UK National Screening Committee

Screening for Prostate Cancer

External review against programme appraisal criteria for the UK National Screening Committee

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The UK National Screening Committee secretariat is hosted by Public Health England.

About the UK National Screening Committee (UK NSC)

The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes. Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

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Plain English summary

There is currently no population screening programme for prostate cancer in the UK. Now in the UK, healthy men over 50 can ask their general practitioner (GP) for a test to measure their prostate-specific antigen (PSA) levels. Before they have the test, they receive all relevant information they need about it and what happens if the test is positive. This review looked to see if screening for prostate cancer in men who do not have symptoms should be recommended in the UK. Prostate cancer is the most common cancer in men in the UK. Of all male cancer diagnoses, 26% are prostate cancer. The risk of getting prostate cancer is higher in older men and in men of black ethnicity. The treatment for prostate cancer can be surgery, radiotherapy or hormone therapy. But some patients are only monitored without receiving treatment.

The most common way to screen for prostate cancer is to measure the levels of the protein called PSA in the blood. But this method has many problems. For example, it can incorrectly diagnose prostate cancer in men who do not actually have it. It could also detect prostate cancer that is benign and would never cause any problems. These men may end up undergoing testing and treatment that they did not need. There is also a chance that the PSA test might miss some cancers. These men might not get the treatment that they need.

This review aimed to find evidence on:

- how PSA screening can reduce prostate cancer becoming more severe and prevent deaths from prostate cancer
- what harms PSA screening can cause
- if there are other tests that are better than PSA to screen for prostate cancer
- how effective treatments for early-stage prostate cancer are (considering balance of harms and benefits).

Based on what the review found, a screening programme for prostate cancer in the UK is not recommended. This is because:

- it is unclear how PSA screening impacts prostate cancer outcomes, specifically death due to prostate cancer
- there are many harms of PSA screening, such as incorrect diagnosis and complications from further testing and treating
- there is not enough evidence at present to show that there are better tests than PSA
- there is no single treatment that is definitely better for patients with early-stage prostate cancer. So, finding these patients by screening would not be worthwhile.

This topic will be reviewed again in 3 years time.

Executive summary

Purpose of the review

This review was conducted to assess whether there is sufficient evidence to consider introducing a population screening programme for prostate cancer in asymptomatic men.

Background

The prostate is a walnut-sized gland located in the pelvis, which forms part of the male reproductive system. Its function is to secrete prostatic fluid, one of the principal components of semen, together with spermatozoa and seminal vesicle fluid. Common disorders of the prostate gland are enlargement (benign prostatic hyperplasia [BPH]), inflammation (prostatitis) and cancer.[1]

Prostate cancer is the most common cancer amongst men in the UK, where it accounts for 26% of all male cancer diagnoses, 14% of male cancer deaths, 13% of total cancer diagnoses and 7% of total cancer deaths in the UK.[2] Localised and locally advanced prostate cancer are more frequently diagnosed than metastatic cancer, which accounted for 16% of new diagnoses in England and Wales in 2016–17.[3] In most cases, prostate cancer progresses slowly and will not cause morbidity or mortality during a man's natural lifetime.[4]

The most commonly used screening tool for prostate cancer is the determination of prostate-specific antigen (PSA) concentration in the blood. PSA, also known as human kallikrein 3 (hK3), is a serine protease enzyme secreted by the epithelial cells in the prostate gland.[5] Elevated serum PSA levels are thought to be indicative of prostate disease, including benign enlargement, prostate infection, and prostate cancer, with between 3 and 4 ng/mL the traditional threshold for the definition of elevated PSA in a screening context.[5, 6]

The incidence of prostate cancer in the UK increased by 41% between 1993–95 and 2014–16;[2] this likely reflects increased detection due to the widespread use of PSA testing and the increased use of surgery to treat benign prostate diseases, which can lead to incidental detection of prostate cancer through examination of tissue samples that are routinely sent for pathological evaluation.[6] However, despite its common use, there are several limitations to using the PSA test for screening. For example, elevated PSA levels are not exclusively indicative of prostate cancer, particularly clinically significant prostate cancer. Therefore, there is the risk of false positive results, along with the adverse implications of identifying clinically insignificant, indolent cancer (slow-progressing disease that will not cause morbidity or mortality during the man's natural lifetime). It has been suggested that overall, the harms of diagnosing and treating

clinically insignificant cancer may outweigh the benefits of screening.[6-8] In addition, paradoxically, the PSA test may not identify a subset of low-PSA (below the cut-off threshold), high-grade prostate cancers with a high risk for prostate cancer specific mortality.[9] There is now growing interest in the use of other tools for screening and identifying those at risk, such as multiparametric magnetic resonance imaging (mpMRI), novel blood or urine-based biomarkers, or risk calculators. Risk calculators incorporate a range of clinical variables such as age; family history; PSA; other biomarkers, including genetic; digital rectal examination (DRE); and imaging results.

Once diagnosed, there are multiple possible treatments for prostate cancer, including radical prostatectomy, radiotherapy, and/or androgen deprivation therapy, which may have adverse side-effects including toxicity, urinary and erectile dysfunction and psychological impacts. Some patients may receive monitoring instead of active treatment, such as active surveillance (regular monitoring of disease in a hospital setting) or watchful waiting (less frequent monitoring, usually in primary care). The most suitable options are dependent on multiple patient-specific factors, including disease stage, Gleason score, general health, age and life expectancy, and a man's personal preferences and choices about treatment.

Focus of the review

This review aimed to identify studies published since the most recent UK NSC review (2015) in order to provide evidence on screening and interventions for prostate cancer. Specifically, new evidence was collected to answer the following 4 questions:

1. Does screening based on PSA reduce short- or long-term prostate cancer morbidity and mortality and all-cause mortality?
2. What are the harms of PSA-based screening for prostate cancer and diagnostic follow-up, with particular reference to overdiagnosis?
3. Is there evidence that screening using risk algorithms or inclusion of markers other than PSA alone can better identify men with clinically significant prostate cancer, or improve screening efficiency?
4. What are the harms and benefits of currently available treatment approaches for early-stage prostate cancer to reduce morbidity and mortality?

Recommendation under review

Based on the 2015 UK NSC review of the evidence, PSA-based screening for prostate cancer in asymptomatic men is not currently recommended in the UK.

Findings and gaps in the evidence of this review

Within the scope of the review, 76 articles were included. Summaries of the question level results are presented below.

Question 1: *Does screening based on PSA reduce short- or long-term prostate cancer morbidity and mortality and all-cause mortality?*

Thirty-one articles reporting on the European Randomized Study of Screening for Prostate Cancer (ERSPC), USA Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial and the UK-specific Cluster Randomised Trial of PSA Testing for Prostate Cancer (CAP) randomised controlled trials (RCTs) were identified for question 1.

All studies reported a significantly higher incidence rate of prostate cancer diagnosis with PSA-based screening compared with no screening or usual care. Nevertheless, due to limited conflicting evidence, it is not possible to conclusively evaluate the impact of PSA-based screening on the diagnosis of prostate cancer stratified by clinical staging. The evidence also remains inconsistent on the effect of PSA-based screening on prostate cancer mortality, compared with no screening or usual care. The ERSPC trial saw a significant reduction in prostate cancer deaths in the screening arm,[10] which was increased to as high as 51% when adjusted for control arm contamination and non-attendance at a 13 year median follow-up,[11] but no such finding was seen in the USA PLCO or UK CAP trials.[12, 13] In both the PLCO and CAP trials, which reported on 15–17 and 10-year median follow-ups, respectively, there was little evidence of a reduction in prostate cancer specific mortality.

It should be considered that the direct comparison of mortality rates between trials is complicated by different screening intervals and PSA thresholds, along with different lengths of follow-up in the different trials. Furthermore, control arm contamination was a significant issue for the PLCO and ERSPC trials, reported to be as high as 62.7% in ERSPC and 54.8% in a study identified in the rapid review for PLCO.[14, 15] Furthermore, a subsequent re-evaluation of control arm contamination of the PLCO concluded that the value was closer to 90%.[16] It is likely that the large number of men assigned to the control arm who nevertheless attended screening appointments (opportunistic screening) diluted the perceived effectiveness of screening in preventing prostate cancer-related deaths. Control arm contamination varied between the PLCO and ERSPC trials, which may also be a contributing factor to the difference in the conclusions drawn about prostate-cancer-specific mortality in these 2 studies.

Question 2: *What are the harms of PSA-based screening for prostate cancer and diagnostic follow-up, with particular reference to overdiagnosis?*

Nine articles reporting on the ERSPC and PLCO trials reported outcomes relevant to Q2.

Harms of screening that were evaluated were overdiagnosis,[17-19] complications associated with biopsy,[20, 21] and quality of life (QoL).[22] Based on the findings of this review, there was evidence to suggest that PSA-based screening may be associated

with overdiagnosis and biopsy-related complications. However, there was no clear effect of PSA-based screening on quality of life. The small number of studies that reported on harms and the wide ranges reported for overdiagnosis (10% to 42%)[18, 19] and biopsy complications (20.2 complications per 1000 biopsies to 67.9%)[20, 23] make it difficult to draw robust conclusions.

Question 3: *Is there evidence that screening using risk algorithms or inclusion of markers other than PSA alone can better identify men with clinically significant prostate cancer, or improve screening efficiency?*

A total of 19 publications reporting on 11 unique studies were initially included in the review for this question. Twelve included studies were deprioritised for extraction as they did not compare a relevant screening test to PSA-based screening or lacked a comparator altogether. Ultimately, 7 primary publications reporting on 6 unique studies were extracted, which compared screening tests for prostate cancer with standard PSA testing. Evidence on the following screening tests was identified: percent free PSA test, digital rectal examination (DRE), PSA test with DRE and prostate cancer antigen 3 (PCA3) test, MRI, PSA test with MRI, and the Stockholm 3 (STHLM3) model.

Two studies evaluated sequential screening methods.[24, 25] The addition of PCA3 was found to significantly improve the area under the curve (AUC) compared with PSA/DRE alone (0.601 vs 0.748; p=0.008), although specificity was low (57.1% at a cut-off of PCA3 ≥35), resulting in a high number of unnecessary biopsies. In the Göteborg pilot study, the PSA ≥1.8 ng/mL followed by MRI screening strategy appeared superior at detecting prostate cancer to PSA ≥3.0 ng/mL followed by MRI, with a sensitivity of 0.73 (95% CI 0.56–0.90) vs 0.46 (95% CI 0.27–0.65) (p=0.08), but had a lower specificity (0.79 [95% CI 0.70–0.87] vs 0.92 [95% CI 0.86–0.97], p<0.001).[24] These findings are yet to be validated in independent populations. MRI alone may be more accurate than PSA testing; however, confidence in these findings is limited by a small sample size of 50 participants.[26] The STHLM3 predictive model represents a promising screening tool that should be subjected to further validation. The AUC for the STHLM3 model was superior to that for the PSA test for the prediction of high-grade (Gleason score ≥7) cancers (AUC 0.75 [95% CI 0.73–0.77] vs 0.58 [95% CI 0.57–0.60]).[27]

In summary, evidence gathered in the current review suggests that MRI (either added to PSA-based screening or alone) and the STHLM3 predictive model may offer greater diagnostic accuracy relative to prostate cancer screening with the PSA test only.

Question 4: *What are the harms and benefits of currently available treatment approaches for early-stage prostate cancer to reduce morbidity and mortality?*

Five systematic literature reviews (SLRs) and 19 publications on 17 RCTs were initially included. The SLRs (2 of which were from the most recent National Institute for Health and Care Excellence (NICE) guidance for managing prostate cancer [NG131]) included 13 unique RCTs. Due to the high volume of evidence identified, a prioritisation strategy

was applied; data was extracted, and studies were included in the evidence synthesis if they compared one relevant intervention to a different relevant intervention or to 'no treatment'. Studies that compared different iterations of the same intervention (e.g. different approaches to performing prostatectomy) were deprioritised from evidence synthesis. Ultimately, 5 SLRs including 13 RCTs and 12 publications on 6 unique RCTs were selected for extraction, resulting in a total of 19 RCTs.

High quality evidence was found for the following treatment comparisons: observation (watchful waiting or active surveillance) vs radiotherapy (RT); observation vs prostatectomy; RT vs prostatectomy; androgen deprivation therapy (ADT) plus RT vs RT and different types of RT. Prostatectomy and RT had some benefit at treating prostate cancer in terms of improving disease progression compared to observation (active surveillance or watchful waiting). However, this was at the consequence of worse adverse events, including urinary and erectile dysfunction and gastrointestinal (GI) and genitourinary (GU) toxicity. There was a lack of evidence distinguishing the effects of treatment for low-, intermediate- and high-risk disease. It is therefore unclear whether the potential benefits of radical treatments on disease progression in comparison to observation can offset the increased rate of adverse events, particularly for men who may never have clinically important disease.

Recommendations on screening

Based on the overall synthesis of evidence against the UK NSC criteria, PSA-based screening of asymptomatic men is still not recommended.

For question 1, overall, the direction of evidence would suggest that whilst PSA-based screening increases the incidence of prostate cancer, the effect on prostate cancer-specific mortality in comparison with no screening or usual care is unclear. Therefore, it is deemed that criterion 11 is not met.

For question 2, overall, it is unclear whether benefit gained from PSA-based screening programmes outweighs harms, particularly overdiagnosis and the complications that could subsequently arise from unnecessary biopsy; thus, criterion 13 is not met.

For question 3, although the evidence is promising, the lack of consistency precludes drawing robust conclusions on the appropriateness of any test as a screening measure to detect prostate cancer. Further studies could confirm the superiority of MRI over PSA-based screening, especially because PSA-based screening also does not meet criteria 11 and 13, investigated in the first part of this review. As such, criteria 4 and 5 are also not met.

For question 4, results for prostatectomy vs RT and comparisons between different RT types were inconclusive. A possible benefit was seen in the addition of ADT to RT compared with RT alone, however, this is incremental and does not inform on how ADT would perform alone or in comparison to other treatments. Overall, of the treatments

that are currently recommended by NICE (those constituting 'usual care'), no intervention could be identified as conclusively superior. Better disease progression offered with RT or prostatectomy vs observation has to be balanced against increased adverse events, particularly in men who may not go on to develop clinically significant disease. It is thus unclear whether early identification of men with prostate cancer would provide them with a therapeutic advantage, and criterion 9 is also not met.

Limitations

Methodological limitations included limiting the searches to only including peer-reviewed, English-language journal articles. The titles, abstracts and full texts were screened by one reviewer, with a second reviewer verifying all included, 10% of excluded decisions and any articles where there was uncertainty about their inclusion.

Evidence uncertainties

Q1 and Q2

The direct comparison of outcomes between trials is complicated by different screening intervals and PSA thresholds, different durations of follow-up which may not be long enough to capture the effects of screening on mortality, and the issue of control arm contamination, particularly in the ERPSC and PLCO trials. It is likely that the relatively large number of men from control arms attending screening appointments (opportunistic screening) has diluted the perceived effectiveness of screening in preventing prostate cancer-related deaths. While contamination in the CAP trial was estimated to be lower at approximately 15%, this still may have influenced mortality.[28] Longer follow-up of the CAP trial may also demonstrate a greater effect of screening.

The majority of screening protocols used a threshold of PSA >3 ng/mL to classify results as positive. Thresholds of 4 ng/mL and 2.5 ng/mL were used in the PLCO and Swedish ERSPC cohorts, respectively. The screening interval varied between trials, from annual screening (PLCO) to once every 7 years (Belgian ERSPC cohort).[10, 12] By contrast, the CAP trial involved a single screening invitation at the start of the study.[12] The comparability between the different thresholds or the influence of the screening interval or biopsy protocol on prostate cancer incidence or mortality is unclear.

The inconsistency in the harm outcomes reported for question 2 makes it difficult to draw robust conclusions on the harms and benefits of screening, as findings are not supported by multiple sources. Further analyses, where possible, are required to further explore harms and benefits such as false-negative results, psychological harms and overtreatment associated with PSA-based screening, in order to confirm the findings of the PLCO and ERSPC trials thus far.

Q3

The comparison of results between the studies is complicated by the use of varying thresholds for the PSA test comparator (3 studies used a PSA threshold of 3 ng/mL, whilst the other 3 studies used 4 ng/mL). The previous UK NSC review found that the use of a 3 ng/mL threshold increased sensitivity for the detection of prostate cancer, but also increased false positive cases and overdiagnosis vs a higher threshold. Furthermore, none of the identified studies characterised the distribution of index test values in the target population. Only one study reported relevant outcomes for more than 2 index test thresholds in an effort to determine the most appropriate threshold. Most notably, none of the studies evaluated the ability of the screening tests to distinguish between insignificant and clinically significant prostate cancer. All but one study applied the reference standard (biopsy) only to the screen-positives, thereby making it impossible to determine the true sensitivity of the test.

Ultimately, as no 2 studies evaluated the same index test(s) and comparator(s), no screening approach was validated by a second, independent study.

Q4

For the majority of treatment comparisons for early prostate cancer (observation vs RT; observation vs prostatectomy; RT vs prostatectomy), conclusions about the consistency of the evidence could not be drawn because the comparison was only reported in one RCT. Whilst RT and prostatectomy were found to be superior to observation (watchful waiting or active surveillance) in terms of disease progression outcomes, this was with the consequence of worse adverse events, including GI and GU toxicity.

There was also very little evidence which stratified by prostate cancer risk group (low-, intermediate- or high-risk; only reported in 2 studies), which adds to the uncertainty of choosing radical treatment over observation treatment in men who may not suffer from clinically significant disease.

Introduction and approach

Background

The prostate is a walnut-sized gland located in the pelvis, which forms part of the male reproductive system. Its function is to secrete prostatic fluid, one of the principal components of semen, together with spermatozoa and seminal vesicle fluid. Common disorders of the prostate gland are enlargement (benign prostatic hyperplasia [BPH]), inflammation (prostatitis) and cancer.[1]

In clinical practice, prostate cancer is typically evaluated according to the Tumour, Node, Metastasis (TNM) staging system, whereby cancer is classified according to the size of the tumour, whether it has metastasised to a different part of the body, and whether it has spread to the lymph nodes.[29] Prostate cancer can also be labelled as localised, denoting cancer that remains fully contained within the prostate gland; locally advanced, reflecting cancer that has broken through the capsule (outer layer) of the prostate gland; or advanced, representing cancer that has spread to other parts of the body. The latter might entail direct growth into the nearby bladder or rectum, and/or metastasis to the lymph nodes, bones, or other body tissues.[29] In its early stages, prostate cancer is often asymptomatic, with symptoms emerging as the disease progresses. If symptoms do occur, these typically affect urinary function due to the proximity of the prostate gland to the urethra, and include frequent urination, increased urination at night (nocturia), difficulty starting or maintaining a urine stream (urinary hesitancy), blood in the urine (haematuria), and painful urination (dysuria). However, these are also common consequences of the normal enlargement of the prostate gland that occurs with ageing, and therefore do not necessarily indicate the presence of prostate cancer.[30, 31] Symptoms that often accompany locally advanced or metastatic prostate cancer are erectile dysfunction, as well as back, hip and pelvic pain, blood in the urine or semen, and unexplained weight loss.[30]

Burden

Prostate cancer is the most common cancer amongst men in the UK, where it accounts for 26% of all male cancer diagnoses and 14% of male cancer deaths, and 13% of total cancer diagnoses and 7% of total cancer deaths in the UK.[2] There were 47,740 new diagnoses and 11,714 deaths from prostate cancer in 2016 in the UK and approximately 400,000 men in the UK have a current or previous diagnosis of the disease.[1 2, 31] Localised and locally advanced prostate cancer are more frequently diagnosed than metastatic cancer, which accounted for 16% of new diagnoses in England and Wales in 2016–17.[3]

The burden is particularly high in men with risk factors. In England, the lifetime risk of prostate cancer diagnosis is 29% for black men, in comparison with 13% for white men and 8% for Asian men.[32] Prostate cancer burden also increases with age, becoming the most common cancer in men aged >45,[33] and with mortality rates in the UK highest in men aged >90.[2]

Internationally, there were approximately 1.3 million new prostate cancer diagnoses and 350,000 prostate cancer deaths in 2018, representing 7.1% and 3.8% of total cancer diagnoses and deaths respectively.[34] Age-standardised prostate cancer incidence was highest in Australia, New Zealand, Northern Europe, Western Europe and North America, and lowest in South-Central Asia, whereas age-standardised prostate cancer mortality was highest in South America and the Caribbean, and lowest in South-Central Asia.[34]

The incidence of prostate cancer in the UK increased by 41% between 1993–95 and 2014–16;[2] this likely reflects increased detection due to the increasing and widespread use of PSA testing and the increased use of surgery to treat benign prostate diseases, which can lead to incidental diagnoses of prostate cancer.[6]

Natural history and aetiology

Around 95% of prostate cancers are adenocarcinomas,[35] with approximately 70% of these originating in the largest part of the prostate, the peripheral zone.[36] Prostatic intraepithelial neoplasia (PIN) has been identified as a possible precursor to prostate cancer, as it is most commonly found in the peripheral zone and possesses a phenotype that is intermediate between benign and cancerous epithelial tissue.[37] Following detection of high-grade PIN, more than 30% of patients are diagnosed with prostate cancer during the subsequent year.[38] Additionally, the androgen receptor signalling pathway, including 2 major androgens, testosterone and dihydrotestosterone (DHT), may be implicated in prostate cancer progression and the survival of prostate cancer cells. This is based on the observations that 90–95% of testosterone is produced in the testicles and prostate cancer is rarely observed in eunuchs, and similarly, that prostate cancer is not seen in men deficient in 5-α-reductase, an enzyme that converts testosterone to DHT.[37, 39] Furthermore, androgen administration triggers prostate enlargement, whereas removal of the testicles (orchidectomy) and androgen deprivation therapy cause prostate cancer to regress.[37, 39, 40]

Prostate cancer is associated with both modifiable (body mass index [BMI], diet) and unmodifiable risk factors (age, ethnicity and genetics).[6, 41] For example, the disease becomes increasingly common with advancing age, with just 1% of diagnoses occurring in men <50 years[6] and only 25% of cases affecting men <65 years,[42] meanwhile, black men are at roughly twofold increased risk relative to white men.[32]

Multiple genes have been implicated in prostate cancer risk, including rare mutations in *BRCA1* and *BRCA2*, which are also risk factors for breast and ovarian cancer in women. Men with a mutation in *BRCA2* have a significantly increased risk of prostate cancer and a greater likelihood of diagnosis with clinically significant disease.[43, 44] There are many more (upwards of 100) mutations that are more common (allele frequencies of ≥5%). Individually, these more common alleles confer a low-to-moderate risk (per-allele odds ratios [ORs] in the region of 1.06 to 1.14),[45] but cumulatively contribute to a higher risk of prostate cancer development in a log-additive or multiplicative fashion.[46, 47] Some variants may also be predictive of more aggressive disease.[47] Prostate cancer risk is also increased in individuals with family history of the disease, further highlighting the contribution of genetic factors to the disease risk.[48-50] Among modifiable risk factors, a higher BMI is associated with an increased risk of diagnosis with advanced disease over earlier-stage disease,[51, 52] and high exposure to pesticides has been shown to increase overall prostate cancer risk.[53]

In most cases, prostate cancer progresses slowly and will not cause morbidity or mortality during the patient's natural lifetime. This is known as indolent or clinically insignificant prostate cancer.[54] By contrast, a minority of cancers are aggressive and progress rapidly to metastasis and death; these are known as clinically significant cancers.[6] In clinical practice, men are regularly stratified into groups at low, medium or high risk of progression, based on multiple clinical parameters using risk assessment tools such as the D'Amico classification system or the Cancer of the Prostate Risk Assessment (CAPRA) score.[41] The D'Amico classification system assesses the 5-year risk of treatment failure based on clinical stage, Gleason score (histopathological analysis of prostate tissue with higher scores indicative of a worse prognosis)[55] and levels of prostate-specific antigen (PSA) in the blood.[56, 57] Nonetheless, the likelihood of disease progression remains difficult to predict, and existing risk stratification tools are relatively inaccurate at differentiating clinically significant and insignificant prostate cancer.[58] Consequences of this may include the unnecessary treatment of patients with clinically insignificant cancer or conversely, the delayed initiation of necessary treatment for significant disease, as described in further detail below.

Prostate-specific antigen (PSA) test

The most commonly used screening tool for prostate cancer is the determination of PSA concentration in the blood. PSA, also known as human kallikrein 3 (hK3), is a serine protease enzyme secreted by the epithelial cells in the prostate gland.[5] In prostate cancer, the architecture of these epithelial cells is disrupted, allowing PSA to leak into the extracellular space and escape into the circulation,[5] hence elevated serum PSA levels are thought to be indicative of prostate cancer, with 3–4 ng/mL the traditional threshold for the definition of elevated PSA.[5, 6]

Limitations

Despite its common use, there are several limitations to PSA screening. Firstly, elevated PSA levels are not exclusively indicative of prostate cancer; they are also associated with benign conditions such as BPH and prostatitis,[6, 41, 59] and other factors/exposures including urinary infection, vigorous exercise, recent ejaculation, bladder or prostate gland surgery, digital rectal examination (DRE) and previous prostate biopsy.[60] Conversely, prostate cancer (including aggressive disease) can be present in the absence of elevated PSA[9] which may be due to the PSA-lowering effects of comorbid conditions such as obesity,[61] or of 5-α-reductase inhibiting drugs such as finasteride and dutasteride,[60] which are commonly prescribed to treat BPH in elderly men. Consequently, the PSA test is vulnerable to both false positive and false negative results; in the US-based Prostate Cancer Prevention Trial (PCPT), PSA had a sensitivity of 21% (79% false negative rate), a specificity of 91% (9% false positive rate), a positive predictive value (PPV) of 30%, and a negative predictive value (NPV) of 85% using a 4 ng/mL cut-off. The lower threshold of 3 ng/mL PSA had a higher sensitivity of 32% (68% false negative rate) but at the cost of a lower specificity of 85% (15% false positive rate.[62-64] High rates of false positives and false negatives have multiple adverse implications for patients. For example, in the event of a false positive, the patient is unnecessarily exposed to the physical and psychological side-effects of the highly invasive prostate needle biopsy procedure that is typically used to confirm diagnosis,[7, 8] whereas in the event of a false negative, the patient is given false assurances which can delay detection of the disease and may worsen their prognosis. Indeed, it has been suggested that the delayed detection of prostate cancer in obese men may contribute to the worse clinical outcomes observed in this subpopulation.[61, 65] In addition, the PSA test cannot reliably distinguish between patients with clinically significant and insignificant prostate cancer.[6] Use of the PSA test may therefore lead to overdiagnosis and subsequent overtreatment; that is, the diagnosis of prostate cancer that would be unlikely to cause overt symptoms during a patient's lifetime or to shorten their life expectancy that is then unnecessarily treated, exposing men to the adverse effects of radical treatment for no benefit. Multiple investigations have suggested that overall, the harms of diagnosing and treating clinically insignificant cancer may outweigh the benefits of screening.[6-8]

Current recommendations on the use of PSA-based screening

Major ongoing RCTs of PSA-based screening, the ERSPC, the US-based PLCO Cancer Screening Trial and the UK-based CAP trial, have so far produced conflicting results in terms of the impact of screening on prostate cancer mortality.[12, 68-70] Faced with inconclusive data regarding the effectiveness of PSA-based screening, many major health organisations recommend against systematic population screening for prostate cancer with the PSA test. The majority suggest that an individualised discussion-based approach is more appropriate, although the exact recommendations vary between organisations, as detailed in Table 1.[59]

For those men who do opt to undergo screening, there is also some heterogeneity in the recommendations around PSA-based testing practice. For example, some organisations advocate the use of age-specific PSA thresholds, while race-specific PSA thresholds have also been proposed in the USA.[41] There is also disagreement regarding the optimal interval for PSA screening. Recommendations from different organisations range from one to 4 years, but there is limited evidence regarding the harms and benefits of different screening intervals.[66] Risk-adapted screening, whereby the regularity of screening is individually determined based on an initial midlife PSA test, is currently under investigation in PROBASE, a randomised controlled trial (RCT) in Germany.[67]

The existing recommendation from the UK NSC is that systematic population screening for prostate cancer should not be offered, due to the inaccuracy of the PSA test as a screening tool, its inability to distinguish clinically significant from insignificant prostate cancer, and the possibility that the harms of PSA screening (including adverse effects of biopsy and treatment) may outweigh its benefits.[71] This recommendation was based on a 2015 UK NSC review, which concluded that the evidence base regarding population screening for prostate cancer had not altered significantly since the preceding UK NSC review, published in 2010. The 2010 and 2015 UK NSC reviews cite the findings of a University of Sheffield School of Health and Related Research (ScHARR) model, first published in 2009 and updated in 2013, which estimated that the harms of the adverse effects of treatment outweigh the potential survival benefits of systematic prostate cancer screening.[72]

Even though population screening is not recommended in the UK, the Prostate Cancer Risk Management Programme (PCRMP) recommends that any asymptomatic man aged 50 or over should be able to request a PSA test after careful discussion with his general practitioner (GP) and consideration of the implications.[73] The PCRMP provides GPs and primary care professionals with information to counsel asymptomatic men aged 50 and over that enquire about PSA testing, although GPs are advised against proactively encouraging PSA testing in asymptomatic men.[73]

Table 1: Current recommendations for PSA screening

Organisation	Country	Year	Age	Recommendation(s)	Notes
UK National Screening Committee[6, 71]	UK	**2016**	All ages	Recommend against systematic population screening	
Prostate Cancer Risk Management Programme[73]	UK	**2016**	≥50	Screening discussions	Asymptomatic men aged 50 or over should be able to request a PSA test after careful discussion with their GP and consideration of the implications
Canadian Task Force on Preventive Health Care[74]	Canada	**2014**	55–69	Recommend against routine screening	Weak recommendation with moderate quality evidence
			<55 or ≥70	Recommend against routine screening	Strong recommendation with low quality evidence
European Association of Urology[75]	Europe	**2018**	All ages	Screening discussions	Recommend against PSA screening without prior counselling on potential risks and benefits, but offer an individualised, risk-adapted strategy for early detection to well-informed men with good performance status and life expectancy ≥10–15 years Recommend against routine screening in all men with life expectancy of <15 years
			>50	Offer early PSA testing	In well-informed men
			>45 and African-American ethnicity or positive family history	Offer early PSA testing	In well-informed men
European Society for Medical Oncology[76]	Europe	**2015**	All ages	Recommend against population-based screening	Also specify that testing for prostate cancer in asymptomatic men should not be done in men over 70 years old
American Academy of Family Physicians[77]	USA	**2019**	<55 or ≥70	Recommend against routine screening	Strong recommendation with low quality evidence
			≥70	Recommend against screening	Rationale: lower benefit of screening due to risk of mortality from other non-prostate cancer causes and increased risk of harms from screening in older men
American Cancer Society[78]	USA	**2016**	50 at average risk	Screening discussions	Average risk and expected to live at least 10 more years
			45 at high risk	Screening discussions	High risk: African-American ethnicity; first degree relative with prostate cancer diagnosed at <65 years old
			40 at very high risk	Screening discussions	Very high risk: >1 first degree relative with prostate cancer diagnosed at <65 years old
	USA	**2015**	50–69	Shared decision making	

Organisation	Country	Year	Age	Recommendation(s)	Notes
American College of Physicians[79]			<50 or ≥70	Recommend against routine screening	This recommendation also applies to those men with a life expectancy of <10 years and those who had not had an informed discussion
American Urological Association[80]	USA	**2013**	55–69	Shared decision making	
			40–54	Recommend against routine screening for men at average risk	However, recommends that decisions regarding prostate cancer screening should be individualised for men at higher risk e.g. positive family history or African-American race
			<40	Recommend against routine screening	This recommendation also applies to those men with a life expectancy of <10–15 years
US National Comprehensive Cancer Network[81]	USA	**2018**	45–75	Offer screening	Begin discussing PSA screening with African-American men several years earlier than white men
			>75	Continue screening with caution in healthy patients with little or no comorbidity	
US Preventive Services Task Force[8]	USA	**2018**	55–69	Screening discussions	Provide information about the benefits and harms of screening
			≥70	Recommend against screening	

Source: Updated and adapted from Tikkinen 2018[59]

Novel biomarkers, diagnostic and risk stratification tools

Given the inherent limitations of the PSA test, there is growing interest in its use in combination with other risk stratification tools prior to definitive diagnostic evaluation with prostate biopsy.[82-84] The 2019 National Institute for Health and Care Excellence (NICE) guidance document (NG131) recommends that a multiparametric magnetic resonance imaging (mpMRI) scan is performed prior to biopsy in patients with suspected localised prostate cancer that are eligible for radical treatment.[85] Two RCTs (Prostate MRI Imaging Study [PROMIS] and PRECISION) concluded that mpMRI scanning could allow more than 25% of suspected prostate cancer patients to avoid an unnecessary biopsy.[86, 87] MpMRI offers high resolution visualisation of the prostate gland, enabling clinicians to detect suspicious lesions and, following standardised guidelines known as the Prostate Imaging Reporting and Data System (PI-RADS), to assess the likelihood of clinically significant prostate cancer on a 5-point scale.[88] It also aids the staging of prostate cancer through the evaluation of locoregional extension, lymph node involvement and bone metastases in the pelvic region.[88] However, there is little evidence on whether a strategy using mpMRI reduces prostate cancer metastases or mortality.

In addition, considerable research effort has been invested in the identification of novel biomarkers for prostate cancer. Like mpMRI scanning, these have largely been used to triage patients with elevated PSA levels, with the aim of avoiding unnecessary biopsies, rather than as a direct replacement for the PSA test.[82, 83] Firstly, it has been argued that alternative PSA indices could improve the accuracy of PSA testing; these include PSA velocity, PSA density, and free PSA (fPSA) and its many subtypes and derivatives, such as the ratio of free-to-total PSA (%fPSA), intact PSA (iPSA), precursor PSA (proPSA), p2PSA, and the ratio of p2PSA-to-fPSA (%p2PSA). There is some evidence that these indices offer greater diagnostic accuracy than total PSA alone.[82, 83, 89, 90] Secondly, the Prostate Health Index (PHI) is an algorithm that combines 3 PSA measures (total PSA, free PSA and p2PSA) into a single score (Carlsson and Roobol 2017), and it has been found that calculating PHI after a positive PSA test might avoid 36–41% of unnecessary biopsies.[91] Thirdly, urinary biomarkers such as PCA3 and TMPRSS2:ERG are prostate-enriched genes whose mRNA can be detected in urine after DRE, and whose expression levels are associated with prostate cancer.[82, 83] Fourthly, the Mi-Prostate Score (MiPs) tool measures the urinary mRNA levels of both genes, together with serum PSA. It has shown early diagnostic promise, but has yet to be tested in large prospective studies.[82, 83] Finally, a 2015 systematic review by NICE in collaboration with the National Institute for Health Research (NIHR) found that the clinical benefit of using the PCA3 assay or the PHI in combination with existing screening tests had yet to be confirmed.[92]

Alternatives to the use of the PSA test alone are nomograms or risk calculators, which incorporate a range of clinical variables, such as age, family history of prostate cancer, PSA indices, DRE findings, germline genotyping, proteomics, and imaging results such as prostate volume. Examples include the ERSPC Risk Calculator (ERSPC-RC) and the Prostate Cancer Prevention Trial Risk Calculator (PCPT-RC).[64, 82, 83, 93] Recent data show that the diagnostic accuracy of risk calculators can be improved through their amalgamation with more modern tools such as the PHI. More contemporary risk calculators have also been introduced, such as 4Kscore, the SelectMDx® tool, and the Stockholm-3 (STHLM3) risk calculator or Stockholm-3 model (S3M).[82, 83] Full details of common risk calculators and their clinical parameters can be found in Table 2.

Meta-analyses have shown that most risk calculators offer better diagnostic accuracy than total PSA alone,[94] and studies have shown that they are able to achieve a significant reduction in unnecessary biopsies.[82, 95-97] Furthermore, risk calculators are extremely accessible since they involve readily available clinical parameters and can be calculated simply using mobile apps or web-based tools,[83] although Western risk calculators show limited diagnostic efficacy when applied to Asian populations.[98] In the UK, the use of prostate cancer nomograms by clinicians is currently recommended by NICE to help patients make treatment decisions, and to predict biopsy results, pathological stage and risk of treatment failure.[85]

Table 2: Risk calculators/nomograms for prostate cancer detection

Risk calculator/ nomogram	Details	Source
ERSPC-RC	PSA, ultrasound prostate volume, clinical stage, prostate biopsy Gleason grade, total length of cancer and noncancer tissue in biopsy cores	[93]
PCPT-RC	Age at biopsy, race, family history of prostate cancer, PSA level, PSA velocity, DRE result, and previous prostate biopsy	[64]
PHI	Total PSA, fPSA and p2PSA	[99]
MiPS	Urinary mRNA levels of PCA3 and *TMPRSS2:ERG,* together with serum PSA	[100]
4Kscore	Combined measurement of age, DRE, prior biopsy results and total PSA, fPSA, iPSA and hK2	[101]
SelectMDx®	Urinary mRNA levels of *HOXC6* and *DLX1* normalised to levels of *KLK3*, alongside PSA, DRE, prostate volume and family history	[96]
STHLM3 or S3M	Clinical parameters (age, family history, previous prostate biopsy, prostate exam), plasma protein biomarkers (PSA, fPSA, iPSA, hK2, MSMB, MIC1) and >200 SNPs	[97]

Abbreviations: *DLX1, distal-less homeobox 1*; DRE, digital rectal examination; ERSPC-RC, European Randomised Study of Screening for Prostate Cancer Risk Calculator; fPSA, free prostate-specific antigen; hK2, human glandular kallikrein; *HOXC6, homeobox C6*; iPSA, intact prostate-specific antigen; *KLK3, kallikrein-3*; MIC1, macrophage inhibitory cytokine; MiPS, Michigan Prostate Score; mRNA, messenger ribonucleic acid; MSMB, microseminoprotein Beta; p2PSA, [-2]pro prostate-specific antigen; PCA3, prostate cancer antigen 3; PCPT-RC, Prostate Cancer Prevention Trial

Risk Calculator; PHI, Prostate Health Index; PSA, prostate-specific antigen; S3M, Stockholm 3 Model; SNP, single nucleotide polymorphism; STHLM3, Stockholm 3; *TMPRSS2:ERG, transmembrane protease serine 2:v-ets erythroblastosis virus E26 oncogene homolog*

Finally, standalone single nucleotide polymorphism (SNP) panels have also been the subject of recent interest, but have yet to yield conclusive results.[102] Other nascent diagnostic approaches include the epigenetic profiling of prostate biopsy tissue,[103] the genetic profiling of microRNAs released by cancer cells in the blood and other biofluids[104] and the genetic profiling of mitochondrial DNA (mtDNA) isolated from blood samples.[105]

Treatment for prostate cancer

There are multiple possible treatments for prostate cancer, but the available options are dependent on multiple patient-specific factors, including disease stage, Gleason score, general health, age and life expectancy. In many cases, there is no indicated 'best option' for a particular stage, so as with PSA screening, patients can be educated about the strengths and limitations of each option, and encouraged to make an informed decision.[85, 106]

Some patients may receive conservative monitoring instead of radical treatment. This conservative treatment could involve active surveillance, which entails regular monitoring of the disease in a hospital outpatient setting, with the intention of initiating curative treatment in the event of disease progression,[8, 106] or watchful waiting that involves less regular monitoring, usually in a primary care setting, with the intention of starting palliative treatment in the event of disease progression.[106] Other patients with primary prostate cancer may receive an active interventional treatment, which could include radical prostatectomy (the surgical removal of the entire prostate gland) and/or radiotherapy (with several different modalities in terms of dosage, method of delivery) with or without adjunctive androgen deprivation therapy.[85, 106] External beam radiotherapy involves the delivery of high-energy X-rays to the prostate from outside the body, whereas brachytherapy entails the internal application of a radiation source, via permanent implantation (seed brachytherapy) or temporary delivery through a tube (high dose-rate brachytherapy).[106] Androgen deprivation therapy by itself is not curative; instead, it aims to delay or manage symptoms, and is often used in combination with other interventions to improve their effectiveness.[106] For metastatic prostate cancer, possible treatments include the chemotherapy drug docetaxel, orchidectomy and androgen deprivation therapy.[85] Current treatment recommendations for the UK by specific cancer stage are summarised in Table 3.

Table 3: NICE treatment recommendations for prostate cancer

Stage of prostate cancer	Recommended treatment options notes
Low-risk localised	• Active surveillance • Radical prostatectomy • Radical radiotherapy
Intermediate-risk localised	• Active surveillance (considered in those who do not choose immediate radical treatment) • Radical prostatectomy • Radical radiotherapy
High-risk localised	When likely that disease can be controlled in the long-term: • Radical prostatectomy • Radical radiotherapy
Locally advanced	• Radical radiotherapy, including considering pelvic radiotherapy for men with >15% risk of pelvic lymph node involvement • Hormonal therapy
Metastatic	• Docetaxel chemotherapy • Bilateral orchidectomy, offered as an alternative to continuous luteinising hormone-releasing hormone agonist therapy • Anti-androgen monotherapy with bicalutamide • Androgen deprivation therapy

Source: NICE guideline NG131[85]

More recently-developed treatments for localised prostate cancer include focal ablative therapy, which involves the targeted destruction of a prostate lesion with a laser, electromagnetic energy (radiofrequency ablation), electrical currents (irreversible electroporation), rapid cooling (cryoablation), light-activated generation of reactive oxygen species (photodynamic therapy) or high-intensity focused ultrasound (HIFU).[107] These techniques are relatively novel, and with the exception of HIFU, are not yet widely available in the UK.[106]

Existing prostate cancer treatments are associated with a range of adverse effects.[6-8, 41, 85] Radiotherapy and radical prostatectomy can lead to urinary, bowel and sexual disorders; for example, 1 in 6 men receiving radiotherapy suffer from bowel urgency and faecal incontinence, while more than half develop erectile dysfunction. In radical prostatectomy, 3 in 1,000 suffer perioperative death, 50 in 1,000 have serious surgical complications, 1 in 5 develop urinary incontinence and 2 in 3 develop erectile dysfunction.[8] Furthermore, postoperative infections are experienced by 1–5 in 100 men following radical prostatectomy.[106] The side effects of androgen deprivation therapy include hot flushes, gynecomastia, sexual dysfunction, osteoporosis and fatigue.[85] The treatment of prostate cancer is also associated with psychological side-effects, such as anxiety and depression; the risk of depression is particularly high with post-surgery androgen deprivation therapy.[108, 109] This array of adverse effects underscores why overtreatment is such a serious issue in prostate cancer.

Current policy context and previous reviews

The existing recommendation from the UK NSC is that systematic population screening for prostate cancer should not be offered, based on the inaccuracy of the PSA test as a diagnostic tool, its inability to distinguish clinically significant from insignificant prostate cancer, and the possibility that the harms of PSA screening may outweigh its benefits.[71] Nonetheless, prostate cancer remains a substantial public health burden, and significant research effort is being invested in the disease throughout the world, particularly towards the development of novel diagnostic tools.

This rapid review aims to identify evidence published since the most recent UK NSC review,[6] including the most recent results of trials that were not captured by the previous review (ERSPC, PLCO and CAP), to provide an overview of the current landscape of screening and interventions for prostate cancer. Specifically, new evidence will be collected to answer the following four questions:

1. Does screening based on PSA reduce short- or long-term prostate cancer morbidity and mortality and all-cause mortality?
2. What are the harms of PSA-based screening for prostate cancer and diagnostic follow-up, with particular reference to overdiagnosis?
3. Is there evidence that screening using risk algorithms or inclusion of markers other than PSA alone can better identify men with clinically significant prostate cancer, or improve screening efficiency?
4. What are the harms and benefits of currently available treatment approaches for early-stage prostate cancer to reduce morbidity and mortality?

A key focus will be on the differentiation of clinically significant and insignificant disease, as the current inability to predict which cases of prostate cancer will experience disease progression poses a considerable challenge for disease management.

Objectives

This review aims to assess whether there is sufficient evidence to consider introducing a screening programme for prostate cancer in asymptomatic men. The review will appraise evidence on the questions in Table 4, which each relate to the criteria set out by the UK NSC for assessing the suitability of a screening programme.

Table 4. Key questions for the evidence summary, and relationship to UK NSC screening criteria

	Criterion	Key questions	Studies included
	THE TEST		
4	There should be a simple, safe, precise and validated screening test.	Is there evidence that screening using risk algorithms or inclusion of markers other than PSA alone can better identify men with clinically significant prostate cancer, or improve screening efficiency? **(Q3)**	19 publications on 11 unique cohorts
5	The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.	Is there evidence that screening using risk algorithms or inclusion of markers other than PSA alone can better identify men with clinically significant prostate cancer, or improve screening efficiency? **(Q3)**	
	THE INTERVENTION		
9	There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.	What are the harms and benefits of currently available treatment approaches for early-stage prostate cancer to reduce morbidity and mortality? **(Q4)**	5 SLRs and 19 publications on 17 RCTs
	THE SCREENING PROGRAMME		
11	There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (such as Down's syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value	Does screening based on PSA reduce short- or long-term prostate cancer morbidity and mortality and all-cause mortality? **(Q1)**	31 publications on 3 unique RCTs

	Criterion	Key questions	Studies included
	and readily understood by the individual being screened.		
13	The benefit gained by individuals from the screening programme should outweigh any harms, for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications	What are the harms of PSA-based screening for prostate cancer and diagnostic follow-up, with particular reference to overdiagnosis? **(Q2**)	9 publications on 2 unique studies

Methods

The current review was conducted by Costello Medical, in keeping with the UK National Screening Committee evidence review process. Database searches were conducted on 2 September 2019 to identify studies relevant to the questions detailed in Table 4.

Eligibility for inclusion in the review

The following review process was followed:

1. Each abstract was reviewed against the inclusion/exclusion criteria by one reviewer. Where the applicability of the inclusion criteria was unclear, the article was included at this stage in order to ensure that all potentially relevant studies are captured. A second independent reviewer provided input in cases of uncertainty and validated all included and 10% of excluded articles. Any disagreements were resolved by discussion until a consensus was met.
2. Full-text articles required for the full-text review stage were acquired if freely available online or through the Cambridge University Library. Any paywalled articles unavailable at the Cambridge University Library were purchased.
3. Each full-text article was then reviewed against the inclusion/exclusion criteria by one reviewer, who determined whether the article was relevant to one or more of the review questions. A second independent reviewer provided input in cases of uncertainty and validated all included and 10% of excluded articles. Any disagreements were resolved by discussion until a consensus was met.

Eligibility criteria for each question are presented in Table 5,
Table 6 and Table 7 below. For all questions, systematic literature reviews (SLRs) and meta-analyses (MAs) were considered for inclusion. If the scope of an SLR or MA was very closely aligned to one of the topics of this review, it was included in its own right. However, where the scope was not closely aligned to one of the topics of this review but some of the included articles may have been of interest, the reference list of the SLR or MA was hand-searched. Any relevant primary research articles identified were included, but the SLR itself was excluded.

Table 5. Inclusion and exclusion criteria for question 1 and 2

Domain	Population	Intervention	Comparator	Outcome	Study type	Setting	Other considerations
Inclusion criteria	Asymptomatic unselected adult men in primary care settings	PSA-based screening programme, including but not limited to Single-threshold PSA test Age-specific thresholds Variable screening intervals	No screening or usual care	Q1: Short- or long-term morbidity/mortality outcomes, including but not limited to: Prostate cancer mortality Prostate cancer-specific morbidity, including but not limited to: Bone pain from metastases Urinary dysfunction Incidence of advanced-stage cancer All-cause mortality Q2: Harms of PSA-based screening for prostate cancer, including but not limited to: False-positive results False-negative results Physical harms of screening or biopsy Psychological harms Overdiagnosis, particularly in terms of over-detection of clinically insignificant disease (i.e. those that need not even be followed by active surveillance) Overtreatment of clinically relevant but low-risk disease (i.e. treatment where active surveillance would be suitable)	RCTs, meta-analyses, systematic reviews (of included study designs)	Any country	Articles published in the English language and since January 2014
Exclusion criteria	Men with symptoms that are highly suspicious for prostate cancer or not in primary care settings Men specifically selected for the presence of another condition or risk factor, e.g. other types of cancer, men working with chemicals known to be carcinogenic, men with known genetic risk of prostate cancer	Any other type of screening programme	Any other comparator	Any other outcomes	Any other study design, including non-randomised trials or interventional studies, cohort studies, case-control studies, case reports, case series, narrative reviews, editorials, commentaries, letters, conference abstracts or other publication types that have not been peer-reviewed	N/A	Studies with full text not in the English language Studies published pre-2014

Abbreviations: N/A, not applicable; RCT, randomised controlled trial.

Table 6. Inclusion and exclusion criteria for question 3

Domain	Population	Intervention	Comparator	Outcome	Study type	Setting	Other considerations
Inclusion criteria	Asymptomatic unselected adult men in primary care settings	**Index test** Tests used alone, sequentially or in combination to predict prostate cancer, including but not limited to: • Clinical variables (e.g. age, family history of prostate cancer, a previous biopsy) • Ratio of free to total PSA • Blood biomarkers (PSA, MIC1 etc.) or biomarker panels (4K panel, STHLM3 panel) • Urine biomarkers • Genetic markers • DRE • Prostate volume • Imaging markers/techniques (e.g. mp-MRI) • Nomograms combining one or more of the above variables or tests **Reference standard** Confirmed prostate cancer diagnosis via: • TPM biopsy or TRUS-guided biopsy • National cancer	**Tier 1:** • PSA-based screening only (including single-threshold PSA test, age-specific thresholds, variable screening intervals) • Usual care **Tier 2:** • No comparator • Another relevant screening test	Measures of screening accuracy: • Test performance (e.g. AUC, sensitivity, specificity, PPV, NPV) Disease-related outcomes: • Prostate cancer mortality • Cancer stage shift e.g. reduction in stage IV prostate cancers	RCTs, meta-analyses and systematic reviews, observational studies with consecutively enrolled populations	Any country	Articles published in the English language and since January 2014

Domain	Population	Intervention	Comparator	Outcome	Study type	Setting	Other considerations
		registry reported cases					
Exclusion criteria	Men with symptoms that are highly suspicious for prostate cancer or not in primary care settings Men specifically selected for the presence of another condition or risk factor, e.g. other types of cancer, men working with chemicals known to be carcinogenic, men with known genetic risk of prostate cancer	Irrelevant index tests	Any other comparators	Any other outcomes	Any other study design, including case reports, case series, narrative reviews, editorials, commentaries, letters, conference abstracts or other publication types that have not been peer-reviewed	N/A	Studies with full text not in the English language Studies published pre-2014

Abbreviations: AUC, area under the curve; DRE, digital rectal examination; MIC1, macrophage inhibitory cytokine**;** mp-MRI, multi-parametric magnetic resonance imaging; N/A, not applicable; NPV, negative predictive value; PPV, positive predictive value; PSA, prostate specific antigen; RCT, randomised controlled trial; STHLM3, Stockholm3; 4K, 4-kallikrein; TPM biopsy, template prostate mapping biopsy; TRUS-guided biopsy, transrectal ultrasound-guided prostate.

Table 7. Inclusion and exclusion criteria for question 4

Domain	Population	Intervention	Comparator	Outcome	Study type	Setting	Other considerations
Inclusion criteria	Adult men with early-stage (stage I or stage II or 'localised'[a]) prostate cancer, including those for which the definition of 'early' or	Any of the following interventions, alone or in combination Curative interventions: • Surgery (radical prostatectomy, including different surgical techniques) • High-intensity focused	**Tier 1:** No treatment Any eligible intervention used as a comparator **Tier 2:** The same intervention with	Effects of treatment approaches: • Mortality (overall and disease-specific) • Metastasis-free survival (or rate of metastasis development) • Quality of life (overall and disease-specific) • Functioning (overall and disease-specific)	RCTs, meta-analyses and systematic reviews	Any country	Articles published in the English language and since January 2018 for the interventions of interest that were included in the NICE SLRs, and since

Domain	Population	Intervention	Comparator	Outcome	Study type	Setting	Other considerations
	'localised' is unclear	ultrasonography • Radiation therapy (external-beam radiation therapy, proton beam therapy, brachytherapy, combination therapies) • Ablative therapy Adjunctive therapy: • Hormone therapy (androgen deprivation therapy) Monitoring: • Watchful waiting • Active surveillance	a minor difference e.g. in dose, schedule, modality	• Bowel, urinary and sexual dysfunction • Psychological effects (e.g. depression) • Endocrinological effects (e.g. bone health, hot flashes, gynaecomastia) • Surgical complications • Rate of disease recurrence – after successful initial treatment • Radiotherapy complications • Complications from active surveillance (e.g. infections and other side effects due to more frequent biopsies)			January 2014 (date of the searches for the previous UK NSC review) for the interventions of interest that were not included in the NICE SLRs (high-intensity focused ultrasonography, ablative therapy, hormone therapy)
Exclusion criteria	Men without prostate cancer or men with advanced or later-stage prostate cancer	Any other interventions	Any other comparators	Any other outcomes	Any other study design, including case reports, case series, narrative reviews, editorials, commentaries, letters, conference abstracts or other publication types that have not been peer-reviewed	N/A	Studies will full text no in the English language Studies published pre-2018 or pre-2014 for the specific interventions not included in the NICE SLRs

[a]Localised prostate cancer included stage T3a in the authors' definition in 2 SLRs and 2 primary RCTs.[110-113]

Abbreviations: N/A, not applicable; NICE, National Institue for Health and Care Excellence; RCT, randomised controlled trial; SLR, systematic literature review; UK NSC, UK National Screening Committee

Appraisal for quality/risk of bias tool

The following tools were used to assess the quality and risk of bias of each study included in the review:

- RCTs: adapted Cochrane Risk of Bias tool (RoB)[114]
- Diagnostic accuracy studies: adapted Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool[115]
- PROBAST tool[116]

The full guidance used for the quality assessments is available in Table 42 – Table 45 in Appendix 4 – Guidance on quality assessments.

Databases/sources searched

The following databases were searched:

- MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print
- Embase
- The Cochrane Library, including the following:
    - Cochrane Database of Systematic Reviews (CDSR)
    - Cochrane Central Register of Controlled Trials (CENTRAL)
- Database of Abstracts of Reviews of Effects (DARE)

Searches were run on 2nd September 2019. Full details of the searches, including the search strategy for each database, are presented in Appendix 1 — Search strategy
.

Overall results

Database searches yielded 9,729 results, of which 74 articles were judged to be relevant to one or more questions. An additional 2 references were identified through hand-searching reference lists, so 76 articles were ultimately included.

Appendix 2 — Included and excluded studies – contains full PRISMA flow diagrams, along with tables of the included publications and details of which questions these publications were identified as being relevant for (Table 34 and Table 35).

Question level synthesis

Criteria 11 and 13 – Efficacy, harms and benefits of PSA-based screening

Criterion 11 – Effect of PSA-based screening for prostate cancer on mortality and morbidity

11: 'There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (such as Down's syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.'

In the last external review conducted for the UK NSC in 2015 (with searches in 2014) (Louie 2015), a meta-analysis of 5 trials was identified for Criterion 11: it compared PSA screening (with or without DRE) with usual care.[7] The identified trials were the ERSPC trial, the PLCO trial, and the Stockholm, Norrkoping and Quebec screening trials.[117-121] Of these trials, only results from the ERSPC study detected a significant reduction in mortality rate compared with standard care.[119] The meta-analysis found that PSA-based screening does not reduce prostate-cancer specific or all-cause mortality, although prostate cancer incidence was higher among men in the screened arm than controls.[7]

This review update searched for relevant data published since 2014 relating to the effect of PSA-based screening on mortality or morbidity, answered through the question (Q1):

Question 1: Does screening based on PSA reduce short- or long-term prostate cancer morbidity and mortality and all-cause mortality?

Criterion 13 – Harms of PSA-based screening for prostate cancer and diagnostic follow-up

13: 'The benefit gained by individuals from the screening programme should outweigh any harms, for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications."

The 2015 UK NSC external review also addressed Criterion 13 and considered harms of screening programmes in terms of the test, diagnostic procedures and treatment.[7] Publications on one systematic review and 4 primary trials (ERSPC, PLCO, Prostate Biopsy Effects [ProBE] and ProtecT) were discussed. Regarding harms of screening tests, there was no excess mortality in PSA screen-positive patients who did not

undergo biopsy, compared with controls in the ERSPC trial. In the PLCO trial, PSA testing was associated with a complication rate of 26.2 per 10,000 screenings, primarily including dizziness, bruising, haematoma and fainting, whereas incidence of pain or bleeding resulting from DRE was 0.3 per 10,000 screenings.

Complications related to biopsies were largely minor. Complications, such as haematuria and haematospermia were reported in the ERSPC, ProBE and PLCO trials, at a frequency ranging from upwards of 50% in ERSPC and ProBE to 68 in 10,000 in the PLCO trial. No deaths attributable to biopsy occurred during the ERSPC trial, and major complications were rare. The included systematic review evaluated overdiagnosis and overtreatment of prostate cancer and reported that overdiagnosis can range from 1.7% to 67% as a result of screening.[122] This can be influenced by patient characteristics, the screening protocol and background incidence of prostate cancer,[122] with the ProtecT study finding that the probability of overdiagnosis increases with age.[123]

Limited data on the impact of PSA-based screening on quality of life was identified. A model based on ERSPC data from the Rotterdam and Sweden centres was developed to predict the impact of the presence or absence of annual screening over the lifetime of 1000 men (aged 55–69). The study concluded that the benefits of screening were outweighed by the impact of overdiagnosis and overtreatment on quality of life (estimated through loss of quality-adjusted life years [QALYs] associated with screening).[124]

This review update searched for relevant data published since 2014 relating to the harms and benefits associated with PSA-based screening, answered through the question (Q2):

Question 2 – What are the harms of PSA-based screening for prostate cancer and diagnostic follow-up, with particular reference to overdiagnosis?

Eligibility for inclusion in the review

This review searched for RCTs and SLRs/MAs of RCTs. Studies were included if the population comprised asymptomatic, unselected men in the primary care setting. Interventions of interest were PSA-based screening, including but not limited to tests evaluating, single-threshold PSA, age-specific thresholds, and variable screening intervals. Outcomes of interest for question 1 were short- or long-term morbidity/mortality outcomes, such as prostate cancer-mortality, all-cause mortality and prostate cancer-specific morbidity. Outcomes of interest for question 2 were any harms of PSA-based screening, including false-positive or false-negative results, overdiagnosis, and physical or psychological harms. Studies were not restricted geographically. Full details of the eligibility criteria are presented in Table 5.

Description of the evidence

Overall

A total of 35 publications on 3 RCTs were included in the review: ERSPC, PLCO and CAP. Within the ERSPC study, 23 publications were included on 5 distinct geographic sections (see further details in Characteristics of included studies (Q1 and Q2)). Ten publications reported on results of the PLCO trial, and one publication on the CAP trial. One publication reported on a separate analysis of the ERSPC and PLCO results.

No systematic reviews that closely aligned with the scope of questions 1 and/or 2 were identified; the main reason for this was that the majority of studies included in the systematic reviews identified as potentially relevant were conducted prior to 2014, and enrolled selective populations. A list of all studies included in the review is available in Table 8.

Question 1

Ultimately, 31 articles reporting on 3 unique RCTs were selected for extraction for question 1: the ERSPC trial (N=20),[10, 11, 14, 70, 125-140] PLCO (N=9),[13, 18, 20, 141-146] and the Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) trial (N=1).[12] One article conducted an analysis of ERSPC and PLCO. [147] All RCTs compared a PSA-based screening programme with 'no screening' or 'usual care'.

Question 2

Nine articles reporting on 2 RCTs, ERSPC (N=7),[10, 19, 22, 23, 125, 130, 135] and PLCO (N=2),[17, 20] reported outcomes relevant to Q2.

Five records reported outcomes for both question 1 and 2 (4 for ERSPC and 1 for PLCO).[10, 20, 125, 130, 135]

Characteristics of included studies (Q1 and Q2)

In total, 11 publications reported on results from the PLCO study (one was an analysis of PLCO and ERSPC results).[13, 17, 18, 20, 141-147]

PLCO

Between 1993 and 2001 in the PLCO trial, 76,683 men aged 55 to 74 years old from 10 US health centres were randomised to a screening intervention or usual care. The screening intervention comprised PSA testing at baseline and annually for 5 years thereafter, in addition to DREs performed at baseline and for the following 3 years. Men with positive PSA results (>4 ng/mL) then underwent a diagnostic process managed by the man's healthcare provider, external to the trial setting. At 13 years of follow-up, 4836 out of 10,798 (~45%) men with any positive screens received a follow-up prostate

biopsy.[20] Follow-up is ongoing, with the latest analyses reporting data at approximately 17 years of follow-up.[13]

ERSPC

The ERSPC study was conducted across 8 European countries: Belgium, Finland, Italy, The Netherlands, Spain, Sweden, Switzerland and France. The Swedish arm of the ERSPC is also referred to as the Göteborg screening trial, which commenced in 1995 (before the ERSPC was established), with the Göteborg cohort being incorporated into the Swedish ERSPC section since 1996.[131] Seven publications identified by this review reported on results from multiple centres of the ERSPC study,[10, 70, 125-129] with the remaining publications reporting on the Finnish (N=9),[14, 19, 22, 133-138] Swedish (N=2),[130, 131] Dutch (N=3),[11, 23, 132] and Spanish (N=2) cohorts.[139, 140] No standalone publications that specifically reported on the Belgium, Italy or Switzerland centres were identified, and data on the French cohort was not reported in any publications included in this review; it was excluded from analyses conducted for the multicentre publications due to short follow-up time and failure to achieve >50% screening attendance.[10, 125] Following exclusion of 86,379 men from French ERSPC centres and with 148 deaths occurring during the randomisation process, 162,389 men in the core age group (55 to 69 years) underwent randomisation, with 72,890 men allocated to the screening group and 89,351 to the control group.[10] Men assigned to the screening group were provided with information about PSA screening and were invited to undergo PSA testing every 2 or 4 years (all centres used 4 years except for Sweden and France) until an upper age limit of 69 years. Men with PSA at or above threshold (≥3.0 ng/mL for most centres, excluding Sweden [≥2.5 ng/mL]) were recommended to undergo clinical follow-up including DRE, transrectal ultrasound of the prostate and systematic sextant biopsy (6 cores). Those with PSA results below the threshold or with a benign biopsy were re-invited after 2 or 4 years. Follow-up data is currently published up to 16 years of follow-up.[69] Up to this point, (across all centres excluding France) there were 16,988 (23%) men with positive tests, of which 15,116 (89%) of men received at least one biopsy.[69]

CAP

One publication reported on the CAP study, a primary care-based cluster randomised trial of PSA testing in England and Wales.[12] In total, 911 primary care practices were randomised, including 408,825 men (189,386 in the screening arm; 219,439 in the control arm). At the practices assigned to the screening arm, men aged 50 to 69 years were invited to a nurse-led clinic appointment where they were informed about the potential benefits and harms of PSA testing, and were offered screening. Men who tested positive (PSA ≥3.0 ng/mL) were referred for biopsy. Men diagnosed with localised prostate cancer, and who met eligibility crietria, were invited to participate in the ProtecT randomised clinical trial of active monitoring, radical prostatectomy and external-beam radiotherapy, which is reported in further detail in the Characteristics of included studies (Q4) section on the harms and benefits of treatment approaches in early-stage prostate cancer. Controls received standard NHS care (the Prostate Cancer Risk Management

Programme),[148] and information about PSA screening was only provided on request. The median length of follow-up in the first reporting of results was 10 years,[12] with results from a further 15 years median follow-up expected in the future.

Table 8. Summary of records included for questions 1 and 2

Trial	Cohort (if multiple)	Number screened	Number of controls	Age for screening (years)	Screening interval	Screening test	Outcomes
CAP[12] (UK)	-	189,386	219,439	50–69	Single invitation	PSA (positive result >3.0 ng/mL)	**Q1**: PCa-related mortality; all-cause mortality
ERSPC[10, 130]	All centres (excluding France)[a]	72,890	89,351	55–69	2, 4 (most centres) or 7 years	PSA (positive result >3.0 ng/mL)	**Q1**: Cumulative PCa-specific incidence, PCa-specific mortality **Q2:** Overdiagnosis
	Belgium	4307	4255	55–69	7 years	PSA (positive result >3.0 ng/mL)	
	Finland (FinRSPC)	31,970	48,409	55–69	4 years	PSA (positive result >3.0 ng/mL)	
	Italy	7265	7250	55–69	4 years	PSA (positive result >3.0 ng/mL)	
	Sweden (Göteborg screening trial)	5901	5951	50–64	2 years	PSA (positive result >2.5 ng/ml)	
	The Netherlands	17,443	17,390	55–74	4 years	PSA (positive result >3.0 ng/mL)	
	Spain	1056	1141	55–69	4 years	PSA (positive result >3.0 ng/mL)	
	Switzerland	4948	4955	55–69	4 years	PSA (positive result >3.0 ng/mL)	
PLCO[13] (USA)	-	38,340	38,343	55–74	Annually for 5 years	PSA (5 years; positive result >4 ng/mL) and DRE (3 years)	**Q1**: PCa incidence, metastatic PCa incidence, PCa-related mortality, all-cause mortality **Q2**: Complications in the screening arm, overdiagnosis rate and false-positive results (by ethnicity)

[a]Data from the French centres was excluded from the analysis due to insufficient follow-up time and a failure to achieve >50% screening attendance.
Abbreviations: CAP, Cluster Randomized Trial of PSA Testing for Prostate Cancer; DRE, digital rectal examination; ERSPC, European Randomised Screening for Prostate Cancer Trial; FinRSPC, Finnish Randomised Screening for Prostate Cancer Trial; PCa, prostate cancer; PSA, prostate-specific antigen

Full study results, including different follow-up periods, and study details are presented in the evidence tables in Appendix 3 — Summary and appraisal of individual studies (Table 39a–h).

Summary of findings

Quality assessment (Q1 and Q2)

The quality of the 3 included unique RCTs was appraised using an adapted Cochrane Risk of Bias 2 checklist,[149] (Table 43). A summary of the risk of bias is presented in Table 9, and the full appraisal is presented in Table 46.

Table 9. Summary of Cochrane Risk of Bias assessments for RCTs comparing PSA-based screening to usual care for detection of prostate cancer

Risk of bias	CAP[12]	ERSPC[10]	PLCO[13]
Randomisation process	Low	Some concerns	Low
Effect of assignment to intervention	Some concerns	High	High
Missing outcome data	Low	Low	Low
Measurement of outcome	Low	Low	Low
Selection of the reported result	Low	Low	Some concerns
Overall risk of bias	**Low**	**Some concerns**	**Some concerns**

Randomisation process

The risk of bias arising from the randomisation process was judged to be low in the CAP and PLCO trials, as although details of allocation concealment were not provided, the method of randomisation was clearly reported and there were no significant differences between the study arms in baseline characteristics.[12] There were some concerns of bias in the ERSPC trial; no baseline characteristics were provided overall or for individual study centres, so the effectiveness of the randomisation process in the ERPSC could not be assessed.[10] Additionally, computer-randomisation was performed either pre-consent (or an effectiveness design; Finland, Italy, Sweden) or post-consent (or an efficacy design; Belgium, the Netherlands, Switzerland and Spain) depending on the study centre, due to the specific national regulations. Post-consent randomisation may give lower coverage of the target population and be at higher risk of bias due to the 'healthy volunteer effect' in that only those who had already indicated willingness to participate were randomised (likely leading to lower non-adherence). Pre-consent randomisation may be better-suited to address the question of the effect of a population-wide screening programme.[128] The use of different designs may also reduce the comparability of the results in each of the study centres. However, a sub-analysis including 6 of the ERSPC centres (3 with pre-consent design, 3 with post-consent design) was conducted that corrected for the randomisation design. This found that the correction did not reduce variation between the individual centres, suggesting that randomisation method did not greatly influence differences between centres.[128]

Effect of assignment to intervention

Due to the nature of the screening intervention, it was not possible to conceal study arm assignment to participants or carers in any of the trials. All trials analysed outcomes based on the intention-to-screen (ITS) principle. However, the ERSPC and PLCO trials were both judged to be at a high risk of bias for this domain. In both trials, men in the control arm attended screening appointments (opportunistic screening), leading to significant study arm contamination.[10, 13] The degree of contamination in the control arms for each trial was reported to be as high as 62.7% in the Finnish section of ERSPC at 12 years of follow-up,[14] and 54.8% in the PLCO trial,[15] in studies identified in the rapid review. It may be as high as 90% in the PLCO trial over the course of the whole trial.[16] This is recognised to likely dilute the measured effect of the screening intervention on primary study outcomes such as prostate cancer incidence and mortality. One publication associated with the ERSPC trial (Dutch section) demonstrated the impact of this when they conducted a sub-analysis to adjust for biopsy contamination in the control arm (along with nonattendance in the screening arm) and found that the improvement in relative risk (screening vs control) was greater after correction for contamination and nonattendance than in the ITS analysis (RR 0.68 [95% CI 0.51–0.93] vs 0.49 [95% CI 0.27–0.87]; p=0.015), although the confidence intervals (CIs) were wide and overlapping.[11] An additional modelling analysis of the PLCO trial, which was not included in the rapid review, virtually reproduced the PLCO trial and concluded that contamination substantially limited the ability of the trial to identify a clinically significant screening benefit.[150] As the CAP trial recruited participants based on primary care practice clusters, volunteer bias was reduced, and this reportedly reduced PSA testing contamination in the control group. However, the presence of an estimate 10–15% contamination still carries some concerns for risk of bias.[12]

Missing outcome data

In the CAP trial, all randomised patients were included in the analyses with minimal missing data reported, obliviating the need for multiple imputation analyses.[12] This study is therefore at low risk of bias for this domain. Similarly, all randomised patients appear to be included in the ERSPC and PLCO analyses.[10, 13]

Measurement of outcome

All 3 unique trials were at low risk of bias for this domain, due to assessment of objective study outcomes, with sufficient description of data collection methods that was consistent across study arms. Additionally, mortality was assessed by personnel blinded to trial group assignment in all 3 trials. In the ERSPC, the potential bias introduced by misclassification of cause of death was assessed in a sub-analysis. Whilst it was reported that there was some variation in the accuracy of cause of death adjudication, corrections for this had no impact on the estimated mortality reduction effect of screening.[129] Similarly, an analysis of the Finnish section of the ERSPC (FinRSPC) alone found that some attribution bias (where it is more likely that a diagnosed condition

will be judged as cause of death even if it is not part of the chain of events that led to death) was present in both the screening and control arm, but more so in the screening arm (7.4% vs 3.1%) – ascribed by the authors as being due to screened men being more likely to be diagnosed with prostate cancer. However, correcting for this resulted in only a small decrease in the hazard ratio for prostate cancer-related death, from 0.94 to 0.92.[135]

Selection of the reported result

For all trials, there was low concern that multiple outcome measurements were taken or that multiple outcome analyses were conducted. A statistical analysis plan (SAP) was provided for the CAP trial,[151] and the ERSPC trial analysis was protocol-based,[152] allowing for confirmation that the reported results were unselected. However, there were some concerns about bias for the PLCO trial in the selection of the reported result, due to unavailability of a pre-specified SAP.

Results (Q1)

Key results are presented in Table 10 and Table 11. Full details of the included studies and their results can be found in in Appendix 3 — Summary and appraisal of individual studies (Table 39a–h).

Prostate cancer incidence

Eleven publications reporting on the PLCO, ERSPC and CAP screening studies reported on the incidence of prostate cancer for PSA-based screening compared with usual care.[13, 28, 69, 126, 127, 132, 136, 137, 139, 146, 153] While all 3 trials reported on the incidence rate of prostate cancer, the ERSPC analyses also reported on risk of prostate cancer diagnosis (Table 39b; Appendix 3 — Summary and appraisal of individual studies). The rate ratio (RaR) is calculated by dividing the incidence rate in the intervention group by the incidence rate in the control group. No other morbidity outcomes were reported by the identified publications.

At the latest follow-up analyses, all studies found that the incidence rate of prostate cancer was significantly higher in the screening arm than in usual care, although the effect size was generally small (Table 10). The largest effect size of screening on the incidence of prostate cancer was detected in the Netherlands ERSPC cohort, with a RaR of 1.89 per 1000 person-years (95% CI 1.77 to 2.03; p=0.000), over 16-years follow-up. This finding suggests that the rate of prostate cancer diagnosis in the screening arm was 1.89 times the rate of diagnosis in the usual care arm. Arnsrud Godtman 2015 reported that at 18 years follow-up in the Göteborg screening trial, prostate cancer incidence was significantly higher in the screening arm (RaR 1.51, 95% CI 1.39 to 1.64). While still statistically significant, Pinsky 2019 reported a smaller

incidence RaR of 1.05 (95% CI 1.01 to 1.09; p<0.001) per 1000 person-years over 17-years follow-up in the PLCO study.[13] In the CAP trial, the between-group difference for incidence rate was 0.65 per 1000 person-years (95% CI 0.52 to 0.78; p<0.001; RaR not reported) over 10 years of follow-up.[28]

Hugossen 2019 (ERSPC) also reported on cumulative incidence over the 16-year follow-up period (at years 1 to 9, 1 to 11, 1 to 13 and 1 to 16).[10] In the screening arm, the cumulative incidence of prostate cancer was highest in the first 9 years following screening (10.55 per 1000 person-years), decreasing for years 1 to 11, 1 to 13, and 1 to 16 (9.20 per 1000 person-years). By contrast, the incidence rate of prostate cancer in the control group was lowest in the first 9 years following randomisation (5.65 per 1000 person-years; RaR for screening vs control 1.90 per 1000 person-years), eventually rising over the 16 years of study follow-up period (6.65 per 1000 person-years; RaR for screening vs control 1.41 per 1000 person-years). A similar trend was observed in an analysis stratified by age at screening, in the Göteborg ERSPC screening study cohort. The incidence rate ratio decreased with increasing age intervals (50 to 54, to 55 to 59, to 60 to 64 years; Table 39c; Appendix 3 — Summary and appraisal of individual studies) illustrating that the difference in PCa diagnosis rates between screening and usual care narrowed with increasing age, although this difference still remained statistically significant for each age group.[10]

Three publications on the PLCO trial and one on the ERSPC trial reported incidence of metastatic prostate cancer.[126, 142, 143, 146] In the PLCO, no significant difference in the incidence of metastatic prostate cancer at diagnosis was detected at 17 years (RaR 0.85, 95% CI 0.67 to 1.06), although a small, but significant, increase in Gleason grade 2–6 (low risk) prostate cancer was detected in the screening arm compared with usual care (RaR 1.17, 95% CI 1.11 to 1.23).[143] Pinsky 2017 found that there was no difference in incidence of metastatic disease (whether at diagnosis or progression) between study arms at a 15-year follow-up.[143, 146] By contrast, in the ERSPC analysis at 13 years of follow-up, the RaR for metastatic cancer was 0.56 (95% 0.48 to 0.65; Table 39b; Appendix 3 — Summary and appraisal of individual studies) in the screening arm compared with the control arm.[126]

Table 10. Incidence rate of prostate cancer as reported by the ERSPC and PLCO trials

Outcome	Trial (cohort)	Follow-up (yrs)	Incidence rate per 1000 person-years (95% CI)		Rate ratio (95% CI)	Rate difference/person-years (95% CI)	p-value
			Screening arm	Control arm			
Prostate cancer incidence	CAP[28]	10	4.45 (4.36–4.55)	3.80 (3.72–3.89)	NR	**0.65 (0.52–0.78)**	**<0.001**
	ERSPC[10] [a]	16	9.20 (NR)	6.65 (NR)	**1.41 (1.36–1.45)**	**2.66 (2.42–2.90)**	NR
	ERSPC (Belgium) [10]	16	NR	NR	1.22 (1.07–1.40)	NR	0.003
	ERSPC (Finland) [10]	16	NR	NR	1.19 (1.14–1.24)	NR	0.000
	ERSPC (Italy) [10]	16	NR	NR	1.24 (1.10–1.41)	NR	0.001
	ERSPC (Netherlands) [10]	16	NR	NR	1.89 (1.77–2.03)	NR	0.000
	ERSPC (Spain) [10, 139]	16	NR	NR	1.72 (1.24–2.39)	NR	0.001
	ERSPC (Sweden) [10]	16	NR	NR	1.44 (1.30–1.60)	NR	0.000
	ERSPC (Switzerland) [10]	16	NR	NR	1.78 (1.57–2.03)	NR	0.000
	Göteberg screening trial (ERSPC, Sweden)[130]	18	9.7 (NR)	6.5 (NR)	**1.51 (1.39–1.64)**	NR	NR
	PLCO[13] [b]	17	10.6 (NR)	10.1 (NR)	**1.05 (1.01–1.09)**	NR	**<0.001**
Metastatic prostate cancer incidence[c]	PLCO[142] [b]	15	0.47 (NR)	0.48 (NR)	0.98 (0.81–1.18)	NR	NR
Metastatic at diagnosis	PLCO[142] [b]	15	0.25 (NR)	0.27 (NR)	0.91 (0.70–1.17)	NR	NR
Progression to metastatic	PLCO[141] [b]	15	0.23 (NR)	0.21 (NR)	1.07 (0.81–1.41)	NR	NR

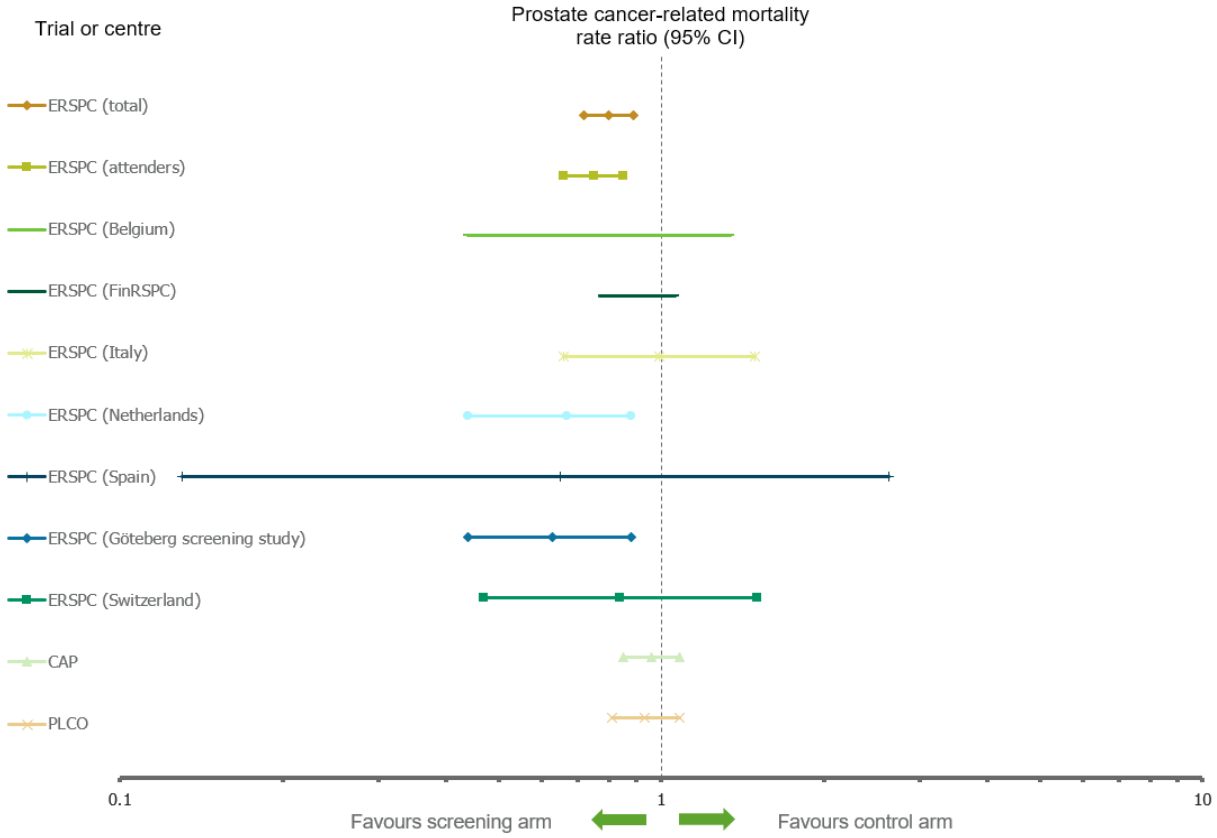
Values in bold indicate statistical significance.
[a] All centres excluding France. [b] Results converted from 10,000 person-years to 1000 person-years. [c] Includes metastatic disease at diagnosis and progression to metastatic disease.
Abbreviations: CAP, Cluster Randomized Trial of PSA Testing for Prostate Cancer; CI, confidence interval; ERSPC, European Randomized study of Screening for Prostate Cancer trial; NR, not reported; PLCO, Prostate, Lung, Colorectal and Ovarian trial

Prostate cancer mortality

All 3 trials reported on the rate of prostate cancer mortality. Only one study, the ERSPC trial, found that PSA screening significantly reduced prostate cancer-related mortality compared with standard care (Table 11).[10, 130]

A multicentre analysis of the ERPSC trial (included all centres excluding France due to lack of compliance with quality criteria and short follow-up duration) reported that prostate cancer-specific mortality rate was significantly lower in men who underwent screening (0.53 per 1000 person-years) than those in usual care (0.66 per 1000 person-years) after 16 years of follow-up, resulting in a RaR of 0.80 (95% CI 0.72 to 0.89; p<0.001)[10] and indicating that mortality rate was 20% lower in the screening arm compared with the usual care arm. However, this finding was not consistent across the individual ERSPC centres; statistically significant differences in prostate cancer-specific mortality were only reported in the Netherlands (RaR 0.67, 95% CI 0.53 to 0.85, p=0.001) and Sweden centres (RaR 0.63, 95% CI 0.44 to 0.88, p=0.008) at 16 years of follow-up. However, lack of statistical significance in the other centres may be an artefact due to underpowering and the effect sizes are comparable in most centres (Figure 1).

Figure 1. Forest plot of rate ratios for prostate cancer-specific mortality



Results are for 16, 10 and 17 years of follow-up for the ERSPC, CAP and PLCO trials respectively.

Abbreviations: CAP, Cluster Randomized Trial of PSA Testing for Prostate Cancer; CI, confidence interval; ERSPC, European Randomized study of Screening for Prostate Cancer; FinRSPC, Finnish Randomised Screening of Prostate Cancer Trial; PLCO, Prostate, Lung, Colorectal and Ovarian tria

In the Sweden centre (Göteborg cohort), a significant reduction in mortality in the PSA screening arm compared with the control arm was also detected at the latest follow-up analysis of 18-years, with a mortality RaR of 0.65 per 1000 person-years (95% CI 0.48 to 0.87).[131] An analysis stratified by age at screening found that PSA-based screening significantly reduced prostate cancer mortality in the 55 to 69 year age group (RaR 0.47, 95% CI 0.28 to 0.79) but not in the 60 to 64 (RaR 0.85, 95% CI 0.56 to 1.28) age groups, although it is noteworthy that the CIs are wide and overlapping. The reduction was not significant in the 50 to 54 year age group (RaR 0.50, 95% CI 0.20 to 1.16), however the authors noted that this was likely due to a problem of power with few deaths in this subgroup (aged 68–72 at follow-up). Age-stratified results were also reported at 14-year and 16-year follow-up analyses (Table 39c; Appendix 3 — Summary and appraisal of individual studies).[131] A sensitivity analysis estimated the effect on the risk of prostate cancer death if screening was attended at least twice, compared with a single PSA test, assuming 'various effects' which were unspecified in the source. This ranged from a 48% reduction for those attending twice if no mortality reduction was postulated from attending one screening test (risk ratio [RR] 0.52, 95% CI 0.42 to 0.63 vs an assumed RR of 1.00) to a 25% reduction for those attending twice if it was postulated that first screening was as effective as following rounds (RR 0.75, 95% CI 0.60 to 0.92 vs an assumed RR of 0.75).[69] This finding was supported by the Pakarainen 2019 sub-analysis of the FinRSPC cohort, which found that attending screening 3 times reduced prostate cancer-specific mortality most substantially (2 times: hazard ratio [HR] 0.48, 95% CI 0.35 to 0.66, 3 times: HR 0.17, 95% CI 0.09 to 0.33).[138] Other mortality outcomes reported by Arnsrud Godtman 2015 (ERSPC, Sweden) at 18 years of follow-up included absolute mortality reduction (ARR; 0.72%, 95% CI 0.50 to 0.94%) and relative risk reduction (RRR; 42%, 95% CI 28 to 54%).[130] An ARR of 0.72% suggests that if 1000 men were screened based on PSA testing, it would be expected that 7 participants would be prevented from dying due to prostate cancer after 18 years of follow-up. The RRR of 42% suggests that by undergoing PSA screening, individual participants would have a 42% lower risk of prostate cancer-related death after 18 years of follow-up. However, this is just one subgroup of the multicountry ERSPC trial, and the results for the whole trial carry more weight. These show an ARR of 0.18% suggesting that if 1000 men were screened based on PSA testing, it would be expected that 2 participants would be prevented from dying due to prostate cancer after 16 years of follow-up.[69]

By contrast, no significant difference was detected between the screening and usual care groups in either the CAP (RaR 0.96, 95% CI 0.85 to 1.08, p=0.50) or PLCO (RaR 0.93, 95% CI 0.81 to 1.08, p=0.11) trials after 10 and 17 years of follow-up, respectively, demonstrating very similar results.[12, 13]

Tsodikov and colleagues used data with a cut-off of 11 years of follow-up from the PLCO and ERSPC trials and performed an analysis that aimed to evaluate whether the effects of screening on prostate cancer-related mortality differed between the 2 trials. They

performed Cox regression analyses, adjusting for age and trial, along with extended analyses that accounted for increased incidence due to screening and diagnostic workup using mean lead times (MLTs). Based on their analysis, they concluded that after accounting for differences in implementation and settings, the ERPSC and PLCO provide compatible evidence that screening reduces prostate cancer mortality (estimated 25 to 31% and 27 to 32% lower risk of death in the ERSPC and PLCO screening arms of the trials, respectively). It would be useful to apply a similar approach to the CAP trial. However, the authors note that the use of MLT has limitations because it is a simplified metric of screening.[147]

It should be noted that the effect of risk stratified screening e.g. based on genetics, biomarkers, family history, or ethnicity, has never been tested.

All-cause mortality

All 3 RCTs reported on all-cause mortality, outlining very similar results (Table 11). No significant differences were detected between the screening and usual care groups in either the CAP (RaR 0.99, 95% CI 0.94 to 1.03, p=0.49), PLCO (RaR 0.98, 95% CI 0.95 to 1.00, p=0.11) nor the Spanish ERSPC (RaR 0.92, 95% CI 0.78 to 1.08) trials.[12, 13, 140]

Table 11. Mortality rate and effectiveness of screening outcomes as reported by the CAP, ERSPC and PLCO trials

Outcome	Trial (Cohort)	Follow-up (yrs)	Mortality rate per 1000 person-years (95% CI)		Rate ratio (95% CI) [reference: control arm]	p-value
			Screening arm	Control arm		
Prostate cancer-specific mortality	CAP[12]	10	0.30 (0.27–0.32)	0.31 (0.29–0.33)	0.96 (0.85–1.08)	0.50
	ERSPC[10a]	16	0.53 (NR)	0.66 (NR)	Total: **0.80 (0.72–0.89)** Attenders: **0.75 (0.66–0.85)**	**<0.001** **<0.001**
	ERSPC (Belgium) [10]	16	NR	NR	0.78 (0.44–1.34)	0.364
	ERSPC (FinRSPC) [10]	16	NR	NR	0.91 (0.77–1.06)	0.210
	ERSPC (Italy) [10]	16	NR	NR	0.99 (0.66-1.49)	0.958
	ERSPC (Netherlands) [10]	16	NR	NR	**0.67 (0.53–0.85)**	**0.001**
	ERSPC (Spain) [10]	16	NR	NR	0.65 (0.13–2.63)	0.550
	ERSPC (Göteberg screening study) [10]	16	NR	NR	**0.63 (0.44–0.88)**	**0.008**
	ERSPC (Switzerland) [10]	16	NR	NR	0.84 (0.47–1.50)	0.556
	Göteberg screening study (ERSPC, Sweden)[130]	18	0.51 (NR)	0.79 (NR)	**0.65 (0.48–0.87)**	NR
	PLCO[13b]	17	0.55 (NR)	0.59 (NR)	0.93 (0.81–1.08)	0.38
All-cause mortality	ERSPC (Spain)[140]	15.2	8.60 (NR)	9.38 (NR)	0.92 (0.78–1.08)	NR
	CAP[12]	10	13.74 (NR)	13.51 (NR)	0.99 (0.94–1.03)	0.49
	PLCO[143c]	15	17.29 (NR)	17.69 (NR)	0.98 (0.95–1.00)	0.11

Values in bold indicate statistical significance
[a] All centres excluding France [b] Converted from 100,000 person-years to 1000 person-years [c] Converted from 10,000 person-years to 1000 person-years
Abbreviations: CAP, Cluster Randomized Trial of PSA Testing for Prostate Cancer**;** CI, confidence interval; ERSPC, European Randomized study of Screening for Prostate Cancer; FinRSPC**,** Finnish Randomised Screening of Prostate Cancer Trial; NR, not reported; PLCO, Prostate, Lung, Colorectal and Ovarian trial

Conclusions (Q1)

Moderate-to-high quality evidence was available for mortality and morbidity outcomes through 3 RCTs included for this question.

All studies reported a significantly higher incidence rate of prostate cancer diagnosis with PSA-based screening compared with no screening or usual care. However, no significant difference in the incidence of metastatic prostate cancer at diagnosis was detected in the PLCO study, though metastatic cancer was more frequently diagnosed in the screening arm in the ERSPC study. Given the inconsistent evidence, it is not possible to conclusively evaluate the impact of PSA-based screening on the diagnosis of prostate cancer stratified by clinical staging.

Conflicting conclusions were reported for prostate cancer-specific mortality. While overall data from the ERSPC cohorts showed significant reduction, including a 42% relative risk reduction of death in the Göteborg cohort, these findings were not detected in the PLCO or CAP trials. The direct comparison of prostate cancer-specific mortality rates between trials is complicated by different screening intervals and PSA thresholds, length of follow-up and more substantially, the issue of control arm contamination. Control arm contamination has been shown to reduce the perceived effect of screening on mortality by separate analyses on both the ERSPC and PLCO trials. In addition, the fact that this contamination could have occurred at different levels and stages of the PLCO and ERSPC trials, has been attributed as a possible reason for the different conclusions found between the 2 studies (along with different protocols, practice settings, pre-trial screening and primary treatments).[68, 154] For example, up to 44% of men had already undergone a PSA test before enrolment in PLCO and contamination was reported at as high as 57.4% in the studies identified by the rapid review,[13] and may be as high as 90% overall.[16] Meanwhile, contamination was reported at as high as 62.9% in the studies identified by the rapid review for ERSPC.[14] It is noteworthy that even despite the contamination, there was a demonstrable effect on prostate cancer incidence and mortality in the ERSPC trial. The result is also further supported by results from an analysis of PLCO and ERSPC, which adjusted for factors like trial setting. This supported the conclusions of the ERSPC trial in that screening resulted in a significant reduction in mortality. While contamination in the CAP trial was estimated to be lower at approximately 15%, this still may have influenced mortality and a longer follow-up in the CAP trial may show more of an effect. Although a meta-analysis would confirm the direction of the effect from the available data, this would not necessarily enable an unequivocal conclusion, given the limited number of studies from which the evidence is derived, despite the large sample size included in each. It would also not avoid the issue of control arm contamination and other differences such as screening strategy, follow-up PSA testing, biopsy rates and post-diagnosis treatment strategy, without specific adjustments.

An exploratory ERSPC analysis reported that the risk of prostate cancer-death was lower if screening was attended at least twice, compared with only once (Table 39b; Appendix 3 — Summary and appraisal of individual studies). However, more data is required to investigate whether screening interval affects mortality between PSA-based screening and usual care, and the most effective screening interval at which mortality could be reduced while minimising overdiagnosis.

Results for all-cause mortality were consistent, with all 3 trials finding no significant difference between the screening and control arms. This was not unexpected as none of the studies could be powered to detect a difference in all-cause mortality.

Overall, based on the findings of this review, the evidence remains inconsistent on the effect of PSA-based screening on prostate cancer-specific mortality, compared with no screening or usual care. This is consistent with the conclusion of the previous UK NSC review (2015), indicating that the longer follow-up period for the trials has not abated the impact of contamination.

Summary of findings relevant to criterion 11: Criterion not met[1]

Quantity: A moderate volume of evidence was available to assess criterion 11, consisting of a total of 3 unique RCTs (31 publications). The RCTs were large, multi-centre (CAP and PLCO) or international (ERSPC) studies covering a large geographical area, with long follow-up periods (10 to 18 years). Analyses included patient numbers which ranged from 2,197 (ERSPC Spanish centre)[10] to 408,825 (CAP) participants.[12]

Quality: The PLCO and ERSPC trials were both judged to be at some concern of risk of bias overall, primarily because allocation of the intervention (screening) could not be concealed from the participants and the high rate of contamination due to men in the control arm attending opportunistic screening over the years of follow-up (a substantial proportion of >50%), which could result in underestimating the effect of screening in the screening arm and may be responsible for the perceived lack of effect of screening on prostate cancer-specific mortality in the PLCO trial. There were low concerns for risk of bias for the majority of other domains. The CAP trial was judged to be at low risk of bias overall; concerns for contamination were lower in the CAP trial due to recruitment based on primary care practice clusters, although could still have been up to 15%.

Applicability: All studies were judged to be of high applicability to the review question, as they recruited asymptomatic men from a primary care setting in the UK (N=1) or in one or more high-income countries considered to be reflective of the UK setting (N=2).

Consistency: The majority of screening protocols used a threshold of PSA ≥3 ng/mL to classify results as positive. Thresholds of 4 ng/mL and 2.5 ng/mL were used in the PLCO and Swedish ERSPC cohorts, respectively. The screening interval varied between trials, from annual screening (PLCO) to once every 7 years (Belgian ERSPC cohort).[10, 12] By contrast, the CAP trial involved a single screening invitation at the start of the study.[12] The comparability between the different thresholds or the influence of the screening interval on prostate cancer incidence or mortality is unclear. However, a sensitivity analysis of ERSPC data found that repeat PSA screening (at least twice) reduced prostate cancer mortality, in comparison with one single PSA-test. It is therefore possible that this may complicate comparison of results from the CAP trial (single screen) with the ERSPC and PLCO trials (repeat screening).

Conclusions: Based on the moderate-to-high quality evidence across the 3 trials, findings for incidence and all-cause mortality were generally consistent. Incidence of prostate cancer was seen to increase with screening, although no difference was observed when evaluating the incidence of metastatic cases specifically. In both the PLCO and CAP trials there was no difference in all-cause mortality between screening and control arms. However, results for prostate cancer-specific mortality were inconsistent. The ERSPC trial saw a significant

[1] **Guidance for judging whether a criterion is met, not met or uncertain. Met** – for example, this should be applied in circumstances in which there is a sufficient volume of evidence of sufficient quality to judge an outcome or effect which is unlikely to be changed by further research or systematic review; **Not Met** – for example, this should be applied in circumstances where there is insufficient evidence to clearly judge an outcome or effect or where there is sufficient evidence of poor performance; **Uncertain** – for example, this should be applied in circumstances in which the constraints of an evidence summary prevent a reliable answer to the question. An example of this may be when the need for a systematic review and meta-analysis is identified by the rapid review.

reduction in prostate cancer deaths in the screening arm, which was increased to as high as 51% when adjusted for control arm contamination,[11] but no such finding was seen in PLCO or CAP.[12, 13]

Overall, the direction of evidence would suggest that whilst PSA-based screening increases the incidence of prostate cancer, the effect on prostate cancer-specific mortality in comparison with no screening or usual care is unclear. Furthermore, a reduction in mortality may still be insufficient to justify the potential harms of screening. Therefore, it is deemed that criterion 11 is not met.

Results (Q2)

Harms of screening that were reported amongst the included RCTs were overdiagnosis (N=3),[17-19] complications associated with biopsy (N=2),[20, 21] and QoL (N=1).[22] No harms of screening were investigated in the CAP trial.[12]

Overdiagnosis

Overdiagnosis is defined as "the diagnosis of a condition that, if unrecognised, would not cause symptoms or harm a patient during his or her lifetime".[155] Overdiagnosis, calculated by the difference in cumulative incidence of prostate cancer between the screening and usual care arms following screening, was reported by 2 publications on the PLCO trial (Table 12).[17, 18] Prorok 2018 reported a statistically significant and persistent excess (10%) of prostate cancer diagnoses in the screening arm compared with controls during 13 years of follow-up.[18] Furthermore, at 19 years of follow-up, the PLCO trial compared estimates of overdiagnosis in white and black screen-detected populations, finding that overdiagnosis rate in white men was higher (20.6% vs 1.3%) although the authors noted that this was not statistically significant (difference 19.3% [95% CI –11.1 to 56.4%], p value not reported).[17] In the same trial, false-positive results were also compared between white and black men. Interestingly, false positive results for PSA were relatively higher in the black population compared with white (13.6 to 14.5% vs 11.1 to 12.4%, $p<0.05$), but false positive results for DRE were lower (10.3 to 10.9% vs 13.3 to 14.2%, $p<0.001$) although in absolute terms the differences were very small.[17] The Finnish arm of the ERSPC trial (FinRSPC) also reported estimated overdiagnosis, with an average value of 42% (95% CI 37 to 52), which was higher for the subgroup of men at lower polygenic risk for prostate cancer (58%, 95% CI 54 to 65)(Table 12).[19]

Several publications for the ERSPC trial explored the benefits and harms of PSA-based screening using the absolute measures, number needed to invite (NNI; the number of men required to be randomised to avert a prostate cancer-related death); number needed for overdetection (NNO; the number of screened men for which there is one excess 'detected' case) and number needed to detect (NND; a measure of the overall impact of screening as a ratio of the reduction in prostate cancer mortality to the excess

incidence) (Table 12).[10, 125, 130] An analysis of all ERSPC centres (excluding France) at 16 years of follow-up reported an NNI of 570 (95% CI 380 to 1137) and NND of 18: on average, it would be expected that 570 men would have to be invited to undergo screening, or 18 men would have to be diagnosed through screening, to prevent one death due to prostate cancer. The largest benefit of screening on prostate cancer-mortality was detected in the Swedish cohort, with an NND of 7 and NNI of 189 (95% CI 109 to 703), with the least benefit observed in the Italian cohort (NNI 44,232, 95% CI 369 to infinity; NND 673), demonstrating variation between study centres.[10] However, at an earlier analysis at 13-years of follow-up, results for the Italian cohort were not substantially different from the other centres (NNI 1198, 95% CI 349 to not determined; NND 29), with results from the Finnish centre demonstrating the least benefit (NNI 1821, 95% CI 631 to not determined; NND 37) (Table 39b, Appendix 3 — Summary and appraisal of individual studies).[125] The reason for the large difference in findings between 13- and 16-year follow-up analyses is unclear.

Table 12. Overdiagnosis outcomes associated with PSA-based screening

Outcome	Study	Follow-up (yrs)	Study arm/subgroup	Outcome Value	Comparison
Overdiagnosis	PLCO[17, 18]	13	Overall	Overdiagnosis, %: 10	NR
		19	White, screen-detected cases (N=3891)	Overdiagnosis, %: 20.6	Difference: 19.3 (95% CI –11.1–56.4)
			Black, screen-detected cases (N=252)	Overdiagnosis, %: 1.3	
			White, screened population (N=33,043)	Overdiagnosis, %: 1.2	Difference: 1.1 (95% CI –6.3–8.2)
			Black, screened population (N=1713)	Overdiagnosis, %: 0.1	
	FinRSPC[19]	13	Overall	Overdiagnosis, % (95% CI): 42 (37–52)	NR
			Lower polygenic risk group[1]	Overdiagnosis, % (95% CI): 58 (54–65)	
			Higher polygenic risk group[1]	Overdiagnosis, % (95% CI): 37 (31–47)	
	ERSPC[10]	16	Total	NNI, n (95% CI): 570 (380–1137) NND, n: 18	NR
			Belgium	NNI, n (95% CI): 678 (209–inf) NND, n: 13	
			Finland (FinRSPC)	NNI, n (95% CI): 1206 (471–inf) NND, n: 19	
			Italy	NNI, n (95% CI): 44232 (369–inf) NND, n: 673	
			Netherlands	NNI, n (95% CI): 303 (191–731) NND, n: 18	
			Spain	NNI, n (95% CI): 647 (153–inf) NND, n: 22	
			Sweden (Göteborg screening trial)	NNI, n (95% CI): 189 (109–703) NND, n: 7	
			Switzerland	NNI, n (95% CI): 1244 (285–inf) NND, n: 65	
	Göteberg screening study[130]	18	Screening arm	NNI, n: 139 NND, n: 13	NR
			Control arm	NNI, n: 493 NND, n:23	
	ERSPC[125]	13	Belgium	NNO, n: 47	NR

Outcome	Study	Follow-up (yrs)	Study arm/subgroup	Outcome Value	Comparison
			Finland (FinRSPC)	NNO, n: 51	
			Italy	NNO, n: 69	
			Netherlands	NNO, n: 16	
			Spain	NNO, n: 28	
			Sweden (Göteborg screening trial)	NNO, n: 22	
			Switzerland	NNO, n: 18	
False-positives	PLCO[17]	19	Black, screen-positive population	PSA+ (any DRE result), n (%): 228 (14.5)	p=0.02 (vs white)
				PSA+/DRE–, n (%): 215 (13.6)	p=0.002 (vs white)
				DRE+ (any PSA result), n (%): 172 (10.9)	p<0.001 (vs white)
				DRE+/PSA−, n (%): 162 (10.3)	p<0.001 (vs white)
				PSA+ or DRE+, n (%): 377 (23.9)	p=0.60 (vs white)
			White, screen-positive population	PSA+ (any DRE result), n (%): 3915 (12.4)	NR
				PSA+/DRE–, n (%): 3508 (11.1)	
				DRE+ (any PSA result), n (%): 4462 (14.2)	
				DRE+/PSA−, n (%): 4195 (13.3)	
				PSA+ or DRE+, n (%): 7703 (24.5)	

[1] Polygenic risk score (PRS) was calculated based on the genotypes of 66 known PCa loci for 4,967 men from the Finnish section of the ERSPC and the 72,072 men in the trial were stratified into those with polygenic risk above and below the median.

Abbreviations: DRE, digital rectal examination; inf, infinite; NND, number needed to detect (measure of the overall impact of screening as a ratio of the reduction in prostate cancer mortality to the excess incidence); NNI, number needed to invite (number of men needed to be randomised to prevent 1 prostate cancer-related death); NNO, number needed for overdiagnosis (number of screened men for which there is 1 excess detected case); NR, not reported; PSA, prostate-specific antigen.

Biopsy complications and mortality

One publication on the PLCO trial reported on mortality and complications associated with biopsy.[20] At both 120 and 180 days post-biopsy, there was no significant difference in mortality between men who received biopsy and men who did not (negative screen group) (Table 13).[20] In the PLCO study, of 3706 men who screened positive and underwent a single follow-up biopsy (with no accompanying prostate cancer diagnosis during that study year), 75 experienced complications, generating a complication rate of 20.2 per 1000 biopsies. This included non-infectious (N=48; 13.0 per 1000 biopsies) and infectious (N=29; 7.8 per 1000 biopsies) events. Non-infectious complications included urinary-related (N=19) and bleeding-related complications (N=14) and the remaining causes were not specified.[20]

A publication from the Rotterdam section of the ERSPC also reported on biopsy-related complications. Out of 10,747 biopsies in the ERSPC study, over half (67.9%) were associated with any complications, the majority of which were pain (50.0%) and haematuria (25.4%) and much more rarely reported fever (3.9%) and hospital admission (0.9%) (Table 13).[23] This marked difference between ERSPC and PLCO studies is likely due to the method of assessing biopsy complications. In the PLCO analysis, medical record data wasused to code complications into circa 30 categories, whereas for the ERSPC analysis, information on complications was self-reported through questionnaires sent to participants 2 weeks post-biopsy.[20, 23]

Table 13. Biopsy complication outcomes

Outcome	Study	Follow-up	Study arm/subgroup	Outcome value	Comparison
Post-biopsy mortality	PLCO[20]	120 days post-biopsy or negative screen	Biopsy group (N=6295)	Number of deaths: 6 Rate: 0.95 per 1000 biopsies	**Rate ratio (95% CI)** Univariate analysis: 0.52 (0.2–1.2) Multivariate analysis: 0.49 (0.2–1.1)
			No biopsy group (negative screen; N=139931)	Number of deaths: 255 Rate: 1.8 per negative screens	
		180 days post-biopsy or negative screen	Biopsy group (N=6295)	Number of deaths: 14 Rate: 2.2 per 1000 biopsies	**Rate ratio (95% CI)** Univariate analysis: 0.76 (0.4–1.3) Multivariate analysis: 0.70 (0.4–1.2)
			No biopsy group (negative screen; N=139931)	Number of deaths: 411 Rate: 2.9 per negative screens	
Biopsy-related complications	PLCO[20]	13 years	Total biopsies (N=3706)	**All complications**: 20.2 per 1000 biopsies **Infectious complications**: 7.8 per 1000 biopsies **Non-infectious complications**: 13.0 per 1000 biopsies	N/A
	Netherlands ERSPC[23]	13 years	Total biopsies (N=10747)	**Any complications, n (%)**: 7294 (67.9) **Fever, n (%)**: 424 (3.9) **Haematuria, n (%)**: 2733 (25.4) **Pain, n (%)**: 5369 (50.0) **Hospital admission, n (%)**: 92 (0.9)	N/A

Abbreviations: CI, confidence interval; ERSPC, European Randomized study of Screening for Prostate Cancer; PLCO, Prostate, Lung, Colorectal and Ovarian trial; N/A, not applicable.

Quality of life

Only one publication reporting on the ERSPC Finnish cohort (FinRSPC) investigated the impact of screening on the QoL of participants.[22] Three questionnaires, the RAND 36-Item Short Form Health Survey, the 15D health state description system, and the EQ-5D instrument, were administered to all men who had been diagnosed with prostate cancer during the trial by 1998, 1999, 2003 and 2011, and to a random sample of men ("trial subsample") inducted to the FinRSPC in 1998 (1100 men from the screening arm and 1100 men from the control arm). Cross-sectional analyses at 13 years of follow-up detected a statistically significant difference in mean EQ-5D score between trial arms among men diagnosed with prostate cancer (increment of 0.016 in favour of the screening arm [p=0.017]). This finding was robust to analyses adjusting for time since diagnoses and prostate cancer stage. There was no difference between QoL between trial arms within the trial subsample, although when men with prostate cancer were excluded, the EQ-5D score was slightly higher in the control arm (0.830 vs 0.857, p=0.04). Longitudinal analysis over 13-year follow-up revealed that mean 15D scores were significantly higher in the screening arm (by 0.01) than the control arm, after adjusting for age, domicile and socioeconomic status. This finding was more pronounced when only comparing screen-positive prostate cancer to men diagnosed with prostate cancer in the control arm (0.016 increment). While a small benefit in mean QoL score measured by the EQ-5D instrument was observed in the screening arm compared with the control arm among men who had been diagnosed with PCa, there was little evidence to support that QoL differed between the screening and control arm in general.

Conclusions (Q2)

Moderate quality evidence on the harms in relation to the benefits of PSA-based screening was available from 2 large RCTs, ERSPC and PLCO. Across both trials, estimates for overdiagnosis ranged from 10% to 58% (for men at low polygenic risk in the Finnish section of ERSPC).[17-19] Several publications on the ERSPC also quantified overall benefit of screening by calculating NND, the number of cases that would need to be detected by screening to prevent one prostate cancer-related death and found this to be an average of 18 across all centres, and the authors postulated that this number will continue to decrease with longer follow-up. At 16 years of follow-up, the largest benefit was seen in Sweden (NND=7) and the smallest in Italy (NND=673), but even the smallest NND indicates a substantial rate of overdiagnosis, even with many years of follow-up.[10] Pain and haematuria were the most commonly-reported biopsy complications amongst 10,747 biopsies from the ERSPC study (50.0% and 24.5% respectively),[23] with other complications reported at a lower frequency, including any complications in the PLCO trial (overall rate of 20.2 complications per 1000 biopsies).[17] PLCO also found no significant difference in mortality associated with biopsy between those who received it and those who did not.[17] One study assessed quality of life

(FinRSPC) and found it not to be substantially different between the screening and control arm, albeit with a small benefit being seen in the screening arm in some analyses (e.g., cross-sectional EQ-5D score and longitudinal 15D score after adjustments for age, domicile and socioeconomic status). This would imply that screening does not adversely impact QoL; however, this should be interpreted with caution and as the evidence is only based on a sub-analysis from one study.[22]

Overall, these results are largely similar to those found in the previous UK NSC review in 2015, with overdiagnosis being the most common harm associated with screening (see ***Overdiagnosis*** section), apart from QoL where the last review found that overdiagnosis and overtreatment had an adverse impact on QoL.[7]

Summary of findings relevant to criterion 13: Criterion not met

Quantity: Overall, 2 RCTs reported evidence on overdiagnosis,[18, 19] 2 on biopsy complications,[20, 23] and one on QoL, in order to address criterion 13.[22] The sample sizes included in the analyses ranged from ~20,000 in the Göteborg screening study (Swedish ERSPC section)[130] to >160,000 for the overall ERSPC analysis,[131] and from 3,706 to 10,747 biopsies in the PLCO and Rotterdam ERSPC respectively.[20, 23]

Quality: The 2 trials (PLCO and ERSPC) were both judged to be at some concern of risk of bias overall, primarily because allocation of the intervention (screening) could not be concealed from the participants and the high rate of contamination due to men in the control arm attending opportunistic screening over the years of follow-up (a substantial proportion of >50%), which could result in underestimating the effect of screening in the screening arm. There were low concerns for risk of bias in the majority of other domains.

Applicability: Both studies were judged to be of high applicability to the review question, as they recruited asymptomatic men from a primary care setting in one or more high-income countries considered to be reflective of the UK setting (N=2).

Consistency: Overdiagnosis was measured by calculating the difference across arms in the number of prostate cancer cases diagnosed and dividing by the number of screen-detected cases in the screening arm in PLCO.[17] Conversely, in the FinRSPC, a statistical method (Walter and Day) using mean sojourn time and sensitivity of PSA was used to estimate overdiagnosis.[19, 156] In the Rotterdam section of the ERSPC, biopsy complications were assessed by questionnaire given 2 weeks post-biopsy follow-up.[23] By contrast, biopsy complications were assessed in the PLCO analysis by examining medical records where complications were coded into categories.[32] These differences limit the comparability of the results.

For QoL and the use of absolute measures to quantify the impact of screening (NNI, NNO, NND), conclusions about consistency could not be drawn because these were only reported in one trial.

Conclusions: Despite the large size of the PLCO and ERSPC trials, the inconsistency in outcomes reported makes it difficult to draw robust conclusions on the harms and benefits of

screening, as findings are not supported by multiple sources. Further analyses, where possible, are required to further explore harms and benefits such as false-negative results, psychological harms and overtreatment associated with PSA-based screening, in order to confirm the findings of the PLCO and ERSPC trials thus far. In both trials, the main quality issue of control arm contamination also has implications for comparisons between screening and control arms. Nonetheless, the screening arms were still affected by overdiagnosis that was further quantified by the measure of overall absolute effect of screening, NND, ranging from 7–673 across centres (men who would need to be screened to avert one prostate cancer-related death), judged to reflect substantial overdiagnosis by the study authors.[10] The extent of complications due to biopsy was also inconclusive, with one study reporting an overall rate of 20.2 per 1000 biopsies (2%)[17] and another a much higher 67.9%, thought to be due to the different methods of assessing complications (medical records vs questionnaire).[23] No substantial difference between the screening and control arms was detected for QoL, indicating that PSA-based screening does not have an adverse impact on QoL, however this was only reported in one analysis of the Finnish section of the ERSPC trial.

Based on the findings of this review, there was evidence to suggest that PSA-based screening may be associated with overdiagnosis and biopsy-related complications. However, there was no clear effect of PSA-based screening on quality of life.

Overall, it is unclear whether benefit gained from PSA-based screening programmes outweighs harms, particularly overdiagnosis and the complications that could subsequently arise from unnecessary biopsy; thus, criterion 13 is not met.

Criteria 4 and 5 – Screening tests and cut-off values for prostate cancer

Criterion 4 – Screening tests for prostate cancer

4: 'There should be a simple, safe, precise and validated screening test.'

Criterion 5 – Screening test values for prostate cancer

5: 'The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed.'

In the last external review conducted for the UK NSC in 2015 (with searches in 2014),[6] evidence for criterion 4 was identified and synthesised for PSA testing, DRE, transrectal ultrasound (TRUS), prostate cancer prediction models and triage biomarkers for diagnosing prostate cancer.

A pooled analysis of studies that evaluated the trade-offs of test-performance between using a PSA cut-off of 4.0 vs 3.0 ng/mL found that whilst there was a higher sensitivity with a 3.0 ng/mL cut-off (68%), there was a lower specificity (85%). At both cut-offs, the PPV was low (28% and 30%, respectively), indicative of high false-positive screening results (≥70%). The review concluded that there was no distinct PSA cut-off to distinguish between the presence and absence of prostate cancer. A meta-analysis of 47,791 men who had undergone DRE as an index test, resulted in a pooled sensitivity of 53.2%, specificity of 83.6%, and PPV of 17.8%. PSA had higher predictive values than DRE when compared to a meta-analysis of PSA in the same study (PPV 25.1% vs 17.8%). Furthermore, there were no RCTs to support that DRE testing reduces morbidity or mortality. Several studies were also identified that combined PSA and DRE, and found that this may improve overall detection of prostate cancer, however again, RCTs to assess the effect of this on morbidity or mortality of prostate cancer were not identified. Little evidence was identified for TRUS, but it was noted that it is not a reliable method to exclude the presence of prostate cancer, with as many as 40% of tumours being missed if the performance of biopsy was only dependent on TRUS.

Six prostate cancer prediction models, identified from a previous review and meta-analysis conducted in 2014 which were evaluated in ≥5 study populations and included variables such as DRE, percent free PSA (fPSA) and transrectal ultrasound prostate volume (TRUS-PV) (PCPT, Finne, Karakiewicz, Chun, Prostataclass, ERSPC RC3) were compared to PSA testing alone.[94] They were generally found to have a higher predictive accuracy to detect any prostate cancer, with results of the meta-analysis suggesting that prediction models have the potential to double the sensitivity of PSA testing (44% vs 21%), however it was noted that further investigation is needed to assess the utility of such models for detecting clinically significant prostate cancer (rather than just any prostate cancer) and for use in clinical practice. The last review also

identified PCA3 and fusion gene TMPRSS2:ERG as promising urinary RNA biomarkers to identify men with both indolent (low-risk) and clinically significant (aggressive) cancers.[6]

Evaluation of criterion 5 was limited to the perspective of PSA and repeat PSA testing. For PSA testing, the lack of consensus surrounding PSA referral values was discussed, however it was noted that referral values were being realigned to the evidence emerging from the large PLCO and ERSPC trials (biopsy referral with PSA ≥3.0 ng/mL).

This review update searched for relevant data published since 2014 relating to screening tests or prognostic models for prostate cancer, which compared results to PSA testing, answered through the question (Q3):

Question 3 – Is there evidence that screening using risk algorithms or inclusion of markers other than PSA alone can better identify men with clinically significant prostate cancer, or improve screening efficiency?

Eligibility for inclusion in the review

This review searched for RCTs, observational studies with consecutively enrolled populations, and SLRs and MAs of these relevant study types. Studies were included if the population comprised asymptomatic, unselected men in the primary care setting. Screening tests of interest were defined as any single test or combination of tests, including but not limited to those evaluating clinical variables, the ratio of free PSA to total PSA, blood/urine/genetic biomarkers or biomarker panels, DRE, prostate volume, imaging markers/techniques, and nomograms combining more than one of these variables. For a study to be included, the performance of the screening test had to be evaluated using an appropriate reference standard (confirmation of prostate cancer diagnosis via template prostate mapping (TPM) or transrectal ultrasound (TRUS)-guided prostate biopsy, or via a national cancer registry). Outcomes of interest for question 3 were measures of screening accuracy (e.g. area under the curve [AUC], sensitivity, specificity, positive predictive value [PPV] and negative predictive value [NPV]) and disease-related outcomes (prostate cancer mortality or a cancer stage shift, such as a reduction in stage IV cancers). Studies were not restricted geographically. Full details of the eligibility criteria are presented in Table 6.

Whilst studies performed in men already suspected of having prostate cancer were not eligible for inclusion as they did not fulfil the eligibility criterion of unselected men in a primary care setting, such as the PROMIS trial, a summary of the evidence identified from these is presented later in ***Studies excluded due to use of a pre-selected population*** section.

Description of the evidence

Overall

A total of 19 publications on 11 unique studies were included. A prioritisation strategy was applied to focus on the most relevant comparisons; data was extracted and studies were included in the evidence synthesis if they compared a relevant screening test to PSA-based screening alone or usual care, whereas studies with no comparator or another comparator (e.g. a study comparing 2 nomograms) were deprioritised from synthesis, and are summarised in the “Studies without a PSA comparator” section. No systematic reviews that closely aligned with the scope of question 3 were identified; the main reasons for this were that the SLRs included studies which were conducted prior to 2014 and/or enrolled pre-selected populations, for example, men with suspicion of prostate cancer rather than men in a general population primary care setting. A list of all studies included in the review is available in Table 14.

Ultimately, 7 articles on 6 unique studies were selected for extraction for question 3: 3 articles reporting on 3 RCTs[24, 25, 157] and 4 articles reporting on 3 observational studies.[26, 27, 97, 158] The smallest study recruited 50 participants[26] and the largest study recruited 47,688 participants.[97] Evidence was found for the following screening tests: percent-free PSA test, DRE, PSA test with DRE and PCA3 test, MRI, PSA test with MRI, and the Stockholm 3 (STHLM3) model. In each case, the screening test was compared to the standard PSA test alone.

Characteristics of included studies (Q3)

The 3 RCTs included for question 3 were the Göteborg prostate cancer screening trial performed in Sweden,[24] the PLCO cancer screening trial conducted in the USA,[157] and Rubio-Briones 2014 investigating opportunistic prostate cancer screening in Spain.[25]

In the Göteborg trial, 20,000 men aged between 50 and 64 years were randomised to PSA screening or control arms in 1995, with individuals in the screening group invited to biennial PSA screening.[24] The record with evidence relevant for question 3 reports on a pilot study involving 384 attendees of the tenth and final screening round, which took place from 2013 to 2014. Men with PSA <1.8 ng/mL underwent no further testing, whereas men with PSA ≥1.8 ng/ml were referred for evaluation with 3Tesla MRI, representing a sequential screening strategy. Those with a positive MRI and/or PSA ≥3 ng/mL were referred for prostate biopsy. A 10-core TRUS-guided biopsy was performed first, blinded to MRI results, before an MRI-targeted biopsy was performed in all participants with a positive MRI result.

Between 1993 and 2001, men in the PLCO trial were randomised to routine prostate cancer screening with DRE and PSA, or usual care.[157] Participants were aged between 55 and 74 years. Men in the screening arm underwent annual DRE for the first 4 years and annual PSA screening for the first 6 years of the trial. In the event of a positive

screening test, the diagnostic and therapeutic course of the patient was determined by their physician. Outcomes reported were clinical endpoints, including prostate cancer specific mortality, obtained over ≤13 years of follow-up in 35,350 men from the screening arm.

The Rubio-Briones 2014 RCT, conducted from 2010 to 2012, included 2,366 healthy men aged 40 to 75 years and evaluated a sequential screening strategy.[25] During an initial visit, participants had a PSA test and DRE performed by a urologist. Men with normal DRE and PSA results (<3 ng/mL) proceeded to a repeat PSA test and DRE after 1, 2, 3 or 4 years if their PSA level was 2 to 3, 1 to 2, 0.5 to 1 or <0.5 ng/mL, respectively. Men with PSA ≥3 ng/mL and/or abnormal DRE results (at either an initial or repeat visit) underwent another DRE, and a further test to determine their PCA3 levels. Individuals with PCA3 ≥35 (ratio of PCA3 to PSA) were referred for a 12-core prostate biopsy, whereas those with PCA3 levels <35 were blindly randomised 1:1 to 12-core prostate biopsy or observation.

The 3 observational studies included for question 3 were: the San Antonio Biomarkers Of Risk (SABOR) study, a prospective cohort study performed in the USA;[158] the STHLM3 study, a prospective, population-based, diagnostic study conducted in Sweden;[27, 97] and Nam 2016, a small prostate cancer screening pilot study based in Canada.[26]

In the SABOR study, conducted between 2000 and 2010, men underwent annual PSA and DRE screening, with subsequent biennial screening for those deemed to be at low risk of prostate cancer based on their PSA levels.[158] From 2007 onwards, a percent-free PSA test was incorporated into screening visits. The article included for question 3 reports on 2,183 SABOR participants with at least one pair of PSA and percent-free PSA values collected at the same clinical visit. Men with PSA >2.5 ng/mL or an abnormal DRE were referred for prostate biopsy.

The STHLM3 study aimed to develop and validate a new model to identify high-risk prostate cancer (Gleason score ≥7) with better test characteristics than the PSA test alone.[27, 97] The original STHLM3 model was developed with a training cohort of 11,130 men recruited in 2012–2013, and tested in a validation cohort of 47,688 men recruited in 2013 to 2014.[97] All participants were aged 50 to 69 years. The model itself consists of a combination of plasma protein biomarkers (PSA, free PSA, intact PSA, hK2, MSMB, and MIC1), genetic markers (232 single nucleotide polymorphisms [SNPs]), clinical variables (age, family history, previous prostate biopsy) and a prostate exam (DRE and prostate volume). In the validation cohort, all men underwent a PSA test; genetic and plasma protein biomarkers were subsequently evaluated in men with PSA ≥1 ng/mL. If the STHLM3 model indicated ≥10% risk of high-grade prostate cancer, patients were referred to a urologist who performed a DRE, prostate volume measurement and 10- or

12-core transrectal prostate biopsy. Of note, DRE and prostate volume measurements were only performed in patients after selection for biopsy.

In the Nam 2016 prostate cancer screening pilot study, men aged between 50 and 75 years were solicited to undergo MRI and prostate biopsy irrespective of their PSA levels or MRI results.[26] Fifty volunteers were recruited, of whom 47 underwent both MRI and prostate biopsy. Those with a negative MRI result had a 12-core TRUS-guided biopsy, whereas those with a positive MRI result had an MRI-targeted biopsy in addition to the 12-core biopsy.

Table 14. Summary of records included for question 3

Study	Design	Partici-pants	Dates	Country	Age[a] (years)	Index test	Index test threshold(s)	Reference standard(s)	Comparator	Comparator threshold(s)	Outcomes
Göteborg [24]	RCT	384	2013 to 2014	Sweden	50 to 64	PSA with MRI	PSA ≥3 ng/mL and/or PSA ≥1.8 ng/mL with positive MRI (Likert score ≥3)	TRUS-guided biopsy, or TRUS-guided biopsy and MRI-targeted biopsy	PSA	PSA ≥3 ng/mL	Sensitivity, specificity, PPV, NPV
PLCO[157]	RCT	35,350	1993 to 2001[b]	USA	55 to 74	DRE	Examination by clinician[c]	Prostate biopsy	PSA	PSA ≥4 ng/mL	PCSM
Rubio-Briones 2014[25]	RCT	2,366	2010 to 2012	Spain	40 to 75	PSA with DRE and PCA3	PSA ≥3 ng/mL and/or abnormal DRE with PCA3 ≥35[d]	Prostate biopsy	PSA	PSA ≥3 ng/mL	True positives, false negatives, AUC, sensitivity, specificity
SABOR[15, 8]	Prospective cohort study	2,183	2007 to 2010	USA	NR	Percent-free PSA	<25% or <15%	Prostate biopsy	PSA	PSA ≥4 ng/mL	Reduction in false positives if used as a reflex test after PSA
STHLM3[2, 7, 97]	Prospective population-based diagnostic study	11,130 (training) 47,688 (validation)	2013 to 2014[e]	Sweden	50 to 69	STHLM3 predictive model[f]	≥10% risk of high-grade prostate cancer[g]	Prostate biopsy	PSA	PSA ≥3 ng/mL	AUC
Nam 2016[26]	Screening pilot study	50	NR	Canada	50 to 75	MRI	Positive MRI (Likert score ≥4)	TRUS-guided biopsy, or TRUS-guided biopsy and MRI-targeted biopsy	PSA	PSA ≥4 ng/mL	AUC, PPV, NPV

[a]At recruitment. [b]Does not include follow-up (≤13 years). [c]DRE was considered positive or suspicious in the presence of induration, nodularity, significant asymmetry or loss of anatomical landmarks. [d]Eight other PCA3 thresholds are considered in post-hoc analyses. [e]Dates for the recruitment of the validation cohort; the training cohort was recruited in 2012–2013. [f]Original STHLM3 model includes plasma protein biomarkers (PSA, free PSA, intact PSA, hK2, MSMB, and MIC1), genetic markers (232 single nucleotide polymorphisms [SNPs]), clinical variables (age, family history, previous prostate biopsy) and a prostate exam (DRE and prostate volume). [g]Gleason score ≥7. **Abbreviations**: AUC, area under the curve; DRE, digital rectal examination; MRI, magnetic resonance imaging; NPV, negative predictive value; NR, not reported; PPV, positive predictive value; PCA3, prostate cancer antigen 3; PCSM, prostate cancer-specific mortality; PLCO, prostate, lung, colorectal and ovarian; PSA, prostate-specific antigen; RCT, randomised controlled trial; SABOR, San Antonio Biomarkers Of Risk; STHLM3, Stockholm 3; TRUS, transrectal ultrasound.

Full details regarding study designs, population characteristics, methods, results and authors' conclusions are presented in the evidence tables in Appendix 3 — Summary and appraisal of individual studies (Table 40a–f).

Summary of findings

Quality assessment (Q3)

Studies on single tests

The quality of the 5 included studies that assessed single tests was appraised using an adapted QUADAS-2 checklist (Table 44; Appendix 4 – Guidance on quality assessments). The quality of the one study that assessed a prognostic model was appraised using an adapted PROBAST tool checklist (Table 45; Appendix 4 – Guidance on quality assessments). A summary of the risk of bias and applicability to the UK setting is presented in Table 15 and Table 16, and the full appraisals are presented in Table 47 and Table 48 (Appendix 5 – Appraisal for quality and risk of bias).

Table 15. Summary of QUADAS-2 assessments for prostate cancer screening studies

Question	Ankerst 2016 (SABOR)[158]	Grenabo Bergdahl 2016 (Göteborg)[24]	Halpern 2017 (PLCO)[157]	Nam 2016[26]	Rubio-Briones 2014[25]
PARTICIPANT SELECTION					
Risk of bias	Unclear	Unclear	Low	Unclear	Unclear
Concern about applicability	Low	High	Low	High	High
INDEX TESTS					
Risk of bias	Low	Low	Low	Low	Low
Concern about applicability	Low	Low	Low	Low	Low
REFERENCE STANDARD					
Risk of bias	Unclear	Low	Unclear	High	Unclear
Concern about applicability	Unclear	Low	Unclear	Low	Unclear
PARTICIPANT FLOW					
Risk of bias	High	High	Unclear	High	High

Participant selection

Overall, the risk of bias was judged low in one out of 5 studies; the low risk of bias study (PLCO) enrolled unselected men without a history of prostate cancer in a consecutive or random manner and did not make any inappropriate exclusions.[157] Four studies were judged to be at an unclear risk of bias; in SABOR and Göteborg, recruitment methods and eligibility criteria were not clearly reported,[24, 158] whereas Nam 2016 and Rubio-Briones 2014 enrolled men on a volunteer basis (opportunistic screening), which may

raise concerns for bias due to the healthy volunteer effect.[25, 26] In addition, Nam 2016 was a small pilot study enrolling just 50 men.[26] The risk of bias for Nam 2016 and Rubio-Briones 2014 studies was therefore also judged to be unclear.[25, 26] A case-control design was avoided in all 5 studies (3 RCTs[24, 25, 157] and 2 prospective cohort studies).[26, 158]

The PLCO and SABOR studies enrolled asymptomatic or healthy men from primary care settings, closely aligning with the population of interest for this review.[157, 158] For the 2 studies that used opportunistically screened healthy men, either via newspaper advertisements,[26] or unreported methods,[25] the concern for applicability was high, as these studies did not recruit from a primary care setting and volunteers may differ from random or consecutively selected participants (volunteer bias).[25, 26] Grenabo-Beghdahl 2016 is a pilot study recruiting men from the tenth round of screening of the Göteborg screening trial (ERSPC, Sweden). It was unclear if exclusion criteria were applied to this cohort, and this study is therefore at an unclear risk of selection bias. However, it was reported that the enrolled men had been invited to PSA screening appointments up to 9 times over a period of 19-years, with only 2% of the cohort being screened for the first time during the pilot study. While originally unselected from a primary care setting, the majority of the study population had undergone substantial repeat screening over a long period of time, and are therefore not representative of the general population. There is therefore high concern about applicability for this study.

Index tests

All 5 studies were judged to be at low risk of bias for this domain.[24-26, 157, 158] Index test thresholds or criteria were pre-specified, thereby demonstrating that the thresholds were not able to be influenced by the reference standard results, minimising the risk of over-estimation of test accuracy.

There was little concern that the index tests may have differed from the review question in all of the included studies; all evaluated relevant tests are covered in the NICE NG131 guideline.

Reference standard

The biopsy procedures, including information on the type of biopsy and who conducted the procedure, were poorly described in 3 studies.[25, 157, 158] In the PLCO trial, it was reported that further diagnostic investigations in screen-positive men were continued under physician care, and therefore may differ between study participants from different primary care centres. It was, however, reported that examiners were blinded to PSA results, and mortality was assessed by a blinded verification process.[24] No details on the biopsy procedure or blinding to index test results were reported in the SABOR and Rubio-Briones 2014 studies.[25, 158] Overall, these studies were therefore at an unclear risk of bias.

In Grenabo-Bergdahl 2016 (Göteborg pilot study), all screen-positive men first underwent TRUS-guided systematic biopsy, conducted by a single urologist blinded to the MRI results.[24] In men with abnormal findings on MRI, MRI-targeted biopsy was then performed unblinded to the MRI results to allow for the approach of "cognitive" targeting. As knowledge of MRI data is required for this targeted biopsy procedure, this study was therefore at a low risk of bias for this domain.[24] Similarly in the Nam 2016 study, all screen-positive men underwent random 12-core TRUS-guided biopsy, and men who had a region identified on MRI additionally underwent targeted MRI-guided biopsy, however no blinding was reported for the first TRUS-guided biopsy procedure.[26] As knowledge of the PSA results may influence biopsy assessment and the experience level of the staff who performed the biopsy is unknown, this study was judged to be at a high risk of bias.

There was no concern about applicability of the reference standard in 2 studies, as widely used biopsy approaches were used to confirm the diagnosis (e.g. TRUS-guided systematic biopsy or MRI-targeted biopsy).[24, 26] Nevertheless, it should be noted that it was not explicitly stated if biopsy was performed by experienced clinicians in the Nam 2016 study. In the 3 studies that did not report any details on the biopsy approach, applicability to the review question was unclear.[25, 157, 158]

Participant flow

Four studies were at a high risk of bias for this domain. Information on the type of biopsy performed in screen-positive men and whether this was conducted by hospital staff or the researchers was not provided in 3 studies.[25, 157, 158] This increases the risk of bias, as it is unknown if all participants received the same reference standard, and there may have been differences in the methods of diagnosis between staff of different hospitals or with different training backgrounds. Furthermore, in the Nam 2016 study, men with PSA >10 ng/mL were not offered MRI, potentially increasing bias against the screening performance of PSA.[26]

In the SABOR study, a considerable number of enrolled men were not included in the analysis for unknown reasons.[158] This could have introduced selection bias, potentially leading to under- or over-estimation of test accuracy.

In all studies, the index tests were conducted before the reference standard (biopsy), and there was no evidence of preventive treatment in the intervening time period,[25, 26, 157, 158] or in one study, men who had received such treatment were excluded.[24] However, only screen-positive men received biopsy in the majority of studies. This would be expected considering the concerns surrounding the harms of low-risk men undergoing biopsy, however it is still important to acknowledge that this prevents screen-negative cases from being confirmed as true-negatives cases, which may influence test accuracy measures via verification bias. This is a particular risk of sequential testing, where screen-negative men may be excluded at the first negative index test result. Grenabo-

Bergdahl 2016 conducted a sensitivity analysis to investigate the potential impact of this on screening accuracy within the Göteborg screening cohort, finding that the significant differences between the 3 screening strategies evaluated remained unchanged for specificity, but at a reduced sensitivity.[97] In the Nam 2016 study, all screened men were planned to undergo biopsy, however, a small sample of 50 men were included (with only 47 undergoing both MRI and biopsy), and thus this study was judged to be at a high risk of bias for this domain.

Predictive model studies

The review identified one predictive model study, STHLM3, the quality of which was assessed with the PROBAST checklist and is summarised in Table 16.

Table 16. PROBAST quality assessment of the STHLM3 predictive study

Question	Grönberg 2015 (STHLM3)[97]
Type of prediction study	Development and validation study
PARTICIPANTS	
Risk of bias	Low
Concern about applicability	Low
PREDICTORS	
Risk of bias	Low
Concern about applicability	Low
OUTCOME	
Risk of bias	Low
Concern about applicability	Low
ANALYSIS	
Risk of bias	Unclear
OVERALL ASSESSMENT	Low

Participants

The data for the model was sourced from the Stockholm 3 (STHLM3) study, a prospective, population-based cohort study in randomly selected men aged 50 to 69 years without a previous diagnosis of prostate cancer. Risk of selection bias was therefore low. While men were not recruited from primary care, they were randomly selected from the Swedish Population Register by date of birth and invited via postal invitation. This population was therefore representative of an unselected, asymptomatic cohort not recruited from secondary or tertiary care setting, in alignment with the review question.

Predictors

The predictors in the STHLM3 model were adequately described, and samples were collected and analysed in a consistent way for all study participants. The predictors were selected based on findings of a systematic literature search, and 2 validation studies. Testing for PSA and other biomarkers was conducted before biopsy, as index PSA test results were required to determine whether biopsy was indicated. However, DRE and

prostate volume measurements were only conducted in men selected for biopsy, which is after the time that the model is intended to be used. As this was reflected in the model by the order of predictors, and the results were shown to be robust to the removal of these predictors from the model, this study is considered to be at low risk of bias for this domain. There is also low concern that overall, the definition, assessment or timing of predictors in the model do not match the review question.

Outcome

There was low risk of bias introduced by determination of the outcome. The outcome of high-risk prostate cancer was pre-defined (Gleason score ≥7) and determined appropriately – all participants underwent a standardised biopsy protocol, in which biopsies were assessed by a single pathologist to reduce interobserver variance. Participating investigators (including urologists and pathologists) were blinded to PSA and biomarker results. While the time interval between screening and biopsy were not reported, it is considered unlikely that time was sufficiently long for new prostate cancer to develop or progress to high-risk classification.

The primary outcome of interest was area under the curve (AUC) of the model compared with PSA alone, in line with the review question. There was therefore low concern about applicability in relation to the outcomes.

Analysis

Large numbers of participants were included in both the training (N=11,130) and validation cohorts (N=47,688). Reasons for exclusion of participants from final analyses were sufficiently reported; for example, 6% of the training cohort and 10% of the validation cohort who had undergone biopsy were excluded due to receipt of alpha-reductase inhibitors, which are used to treat enlarged prostate and could confound results. Continuous and categorial predictors were handled appropriately using logistic regression, in which continuous outcomes were modelled using linear effects, and categorical outcomes were included as indicator variables.

However, there was no information on the handling of missing data, accounting for any complexities in the data (such as censoring), or evaluation of model performance measures such as development and calibration. While it was reported that 5-fold cross validation was used to account for model overfitting or optimism in model performance, no information was provided on the predictors and their assigned weights (e.g. no intercepts provided). Due to substantial missing information on the analyses, the risk of bias introduced by the analysis for the STHLM3 study is unclear overall.

Results (Q3)

Key results for each of the screening tests are presented in Table 17. Full details of the included studies and their results can be found in Table 40a–f (Appendix 3 — Summary and appraisal of individual studies).

Sequential screening

PSA test with MRI vs PSA test

The Göteborg pilot study compared 3 different screening strategies: (1) PSA ≥3.0 ng/mL and systematic biopsy; (2) PSA ≥3.0 ng/mL, MRI scan, and MRI-targeted prostate biopsy in the event of a positive MRI scan (Likert score ≥3); and (3) PSA ≥1.8 ng/mL, MRI scan, and MRI-targeted prostate biopsy in the event of a positive MRI scan (Likert score ≥3).[24] The reference screening strategy (1) achieved a sensitivity of 0.64 (95% CI 0.47 to 0.82) and specificity of 0.52 (95% CI 0.43 to 0.62), suggesting that a substantial proportion of screen-positive men based on PSA alone will not have prostate cancer detected on biopsy. This is demonstrated by a low positive predictive value (PPV) of 0.27 (95% CI 0.16 to 0.37) and a higher negative predictive value (NPV) of 0.84 (95% CI 0.75 to 0.93).The addition of MRI as a sequential index test in men with PSA ≥3 ng/mL allowed for further exclusion of low-risk men, demonstrated by a higher specificity of 92% (95% CI 0.86 to 0.97). However, this was at the expense of sensitivity, which decreased to 46% (95% CI 0.27 to 0.65). It was reported that this screening strategy missed 3 cases of significant prostate cancer, demonstrating the potential consequence of a reduction in sensitivity. When the PSA cut-off was lowered to 1.8 ng/mL, both sensitivity and specificity increased (sensitivity 0.73, 95% CI 0.56 to 0.90; specificity 0.79, 95% CI 0.70 to 0.87) in comparison with PSA alone, followed by systematic biopsy. In fact, PSA ≥1.8 ng/mL followed by MRI reduced the proportion of biopsies performed by 26%, with improved detection of significant prostate cancer (by 48%) and prostate cancer with Gleason score ≥7 (by 43%). Measures of test accuracy for prostate cancer by risk of progression or grade were not reported.

PSA test with DRE and PCA3 test vs PSA test

The Rubio-Briones 2014 RCT compared a novel sequential screening strategy (PSA ≥3 ng/mL and/or abnormal DRE, followed by PCA3 ≥35 signifying a positive result) with the standard PSA test (threshold of ≥3 ng/mL).[25] The AUC for the PCA3 strategy (0.748, 95% CI 0.677 to 0.819) was greater than that for the PSA test (0.601, 95% CI 0.514 to 0.689), with a statistically significant difference between the approaches (p=0.008). The PCA3 strategy achieved 78.2% sensitivity and 57.1% specificity, suggesting that while a large proportion of men with prostate cancer will be diagnosed at biopsy, a substantial proportion of screen-positive men will not have prostate cancer, representing unnecessary biopsy. For example, of the 110 men that had PCA3 ≥35 and underwent prostate biopsy, only 43 (39.1%) had prostate cancer (true positives). Conversely, of the

101 men that had PCA3 <35 and were randomised to prostate biopsy, 12 (11.9%) had prostate cancer (false negatives).

Single screening tests

MRI vs PSA test

The Nam 2016 study compared MRI (Likert score ≥4 signified a positive result) with the standard PSA test (with a threshold of ≥4 ng/mL).[26] The AUC for MRI (0.81, 95% CI 0.67 to 0.94) was greater than that for the PSA test (0.67, 95% CI 0.52 to 0.84). When patients were divided into those with negative and positive PSA test results, MRI score was a strong predictor of cancer. Prostate cancer was diagnosed in 9 out of 30 men (30.0%) with a negative PSA test result. For this group, the PPV of MRI was 66.7% (6/9) and the NPV of MRI was 85.7% (18/21, p=0.004). Prostate cancer was also diagnosed in 9 out of 17 men (52.9%) with a positive PSA test result. For this group, the PPV of MRI was 75.0% (6/8) and the NPV of MRI was 66.7% (6/9, p=0.08).

DRE vs PSA test

The PLCO study compared DRE with the standard PSA test (with a threshold of ≥4 ng/mL).[157] During follow-up (≤13 years) there were 64 prostate cancer-specific deaths. Suspicious DRE was significantly associated with prostate cancer-specific mortality on univariate analysis (HR 3.49, 95% CI 1.96 to 6.23, p<0.001) and on multivariate analysis, after adjustment for age and intra-study PSA (HR 2.54, 95% CI 1.41 to 4.58, p=0.002). Nonetheless, abnormal PSA was even more strongly associated with prostate cancer-specific mortality on multivariate analysis (HR 5.23, 95% CI 3.08 to 8.88, p<0.001). Hence, PSA is likely to be a better predictor of prostate cancer-specific mortality than DRE.

Percent-free PSA test vs PSA test

The SABOR study compared the percent-free PSA test (with a threshold of <25% or <15%) with the standard PSA test (with a threshold of ≥4 ng/mL).[158] Of the 79 men that had a negative biopsy after a positive PSA test, 25 (31.6%) and 52 (65.8%) tested negative on the percent-free PSA test by exceeding the thresholds of 25% and 15%, respectively. Hence, the use of the percent-free PSA test as a reflex test after the standard PSA test would have spared 65.8% of unnecessary biopsies. Conversely, of the 41 men that had a positive biopsy after a negative PSA test, 35 (85.4%) and 18 (43.9%) tested positive on the percent-free PSA test by failing to exceed the thresholds of 25% and 15%, respectively.

STHLM3 model vs PSA test

The STHLM3 study compared the STHLM3 model (≥10% risk of high-grade [Gleason score ≥7] prostate cancer signified a positive result) with the standard PSA test (with a threshold of ≥3 ng/mL).[97] The AUC for the original STHLM3 model was greater than that for the PSA test alone for the prediction of all cancers (0.69 [95% CI 0.68 to 0.71] vs

0.52 [95% CI 0.50 to 0.53], p value not reported), the prediction of high-grade (Gleason score ≥7) cancers (0.74 [95% CI 0.72 to 0.75] vs 0.56 [95% CI 0.54 to 0.59], p<0.0001), the prediction of all cancers excluding very low-risk cancers (CAPRA score 0 to 2) (0.78 [95% CI 0.76 to 0.80] vs 0.64 [95% CI 0.62 to 0.67], p value not reported), and the prediction of cancers with a Gleason score ≥(4 + 3) (0.74 [95% CI 0.71 to 0.77] vs 0.60 [95% CI 0.56 to 0.64], p value not reported). Note, however, that the DRE and prostate volume measurements were only performed in patients after selection for biopsy. When considering only the components of the STHLM3 model that were measured prior to selection for biopsy (i.e. total PSA, risk factors, genetic markers and plasma protein biomarkers), the AUC for the original STHLM3 model for the prediction of high-grade (Gleason score ≥7) cancers was reduced from 0.74 (95% CI 0.72–0.75) to 0.70 (95% CI 0.68–0.72). Nonetheless, the AUCs for both the former and the latter were significantly greater than the AUC for the PSA test alone (p<0.0001).

The original STHLM3 model was later updated with the removal of specific variables (e.g. intact PSA) and the addition of others (e.g. a rare germline mutation of the *HOXB13* gene).[27] The updated STHLM3 model performed slightly better than the original one. Based on analyses including all biopsied participants from the STHLM3 pilot study and validation study, the AUC for the updated STHLM3 model for the prediction of high-grade (Gleason score ≥7) cancers was 0.75 (95% CI 0.73 to 0.77), while the AUC for the PSA test was 0.58 (95% CI 0.57 to 0.60). Further analyses were performed to evaluate the usage of the updated STHLM3 model as a reflex test in patients with PSA ≥3ng/mL only. In this context, the AUC for the updated STHLM3 model for the prediction of high-grade (Gleason score ≥7) cancers rose to 0.76 (95% CI 0.74 to 0.77).

Table 17. Diagnostic performance of screening tests

Study	Test	Threshold(s)	Reference standard(s)	Outcome							
				Sens. (95% CI)	Spec. (95% CI)	PPV (95% CI)	NPV (95% CI)	False positive	False negative	AUC (95% CI)	PCSM, HR (95% CI)
Göteborg[24]	Strategy 1: PSA	PSA ≥3 ng/mL	TRUS-guided biopsy	0.64 (0.47–0.82)	0.52 (0.43–0.62)	0.27 (0.16–0.37)	0.84 (0.75–0.93)	NR	NR	NR	NR
	Strategy 2: PSA + MRI	PSA ≥3 ng/mL with positive MRI (Likert score ≥3)	MRI-targeted biopsy	0.46 (0.27–0.65)	0.92 (0.86–0.97)	0.60 (0.39–0.81)	0.87 (0.80–0.93)	NR	NR	NR	NR
	Strategy 3: PSA + MRI	PSA ≥1.8 ng/mL with positive MRI (Likert score ≥3)	MRI-targeted biopsy	0.73 (0.56–0.90)	0.79 (0.70–0.87)	0.48 (0.32–0.63)	0.92 (0.86–0.98)	NR	NR	NR	NR
PLCO[157]	PSA	PSA ≥4 ng/mL	Prostate biopsy	NR	NR	NR	NR	NR	NR	NR	**5.23 (3.08–8.88), p<0.001**
	DRE	Examination by clinician[a]	Prostate biopsy	NR	NR	NR	NR	NR	NR	NR	**2.54 (1.41–4.58, p=0.002)**
Rubio-Briones 2014[25]	PSA	PSA ≥3 ng/mL	Prostate biopsy	NR	NR	NR	NR	NR	NR	0.601 (0.514–0.689)	NR
	PSA with DRE, followed by PCA3	PSA ≥3 ng/mL and/or abnormal DRE, with PCA3 ≥35[b]	Prostate biopsy	78.2	57.1	NR	NR	NR	11.9%	0.748 (0.677–0.819)	NR
SABOR[158]	PSA vs percent-free PSA	PSA ≥4 ng/mL vs percent-free PSA <25% or <15%	Prostate biopsy	NR	NR	NR	NR	417 false positives (≥1 biopsies) PSA screen-positive and negative biopsy (N=79): 25 (31.6%) screened negative at percent-free PSA 25% threshold; 52	PSA screen-negative and positive biopsy (N=41): 35 (85.4%) screened positive at percent-free PSA 25% threshold;18 (43.9%) at	NR	NR

Study	Test	Threshold(s)	Reference standard(s)	Outcome							
				Sens. (95% CI)	Spec. (95% CI)	PPV (95% CI)	NPV (95% CI)	False positive	False negative	AUC (95% CI)	PCSM, HR (95% CI)
								(65.8%) at percent-free PSA 15% threshold	percent-free PSA 15% threshold		
Gronberg 2016 (STHLM3)[97]	PSA	PSA ≥3 ng/mL	Prostate biopsy	NR	NR	NR	NR	NR	NR	All PCa: 0.52 (0.50–0.53) High grade[c] PCa: 0.56 (0.54–0.59) Excluding very low-risk[d] PCa: 0.64 (0.62–0.67) Gleason score ≥(4 + 3) PCa: 0.60 (0.56–0.64)	NR
	STHLM3 predictive model[e]	≥10% risk of high-grade prostate cancer[c]	Prostate biopsy	NR	NR	NR	NR	NR	NR	All PCa: 0.69 (0.68–0.71) High grade[c] PCa: 0.74 (0.72–0.75) Excluding very low-risk[d] PCa: 0.78 (0.76–0.80) Gleason score ≥(4 + 3) PCa: 0.74 (0.71–77)	NR
Strom 2018 (STHLM3)[27]	PSA	PSA ≥3 ng/mL	Prostate biopsy	NR	NR	NR	NR	NR	NR	High risk PCa[c] 0.58 (0.57–0.60)	NR

Study	Test	Threshold(s)	Reference standard(s)	Outcome							
				Sens. (95% CI)	Spec. (95% CI)	PPV (95% CI)	NPV (95% CI)	False positive	False negative	AUC (95% CI)	PCSM, HR (95% CI)
	Updated STHLM3 predictive model[f]	≥10% risk of high-grade prostate cancer[c]	Prostate biopsy	NR	NR	NR	NR	NR	NR	High risk PCa[c] 0.75 (0.73–0.77)	
Nam 2016[26]	PSA	PSA ≥4 ng/mL	TRUS-guided biopsy after negative MRI, TRUS-guided biopsy and MRI-targeted biopsy after positive MRI	NR	NR	NR	NR	NR	NR	0.67 (0.52–0.84)	NR
	MRI	Positive MRI (Likert score ≥4)	TRUS-guided biopsy after negative MRI, TRUS-guided biopsy and MRI-targeted biopsy after positive MRI	NR	NR	66.7% in men with a negative PSA test. 75.0% in men with a positive PSA test.	85.7% in men with a negative PSA test. 66.7% in men with a positive PSA test.	NR	NR	0.81 (95% CI 0.67–0.94)	NR

[a]DRE was considered positive or suspicious in the presence of induration, nodularity, significant asymmetry or loss of anatomical landmarks. [b]Eight other PCA3 thresholds are considered in post-hoc analyses. [c]Gleason score ≥7. [d]CAPRA score 0–2. [e]Original STHLM3 model includes plasma protein biomarkers (PSA, free PSA, intact PSA, hK2, MSMB, and MIC1), genetic markers (232 single nucleotide polymorphisms [SNPs]), clinical variables (age, family history, previous prostate biopsy) and a prostate exam (DRE and prostate volume). [f]Updated STHLM3 model involved the removal of specific variables (e.g. intact PSA) and the addition of others (e.g. a rare germline mutation of the *HOXB13* gene). **Abbreviations**: AUC, area under the curve; CAPRA, Cancer of the Prostate Risk Assessment; CI, confidence interval; DRE, digital rectal examination; HR, hazard ratio; MRI, magnetic resonance imaging; NPV, negative predictive value; NR, not reported; PPV, positive predictive value; PCa, prostate cancer; PCA3, prostate cancer antigen 3; PCSM, prostate cancer specific mortality; PLCO, prostate, lung, colorectal and ovarian; PSA, prostate-specific antigen; SABOR, San Antonio Biomarkers Of Risk; STHLM3, Stockholm 3; TRUS, transrectal ultrasound.

Studies without a PSA comparator

Twelve included studies were deprioritised for extraction as they did not compare a relevant screening test to PSA-based screening, or lacked a comparator altogether. Eleven studies reported on the accuracy of one or more predictive models for prostate cancer, mostly in the context of triaging risk of high-grade cancer in men referred for biopsy. These are summarised below, however, they have not been included in the consideration of whether criteria 4 and 5 are met, as comparison to PSA is not feasible.

Four publications by Ankerst and colleagues reported on development and modification of the Prostate Cancer Prevention Trial risk calculator (PCPTRC) tool,[159-162] including addition of PCA3 data obtained from the SABOR cohort, which significantly improved prediction of high-grade prostate cancer.[159, 160] Incorporation of the TMPRSS2:ERG urinary assay results in the model did not improve detection any further after the addition of PCA3.[160] Ankerst 2018 compared the PCPTRC to the newly developed Prostate Biopsy Collaborate Group (PBCG) model, in the estimation of the risks associated with high-grade prostate cancer on biopsy.[162] The PBCG model was constructed by Ankerst et al based on data from 15,611 men undergoing biopsy at 8 North American centres. It was concluded that the PBCG model was superior over the PCPTRC for prediction of prostate biopsy outcome in terms of clinical net benefit, with an improvement in AUC (75.5%, 95% CI 74.2 to 76.8 vs. 72.3%, 95% CI 70.9 to 73.7, respectively). Based on a risk threshold of 10%, the use of the PBCG model would lead to 25 fewer biopsies per 1000 men, without missing any cases of high-grade prostate cancer. These findings were further validated on a cohort of 10,377 European biopsies.[162]

Two studies used data from the screening arm of the PLCO trial.[163, 164] Kim 2017 compared the performance of the four-kallikrein (4K) panel in predicting high-grade prostate cancer with that of the Prostate Cancer Prevention Trial (PCPT) risk calculator, finding that the 4K panel was a superior predictor of high-grade prostate cancer (AUC, 4K 0.79 vs PCPT 0.73). The addition of microseminoprotein-beta (MSP) as a predictor further improved risk discrimination in comparison with 4K alone (AUC 0.81).[163] Shoaibi 2017 investigated the performance of PSA rate based on a PSA growth curve model. A PSA rate threshold of 0.37 ng/ml/year achieved an optimal combination of 97.2% sensitivity and 97.3% specificity for detection of high-risk prostate cancer. The study also found that PSA rate was a better predictor that a single PSA value from the last test, although these findings are yet to be validated.[164]

Four studies evaluated the ERSPC Rotterdam risk calculator.[165-168] Roobol 2017 reported that an updated version of the ERSPC risk calculator number 3 (RC3), achieved an AUC of 0.70 (95% CI 0.68 to 0.72), reducing unnecessary biopsies by 34% at a 1% risk threshold, while missing only 2% of high-risk prostate cancer cases.[165] Vedder 2014 compared the predictive performance of percent-free PSA, PCA3, 4K-panel and the ERSPC risk calculator (original model and with DRE), and combinations

of these models, in detection of prostate cancer. The addition of PCA3 and the 4K panel to the DRE-based ERSPC risk calculator improved predictive performance (AUC 0.80, 95% CI 0.72 to 0.87 vs AUC 0.76, 95% CI 0.68 to 0.83).[166] The utility of the RPCRC and 4K panel predictive models in reducing unnecessary biopsy and overdiagnosis were found to be comparable by Verbeek 2018, with enhanced efficacy when used together. One study compared the predictive accuracy of the RC3 model with PSA alone, although the only outcome reported for this comparison was the concordance index (RC3 0.810 vs PSA 0.767; p<0.001).[168]

One study, Van der Leest 2019, evaluated 3 MRI protocols as a primary screening test for detecting high-grade prostate cancer in biopsy-naïve men:[169] monoplanar ("fast" biparametric MRI [bp-MRI]) and triplanar nonconstrast bp-MRI were compared with current contrast-enhanced multiparametric MRI. All 3 MRI approaches achieved a sensitivity of 95% in the detection of high-grade prostate cancer, although this was at the expense of specificity, which was lowest for fast bp-MRI (65%) in comparison with bp-MRI and mp-MRI (both 69%). It was concluded that while fast bp-MRI is associated with lower direct costs which could improve accessibility in clinical practice, it is estimated that the use of this protocol could lead to 2% more biopsies, with ~1% more overdiagnosis of low-grade prostate cancer.[169]

Studies excluded due to use of a pre-selected population

Many records (>600) were excluded from this review due to having a pre-selected population that was not in a primary care setting. A key example of this is the PROMIS study, which used mpMRI as a triage test in men who had been advised to have a prostate biopsy due to a clinical suspicion of prostate cancer.[170] Suspicion included elevated serum PSA (up to 15 ng/mL), suspicious DRE, suspected organ confined stage ≤T2 on rectal examination, or family history. A total of 576 eligible participants underwent 3 tests, 1) mpMRI (the index test), 2) TRUS-guided biopsy (the current standard), 3) TPM biopsy (the reference test). For clinically significant prostate cancer (which was defined by validated criteria for use with TPM-biopsy for detection of primary Gleason grade ≥4 and cancer core length predictive for the presence of lesions ≥0.5 mL), mpMRI had a sensitivity of 93% (95% CI 88 to 96), specificity of 41% (95% CI 36 to 46), PPV of 51% (95% CI 46 to 56) and NPV of 89% (95% CI 83 to 94), compared to 48% (sensitivity), 96% (specificity), 90% (PPV) and 89% (NPV) for TRUS-guided biopsy. In an economic evaluation, the most cost-effective strategy was testing all men with mpMRI, followed by MRI-guided TRUS biopsy in those with clinically significant cancer and re-biopsy if clinically significant cancer was not detected. The authors concluded that incorporating mpMRI into the diagnostic pathway may reduce the proportion of men having unnecessary biopsies, improve the detection of clinically significant prostate cancer and increase cost-effectiveness of the diagnostic and therapeutic pathway. However, caution must still be taken as a negative mpMRI scan was recorded for 158 (27%) men, 17 of whom (11%) were found to have clinically significant prostate cancer upon biopsy.[86, 170]

Conclusions (Q3)

The review included 5 moderate-to-low quality studies investigating screening tests and one high-quality study investigating a model for detecting prostate cancer. A large number of studies were excluded due to the index test being used in selected populations, i.e. in patients selected for biopsy based on prior suspicious DRE and/or PSA testing. Each study evaluated different screening tests or sequential test strategies, thus, no index test was validated in an independent study.

Two studies evaluated sequential screening methods; the Göteborg pilot study assessed the addition of MRI to PSA screening,[24] while Rubio-Briones 2014 assessed the addition of PCA3 testing to the PSA test and DRE.[25] The addition of PCA3 was found to significantly improve the AUC compared with PSA or DRE alone, although specificity was low (high false positive rate), reflecting a high number of unnecessary biopsies. In the Göteborg pilot study, the most clinically useful screening strategy evaluated was PSA ≥1.8 ng/mL followed by MRI (strategy 3), which was superior to both PSA ≥3.0 ng/mL followed by MRI (strategy 2) and PSA testing alone (strategy 1). However, these findings are yet to be validated in the larger Göteborg 2 trial, which is anticipated to involve 40,000 participants and run until 2040.

Among studies that evaluated single tests, MRI, DRE and %fPSA were investigated with comparisons to PSA. The results of Nam 2016 support the conclusions of the aforementioned Göteborg pilot study and suggest that MRI alone may be more accurate than PSA testing, and identifying 6/9 cases of prostate cancer in men who screened negative based on PSA. However the small sample size of this pilot study (50 participants) limits the robustness of the conclusion that can be drawn.[26] The use of %fPSA may also improve specificity; it was reported that it could spare approximately two-thirds of unnecessary biopsies, but this would also come at the cost of a decreased ability to detect true positive cases. DRE is less promising, being shown to be a significantly worse predictor of prostate cancer-specific mortality over 13 years of follow-up in the PLCO trial.

The STHLM3 predictive model represents a promising screening tool that should be subjected to further validation. The AUC for the STHLM3 model was superior to that for the PSA test for both the prediction of all cancers and the prediction of high-grade (Gleason score ≥7) cancers.

Comparison of the results from the different studies is confounded by the fact that they used different thresholds for the PSA test; 3 studies used PSA 3 ng/mL, whereas the other 3 studies used 4 ng/mL. The previous UK NSC review found that the use of a 3 ng/mL threshold increased sensitivity for the detection of prostate cancer, but also increased false positive cases and overdiagnosis. The overall conclusion was that there was no consensus on appropriate PSA cut-off thresholds for the detection of prostate

cancer; while a review was identified that reported age-specific reference ranges for PSA, these had not been validated. Likewise, in the current review, there was very little evidence on whether the thresholds employed for the various index tests were the most appropriate thresholds. None of the studies described the distribution of index test values in the target population, and only 3 studies reported relevant outcomes for more than one index test threshold (SABOR, Göteborg and the Rubio-Briones 2014). Only one study reported relevant outcomes for more than 2 index test thresholds in an effort to determine the most appropriate threshold (Rubio-Briones 2014). Another key issue is that it is unclear weather the application of these models reduces prostate cancer metastases or mortality in the longer term. This question could be addressed by an evidence synthesis similar to that addressing criteria 11 and 13 in this review, except for looking at studies comparing screening using these models vs screening with PSA, rather than PSA vs no screening.

Summary of findings relevant to criteria 4 and 5: Criteria not met

Quantity: A small volume of evidence on the diagnostic performance of screening tests compared with PSA screening in unselected men was identified. In total, 7 articles reporting on 6 unique screening tests were included (note also that the 2 STHLM3 articles report on slightly different iterations of the STHLM3 model), although none distinguished between insignificant and clinically significant disease. No identified studies describe the distribution of index test values in the target population. Only 3 studies report relevant outcomes for more than one index test threshold (SABOR, Göteborg and Rubio-Briones 2014), and only one study reports relevant outcomes for more than 2 index test thresholds in an attempt to determine the most appropriate threshold (Rubio-Briones 2014).

Quality: All 5 studies reporting on single or sequential screening tests had low risk of bias associated with conduct of the index test(s). However, the level of reporting on the reference standard was generally poor, with only 2 studies describing the biopsy procedure in sufficient detail. These 2 studies were therefore at unclear risk of bias for measurement of the reference standard. Regarding the evidence on diagnostic test accuracy, all participants in an ideal screening test study should undergo biopsy regardless of their index test/PSA test results; however, with the exception of one of the included studies, participants only underwent biopsy if a specific threshold was met, preventing the derivation of complete data on true negatives and false negatives. The one study where all participants underwent biopsy regardless of screening test results only recruited 50 participants, and this study was at high risk of bias related to participant enrolment, participant flow and the reference standard (Nam 2016). Nonetheless, it is acknowledged that this approach does not align with recommended clinical practice and could not be implemented as a screening test due to concerns regarding the potential harms of unnecessary biopsies.

Applicability: Two studies enrolled unselected men from primary care settings. There were concerns related to participant enrolment in 2 studies that evaluated opportunistic screening for prostate cancer, with participants recruited through volunteer sampling or unreported

methods. All studies evaluated relevant screening tests for prostate cancer covered by the NG131 guideline, and 2 studies evaluated the STHLM3 model which includes relevant biomarker predictors. All studies were conducted in high-income countries that are judged to be applicable to the UK setting.

Consistency: While all studies compared an index test to PSA testing, no 2 studies evaluated the same index test(s) and comparator(s), and therefore no screening approach has been validated by a second, independent study. Moreover, comparison of the results from different studies is complicated by the use of different thresholds for the PSA test.

Conclusions: Evidence gathered in the current review suggests that MRI (either added to PSA-based screening or alone) and the STHLM3 predictive model may offer greater diagnostic accuracy relative to prostate cancer screening with the PSA test only. Nevertheless, comparison of results between the studies is complicated by the use of varying thresholds for the PSA test comparator. None of the identified studies characterised the distribution of index test values in the target population, and only one study reported relevant outcomes for more than 2 index test thresholds in an effort to determine the most appropriate threshold. Most notably, none of the studies evaluated the ability of the screening tests to distinguish between insignificant and clinically significant prostate cancer. All but one studies also applied the reference standard (biopsy) only to the screen-positives, thereby making it impossible to determine the true sensitivity of the test (e.g. false negatives are not picked up).

Although the evidence is promising, the lack of consistency precludes drawing robust conclusions on the appropriateness of any test as a screening measure to detect prostate cancer. Further studies could confirm the superiority of MRI over PSA-based screening in terms of detecting high grade disease, especially in light of the fact that PSA-based screening also does not meet criteria 11 and 13, investigated in the first part of this review. As such, criteria 4 and 5 are also not met.

Criterion 9 – Harms and benefits of treatment approaches for early-stage prostate cancer

9: 'There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme should not be further considered'

In the last external review conducted for the UK NSC in 2015 (with searches in 2014) (Louie 2015), a meta-analysis of 16 RCTs was identified for Criterion 9;[171] it compared the efficacy and safety of observation (NICE uses the term, 'observation' to group together active surveillance and watchful waiting. These are both methods of monitoring prostate cancer. The key difference between the 2 approaches is that watchful waiting involves fewer tests than active surveillance, with check-ups usually taking place at the GP surgery rather than at hospital)[172, 173], prostatectomy and different types of radiotherapy (RT) in men with localised prostate cancer. The meta-analysis found no reduction in 5-year all-cause mortality for any compared treatment groups, but reported that prostate cancer-specific mortality was lower in patients treated with prostatectomy vs observational management and with conformal RT vs conventional RT. In addition, 3 large RCTs with longer follow-up were also identified: the Scandinavian Prostate Cancer Group Study 4 (SPCG-4),[174] US-based Prostate Cancer Intervention versus Observation Trial (PIVOT),[175] and the UK-based ProtecT trial.[4] SPCG-4 and PIVOT both compared radical prostatectomy with watchful waiting; SPCG-4 found that prostatectomy significantly reduced prostate cancer mortality compared with watchful waiting (at 23-year follow-up) whilst PIVOT saw no significant difference for the same comparison (at 12-year follow-up). Lastly, ProtecT is a large 3-arm RCT comparing monitoring, radical prostatectomy or radical radiotherapy for localised prostate cancer detected after PSA testing, but no results had been posted at the time of the previous UK NSC review.

This update review searched for relevant data published since 2014 relating to the harms and benefits for interventions to treat early-stage prostate cancer, including the evidence reviewed for the recent NICE NG131 (2019)[85] guidance and any new analyses for the focal SPCG-4, PIVOT and ProtecT trials.

Question 4 – What are the harms and benefits of currently available treatment approaches for early-stage prostate cancer to reduce morbidity and mortality?

Eligibility for inclusion in the review

This review searched for RCTs and SLRs and MAs of RCTs. Studies were included if the population comprised men with early-stage or localised prostate cancer (stage T1–T3a) eligible for primary treatment. Treatment interventions of interest were

prostatectomy, high-intensity ultrasonography, radiation therapy (including conventional, hypofractionated, external-beam, brachytherapy and combinations), ablative therapy, androgen suppression and observation (watchful waiting or active surveillance). Active surveillance and watchful waiting are different in that active surveillance is proactive monitoring whilst watchful waiting is passive, however, they were grouped together under the umbrella term of 'observation' in the SLRs that informed the most recent guidance as 2 methods of conservative treatment. Outcomes of interest included disease-specific outcomes (survival, biochemical failure, metastasis), toxicity/treatment complications and quality of life (QoL)/functioning. Studies were not restricted geographically. Full details of the eligibility criteria are presented in Table 7.

For this question, 2 SLRs informing the most recently-published NICE guidance (NG131 2019)[85] for the diagnosis and management of prostate cancer were updated; the interventions investigated were RT, observation (active surveillance or watchful waiting) and prostatectomy. If any RCTs were captured in either of these, details of the study were only extracted from the SLR publication, and results only included as part of any pooled/meta-analyses conducted in the SLR (please see the Methods section for further details), to avoid duplicate inclusion of the same trial. If the same trials were included in different SLRs, results from both SLRs were extracted on the basis that the analyses may have differed, but this was taken into consideration when interpreting the results. For any interventions of interest that were not included in the NICE SLRs, evidence was searched for since 2014, when the previous UK NSC review searches were run.

Description of the evidence

Characteristics of included studies (Q4)

Overall

A total of 5 SLRs and 19 publications on 17 RCTs were included. The SLRs (2 of which were from NG131) included 13 unique RCTs. Due to the high volume of evidence identified, a prioritisation strategy was applied; data was extracted, and studies were included in the evidence synthesis if they compared one relevant intervention to a different relevant intervention or to 'no treatment'. Studies that compared different iterations of the same intervention (e.g. different drugs to achieve androgen deprivation or different approaches to performing prostatectomy) were deprioritised for data extraction, and are summarised in "***Deprioritised records***" section. A list of all included studies is available in Table 35 (Appendix 2 — Included and excluded studies).

Ultimately, 5 SLRs including 13 RCTs and 12 publications on 6 unique RCTs were selected for extraction, resulting in a total of 19 RCTs (Table 18). Localised prostate cancer included stage T3a in the authors' definition in 2 SLRs and 2 primary RCTs.[110-113] Patient numbers included in the analyses ranged from 89 to 7,050 (a pooled analysis in an

SLR)[111, 113] and the largest single RCT included 1,979 patients.[176] Evidence was found for most interventions, except for high intensity ultrasonography or ablative therapy.

Table 18. Summary of treatment comparisons in records ultimately prioritised for extraction

Broad category	Treatment comparison	N studies*	Study names
Different types of RT	Conventional RT vs hypofractionated RT	2 **SLRs** (10 RCTs)	**NG131 Evidence Review C (NICE 2019)**[a] (RENCI; HYPRO; PROFIT; CHHiP; Hoffman 2014; RTOG 0415; Marzi 2009; Norkus 2009; Norkus 2013; FCCC) **Yin 2019**[c] (Hoffman 2018; PROFIT; RTOG 0415; CHHiP; HYPRO; Pollack 2013; RENCI)
	EBRT vs EBRT + LDR-BT	2 **SLRs** (1 RCT)	**NG131 Evidence Review C (NICE 2019)**[a] (ASCENDE-RT) **Chin 2017**[c] (ASCENDE-RT)
	EBRT + LDR-BT vs LDR-BT	1 **SLR** (1 RCT)	**Chin 2017**[c] (RTOG 0232)
Observation vs RT	Active surveillance vs RT	1 **SLR** (1 RCT)	**NG131 Evidence Review G (NICE 2019)**[b] (ProtecT)
	Watchful waiting vs RT	1 RCT	Hackman 2019
Observation vs prostatectomy	Active surveillance vs prostatectomy	1 **SLR** (1 RCT)	**NG131 Evidence Review G (NICE 2019)**[b] (ProtecT)
	Watchful waiting vs prostatectomy	1 **SLR** (2 RCTs)	**NG131 Evidence Review G (NICE 2019)**[b] (SPCG-4, PIVOT)
N/A	RT vs prostatectomy	1 **SLR** (1 RCT) 1 RCT	**NG131 Evidence Review G (NICE 2019)**[b] (ProtecT) Lennernas 2015
N/A	ADT + RT vs RT	5 RCTs	NCT00116220 PMH 9907 EORTC Trial 22991 Voog 2016
N/A	"Conservative" treatment vs "radical" treatment[d]	1 **SLR** (3 RCTs)	**Ng 2019**[c] (SPCG-4, PIVOT, ProtecT)

Bold represents SLRs included in the review, followed by the studies included in each SLR
* The number of studies recorded is the number of unique SLRs or RCTs for each treatment comparison (i.e. some SLRs contained the same study/ies).
[a] SLR from NG131 which was updated as part of this review, and included 11 unique RCTs overall. The specific studies for each treatment comparison are listed in brackets.
[b] SLR from NG131 which was updated as part of this review, and included 3 unique RCTs overall. The specific studies for each treatment comparison are listed in brackets.
[c] SLR identified as being closely aligned with the review question and included in its own right.
[d] Outcomes for patients assigned to watchful waiting or active surveillance were grouped together as 'conservative treatment', and outcomes for patients assigned to prostatectomy or radiotherapy were grouped together as 'radical treatment'.
Abbreviations: ADT, androgen deprivation therapy; EBRT, external-beam radiation therapy; LDR-BT, low-dose-rate brachytherapy; N/A, not applicable; NICE, National Institute for Health and Care Excellence; NG131, NICE Guidance 131; RCT, randomised controlled trial; RT, radiotherapy/radiation therapy; SLR, systematic literature review.

The most commonly reported outcomes were overall and prostate cancer-specific survival and mortality (including time to event outcomes); disease progression (e.g. biochemical failure) and development of distant metastases; gastrointestinal (GI) and genitourinary (GU) adverse events; urinary, sexual and bowel functioning and impacts on quality of life. Full study results including different follow-up periods and study details are presented in the evidence tables in Table 41a–k (Appendix 3 — Summary and appraisal of individual studies).

NG131 SLRs

In 2018 NICE conducted 8 SLRs to inform the NG131 (published in 2019) guidance. Of these, 2 were identified as being closely aligned with the scope of this question, one on "radical radiotherapy",[113] and the other on "active surveillance, radical prostatectomy or radical radiotherapy",[177] and it was therefore decided that these would form the evidence base for the relevant treatments and be updated for this rapid review. Full details of the SLRs can be found in Table 41a–e, whilst brief details of the eligibility (PICOS) criteria and study flow are reported below in Table 19. Both included meta-analyses of pooled data. The quality and risk of bias of the SLRs were assessed using the AMSTAR 2 checklist and are summarised in the following section.

Table 19. PICOS criteria of NG131 SLRs updated in this review

Radical RT	Observation, radical prostatectomy or radical radiotherapy
PICOS P: Localised PCa (T1b–T3a N0 M0) I: Hypofractionated RT; brachytherapy + EBRT C: Conventional fractionation with external beam therapy O: PCa-specific mortality; OS; metastasis-free survival; treatment-related morbidity; HRQoL S: RCTs; SLRs of RCTs	**PICOS** P: Localised PCa (T1–T2) I: Observation; radical RT (alone or in combination with brachytherapy); radical prostatectomy C: Relevant interventions compared to one another; alternative protocols within the intervention class O: PCa-specific mortality; OS; metastasis-free survival; treatment-related morbidity; severe AEs; treatment discontinuations due to severe AEs; HRQoL S: RCTs, SLRs of RCTs
Included articles Conventional vs hypofractionated RT = 22 articles on 10 RCTs EBRT alone vs EBRT + LDR-BT boost = 2 articles on 1 RCT Brachytherapy alone = 0 articles	**Included articles** 13 articles on 3 RCTs (ProtecT, PIVOT and SPCG-4)

Abbreviations: AE, adverse event; EBRT, external beam radiation therapy; HRQoL, health-related quality of life; LDR-BT, low-dose-rate brachytherapy; OS, overall survival; PCa, prostate cancer; PICOS, population, intervention, comparator, outcomes, study type; PIVOT, Prostate Intervention Versus Observation Trial; RCT, randomised controlled trial; RT, radiation therapy/radiotherapy; SLR, systematic literature review; SPCG-4, Scandinavian Prostate Cancer Group Study 4.

Based on the identified evidence, NG131 currently recommends that men with low-risk localised prostate cancer receive the informed option of active surveillance, radical prostatectomy or radical RT and intermediate- and high-risk localised prostate cancer receive radical prostatectomy or radical RT.[85]

Trials included in the updated SLRs

Three major RCTs were included in the updated NG131 SLRs, and are described below.

Prostate Testing for Cancer and Treatment (ProtecT) Trial

The aim of the ProtecT trial (NCT00632983) was to evaluate the effectiveness, cost-effectiveness and acceptability of treatments for men with localised prostate cancer (not further defined), comparing active surveillance, radical prostatectomy and radical radiotherapy. It is being conducted in the UK, supported by the National Institute for Health Research (NIHR).[4, 178]

Participants of ProtecT are men 50–69 years of age in 9 centres across the UK, invited from general practice to attend prostate cancer check-ups. Men with a raised PSA result of ≥3.0 ng/mL and <20 ng/mL from the Prostate Check Clinic PSA test were referred for

diagnostic testing including biopsy. Those confirmed to have localised prostate cancer were invited to participate in the RCT component of the study.

Of 82,849 men who had PSA testing, 2417 men were diagnosed with localised prostate cancer. Of these, 1643 participants were randomised to active surveillance, radical prostatectomy or radical radiotherapy.[4] The primary outcome was definite or probable prostate cancer mortality (including intervention related-mortality) at a median of 10 years' follow-up, with a survival analysis at 15-year follow-up now planned (expected June 2021).[178] Secondary outcomes include disease progression (biochemical and clinical), treatment complications, lower urinary tract symptoms, psychosocial impact of treatment, including generic health status, quality of life and sexual function.[178]

The Prostate Cancer Intervention versus Observation Trial (PIVOT)
PIVOT was an RCT of 731 men with localised prostate cancer (stage T1-T2NxM0, American Joint Committee on Cancer),[179] randomised to radical prostatectomy or observation. Men were recruited from the Department of Veterans Affairs and National Cancer Institute medical centres in the United States.[175] The primary outcome was all-cause mortality at a minimum of 8 years and maximum of 15 years, or until the patient had died. Secondary outcomes included prostate-cancer mortality, disease progression, treatments received, and patient-reported health outcomes (perioperative harms, urinary incontinence, and erectile and bowel dysfunction, systematically evaluated until 2010).[175]

The Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4)
The SPCG-4 trial is an RCT of 795 men aged less than 75 years old with localised prostate cancer (T0d [later named T1b], T1, or T2 as defined by 1978 criteria of the International Union against Cancer, followed by inclusion of T1c tumours after 1994),[180, 181] who were randomised to radical prostatectomy or watchful waiting between October 1989 and December 1999.[182] Patients were recruited from Sweden, Finland and Iceland. Clinical outcomes included all-cause mortality, prostate-cancer mortality and development of distant metastases. Follow-up examinations were conducted bi-annually for the first 2 years, and annually thereafter. The last analyses were performed at 29 years of follow-up.[183]

Summary of findings

Quality assessments (Q4)

SLRs

The quality of the 5 included SLRs was appraised using the AMSTAR 2 checklist;[184] a summary is presented in Table 20 and the full appraisal is presented in Table 49 (Appendix 5 – Appraisal for quality and risk of bias).

Table 20. Summary of AMSTAR 2 assessments for SLRs evaluating treatment approaches in early-stage prostate cancer

Question	NG131C – radical RT[113]	NG131G – observation, RT and prostatectomy[1] [77]	Ng 2019[185]	Yin 2019[110]	Chin 2017[186]
Did the research questions and inclusion criteria for the review include the components of PICO? (Yes/No)	Yes	Yes	Yes	Yes	No
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? (Yes/Partial Yes/No)	Yes	Yes	Yes	Yes	Partial Yes
Did the review authors explain their selection of the study designs for inclusion in the review? (Yes/No)	No	No	No	No	No
Did the review authors use a comprehensive literature search strategy? (Yes/Partial Yes/No)	Yes	Yes	Yes	No	No
Did the review authors perform study selection in duplicate? (Yes/No)	Yes	Yes	Yes	Yes	Unclear
Did the review authors perform data extraction in duplicate? (Yes/No)	Unclear	Unclear	Unclear	Unclear	Yes
Did the review authors provide a list of excluded studies and justify the exclusions? (Yes/Partial Yes/No)	Yes	Yes	Yes	No	No
Did the review authors describe the included studies in adequate detail? (Yes/Partial Yes/No)	Yes	Partial Yes	Partial Yes	Yes	Yes
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? (Yes/Partial Yes/No)	Yes	Yes	Yes	No	Yes
Did the review authors report on the sources of funding for the studies included in the review? (Yes/No)	Yes	Yes	Yes	No	No
If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? (Yes/No/No meta-analysis conducted)	Yes	Yes	Yes	Yes	No meta-analysis conducted
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? (Yes/No/No meta-analysis conducted)	Yes	Yes	Yes	No	No meta-analysis conducted
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? (Yes/No)	Yes	Yes	Yes	No	Yes
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? (Yes/No)	Yes	Yes	Yes	No	No

Question	NG131C – radical RT[113]	NG131G – observation, RT and prostatectomy[1][77]	Ng 2019[185]	Yin 2019[110]	Chin 2017[186]
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? (Yes/No/No meta-analysis conducted)	No	No	Yes	No	No meta-analysis conducted
Did the review authors report any potential sources of conflict of interest, including any funding they received for the review? (Yes/No)	Yes	Yes	Yes	Yes	Yes

Objectives and eligibility criteria

Four of the included SLRs sufficiently described the objectives and inclusion criteria using the PICO framework, and had their methods established prior to commencing the review as evidenced by the availability of protocols.[110, 113, 177, 185] Chin 2017 did not adequately define the research question and although a protocol was available, it was not registered with an independent body, resulting in a 'partial yes' answer to this question.[186] It should be noted that although the eligibility criteria for the NG131 SLRs stated that 'localised prostate cancer' (defined explicitly as stage T2–3a in one case) was eligible for inclusion,[113] some of the included studies recruited some patients with stages T3 or T4. This is a possible limitation of the analyses conducted in these SLRs. None of the included SLRs sufficiently justified selection of eligible study designs for inclusion.

Search strategy

A comprehensive search strategy was used in 3 of the 5 included SLRs.[110, 113, 177] Ng 2019 and Chin 2017 did not justify the use of a language restriction,[185, 186] thereby not meeting criteria for this domain.

Record review and extraction

Four of the SLRs reported the use of a second independent review at the title/abstract and full-text review stages; however, it was unclear if extractions of the selected studies were performed in duplicate.[110, 113, 177, 185] By contrast, the Chin 2017 SLR did not clarify whether study selection was performed in duplicate, but did state that extractions were undertaken by one reviewer and checked for accuracy by another reviewer.[186]

Results and meta-analysis

Three out of 5 SLRs presented a list of included and excluded studies and reported on the source of funding for included studies.[113, 177, 185] The NG131C, Chin 2017 and Yin 2019 SLRs fully described the results of the included studies, whereas NG131G and Ng 2019 only partially described the results. Yin 2019 was the only SLR that failed to report on the results of the quality assessment of included studies, despite reporting use of the Cochrane Risk of Bias tool.[110] Four of the included SLRs conducted meta-analyses,[113, 177, 185, 186] and no meta-analysis component was included in the Chin 2017 SLR. All 4 meta-analyses used appropriate statistical methods ,[110, 113, 177, 185] however, only 3 sufficiently assessed the risk of bias of the individual studies and the potential impact on results.[113, 177, 185]

Disclosures

All SLRs reported on conflicts of interest and any funding provided.[110, 113, 177, 185, 186]

RCTs reported in each of the SLRs included in this review

A summary of the study quality of the RCTs that were included in the relevant SLRs (as judged by the SLR authors), is presented in Table 21.

Table 21. Summary of study quality of RCTs reported in the SLRs included in this rapid review

	NG131C – radical RT[113]	**NG131 G – observation, RT and prostatectomy[177]**	**Ng 2019[185]**	**Chin 2017[186]**	**Yin 2019[110]**
Quality assessment tool	Cochrane Risk of Bias Tool	Cochrane Risk of Bias Tool	Cochrane Risk of Bias Tool	Unclear	Cochrane Risk of Bias Tool
Included RCTs	**9[a]**	**3**	**4**	**5**	NR
High risk of bias	3	0	1	0	NR
Moderate risk of bias	6	3	0	1	NR
Low risk of bias	0	0	3	4	NR

No quality assessment process was reported in the Yin 2019 SLR.
[a] 11 RCTs were included in the SLR, but 2 were not included in the evidence table, leaving 9 studies for quality assessment.

NG131C

Three studies included in the NG131C SLR for conventional RT vs hypofractionated RT were judged to be at high risk of bias due to the lack of blinding procedures and assessment of subjective patient-reported outcomes. The remaining 6 were at a moderate risk of bias, as it was judged the lack of blinding would have only had a low-to-moderate impact due to assessment of objective or physician-assessed outcomes.[113]

NG131G

All 3 studies were judged to be at a moderate risk of bias, due to lack of blinding of participants.[187]

Ng 2019

All 3 studies at low risk of bias. While all 3 studies were not blinded, the review authors judged that the outcomes were not likely to be influenced by lack of blinding.[185]

Chin 2017

Of the 5 included RCTs, 4 were judged to be at a low risk of bias, with the remaining one study at a moderate risk of bias, likely due to concerns about allocation concealment and blinding, though the reasoning behind the judgement is unclear as the authors do not provide any discussion on the quality of the studies they included.[186]

Yin 2019

Yin 2019 did not report on the results of the risk of bias assessment for the included studies.[110]

RCTs

The quality of the 6 included RCTs (reported through 12 publications) was appraised using an adapted Cochrane Risk of Bias checklist,[149] (Table 43; Appendix 4 – Guidance on quality assessments). A summary of the risk of bias is presented in Table 22, and the full appraisal is presented in Table 50 (Appendix 5 – Appraisal for quality and risk of bias).

Table 22. Summary of Cochrane Risk of Bias assessments for RCTs evaluating treatment approaches in early-stage prostate cancer

Risk of bias	Bolla 2016 (EORTC Trial 22991)[188]	Hackman 2019 (FinnProstate and Finnish Radiation Oncology Groups trial)[112]	Lennernäs 2015[111]	McPartlin 2016 (PMH 9907)[189]	Sanford 2017[190]	Voog 2016 (RTOG 94-08)[176]
Randomisation process	Low	Low	Low	Low	Low	Low
Effect of assignment to intervention	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Missing outcome data	Low	Low	High	Low	Low	Low
Measurement of outcome	Low	Some concerns	Some concerns	Low	Low	Low
Selection of the reported result	Low	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns
Overall risk of bias	**Some concerns**	**Some concerns**	**High**	**Some concerns**	**Some concerns**	**Some concerns**

Randomisation process

The risk of bias arising from the randomisation process was judged to be low across all 6 trials. All trials were randomised, although the specific approaches used for randomisation and allocation concealment were poorly reported in 3 of 6 trials.[112, 189, 190] However, randomisation was deemed appropriate as demonstrated by similar baseline characteristics between treatment arms.

Effect of assignment to intervention

There were some concerns for risk of bias in all 6 included trials for this domain.[111, 112, 176, 188-190] None of the studies were reported to have been blinded, and therefore study personnel and participants were likely aware of treatment allocation. The impact of this on the risk of bias was judged as carrying 'some concerns' in all 6 trials, as deviations to intervention received may have arisen due to knowledge of the intervention,[111, 112, 188-190] or insufficient information was provided to assess this risk.[176] However, all trials analysed outcome data on an intention-to-treat (ITT) or modified ITT basis, demonstrating appropriate analysis methods.

Missing outcome data

Five included trials were judged to be at a low risk of bias due to missing outcome data, as all or nearly all (>95%) randomised participants were included in the analyses.[176, 188-191] Royce 2017, a subgroup analysis of the Sanford 2017 trial, excluded participants with missing data on baseline characteristics, however these patients comprised <5% of the study cohort.[191] In the Lennernäs 2015 study, only 66% of participants completed outcome questionnaires at all 3 assessment timepoints, and no corrective or sensitivity analyses were performed to adjust or examine the impact of this.[111] This study was therefore judged to be at high risk of bias for this domain.

Measurement of outcome

Two studies had some concerns for risk of bias,[111, 112] and the remaining 4 trials were at a low risk of bias for this domain.[176, 188-190] Hackman 2018 and Lennernäs 2015 evaluated adverse events and treatment-related complications, the assessment of which may have been influenced by patients' and study personnel's knowledge of the assigned intervention.[111, 112] Rates of adverse events were significantly higher in the RT arm than the observation arm (Hackman 2018), with some statistical differences in toxicity symptoms assessed using questionnaires. Though lack of blinding procedures may have influenced reporting of symptoms by participants, it is also expected that patients in the RT arm would have experienced significantly more toxicity than those in the observation arm, so this study was judged to have some concerns for bias. It was deemed somewhat unlikely that lack of blinding procedures affected the results of Lennernäs 2015 as there were no significant differences detected between study arms, and so this trial was judged to have some concerns for bias also.[111] Sanford 2017 and Voog 2016 evaluated criteria-defined objective outcomes, such as mortality and survival, and therefore knowledge of the assigned intervention would have been very unlikely to have affected the result.[176, 190] Methods of outcome measurement were deemed appropriate and did not differ between study arms in all in 6 trials.

Selection of the reported result

All but one trial carried some concerns for bias for selection of the reported result, due to unavailability of a pre-specific analysis plan. Bolla 2016 reported a pre-specified analysis plan, allowing for confirmation that the reported results were unselected.[188] For all trials, the concern that multiple outcome measurements were taken or multiple outcome analyses were conducted was low.

Results (Q4)

Key results for each of the treatment comparisons are presented in Table 23, Table 24, Table 25, Table 26 and Table 27. Full details of the included studies and their results can be found in Table 41a–k (Appendix 3 — Summary and appraisal of individual studies).

Prostatectomy vs observation

The SLR conducted for NG131 included one RCT comparing active surveillance with prostatectomy (ProtecT) and 2 RCTs comparing watchful waiting with prostatectomy (SPCG-4 and PIVOT), all of which reported outcomes at multiple points of follow-up.[177] Separate analyses were performed for the respective treatment comparisons. One additional record for a 29-year follow-up of SPCG-4, which was published after the database searches for NG131, was identified in this rapid review, but no additional novel RCTs were included for observation vs prostatectomy.[192] Another SLR conducted in 2019 included the same 3 major studies (ProtecT, SPCG-4 and PIVOT); however, given that outcomes for patients randomised to prostatectomy and RT were pooled in this SLR, it is considered separately in *Conservative vs radical treatment* section.[69]

NG131 summarised evidence from ProtecT with data on 1643 men with stage T1c–T2 localised prostate cancer (majority with low-risk disease at randomisation)[193] and found that men who received radical prostatectomy had a lower relative risk of disease progression (RR 0.39, 95% CI 0.27 to 0.56) and developing distant metastases (RR 0.39, 95% CI 0.21 to 0.73) at a median 10 years follow-up compared with active surveillance, but an increased risk of severe urinary incontinence (RR 1.37, 95% CI 1.23 to 1.53), erectile dysfunction adverse events (RR 1.19, 95% CI 1.10 to 1.28) and sexual dysfunction (mean difference of –8.30 points on the Expanded Prostate Cancer Index Composite [EPIC] summary score) at 6 to 8 years. No significant differences were identified for other outcomes, including urinary function and bowel function.[177]

Pooled evidence from SPCG-4 and PIVOT (including 1429 men with stage T1–T2 localised prostate cancer) revealed that risk of both prostate cancer-specific and overall mortality was decreased at 12 to 14 years follow-up for prostatectomy compared with watchful waiting (prostate cancer-specific HR 0.61, 95% CI 0.45 to 0.83 and overall HR 0.86, 95% CI 0.75 to 0.98). The longest follow-up (18 years) included in NG131 for SPCG-4 demonstrated a consistent/improving trend (HR 0.56, 95% CI 0.41 to 0.76 and HR 0.71, 95% CI 0.59 to 0.95),[177] which was maintained at the later-published 29-year follow-up (HR 0.55, 95% CI 0.41 to 0.74 and HR 0.74, 95% CI 0.62 to 0.87).[192] Similar to the comparison versus active surveillance, those receiving prostatectomy had higher urinary incontinence (RR 2.98, 95% CI 1.85 to 4.78) and erectile dysfunction (RR 1.69, 95% CI 0.50 to 5.78) at 12+ years than those under watchful waiting. Notably, no significant difference in mortality was identified between treatment arms until 4 to 6 years of follow-up.[177]

Table 23. Outcomes for prostatectomy vs observation

Outcome	Study	Follow-up or subgroup	Reporting of outcome	Prostatectomy	Observation		Comparison	P value
					Watchful waiting	Active surveillance		
		(n) if different from randomised					*Effect size (95% CI)*	
Disease-related								
PCa-related death	NG131 (SLR)	1 study (SPCG-4) 18 years	N/A	NR	NR	-	**HR: 0.56 (0.41–0.76)** HR <1 favours prostatectomy	0.0003
	SPCG-4	Endpoint estimates at 23 years, RR over 29 years	Events, n/total N	71/347	110/348	-	**RR: 0.55 (0.41–0.74)** RR <1 favours prostatectomy	<0.001
All-cause mortality	NG131 (SLR)	1 study (SPCG-4) 18 years	N/A	NR	NR	-	**HR: 0.71 (0.59–0.95)** HR <1 favours prostatectomy	0.0003
	SPCG-4	Endpoint estimates at 23 years, RR over 29 years	Events, n/total N	261/347	292/348	-	**RR: 0.74 (0.62–0.87)** RR <1 favours prostatectomy	<0.001
AOS	NG131	10 years	N/A	NR	-	NR	HR: 0.93 (0.65–1.33) HR <1 favours prostatectomy	NR
DFS	No outcomes reported							
Biochemical failure	NG131	Disease progression	N/A	NR	-	NR	HR: 0.39 (0.27–0.56) HR <1 favours prostatectomy	NR
	NG131	Disease progression (6.2–19.5 years)	N/A	NR	NR	-	HR: 0.37 (0.29–0.47) HR <1 favours prostatectomy	NR
Metastasis	NG131 (SLR)	2 studies in MA 10 years	N/A	NR	-	NR	RR 0.39 (0.21–0.73) RR <1 favours prostatectomy	NR
	NG131 (SLR)	1 study (SPCG-4) 18 years	Events, n/total N	89/347	138/348	-	**RR: 0.65 (0.52–0.81)** RR <1 favours prostatectomy	0.0001
	SPCG-4	Endpoint estimates at 23 years, RR over 29 years	Events, n/total N	92/347	150/348	-	**0.54 (0.42–0.70)** RR <1 favours prostatectomy	<0.001
Toxicity/treatment complications								
Overall AEs	No outcomes reported							
Urinary AEs	NG131 (SLR)	Severe incontinence AEs (6 years)	Events, n/total N	318/463	-	226/451	**RR: 1.37 (1.23–1.53)** RR >1 favours observation	<0.00001

Outcome	Study	Follow-up or subgroup	Reporting of outcome	Prostatectomy	Observation		Comparison	P value
					Watchful waiting	Active surveillance		
		(n) if different from randomised					*Effect size (95% CI)*	
Erectile dysfunction	NG131 (SLR)	Severe incontinence AEs (12+ years)	Events, n/total N	156/537	52/531	-	**RR: 2.98 (1.85–4.78)** RR >1 favours observation	<0.00001
	NG131 (SLR)	Severe AEs (6–8 years)	Events, n/total N	385/461	-	318/452	**RR: 1.19 (1.10–1.28)** RR >1 favours observation	<0.00001
	NG131 (SLR)	Severe AEs (12–18 years)	Events, n/total N	199/537	142/540	-	**RR: 1.69 (0.50–5.78)** RR >1 favours observation	0.002
GI toxicity	No outcomes reported							
GU toxicity	No outcomes reported							
QoL/functioning								
Overall QoL	No outcomes reported							
Overall functioning	No outcomes reported							
Urinary function	NG131 (SLR)	6 years	EPIC score, mean (SD)	88.7 (11.3)	-	89 (12.5)	MD: 0.30 (–1.25–1.85)	0.70
Sexual function	NG131 (SLR)	6 years	EPIC score, mean (SD)	32.3 (23.2)	-	40.6 (26.7)	**MD: 8.30 (5.01–11.59)**	<0.00001
Bowel function	NG131 (SLR)	6 years	EPIC score, mean (SD)	93.2 (8.7)	-	93 (9.8)	MD: –0.20 (–1.40–1.00)	0.74
Anxiety	NG131 (SLR)	6 years	HADS score, mean (SD)	3.7 (3.5)	-	4.1 (3.9)	MD: 0.40 (–0.08–0.88)	0.10
	NG131 (SLR)	12 years	N/A	NR	NR	-	RR: 1.01 (0.79–1.10) No treatment favoured	NR
Depression	NG131 (SLR)	6 years	HADS score, mean (SD)	2.7 (3.1)	-	3.1 (3.4)	MD: 0.40 (–0.02–0.82)	0.06
	NG131 (SLR)	12 years	N/A	NR	NR	-	RR: 0.92 (0.74–1.14) RR <1 favours prostatectomy	NR

Footnotes: Values in **bold** indicate statistically significant results.
Abbreviations: AE: adverse event; CI: confidence interval; DFS: disease-free survival; EPIC: Expanded Prostate Cancer Index Composite; GI: gastrointestinal; GU: genitourinary; HADS: Hospital Anxiety and Depression Scale; HR: hazard ratio; IIEF: International Index of Erectile Function; LENT-SOMA: Late Effects Normal Tissue Task Force - Subjective, Objective, Management, Analytic Scale; N/A: not applicable; NR: not reported; MD: mean difference; OR: odds ratio; OS: overall survival; PCa: prostate cancer; QOL: quality of life; RT: radiotherapy; SD: standard deviation; SLR: systematic literature review.

RT vs observation

In addition to a prostatectomy arm, ProtecT (as reported in the SLR for NG131) also compared active surveillance with radical RT.[177] The Ng 2019 SLR also included ProtecT, but performed a pooled analysis of the RT and prostatectomy treatment arms that is discussed in the ***Conservative vs radical treatment*** section.[185] One additional primary RCT (Hackman 2019) compared watchful waiting with RT.[112]

Patients who received RT in ProtecT were reported to have a lower risk of disease progression (HR 0.39, 95% CI 0.27 to 0.56) and distant metastases (RR 0.48, 95% CI 0.27 to 0.87) than patients under active surveillance, but no difference in all-cause mortality (HR 0.94, 95% CI 0.65 to 1.36) (follow-up not specified in NG131). There was also a lower risk of prostate cancer-related death (HR 0.51, 95% CI 0.15 to 1.73), however the wide confidence intervals decrease the confidence in this result. Similar findings in favour of RT were reported by Hackman 2019 for a trial including 157 patients with stage T2–T3a, comparing RT with watchful waiting, for biochemical failure (HR 0.30, 95% CI 0.16 to 0.53) and metastasis (HR 0.49, 95% CI 0.09 to 2.68) but not prostate cancer-related death, where no difference was seen (HR 1.00, 95% CI 0.06 to 15.91) at 9.3 years of follow-up.[112]

For both trials, urinary adverse events were more common in the RT arm than the observation arm, whilst erectile dysfunction was only significantly worse in watchful waiting compared with RT (OR 0.75, 95% CI 0.56 to 1.00) but not for RT compared to active surveillance (RR 1.03, 95% CI 0.95 to 1.12). Hackman 2019 also reported increased overall adverse events and GI adverse events in the RT arm ($p \leq 0.05$), whereas urinary function, bowel function, anxiety and depression were significantly worse for ProtecT participants who received RT than active surveillance ($p \leq 0.05$).[112, 177]

Table 24. Outcomes for RT vs observation

Outcome	Study	Follow-up or subgroup	Reporting of outcome	RT	Observation		Comparison	P value
					Watchful waiting	Active surveillance		
		(n) if different from randomised					*Effect size (95% CI)*	
Disease-related								
PCa-related death	Hackman 2019	Median 9.3 years	Events, n	1	1	-	HR: 1.00 (0.06–15.91) No favoured treatment	1.00
	NG131	NR	N/A	NR	-	NR	HR: 0.51 (0.15–1.73) HR <1 favours RT	NR
All-cause mortality	Hackman 2019	Median 9.3 years	Events, n	10	13	-	HR: 0.76 (0.33–1.72) HR <1 favours RT	0.5
	NG131	NR	N/A	NR	-	NR	HR: 0.94 (0.65–1.36) HR <1 favours RT	NR
OS	No outcomes reported							
DFS	No outcomes reported							
Biochemical failure	Hackman 2019	Median 9.3 years	Events, n	15	43	-	**HR: 0.30 (0.16–0.53)** HR <1 favours RT	<0.001
	NG131	Disease progression	N/A	NR	-	NR	HR: 0.39 (0.27–0.56) HR <1 favours RT	NR
Metastasis	Hackman 2019	Median 9.3 years	Events, n	2	4	-	HR: 0.49 (0.09–2.68) HR <1 favours RT	0.4
	NG131	NR	N/A	NR	-	NR	RR: 0.48 (0.27–0.87) RR <1 favours RT	NR
Other (castration resistance)	Hackman 2019	Median 9.3 years	Events, n	3	6	-	HR: 0.47 (0.12–1.88) HR <1 favours RT	0.3
Toxicity/treatment complications								
Overall AEs[a]	Hackman 2019	Grade 1 Grade 2 Grade 3 Grade 4	Events, n (%)	121 (96) 115 (91) 70 (56) 1 (1)	105 (85) 107 (87) 50 (40) 0 (0)	-	**OR: 0.71 (0.55–0.92)** OR <1 favours observation	0.009
Urinary AEs[a]	Hackman 2019	Grade 1 Grade 2 Grade 3 Grade 4	Events, n (%)	111 (88) 72 (57) 18 (14) 0 (0)	77 (62) 47 (38) 7 (6) 0 (0)	-	**OR: 0.48 (0.36–0.64)** OR <1 favours observation	<0.001
				NR	NR			
		Estimate at 10-year follow-up	Predicted probability (OR [95% CI]) of severity of urinary	NR	NR	-	OR: 0.51 (0.25–1.03) OR <1 favours observation	0.061

Outcome	Study	Follow-up or subgroup	Reporting of outcome	RT	Observation		Comparison	P value
					Watchful waiting	Active surveillance		
		(n) if different from randomised					*Effect size (95% CI)*	
			symptoms (IPSS scale)					
		Estimate at 10-year follow-up	Predicted probability (OR [95% CI]) of severity of urinary toxicity (LENT-SOMA scale)	NR	NR	-	OR: 0.76 (0.40–1.42) OR <1 favours observation	0.4
	NG131	Moderate/severe incontinence (6 years)	Events, n/Total N	21/458	-	38/455	**RR: 0.55 (0.33, 0.92)** RR <1 favours RT	0.02
Erectile dysfunction[a]	Hackman 2019	Grade 1 Grade 2 Grade 3 Grade 4	Events, n (%)	71 (56) 94 (75) 47 (37) 0 (0)	52 (42) 95 (77) 35 (28) 0 (0)	-	**OR: 0.75 (0.56–1.00)** OR <1 favours observation	0.05
		Estimate at 10-year follow-up	Predicted probability (OR [95% CI]) of severity of erectile dysfunction (IIEF-5 scale)	NR	NR	-	OR: 0.70 (0.29–1.68) OR <1 favours observation	0.4
	NG131	Severe AEs (6 years)	Events, n/total N	331/456	-	248/452	RR: 1.03 (0.95–1.12) RR >1 favours observation	0.46
GI toxicity[a]	Hackman 2019	Grade 1 Grade 2 Grade 3 Grade 4	Events, n (%)	97 (77) 29 (23) 1 (1) 0 (0)	16 (13) 4 (3) 1 (1) 0 (0)	-	**OR: 0.12 (0.07–0.19)** OR <1 favours observation	<0.001
		Estimate at 10-year follow-up	Predicted probability (OR [95% CI]) of severity of urinary toxicity (LENT-SOMA scale)	NR	NR	-	**OR: 0.04 (0.00–0.43)**	0.008
GU toxicity	Hackman 2019	Most common LENT-SOMA grade 4 toxicities	Number of patients, n	Kidney-related toxicity: 18 Urinary incontinence: 7	Kidney-related toxicity: 15 Urinary incontinence: 5	-	NR	NR

Outcome	Study	Follow-up or subgroup	Reporting of outcome	RT	Observation		Comparison	P value
					Watchful waiting	Active surveillance		
		(n) if different from randomised					*Effect size (95% CI)*	
				Urinary frequency: 5	Urinary frequency: 2			
QoL/functioning								
Overall QoL	No outcomes reported							
Overall functioning	No outcomes reported							
Urinary function	NG131	6 years	EPIC score, mean (SD)	91.4 (9.2)	-	89 (12.5)	**MD: –2.40 (–3.83– –0.97)**	0.001
Sexual function	NG131	6 years	EPIC score, mean (SD)	41.3 (24.9)	-	40.6 (26.7)	MD: –0.70 (–4.12–2.72)	0.69
Bowel function	NG131	6 years	EPIC score, mean (SD)	91.2 (10.9)	-	93 (9.8)	**MD: 1.80 (0.46–3.14)**	0.008
Anxiety	NG131	6 years	HADS score, mean (SD)	4.1 (3.9)	-	3.4 (3.2)	**MD: 0.70 (0.24–1.16)**	0.003
Depression	NG131	6 years	HADS score, mean (SD)	2.7 (2.9)	-	3.1 (3.4)	**MD: 0.40 (–0.01–0.81)**	0.05

Footnotes: Values in **bold** indicate statistically significant results.
[a]Adverse event grades measure with CTCAE v4.03
Abbreviations: AE: adverse event; CI: confidence interval; CTCAE: Common Toxicity Criteria for Adverse Events; DFS: disease-free survival; EPIC: Expanded Prostate Cancer Index Composite; GI: gastrointestinal; GU: genitourinary; HADS: Hospital Anxiety and Depression Scale; HR: hazard ratio; IIEF: International Index of Erectile Function; LENT-SOMA: Late Effects Normal Tissue Task Force - Subjective, Objective, Management, Analytic Scale; NR: not reported; MD: mean difference; OR: odds ratio; OS: overall survival; PCa: prostate cancer; QOL: quality of life; RT: radiotherapy; SD: standard deviation.

RT vs prostatectomy

Comparison between RT and prostatectomy was performed in the ProtecT RCT, reported through the NG131 and Ng 2019 SLRs (the latter discussed in the ***Conservative vs radical treatment*** section),[177, 185] and in a small primary RCT conducted in Sweden (prostatectomy compared to a combination of high-dose rate brachytherapy and external-beam radiation therapy [EBRT]).[111]

In ProtecT, men who underwent prostatectomy had a similar risk of developing distant metastases relative to men who received RT (RR 1.25, 95% CI 0.61 to 2.57) and a significantly higher risk of severe erectile dysfunction adverse events at 6 years (RR 1.15, 95% CI 1.07 to 1.23). Urinary and sexual function at 6 years were also significantly worse in the prostatectomy group (mean differences of –2.70 and –9.00 points on the EPIC summary score respectively). Concomitantly, no difference was observed in the HR for prostate cancer-related death (HR 0.80, 95% CI 0.22 to 2.91) between prostatectomy and RT. Bowel function at 6 years was, however, significantly better in the prostatectomy group (mean difference of 2.00 on the EPIC summary score). No significant differences were identified for anxiety, depression or the risk of moderate/severe urinary incontinence. The risk of disease progression in the 2 groups was also similar (HR 0.99, 95% CI 0.67 to 1.46).[177]

The Swedish RCT found no statistically significant differences between the 2 treatment groups at 24 months in terms of global quality of life, fatigue, pain, insomnia, constipation or diarrhoea, or in physical, role (work and household activities), emotional, cognitive or social functioning. Likewise, there were no significant differences at 24 months in prostate cancer specific-complications, including urinary urgency and incontinence, bowel blood and incontinence, hot flushes, erectile dysfunction and sexual interest. Few patients died during the 10-year follow-up and the study was insufficiently powered to compare all-cause or prostate cancer mortality.[111]

Table 25. Outcomes for RT vs prostatectomy

Outcome	Study	Follow-up or subgroup	Reporting of outcome	RT	Prostatectomy	Comparison	P value
		(n) if different from randomised				*Effect size (95% CI)*	
Disease-related							
PCa-related death	Lennernäs 2015	10 years	Events, n	2	6	NR	NR
	NG131 (SLR)	NR	N/A	NR	NR	HR: 0.80 (0.22–2.91) HR <1 favours prostatectomy	NR
All-cause mortality	Lennernäs 2015	10 years – excluding PCa-related	Events, n	7	6	NR	NR
OS	No outcomes reported						
DFS	No outcomes reported						
Biochemical failure	NG131 (SLR)	Disease progression	N/A	NR	NR	HR 0.99 (0.67–1.46) HR <1 favours prostatectomy	NR
Metastasis	NG131 (SLR)	NR	N/A	NR	NR	RR: 1.25 (0.61–2.57) RR >1 favours RT	NR
Toxicity/treatment complications							
Overall AEs	No outcomes reported						
Urinary AEs	Lennernäs 2015	Urgency – 24 months/ Incontinence – 24 months	% category 1 % category 2 % category 3 % category 4	39/61 32/29 26/5 3/5	59/46 26/41 10/5 5/8	NR	NR
	NG131	Moderate/severe incontinence (6 years)	Events, n/total N	58/464	58/464	1.00 (0.71–1.41) No treatment favoured	1.00
Erectile dysfunction	Lennernäs 2015	24 months	% (category scores 1–4)	5, 19, 19, 57	31, 36, 22, 11	NR	NR
	NG131	Severe AEs (6 years)	Events, n/total N	331/456	385/461	**RR: 1.15 (1.07–1.23)** RR >1 favours RT	<0.00001
GI toxicity	No outcomes reported						
GU toxicity	No outcomes reported						
QoL/functioning							
Overall QoL	Lennernäs 2015	Score at 24 months (RT n=24, prostatectomy n=31)	Mean (SD)	75 (20)	77 (21)	NR	NR

Outcome	Study	Follow-up or subgroup	Reporting of outcome	RT	Prostatectomy	Comparison	P value
		(n) if different from randomised				*Effect size (95% CI)*	
Overall functioning	No outcomes reported						
Urinary function	NG131	6 years	EPIC score, mean (SD)	91.4 (9.2)	88.7 (11.3)	**MD: 2.70 (1.36–4.04)**	<0.0001
Sexual function	NG131	6 years	EPIC score, mean (SD)	41.3 (24.9)	32.3 (23.2)	**MD: 9.00 (5.84–12.16)**	<0.0001
Bowel function	NG131	6 years	EPIC score, mean (SD)	91.2 (10.9)	93.2 (8.7)	**MD: –2.00 (–3.27– –0.73)**	0.002
Anxiety	NG131	6 years	HADS score, mean (SD)	3.4 (3.2)	3.7 (3.5)	MD: 0.30 (–0.13–0.73)	0.17
Depression	NG131	6 years	HADS score, mean (SD)	2.7 (2.9)	2.7 (3.1)	MD: 0.00 (–0.39–0.39)	1.00

Footnotes: Values in **bold** indicate statistically significant results.
Abbreviations: AE: adverse event; CI: confidence interval; DFS: disease-free survival; GI: gastrointestinal; GU: genitourinary; HR: hazard ratio; N/A: not applicable; NR: not reported; OS: overall survival; MD: mean difference; PCa: prostate cancer; QOL: quality of life; RR: risk ratio; RT: radiotherapy; SD: standard deviation.

Androgen suppression and RT vs RT alone

Androgen suppression (also referred to as androgen deprivation therapy [ADT]) was not included as an intervention of interest in any of the NG131 SLRs, and no other SLRs matching the scope of the question and including androgen suppression as an intervention were included. As such, results for this comparison are derived from 4 RCTs reported through 5 publications.[176, 188-190, 194] In each of these RCTs, the combination of ADT and RT was compared with RT alone. Relative to ADT and RT, patients treated with RT alone had a significantly increased risk of prostate cancer-related death (HR 1.87, 95% CI not reported, p=0.001) and all-cause mortality (HR 1.17, 95% CI 0.81 to 1.42) over a 10-year follow-up.[176] Overall survival rate was lower with RT alone in 2 of the 3 studies in which it was reported,[176, 188, 189] and biochemical failure rate was higher with RT alone in all 3 studies that reported it.[188, 189, 194] In the EORTC Trial 22991, biochemical disease-free survival rate was significantly lower and the development of metastases was significantly higher at 5 years with RT alone. In the same trial, patients suffered a greater decline in overall QoL at 3 years with RT alone, but a lesser decline in sexual function.[188] Where reported, GI and GU toxicity did not differ significantly between patients in the 2 treatment groups.[189]

Table 26. Outcomes for ADT + RT vs RT alone

Outcome	Study	Follow-up or subgroup	Reporting of outcome	ADT + RT	RT	Comparison	P value
		(n) if different from randomised				*Effect size (95% CI)*	
Disease-related							
PCa-related death	Voog 2016	10 years	Events, n	40	74	**HR: 1.87** HR >1 favours ADT + RT	0.001
All-cause mortality	Voog 2016	10 years	Events, n	359	404	**HR: 1.17 (0.81–1.42)** HR >1 favours ADT + RT	0.03
OS	EORTC Trial 22991	5 years	Rate, % (95% CI)	91.3 (88.0–93.7)	88.4 (84.7–91.3)	NR	NR
	PMH 9907[a]	9 years	Rate, % (95% CI)	82 (75–90)	86 (80–94)	HR: 1.33 (0.72–2.47) HR >1 favours RT	0.37
	Voog 2016	10 years	Events, n	628	588	NR	NR
DFS	EORTC Trial 22991	Biochemical DFS – 5 years	Events, n (%) Rate, % (95% CI)	118 (410) 82.6 (78.4–86.1)	201 (49.1) 69.8 (64.9–74.2)	**0.52 (0.41–0.66)**	<0.001
Biochemical failure	EORTC Trial 22991	Cumulative local relapse rate – 5 years	Rate, % (95% CI)	2.1 (0.7–3.6)	6.6 (4.1–9.1)	**0.37 (0.21–0.68)**	0.001
	PMH 9907[a]	9 years	Rate, % (95% CI)	40 (31–51)	47 (37–58)	HR: 0.82 (0.55–1.21) HR <1 favours ADT + RT	0.32
	Royce 2017	PSA failure	Events, n (%)	36 (32.05)	60 (65.95)	NR	NR
Metastasis	EORTC Trial 22991	5 years	Events, n (%)	**18 (4.4)**	**31 (7.6)**	NR	0.05
Toxicity/treatment complications							
Overall AEs	No outcomes reported						
Urinary AEs	No outcomes reported						
Erectile dysfunction	No outcomes reported						
GI toxicity	PMH 9907[a]	Acute; Grade 3 AE Late; Grade 3 AE	Events, n (%)	0 (0) 2 (1.8)	0 (0) 0 (0)	NR	0.83 >0.99
GU toxicity	PMH 9907[a]	Acute; Grade 3 AE Late; Grade 3 AE	Events, n (%)	0 (0) 13 (11.4)	1 (0.8) 14 (11)	NR	0.55 0.41
QoL/functioning							
Overall QoL	EORTC Trial 22991	3 years	Score change from baseline, mean (SD)	–2.29 (19.60)	–2.91 (21.08)	NR	NR
Overall functioning	No outcomes reported						

Outcome	Study	Follow-up or subgroup	Reporting of outcome	ADT + RT	RT	Comparison	P value
		(n) if different from randomised				*Effect size (95% CI)*	
Urinary function	No outcomes reported						
Sexual function	EORTC Trial 22991	3 years	Score change from baseline, mean (SD)	–15.56 (34.95)	–13.96 (34.64)	NR	NR
Bowel function	No outcomes reported						
Anxiety	No outcomes reported						
Depression	No outcomes reported						

Footnotes: Values in **bold** indicate statistically significant results.
Abbreviations: ADT: androgen deprivation therapy; AE: adverse event; CI: confidence interval; DFS: disease-free survival; GI: gastrointestinal; GU: genitourinary; NR: not reported; OS: overall survival; PCa: prostate cancer; QOL: quality of life; RT: radiotherapy; SD: standard deviation.

RT types

Three distinct comparisons were made within different types of RT, including conventional vs hypofractionated RT (2 SLRs including 10 unique RCTs),[110, 113] EBRT vs EBRT plus low-dose-rate brachytherapy (LDR-BT) (2 SLRs, both including the same single RCT)[113, 186] and EBRT plus LDR-BT vs LDR-BT alone (1 SLR including a single RCT).[186]

For conventional RT compared to hypofractionated RT, the NG131 C SLR carried out outcome analyses with up to 10 RCTs comprising a pooled dataset of 7050 men and a second SLR included a subset of 7 of the same RCTs (pooled dataset of 6843 men).[110, 113] It should be noted that although the eligibility criteria for the SLRs stated 'localised prostate cancer' (defined explicitly as stage T2–3a in one case),[113] some of the included studies enrolled some patients with any stage T3 or T4, which are not recognised as localised disease. This presents as a possible limitation of the analyses conducted. Meta-analyses found no differences between conventional and hypofractionated RT arms for overall survival, biochemical failure, biochemical clinical failure, GU toxicity and late GI toxicity (RRs 1.01 to 1.07, p>0.05), the only significant difference being for higher acute GI toxicity in men receiving hypofractionated RT compared with conventional (RR 1.42, 95% CI 1.29 to 1.59). Conversely, whilst seeing a similar insignificant result for overall survival, analyses conducted in Yin 2019 (which included a subset of the same studies as NG131) did find that the risk of biochemical failure was decreased in men receiving hypofractionated RT compared with conventional RT (OR 0.80, 95% CI 0.68 to 0.95, p=0.009).[110]

One RCT (ASCENDE-RT) including 398 participants with intermediate-to-high risk prostate cancer was included in 2 SLRs for the comparison of EBRT alone to EBRT plus LDR-BT. Consistent results were reported across both publications, reporting on higher GU toxicity associated with LDR-BT boost and usage of pads for urinary incontinence, but otherwise finding no significant differences between major outcomes.[113, 186]

A final SLR (Chin 2017) reported on RTOG 0232, which compared EBRT plus LDR-BT with LDR-BT alone in 588 patients and found comparable rates of 5-year progression-free survival (86% vs 85%) and grade 3 GU and GI toxicity (3% vs 7% and 3% vs 2%, respectively) across LDR-BT alone compared to LDR-BT in combination with EBRT.[186]

Table 27. Outcomes for radiation type

Outcome	Study	Follow-up or subgroup	Reporting of outcome	Hypofractionated	Conventional	EBRT	EBRT + LDR-BT	LDR-BT	Comparison	P value
		(n) if different from randomised							*Effect size (95% CI)*	
Disease-related										
PCa-related death	Chin 2017 (SLR)	1 study (ASCENDE-RT) Median 78 months	Events, n (%)	-	-	11 (5.5)	7 (3.5)	-	NR	0.32
All-cause mortality	No outcomes reported									
OS	NG131 (SLR)	7 studies in MA	Events, n/total N	3569/ 3950	2522/ 2839	-	-	-	RR: 1.01 (0.99– 1.03) RR >1 favours conventional	0.33
	NG131 (SLR)	1 study (ASCENDE-RT) Freedom from PCa-related death	N/A	-	-	NR	NR	-	RR: 1.02 (0.98– 1.06) RR >1 favours LDR-BT arm	NR
	Chin 2017 (SLRT)	1 study (ASCENDE-RT) 7-year OS	Events, %	-	-	74	78	-	NR	0.29
	Yin 2019 (SLR)	6 studies in MA	Events, n	372	411	-	-	-	OR 0.89 (0.78– 1.02) OR <1 favours H-RT	0.10
DFS	NG131 (SLR)	3 studies in MA Freedom from biochemical failure	Events, n/total N	1424/ 1648	1365/ 1622	-	-	-	RR: 1.03 (1.00– 1.06) RR >1 favours hypo	0.07
	NG131 (SLR)	6 studies in MA Freedom from biochemical-clinical failure	Events, n/total N	3346/ 3876	2319/ 2754	-	-	-	RR: 1.01 (0.99– 1.03) RR >1 favours conventional	0.27
	Chin 2017 (SLR)	1 study (ASCENDE-RT) 9-year DFS	Events, %	-	-	**62**	**83**	-	NR	<0.001
Biochemical failure	Yin 2019 (SLR)	4 studies in MA	Events, n	219	254	-	-	-	**OR 0.80 (0.68–0.95)** OR <1 favours H-RT	0.009
Metastasis	No outcomes reported									
Other	Yin 2019 (SLR) Biochemical and clinical disease failure, hypofractionated vs conventional RT: OR 0.92 (0.82–1.02), p=0.12 Chin 2017 (SLR) 1 study (RTOG 0232) 5-year PFS, EBRT + LDR-BT vs LDR-BT: HR 1.02 1 study (ASCENDE-RT) metastasis-free survival EBRT vs EBRT + LDR-BT: p=0.83									
Toxicity/treatment complications										

Outcome	Study	Follow-up or subgroup	Reporting of outcome	Hypofractionated	Conventional	EBRT	EBRT + LDR-BT	LDR-BT	Comparison	P value
		(n) if different from randomised							*Effect size (95% CI)*	
Overall AEs	No outcomes reported									
Urinary AEs	No outcomes reported									
Erectile dysfunction	No outcomes reported									
GI toxicity	NG131 (SLR)	Acute GI toxicity 9 studies in MA	Events, n/total N	945/ 3235	470/ 2474	-	-	-	**RR: 1.42 (1.29– 1.59)** RR >1 favours conventional	<0.00001
	NG131 (SLR)	Late GI toxicity 9 studies in MA	Events, n/total N	518/ 4071	396/ 2979	-	-	-	RR: 1.03 (0.91– 1.16) RR >1 favours conventional	0.65
	NG131 (SLR)	Acute GI toxicity 1 study (ASCENDE-RT)	N/A	-	-	NR	NR	-	RR: 1.01 (0.82– 1.25) RR >1 favours EBRT alone	NR
	Chin 2017 (SLR)	1 study (ASCENDE-RT) Grade 3 Grade 4	Events, %	-	-	4 0	9 1	-	NR	NR
	Yin 2019 (SLR)	5 studies in MA	Events, n	402	406	-	-	-	OR 0.97 (0.71– 1.33) OR <1 favours H-RT	0.85
	Chin 2017 (SLR)	1 study (RTOG 0203) Grade 3	Events, %	-	-	-	3	3	NR	NR
GU toxicity	NG131 (SLR)	Acute GU toxicity 9 studies in MA	Events, n/total N	1347/ 3236	984/ 2474	-	-	-	RR: 1.01 (0.95– 1.07) No treatment arm favoured	0.82
	NG131 (SLR)	Late GU toxicity 9 studies in MA	Events, n/total N	699/ 3990	578/ 2898	-	-	-	RR: 1.07 (0.97– 1.18) RR >1 favours conventional	0.16
	NG131 (SLR)	Acute GU toxicity 1 study (ASCENDE-RT)	N/A	-	-	NR	NR	-	RR: 2.24 (1.55– 3.23) RR >1 favours EBRT alone	NR
	Chin 2017 (SLR)	1 study (ASCENDE-RT) Grade 3 Grade 4	Events, %	-	-	5 1	19 1	-	NR	NR
	Yin 2019 (SLR)	5 studies in MA	Events, n	469	415	-	-	-	OR 1.04 (0.87– 1.24) OR >1 favours C-RT	0.69

Outcome	Study	Follow-up or subgroup	Reporting of outcome	Hypofractionated	Conventional	EBRT	EBRT + LDR-BT	LDR-BT	Comparison	P value
		(n) if different from randomised							*Effect size (95% CI)*	
	Chin 2017 (SLR)	1 study (RTOG 0232) Grade 3	Events, %	-	-	-	7	3	NR	NR

Footnotes: Values in **bold** indicate statistically significant results.
Abbreviations: AE: adverse event; CI: confidence interval; DFS: disease-free survival; EBRT: external-beam radiation therapy; GI: gastrointestinal; GU: genitourinary; LDR-BT: low dose rate brachytherapy; N/A: not applicable; NR: not reported; OS: overall survival; PCa: prostate cancer; PFS: progression-free survival; QOL: quality of life; RR: risk ratio; RT: radiotherapy; SD: standard deviation; SLR: systematic literature review.

Conservative vs radical treatment

The Ng 2019 SLR included 3 RCTs: SPCG-4, PIVOT and ProtecT.[185] The primary aim of this SLR was to compare key clinical outcomes between conservatively and radically treated localised prostate cancer patients. For conservative treatment, the watchful waiting arms of SPCG-4 and PIVOT were grouped with the active surveillance arm of ProtecT. For radical treatment, outcomes from the RT and prostatectomy arms of ProtecT were pooled and grouped with outcomes from the prostatectomy arms of SPCG-4 and PIVOT. The meta-analysis revealed that, relative to radically treated patients, conservatively treated patients had a significantly increased risk of prostate cancer-related death (OR 1.74, 95% CI 1.31 to 2.30, absolute risk difference: 37 [16 to 63] more per 1000), all-cause mortality (OR 1.37, 95% CI 1.14 to 1.64, absolute risk difference: 69 [28 to 112] more per 1000) and development of distant metastases (OR 1.87, 95% CI 1.48 to 2.36, absolute risk difference: 63 [36 to 95] more per 1000), but a significantly decreased risk of urinary adverse events (OR 0.42, 95% CI 0.21 to 0.86, absolute risk difference: 72 [101 to 16] fewer per 1000) and erectile dysfunction (OR 0.62, 95% CI 0.39 to 0.98, absolute risk difference: 118 [223 to 5] fewer per 1000).[185]

Influence of prostate cancer risk level

Two studies presented stratified analyses by prostate cancer risk group (low-, intermediate- or high-risk). In the EORTC trial, exploratory heterogeneity tests (National Comprehensive Cancer Network or D'Amico) found that there was no statistically significant impact of the risk group on the unadjusted treatment effect on biochemical disease free survival (DFS) or clinical DFS.[188] On the other hand, an interaction analysis of RTOG 94-08 suggested that there was a relationship between disease-specific survival and intermediate-risk patients and treatment arm (androgen suppression plus RT), with a HR of 3.89 (95% CI 1.14 to 13.21). In other terms, the benefits of short-course androgen deprivation therapy in combination with RT were seen more strongly in intermediate-risk patients.[176]

The NG131 NICE guidance presents its recommendations by risk group, however, no specific analysis by risk group was conducted in the SLRs.

Deprioritised records

A total of 7 publications were identified comparing different iterations of RT, active surveillance, prostatectomy and hormonal therapy for localised prostate cancer. Comparison between standard and dose-escalated RT in intermediate-risk patients yielded mixed results; dose-escalation reduced biochemical failure and distant metastases, and reduced the rate of salvage therapy, but caused more late toxic effects and did not improve overall survival.[195]

Another RCT compared 2 high dose-rate brachytherapy regimens in low- and intermediate-risk patients: one fraction at 19 Gy or 2 fractions at 13.5 Gy one week apart.[196] Urinary symptoms and erectile dysfunction were more common during the first 12 months in the two-fraction arm.

One Swedish RCT with low-risk prostate cancer patients compared standard active surveillance with a modified protocol, consisting of a more extensive repeat transrectal biopsy and less frequent follow-up, and the results did not support general use of the modified protocol.[197] A significant difference was found when traditional trans-Retzius robot-assisted laparoscopic radical prostatectomy (RALP) was compared with Retzius-sparing RALP[198], with the latter approach resulting in the earlier recovery of urinary continence. However, at a 12-week follow-up of a different RCT comparing robot-assisted laparoscopic prostatectomy and radical retropubic prostatectomy, no significant differences were seen in urinary or sexual function scores between arms.[199]

Another deprioritised RCT investigated 60 patients with stage T1c–T2b cancer randomised to dutasteride and bicalutamide or luteinizing hormone releasing hormone (LHRH) agonist and bicalutamide prior to starting brachytherapy. No significant differences were seen in reduction of prostate volume or International Prostate Symptom Score (IPPS), but the EPIC sexual summary score was significantly better in the dutasteride and bicalutamide group.[200] Finally, comparison of short-term (4 months) and long-term (24 months) ADT in patients receiving high-dose RT showed that long-term ADT improved 5-year overall survival, biochemical disease-free survival and metastasis-free survival, particularly in those with high-risk disease, with no increase in late radiation toxicity.[201]

Conclusions (Q4)

High quality evidence was found comparing across prostatectomy, RT and observation (watchful waiting or active surveillance), as well as on androgen deprivation added to RT against RT and between different types of RT.

Two SLRs, including the key trials of interest (ProtecT, SPCG-4, PIVOT), compared the effectiveness of prostatectomy with either watchful waiting or active surveillance. The key findings were a lower risk of disease progression/metastases with prostatectomy than either watchful waiting or active surveillance. Improved prostate cancer-specific and overall mortality were also observed against watchful waiting, but only after 4 to 6 years of follow-up. As expected, patients undergoing prostatectomy had an increased frequency of adverse events including GI and GU toxicity. Overall, the possible benefit in disease progression outcomes may not outweigh the risk of increased rate of adverse events, particularly given the lack of evidence that explores this in clinically insignificant compared

to clinically significant subgroups of the disease. In other terms, men may receive treatment but never go on to develop clinically significant prostate cancer. There is a trade-off between benefits and risks and ultimately it will be necessary for patients to make an informed choice.

The comparison of RT with observation was reported through the ProtecT trial in one NG131 SLR (active surveillance, high quality), supplemented with Hackman 2019 (watchful waiting, some concerns about risk of bias). Disease progression, distant metastases and biochemical failure were decreased in patients treated with RT arm compared with observation. Prostate cancer-related death was decreased on average when comparing RT with active surveillance in ProtecT, however the upper limit of the wide CIs was also consistent with an increase in prostate cancer-related death. Overall mortality was unchanged. Hackman 2019 saw no difference in prostate cancer-related death when comparing RT with watchful waiting, thus leaving the direction of evidence unclear for mortality outcomes. As expected, adverse events were more common in RT arms, resulting in a similar conclusion as for prostatectomy vs observation, with a lack of evidence exploring outcomes in clinically significant vs insignificant disease.

Results of the comparison of RT with prostatectomy were reported in the ProtecT trial (through NG131 and Ng 2019 SLRs), and in a small RCT judged to be at high risk of bias (Lennernäs 2015). Interestingly, the results were similar to those seen in the separate comparisons made for each intervention against observation. In ProtecT, prostatectomy had a higher risk of metastases, erectile AEs, and urinary and sexual dysfunction, but a lower risk of prostate cancer-related death and better bowel function. The risk of disease progression was similar for both treatments.
Given that no significant differences between treatments were reported in Lennernäs 2015, the overall results do not conclusively point to either treatment as being superior; rather, each treatment has a different efficacy and safety profile.

Four RCTs of moderate quality provided results on the efficacy of ADT + RT compared with RT only. In general, ADT conferred benefits for prostate cancer-related death, all-cause mortality, overall survival, biochemical failure rate, disease-free survival and metastases, and no significant difference in GI/GU toxicity. This is a suggestive of an incremental benefit of the addition of ADT to RT, but is not informative regarding how ADT would compare to RT alone, or indeed as an addition to prostatectomy.

Different types of RT were compared in 2 SLRs, one high quality (NG131), the other with concerns for being at risk of bias (Yin 2019) and which included several of the same RCTs. For most outcomes, the results were not significant (and consistent across both SLRs), with only a few outcomes having significantly different results (e.g. Yin 2019 found that the risk

of biochemical failure was decreased in men receiving hypofractionated RT compared with conventional RT, but no significant difference was found for this outcome in the NG131 SLR). Overall, no type of RT was conclusively better than another.

Whilst prostatectomy and RT have benefits vs observation for treating prostate cancer (including the additional benefit of using androgen suppression in conjunction with RT), it remains unclear how these benefits weigh up against the risks of the treatment compared with observation. This is particularly important in the context of men with clinically insignificant disease who would not require treatment.

Summary of findings relevant to criterion 9: Criterion not met

Quantity: Including the data in the included SLRs, a high volume of evidence was available to assess Criterion 9, consisting of a total of 19 RCTs reported across 5 SLRs and 12 primary publications. Evidence was identified for 10 different direct treatment comparisons and 14 publications across 2 SLRs were included for the 3 major prostate cancer trials (ProtecT, SPCG-4, PIVOT) that were identified in the previous UK NSC review. This allowed for the most relevant evidence to be prioritised for extraction and synthesis. However, no evidence was identified for high-intensity ultrasonography or ablative therapy. This should be noted because, with the exception of ADT, the treatments for which evidence was available (observation, prostatectomy, RT) are already recommended by NICE as 'usual care' for localised prostate cancer. The majority of the RCTs included stage T1–T2 prostate cancer and 2 SLRs and 2 RCTs extended the definition of localised to include stage T3a.[110-113] Analyses included patient numbers which ranged from 89 to 7050 (pooled) participants.[111, 113]

Quality: Three SLRs were judged to be at a low risk of bias.[69, 113, 177] For the other 2 there were some concerns, particularly for domains including the search strategy, justification for study exclusion and assessment of the risk of bias and heterogeneity of the included studies.[110, 186] Two primary RCTs were at a high risk of bias due to the possible influence on outcome measurement arising from lack of blinding procedures, or because of missing outcome data.[111, 112] There were some concerns about the risk of bias in the remaining 4 RCTs, particularly for the effect of assignment to the interventions, and selection of the reported result due to unavailability of statistical analysis plans.[176, 188-190]

Applicability: The main concern regarding applicability arises from the inclusion of some patients whose cancer was beyond stage T3a in studies included in 2 of the SLRs;[110, 113] these patients would likely be at higher baseline risk of adverse outcomes and may have a lower treatment success. However, this only implicates a minority of the overall evidence for the within-RT treatment comparison. The remaining studies were judged to be of high applicability to the

review question as they included men with localised prostate-cancer (in some cases following screen-detection) in primary care settings.

Consistency: Three of the 5 included SLRs provided satisfactory discussions of the heterogeneity of their included studies,[113, 177, 185] whilst 2 did not.[110, 186] There are low concerns regarding the approach to data analyses conducted in different SLRs, given that largely similar results were reported for the same comparisons, despite the SLRs not always including the same RCTs or sub-analyses of RCTs. For the majority of treatment comparisons, conclusions about consistency of RCTs could not be drawn because only one RCT was included. For ADT + RT vs RT alone, the 4 included RCTs used similar treatment schedules for ADT, consisting of flutamide or bicalutamide in combination with goserelin or leuprolide and RT, although note that one RT schedule was dose-escalated.[189]

Conclusions: Evidence for all treatment comparisons was identified from at least one high quality SLR, except for androgen suppression + RT vs RT alone, which came from 4 moderate quality RCTs. Compared with observation, both RT and prostatectomy had improved disease progression outcomes, increased adverse events and inconclusive results for survival. Results for prostatectomy vs RT and comparisons between different RT types were inconclusive. A possible benefit was seen in the addition of ADT to RT compared with RT alone, however, this is incremental and does not inform on how ADT would perform alone or in comparison to other treatments. Overall, of the treatments that are currently recommended by NICE (those constituting 'usual care'), no particular intervention could be identified as conclusively superior. Better disease progression offered with RT or prostatectomy vs observation has to be balanced against increased adverse events and the consideration that there is still a lack of evidence comparing outcomes in clinically significant and insignificant disease, likely largely due to difficulties in predicting which cases will be significant at an early stage. It is thus unclear whether early identification of patients with prostate cancer would provide them with a therapeutic advantage that outweighs the risks of adverse events.

Review summary

Conclusions and implications for policy

Based on the overall synthesis of evidence against the UK NSC criteria, screening of men for prostate cancer should still not be recommended.

Four questions were considered in this rapid review: (1) Does screening based on PSA reduce short- or long-term prostate cancer morbidity and mortality and all-cause mortality?; (2) What are the harms of PSA-based screening for prostate cancer and diagnostic follow-up, with particular reference to overdiagnosis?; (3) Is there evidence that screening using risk algorithms or inclusion of markers other than PSA alone can better identify men with clinically significant prostate cancer, or improve screening efficiency?; and (4) What are the harms and benefits of currently available treatment approaches for early-stage prostate cancer to reduce morbidity and mortality?

Studies evaluating the performance of screening tests compared with PSA investigated 3 different single screening tests (percent-free PSA,[158] DRE,[157] and MRI[26]), as well as the addition of PCA3 to follow PSA and DRE tests.[25] One study evaluated the prognostic STHLM3 model compared with PSA.[97] While the lack of studies reporting on the same tests limits the robustness of the conclusions about any particular test, based on the findings of this review, the STHLM3 model and MRI represent the most promising screening methods compared with PSA alone. MRI, either alone or as a sequential screening test following PSA, achieved greater accuracy than PSA alone in 2 studies,[24, 26] although confidence in these findings is limited by a high risk of bias[26] (Nam 2016) and lack of further validation of results (both studies). Nevertheless, an evaluation of sequential MRI-based screening for prostate cancer in unselected men is already underway in the Göteborg 2 trial, which could provide further evidence on the usefulness of MRI screening for prostate cancer in unselected men.[202] Overall, few studies reported eligible screening accuracy outcomes for detection of prostate cancer distinguished by insignificant or significant disease, and therefore this component of the criteria remains unclear. The Göteborg study reported that the detection rate of prostate cancer was higher using the PSA (≥1.8 ng/mL) and MRI strategy for both significant (48%) and high-risk (38%) cancer, compared with PSA alone. Furthermore, the STHLM3 study measured the predictive capabilities of the model for all cancers (AUC 0.69, 95% CI 0.68 to 0.71) and high-grade cancers (AUC 0.74, 95% CI 0.72 to 0.75). Additionally, a number of identified studies evaluated screening using predictive models or MRI for detection of “high-grade” prostate cancer specifically, although as the index test was not compared with PSA or any other test, these studies were deprioritised in

evidence synthesis, especially considering that the model was not necessarily aiming at comparing test accuracy between detection of high and low grade cancer.
Another important limitation of the evidence, which is relevant across questions 1 to 3, is that different studies use different thresholds to classify the comparator PSA level is a screen-positive result (PSA 3 ng/mL vs 4 ng/mL). The previous UK NSC review found that the use of a 3 ng/mL threshold increased sensitivity for the detection of prostate cancer, but also increased false positive cases and overdiagnosis. Overall, it was concluded that there was no consensus on the most appropriate threshold for the detection of prostate cancer, and that age-specific reference ranges for PSA remain unvalidated. Findings of this review similarly show that there is still very little evidence on whether the thresholds employed for the various index tests were the most appropriate ones. Finally, due to the invasive nature of the reference standard (biopsy), this was only administered to men considered "screen-positive" (i.e. at a higher risk than normal men), precluding the investigation of false negatives. This is a limitation of the reference standard, rather than the included studies, as applying biopsy to all men would be both less feasible and unethical, considering the high risk of complications of the procedure alone.

Based on moderate-to-high quality evidence, PSA-based screening significantly increases the incidence rate of prostate cancer in comparison with no screening or usual care. Though no conclusions can be made about the stratification of the diagnosis by clinical staging due to inconsistent and lacking evidence, it appears that metastatic cases' incidence is affected by screening, with no difference found in the PLCO trial but a lower reported incidence in the screening arm of the ERSPC trial (RaR <1 vs screening).[126] The impact of PSA-based screening on prostate cancer-specific mortality also remains unclear due to conflicting evidence across the 3 included RCTs (ERSPC reports a significant reduction after 16 years of follow-up, whereas CAP and PLCO detect no difference after 10 and 17 years of follow-up, respectively). This is in alignment with the findings of the last (2015) UK NSC review, however longer-follow-up in CAP and lower contamination in PLCO could show an effect. Comparing harms and benefits of PSA-based screening, the findings of this review are also largely similar to those found in the previous UK NSC review in 2015, with overdiagnosis being the most common harm associated with screening, based on evidence from the ERSPC and PLCO. Furthermore, no significant difference between the screening and usual care groups was found in QoL in a subgroup analysis of the FinRSPC cohort (the single report on this outcome), which is in contrast to the findings of the last review where overdiagnosis and overtreatment were found to have an adverse impact on QoL.[7]

An important limitation of the evidence is the high level of contamination of PSA-based screening within the control arm of the ERSPC and PLCO trials. If men in both study groups received the screening intervention, it is possible that the measured intervention effect on

outcomes of interest is diluted or equalised, which may be the case for prostate cancer-specific mortality. Previous analyses have reported that the effect of contamination is likely to be minimal (below 20%),[203] but the degree of contamination in the control arm has been reported to be as high as 62.7% in ERSPC,[14] and 90% in PLCO.[16] Subsequently, multiple sub-analyses have demonstrated the impact of control arm contamination on effect dilution; for example, Gulati 2012 concluded that due to contamination, the PLCO trial would not be able to accurately detect a clinically significant screening benefit, preventing conclusions from being drawn.[150] The fact that the ERSPC trial demonstrated differences in incidence in the screening and control arms could indicate a lower effect of contamination. It should be noted that CAP also found no significant reduction in mortality, despite a lower contamination level of 10 to 15%, although this may be a result of the shorter follow-up period compared to the other trials. Conversely, an analysis of PLCO and ERSPC trials concluded that mortality was significantly lower in the screening arms.[147] Due to the nature of the intervention (i.e. screening), it appears that contamination is a limitation of the evidence and it may not be possible to arrive at a conclusive answer to Question 1 other than through further large studies and/or modelling exercises, if the results of these are then synthesised through appropriate statistical methodology.

A high volume of evidence was identified to evaluate treatment options for early-stage or localised prostate cancer. Moreover, apart from the comparison of androgen deprivation and radiotherapy with radiotherapy alone, all evidence was based on at least one high-quality SLR. Nevertheless, a large limitation is that the majority of comparisons are reported through a single RCT only. A possible benefit was seen in the addition of adjunctive androgen deprivation to radiotherapy; however, this is only in comparison to radiotherapy alone and as such is incremental. It appears that both prostatectomy and radiotherapy are more effective than observation at decreasing disease progression, though this comes at a price of increased adverse events. Furthermore, the benefit to survival is unclear when either treatment is compared with observation or when they are compared to each other.[177]

Overall, of the treatments that are currently recommended by NICE (those constituting 'usual care'), no particular intervention (radical RT, radical prostatectomy, active surveillance or watchful waiting) was identified as superior. A reduction in disease progression offered with RT or prostatectomy compared with observation has to be balanced against increased adverse events and the consideration that there is still a lack of an unequivocal improvement in survival with any of these treatments. It is thus unclear whether early identification of patients with prostate cancer would provide them with a therapeutic advantage.

Despite a large volume of studies found, evidence on treatment effectiveness is limited. Firstly, no evidence on treatments not currently recommended by NICE as ‘usual care’ for

early prostate cancer, such as high intensity ultrasonography and ablative therapy, was identified in this review. The efficacy of these interventions, along with the balance between any harms and benefits, remains unclear. Secondly, it should be noted that patients with T3a stage were included in some analyses, although the impact of this on the results is expected to be minimal.

In summary, screening for prostate cancer in unselected men is associated with increased incidence of prostate cancer diagnoses and the impact of PSA-based screening on prostate cancer-specific mortality remains unclear. Supporting findings of the previous review, overdiagnosis associated with PSA-based screening is still a concern as a harm of screening, although the effects of this and biopsy-related complications on QoL remain unclear. No robust conclusions can be made about tests superior to PSA, though it appears that adding MRI to PSA may improve test performance. A key limitation of the evidence overall is the lack of differentiation between insignificant and clinically significant disease, and so the benefit that screening would provide in terms of identifying those most in need of treatment remains particularly unclear. Finally, interventions recommended by NICE for the treatment of early-stage prostate cancer can slow down disease progression compared with observation, but have a similar effect on prostate cancer-specific mortality and more adverse events.

Limitations

This section considers limitations of the review methodology. Limitations of the evidence and evidence gaps are discussed in the section above.

This rapid review was conducted in line with the UK NSC requirements for evidence summaries, as described at https://www.gov.uk/government/publications/uk-nsc-evidence-review-process/appendix-f-requirements-for-uk-nsc-evidence-summaries. All items on the UK NSC Reporting Checklist for Evidence Summaries have been addressed in this report. A summary of the checklist, along with the page or pages where each item can be found in this report, is presented in Table 51 (Appendix 6 – UK NSC reporting checklist for evidence summaries). Database search terms were restricted by study design, screening terms and limited to studies published since 2014 (date of searches conducted for the previous UK NSC review) for questions 1 to 3. Database search terms were restricted by study design and intervention terms for question 4, as well as limited to records published since 2016 for interventions included in NICE NG131 SLRs (which were included in this review) or to records published since 2014 for interventions not covered in the NICE NG131 SLRs. Published and well validated filters were used to limit by study design and searches were supplemented with SLR reference list searches.

Included publication types

This review only included peer-reviewed journal publications and excluded publications that were not peer-reviewed and grey literature. This may have led to the exclusion of relevant evidence. However, this is an accepted methodological adjustment for a rapid review and is unlikely to miss any pivotal studies.

Language

Only studies published in English were included. There is a possibility that some evidence reported in a language other than English was missed. However, this review was ultimately focusing on evidence relevant to the UK setting, and it could be supposed that publications in non-English languages may be more focused on results applicable to other countries. It is anticipated that this limitation should not exclude any pivotal studies.

Review methodology

Articles were reviewed by a single reviewer in the first instance. A second reviewer examined all included articles, 10% of excluded articles, and any articles where there was uncertainty about inclusion. This is a pragmatic strategy that should have minimised the risk of errors and is an accepted methodological adjustment for a rapid review.

Articles not freely available

Searches for full-text articles were carried out at Cambridge University Library. Any unavailable articles were purchased (unless they were not selected for extraction based on study design or intervention, see the Methods section and below).

Study prioritisation

Due to a sufficiently high number of studies initially included in the review for questions 3 and 4, only studies focusing on comparison to PSA-based screening (question 3) or comparing 2 different interventions (question 4) were ultimately selected for data extraction. This tiered approach to the study selection process was pre-specified and was utilised so that only the most relevant evidence is initially considered in the review.

Appendix 1 — Search strategy

Electronic databases

The search strategy included searches of the databases shown in Table 28. MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print and Embase were searched simultaneously using Ovid SP. The Cochrane Library databases were searched simultaneously via the Wiley Online platform. Database of Abstracts of Reviews of Effects (DARE) was searched via the Centre for Reviews and Dissemination (CRD) website. For both Ovid SP and the Wiley Online platform, separate searches were performed for Questions 1–3 and Question 4.

Table 28. Summary of electronic database searches and dates

Database	Platform	Searched on date	Date range of search
MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print	Ovid SP	September 2nd 2019	1946 to August 30th 2019
Embase	Ovid SP	September 2nd 2019	1974 to August 30th 2019
The Cochrane Library, including: - Cochrane Database of Systematic Reviews (CDSR) - Cochrane Central Register of Controlled Trials (CENTRAL)	Wiley Online	September 2nd 2019	CDSR: Issue 9 of 12, September 2019 CENTRAL: Issue 9 of 12, September 2019
Database of Abstracts of Reviews of Effects (DARE)	Centre for Reviews and Dissemination, University of York	September 2nd 2019	DARE: Issue 2 of 4, April 2015

Search terms

Search terms included combinations of free text and subject headings (Medical Subject Headings [MeSH] for MEDLINE, and Emtree terms for Embase), grouped into the following categories:

- disease area: prostate cancer
- study design: RCTs, non-RCTs and observational studies
- other term group: interventions
    - screening terms (for questions 1–3)
    - intervention terms (for question 4)

Search terms for MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print and Embase are shown in Table 29 (Questions 1–3) and Table 30 (Question 4), search

terms for the Cochrane Library databases are shown in Table 31 (Questions 1–3) and Table 32 (Question 4), and search terms for DARE are shown in Table 33.

Table 29. Search strategy for MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print and Embase (Searched via Ovid SP; Questions 1–3)

Term group	#	Search terms	Results
Prostate cancer terms	1	exp Prostatic Neoplasms/ or exp Prostate Tumor/	352524
	2	(prostat$ adj4 (neoplas$ or cancer$ or carcinoma$ or adenocarcinom$ or tumour$ or tumor$ or malignan$ or metasta$ or angiosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytic$ or leiomyosarcoma$ or lump$)).ti,ab.	346469
	3	PIN.ab,ti,kw,kf.	30247
	4	or/1-3	444343
Screening terms	5	mandatory testing/ or mass screening/	152726
	6	(Sensitivity.mp. and Specificity/) or (detect$ or identif$ or diagnos$ or test$ or screen$).ti. or (sensitiv$ or specific$ or accura$ or precis$ or NPV or PPV or predictive value$ or likelihood ratio$).ti,ab.	12882162
	7	or/5-6	12931110
	8	((screen$ or test$) adj2 prostat$).ti,ab.	16280
	9	*Prostate-Specific Antigen/ or *prostate specific antigen/	25525
	10	(prostate specific antigen or psa).ti,ab.	118453
	11	Magnetic Resonance Imaging/ or nuclear magnetic resonance imaging/	1124906
	12	(magnet$ adj2 (resonance$ or imag$ or scan$ or spectroscop$)).ti,ab.	720375
	13	(MR adj2 (resonance$ or imag$ or scan$ or spectroscop$)).ti,ab.	159242
	14	(Dynamic contrast$ enhanc$ adj2 (MR$ or magnet$)).ti,ab.	10768
	15	(contrast$ adj2 (imag$ or scan$)).ti,ab.	44347
	16	((MRI or MRSI or MP-MR$ or MPMR$) adj4 prostat$).ti,ab.	7021
	17	turbo spin echo$.ti,ab.	4750
	18	((diffusion$ or weight$) adj2 imag$).ti,ab.	112689
	19	((DWI or DCE-MRI or T2W or TSE or T2-weighted MRI$) adj3 prostat$).ti,ab.	480
	20	(Multi-parametric or multiparametric$ or biparametric$ or bi-parametric$).ti,ab.	18622
	21	*Digital Rectal Examination/	831
	22	(digital rectal examination or DRE).ti,ab.	13664
	23	((transrectal ultrasound$ or trans-rectal ultrasound$ or TRUS or TRUSB) adj4 prostat$).ti,ab.	7054
	24	*Biomarkers/ or *biological marker/ or *biochemical marker/ or *Genetic Testing/ or *genetic screening/	146684
	25	((biological or serum) adj2 (marker$ or biomarker$)).ti,ab.	70822
	26	(urine adj (measur$ or analy$ or test$ or collect$)).ti,ab.	30676
	27	(urinalys$ or pca3 or pca 3 or dd3 or 4kscore or 4k score or prostate health index or four-kallikrein panel).ti,ab.	23453
	28	*Risk assessment/ or *Risk factors/ or *Medical history/	119571

Term group	#	Search terms	Results
	29	or/8-28	2026969
	30	7 and 29	706840
	31	Randomized Controlled Trials as Topic/	228510
	32	Randomized Controlled Trial/	1056169
	33	Random Allocation/	180386
	34	Randomization/	184123
	35	Double Blind Method/	284385
	36	Single Blind Method/	61717
	37	Single Blind Procedure/	36423
	38	Double Blind Procedure/	165026
	39	Crossover Procedure/	60512
	40	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).ab,ti,kw,kf.	395293
	41	exp Clinical Trial/	2260726
	42	Clinical trial, phase i.pt.	19251
	43	Clinical trial, phase ii.pt.	31078
	44	Clinical trial, phase iii.pt.	15457
	45	Clinical trial, phase iv.pt.	1741
	46	Phase 1 Clinical Trial/ or exp Clinical trial, phase I/	73316
	47	Phase 2 Clinical Trial/ or exp Clinical trial, phase II/	106337
	48	Phase 3 Clinical Trial/ or exp Clinical trial, phase III/	57724
	49	Phase 4 Clinical Trial/ or exp Clinical trial, phase IV/	5320
	50	Controlled clinical trial.pt.	93253
Study design terms: RCTs	51	Randomized controlled trial.pt.	488336
	52	Multicenter study.pt.	255701
	53	Comparative study.pt.	1838619
	54	Clinical trial.pt.	517688
	55	Clinical Trials as Topic/	263030
	56	trial$.ti.	643311
	57	(clinical adj trial$).ab,ti,kw,kf.	851732
	58	Placebos/	318505
	59	Placebo/	340976
	60	placebo$.ab,ti,kw,kf.	504376
	61	randomly allocated.ab,ti,kw,kf.	60262
	62	(allocated adj2 random$).ab,ti,kw,kf.	67249
	63	random allocation.ab,ti,kw,kf.	3702
	64	random assignment.ab,ti,kw,kf.	5022
	65	randomized.ti,ab.	1193166
	66	randomised.ti,ab.	241527
	67	randomisation.ab,ti,kw,kf.	20608
	68	randomization.ab,ti,kw,kf.	68607
	69	randomly.ti,ab.	738625
	70	RCT.ab,ti,kw,kf.	55985
	71	Open-label trial$.ab,ti,kw,kf.	8978
	72	Open-label stud$.ab,ti,kw,kf.	20696

Term group	#	Search terms	Results
	73	Non-blinded stud$.ab,ti,kw,kf.	299
	74	or/31-73	6016472
	75	Cohort Studies/	616210
Study design terms: non-RCTs and observational studies	76	Cohort Analysis/	748574
	77	cohort analy$.ab,ti,kw,kf.	19696
	78	(cohort adj (study or studies)).ab,ti,kw,kf.	460433
	79	Cross-sectional studies/	489137
	80	(cross-sectional adj (study or studies)).ab,ti,kw,kf.	346377
	81	Longitudinal Studies/ or exp Longitudinal study/	256105
	82	Longitudinal.ab,ti,kw,kf.	541456
	83	Follow-Up Studies/	1614648
	84	Follow-Up/	1450352
	85	(follow up adj (study or studies)).ab,ti,kw,kf.	112937
	86	Prospective Studies/ or exp Prospective study/	1059315
	87	(Prospective adj (study or studies)).ab,ti,kw,kf.	415795
	88	(evaluation adj (study or studies)).ab,ti,kw,kf.	14158
	89	Retrospective Studies/ or exp Retrospective study/	1585707
	90	retrospective$.ti,ab.	1807553
	91	(chart adj3 review).ab,ti,kw,kf.	111837
	92	Observational studies/ or exp Observational study/	247630
	93	(observational adj (study or studies)).ab,ti,kw,kf.	248797
	94	((single arm or single-arm) adj3 (study or studies or trial$)).ab,ti,kw,kf.	14444
	95	or/75-94	6413342
Exclusion terms	96	("Conference Abstract" or "Conference Review" or comment or letter or editorial or note or case reports).pt.	9637783
	97	(case stud$ or case report$).ti.	619911
	98	Letter/ or historical article/ or case study/	4313520
	99	Animals/ not Humans/	5545185
	100	or/96-99	15770497
Combined and total Q1-Q3 (RCTs only)	101	4 and 30 and 74	19503
	102	101 not 100	15712
	103	limit 102 to yr=2014-2019	4301
Combined and total Q3 (non-RCTs/observational studies only)	104	4 and 30 and 95	28493
	105	104 not 100 not 102	15305
	106	limit 105 to yr=2014-2019	6665
Remove duplicates	107	limit 106 to yr=2016-2019	4610
	108	106 not 107	2055
	109	remove duplicates from 103	2819
	110	remove duplicates from 107	3144
	111	remove duplicates from 108	1404
Total	112	109 or 110 or 111	7367

Table 30. Search strategy for MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print and Embase (Searched via Ovid SP; Question 4)

Term group	#	Search terms	Results
Prostate cancer terms	1	exp Prostatic Neoplasms/ or exp Prostate Tumor/	352524
	2	(prostat$ adj4 (neoplas$ or cancer$ or carcinoma$ or adenocarcinom$ or tumour$ or tumor$ or malignan$ or metasta$ or angiosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytic$ or leiomyosarcoma$ or lump$)).ti,ab.	346469
	3	PIN.ab,ti,kw,kf.	30247
	4	or/1-3	444343
	5	(stage I or stage II or stage 1 or stage 2 or early or local or localised or localized).ti,ab.	5310305
	6	4 and 5	83490
Intervention terms (in NICE guidelines SLR) (Q4)	7	*Watchful Waiting/	2505
	8	((active$ or watch$ or expect$ or conservat$) adj (surveillan$ or monitor$ or observat$ or wait$ or manag$)).ti,ab.	76127
	9	((deferr$ or delay$) adj1 (treat$ or therap$)).ti,ab.	22232
	10	or/7-9	98943
	11	prostatic neoplasm/su	21462
	12	*Prostatectomy/	41403
	13	(radical adj4 prostatectom$).ti,ab.	56769
	14	or/11-13	78822
	15	*Radiotherapy/	71631
	16	radiotherap$.ti,ab.	403113
	17	(radiat$ adj4 (therap$ or treatment$)).ti,ab.	234657
	18	((external$ or conformal$) adj4 (irradiat$ or therap$ or treat$)).ti,ab.	49935
	19	((interstitial$ or intracavit$ or implant$ or surface$ or internal$) adj4 (irradiat$ or radiation$)).ti,ab.	19886
	20	curietherap$.ti,ab.	865
	21	(radioisotope$ adj4 (irradiat$ or therap$ or treat$)).ti,ab.	1274
	22	((seed$ or permanent$) adj2 implant$).ti,ab.	14677
	23	or/15-22	651557
	24	*Brachytherapy/	32353
	25	brachytherap$.ti,ab.	45778
	26	(hyperfraction$ or hyper fraction$ or hypofraction$ or hypo fraction$).ti,ab.	15018
	27	((optim$ or fraction$ or respons$ or relation$ or dependence$ or effect$ or scheme$ or curve$) adj4 (dose$ or dosage or schedule$)).ti,ab.	602818
	28	((high$ or full$ or maximum$ or larg$ or escalat$ or supplement$ or low$ or minimum$ or small$) adj4 (dose$ or dosage$ or schedule$)).ti,ab.	1011884
	29	(HDR or LDR).ti,ab.	15021
	30	or/24-29	1452221
	31	23 and 30	127573

Term group	#	Search terms	Results
	32	10 or 14 or 31	297556
Intervention terms (not in NICE guidelines SLR) (Q4)	33	*High-Intensity Focused Ultrasound Ablation/ or *High Intensity Focused Ultrasound/ or *Ultrasound, High-Intensity Focused, Transrectal/ or *Transrectal High Intensity Focused Ultrasound/	4731
	34	((ultrasonograp$ or ultrasound) adj2 (high intensity or high-intensity)).ti,ab.	7909
	35	HIFU.ti,ab.	5853
	36	*Ablation therapy/ or *Catheter Ablation/	44599
	37	ablati$ therapy.ti,ab.	8853
	38	(radiofrequency ablation$ or radio frequency ablation$ or catheter ablation$ or rfta or RFA).ti,ab.	68442
	39	(thermoablation$ or thermo ablation or thermo destruc$ or thermal destruc$ or thermo coag$ or thermal coag$ or electrocoag$ or transvenous ablation$).ti,ab.	9405
	40	*Androgen deprivation therapy/ or *Antineoplastic agent/ or *Androgen antagonist/ or *Antiandrogen/ or *Antineoplastic agents/ or *Androgen antagonists/ or *Antiandrogens/	331618
	41	antiandrogen$.ti,ab.	11747
	42	((androgen$ or hormon$) adj3 (ablati$ or block$ or withdraw$ or depriv$ or suppress$)).ti,ab.	46595
	43	(gonadotrophin releasing hormone analogue$ or GRHA or luteini$ing hormone-releasing hormone or LHRH).ti,ab.	14717
	44	*Goserelin/ or *Cyproterone/ or *Estrogen/ or *Estrogens/ or *Leuprolide/ or *Leuprorelin/ or *Flutamide/ or *Diethylstilbestrol/ or *Progestins/ or *Gestagen/ or *Finasteride/ or *Bicalutamide/ or *Nilutamide/ or *Megesterol/	109988
	45	(Goserelin or Cyproterone or Leuprolide or Leuprorelin or Flutamide or Diethylstilbestrol or Progestin$ or Gestagen or Finasteride or bicalutamide or oestrogen$ or estrogen$ or leuprorelin or enantone or a-43818 or lupron or tap-144 or niftolid$ or zoladex or eulexin or casodex or nilutamide or nilandrone or megestrol or proscar).ti,ab.	388205
	46	or/33-45	893468
Study design terms: RCTs and non-RCTs	47	Randomized Controlled Trials as Topic/	228510
	48	Randomized Controlled Trial/	1056169
	49	Random Allocation/	180386
	50	Randomization/	184123
	51	Double Blind Method/	284385
	52	Single Blind Method/	61717
	53	Single Blind Procedure/	36423
	54	Double Blind Procedure/	165026
	55	Crossover Procedure/	60512
	56	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).ab,ti,kw,kf.	395293
	57	exp Clinical Trial/	2260726
	58	Clinical trial, phase i.pt.	19251

Term group	#	Search terms	Results
	59	Clinical trial, phase ii.pt.	31078
	60	Clinical trial, phase iii.pt.	15457
	61	Clinical trial, phase iv.pt.	1741
	62	Phase 1 Clinical Trial/ or exp Clinical trial, phase I/	73316
	63	Phase 2 Clinical Trial/ or exp Clinical trial, phase II/	106337
	64	Phase 3 Clinical Trial/ or exp Clinical trial, phase III/	57724
	65	Phase 4 Clinical Trial/ or exp Clinical trial, phase IV/	5320
	66	Controlled clinical trial.pt.	93253
	67	Randomized controlled trial.pt.	488336
	68	Multicenter study.pt.	255701
	69	Clinical trial.pt.	517688
	70	Clinical Trials as Topic/	263030
	71	trial$.ti.	643311
	72	(clinical adj trial$).ab,ti,kw,kf.	851732
	73	Placebos/	318505
	74	Placebo/	340976
	75	placebo$.ab,ti,kw,kf.	504376
	76	randomly allocated.ab,ti,kw,kf.	60262
	77	(allocated adj2 random$).ab,ti,kw,kf.	67249
	78	random allocation.ab,ti,kw,kf.	3702
	79	random assignment.ab,ti,kw,kf.	5022
	80	randomized.ti,ab.	1193166
	81	randomised.ti,ab.	241527
	82	randomisation.ab,ti,kw,kf.	20608
	83	randomization.ab,ti,kw,kf.	68607
	84	randomly.ti,ab.	738625
	85	RCT.ab,ti,kw,kf.	55985
	86	Open-label trial$.ab,ti,kw,kf.	8978
	87	Open-label stud$.ab,ti,kw,kf.	20696
	88	Non-blinded stud$.ab,ti,kw,kf.	299
	89	or/47-88	4479557
Study design terms: Non-RCTs and observational studies	90	Cohort Studies/	616210
	91	Cohort Analysis/	748574
	92	cohort analy$.ab,ti,kw,kf.	19696
	93	(cohort adj (study or studies)).ab,ti,kw,kf.	460433
	94	Cross-sectional studies/	489137
	95	(cross-sectional adj (study or studies)).ab,ti,kw,kf.	346377
	96	Longitudinal Studies/ or exp Longitudinal study/	256105
	97	Longitudinal.ab,ti,kw,kf.	541456
	98	Follow-Up Studies/	1614648
	99	Follow-Up/	1450352
	100	(follow up adj (study or studies)).ab,ti,kw,kf.	112937
	101	Prospective Studies/ or exp Prospective study/	1059315
	102	(Prospective adj (study or studies)).ab,ti,kw,kf.	415795

Term group	#	Search terms	Results
Exclusion terms	103	(evaluation adj (study or studies)).ab,ti,kw,kf.	14158
	104	Retrospective Studies/ or exp Retrospective study/	1585707
	105	retrospective$.ti,ab.	1807553
	106	(chart adj3 review).ab,ti,kw,kf.	111837
	107	Observational studies/ or exp Observational study/	247630
	108	(observational adj (study or studies)).ab,ti,kw,kf.	248797
	109	((single arm or single-arm) adj3 (study or studies or trial$)).ab,ti,kw,kf.	14444
	110	or/90-109	6413342
	111	("Conference Abstract" or "Conference Review" or comment or letter or editorial or note or case reports).pt.	9637783
	112	(case stud$ or case report$).ti.	619911
	113	Letter/ or historical article/ or case study/	4313520
	114	Animals/ not Humans/	5545185
	115	or/111-114	15770497
Combined	116	6 and 32 and 89	6804
	117	6 and 46 and 89	4492
	118	6 and (32 or 46) and 110	16296
	119	116 not 115	5120
	120	117 not 115	3380
	121	118 not 115	11055
	122	limit 119 to yr=2018-current	475
	123	limit 120 to yr=2014-current	940
	124	limit 121 to yr=2014-current	3951
Total RCTs	125	122 or 123	1292
	126	remove duplicates from 125	808
Total non-RCTs/observational	127	remove duplicates from 124	2561

Table 31. Search strategy for the Cochrane Library databases (Searched via the Wiley Online platform; Questions 1–3)

Term group	#	Search terms	Results
Prostate cancer terms	1	[mh "Prostatic Neoplasms"]	4984
	2	(prostat* NEAR/4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or leiomyosarcoma* or lump*)):ti,ab	11843
	3	PIN:ti,ab,kw	1076
	4	{or #1-#3}	13347
Screening terms	5	[mh ^"mandatory testing"] or [mh ^"mass screening"]	2984
	6	[mh ^"Sensitivity and Specificity"] or (detect* or identif* or diagnos* or test* or screen*).ti or (sensitiv* or specific* or accura* or precis* or NPV or PPV or "predictive value*" or "likelihood ratio*"):ti,ab	672027
	7	{or #5-#6}	672027
	8	((screen* or test*) NEAR/2 prostat*):ti,ab	909

Term group	#	Search terms	Results
	9	[mh ^"Prostate-Specific Antigen"]	1249
	10	("prostate specific antigen" or psa):ti,ab	6756
	11	[mh ^"Magnetic Resonance Imaging"]	6850
	12	(magnet* NEAR/2 (resonance* or imag* or scan* or spectroscop*)):ti,ab	15490
	13	(MR NEAR/2 (resonance* or imag* or scan* or spectroscop*)):ti,ab	2282
	14	("Dynamic contrast* enhanc*" NEAR/2 (MR* or magnet*)):ti,ab	0
	15	(contrast* NEAR/2 (imag* or scan*)):ti,ab	843
	16	((MRI or MRSI or MP-MR* or MPMR*) NEAR/4 prostat*):ti,ab	220
	17	"turbo spin echo*":ti,ab	85
	18	((diffusion* or weight*) NEAR/2 imag*):ti,ab	1663
	19	((DWI or DCE-MRI or T2W or TSE or "T2-weighted MRI*") NEAR/3 prostat*):ti,ab	8
	20	(Multi-parametric or multiparametric* or biparametric* or bi-parametric*):ti,ab	382
	21	[mh ^"Digital Rectal Examination"]	41
	22	("digital rectal examination" or DRE):ti,ab	592
	23	(("transrectal ultrasound*" or "trans-rectal ultrasound*" or TRUS or TRUSB) NEAR/4 prostat*):ti,ab	494
	24	[mh ^"Biomarkers"] or [mh ^"Genetic Testing"]	13557
	25	((biological or serum) NEAR/2 (marker* or biomarker*)):ti,ab	3392
	26	(urine NEXT (measur* or analy* or test* or collect*)):ti,ab	3273
	27	(urinalys* or pca3 or "pca 3" or dd3 or 4kscore or "4k score" or "prostate health index" or "four-kallikrein panel"):ti,ab	2308
	28	[mh ^"Risk assessment"] or [mh ^"Risk factors"]	29554
	29	{or #8-#28}	75919
	30	#7 and #29	53163
Combined	31	#4 and #30	4809
	32	limit #31 to Cochrane Library publication data from Jan 2014 to Dec 2019, in Cochrane Reviews limit #31 to publication year from 2014 to 2019, in Trials	6 2325

Table 32. Search strategy for the Cochrane Library databases (Searched via the Wiley Online platform; Question 4)

Term group	#	Search terms	Results
Prostate cancer terms	1	[mh "Prostatic Neoplasms"]	4984
	2	(prostat* NEAR/4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or leiomyosarcoma* or lump*)):ti,ab	11843
	3	PIN:ti,ab,kw	1076
	4	{or #1-#3}	13347
	5	("stage I" or "stage II" or "stage 1" or "stage 2" or early or local or localised or localized):ti,ab	166628

Term group	#	Search terms	Results
	6	#4 and #5	3521
Intervention terms (in NICE guidelines SLR) (Q4)	7	[mh ^"Watchful Waiting"]	275
	8	((active* or watch* or expect* or conservat*) NEXT (surveillan* or monitor* or observat* or wait* or manag*)):ti,ab	3589
	9	((deferr* or delay*) NEXT (treat* or therap*)):ti,ab	1085
	10	{or #7-#9}	4782
	11	[mh ^"prostatic neoplasm"/su]	688
	12	[mh ^Prostatectomy]	1317
	13	(radical NEAR/4 prostatectom*):ti,ab	2286
	14	{or #11-#13}	3166
	15	[mh ^Radiotherapy]	1155
	16	radiotherap*:ti,ab	21030
	17	(radiat* NEAR/4 (therap* or treatment*)):ti,ab	9747
	18	((external* or conformal*) NEAR/4 (irradiat* or therap* or treat*)):ti,ab	2353
	19	((interstitial* or intracavit* or implant* or surface* or internal*) NEAR/4 (irradiat* or radiation*)):ti,ab	433
	20	curietherap*:ti,ab	18
	21	(radioisotope* NEAR/4 (irradiat* or therap* or treat*)):ti,ab	25
	22	((seed* or permanent*) NEAR/2 implant*):ti,ab	438
	23	{or #15-#22}	29540
	24	[mh ^Brachytherapy]	669
	25	brachytherap*:ti,ab	1617
	26	(hyperfraction* or "hyper fraction*" or hypofraction* or "hypo fraction*"):ti,ab	1386
	27	((optim* or fraction* or respons* or relation* or dependence* or effect* or scheme* or curve*) NEAR/4 (dose* or dosage or schedule*)):ti,ab	48993
	28	((high* or full* or maximum* or larg* or escalat* or supplement* or low* or minimum* or small*) NEAR/4 (dose* or dosage* or schedule*)):ti,ab	86887
	29	(HDR or LDR):ti,ab	423
	30	{or #24-#29}	117871
	31	#23 and #30	6067
	32	#10 or #14 or #31	13669
Intervention terms (not in NICE guidelines SLR) (Q4)	33	[mh ^"High-Intensity Focused Ultrasound Ablation"] or [mh ^"Ultrasound, High-Intensity Focused, Transrectal"]	65
	34	((ultrasonograp* or ultrasound) NEAR/2 ("high intensity")):ti,ab	184
	35	HIFU:ti,ab	162
	36	[mh ^"Catheter Ablation"]	1387
	37	("ablati* therapy"):ti,ab	1
	38	("radiofrequency ablation*" or "radio frequency ablation*" or "catheter ablation*" or rfta or RFA):ti,ab	3007
	39	(thermoablation* or "thermo ablation" or "thermo destruc*" or "thermal destruc*" or "thermo coag*" or "thermal coag*" or electrocoag* or "transvenous ablation*"):ti,ab	270
	40	[mh ^"Antineoplastic agents"] or [mh ^"Androgen antagonists"]	7271

Term group	#	Search terms	Results
Combined	41	antiandrogen*:ti,ab	796
	42	((androgen* or hormon*) NEAR/3 (ablat* or block* or withdraw* or depriv* or suppress*)):ti,ab	2902
	43	("gonadotrophin releasing hormone analogue*" or GRHA or "luteini*ing hormone-releasing hormone" or LHRH):ti,ab	886
	44	[mh ^Goserelin] or [mh ^Cyproterone] or [mh ^Estrogens] or [mh ^Leuprolide] or [mh ^Flutamide] or [mh ^Diethylstilbestrol] or [mh ^Progestins] or [mh ^Finasteride]	3703
	45	(Goserelin or Cyproterone or Leuprolide or Leuprorelin or Flutamide or Diethylstilbestrol or Progestin* or Gestagen or Finasteride or bicalutamide or oestrogen* or estrogen* or leuprorelin or enantone or "a-43818" or lupron or "tap-144" or niftolid* or zoladex or eulexin or casodex or nilutamide or nilandrone or megestrol or proscar):ti,ab	15384
	46	{or #33-#45}	29332
	47	#6 and #32 with Cochrane Library publication date Between Jan 2018 and Dec 2019, in Cochrane Reviews	3
	48	#6 and #32 with Publication Year from 2018 to 2019, in Trials	161
	49	#6 and #46 with Cochrane Library publication date Between Jan 2014 and Dec 2019, in Cochrane Reviews	3
	50	#6 and #46 with Publication Year from 2014 to 2019, in Trials	458
Total	51	#47 or #48 or #49 or #50 in Cochrane Reviews, Trials	579

Table 33. Search strategy for Database of Abstracts of Reviews of Effects (Searched via the Centre for Reviews and Dissemination website; Questions 1–4)

Term group	#	Search terms	Results
Prostate cancer terms	1	MeSH DESCRIPTOR Prostatic Neoplasms EXPLODE ALL TREES	709
	2	((prostat* NEAR4 (neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump*)) or ((neoplas* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metasta* or angiosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcino* or leiomyosarcoma* or lump*) NEAR4 prostat*))	909
	3	(PIN)	32
	4	(#1 or #2 or #3) IN DARE FROM 2014 TO 2019	103

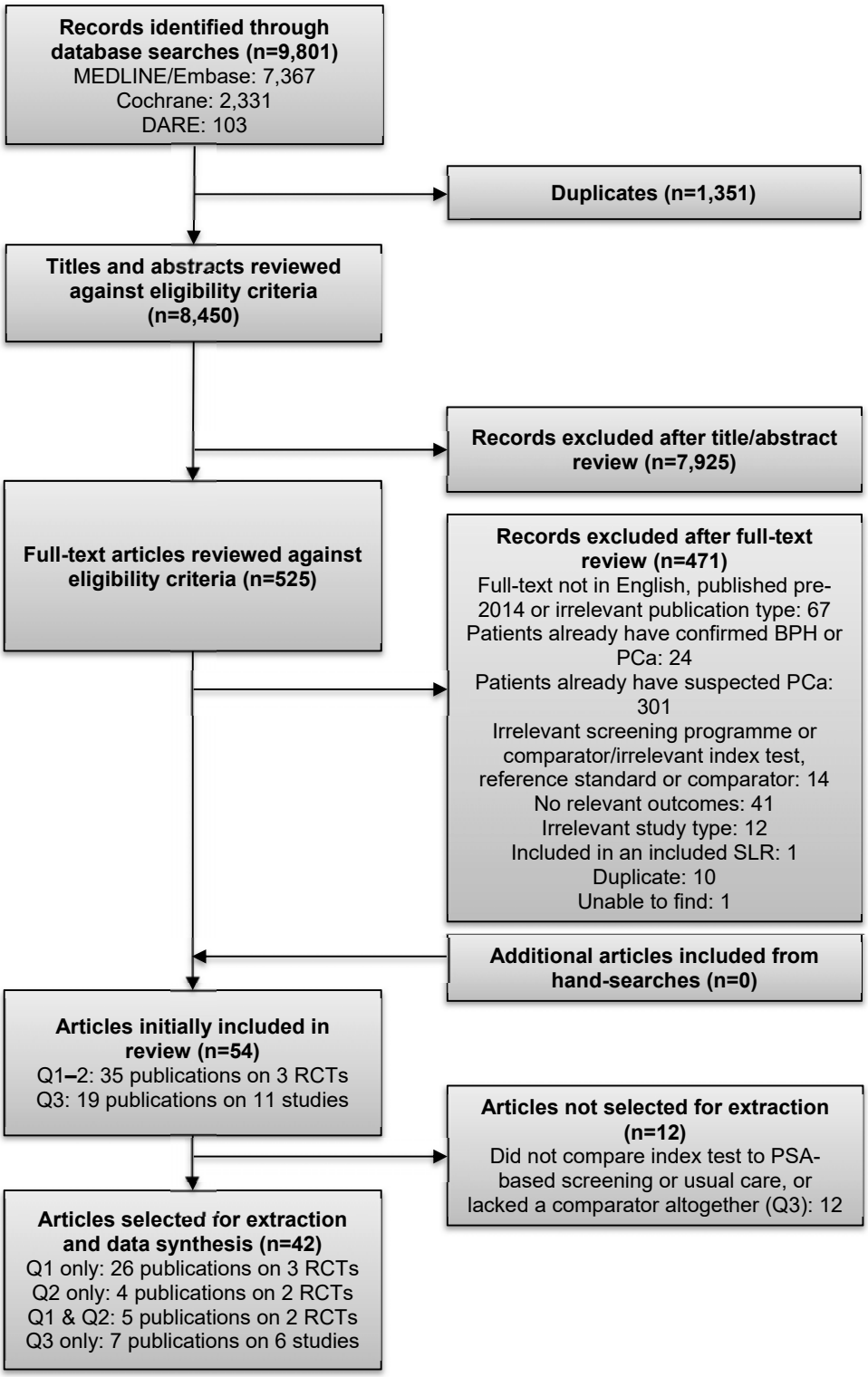
Results were imported into EndNote and de-duplicated.

Appendix 2 — Included and excluded studies

PRISMA flowcharts

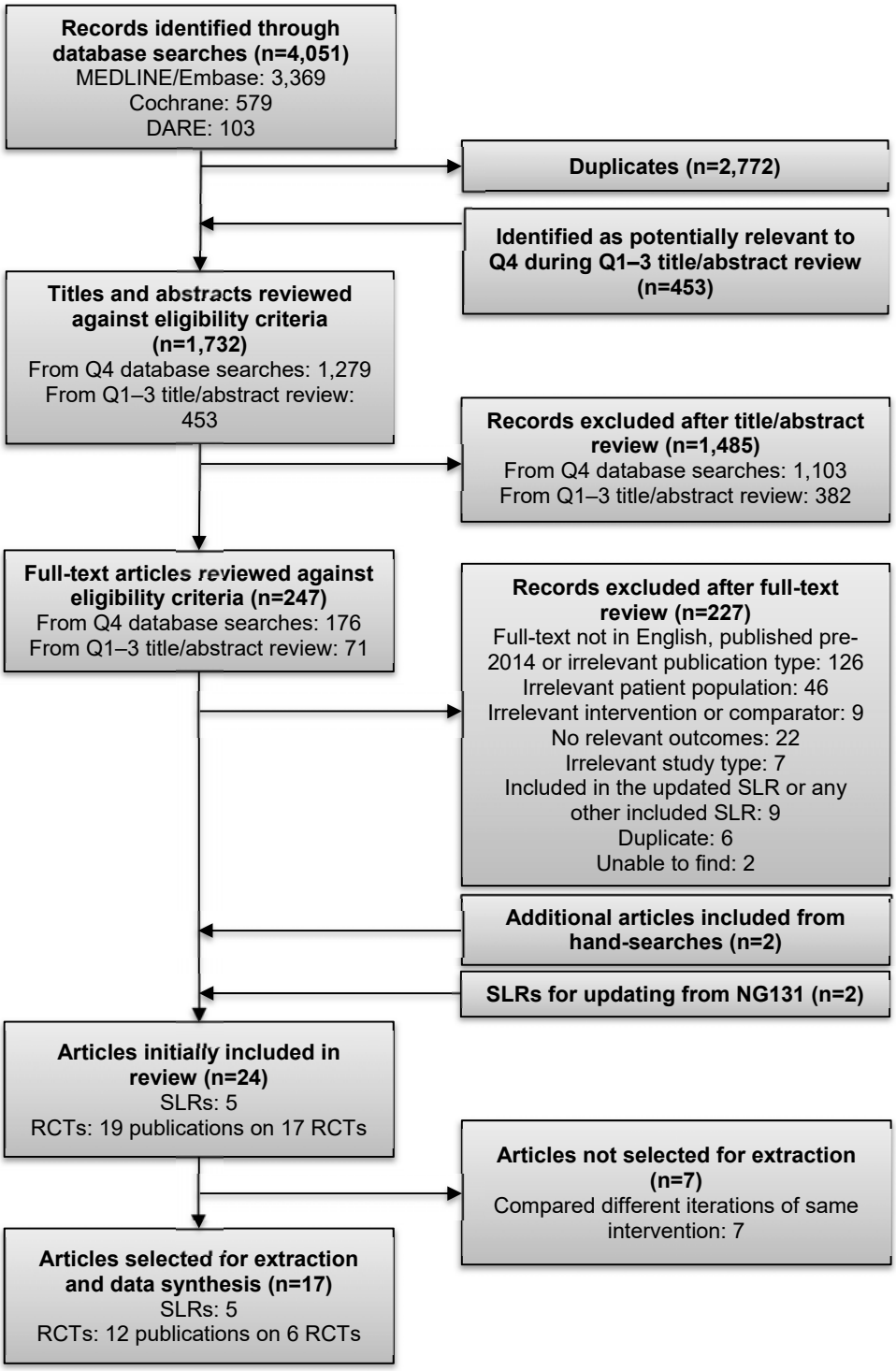
Figure 2 and Figure 3 summarise the volume of publications included and excluded at each stage of the review for questions 1–3 and question 4, respectively. For questions 1–3, a total of 54 publications were ultimately judged to be relevant to one or more review questions and were considered for extraction, 42 of which were ultimately extracted and synthesised. For question 4, a total of 24 publications were ultimately judged to be relevant to the review question and were considered for extraction, 17 of which were ultimately extracted and synthesised. Publications that were included or excluded after the review of full-text articles are detailed below.

Figure 2. Summary of publications included and excluded at each stage of the review (questions 1–3)



Abbreviations: BPH, benign prostatic hyperplasia; DARE, Database of Abstracts of Reviews of Effects; PCa, prostate cancer; PSA, prostate-specific antigen; Q1/2/3, questions 1/2/3; RCT, randomised controlled trial; SLR, systematic literature review.

Figure 3. Summary of publications included and excluded at each stage of the review (question 4)



Abbreviations: DARE, Database of Abstracts of Reviews of Effects; NG131, National Institute for Health and Care Excellence (NICE) guidance document 131; Q1/2/3/4, questions 1/2/3/4; RCT, randomised controlled trial; SLR, systematic literature review.

Publications included after review of full-text articles

The 54 publications included after review of full-texts for questions 1–3 are summarised in Table 34 and the 24 publications included after review of full-texts for question 4 are summarised in Table 35 below. Studies were prioritised for extraction and data synthesis. The following criteria were applied after assessing the overall volume of evidence identified in the review:

1. For questions 1 and 2, all included studies were extracted.
2. For question 3, an included study was extracted if it compared a relevant index test to PSA-based screening alone or usual care, whereas studies with no comparator or another comparator (e.g. a study comparing 2 nomograms) were deprioritised and not extracted.
3. For question 4, an included study was extracted if it compared one relevant intervention to a different relevant intervention or to 'no treatment', whereas studies that compared different iterations of the same intervention (e.g. different drugs to achieve androgen deprivation or different approaches to performing prostatectomy) were deprioritised and not extracted.

Publications not selected for extraction and data synthesis are clearly detailed in Table 34 and Table 35 below.

Table 34. Summary of publications included after review of full-text articles for questions 1–3

Study	Question	Intervention (Q1–2), index test (Q3) or reason for deprioritisation	Study name
STUDIES SELECTED FOR EXTRACTION			
Schroder 2014[70]	Q1	PSA-based screening vs usual care	ERSPC
Buzzoni 2015[126]	Q1	PSA-based screening vs usual care	ERSPC
Carlsson 2019[127]	Q1	PSA-based screening vs usual care	ERSPC
Hakama 2017[128]	Q1	PSA-based screening vs usual care	ERSPC
Walter 2017[129]	Q1	PSA-based screening vs usual care	ERSPC
Hugosson 2018	Q1	PSA-based screening vs usual care	ERSPC
Bokhorst 2014[11]	Q1	PSA-based screening vs usual care	ERSPC
Bokhorst 2015[132]	Q1	PSA-based screening vs usual care	ERSPC
Neupane 2018[133]	Q1	PSA-based screening vs usual care	ERSPC
Kilpelainen 2015[134]	Q1	PSA-based screening vs usual care	ERSPC
Kilpelainen 2017[14]	Q1	PSA-based screening vs usual care	ERSPC
Lindberg 2019[136]	Q1	PSA-based screening vs usual care	ERSPC
Pakarainen 2016[137]	Q1	PSA-based screening vs usual care	ERSPC
Pakarainen 2019[138]	Q1	PSA-based screening vs usual care	ERSPC
Luján 2015	Q1	PSA-based screening vs usual care	ERSPC
Luján 2014[140]	Q1	PSA-based screening vs usual care	ERSPC
Pinsky 2019[13]	Q1	PSA-based screening vs usual care	PLCO
Pinsky 2019	Q1	PSA-based screening vs usual care	PLCO
Pinsky 2019[142]	Q1	PSA-based screening vs usual care	PLCO

Study	Question	Intervention (Q1–2), index test (Q3) or reason for deprioritisation	Study name
Pinsky 2017[143]	Q1	PSA-based screening vs usual care	PLCO
Lewicki 2017[144]	Q1	PSA-based screening vs usual care	PLCO
Shoag 2016[145]	Q1	PSA-based screening vs usual care	PLCO
Prorok 2018[18]	Q1	PSA-based screening vs usual care	PLCO
Kelly 2017[146]	Q1	PSA-based screening vs usual care	PLCO
Martin 2018	Q1	PSA-based screening vs usual care	CAP
Tsodikov 2017[147]	Q1	PSA-based screening vs usual care	ERSPC and PLCO
Chiu 2017	Q2	PSA-based screening vs usual care	ERSPC
Pashayan 2015[19]	Q2	PSA-based screening vs usual care	ERSPC
Booth 2014[22]	Q2	PSA-based screening vs usual care	ERSPC
Miller 2018[17]	Q2	PSA-based screening vs usual care	PLCO
Auvinen 2016[125]	Q1 & Q2	PSA-based screening vs usual care	ERSPC
Hugosson 2019	Q1 & Q2	PSA-based screening vs usual care	ERSPC
Arnsrud Godtman 2015[130]	Q1 & Q2	PSA-based screening vs usual care	ERSPC
Kilpelainen 2016	Q1 & Q2	PSA-based screening vs usual care	ERSPC
Pinsky 2014[20]	Q1 & Q2	PSA-based screening vs usual care	PLCO
Grenabo Bergdahl 2016[24]	Q3	PSA with MRI	Göteborg
Halpern 2017[157]	Q3	DRE	PLCO
Rubio-Briones 2014[25]	Q3	PSA with DRE and PCA3	NR
Ankerst 2016[158]	Q3	Percent-free PSA	SABOR
Gronberg 2015	Q3	STHLM3 predictive model	STHLM3
Strom 2018[27]	Q3	STHLM3 predictive model	STHLM3
Nam 2016[26]	Q3	MRI	NR
STUDIES NOT SELECTED FOR EXTRACTION			
Ankerst 2014[159]	Q3	Does not compare index test to PSA-based screening	PBCG, SABOR and EDRN
Ankerst 2019[160]	Q3	Does not compare index test to PSA-based screening	Michigan cohort with PCPTRC
Ankerst 2014[161]	Q3	Does not compare index test to PSA-based screening	Prostate Biopsy Collaborative Group
Ankerst 2018[162]	Q3	Does not compare index test to PSA-based screening	European and North American cohorts
Kim 2017[163]	Q3	Does not compare index test to PSA-based screening	PLCO
Shoaibi 2017[164]	Q3	Does not compare index test to PSA-based screening	PLCO
Roobol 2017[165]	Q3	Does not compare index test to PSA-based screening	ERSPC, RC3
Vedder 2014[166]	Q3	Does not compare index test to PSA-based screening	ERSPC, RC3
Verbeek 2019[167]	Q3	Does not compare index test to PSA-based screening	ERSPC, RC3
Verbeek 2019[168]	Q3	Does not compare index test to PSA-based screening	ERSPC, RC3

Study	Question	Intervention (Q1–2), index test (Q3) or reason for deprioritisation	Study name
van der Leest 2019[169]	Q3	Does not compare index test to PSA-based screening	NR
Nieboer 2015[204]	Q3	Does not compare index test to PSA-based screening	NR

CAP, Cluster Randomized Trial of PSA Testing for Prostate Cancer; EDRN, Early Detection Research Network; ERSPC, European Randomised study of Screening for Prostate Cancer; NR, not reported; PBCG, Prostate Biopsy Collaborative Group; PCPTRC, Prostate Cancer Prevention Trial Risk Calculator; PLCO, Prostate, Lung, Colorectal and Ovarian (Cancer Screening Trial); RC3, risk calculator 3; SABOR, San Antonio Biomarkers Of Risk; STHLM3, Stockholm-3.

Table 35. Summary of publications included after review of full-text articles for question 4

Study	Question	Treatment comparison or reason for deprioritisation	Study name
STUDIES SELECTED FOR EXTRACTION			
NG131 [C] 2019[113]	Q4	Hypofractionated RT vs conventional RT	NA (SLR)
NG131 [G] 2019[160]	Q4	Active surveillance vs RT vs radical prostatectomy	NA (SLR)
Ng 2019[185]	Q4	Prostatectomy and/or RT vs watchful waiting/observation/active monitoring	NA (SLR)
Yin 2019[205]	Q4	Moderate hypofractionated RT vs conventional fractionated RT	NA (SLR)
Chin 2017[186]	Q4	Dose-escalated EBRT vs standard brachytherapy	NA (SLR)
Bill-Axelson 2018[166]	Q4	Radical prostatectomy vs watchful waiting	SPCG-4
Lane 2016[193]	Q4	Active monitoring vs surgery vs RT	ProtecT
Lane 2014[206]	Q4	Active monitoring vs surgery vs RT	ProtecT
Royce 2017[191]	Q4	RT + full ADT (leuprolide/goserelin and flutamide) vs RT + partial ADT vs RT + no ADT	NR (NCT00116220)
Sanford 2017[190]	Q4	RT + full ADT (leuprolide/goserelin and flutamide) vs RT + partial ADT vs RT + no ADT	NR (NCT00116220)
McPartlin 2016[189]	Q4	Bicalutamide + dose-escalated EBRT vs dose-escalated EBRT alone	PMH 9907
Bolla 2016[188]	Q4	Androgen suppresion + RT vs RT alone	EORTC 22991
Hackman 2019[112]	Q4	Radical prostatectomy + adjuvant RT vs radical prostatectomy alone	FinnProstate and Finnish Radiation Oncology Groups (NCT02668718)
Voog 2016[176]	Q4	RT + hormone therapy vs RT alone	RTOG 9408
Lennernas 2014[207]	Q4	HDR brachytherapy + RT vs open surgery	NR
Hoffman 2018[208]	Q4	Conventionally fractionated IMRT vs dose-escalated hypofractionated IMRT	NR
Johansson 2018[209]	Q4	Radical prostatectomy (with or without ADT) vs watchful waiting (with or without ADT)	NR
STUDIES NOT SELECTED FOR EXTRACTION			

Study	Question	Treatment comparison or reason for deprioritisation	Study name
Michalski 2018[195]	Q4	Compares different iterations of same intervention	RTOG 0126
Morton 2017[196]	Q4	Compares different iterations of same intervention	NR
Bratt 2019[197]	Q4	Compares different iterations of same intervention	SAMS
Asimakopoulos 2019[198]	Q4	Compares different iterations of same intervention	NR
Yaxley 2016[199]	Q4	Compares different iterations of same intervention	NR
Gaudet 2016[200]	Q4	Compares different iterations of same intervention	NR
Zapatero 2015[201]	Q4	Compares different iterations of same intervention	AADLPC

AADLPC, Adjuvant Androgen Deprivation in Localized Prostate Cancer; ADT, androgen deprivation therapy; EBRT, external beam radiation therapy; EORTC, European Organisation for Research and Treatment of Cancer; HDR, high dose-rate; IMRT, intensity-modulated radiation therapy; NA, not applicable; NR, not reported; PMH, Princess Margaret Hospital; ProtecT, Prostate Testing for Cancer and Treatment; RT, radiotherapy; RTOG, radiation therapy oncology group; SAMS, Study of Active Monitoring in Sweden; SLR, systematic literature review; SPCG-4, Scandinavian Prostate Cancer Group Study Number 4.

Table 36. Unavailable publications not reviewed for eligibility at full-text stage

Question(s)	Reference
1–3	Pabame HK, Simo RT, Kamdje AHN, et al. Interests in the use of rapid prostate antigen screening test in the North-Cameroon. Journal of Analytical Oncology 2018;7:43-46.
4	Isrctn. Partial prostate Ablation versus Radical prosTatectomy. Http://www.who.int/trialsearch/trial2.aspx? Trialid=isrctn99760303 2014.
4	Jprn U. Study of the usefulness of neoadjuvant chemo-hormone therapy for high-risk prostate cancer. Http://www.who.int/trialsearch/trial2.aspx? Trialid=jprn-umin000030346 2017.

Publications excluded after review of full-text articles

Of the 772 publications included after the review of titles and abstracts (525 for questions 1–3 and 247 for question 4), 16 were found to be duplicates at the full-text review stage (10 for questions 1–3 and 6 for question 4), while 3 full-texts could not be found (1 for questions 1–3 and 2 for question 4; see Table 36 above). Of the remaining 753 publications, 679 were ultimately judged not to be relevant to this review (460 for questions 1–3 and 219 for question 4). These publications, along with reasons for exclusion, are listed in Table 37 and Table 38 below.

Table 37. Publications excluded after review of full-text articles for questions 1–3

Reference	Reason for exclusion
Abd-Alazeez M, Ahmed HU, Arya M, et al. Can multiparametric magnetic resonance imaging predict upgrading of transrectal ultrasound biopsy results at more definitive histology? Urologic Oncology: Seminars and Original Investigations 2014;32:741-747.	Patients already have suspected PCa
Abraham NE, Mendhiratta N, Taneja SS. Patterns of repeat prostate biopsy in contemporary clinical practice. Journal of Urology 2015;193:1178-1184.	Patients already have suspected PCa
Adhyatma KP, Warli SM. Diagnostic value of platelet-to-lymphocyte ratio in prostate cancer. Open Access Macedonian Journal of Medical Sciences 2019;7:1093-1096.	Patients already have suspected PCa
Adhyatma KP, Prapiska FF, Siregar GP, et al. Systemic inflammatory response in predicting prostate cancer: The diagnostic value of neutrophil-To-Lymphocyte Ratio. Open Access Macedonian Journal of Medical Sciences 2019;7:1628-1630.	Patients already have suspected PCa
Akizhanova M, Iskakova EE, Kim V, et al. PSA and Prostate Health Index based prostate cancer screening in a hereditary migration complicated population: Implications in precision diagnosis. Journal of Cancer 2017;8:1223-1228.	Patients already have suspected PCa
Alberts AR, Roobol MJ, Verbeek JFM, et al. Prediction of High-grade Prostate Cancer Following Multiparametric Magnetic Resonance Imaging: Improving the Rotterdam European Randomized Study of Screening for Prostate Cancer Risk Calculators. European Urology 2019;75:310-318.	Patients already have suspected PCa
Alberts AR, Schoots IG, Bokhorst LP, et al. Characteristics of Prostate Cancer Found at Fifth Screening in the European Randomized Study of Screening for Prostate Cancer Rotterdam: Can We Selectively Detect High-grade Prostate Cancer with Upfront Multivariable Risk Stratification and Magnetic Resonance Imaging? European Urology 2018;73:353-360.	Irrelevant screening programme or comparator/irrelevant index test, reference standard or comparator
Alberts AR, Schoots IG, Bokhorst LP, et al. Risk-based Patient Selection for Magnetic Resonance Imaging-targeted Prostate Biopsy after Negative Transrectal Ultrasound-guided Random Biopsy Avoids Unnecessary Magnetic Resonance Imaging Scans. European Urology 2016;69:1129-1134.	Patients already have suspected PCa
Aliukonis P, Letauta T, Briediene R, et al. The role of different PI-RADS versions in prostate multiparametric magnetic resonance tomography assessment. Acta Medica Lituanica 2017;24:44-50.	Patients already have suspected PCa
Amini E, Pishgar F, Ayati M, et al. Transition Zone Prostate-specific Antigen Density Could Better Guide the Rebiopsy Strategy in Men With Prostate Inflammation at Initial Biopsy. Urology 2015;86:985-90.	Patients already have suspected PCa
Aminsharifi A, Howard L, Wu Y, et al. Prostate Specific Antigen Density as a Predictor of Clinically Significant Prostate Cancer When the Prostate Specific Antigen is in the Diagnostic Gray Zone: Defining the Optimum Cutoff Point Stratified by Race and Body Mass Index. Journal of Urology 2018;200:758-766.	Patients already have suspected PCa
An JY, Sidana A, Holzman SA, et al. Ruling out clinically significant prostate cancer with negative multi-parametric MRI. International Urology and Nephrology 2018;50:7-12.	Patients already have suspected PCa
Anastasiadis E, Charman SC, Arumainayagam N, et al. What Burden of Prostate Cancer Can Radiologists Rule Out on Multiparametric Magnetic Resonance Imaging? A Sensitivity Analysis Based on Varying the Target Condition in Template Prostate Mapping Biopsies. Urology 2015;86:544-551.	Patients already have suspected PCa
Anonymous. Correction: Absolute Effect of Prostate Cancer Screening: Balance of Benefits and Harms by Center within the European Randomized Study of Prostate Cancer Screening. Clinical Cancer Research 2016;22:3702.	Full-text not in English, published pre-2014 or irrelevant publication type
Anonymous. Erratum: Absolute Effect of Prostate Cancer Screening: Balance of Benefits and Harms by Center within the European Randomized Study of Prostate Cancer Screening (Clinical Cancer Research (2016) 22 (243-249)). Clinical Cancer Research 2016;22:3702.	Full-text not in English, published pre-2014 or irrelevant publication type
Anonymous. Correction: Screening for prostate cancer: Is the third trial the charm? (JAMA - Journal of the American Medical Association (2018) 319:9 (868-869) DOI: 10.1001/jama.2018.0153). JAMA - Journal of the American Medical Association 2018;319:1510.	Full-text not in English, published pre-2014 or irrelevant publication type
Auffenberg GB, Merdan S, Miller DC, et al. Evaluation of Prostate Cancer Risk Calculators for Shared Decision Making Across Diverse Urology Practices in Michigan. Urology 2017;104:137-142.	Patients already have suspected PCa

Reference	Reason for exclusion
Auvinen A, Rannikko A, Taari K, et al. A randomized trial of early detection of clinically significant prostate cancer (ProScreen): study design and rationale. European journal of epidemiology 2017;32:521-527.	Full-text not in English, published pre-2014 or irrelevant publication type
Baldisserotto M, Neto EJD, Carvalhal G, et al. Validation of PI-RADS v.2 for prostate cancer diagnosis with MRI at 3T using an external phased-array coil. Journal of Magnetic Resonance Imaging 2016;44:1354-1359.	Patients already have suspected PCa
Baur ADJ, Daqqaq T, Wagner M, et al. T2- and diffusion-weighted magnetic resonance imaging at 3 T for the detection of prostate cancer with and without endorectal coil: An intraindividual comparison of image quality and diagnostic performance. European Journal of Radiology 2016;85:1075-1084.	Patients already have suspected PCa
Baur ADJ, Maxeiner A, Franiel T, et al. Evaluation of the prostate imaging reporting and data system for the detection of prostate cancer by the results of targeted biopsy of the prostate. Investigative Radiology 2014;49:411-420.	Patients already have suspected PCa
Baur ADJ, Schwabe J, Rogasch J, et al. A direct comparison of contrast-enhanced ultrasound and dynamic contrast-enhanced magnetic resonance imaging for prostate cancer detection and prediction of aggressiveness. European Radiology 2018;28:1949-1960.	Patients already have suspected PCa
Becker AS, Cornelius A, Reiner CS, et al. Direct comparison of PI-RADS version 2 and version 1 regarding interreader agreement and diagnostic accuracy for the detection of clinically significant prostate cancer. European Journal of Radiology 2017;94:58-63.	Patients already have suspected PCa
Bergdahl AG, Wilderang U, Aus G, et al. Corrigendum re: "Role of Magnetic Resonance Imaging in Prostate Cancer Screening: a Pilot Study Within the Goteborg Randomised Screening Trial". European urology 2016;(no pagination).	Full-text not in English, published pre-2014 or irrelevant publication type
Bergdahl AG, Wilderang U, Aus G, et al. Corrigendum re: "Role of Magnetic Resonance Imaging in Prostate Cancer Screening: A Pilot Study Within the Goteborg Randomised Screening Trial" (Eur Urol (2016) 70 (566-573) (S0302283815012142) (10.1016/j.eururo.2015.12.006)). European Urology 2017;71:e81.	Full-text not in English, published pre-2014 or irrelevant publication type
Bermejo P, Vivo A, Tarraga PJ, et al. Development of interpretable predictive models for BPH and prostate cancer. Clinical Medicine Insights: Oncology 2015;9:15-24.	Patients already have suspected PCa
Bhakdi SC, Suriyaphol P, Thaicharoen P, et al. Accuracy of tumour-associated circulating endothelial cells as a screening biomarker for clinically significant prostate cancer. Cancers 2019;11 (8) (no pagination).	Patients already have suspected PCa
Bhat NR, Vetter JM, Andriole GL, et al. Magnetic Resonance Imaging-Defined Prostate-Specific Antigen Density Significantly Improves the Risk Prediction for Clinically Significant Prostate Cancer on Biopsy. Urology 2019;126:152-157.	Patients already have suspected PCa
Bhindi B, Jiang H, Poyet C, et al. Creation and internal validation of a biopsy avoidance prediction tool to aid in the choice of diagnostic approach in patients with prostate cancer suspicion. Urologic Oncology: Seminars and Original Investigations 2017;35:604.e17-604.e24.	Patients already have suspected PCa
Blomqvist L, Carlsson S, Gjertsson P, et al. Limited evidence for the use of imaging to detect prostate cancer: a systematic review. European Journal of Radiology 2014;83:1601-1606.	Full-text not in English, published pre-2014 or irrelevant publication type
Boegemann M, Stephan C, Cammann H, et al. The percentage of prostate-specific antigen (PSA) isoform [-2]proPSA and the Prostate Health Index improve the diagnostic accuracy for clinically relevant prostate cancer at initial and repeat biopsy compared with total PSA and percentage free PSA in men aged <=65 years. BJU International 2016;117:72-79.	Patients already have suspected PCa
Bokhorst LP, Kranse R, Venderbos LDF, et al. Differences in Treatment and Outcome after Treatment with Curative Intent in the Screening and Control Arms of the ERSPC Rotterdam. European urology 2015;68:179-182.	No relevant outcomes
Bokhorst LP, Zappa M, Carlsson SV, et al. Correlation between stage shift and differences in mortality in the European Randomised study of Screening for Prostate Cancer (ERSPC). BJU International 2016;118:677-680.	Patients already have confirmed BPH or PCa
Boniol M, Autier P, Perrin P, et al. Variation of Prostate-specific Antigen Value in Men and Risk of High-grade Prostate Cancer: Analysis of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Study. Urology 2015;85:1117-1122.	Irrelevant screening programme or comparator/irrelevant index test, reference standard or comparator
Bonn SE, Sjolander A, Tillander A, et al. Body mass index in relation to serum prostate-specific antigen levels and prostate cancer risk. International Journal of Cancer 2016;139:50-57.	Patients already have suspected PCa
Borque-Fernando A, Esteban-Escano LM, Rubio-Briones J, et al. A Preliminary Study of the Ability of the 4Kscore test, the Prostate Cancer Prevention Trial-Risk Calculator and the	Patients already have suspected PCa

Reference	Reason for exclusion
European Research Screening Prostate-Risk Calculator for Predicting High-Grade Prostate Cancer. Actas urologicas espanolas 2016;40:155-163.	
Boyle P, Koechlin A, Bota M, et al. Endogenous and exogenous testosterone and the risk of prostate cancer and increased prostate-specific antigen (PSA) level: a meta-analysis. BJU International 2016;118:731-741.	Full-text not in English, published pre-2014 or irrelevant publication type
Breza J, Subin F, Bernadic M, et al. The use of European Randomized study of Screening for Prostate Cancer calculator as a diagnostic tool for prostate biopsy indication. Bratislavske lekarske listy 2019;120:331-335.	Patients already have suspected PCa
Brikun I, Nusskern D, Freije D. An expanded biomarker panel for the detection of prostate cancer from urine DNA. Experimental Hematology and Oncology 2019;8 (1) (no pagination).	Patients already have suspected PCa
Brikun I, Nusskern D, Decatus A, et al. A panel of DNA methylation markers for the detection of prostate cancer from FV and DRE urine DNA. Clinical Epigenetics 2018;10 (1) (no pagination).	Patients already have suspected PCa
Brock M, Loppenberg B, Roghmann F, et al. Impact of real-time elastography on magnetic resonance imaging/ultrasound fusion guided biopsy in patients with prior negative prostate biopsies. Journal of Urology 2015;193:1191-1197.	Patients already have suspected PCa
Brooks MA, Carlsson SV, Zajichek A, et al. Development of prostate-specific antigen (PSA) screening nomograms for 15-year prediction of prostate cancer diagnosis (PCDx), mortality (PCM), and all-cause mortality (ACM). Journal of clinical oncology 2018;36.	Full-text not in English, published pre-2014 or irrelevant publication type
Caglayan V, Onen E, Avci S, et al. Lymphocyte-to-monocyte ratio is a valuable marker to predict prostate cancer in patients with prostate specific antigen between 4 and 10 ng/dl. Archivio Italiano di Urologia e Andrologia 2018;90:270-275.	Patients already have suspected PCa
Cai Q, Wang Z, Zhang W, et al. Association between glutathione S-transferases M1 and T1 gene polymorphisms and prostate cancer risk: a systematic review and meta-analysis. Tumor Biology 2014;35:247-256.	Full-text not in English, published pre-2014 or irrelevant publication type
Calio B, Sidana A, Sugano D, et al. Changes in prostate cancer detection rate of MRI-TRUS fusion vs systematic biopsy over time: Evidence of a learning curve. Prostate Cancer and Prostatic Diseases 2017;20:436-441.	Patients already have suspected PCa
Caliskan S. Diagnostic efficacy of free prostate-specific antigen/total prostate-specific antigen ratio for the diagnosis of prostate cancer in low concentration (<=4 ng/ml) and intermediate levels of total prostate-specific antigen (4.01-10.0 ng/ml). Journal of Cancer Research and Therapeutics 2017;13:279-283.	Patients already have suspected PCa
Caliskan S, Sungur M. The clinical importance of percentage free prostate-specific antigen (PSA) in the PSA level of 4-20 ng/ml. Kuwait Medical Journal 2018;50:316-319.	Patients already have suspected PCa
Campi R, Brookman-May SD, Subiela Henriquez JD, et al. Impact of Metabolic Diseases, Drugs, and Dietary Factors on Prostate Cancer Risk, Recurrence, and Survival: A Systematic Review by the European Association of Urology Section of Oncological Urology. European Urology Focus. 2018.	No relevant outcomes
Canat L, Atalay HA, Can O, et al. Serum procalcitonin levels in prostate cancer: A new biomarker? Urologia Journal 2018;85:46-50.	Patients already have suspected PCa
Carlsson S, Arnsrud Godtman R, Holmberg E, et al. At what age should a PSA-based screening program start? 20-year results from the Göteborg randomized population-based prostate cancer screening study. European urology, supplements 2017;16:e406-e408.	Full-text not in English, published pre-2014 or irrelevant publication type
Carlsson S, Assel M, Sjoberg D, et al. Influence of blood prostate specific antigen levels at age 60 on benefits and harms of prostate cancer screening: Population based cohort study. BMJ (Online) 2014;348 (no pagination).	Irrelevant study type
Carlsson S, Assel M, Ulmert D, et al. Screening for Prostate Cancer Starting at Age 50-54 Years. A Population-based Cohort Study. European urology 2017;71:46-52.	Irrelevant study type
Castro HAS, Iared W, Santos JEM, et al. Impact of PSA density of transition zone as a potential parameter in reducing the number of unnecessary prostate biopsies in patients with psa levels between 2.6 and 10.0 ng/mL. International braz j urol : official journal of the Brazilian Society of Urology 2018;44:709-716.	Patients already have suspected PCa
Ceylan C, Doluoglu OG, Yahsi S. A different perspective: Can urine pH be important in the diagnosis of prostate cancer? Urologia Journal. 2019.	Patients already have suspected PCa
Chamie K, Sonn GA, Finley DS, et al. The role of magnetic resonance imaging in delineating clinically significant prostate cancer. Urology 2014;83:369-375.	Patients already have confirmed BPH or PCa
Chang Y, Chen R, Yang Q, et al. Peripheral zone volume ratio (PZ-ratio) is relevant with biopsy results and can increase the accuracy of current diagnostic modality. Oncotarget 2017;8:34836-34843.	Patients already have suspected PCa

Reference	Reason for exclusion
Chen R, Huang Y, Cai X, et al. Age-specific cutoff value for the application of percent free prostate-specific antigen (PSA) in Chinese men with serum PSA levels of 4.0-10.0 ng/ml. PLoS ONE 2015;10 (6) (no pagination).	Patients already have suspected PCa
Chen R, Xie L, Cai X, et al. Percent free prostate-specific antigen for prostate cancer diagnosis in Chinese men with a PSA of 4.0e10.0 ng/mL: Results from the Chinese Prostate Cancer Consortium. Asian Journal of Urology 2015;2:107-113.	Patients already have suspected PCa
Chen R, Xie L, Xue W, et al. Development and external multicenter validation of Chinese Prostate Cancer Consortium prostate cancer risk calculator for initial prostate biopsy. Urologic Oncology: Seminars and Original Investigations 2016;34:416.e1-416.e7.	Patients already have suspected PCa
Chen R, Zhou LQ, Cai XB, et al. Percent free prostate-specific antigen is effective to predict prostate biopsy outcome in Chinese men with prostate-specific antigen between 10.1 and 20.0 ng ml(-1). Asian Journal of Andrology 2015;17:1017-21.	Patients already have suspected PCa
Chen T, Li M, Gu Y, et al. Prostate Cancer Differentiation and Aggressiveness: Assessment With a Radiomic-Based Model vs. PI-RADS v2. Journal of Magnetic Resonance Imaging 2019;49:875-884.	Patients already have suspected PCa
Cheng YT, Chiang CH, Pu YS, et al. The application of p2PSA% and prostate health index in prostate cancer detection: A prospective cohort in a Tertiary Medical Center. Journal of the Formosan Medical Association 2019;118:260-267.	Patients already have suspected PCa
Chevli KK, Duff M, Walter P, et al. Urinary PCA3 as a predictor of prostate cancer in a cohort of 3,073 men undergoing initial prostate biopsy. Journal of Urology 2014;191:1743-1748.	Patients already have suspected PCa
Chiu PKF, Roobol MJ, Teoh JY, et al. Prostate health index (PHI) and prostate-specific antigen (PSA) predictive models for prostate cancer in the Chinese population and the role of digital rectal examination-estimated prostate volume. International Urology and Nephrology 2016;48:1631-1637.	Patients already have suspected PCa
Chiu PK, Ng CF, Semjonow A, et al. A Multicentre Evaluation of the Role of the Prostate Health Index (PHI) in Regions with Differing Prevalence of Prostate Cancer: Adjustment of PHI Reference Ranges is Needed for European and Asian Settings. European Urology 2019;75:558-561.	Patients already have suspected PCa
Chiu PK, Roobol MJ, Nieboer D, et al. Adaptation and external validation of the European randomised study of screening for prostate cancer risk calculator for the Chinese population. Prostate cancer and prostatic diseases 2016;(no pagination).	Patients already have suspected PCa
Chiu PK, Teoh JY, Chan SY, et al. Role of PSA density in diagnosis of prostate cancer in obese men. International Urology & Nephrology 2014;46:2251-4.	Patients already have suspected PCa
Chiu PK, Teoh JY, Lee WM, et al. Extended use of Prostate Health Index and percentage of [-2]pro-prostate-specific antigen in Chinese men with prostate specific antigen 10-20 ng/mL and normal digital rectal examination. Investigative And Clinical Urology 2016;57:336-42.	Patients already have suspected PCa
Chua ME, Tanseco PP, Mendoza JS, et al. Configuration and validation of a novel prostate disease nomogram predicting prostate biopsy outcome: A prospective study correlating clinical indicators among Filipino adult males with elevated PSA level. Asian Journal of Urology 2015;2:114-122.	Patients already have suspected PCa
Cicione A, Cormio L, Cantiello F, et al. Presence and severity of lower urinary tract symptoms are inversely correlated with the risk of prostate cancer on prostate biopsy. Minerva Urologica e Nefrologica 2017;69:486-492.	Patients already have suspected PCa
Creed J, Klotz L, Harbottle A, et al. A single mitochondrial DNA deletion accurately detects significant prostate cancer in men in the PSA 'grey zone'. World journal of urology 2018;36:341-348.	Patients already have suspected PCa
Cui T, Kovell RC, Terlecki RP. Is it time to abandon the digital rectal examination? Lessons from the PLCO Cancer Screening Trial and peer-reviewed literature. Current Medical Research and Opinion 2016;32:1663-1669.	No relevant outcomes
Cui Y, Cao W, Li Q, et al. Evaluation of prostate cancer antigen 3 for detecting prostate cancer: a systematic review and meta-analysis. Scientific reports 2016;6:25776.	Full-text not in English, published pre-2014 or irrelevant publication type
Cuocolo R, Stanzione A, Ponsiglione A, et al. Clinically significant prostate cancer detection on MRI: A radiomic shape features study. European Journal of Radiology 2019;116:144-149.	Patients already have suspected PCa
Cuocolo R, Stanzione A, Rusconi G, et al. PSA-density does not improve bi-parametric prostate MR detection of prostate cancer in a biopsy naive patient population. European Journal of Radiology 2018;104:64-70.	Patients already have suspected PCa
Dal Moro F, Zecchini G, Morlacco A, et al. Does 1.5 T mpMRI play a definite role in detection of clinically significant prostate cancer? Findings from a prospective study comparing blind 24-	Patients already have suspected PCa

Reference	Reason for exclusion
core saturation and targeted biopsies with a novel data remodeling model. Aging Clinical and Experimental Research 2019;31:115-123.	
Das B, Shoukat S, Bux KI, et al. Correlation between MR spectroscopy and histology in detection of prostatic carcinoma. Journal of the Pakistan Medical Association 2018;68:986-989.	Patients already have suspected PCa
Dasgupta P, Baade PD, Aitken JF, et al. Geographical variations in prostate cancer outcomes: A systematic review of international evidence. Frontiers in Oncology 2019;9 (APR) (no pagination).	Included in an included SLR
Daun M, Fardin S, Ushinsky A, et al. PI-RADS Version 2 Is an Excellent Screening Tool for Clinically Significant Prostate Cancer as Designated by the Validated International Society of Urological Pathology Criteria: A Retrospective Analysis. Current Problems in Diagnostic Radiology. 2019.	Patients already have suspected PCa
Davenport MS, Montgomery JS, Kunju LP, et al. ¹⁸F-choline PET/mpMRI for Detection of clinically significant prostate cancer: Part 1. Improved risk stratification for MRI-guided transrectal prostate biopsies. Journal of Nuclear Medicine 2019;16:16.	Patients already have suspected PCa
De La Calle C, Patil D, Wei JT, et al. Multicenter evaluation of the prostate health index to detect aggressive prostate cancer in biopsy Naive men. Journal of Urology 2015;194:65-72.	Patients already have suspected PCa
De Luca S, Passera R, Bollito E, et al. Comparison of prostate cancer gene 3 score, prostate health index and percentage free prostate-specific antigen for differentiating histological inflammation from prostate cancer and other non-neoplastic alterations of the prostate at initial biopsy. Anticancer Research 2014;34:7159-65.	Patients already have suspected PCa
De Luca S, Passera R, Fiori C, et al. Prostate health index and prostate cancer gene 3 score but not percent-free Prostate Specific Antigen have a predictive role in differentiating histological prostatitis from PCa and other nonneoplastic lesions (BPH and HG-PIN) at repeat biopsy. Urologic Oncology: Seminars and Original Investigations 2015;33:424.e17-424.e23.	Patients already have suspected PCa
De Nunzio C, Lombardo R, Cancrini F, et al. The chun nomogram significantly outperforms the PCPT, ERSPC, kawakami and karakiewicz nomograms in the prediction of prostate cancer: a single center cohort-study. Journal of urology 2018;199:e1109-.	Full-text not in English, published pre-2014 or irrelevant publication type
De Nunzio C, Lombardo R, Leonardo C, et al. Serum levels of 17-beta-estradiol are not predictive of prostate cancer diagnosis and aggressiveness: Results from an Italian biopsy cohort. Urologic Oncology: Seminars and Original Investigations 2014;32:35.e9-35.e13.	Patients already have suspected PCa
De Nunzio C, Lombardo R, Tema G, et al. External validation of Chun, PCPT, ERSPC, Kawakami, and Karakiewicz nomograms in the prediction of prostate cancer: a single center cohort-study. Urologic oncology: seminars and original investigations 2018;(no pagination).	Patients already have suspected PCa
de Rooij M, Hamoen EH, Futterer JJ, et al. Accuracy of multiparametric MRI for prostate cancer detection: a meta-analysis. AJR American Journal of Roentgenology 2014;202:343-351.	Full-text not in English, published pre-2014 or irrelevant publication type
DeFrank JT, Barclay C, Sheridan S, et al. The Psychological Harms of Screening: the Evidence We Have Versus the Evidence We Need. Journal of General Internal Medicine 2014;30:242-248.	Full-text not in English, published pre-2014 or irrelevant publication type
Delgado Oliva F, Arlandis Guzman S, Bonillo Garcia M, et al. Diagnostic performance of power doppler and ultrasound contrast agents in early imaging-based diagnosis of organ-confined prostate cancer: Is it possible to spare cores with contrast-guided biopsy? European Journal of Radiology 2016;85:1778-1785.	Patients already have suspected PCa
Dell'Oglio P, Stabile A, Gandaglia G, et al. Inclusion of mpMRI into the european randomized study of screening for prostate cancer (ERSPC) risk calculator: a new proposal to improve the accuracy of prostate cancer detection. Journal of urology 2017;197:e1027-.	Full-text not in English, published pre-2014 or irrelevant publication type
Deng T, Zhang M, Feng S, et al. Number of screening rounds and risk of prostate cancer: A systematic review and meta-analysis. International Journal of Clinical and Experimental Medicine 2018;11:1-11.	Full-text not in English, published pre-2014 or irrelevant publication type
Drks. Multicenter evaluation of MRI-targeted prostate biopsy. Http://www.who.int/trialsearch/trial2.aspx? Trialid=drks00005986 2014.	Patients already have suspected PCa
Drks. PROKOMB - PROSTATE - COOPERATIVE MRT PROJECT BERLIN. Http://www.who.int/trialsearch/trial2.aspx? Trialid=drks00010726 2016.	Patients already have suspected PCa
Drost FH, Osses DF, Nieboer D, et al. Prostate MRI, with or without MRI-targeted biopsy, and systematic biopsy for detecting prostate cancer. Cochrane Database of Systematic Reviews 2019;4:CD012663.	Patients already have suspected PCa
Drost FJH, Osses D, Nieboer D, et al. Prostate Magnetic Resonance Imaging, with or Without Magnetic Resonance Imaging-targeted Biopsy, and Systematic Biopsy for Detecting Prostate Cancer: A Cochrane Systematic Review and Meta-analysis. European Urology. 2019.	Patients already have suspected PCa

Reference	Reason for exclusion
Drudi FM, Cantisani V, Angelini F, et al. Multiparametric MRI Versus Multiparametric US in the Detection of Prostate Cancer. Anticancer Research 2019;39:3101-3110.	Patients already have suspected PCa
Druskin SC, Tosoian JJ, Young A, et al. Combining Prostate Health Index density, magnetic resonance imaging and prior negative biopsy status to improve the detection of clinically significant prostate cancer. BJU International 2018;121:619-626.	Patients already have suspected PCa
Dwivedi DK, Kumar R, Dwivedi AK, et al. Prebiopsy multiparametric MRI-based risk score for predicting prostate cancer in biopsy-naive men with prostate-specific antigen between 4-10 ng/mL. Journal of Magnetic Resonance Imaging 2018;47:1227-1236.	Patients already have suspected PCa
Ebeid AI, Elshamy AS. Hypoechoic versus hypervascular lesion in the diagnosis of prostatic carcinoma. African Journal of Urology 2018;24:169-174.	Patients already have suspected PCa
Eklund M, Nordstrom T, Aly M, et al. The Stockholm-3 (STHLM3) Model can Improve Prostate Cancer Diagnostics in Men Aged 50-69 yr Compared with Current Prostate Cancer Testing. European Urology Focus 2018;4:707-710.	Patients already have suspected PCa
Elian MMM, Abdel Gawad EA, Fathelbab TKH. Value of functional MRI in evaluation of patients with suspected prostate cancer. Egyptian Journal of Radiology and Nuclear Medicine. 2015;19.	Patients already have suspected PCa
Elkhoury FF, Felker ER, Kwan L, et al. Comparison of Targeted vs Systematic Prostate Biopsy in Men Who Are Biopsy Naive: The Prospective Assessment of Image Registration in the Diagnosis of Prostate Cancer (PAIREDCAP) Study. JAMA Surgery. 2019.	Patients already have suspected PCa
Elwenspoek MMC, Sheppard AL, McInnes MDF, et al. Comparison of Multiparametric Magnetic Resonance Imaging and Targeted Biopsy with Systematic Biopsy Alone for the Diagnosis of Prostate Cancer: A Systematic Review and Meta-analysis. JAMA Network Open 2019;2 (8) (no pagination).	Patients already have suspected PCa
Ergun O, Capar E, Goger YE, et al. Can expressed prostatic secretions effect prostate biopsy decision of urologist? International braz j urol : official journal of the Brazilian Society of Urology 2019;45:246-252.	Patients already have suspected PCa
Euctr ES. Open randomized clinical trial to examine individual pain tolerance in the use of two anesthetic techniques to perform extended prostate biopsy. Http://www.who.int/trialsearch/trial2.aspx? Trialid=euctr2015-003740-39-es 2016.	Irrelevant screening programme or comparator/irrelevant index test, reference standard or comparator
Exterkate L, Wegelin O, Barentsz JO, et al. Is There Still a Need for Repeated Systematic Biopsies in Patients with Previous Negative Biopsies in the Era of Magnetic Resonance Imaging-targeted Biopsies of the Prostate? European Urology Oncology. 2019.	Patients already have suspected PCa
Faiella E, Santucci D, Greco F, et al. Analysis of histological findings obtained combining US/mp-MRI fusion-guided biopsies with systematic US biopsies: mp-MRI role in prostate cancer detection and false negative. Radiologia Medica 2018;123:143-152.	Patients already have suspected PCa
Fan YH, Pan PH, Lin TP, et al. Prostate-Health-Index outperforms other PSA derivatives in predicting a positive biopsy in men with tPSA<10 ng/ml: Largest prospective cohort in Taiwan. Journal of the Chinese Medical Association : JCMA. 2019;22.	Patients already have suspected PCa
Fang D, Ren D, Zhao C, et al. Prevalence and Risk Factors of Prostate Cancer in Chinese Men with PSA 4-10 ng/mL Who Underwent TRUS-Guided Prostate Biopsy: The Utilization of PAMD Score. BioMed Research International 2015;2015:596797.	Patients already have suspected PCa
Fascelli M, Rais-Bahrami S, Sankineni S, et al. Combined Biparametric Prostate Magnetic Resonance Imaging and Prostate-specific Antigen in the Detection of Prostate Cancer: A Validation Study in a Biopsy-naive Patient Population. Urology 2016;88:125-34.	Patients already have suspected PCa
Feibus AH, Sartor O, Moparty K, et al. Clinical Use of PCA3 and TMPRSS2:ERG Urinary Biomarkers in African-American Men Undergoing Prostate Biopsy. Journal of Urology 2016;196:1053-1060.	Patients already have suspected PCa
Fenton JJ, Weyrich MS, Durbin S, et al. Prostate-specific antigen-based screening for prostate cancer evidence report and systematic review for the us preventive services task force. JAMA - Journal of the American Medical Association 2018;319:1914-1931.	Full-text not in English, published pre-2014 or irrelevant publication type
Filella X, Foj L, Auge JM, et al. Clinical utility of %p2PSA and prostate health index in the detection of prostate cancer. Clinical Chemistry and Laboratory Medicine 2014;52:1347-1355.	Patients already have suspected PCa
Foj L, Mila M, Mengual L, et al. Real-time PCR PCA3 assay is a useful test measured in urine to improve prostate cancer detection. Clinica Chimica Acta 2014;435:53-8.	Patients already have suspected PCa
Foley RW, Gorman L, Sharifi N, et al. Improving multivariable prostate cancer risk assessment using the Prostate Health Index. BJU International 2016;117:409-17.	Patients already have suspected PCa

Reference	Reason for exclusion
Foley RW, Lundon DJ, Murphy K, et al. Predicting prostate cancer: analysing the clinical efficacy of prostate cancer risk calculators in a referral population. Irish Journal of Medical Science 2015;184:701-6.	Patients already have suspected PCa
Foley RW, Maweni RM, Gorman L, et al. European Randomised Study of Screening for Prostate Cancer (ERSPC) risk calculators significantly outperform the Prostate Cancer Prevention Trial (PCPT) 2.0 in the prediction of prostate cancer: a multi-institutional study. BJU International 2016;118:706-713.	Patients already have suspected PCa
Force USPST, Grossman DC, Curry SJ, et al. Screening for Prostate Cancer: US Preventive Services Task Force Recommendation Statement. JAMA 2018;319:1901-1913.	Full-text not in English, published pre-2014 or irrelevant publication type
Franlund M, Arnsrud Godtman R, Carlsson SV, et al. Prostate cancer risk assessment in men with an initial P.S.A. below 3 ng/mL: results from the Goteborg randomized population-based prostate cancer screening trial. Scandinavian journal of urology 2018;(no pagination).	No relevant outcomes
Frantzi M, Gomez Gomez E, Blanca Pedregosa A, et al. CE-MS-based urinary biomarkers to distinguish non-significant from significant prostate cancer. British Journal of Cancer 2019;120:1120-1128.	Patients already have suspected PCa
Friedersdorff F, Manus P, Miller K, et al. Serum testosterone improves the accuracy of Prostate Health Index for the detection of prostate cancer. Clinical Biochemistry 2014;47:916-20.	Patients already have suspected PCa
Friedl A, Stangl K, Bauer W, et al. Prostate-specific Antigen Parameters and Prostate Health Index Enhance Prostate Cancer Prediction With the In-bore 3-T Magnetic Resonance Imaging-guided Transrectal Targeted Prostate Biopsy After Negative 12-Core Biopsy. Urology 2017;110:148-153.	Patients already have suspected PCa
Furuya K, Kawahara T, Narahara M, et al. Measurement of serum isoform [-2]proPSA derivatives shows superior accuracy to magnetic resonance imaging in the diagnosis of prostate cancer in patients with a total prostate-specific antigen level of 2-10 ng/ml. Scandinavian Journal of Urology 2017;51:251-257.	Patients already have suspected PCa
Fusco R, Sansone M, Petrillo M, et al. Multiparametric MRI for prostate cancer detection: Preliminary results on quantitative analysis of dynamic contrast enhanced imaging, diffusion-weighted imaging and spectroscopy imaging. Magnetic Resonance Imaging 2016;34:839-845.	Patients already have confirmed BPH or PCa
Gallotta A, Giannarini G, Laurini L, et al. Clinical validation of the iXip index in avoiding unnecessary prostate biopsy: Results from a prospective multicenter study involving 426 patients. Cancer Treatment and Research Communications 2017;10:40-45.	Patients already have suspected PCa
Gao G, Wang C, Zhang X, et al. Quantitative analysis of diffusion-weighted magnetic resonance images: differentiation between prostate cancer and normal tissue based on a computer-aided diagnosis system. Science China 2017;Life sciences. 60:37-43.	Patients already have suspected PCa
Garcia Bennett J, Vilanova JC, Guma Padro J, et al. Evaluation of MR imaging-targeted biopsies of the prostate in biopsy-naive patients. A single centre study. Diagnostic and Interventional Imaging 2017;98:677-684.	Patients already have suspected PCa
Garcia C, Winter M, Bergersen P, et al. Transperineal versus transrectal prostate biopsy in prostate cancer detection: a systematic review with meta-analysis. BJU international. 2016;117:38.	Full-text not in English, published pre-2014 or irrelevant publication type
Gaur S, Harmon S, Mehralivand S, et al. Prospective comparison of PI-RADS version 2 and qualitative in-house categorization system in detection of prostate cancer. Journal of Magnetic Resonance Imaging 2018;48:1326-1335.	Patients already have suspected PCa
Gaur S, Harmon S, Rosenblum L, et al. Can apparent diffusion coefficient values assist pi-rads version 2 dwi scoring? A correlation study using the pi-radsv2 and international society of urological pathology systems. American Journal of Roentgenology 2018;211:W33-W41.	Patients already have confirmed BPH or PCa
Gayet M, Mannaerts CK, Nieboer D, et al. Prediction of Prostate Cancer: External Validation of the ERSPC Risk Calculator in a Contemporary Dutch Clinical Cohort. European Urology Focus 2018;4:228-234.	Patients already have suspected PCa
Gayet M, Van Der Aa A, Beerlage HP, et al. The value of magnetic resonance imaging and ultrasonography (MRI/US)-fusion biopsy platforms in prostate cancer detection: A systematic review. BJU International 2016;117:392-400.	Patients already have suspected PCa
Gaziev G, Wadhwa K, Barrett T, et al. Defining the learning curve for multiparametric magnetic resonance imaging (MRI) of the prostate using MRI-transrectal ultrasonography (TRUS) fusion-guided transperineal prostate biopsies as a validation tool. BJU International 2016;117:80-86.	Patients already have suspected PCa
Giannarini G, Girometti R, Crestani A, et al. A Prospective Accuracy Study of Prostate Imaging Reporting and Data System Version 2 on Multiparametric Magnetic Resonance Imaging in	Patients already have suspected PCa

Reference	Reason for exclusion
Detecting Clinically Significant Prostate Cancer With Whole-mount Pathology. Urology 2019;123:191-197.	
Gielchinsky I, Scheltema MJ, Cusick T, et al. Reduced sensitivity of multiparametric MRI for clinically significant prostate cancer in men under the age of 50. Research and Reports in Urology 2018;10:145-150.	Patients already have confirmed BPH or PCa
Gilbert R, Martin RM, Evans DM, et al. Incorporating known genetic variants does not improve the accuracy of PSA testing to identify high risk prostate cancer on biopsy. PLoS ONE 2015;10 (10) (no pagination).	Patients already have suspected PCa
Glybochko PV, Zezerov EG, Glukhov AI, et al. Telomerase as a tumor marker in diagnosis of prostatic intraepithelial neoplasia and prostate cancer. Prostate 2014;74:1043-1051.	Patients already have suspected PCa
Godtman RA, Carlsson S, Holmberg E, et al. The Effect of Start and Stop Age at Screening on the Risk of Being Diagnosed with Prostate Cancer. Journal of urology 2016;195:1390-1396.	No relevant outcomes
Godtman RA, Holmberg E, Khatami A, et al. Long-term Results of Active Surveillance in the Goteborg Randomized, Population-based Prostate Cancer Screening Trial. European Urology 2016;70:760-766.	Patients already have confirmed BPH or PCa
Godtman R, Holmberg E, Khatami A, et al. An update on the outcome of men on active surveillance in the Gothenburg randomized population-based prostate cancer screening trial. European urology, supplements. 2015;14:e1034-e1034a.	Full-text not in English, published pre-2014 or irrelevant publication type
Goldman H, Singh N, Harding C, et al. Accuracy of multiparametric magnetic resonance imaging to detect significant prostate cancer and index lesion location. ANZ journal of surgery 2019;89:106-110.	Patients already have suspected PCa
Gomez-Gomez E, Carrasco-Valiente J, Blanca-Pedregosa A, et al. European Randomized Study of Screening for Prostate Cancer Risk Calculator: External Validation, Variability, and Clinical Significance. Urology 2017;102:85-91.	Patients already have suspected PCa
Greene DJ, Elshafei A, Nyame YA, et al. External validation of a PCA-3-based nomogram for predicting prostate cancer and high-grade cancer on initial prostate biopsy. Prostate 2016;76:1019-1023.	Patients already have suspected PCa
Gulati R, Morgan TM, A'Mar T, et al. Overdiagnosis and lives saved due to reflex testing men with intermediate prostate-specific antigen levels. Journal of the National Cancer Institute. 2019;21.	Patients already have suspected PCa
Guo J, Yang J, Zhang X, et al. A panel of biomarkers for diagnosis of prostate cancer using urine samples. Anticancer Research 2018;38:1471-1477.	Patients already have suspected PCa
Gupta RT, Brown AF, Silverman RK, et al. Can radiologic staging with multiparametric MRI enhance the accuracy of the partin tables in predicting organ-confined prostate cancer? American Journal of Roentgenology 2016;207:87-95.	Patients already have suspected PCa
Gupta RT, Faridi KF, Singh AA, et al. Comparing 3-T multiparametric MRI and the Partin tables to predict organ-confined prostate cancer after radical prostatectomy. Urologic Oncology: Seminars and Original Investigations 2014;32:1317-1326.	Patients already have suspected PCa
Habchi H, Bratan F, Paye A, et al. Value of prostate multiparametric magnetic resonance imaging for predicting biopsy results in first or repeat biopsy. Clinical Radiology 2014;69:e120-e128.	Patients already have suspected PCa
Hadjipavlou M, Mohamed A, Sriprasad S, et al. Abnormal digital rectal examination (DRE) of the prostate increases the likelihood of future high grade prostate cancer diagnosis in patients with initial benign prostate biopsy. Journal of urology. 2015;193:e900.	Full-text not in English, published pre-2014 or irrelevant publication type
Haese A, Trooskens G, Steyaert S, et al. Multicenter Optimization and Validation of a 2-Gene mRNA Urine Test for Detection of Clinically Significant Prostate Cancer before Initial Prostate Biopsy. Journal of Urology 2019;202:256-262.	Patients already have suspected PCa
Haider MA, Yao X, Loblaw A, et al. Multiparametric Magnetic Resonance Imaging in the Diagnosis of Prostate Cancer: A Systematic Review. Clinical Oncology 2016;28:550-567.	Full-text not in English, published pre-2014 or irrelevant publication type
Halpern JA, Oromendia C, Shoag JE, et al. Use of Digital Rectal Examination as an Adjunct to Prostate Specific Antigen in the Detection of Clinically Significant Prostate Cancer. Journal of Urology 2018;199:947-953.	No relevant outcomes
Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. New England journal of medicine 2016;375:1415-1424.	Patients already have confirmed BPH or PCa
Hamoen EH, de Rooij M, Witjes JA, et al. Use of the Prostate Imaging Reporting and Data System (PI-RADS) for prostate cancer detection with multiparametric magnetic resonance imaging: a diagnostic meta-analysis. European Urology 2014:epub.	Full-text not in English, published pre-2014 or irrelevant publication type

Reference	Reason for exclusion
Hansen NL, Kesch C, Barrett T, et al. Multicentre evaluation of targeted and systematic biopsies using magnetic resonance and ultrasound image-fusion guided transperineal prostate biopsy in patients with a previous negative biopsy. BJU International 2017;120:631-638.	Patients already have suspected PCa
Hara T, Ogata T, Wada H, et al. Prostate cancer detection with multiparametric MRI: A comparison of 1 M-Concentration gadobutrol with 0.5 M-Concentration gadolinium-based contrast agents. Current Urology 2018;11:201-205.	Patients already have suspected PCa
Haring A, Murtola TJ, Talala K, et al. Antidiabetic drug use and prostate cancer risk in the Finnish Randomized Study of Screening for Prostate Cancer. Scandinavian journal of urology 2017;51:5-12.	No relevant outcomes
Haroon A, Ahmed HU, Cathcart P, et al. ¹⁸F-FECH PET/CT to assess clinically signifcant disease in prostate cancer: Correlation with maximum and total cancer core length obtained via MRI-guided template mapping biopsies. American Journal of Roentgenology 2016;207:1297-1306.	Patients already have suspected PCa
Hashimoto M, Matsumura N, Ohzeki T, et al. The Change in Neutrophil Lymphocyte Ratio from the First to the Last Repeat Prostate Biopsy Proposed as a Marker of Carcinogenesis. Urologia Internationalis 2018;101:74-79.	Irrelevant study type
Hegde JV, Veruttipong D, Said JW, et al. Prostate Cancer Antigen 3 Score Does Not Predict for Adverse Pathologic Features at Radical Prostatectomy or for Progression-free Survival in Clinically Localized, Intermediate- and High-risk Prostate Cancer. Urology 2017;107:171-177.	Patients already have confirmed BPH or PCa
Hermie I, Van Besien J, De Visschere P, et al. Which clinical and radiological characteristics can predict clinically significant prostate cancer in PI-RADS 3 lesions? A retrospective study in a high-volume academic center. European Journal of Radiology 2019;114:92-98.	Patients already have suspected PCa
Hofbauer SL, Maxeiner A, Kittner B, et al. Validation of Prostate Imaging Reporting and Data System Version 2 for the Detection of Prostate Cancer. Journal of Urology 2018;200:767-773.	Patients already have suspected PCa
Hotker AM, Dappa E, Mazaheri Y, et al. The influence of background signal intensity changes on cancer detection in prostate MRI. American Journal of Roentgenology 2019;212:823-829.	Patients already have suspected PCa
Hsieh PF, Chang CH, Yang CR, et al. Prostate Health Index (PHI) improves prostate cancer detection at initial biopsy in Taiwanese men with PSA 4-10 ng/mL. Kaohsiung Journal of Medical Sciences 2018;34:461-466.	Patients already have suspected PCa
Hu B, Yang H, Yang H. Diagnostic value of urine prostate cancer antigen 3 test using a cutoff value of 35 micrograms/L in patients with prostate cancer. Tumor Biology 2014;35:8573-8580.	Full-text not in English, published pre-2014 or irrelevant publication type
Huang C, Song G, Wang H, et al. MultiParametric Magnetic Resonance Imaging-Based Nomogram for Predicting Prostate Cancer and Clinically Significant Prostate Cancer in Men Undergoing Repeat Prostate Biopsy. BioMed Research International 2018;2018 (no pagination).	Patients already have suspected PCa
Huang M, Lin Y, Xu A, et al. Percent free prostate-specific antigen does not improve the effectiveness of prostate cancer detection in Chinese men with a prostate-specific antigen of 2.5-20.0 ng/ml: A multicenter study. Medical Oncology 2014;31 (4) (no pagination).	Patients already have suspected PCa
Huang TB, Mao SY, Lu SM, et al. Predictive value of neutrophil-to-lymphocyte ratio in diagnosis of prostate cancer among men who underwent template-guided prostate biopsy: A STROBE-compliant study. Medicine 2016;95:e5307.	Patients already have suspected PCa
Huang Y, Cheng G, Liu B, et al. A prostate biopsy strategy based on a new clinical nomogram reduces the number of biopsy cores required in high-risk patients. BMC Urology 2014;14 (1) (no pagination).	Patients already have suspected PCa
Huang Y, Gu X, Wang Y, et al. Prostate health index is useful for prostate cancer detecting in Chinese people. Translational Cancer Research 2019;8:836-839.	Patients already have suspected PCa
Ilic D, Djulbegovic M, Jung JH, et al. Prostate cancer screening with prostate-specific antigen (PSA) test: A systematic review and meta-analysis. BMJ (Online) 2018;362 (no pagination).	Patients already have suspected PCa
Irct2013090911691N. The Effect of Health Belief Model-Based Training on Prostate Cancer Screening Behaviors among the Retired Clerks of Shiraz Department of Education in 2013; A randomized Controlled Clinical Trial. Http://www.who.int/trialsearch/trial2.aspx? Trialid=irct2013090911691n3 2014.	No relevant outcomes
Ishioka J, Matsuoka Y, Uehara S, et al. Computer-aided diagnosis of prostate cancer on magnetic resonance imaging using a convolutional neural network algorithm. BJU International 2018;122:411-417.	Patients already have suspected PCa
Isrctn. The GÖTEBORG prostate cancer screening 2 trial. Http://www.who.int/trialsearch/trial2.aspx? Trialid=isrctn94604465 2017.	Full-text not in English, published pre-2014 or irrelevant publication type

Reference	Reason for exclusion
Itatani R, Namimoto T, Kajihara H, et al. Triage of low-risk prostate cancer patients with PSA levels 10 ng/mL or less: Comparison of apparent diffusion coefficient value and transrectal ultrasound-guided target biopsy. American Journal of Roentgenology 2014;202:1051-1057.	Patients already have confirmed BPH or PCa
Izumi K, Mizokami A, Lin HP, et al. Serum chemokine (CC motif) ligand 2 level as a diagnostic, predictive, and prognostic biomarker for prostate cancer. Oncotarget 2016;7:8389-98.	Full-text not in English, published pre-2014 or irrelevant publication type
Jansen BHE, Nieuwenhuijzen JA, Oprea-Lager DE, et al. Adding multiparametric MRI to the MSKCC and Partin nomograms for primary prostate cancer: Improving local tumor staging? Urologic Oncology: Seminars and Original Investigations 2019;37:181.e1-181.e6.	Patients already have confirmed BPH or PCa
Jansen BHE, Oudshoorn FHK, Tijans AM, et al. Local staging with multiparametric MRI in daily clinical practice: diagnostic accuracy and evaluation of a radiologic learning curve. World journal of urology 2018;36:1409-1415.	Patients already have confirmed BPH or PCa
Javali TD, Dwivedi DK, Kumar R, et al. Magnetic resonance spectroscopy imaging-directed transrectal ultrasound biopsy increases prostate cancer detection in men with prostate-specific antigen between 4-10ng/mL and normal digital rectal examination. International Journal of Urology 2014;21:257-262.	Patients already have suspected PCa
Jena A, Taneja R, Taneja S, et al. Improving Diagnosis of Primary Prostate Cancer With Combined ⁶⁸Ga-Prostate-Specific Membrane Antigen-HBED-CC Simultaneous PET and Multiparametric MRI and Clinical Parameters. AJR. American Journal of Roentgenology 2018;211:1246-1253.	Patients already have suspected PCa
Jeong CW, Lee S, Jung JW, et al. Mobile application-based Seoul National University prostate cancer risk calculator: Development, validation, and comparative analysis with two western risk calculators in Korean men. PLoS ONE 2014;9 (4) (no pagination).	Patients already have suspected PCa
Jia JB, Houshyar R, Verma S, et al. Prostate cancer on computed tomography: A direct comparison with multi-parametric magnetic resonance imaging and tissue pathology. European Journal of Radiology 2016;85:261-267.	Patients already have suspected PCa
Jia Y, Zhu LY, Xian YX, et al. Detection rate of prostate cancer following biopsy among the northern Han Chinese population: A single-center retrospective study of 1022 cases. World Journal of Surgical Oncology 2017;15 (1) (no pagination).	Patients already have suspected PCa
Jiang X, Zhang J, Tang J, et al. Magnetic resonance imaging - Ultrasound fusion targeted biopsy outperforms standard approaches in detecting prostate cancer: A meta-analysis. Molecular and Clinical Oncology 2016;5:301-309.	Patients already have suspected PCa
John S, Cooper S, Breau RH, et al. Multiparametric magnetic resonance imaging-transrectal ultrasound-guided cognitive fusion biopsy of the prostate: Clinically significant cancer detection rates stratified by the Prostate Imaging and Data Reporting System version 2 assessment categories. Canadian Urological Association Journal 2018;12:401-406.	Patients already have suspected PCa
Johnson DC, Raman SS, Mirak SA, et al. Detection of Individual Prostate Cancer Foci via Multiparametric Magnetic Resonance Imaging. European Urology 2019;75:712-720.	Patients already have suspected PCa
Johnson DC, Yang JJ, Kwan L, et al. Do contemporary imaging and biopsy techniques reliably identify unilateral prostate cancer? Implications for hemiablation patient selection. Cancer 2019;125:2955-2964.	Patients already have suspected PCa
Johnston E, Pye H, Bonet-Carne E, et al. INNOVATE: A prospective cohort study combining serum and urinary biomarkers with novel diffusion-weighted magnetic resonance imaging for the prediction and characterization of prostate cancer. BMC Cancer 2016;16:816.	Patients already have suspected PCa
Johnston MJ, Thorman H, Shah A, et al. Comparing significant prostate cancer detection rates after the introduction of pre-biopsy MRI: turning PROMIS into action. Journal of Clinical Urology 2019;12:341-346.	Patients already have suspected PCa
Johnston TJ, Shaw GL, Lamb AD, et al. Mortality Among Men with Advanced Prostate Cancer Excluded from the ProtecT Trial. European Urology 2017;71:381-388.	Patients already have confirmed BPH or PCa
Johnston T, Shaw G, Lamb A, et al. Detection of asymptomatic locally advanced and high-risk prostate cancer through PSA testing: clinical outcomes in men excluded from the ProtecT Trial. European urology, supplements 2016;15:e95-.	Full-text not in English, published pre-2014 or irrelevant publication type
Jordan EJ, Fiske C, Zagoria R, et al. PI-RADS v2 and ADC values: is there room for improvement? Abdominal Radiology 2018;43:3109-3116.	Patients already have suspected PCa
Jprn U. Effect of PSA decreasing of a pollen extract(Cernilton) for patients with prostate biopsy: multicenter study. Http://www.who.int/trialsearch/trial2.aspx? Trialid=jprn-umin000017593 2015.	Patients already have suspected PCa
Jprn U. Clinical research on proPSA measurement in a diagnosis of prostate cancer: prostate health index trial. Http://www.who.int/trialsearch/trial2.aspx? Trialid=jprn-umin000016934 2015.	Patients already have suspected PCa

Reference	Reason for exclusion
Jprn U. A feasibility study of photoacoustic imaging system for detection of prostate cancer. Http://www.who.int/trialsearch/trial2.aspx? Trialid=jprn-umin000027196 2017.	Patients already have suspected PCa
Jue JS, Barboza MP, Prakash NS, et al. Re-examining Prostate-specific Antigen (PSA) Density: Defining the Optimal PSA Range and Patients for Using PSA Density to Predict Prostate Cancer Using Extended Template Biopsy. Urology 2017;105:123-128.	Patients already have suspected PCa
Junker D, Steinkohl F, Fritz V, et al. Comparison of multiparametric and biparametric MRI of the prostate: are gadolinium-based contrast agents needed for routine examinations? World journal of urology 2019;37:691-699.	Patients already have suspected PCa
Kaapu KJ, Murtola TJ, Maattanen L, et al. Prostate cancer risk among users of digoxin and other antiarrhythmic drugs in the Finnish Prostate Cancer Screening Trial. Cancer Causes and Control 2016;27:157-164.	No relevant outcomes
Kanao K, Komori O, Nakashima J, et al. Individualized prostate-specific antigen threshold values to avoid overdiagnosis of prostate cancer and reduce unnecessary biopsy in elderly men. Japanese Journal of Clinical Oncology 2014;44:852-859.	Patients already have suspected PCa
Karnes RJ, MacKintosh FR, Morrell CH, et al. Prostate-specific antigen trends predict the probability of prostate cancer in a very large U.S. Veterans affairs cohort. Frontiers in Oncology 2018;8 (AUG) (no pagination).	No relevant outcomes
Kasivisvanathan V, Stabile A, Neves JB, et al. Magnetic Resonance Imaging-targeted Biopsy Versus Systematic Biopsy in the Detection of Prostate Cancer: A Systematic Review and Meta-analysis(Figure presented.). European Urology 2019;76:284-303.	Irrelevant screening programme or comparator/irrelevant index test, reference standard or comparator
Kilic O, Akand M, Kulaksizoglu H, et al. Intravenous paracetamol for relief of pain during transrectal-ultrasound-guided biopsy of the prostate: a prospective, randomized, double-blind, placebo-controlled study. The kaohsiung journal of medical sciences 2015;31:572-579.	Patients already have suspected PCa
Kilpelainen TP, Talala K, Raitanen J, et al. Prostate cancer and socioeconomic status in the finnish randomized study of screening for prostate cancer. American Journal of Epidemiology 2016;184:720-731.	No relevant outcomes
Kim SH, Choi MS, Kim MJ, et al. Validation of prostate imaging reporting and data system version 2 using an MRI-Ultrasound fusion biopsy in prostate cancer diagnosis. American Journal of Roentgenology 2017;209:800-805.	Patients already have suspected PCa
Kinnunen PTT, Murtola TJ, Talala K, et al. Anticoagulants and cancer mortality in the Finnish randomized study of screening for prostate cancer. Cancer Causes and Control 2019;30:877-888.	No relevant outcomes
Klein EA, Chait A, Hafron JM, et al. The Single-parameter, Structure-based IsoPSA Assay Demonstrates Improved Diagnostic Accuracy for Detection of Any Prostate Cancer and High-grade Prostate Cancer Compared to a Concentration-based Assay of Total Prostate-specific Antigen: A Preliminary Report. European Urology 2017;72:942-949.	Patients already have suspected PCa
Klinkenberg LJJ, Lentjes EGWM, Boer AK. Clinical interpretation of prostate-specific antigen values: Type of applied cut-off value exceeds methods bias as the major source of variation. Annals of Clinical Biochemistry 2019;56:259-265.	Patients already have suspected PCa
Kordbacheh H, Seethamraju RT, Weiland E, et al. Image quality and diagnostic accuracy of complex-averaged high b value images in diffusion-weighted MRI of prostate cancer. Abdominal Radiology 2019;44:2244-2253.	Patients already have suspected PCa
Korn EL, Dignam JJ, Freidlin B. Assessing treatment benefit with competing risks not affected by the randomized treatment. Statistics in Medicine 2015;34:265-280.	No relevant outcomes
Kukko V, Kaipia A, Talala K, et al. Allopurinol and the risk of prostate cancer in a Finnish population-based cohort. Prostate cancer and prostatic diseases 2019.	Irrelevant screening programme or comparator/irrelevant index test, reference standard or comparator
Kulchenko NG, Kostin AA, Chibisov SM, et al. Modern principles of early diagnosis of prostate cancer. Research Journal of Pharmacy and Technology 2017;10:696-698.	Patients already have confirmed BPH or PCa
Kweldam CF, Kümmerlin IP, Nieboer D, et al. Prostate cancer outcomes of men with biopsy Gleason score 6 and 7 without cribriform or intraductal carcinoma. European journal of cancer (oxford, england : 1990) 2016;66:26-33.	No relevant outcomes
Kweldam CF, Kummerlin IP, Nieboer D, et al. Presence of invasive cribriform or intraductal growth at biopsy outperforms percentage grade 4 in predicting outcome of Gleason score 3+4=7 prostate cancer. Modern pathology 2017;(no pagination).	No relevant outcomes

Reference	Reason for exclusion
Kweldam CF, Kummerlin IP, Nieboer D, et al. Disease-specific survival of patients with invasive cribriform and intraductal prostate cancer at diagnostic biopsy. Modern Pathology 2016;29:630-636.	No relevant outcomes
Laranja WW, Sanches BCF, Voris BRI, et al. The Biopsychosocial Burden of Prostate Biopsy at the Time of Its Indication, Procedure, and Pathological Report. Prostate Cancer 2019;2019 (no pagination).	Patients already have suspected PCa
Lazzeri M, Abrate A, Lughezzani G, et al. Relationship of chronic histologic prostatic inflammation in biopsy specimens with serum isoform [-2]proPSA (p2PSA), %p2PSA, and prostate health index in men with a total prostate-specific antigen of 4-10 ng/mL and normal digital rectal examination. Urology 2014;83:606-612.	Patients already have suspected PCa
Lazzeri M, Lughezzani G, Haese A, et al. Clinical performance of prostate health index in men with tPSA>10 ng/ml: Results from a multicentric European study. Urologic Oncology: Seminars and Original Investigations 2016;34:415.e13-415.e19.	Patients already have suspected PCa
Lee SJ, Oh YT, Jung DC, et al. Combined Analysis of Biparametric MRI and Prostate-Specific Antigen Density: Role in the Prebiopsy Diagnosis of Gleason Score 7 or Greater Prostate Cancer. AJR. American Journal of Roentgenology 2018;211:W166-W172.	Patients already have suspected PCa
Leyten GHJM, Hessels D, Jannink SA, et al. Prospective multicentre evaluation of PCA3 and TMPRSS2-ERG gene fusions as diagnostic and prognostic urinary biomarkers for prostate cancer. European Urology 2014;65:534-542.	Patients already have suspected PCa
Leyten GHJM, Hessels D, Smit FP, et al. Identification of a candidate gene panel for the early diagnosis of prostate cancer. Clinical Cancer Research 2015;21:3061-3070.	Patients already have suspected PCa
Li C, Chen M, Li S, et al. Detection of prostate cancer in peripheral zone: comparison of MR diffusion tensor imaging, quantitative dynamic contrast-enhanced MRI, and the two techniques combined at 3.0 T. Acta Radiologica 2014;55:239-47.	Patients already have suspected PCa
Li M, Huang Z, Yu H, et al. Comparison of PET/MRI with multiparametric MRI in diagnosis of primary prostate cancer: A meta-analysis. European Journal of Radiology 2019;113:225-231.	Patients already have suspected PCa
Li W, Xin C, Zhang L, et al. Comparison of diagnostic performance between two prostate imaging reporting and data system versions: A systematic review. European Journal of Radiology 2019;114:111-119.	Patients already have suspected PCa
Li X, Pan Y, Huang Y, et al. Developing a model for forecasting Gleason score >=7 in potential prostate cancer patients to reduce unnecessary prostate biopsies. International Urology and Nephrology 2016;48:535-540.	Patients already have suspected PCa
Lin WC, Westphalen AC, Silva GE, et al. Comparison of PI-RADS 2, ADC histogram-derived parameters, and their combination for the diagnosis of peripheral zone prostate cancer. Abdominal Radiology 2016;41:2209-2217.	Patients already have confirmed BPH or PCa
Lin YR, Wei XH, Uhlman M, et al. PSA density improves the rate of prostate cancer detection in Chinese men with a PSA between 2.5-10.0 ng ml (-1) and 10.1-20.0 ng ml (-1) : a multicenter study. Asian Journal of Andrology 2015;17:503-7.	Patients already have suspected PCa
Li-Sheng Chen S, Ching-Yuan Fann J, Sipeky C, et al. Risk Prediction of Prostate Cancer with Single Nucleotide Polymorphisms and Prostate Specific Antigen. The Journal of urology 2019;201:486-495.	Patients already have suspected PCa
Little J, Wilson B, Carter R, et al. Multigene panels in prostate cancer risk assessment: A systematic review. Genetics in Medicine 2016;18:535-544.	Full-text not in English, published pre-2014 or irrelevant publication type
Liu B, Pan TJ. Role of PSA-related variables in improving positive ratio of biopsy of prostate cancer within serum PSA gray zone. Urologia 2014;81:173-176.	Patients already have suspected PCa
Liu C, Liu SL, Wang ZX, et al. Using the prostate imaging reporting and data system version 2 (PI-RIDS v2) to detect prostate cancer can prevent unnecessary biopsies and invasive treatment. Asian Journal of Andrology 2018;20:459-464.	Patients already have suspected PCa
Liu C, Zhao J, Tian F, et al. Low-cost thermophoretic profiling of extracellular-vesicle surface proteins for the early detection and classification of cancers. Nature Biomedical Engineering 2019;3:183-193.	No relevant outcomes
Liu J, Wang ZQ, Li M, et al. Establishment of two new predictive models for prostate cancer to determine whether to require prostate biopsy when the PSA level is in the diagnostic gray zone (4-10 ng ml⁻¹). Asian journal of andrology. 2019;04.	Patients already have suspected PCa
Loeb S, Bjurlin MA, Nicholson J, et al. Overdiagnosis and overtreatment of prostate cancer. European Urology 2014;65:1046-1055.	Full-text not in English, published pre-2014 or irrelevant publication type

Reference	Reason for exclusion
Loeb S, Sanda MG, Broyles DL, et al. The prostate health index selectively identifies clinically significant prostate cancer. Journal of urology 2015;193:1163-1169.	Patients already have confirmed BPH or PCa
Loeb S, Shin SS, Broyles DL, et al. Prostate Health Index improves multivariable risk prediction of aggressive prostate cancer. BJU international 2016;(no pagination).	Patients already have suspected PCa
Lopes Vendrami C, McCarthy RJ, Chatterjee A, et al. The Utility of Prostate Specific Antigen Density, Prostate Health Index, and Prostate Health Index Density in Predicting Positive Prostate Biopsy Outcome is Dependent on the Prostate Biopsy Methods. Urology 2019;129:153-159.	Patients already have suspected PCa
Loughlin KR. PSA velocity: A systematic review of clinical applications. Urologic Oncology: Seminars and Original Investigations 2014;32:1116-1125.	Full-text not in English, published pre-2014 or irrelevant publication type
Louie KS, Seigneurin A, Cathcart P, et al. Do prostate cancer risk models improve the predictive accuracy of PSA screening? A meta-analysis. Annals of Oncology 2015;26:848-864.	Full-text not in English, published pre-2014 or irrelevant publication type
Lu AJ, Syed JS, Nguyen KA, et al. Negative Multiparametric Magnetic Resonance Imaging of the Prostate Predicts Absence of Clinically Significant Prostate Cancer on 12-Core Template Prostate Biopsy. Urology 2017;105:118-122.	Patients already have suspected PCa
Lu YF, Zhang Q, Chen HY, et al. Improving the detection rate of prostate cancer in the gray zone of PI-RADS v2 and serum tPSA by using prostate-specific antigen-age volume. Medicine 2019;98:e16289.	Patients already have suspected PCa
Lughezzani G, Lazzeri M, Haese A, et al. Multicenter European external validation of a prostate health index-based nomogram for predicting prostate cancer at extended biopsy. European Urology 2014;66:906-912.	Patients already have suspected PCa
Lui KJ, Chang KC. Test equality between two binary screening tests with a confirmatory procedure restricted on screen positives. Journal of Biopharmaceutical Statistics 2015;25:29-43.	Patients already have suspected PCa
Lujan M, Paez A, Angulo JC, et al. Long-term prostate-specific antigen contamination in the Spanish arm of the European Randomized Study of Screening for Prostate Cancer (ERSPC). Actas urologicas espanolas 2016;40:164-172.	No relevant outcomes
Lundgren PO, Kjellman A, Norming U, et al. Long-Term Outcome of a Single Intervention Population Based Prostate Cancer Screening Study. Journal of urology 2018;200:82-88.	Irrelevant study type
Luo Y, Gou X, Huang P, et al. Prostate cancer antigen 3 test for prostate biopsy decision: a systematic review and meta analysis. Chinese Medical Journal 2014;127:1768-1774.	Full-text not in English, published pre-2014 or irrelevant publication type
Luo Y, Gou X, Huang P, et al. The PCA3 test for guiding repeat biopsy of prostate cancer and its cut-off score: a systematic review and meta-analysis. Asian Journal of Andrology 2014;16:487-492.	Full-text not in English, published pre-2014 or irrelevant publication type
Maeda E, Katsura M, Gonoi W, et al. Abnormal signal intensities of the seminal vesicles in a screening population. Journal of Magnetic Resonance Imaging 2014;39:1426-1430.	Patients already have suspected PCa
Maggi M, Panebianco V, Mosca A, et al. Prostate Imaging Reporting and Data System 3 Category Cases at Multiparametric Magnetic Resonance for Prostate Cancer: A Systematic Review and Meta-analysis. European Urology Focus. 2019.	Patients already have suspected PCa
Mannaerts CK, Gayet M, Verbeek JF, et al. Prostate Cancer Risk Assessment in Biopsy-naive Patients: The Rotterdam Prostate Cancer Risk Calculator in Multiparametric Magnetic Resonance Imaging-Transrectal Ultrasound (TRUS) Fusion Biopsy and Systematic TRUS Biopsy. European Urology Oncology 2018;1:109-117.	Patients already have suspected PCa
Martinez-Gonzalez NA, Neuner-Jehle S, Plate A, et al. The effects of shared decision-making compared to usual care for prostate cancer screening decisions: A systematic review and meta-analysis. BMC Cancer 2018;18 (1) (no pagination).	Full-text not in English, published pre-2014 or irrelevant publication type
Martinez-Gonzalez NA, Plate A, Senn O, et al. Shared decision-making for prostate cancer screening and treatment: A systematic review of randomised controlled trials. Swiss Medical Weekly 2018;128 (7-8) (no pagination).	No relevant outcomes
Martinez-Gonzalez NA, Plate A, Senn O, et al. Shared decision-making for prostate cancer screening and treatment: a systematic review of randomised controlled trials. Swiss Medical Weekly 2018;148:w14584.	Irrelevant screening programme or comparator/irrelevant index test, reference standard or comparator

Reference	Reason for exclusion
Maruf M, Fascelli M, George AK, et al. The prostate cancer prevention trial risk calculator 2.0 performs equally for standard biopsy and MRI/US fusion-guided biopsy. Prostate Cancer and Prostatic Diseases 2017;20:179-185.	Patients already have suspected PCa
Marzouk K, Ehdaie B, Vertosick E, et al. Developing an effective strategy to improve the detection of significant prostate cancer by combining the 4Kscore and multiparametric MRI. Urologic Oncology: Seminars and Original Investigations. 2019.	Patients already have suspected PCa
Mathur S, O'Malley ME, Ghai S, et al. Correlation of 3T multiparametric prostate MRI using prostate imaging reporting and data system (PIRADS) version 2 with biopsy as reference standard. Abdominal Radiology 2019;44:252-258.	Patients already have suspected PCa
Matshela RF, Maree JE, van Belkum C. Prevention and detection of prostate cancer: a pilot intervention in a resource--poor South African community. Cancer Nursing 2014;37:189-97.	No relevant outcomes
McKiernan J, Donovan MJ, Margolis E, et al. A Prospective Adaptive Utility Trial to Validate Performance of a Novel Urine Exosome Gene Expression Assay to Predict High-grade Prostate Cancer in Patients with Prostate-specific Antigen 2-10 ng/ml at Initial Biopsy. European Urology 2018;74:731-738.	Patients already have suspected PCa
Mearini L, Ferri C, Lazzeri M, et al. Evaluation of prostate-specific antigen isoform p2PSA and its derivates, %p2PSA, prostate health index and prostate dimension-adjusted related index in the detection of prostate cancer at first biopsy: An exploratory, prospective study. Urologia Internationalis 2014;93:135-145.	Patients already have suspected PCa
Medina EA, Shi X, Grayson MH, et al. The diagnostic value of adiponectin multimers in healthy men undergoing screening for prostate cancer. Cancer Epidemiology Biomarkers and Prevention 2014;23:309-315.	Irrelevant study type
Mendhiratta N, Meng X, Rosenkrantz AB, et al. Prebiopsy MRI and MRI-ultrasound Fusion-targeted Prostate Biopsy in Men with Previous Negative Biopsies: Impact on Repeat Biopsy Strategies. Urology 2015;86:1192-1198.	Patients already have suspected PCa
Mendhiratta N, Rosenkrantz AB, Meng X, et al. Magnetic resonance imaging-ultrasound fusion targeted prostate biopsy in a consecutive cohort of men with no previous biopsy: Reduction of over detection through improved risk stratification. Journal of Urology 2015;194:1601-1606.	Patients already have suspected PCa
Meng Y, Vetter JM, Parker AA, et al. Improved Detection of Clinically Significant Prostate Cancer With Software-assisted Systematic Biopsy Using MR/US Fusion in Patients With Negative Prostate MRI. Urology 2018;120:162-166.	Patients already have suspected PCa
Merriel SWD, Turner EL, Walsh E, et al. Cross-sectional study evaluating data quality of the National Cancer Registration and Analysis Service (NCRAS) prostate cancer registry data using the Cluster randomised trial of PSA testing for Prostate cancer (CAP). BMJ Open 2017;7 (11) (no pagination).	Irrelevant study type
Meyer AR, Joice GA, Schwen ZR, et al. Initial Experience Performing In-office Ultrasound-guided Transperineal Prostate Biopsy Under Local Anesthesia Using the PrecisionPoint Transperineal Access System. Urology 2018;115:8-13.	Patients already have suspected PCa
Meyrick DP, Asokendaran M, Skelly LA, et al. The role of 68Ga-PSMA-I&T PET/CT in the pretreatment staging of primary prostate cancer. Nuclear Medicine Communications 2017;38:956-963.	Patients already have confirmed BPH or PCa
Miah S, Eldred-Evans D, Simmons LAM, et al. Patient Reported Outcome Measures for Transperineal Template Prostate Mapping Biopsies in the PICTURE Study. Journal of Urology 2018;200:1235-1240.	Patients already have suspected PCa
Milkovic B, Dzamic Z, Pejcic T, et al. Evaluation of free-to-total prostate specific antigen (F/T PSA), prostate specific antigen density (PSAD) and (F/T)/PSAD sensitivity on reduction of unnecessary prostate biopsies for patients with PSA in gray zone. Annali italiani di chirurgia 2014;85:448-453.	Patients already have suspected PCa
Min JH, Park BK, Park JJ, et al. Preoperative assessment of prostate cancer using prebiopsy MRI. American Journal of Roentgenology 2014;203:341-346.	Patients already have suspected PCa
Mirak SA, Shakeri S, Bajgiran AM, et al. Three Tesla Multiparametric Magnetic Resonance Imaging: Comparison of Performance with and without Endorectal Coil for Prostate Cancer Detection, PI-RADSTM version 2 Category and Staging with Whole Mount Histopathology Correlation. Journal of Urology 2019;201:496-502.	Patients already have suspected PCa
Misrai V, Kerever S, Pasquie M, et al. Does mechanical morcellation of large glands compromise incidental prostate cancer detection on specimen analysis? A pathological comparison with open simple prostatectomy. World Journal of Urology 2019;37:1315-1320.	Patients already have suspected PCa

Reference	Reason for exclusion
Moller A, Olsson H, Gronberg H, et al. The Stockholm3 blood-test predicts clinically-significant cancer on biopsy: independent validation in a multi-center community cohort. Prostate Cancer and Prostatic Diseases 2019;22:137-142.	Patients already have suspected PCa
Moraes MO, Roman DHH, Copetti J, et al. Effects of the addition of quantitative apparent diffusion coefficient data on the diagnostic performance of the PI-RADS v2 scoring system to detect clinically significant prostate cancer. World Journal of Urology 2019;07:07.	Patients already have suspected PCa
Morisot A, Bessaoud F, Landais P, et al. Prostate cancer: net survival and cause-specific survival rates after multiple imputation. BMC medical research methodology 2015;15:54.	Patients already have confirmed BPH or PCa
Morote J, Celma A, Planas J, et al. Diagnostic accuracy of prostate health index to identify aggressive prostate cancer. An Institutional validation study. Actas Urologicas Espanolas 2016;40:378-85.	Patients already have suspected PCa
Morrison BF, Aiken WD, Mayhew R, et al. Prostate Cancer Knowledge, Prevention, and Screening Behaviors in Jamaican Men. Journal of cancer education : the official journal of the American Association for Cancer Education 2017;32:352-356.	No relevant outcomes
Morrison BF, Aiken W, Mayhew R, et al. Prostate cancer screening in Jamaica: Results of the largest national screening clinic. Journal of Cancer Epidemiology 2016;2016 (no pagination).	Irrelevant study type
Murray NP, Reyes E, Orellana N, et al. A comparative performance analysis of total PSA, percentage free PSA, PSA velocity, and PSA density versus the detection of primary circulating prostate cells in predicting initial prostate biopsy findings in chilean men. BioMed Research International 2014;2014 (no pagination).	Patients already have suspected PCa
Murray NP, Reyes E, Orellana N, et al. Prostate cancer screening in the fit Chilean elderly: a head to head comparison of total serum PSA versus age adjusted PSA versus primary circulating prostate cells to detect prostate cancer at initial biopsy. Asian Pacific Journal of Cancer Prevention: Apjcp 2015;16:601-6.	Patients already have suspected PCa
Murtola TJ, Karppa EK, Taari K, et al. 5-Alpha reductase inhibitor use and prostate cancer survival in the Finnish Prostate Cancer Screening Trial. International journal of cancer 2016;138:2820-2828.	No relevant outcomes
Murtola TJ, Kasurinen TVJ, Talala K, et al. Serum cholesterol and prostate cancer risk in the Finnish randomized study of screening for prostate cancer. Prostate Cancer and Prostatic Diseases 2019;22:66-76.	No relevant outcomes
Murtola TJ, Salli SM, Talala K, et al. Blood glucose, glucose balance, and disease-specific survival after prostate cancer diagnosis in the Finnish Randomized Study of Screening for Prostate Cancer. Prostate cancer and prostatic diseases 2019.	Patients already have confirmed BPH or PCa
Murtola TJ, Vettenranta AM, Talala K, et al. Outcomes of Prostate-specific Antigen-based Prostate Cancer Screening Among Men Using Nonsteroidal Anti-inflammatory Drugs. European Urology Focus 2018;4:851-857.	No relevant outcomes
Murtola TJ, Vihervuori VJ, Lahtela J, et al. Fasting blood glucose, glycaemic control and prostate cancer risk in the Finnish Randomized Study of Screening for Prostate Cancer. British journal of cancer 2018;118:1248-1254.	No relevant outcomes
Murtola TJ, Virkku A, Talala K, et al. Outcomes of Prostate Cancer Screening by 5α-Reductase Inhibitor Use. Journal of urology 2017;198:305-309.	No relevant outcomes
Murtola T, Salli S, Talala K, et al. Blood glucose balance and disease-specific survival after prostate cancer diagnosis in the Finnish Randomized Study of Prostate Cancer Screening. European urology, supplements 2018;17:e378-.	Full-text not in English, published pre-2014 or irrelevant publication type
Murtola T, Vettenranta A, Talala K, et al. Outcomes of PSA-based prostate cancer screening among men using nonsteroidal anti-inflammatory drugs. European urology, supplements 2017;16:e424-.	Full-text not in English, published pre-2014 or irrelevant publication type
Murtola T, Vihervuori V, Talala K, et al. Fasting blood glucose and prostate cancer risk in the finnish randomized study of screening for prostate cancer. Journal of urology 2017;197:e896-e897.	Full-text not in English, published pre-2014 or irrelevant publication type
Murtola T, Virkku A, Talala K, et al. Effect of 5-alfa reductase inhibitor usage on outcomes of prostate cancer screening. Journal of urology 2017;197:e751-.	Full-text not in English, published pre-2014 or irrelevant publication type
Na R, Ye D, Qi J, et al. Prostate health index significantly reduced unnecessary prostate biopsies in patients with PSA 2-10 ng/mL and PSA >10 ng/mL: Results from a Multicenter Study in China. Prostate 2017;77:1221-1229.	Patients already have suspected PCa
Nason GJ, Selvarajah L, O'Connor EM, et al. The predictive ability of pre-operative magnetic resonance imaging to detect pathological outcomes in prostate cancer. Irish Medical Journal 2018;111:790.	Patients already have suspected PCa

Reference	Reason for exclusion
Nct. Predicting Prostate Biopsy Results With Biomarkers and mpMRI. Https://clinicaltrials.gov/show/nct03730324 2018.	Patients already have suspected PCa
Nct. Prostate Cancer Detection Using the Stockholm3 Test and MR/Fusion Biopsies. Https://clinicaltrials.gov/show/nct03377881 2017.	Full-text not in English, published pre-2014 or irrelevant publication type
Nct. MRI Versus PSA in Prostate Cancer Screening. Https://clinicaltrials.gov/show/nct02799303 2016.	Full-text not in English, published pre-2014 or irrelevant publication type
Nct. A Randomized Trial of Early Detection of Clinically Significant Prostate Cancer (ProScreen). Https://clinicaltrials.gov/show/nct03423303 2018.	Full-text not in English, published pre-2014 or irrelevant publication type
Nct. Improving Prostate Cancer Detection Using MRI-Targeted TRUS-Guided Biopsy. Https://clinicaltrials.gov/show/nct02488096 2015.	Patients already have suspected PCa
Ng CF, Chiu PKF, Lam NY, et al. The Prostate Health Index in predicting initial prostate biopsy outcomes in Asian men with prostate-specific antigen levels of 4-10 ng/mL. International Urology and Nephrology 2014;46:711-717.	Patients already have suspected PCa
Niaf E, Lartizien C, Bratan F, et al. Prostate focal peripheral zone lesions: characterization at multiparametric MR imaging--influence of a computer-aided diagnosis system. Radiology 2014;271:761-9.	Patients already have suspected PCa
Nicholson A, Mahon J, Boland A, et al. The clinical effectiveness and cost-effectiveness of the PROGENSA prostate cancer antigen 3 assay and the prostate health index in the diagnosis of prostate cancer: A systematic review and economic evaluation. Health Technology Assessment 2015;19:1-191.	Full-text not in English, published pre-2014 or irrelevant publication type
Nickens KP, Ali A, Scoggin T, et al. Prostate cancer marker panel with single cell sensitivity in urine. Prostate 2015;75:969-975.	Patients already have suspected PCa
NiMhurchu E, O'Kelly F, Murphy IG, et al. Predictive value of PI-RADS classification in MRI-directed transrectal ultrasound guided prostate biopsy. Clinical Radiology 2016;71:375-80.	Patients already have suspected PCa
Nitta S, Tsutsumi M, Sakka S, et al. Machine learning methods can more efficiently predict prostate cancer compared with prostate-specific antigen density and prostate-specific antigen velocity. Prostate International 2019;7:114-118.	Patients already have suspected PCa
Niu XK, He WF, Zhang Y, et al. Developing a new PI-RADS v2-based nomogram for forecasting high-grade prostate cancer. Clinical radiology 2017;72:458-464.	Patients already have suspected PCa
Niu XK, Li J, Das SK, et al. Developing a nomogram based on multiparametric magnetic resonance imaging for forecasting high-grade prostate cancer to reduce unnecessary biopsies within the prostate-specific antigen gray zone. BMC medical imaging 2017;17:11.	Patients already have suspected PCa
Nnabugwu II, Udeh EI, Ugwumba FO, et al. Predicting Gleason score using the initial serum total prostate-specific antigen in Black men with symptomatic prostate adenocarcinoma in Nigeria. Clinical Interventions in Aging 2016;11:961-966.	Patients already have confirmed BPH or PCa
Nordstrom T, Adolfsson J, Gronberg H, et al. Effects of increasing the PSA cutoff to perform additional biomarker tests before prostate biopsy. BMC Urology 2017;17:92.	No relevant outcomes
Nordstrom T, Jaderling F, Carlsson S, et al. Does a novel diagnostic pathway including blood-based risk prediction and MRI-targeted biopsies outperform prostate cancer screening using prostate-specific antigen and systematic prostate biopsies? Protocol of the randomised study STHLM3MRI. BMJ Open 2019;9 (6) (no pagination).	Full-text not in English, published pre-2014 or irrelevant publication type
Nordstrom T, Picker W, Aly M, et al. Detection of Prostate Cancer Using a Multistep Approach with Prostate-specific Antigen, the Stockholm 3 Test, and Targeted Biopsies: The STHLM3 MRI Project. European Urology Focus 2017;3:526-528.	Full-text not in English, published pre-2014 or irrelevant publication type
Nordstrom T, Vickers A, Assel M, et al. Comparison Between the Four-kallikrein Panel and Prostate Health Index for Predicting Prostate Cancer. European Urology 2015;68:139-46.	Irrelevant study type
Nowroozi MR, Amini S, Kasaeian A, et al. Development, validation and comparison of two nomograms predicting prostate cancer at initial 12-core biopsy. Asia-Pacific Journal of Clinical Oncology 2016;12:e289-97.	Patients already have suspected PCa
Oishi M, Shin T, Ohe C, et al. Which Patients with Negative Magnetic Resonance Imaging Can Safely Avoid Biopsy for Prostate Cancer? Journal of Urology 2019;201:268-277.	Patients already have suspected PCa
Olleik G, Kassouf W, Aprikian A, et al. Evaluation of new tests and interventions for prostate cancer management: A systematic review. JNCCN Journal of the National Comprehensive Cancer Network 2018;16:1340-1351.	Patients already have suspected PCa

Reference	Reason for exclusion
O'Malley PG, Nguyen DP, Al Hussein Al Awamlh B, et al. Racial Variation in the Utility of Urinary Biomarkers PCA3 and T2ERG in a Large Multicenter Study. Journal of urology 2017;(no pagination).	Patients already have suspected PCa
Osses DF, Remmers S, Schroder FH, et al. Results of Prostate Cancer Screening in a Unique Cohort at 19 yr of Follow-up. European Urology 2019;75:374-377.	Full-text not in English, published pre-2014 or irrelevant publication type
Ozcan S, Diri MA, Bagcioglu M, et al. Complications and prostate cancer diagnosis rate of TRUS prostate biopsies using 16 and 18G needles by Clavien scoring. Urologia Journal 2017;84:236-239.	Patients already have suspected PCa
Paez A, Lujan M, Angulo JC, et al. Prostate cancer incidence and mortality in the Spanish section of the European Randomized Study of Screening for Prostate Cancer (ERSPC). European urology, supplements. 2014;13:e849.	Full-text not in English, published pre-2014 or irrelevant publication type
Pakarainen TJ, Tammela T, Raitanen J, et al. Risk of prostate cancer after PSA screening: results from the Finnish section of ERSPC. European urology, supplements. 2015;14:e24.	Full-text not in English, published pre-2014 or irrelevant publication type
Pal RP, Ahmad R, Trecartan S, et al. A Single Center Evaluation of the Diagnostic Accuracy of Multiparametric Magnetic Resonance Imaging against Transperineal Prostate Mapping Biopsy: An Analysis of Men with Benign Histology and Insignificant Cancer following Transrectal Ultrasound Biopsy. Journal of Urology 2018;200:302-308.	Patients already have suspected PCa
Palsdottir T, Nordstrom T, Aly M, et al. A Unified Prostate Cancer Risk Prediction Model Combining the Stockholm3 Test and Magnetic Resonance Imaging. European urology oncology. 2018;08.	Patients already have suspected PCa
Palsdottir T, Nordstrom T, Aly M, et al. Are Prostate Specific-Antigen (PSA) and age associated with the risk of ISUP Grade 1 prostate cancer? Results from 72 996 individual biopsy cores in 6 083 men from the Stockholm3 study. PLoS ONE 2019;14 (6) (no pagination).	Patients already have suspected PCa
Panebianco V, Barchetti G, Simone G, et al. Negative Multiparametric Magnetic Resonance Imaging for Prostate Cancer: What's Next? [Figure presented]. European Urology 2018;74:48-54.	Patients already have suspected PCa
Park H, Lee SW, Song G, et al. Diagnostic Performance of %[-2]proPSA and Prostate Health Index for Prostate Cancer: Prospective, Multi-institutional Study. Journal of Korean medical science 2018;33:e94.	Patients already have suspected PCa
Park JY, Yoon S, Park MS, et al. Development and external validation of the Korean prostate cancer risk calculator for high-grade prostate cancer: Comparison with two western risk calculators in an asian cohort. PLoS ONE 2017;12 (1) (no pagination).	Patients already have suspected PCa
Patrick AL, Nelson JB, Weissfeld JL, et al. Prostate cancer screening in men of African descent: 15-year results of the tobago prostate cancer survey. West Indian Medical Journal 2018;67:334-343.	Irrelevant study type
Pepe P, Garufi A, Priolo G, et al. Can 3-Tesla pelvic phased-array multiparametric MRI avoid unnecessary repeat prostate biopsy in patients with PSA < 10 ng/mL? Clinical Genitourinary Cancer 2015;13:e27-30.	Patients already have suspected PCa
Pereira-Azevedo N, Braga I, Verbeek JFM, et al. Prospective evaluation on the effect of interobserver variability of digital rectal examination on the performance of the Rotterdam Prostate Cancer Risk Calculator. International Journal of Urology 2017;24:826-832.	Patients already have suspected PCa
Pereira-Azevedo N, Osorio L, Fraga A, et al. Rotterdam Prostate Cancer Risk Calculator: Development and Usability Testing of the Mobile Phone App. JMIR Cancer 2017;3:e1.	No relevant outcomes
Pickersgill NA, Vetter JM, Raval NS, et al. The Accuracy of Prostate Magnetic Resonance Imaging Interpretation: Impact of the Individual Radiologist and Clinical Factors. Urology 2019;127:68-73.	Patients already have suspected PCa
Pierre-Victor D, Pinsky PF. Association of Nonadherence to Cancer Screening Examinations with Mortality from Unrelated Causes: A Secondary Analysis of the PLCO Cancer Screening Trial. JAMA Internal Medicine 2019;179:196-203.	No relevant outcomes
Ploussard G, Aronson S, Pelsser V, et al. Impact of the type of ultrasound probe on prostate cancer detection rate and characterization in patients undergoing MRI-targeted prostate biopsies using cognitive fusion. World Journal of Urology 2014;32:977-83.	Patients already have suspected PCa
Ploussard G, Nicolaiew N, Marchand C, et al. Prospective evaluation of an extended 21-core biopsy scheme as initial prostate cancer diagnostic strategy. European Urology 2014;65:154-61.	Patients already have suspected PCa
Pokorny MR, de Rooij M, Duncan E, et al. Prospective study of diagnostic accuracy comparing prostate cancer detection by transrectal ultrasound-guided biopsy versus magnetic resonance	Patients already have suspected PCa

Reference	Reason for exclusion
(MR) imaging with subsequent MR-guided biopsy in men without previous prostate biopsies. European Urology 2014;66:22-9.	
Polanec SH, Pinker-Domenig K, Brader P, et al. Multiparametric MRI of the prostate at 3 T: limited value of 3D (1)H-MR spectroscopy as a fourth parameter. World journal of urology 2016;34:649-656.	Patients already have suspected PCa
Poyet C, Nieboer D, Bhindi B, et al. Prostate cancer risk prediction using the novel versions of the European Randomised Study for Screening of Prostate Cancer (ERSPC) and Prostate Cancer Prevention Trial (PCPT) risk calculators: Independent validation and comparison in a contemporary European cohort. BJU International 2016;117:401-408.	Patients already have suspected PCa
Pron G. Prostate-Specific Antigen (PSA)-Based Population Screening for Prostate Cancer: An Evidence-Based Analysis. Ontario Health Technology Assessment Series 2015;15:1-64.	Full-text not in English, published pre-2014 or irrelevant publication type
Punnen S, Nahar B, Soodana-Prakash N, et al. Optimizing patient's selection for prostate biopsy: A single institution experience with multi-parametric MRI and the 4Kscore test for the detection of aggressive prostate cancer. PLoS ONE [Electronic Resource] 2018;13:e0201384.	Patients already have suspected PCa
Qiu S, Yang L, Wei Q. Magnetic resonance imaging-guided prostate biopsies fail to outperform standard transrectal ultrasound-guided biopsy in detecting high-risk prostate cancer: a Bayesian network meta-analysis of 24 randomised controlled trials. Journal of urology 2017;197:e19-.	Full-text not in English, published pre-2014 or irrelevant publication type
Radtke JP, Wiesenfarth M, Kesch C, et al. Combined Clinical Parameters and Multiparametric Magnetic Resonance Imaging for Advanced Risk Modeling of Prostate Cancer-Patient-tailored Risk Stratification Can Reduce Unnecessary Biopsies. European Urology 2017;72:888-896.	Patients already have suspected PCa
Rahal AK, Badgett RG, Hoffman RM. Screening coverage needed to reduce mortality from prostate cancer: A living systematic review. PLoS ONE 2016;11 (4) (no pagination).	Full-text not in English, published pre-2014 or irrelevant publication type
Rainato G, Fabricio ASC, Zancan M, et al. Evaluating serum insulin-like growth factor 1 and insulin-like growth factor binding protein 3 as markers in prostate cancer diagnosis. International Journal of Biological Markers 2016;31:e317-e323.	Patients already have suspected PCa
Rais-Bahrami S, Siddiqui MM, Vourganti S, et al. Diagnostic value of biparametric magnetic resonance imaging (MRI) as an adjunct to prostate-specific antigen (PSA)-based detection of prostate cancer in men without prior biopsies. BJU International 2015;115:381-388.	Patients already have suspected PCa
Randazzo M, Beatrice J, Huber A, et al. A "PSA pyramid" for men with initial prostate-specific antigen ≤3 ng/ml: a plea for individualized prostate cancer screening. European urology 2015;68:591-597.	Irrelevant screening programme or comparator/irrelevant index test, reference standard or comparator
Randazzo M, Beatrice J, Huber A, et al. Influence of metformin use on PSA values, free-to-total PSA, prostate cancer incidence and grade and overall survival in a prospective screening trial (ERSPC Aarau). World journal of urology 2015;33:1189-1196.	No relevant outcomes
Randazzo M, Müller A, Carlsson S, et al. A positive family history as a risk factor for prostate cancer in a population-based study with organised prostate-specific antigen screening: results of the Swiss European Randomised Study of Screening for Prostate Cancer (ERSPC, Aarau). BJU international 2016;117:576-583.	No relevant outcomes
Ravipaty S, Wu W, Dalvi A, et al. Clinical Validation of a Serum Protein Panel (FLNA, FLNB and KRT19) for Diagnosis of Prostate Cancer. Journal of Molecular Biomarkers & Diagnosis 2017;8.	Patients already have suspected PCa
Remmers S, Verbeek JFM, Nieboer D, et al. Predicting biochemical recurrence and prostate cancer-specific mortality after radical prostatectomy: comparison of six prediction models in a cohort of patients with screening- and clinically detected prostate cancer. BJU International. 2019.	Patients already have confirmed BPH or PCa
Renard-Penna R, Roupret M, Comperat E, et al. Relationship between non-suspicious MRI and insignificant prostate cancer: results from a monocentric study. World journal of urology 2016;34:673-678.	Patients already have suspected PCa
Rienks J, Barbaresko J, Nothlings U. Association of isoflavone biomarkers with risk of chronic disease and mortality: A systematic review and meta-analysis of observational studies. Nutrition Reviews 2017;75:616-641.	Irrelevant screening programme or comparator/irrelevant index test, reference standard or comparator

Reference	Reason for exclusion
Roberts MJ, Chow CWK, Schirra HJ, et al. Diagnostic performance of expression of PCA3, hepsin and mir biomarkers inejaculate in combination with serum PSA for the detection of prostate cancer. Prostate 2015;75:539-549.	Patients already have suspected PCa
Roethke MC, Kuru TH, Mueller-Wolf MB, et al. Evaluation of an automated analysis tool for prostate cancer prediction using multiparametric magnetic resonance imaging. PLoS ONE 2016;11 (7) (no pagination).	Patients already have suspected PCa
Roobol MJ, Vedder MM, Nieboer D, et al. Comparison of Two Prostate Cancer Risk Calculators that Include the Prostate Health Index. European Urology Focus 2015;1:185-190.	Patients already have suspected PCa
Rosenkrantz AB, Rice SL, Wehrli NE, et al. Association between changes in suspicious prostate lesions on serial MRI examinations and follow-up biopsy results. Clinical Imaging 2015;39:264-269.	Patients already have suspected PCa
Rottgen R, Paersch B, Eichstadt H, et al. Perfusion and diffusion in prostate MRI: Computer-based fusion of multiparametric imaging data in the diagnostic evaluation of prostate cancer. Perfusion (Germany) 2016;29:156-162.	Full-text not in English, published pre-2014 or irrelevant publication type
Roumeguere T, Legrand F, Rassy EE, et al. A prospective clinical study of the implications of IL-8 in the diagnosis, aggressiveness and prognosis of prostate cancer. Future Science OA 2018;4 (2) (no pagination).	Patients already have suspected PCa
Rubio-Briones J, Borque A, Esteban LM, et al. Optimizing the clinical utility of PCA3 to diagnose prostate cancer in initial prostate biopsy. BMC Cancer 2015;15 (1) (no pagination).	Patients already have suspected PCa
Rubio-Briones J, Casanova J, Martinez F, et al. PCA3 como biomarcador de segunda linea en un programa de screening oportunista prospectivo, aleatorizado y controlado, PCA3 as a second-line biomarker in a prospective controlled randomized opportunistic prostate cancer screening programme. Actas urologicas espanolas 2017;41:300-308.	Full-text not in English, published pre-2014 or irrelevant publication type
Ruffion A, Perrin P, Devonec M, et al. Additional value of PCA3 density to predict initial prostate biopsy outcome. World journal of urology 2014;32:917-923.	Patients already have suspected PCa
Russo GI, Regis F, Castelli T, et al. A Systematic Review and Meta-analysis of the Diagnostic Accuracy of Prostate Health Index and 4-Kallikrein Panel Score in Predicting Overall and High-grade Prostate Cancer. Clinical Genitourinary Cancer 2017;15:429-439.e1.	Patients already have suspected PCa
Saarimaki L, Hugosson J, Tammela TL, et al. Impact of Prostatic-specific Antigen Threshold and Screening Interval in Prostate Cancer Screening Outcomes: comparing the Swedish and Finnish European Randomised Study of Screening for Prostate Cancer Centres. European urology focus 2017.	Irrelevant screening programme or comparator/irrelevant index test, reference standard or comparator
Saarimaki L, Tammela TL, Maattanen L, et al. Family history in the finnish prostate cancer screening trial. International Journal of Cancer 2015;136:2172-2177.	No relevant outcomes
Sanchis-Bonet A, Barrionuevo-Gonzalez M, Bajo-Chueca A, et al. Does [-2]Pro-Prostate Specific Antigen Meet the Criteria to Justify Its Inclusion in the Clinical Decision-Making Process? Urologia Internationalis 2018;100:146-154.	Patients already have suspected PCa
Sanda MG, Feng Z, Howard DH, et al. Association between combined TMPRSS2:ERG and PCA3 RNA urinary testing and detection of aggressive prostate cancer. JAMA Oncology 2017;3:1085-1093.	Patients already have suspected PCa
Saquib N, Saquib J, Ioannidis JPA. Does screening for disease save lives in asymptomatic adults? Systematic review of meta-analyses and randomized trials. International Journal of Epidemiology 2015;44:264-277.	Full-text not in English, published pre-2014 or irrelevant publication type
Sarre S, Maattanen L, Tammela TLJ, et al. Postscreening follow-up of the Finnish Prostate Cancer Screening Trial on putative prostate cancer risk factors: vitamin and mineral use, male pattern baldness, pubertal development and non-steroidal anti-inflammatory drug use. Scandinavian journal of urology 2016;50:267-273.	Irrelevant screening programme or comparator/irrelevant index test, reference standard or comparator
Sasaki M, Ishidoya S, Ito A, et al. Low percentage of free prostate-specific antigen (PSA) is a strong predictor of later detection of prostate cancer among japanese men with serum levels of total PSA of 4.0 ng/mL or less. Urology 2014;84:1163-1167.	Patients already have suspected PCa
Schalk SG, Huang J, Li J, et al. 3-D Quantitative Dynamic Contrast Ultrasound for Prostate Cancer Localization. Ultrasound in Medicine and Biology 2018;44:807-814.	Patients already have suspected PCa
Schimmoller L, Blondin D, Arsov C, et al. MRI-guided in-bore biopsy: Differences between prostate cancer detection and localization in primary and secondary biopsy settings. American Journal of Roentgenology 2016;206:92-99.	Patients already have suspected PCa

Reference	Reason for exclusion
Schimmoller L, Quentin M, Arsov C, et al. MR-sequences for prostate cancer diagnostics: validation based on the PI-RADS scoring system and targeted MR-guided in-bore biopsy. European Radiology 2014;24:2582-9.	Patients already have suspected PCa
Schoots IG, Roobol MJ, Nieboer D, et al. Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. European Urology 2014:epub.	Patients already have suspected PCa
Schoots IG, Roobol MJ, Nieboer D, et al. Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: a systematic review and meta-analysis. European Urology 2015;68:438-50.	Patients already have suspected PCa
Schwen ZR, Tosoian JJ, Sokoll LJ, et al. Prostate Health Index (PHI) Predicts High-stage Pathology in African American Men. Urology 2016;90:136-140.	Patients already have suspected PCa
Scott E, Adolfsson J, Aly M, et al. Prostate cancer screening in men aged 50 to 69 years (STHLM3): A prospective population-based diagnostic study. Gronberg H, Adolfsson J, Aly M, Nordstrom T, Wiklund P, Brandberg Y, Thompson J, Wiklund F, Lindberg J, Clements M, Egevad L, Eklund M.Lancet Oncol. 2015 Dec;16(16):1667-76. [Epub 2015 Nov 10]. doi: 10.1016/S1470-2045(15)00361-7. Urologic Oncology: Seminars and Original Investigations 2017;35:120.	Full-text not in English, published pre-2014 or irrelevant publication type
Seibert TM, Fan CC, Wang Y, et al. Polygenic hazard score to guide screening for aggressive prostate cancer: development and validation in large scale cohorts. BMJ 2018;360:j5757.	No relevant outcomes
Seisen T, Roupret M, Brault D, et al. Accuracy of the prostate health index versus the urinary prostate cancer antigen 3 score to predict overall and significant prostate cancer at initial biopsy. Prostate 2015;75:103-111.	Patients already have suspected PCa
Shen P, Zhao J, Sun G, et al. The roles of prostate-specific antigen (PSA) density, prostate volume, and their zone-adjusted derivatives in predicting prostate cancer in patients with PSA less than 20.0 ng/mL. Andrology 2017;5:548-555.	Patients already have suspected PCa
Sheridan AD, Nath SK, Aneja S, et al. MRI-ultrasound fusion targeted biopsy of prostate imaging reporting and data system version 2 category 5 lesions found false-positive at multiparametric prostate MRI. American Journal of Roentgenology 2018;210:W218-W225.	Patients already have suspected PCa
Sheridan AD, Nath SK, Syed JS, et al. Risk of clinically signifcant prostate cancer associated with prostate imaging reporting and data system category 3 (equivocal) lesions identifed on multiparametric prostate MRI. American Journal of Roentgenology 2018;210:347-357.	Patients already have suspected PCa
Shin T, Smyth TB, Ukimura O, et al. Diagnostic accuracy of a five-point Likert scoring system for magnetic resonance imaging (MRI) evaluated according to results of MRI/ultrasonography image-fusion targeted biopsy of the prostate. BJU International 2018;121:77-83.	Patients already have suspected PCa
Shin T, Smyth TB, Ukimura O, et al. Detection of prostate cancer using magnetic resonance imaging/ultrasonography image-fusion targeted biopsy in African-American men. BJU International 2017;120:233-238.	Patients already have suspected PCa
Shinmoto H, Tamura C, Soga S, et al. Anterior prostate cancer: Diagnostic performance of T2-weighted MRI and an apparent diffusion coefficient map. American Journal of Roentgenology 2015;205:W185-W192.	Patients already have suspected PCa
Shoag J, Halpern J, Eisner B, et al. Efficacy of Prostate-Specific Antigen Screening: use of Regression Discontinuity in the PLCO Cancer Screening Trial. JAMA oncology 2015;1:984-986.	Full-text not in English, published pre-2014 or irrelevant publication type
Shoag J, Savenkov O, Christos PJ, et al. Vasectomy and risk of prostate cancer in a screening trial. Cancer epidemiology biomarkers and prevention 2017;26:1653-1659.	No relevant outcomes
Shoaibi A, Rao GA, Cai B, et al. The use of multiphase nonlinear mixed models to define and quantify long-term changes in serum prostate-specific antigen: data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Annals of Epidemiology 2016;26:36-42.e2.	Irrelevant study type
Shore N, Hafron J, Langford T, et al. Urinary molecular biomarker test impacts prostate biopsy decision making in clinical practice. Urology Practice 2019;6:256-260.	No relevant outcomes
Sidana A, Watson MJ, George AK, et al. Fusion prostate biopsy outperforms 12-core systematic prostate biopsy in patients with prior negative systematic biopsy: A multi-institutional analysis. Urologic Oncology 2018;36:341.e1-341.e7.	Patients already have suspected PCa
Siddiqui MM, George AK, Rubin R, et al. Efficiency of Prostate Cancer Diagnosis by MR/Ultrasound Fusion-Guided Biopsy vs Standard Extended-Sextant Biopsy for MR-Visible Lesions. Journal of the National Cancer Institute 2016;108 (9) (no pagination).	Patients already have suspected PCa

Reference	Reason for exclusion
Sipeky C, Gao P, Zhang Q, et al. Synergistic interaction of HOXB13 and CIP2A predisposes to aggressive prostate cancer. Clinical Cancer Research 2018;24:6265-6276.	Irrelevant study type
Sjoberg DD, Vickers AJ, Assel M, et al. Twenty-year Risk of Prostate Cancer Death by Midlife Prostate-specific Antigen and a Panel of Four Kallikrein Markers in a Large Population-based Cohort of Healthy Men. European Urology 2018;73:941-948.	No relevant outcomes
Somford DM, Vreuls W, Jansen TS, et al. Incremental value of transition zone and midline apical biopsy at baseline TRUS-guided biopsy for prostate cancer detection. World Journal of Urology 2014;32:461-467.	Patients already have suspected PCa
Sprinkart AM, Marx C, Traber F, et al. Evaluation of Exponential ADC (eADC) and Computed DWI (cDWI) for the Detection of Prostate Cancer. Rofo: Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin 2018;190:758-766.	Patients already have suspected PCa
Spyropoulos E, Kotsiris D, Spyropoulos K, et al. Prostate Cancer Predictive Simulation Modelling, Assessing the Risk Technique (PCP-SMART): Introduction and Initial Clinical Efficacy Evaluation Data Presentation of a Simple Novel Mathematical Simulation Modelling Method, Devised to Predict the Outcome of Prostate Biopsy on an Individual Basis. Clinical Genitourinary Cancer 2017;15:129-138.e1.	Patients already have suspected PCa
Sriplakich S, Lojanapiwat B, Chongruksut W, et al. Prospective performance of the Prostate Health Index in prostate cancer detection in the first prostate biopsy of men with a total prostatic specific antigen of 4-10 ng/mL and negative digital rectal examination. Prostate International 2018;6:136-139.	Patients already have suspected PCa
Stephan C, Wilkosz J, Rozanski W, et al. Urinary thiosulfate as failed prostate cancer biomarker - an exemplary multicenter re-evaluation study. Clinical Chemistry & Laboratory Medicine 2015;53:477-83.	Patients already have confirmed BPH or PCa
Sterling WA, Weiner J, Schreiber D, et al. The impact of African American race on prostate cancer detection on repeat prostate biopsy in a veteran population. International Urology and Nephrology 2016;48:2015-2021.	Patients already have suspected PCa
Steuber T, Tennstedt P, Macagno A, et al. Thrombospondin 1 and cathepsin D improve prostate cancer diagnosis by avoiding potentially unnecessary prostate biopsies. BJU International 2019;123:826-833.	Patients already have suspected PCa
Su R, Xu G, Xiang L, et al. A Novel Scoring System for Prediction of Prostate Cancer Based on Shear Wave Elastography and Clinical Parameters. Urology 2018;121:112-117.	Patients already have suspected PCa
Sutton SS, Crawford ED, Moul JW, et al. Determining optimal prostate-specific antigen thresholds to identify an increased 4-year risk of prostate cancer development: an analysis within the Veterans Affairs Health Care System. World journal of urology 2016;34:1107-1113.	Irrelevant screening programme or comparator/irrelevant index test, reference standard or comparator
Tan TW, Png KS, Lee CH, et al. MRI Fusion-Targeted Transrectal Prostate Biopsy and the Role of Prostate-Specific Antigen Density and Prostate Health Index for the Detection of Clinically Significant Prostate Cancer in Southeast Asian Men. Journal of Endourology 2017;31:1111-1116.	Patients already have suspected PCa
Taverna G, Bozzini G, Grizzi F, et al. Endorectal multiparametric 3-tesla magnetic resonance imaging associated with systematic cognitive biopsies does not increase prostate cancer detection rate: a randomized prospective trial. World journal of urology 2016;34:797-803.	Patients already have suspected PCa
Tewes S, Peters I, Tiemeyer A, et al. Evaluation of MRI/Ultrasound Fusion-Guided Prostate Biopsy Using Transrectal and Transperineal Approaches. BioMed research international 2017;2017:2176471.	Patients already have suspected PCa
Tijani KH, Anunobi CC, Adeyomoye AO, et al. The role of the percentage free PSA in the diagnosis of prostate cancer in Blacks: Findings in indigenous West African men using TRUS guided biopsy. African Journal of Urology 2017;23:14-19.	Patients already have suspected PCa
Tonttila PP, Lantto J, Paakko E, et al. Prebiopsy Multiparametric Magnetic Resonance Imaging for Prostate Cancer Diagnosis in Biopsy-naive Men with Suspected Prostate Cancer Based on Elevated Prostate-specific Antigen Values: Results from a Randomized Prospective Blinded Controlled Trial. European Urology 2016;69:419-425.	Patients already have suspected PCa
Topaktas R, Urkmez A, Kutluhan MA, et al. Does plasma thiol and disulphide be a new marker for prostate cancer in prostate-specific antigen level between 10 and 20 ng/ml? Aging Male. 2019.	Patients already have suspected PCa
Transin S, Souchon R, Gonindard-Melodelima C, et al. Computer-aided diagnosis system for characterizing ISUP grade >= 2 prostate cancers at multiparametric MRI: A cross-vendor evaluation. Diagnostic and Interventional Imaging. 2019.	Patients already have suspected PCa

Reference	Reason for exclusion
Tsivian M, Gupta RT, Tsivian E, et al. Assessing clinically significant prostate cancer: Diagnostic properties of multiparametric magnetic resonance imaging compared to three-dimensional transperineal template mapping histopathology. International Journal of Urology 2017;24:137-143.	Patients already have suspected PCa
Tu X, Liu Z, Chang T, et al. Transperineal Magnetic Resonance Imaging-Targeted Biopsy May Perform Better Than Transrectal Route in the Detection of Clinically Significant Prostate Cancer: Systematic Review and Meta-analysis. Clinical Genitourinary Cancer. 2019.	Patients already have suspected PCa
Turner EL, Metcalfe C, Donovan JL, et al. Design and preliminary recruitment results of the Cluster randomised triAl of PSA testing for Prostate cancer (CAP). British journal of cancer 2014;110:2829-2836.	No relevant outcomes
Ucer O, Muezzinoglu T, Celen I, et al. The effect on the sensitivities of PSA and PSA-age volume score of IPSS and nocturia in predicting positive prostate biopsy findings. African Journal of Urology 2017;23:116-119.	Patients already have suspected PCa
Ucer O, Yucetas U, Celen I, et al. Assessment of PSA-Age volume score in predicting positive prostate biopsy findings in Turkey. International braz j urol : official journal of the Brazilian Society of Urology 2015;41:864-868.	Patients already have suspected PCa
Valerio M, Donaldson I, Emberton M, et al. Detection of clinically significant prostate cancer using magnetic resonance imaging-ultrasound fusion targeted biopsy: a systematic review. European Urology 2014:epub.	Full-text not in English, published pre-2014 or irrelevant publication type
van der Leest M, Cornel E, Israel B, et al. Head-to-head Comparison of Transrectal Ultrasound-guided Prostate Biopsy Versus Multiparametric Prostate Resonance Imaging with Subsequent Magnetic Resonance-guided Biopsy in Biopsy-naive Men with Elevated Prostate-specific Antigen: A Large Prospective Multicenter Clinical Study(Figure presented.). European Urology 2019;75:570-578.	Patients already have suspected PCa
van Hove A, Savoie PH, Maurin C, et al. Comparison of image-guided targeted biopsies versus systematic randomized biopsies in the detection of prostate cancer: a systematic literature review of well-designed studies. World journal of urology 2014;32:847-858.	Irrelevant screening programme or comparator/irrelevant index test, reference standard or comparator
van Leeuwen PJ, Hayen A, Thompson JE, et al. A multiparametric magnetic resonance imaging-based risk model to determine the risk of significant prostate cancer prior to biopsy. BJU International 2017;120:774-781.	Patients already have suspected PCa
Van Neste L, Hendriks RJ, Dijkstra S, et al. Detection of High-grade Prostate Cancer Using a Urinary Molecular Biomarker-Based Risk Score. European urology 2016;70:740-748.	Patients already have suspected PCa
Veitonmaki T, Murtola TJ, Maattanen L, et al. Use of non-steroidal anti-inflammatory drugs and prostate cancer survival in the finnish prostate cancer screening trial. Prostate 2015;75:1394-1402.	No relevant outcomes
Venderbos L, Bangma C, Roobol M. The prevalence and progression of lower urinary tract symptoms in an ageing population-results from the European Randomized study of Screening for Prostate Cancer (Rotterdam). European urology, supplements 2017;16:e689-e690.	Full-text not in English, published pre-2014 or irrelevant publication type
Venderink W, de Rooij M, Sedelaar JPM, et al. Elastic Versus Rigid Image Registration in Magnetic Resonance Imaging-transrectal Ultrasound Fusion Prostate Biopsy: A Systematic Review and Meta-analysis. European Urology Focus 2018;4:219-227.	Irrelevant screening programme or comparator/irrelevant index test, reference standard or comparator
Verma A, St Onge J, Dhillon K, et al. PSA density improves prediction of prostate cancer. The Canadian journal of urology 2014;21:7312-7321.	Patients already have suspected PCa
Verma S, Sarkar S, Young J, et al. Evaluation of the impact of computed high b-value diffusion-weighted imaging on prostate cancer detection. Abdominal Radiology 2016;41:934-45.	Patients already have suspected PCa
Vickers AJ, Sjoberg DD, Ulmert D, et al. Empirical estimates of prostate cancer overdiagnosis by age and prostate-specific antigen. BMC medicine 2014;12:26.	No relevant outcomes
Vlaeminck-Guillem V, Devonec M, Champetier D, et al. Urinary PCA3 to predict prostate cancer in a cohort of 1015 patients. Progres en urologie : journal de l'Association francaise d'urologie et de la Societe francaise d'urologie 2015;25:1160-8, e1-8.	Full-text not in English, published pre-2014 or irrelevant publication type
Vukovic I, Djordjevic D, Bojanic N, et al. Predictive value of [-2]propsa (p2psa) and its derivatives for the prostate cancer detection in the 2.0 to 10.0ng/mL PSA range. International braz j urol : official journal of the Brazilian Society of Urology 2017;43:48-56.	Patients already have suspected PCa

Reference	Reason for exclusion
Walsh AL, Considine SW, Thomas AZ, et al. Digital rectal examination in primary care is important for early detection of prostate cancer: A retrospective cohort analysis study. British Journal of General Practice 2014;64:e783-e787.	No relevant outcomes
Wang BR, Chen CC, Zheng RH, et al. Comparison of cancer detection between 18- and 12-core prostate biopsy in Asian patients with prostate-specific antigen levels of 4-20 ng/mL. Journal of the Chinese Medical Association: JCMA 2018;81:1044-1051.	Patients already have suspected PCa
Wang F, Ren S, Chen R, et al. Development and prospective multicenter evaluation of the long noncoding RNA MALAT-1 as a diagnostic urinary biomarker for prostate cancer. Oncotarget 2014;5:11091-11102.	Patients already have suspected PCa
Wang HY, Hsieh CH, Wen CN, et al. Cancers screening in an asymptomatic population by using multiple tumour markers. PLoS ONE 2016;11 (6) (no pagination).	Patients already have suspected PCa
Wang H, Tai S, Zhang L, et al. Integrated formulas to forecast prostate cancer: The parameters of influencing the prostate specific antigen level as an adjunct to prostate specific antigen and multi-parametric MRI to predict prostate cancer before biopsy. Translational Cancer Research 2017;6:1180-1187.	Patients already have suspected PCa
Wang NN, Teslovich NC, Fan RE, et al. Applying the PRECISION approach in biopsy naive and previously negative prostate biopsy patients. Urologic Oncology: Seminars and Original Investigations 2019;37:530.e19-530.e24.	Patients already have suspected PCa
Wang R, Gao G, Wang H, et al. Evaluation of diagnostic efficacy of Prostate Imaging and Reporting Data System Version 2 in detection of prostate clinically significant cancer. [Chinese]. Chinese Journal of Medical Imaging Technology 2016;32:1799-1802.	Full-text not in English, published pre-2014 or irrelevant publication type
Wang T, Qu X, Jiang J, et al. Diagnostic significance of urinary long non-coding PCA3 RNA in prostate cancer. Oncotarget 2017;8:58577-58586.	Irrelevant study type
Wang W, Wang M, Wang L, et al. Diagnostic ability of %p2PSA and prostate health index for aggressive prostate cancer: a meta-analysis. Scientific Reports 2014;4:5012.	Full-text not in English, published pre-2014 or irrelevant publication type
Wang X, Liu M, Wang J, et al. T2-weighted/diffusion-weighted magnetic resonance imaging as a novel scoring mode for the early detection of prostate cancer. Journal of urology. 2015;193:e121.	Full-text not in English, published pre-2014 or irrelevant publication type
Wang X, Wang JY, Li CM, et al. Evaluation of the prostate imaging reporting and data system for magnetic resonance imaging diagnosis of prostate cancer in patients with prostate-specific antigen <20 ng/ml. Chinese Medical Journal 2016;129:1432-1438.	Patients already have suspected PCa
Washino S, Kobayashi S, Okochi T, et al. Cancer detection rate of prebiopsy MRI with subsequent systematic and targeted biopsy are superior to non-targeting systematic biopsy without MRI in biopsy naive patients: a retrospective cohort study. BMC Urology 2018;18:51.	Patients already have suspected PCa
Wegelin O, van Melick HHE, Hooft L, et al. Comparing Three Different Techniques for Magnetic Resonance Imaging-targeted Prostate Biopsies: A Systematic Review of In-bore versus Magnetic Resonance Imaging-transrectal Ultrasound fusion versus Cognitive Registration. Is There a Preferred Technique? European Urology 2017;71:517-531.	Irrelevant screening programme or comparator/irrelevant index test, reference standard or comparator
Wei JT, Feng Z, Partin AW, et al. Can urinary PCA3 Supplement PSA in the early detection of prostate cancer? Journal of Clinical Oncology 2014;32:4066-4072.	Patients already have suspected PCa
Woo S, Suh CH, Eastham JA, et al. Comparison of Magnetic Resonance Imaging-stratified Clinical Pathways and Systematic Transrectal Ultrasound-guided Biopsy Pathway for the Detection of Clinically Significant Prostate Cancer: A Systematic Review and Meta-analysis of Randomized Controlled Trials. European urology oncology. 2019;13.	Patients already have suspected PCa
Woo S, Suh CH, Kim SY, et al. Head-To-Head Comparison Between High- and Standard-b-Value DWI for Detecting Prostate Cancer: A Systematic Review and Meta-Analysis. AJR. American Journal of Roentgenology 2018;210:91-100.	Patients already have confirmed BPH or PCa
Wu YS, Fu XJ, Na R, et al. Phi-based risk calculators performed better in the prediction of prostate cancer in the Chinese population. Asian journal of andrology. 2019;22.	Patients already have suspected PCa
Wu YS, Wu XB, Zhang N, et al. Evaluation of PSA-age volume score in predicting prostate cancer in Chinese population. Asian Journal of Andrology 2018;20:324-329.	Patients already have suspected PCa
Wulaningsih W, Astuti Y, Matsuguchi T, et al. Circulating Prostate-Specific Antigen and Telomere Length in a Nationally Representative Sample of Men Without History of Prostate Cancer. Prostate 2017;77:22-32.	No relevant outcomes
Xie SW, Dong BJ, Xia JG, et al. The utility and limitations of contrast-enhanced transrectal ultrasound scanning for the detection of prostate cancer in different area of prostate. Clinical Hemorheology and Microcirculation 2018;70:281-290.	Patients already have suspected PCa

Reference	Reason for exclusion
Xu G, Feng L, Yao M, et al. A new 5-grading score in the diagnosis of prostate cancer with real-time elastography. International journal of clinical and experimental pathology 2014;7:4128-4135.	Patients already have suspected PCa
Xu N, Wu YP, Chen DN, et al. Can Prostate Imaging Reporting and Data System Version 2 reduce unnecessary prostate biopsies in men with PSA levels of 4-10 ng/ml? Journal of Cancer Research and Clinical Oncology 2018;144:987-995.	Patients already have suspected PCa
Xue WJ, Ying XL, Jiang JH, et al. Prostate cancer antigen 3 as a biomarker in the urine for prostate cancer diagnosis: A meta-analysis. Journal of Cancer Research and Therapeutics 2014;10:C218-C221.	Full-text not in English, published pre-2014 or irrelevant publication type
Yanai Y, Kosaka T, Hongo H, et al. Evaluation of prostate-specific antigen density in the diagnosis of prostate cancer combined with magnetic resonance imaging before biopsy in men aged 70 years and older with elevated PSA. Molecular and Clinical Oncology 2018;9:656-660.	Patients already have suspected PCa
Yao YH, Wang H, Li BG, et al. Evaluation of the TMPRSS2: ERG fusion for the detection of prostate cancer: a systematic review and meta-analysis. Tumor Biology 2014;35:2157-2166.	Full-text not in English, published pre-2014 or irrelevant publication type
Yeboah FA, Acheampong E, Gyasi-Sarpong CK, et al. Nomogram for predicting the probability of the positive outcome of prostate biopsies among Ghanaian men. African Journal of Urology 2018;24:45-53.	Patients already have suspected PCa
Yerramilli D, Walsh E, Turner E, et al. Cancer-related morbidity at the end of life in men with prostate cancer. Journal of clinical oncology 2018;36.	Full-text not in English, published pre-2014 or irrelevant publication type
Yilmaz H, Ciftci S, Yavuz U, et al. Percentage of free prostate-specific antigen (PSA) is a useful method in deciding to perform prostate biopsy with higher core numbers in patients with low PSA cut-off values. Kaohsiung Journal of Medical Sciences 2015;31:315-319.	Patients already have suspected PCa
Yoneyama T, Tobisawa Y, Kaneko T, et al. Clinical significance of the LacdiNAc-glycosylated prostate-specific antigen assay for prostate cancer detection. Cancer Science 2019;110:2573-2589.	Patients already have suspected PCa
Yong L, Xin G, Peng H, et al. Prostate cancer antigen 3 test for prostate biopsy decision: a systematic review and meta analysis. Chinese Medical Journal 2014;127:1768-1774.	Full-text not in English, published pre-2014 or irrelevant publication type
Yoshida R, Yoshizako T, Katsube T, et al. Computed diffusion-weighted imaging using 1.5-T magnetic resonance imaging for prostate cancer diagnosis. Clinical Imaging 2017;41:78-82.	Patients already have confirmed BPH or PCa
Yu GP, Na R, Ye DW, et al. Performance of the Prostate Health Index in predicting prostate biopsy outcomes among men with a negative digital rectal examination and transrectal ultrasonography. Asian Journal of Andrology 2016;18:633-638.	Patients already have suspected PCa
Yuri P, Wangge G, Abshari F, et al. Indonesian prostate cancer risk calculator (IPCRC): an application for predicting prostate cancer risk (a multicenter study). Acta medica Indonesiana 2015;47:95-103.	Patients already have confirmed BPH or PCa
Zambon JP, Almeida FG, Conceicao RD, et al. Prostate-specific antigen testing in men between 40 and 70 years in Brazil: database from a check-up program. International braz j urol : official journal of the Brazilian Society of Urology 2014;40:745-752.	Patients already have suspected PCa
Zhang L, Chang H, Strauss GM. PSA (Prostate-Specific-Antigen) screening to improve outcome in prostate cancer (PC): reanalysis of the Prostate-Lung-Colorectal- Ovary (PLCO) randomized controlled trial (RCT). Journal of clinical oncology 2018;36.	Full-text not in English, published pre-2014 or irrelevant publication type
Zhang X, Li G, Hu L, et al. Resistive index of prostatic capsular arteries as a predictor of prostate cancer in patients undergoing initial prostate biopsy. Medical Oncology 2014;31:297.	Patients already have suspected PCa
Zhang X, Quan X, Lu S, et al. The clinical value of dynamic contrast-enhanced magnetic resonance imaging at 3.0T to detect prostate cancer. Journal of International Medical Research 2014;42:1077-84.	Patients already have suspected PCa
Zheng Y, Huang Y, Cheng G, et al. Developing a new score system for patients with PSA ranging from 4 to 20 ng/mL to improve the accuracy of PCa detection. Springerplus 2016;5:1484.	Patients already have suspected PCa
Zhu Y, Han CT, Zhang GM, et al. Development and external validation of a prostate health index-based nomogram for predicting prostate cancer. Scientific reports 2015;5:15341.	Patients already have suspected PCa

Table 38. Publications excluded after review of full-text articles for question 4

Reference	Reason for exclusion
Actrn. Randomised phase 3 trial of enzalutamide in androgen deprivation therapy with radiation therapy for high risk, clinically localised, prostate cancer. Http://www.who.int/trialsearch/trial2.aspx? Trialid=actrn12614000126617 2014.	Full-text not in English, published pre-2014 or irrelevant publication type
Actrn. Randomised Study Assessing Urinary Continence following Robotic Radical Prostatectomy with or without an intraoperative 'RoboSling'. http://www.who.int/trialsearch/Trial2.aspx?TrialID=ACTRN12618002058257 2018.	Full-text not in English, published pre-2014 or irrelevant publication type
Adam S, Feller A, Rohrmann S, et al. Health-related quality of life among long-term (>=5years) prostate cancer survivors by primary intervention: A systematic review. Health and Quality of Life Outcomes 2018;16 (1) (no pagination).	Irrelevant study type
Ahlberg MS, Adami HO, Beckmann K, et al. PCASTt/SPCG-17-A randomised trial of active surveillance in prostate cancer: Rationale and design. BMJ Open 2019;9 (8) (no pagination).	Full-text not in English, published pre-2014 or irrelevant publication type
Alder R, Zetner D, Rosenberg J. Incidence of inguinal hernia after radical prostatectomy: a systematic review and meta-analysis. The Journal of urology 2019:101097JU0000000000000313.	Full-text not in English, published pre-2014 or irrelevant publication type
Aluwini S, Pos F, Schimmel E, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): acute toxicity results from a randomised non-inferiority phase 3 trial. The lancet. Oncology 2015;16:274-283.	Irrelevant patient population
Aluwini S, Pos F, Schimmel E, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with prostate cancer (HYPRO): late toxicity results from a randomised, non-inferiority, phase 3 trial. The Lancet Oncology 2016;17:464-474.	Irrelevant patient population
Amin MB, Lin DW, Gore JL, et al. The critical role of the pathologist in determining eligibility for active surveillance as a management option in patients with prostate cancer: consensus statement with recommendations supported by the College of American Pathologists, International Society of Urological Pathology, Association of Directors of Anatomic and Surgical Pathology, the New Zealand Society of Pathologists, and the Prostate Cancer Foundation. Archives of pathology & laboratory medicine 2014;138:1387-1405.	Full-text not in English, published pre-2014 or irrelevant publication type
Arcangeli G, Arcangeli S, Pinzi V, et al. Optimal scheduling of hypofractionated radiotherapy for localized prostate cancer: A systematic review and metanalysis of randomized clinical trials. Cancer Treatment Reviews 2018;70:22-29.	Full-text not in English, published pre-2014 or irrelevant publication type
Asimakopoulos AD, Topazio L, De Angelis M, et al. Retzius-sparing versus standard robot-assisted radical prostatectomy: a prospective randomized comparison on immediate continence rates. Surgical endoscopy 2018;(no pagination).	Irrelevant intervention or comparator
Bahl A, Challapalli A, Greenwood R, et al. Quality of life evaluation of the effect of decapeptyl compared with zoladex preradiotherapy: final results of randomised controlled trial. Journal of clinical oncology 2017;35.	Full-text not in English, published pre-2014 or irrelevant publication type
Benelli A, Varca V, Rosso M, et al. 3D versus 2D laparoscopic radical prostatectomy for organ confined prostate cancer: our experience. Journal of clinical urology 2018.	Irrelevant intervention or comparator
Bhattacharya IS, Taghavi Azar Sharabiani M, Alonzi R, et al. Hypoxia and angiogenic biomarkers in prostate cancer after external beam radiotherapy (EBRT) alone or combined with high-dose-rate brachytherapy boost (HDR-BTb). Radiotherapy and Oncology 2019;137:38-44.	Irrelevant patient population
Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. New England Journal of Medicine 2014;370:932-942.	Included in the updated SLR or any other included SLR
Bokhorst LP, Zappa M, Carlsson SV, et al. Correlation between stage shift and differences in mortality in the European Randomised study of Screening for Prostate Cancer (ERSPC). BJU International 2016;118:677-680.	No relevant outcomes
Bove P, Iacovelli V, Celestino F, et al. 3D vs 2D laparoscopic radical prostatectomy in organ-confined prostate cancer: comparison of operative data and pentafecta rates: a single cohort study. BMC urology 2015;15:12.	Irrelevant intervention or comparator
Carles J, Gallardo E, Domenech M, et al. Phase 2 Randomized Study of Radiation Therapy and 3-Year Androgen Deprivation With or Without Concurrent Weekly Docetaxel in High-Risk Localized Prostate Cancer Patients. International Journal of Radiation Oncology Biology Physics 2019;103:344-352.	Irrelevant patient population
Carneiro A, Deeke Sasse A, Aurel Wagner A, et al. Cardiovascular events associated with androgen deprivation therapy in patients with prostate cancer: a systematic review and meta-analysis. World Journal of Urology 2014:epub.	Full-text not in English, published pre-2014 or irrelevant publication type

Reference	Reason for exclusion
Carvalho IT, Baccaglini W, Claros OR, et al. Genitourinary and gastrointestinal toxicity among patients with localized prostate cancer treated with conventional versus moderately hypofractionated radiation therapy: systematic review and meta-analysis. Acta Oncologica 2018;57:1003-1010.	Full-text not in English, published pre-2014 or irrelevant publication type
Catton CN, Lukka H, Gu CS, et al. Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. Journal of Clinical Oncology 2017;35:1884-1890.	Included in the updated SLR or any other included SLR
Chandra RA, Chen MH, Zhang D, et al. Age, Comorbidity, and the Risk of Prostate Cancer-Specific Mortality in Men with Biopsy Gleason Score 4+3: Implications on Patient Selection for Multiparametric MRI. Clinical Genitourinary Cancer 2015;13:400-405.	No relevant outcomes
Chang K, Qin XJ, Zhang HL, et al. Comparison of two adjuvant hormone therapy regimens in patients with high-risk localized prostate cancer after radical prostatectomy: Primary results of study CU1005. Asian Journal of Andrology 2016;18:452-455.	Irrelevant patient population
Chen CH, Pu YS. Adjuvant androgen-deprivation therapy following prostate total cryoablation in high-risk localized prostate cancer patients - Open-labeled randomized clinical trial. Cryobiology 2018;82:88-92.	Irrelevant patient population
Cheng KKF, Lim EYT, Kanesvaran R. Quality of life of elderly patients with solid tumours undergoing adjuvant cancer therapy: A systematic review. BMJ Open 2018;8 (1) (no pagination).	Full-text not in English, published pre-2014 or irrelevant publication type
Chi CI. The efficiency and safety of transperitoneal versus extraperitoneal robotic-assisted laparoscopic radical prostatectomy for patients with prostate cancer: a single-center, prospective, randomized controlled trial. Http://www.who.int/trialsearch/trial2.aspx?Trialid=chictr-inr-17011299 2017.	Full-text not in English, published pre-2014 or irrelevant publication type
Correction to High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): a randomised, controlled, phase 3 trial. Lancet oncology 2015;16:e262.	Full-text not in English, published pre-2014 or irrelevant publication type
Coughlin GD, Yaxley JW, Chambers SK, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: 24-month outcomes from a randomised controlled study. Lancet oncology 2018;19:1051-1060.	Irrelevant patient population
Crawford ED, Shore ND, Moul JW, et al. Long-term tolerability and efficacy of degarelix: 5-year results from a phase III extension trial with a 1-arm crossover from leuprolide to degarelix. Urology 2014;83:1122-1128.	Irrelevant patient population
Ctri. Prostate Radiotherapy In high risk and node positive disease comparing Moderate & Extreme hypofractionation. Http://www.who.int/trialsearch/trial2.aspx?Trialid=ctri/2018/05/014054 2018.	Full-text not in English, published pre-2014 or irrelevant publication type
Dal Moro F, Crestani A, Valotto C, et al. Anesthesiologic effects of transperitoneal versus extraperitoneal approach during robot-assisted radical prostatectomy: results of a prospective randomized study. International braz j urol 2015;41:466-472.	Irrelevant intervention or comparator
D'Amico AV, Chen MH, Renshaw A, et al. Long-term Follow-up of a Randomized Trial of Radiation With or Without Androgen Deprivation Therapy for Localized Prostate Cancer. JAMA 2015;314:1291-3.	Full-text not in English, published pre-2014 or irrelevant publication type
De Carlo F, Celestino F, Verri C, et al. Retropubic, laparoscopic, and robot-assisted radical prostatectomy: surgical, oncological, and functional outcomes: a systematic review. Urologia Internationalis 2014;93:373-383.	Full-text not in English, published pre-2014 or irrelevant publication type
Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. The Lancet Oncology 2016;17:1047-1060.	Included in the updated SLR or any other included SLR
Dearnaley DP, Jovic G, Syndikus I, et al. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: Long-term results from the MRC RT01 randomised controlled trial. The Lancet Oncology 2014;15:464-473.	Irrelevant patient population
Demanes DJ, Ghilezan MI. High-dose-rate brachytherapy as monotherapy for prostate cancer. Brachytherapy 2014;13:529-541.	Full-text not in English, published pre-2014 or irrelevant publication type
Donis Canet F, Sanchez Gallego MD, Arias Funez F, et al. Cryotherapy versus high-intensity focused ultrasound for treating prostate cancer: Oncological and functional results. Actas Urologicas Espanolas 2017;14:14.	Full-text not in English, published pre-2014 or irrelevant publication type
Donovan JL, Hamdy FC, Lane JA, et al. Patient-Reported Outcomes after Monitoring, Surgery, or Radiotherapy for Prostate Cancer. New England journal of medicine 2016;375:1425-1437.	Included in the updated SLR or any other included SLR

Reference	Reason for exclusion
Dosani M, Morris J, Tyldesley S, et al. The relationship between hot flashes and testosterone recovery following 12 months of androgen suppression for men with localized prostate cancer in a randomized trial. International journal of radiation oncology 2016;96:S126-.	Full-text not in English, published pre-2014 or irrelevant publication type
Dosani M, Morris WJ, Tyldesley S, et al. The Relationship between Hot Flashes and Testosterone Recovery after 12 Months of Androgen Suppression for Men with Localised Prostate Cancer in the ASCENDE-RT Trial. Clinical oncology 2017;29:696-701.	Full-text not in English, published pre-2014 or irrelevant publication type
Drks. Prospective Randomized Study to Compare a Limited versus Extended Pelvine Lymphadenectomy during Prostatectomy - AP 77/13 of AUO. Http://www.who.int/trialsearch/trial2.aspx? Trialid=drks00012763 2017.	Full-text not in English, published pre-2014 or irrelevant publication type
Drks. Randomized, multicenter study comparing robot-assisted and conventional laparoscopic radical prostatectomy. Http://www.who.int/trialsearch/trial2.aspx? Trialid=drks00007138 2014.	Full-text not in English, published pre-2014 or irrelevant publication type
Dubray BM, Salleron J, Guerif SG, et al. Does short-term androgen depletion add to high dose radiotherapy (80 Gy) in localized intermediate risk prostate cancer? Final analysis of GETUG 14 randomized trial (EU-20503/ NCT00104741). Journal of clinical oncology 2016;34.	Full-text not in English, published pre-2014 or irrelevant publication type
Eade T, Hruby G, Booth J, et al. Results of a Prospective Dose Escalation Study of Linear Accelerator-Based Virtual Brachytherapy (BOOSTER) for Prostate Cancer; Virtual HDR Brachytherapy for Prostate Cancer. Advances in Radiation Oncology. 2019.	Irrelevant study type
Efstathiou E, Davis JW, Pisters L, et al. Clinical and Biological Characterisation of Localised High-risk Prostate Cancer: Results of a Randomised Preoperative Study of a Luteinising Hormone-releasing Hormone Agonist with or Without Abiraterone Acetate plus Prednisone. European Urology. 2019.	Irrelevant patient population
Efstathiou E, Davis JW, Titus MA, et al. Neoadjuvant enzalutamide (ENZA) and abiraterone acetate (AA) plus leuprolide acetate (LHRHa) versus AA+ LHRHa in localized high-risk prostate cancer (LHRPC). Journal of clinical oncology 2016;34.	Full-text not in English, published pre-2014 or irrelevant publication type
Euctr FI. A study of efficacy and safety of CAM2032 q1m compared to Eligard® in patients with prostate cancer. Http://www.who.int/trialsearch/trial2.aspx? Trialid=euctr2014-001074-34-fi 2014.	Full-text not in English, published pre-2014 or irrelevant publication type
Euctr FR. A phase II study in low risk prostate cancer patients to compare active surveillance with versus without an antiandrogenic treatment. Http://www.who.int/trialsearch/trial2.aspx? Trialid=euctr2016-001266-29-fr 2017.	Full-text not in English, published pre-2014 or irrelevant publication type
Euctr GB. Research study that is testing a new treatment combination for localised prostate cancer that is going to be treated with radiotherapy. This study is looking at combining a new drug, enzalutamide, with the current best available treatments in order to improve outcomes for men in this situation. This is a randomised controlled trial which means that half the participants on the trial will get enzalutamide and the other half will get current standard of care. Http://www.who.int/trialsearch/trial2.aspx? Trialid=euctr2014-003191-23-gb 2014.	Full-text not in English, published pre-2014 or irrelevant publication type
Euctr LT. Research study to determine whether an investigational product LiprocaÂ® Depot single injected into the prostate is safe, tolerable and effective in treatment of localized prostate cancer for patients assigned to active surveillance and who are at high risk for disease progression â€“ using a single blind and two-stage dose finding study design followed by an open label extension. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2016-002504-43-LT 2018.	Full-text not in English, published pre-2014 or irrelevant publication type
Euctr SE. An Efficacy and Safety Study of JNJ56021927 (ARN509) in High-risk Prostate Cancer Subjects Receiving Primary Radiation Therapy: ATLAS. Http://www.who.int/trialsearch/trial2.aspx? Trialid=euctr2015-003007-38-se 2015.	Full-text not in English, published pre-2014 or irrelevant publication type
Faure Walker NA, Norris JM, Shah TT, et al. A comparison of time taken to return to baseline erectile function following focal and whole gland ablative therapies for localized prostate cancer: A systematic review. Urologic Oncology: Seminars and Original Investigations 2018;36:67-76.	Irrelevant study type
Fazeli F, Nowroozi MR, Ayati M, et al. Comparison of the efficacy of two brands of triptorelin (Microrelin and Diphereline) in reducing prostate-specific antigen and serum testosterone in prostate cancer: A double-blinded randomized clinical trial. Nephro-Urology Monthly 2015;7 (3) (no pagination).	Irrelevant patient population
Fenton JJ, Weyrich MS, Durbin S, et al. Prostate-specific antigen-based screening for prostate cancer evidence report and systematic review for the us preventive services task force. JAMA - Journal of the American Medical Association 2018;319:1914-1931.	Irrelevant study type
Ferreira ASS, Guerra MR, Lopes HE, et al. Brachytherapy and radical prostatectomy in patients with early prostate cancer. Revista da Associacao Medica Brasileira 2015;61:431-439.	Irrelevant patient population

Reference	Reason for exclusion
Feutren T, Herrera FG. Prostate irradiation with focal dose escalation to the intraprostatic dominant nodule: a systematic review. Prostate International 2018;6:75-87.	Irrelevant study type
Fonteyne V, Sarrazyn C, Swimberghe M, et al. 4 Weeks Versus 5 Weeks of Hypofractionated High-dose Radiation Therapy as Primary Therapy for Prostate Cancer: Interim Safety Analysis of a Randomized Phase 3 Trial. International Journal of Radiation Oncology Biology Physics 2018;100:866-870.	Irrelevant patient population
Frey AU, Sonksen J, Fode M. Neglected side effects after radical prostatectomy: a systematic review. Journal of Sexual Medicine 2014;11:374-385.	Full-text not in English, published pre-2014 or irrelevant publication type
Giacalone NJ, Wu J, Chen MH, et al. Prostate-Specific Antigen Failure and Risk of Death Within Comorbidity Subgroups Among Men With Unfavorable-Risk Prostate Cancer Treated in a Randomized Trial. Journal of Clinical Oncology 2016;34:3781-3786.	No relevant outcomes
Giganti F, Gambarota G, Moore CM, et al. Prostate cancer detection using quantitative T2 and T2-weighted imaging: the effects of 5-alpha-reductase inhibitors in men on active surveillance. Journal of magnetic resonance imaging 2017;(no pagination).	No relevant outcomes
Gilbert SM, Dunn RL, Miller DC, et al. Functional Outcomes Following Nerve Sparing Prostatectomy Augmented with Seminal Vesicle Sparing Compared to Standard Nerve Sparing Prostatectomy: Results from a Randomized Controlled Trial. Journal of Urology 2017;198:600-607.	Irrelevant intervention or comparator
Golan R, Bernstein AN, McClure TD, et al. Partial Gland Treatment of Prostate Cancer Using High-Intensity Focused Ultrasound in the Primary and Salvage Settings: A Systematic Review. Journal of Urology 2017;198:1000-1009.	Full-text not in English, published pre-2014 or irrelevant publication type
Greco C, Pimentel N, Pares O, et al. Single-dose radiotherapy (SDRT) in the management of intermediate risk prostate cancer: early results from a phase II randomized trial. Journal of clinical oncology 2018;36.	Full-text not in English, published pre-2014 or irrelevant publication type
Habl G, Hatiboglu G, Edler L, et al. Ion Prostate Irradiation (IPI) - a pilot study to establish the safety and feasibility of primary hypofractionated irradiation of the prostate with protons and carbon ions in a raster scan technique. BMC cancer 2014;14:202.	Full-text not in English, published pre-2014 or irrelevant publication type
Hackshaw-Mcgeagh LE, Penfold CM, Walsh E, et al. Physical activity, alcohol consumption, BMI and smoking status before and after prostate cancer diagnosis in the ProtecT trial: opportunities for lifestyle modification. International journal of cancer 2015;137:1509-1515.	No relevant outcomes
Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. New England journal of medicine 2016;375:1415-1424.	Included in the updated SLR or any other included SLR
Hoffman KE, Voong KR, Levy LB, et al. Randomized Trial of Hypofractionated, Dose-Escalated, Intensity-Modulated Radiation Therapy (IMRT) versus conventionally fractionated IMRT for localized prostate cancer. Journal of Clinical Oncology 2018;36:2943-2949.	Included in the updated SLR or any other included SLR
Hoskin PJ, Rojas AM, Ostler PJ, et al. Dosimetric predictors of biochemical control of prostate cancer in patients randomised to external beam radiotherapy with a boost of high dose rate brachytherapy. Radiotherapy and oncology 2014;110:110-113.	Irrelevant patient population
Hou Z, Li G, Bai S. High dose versus conventional dose in external beam radiotherapy of prostate cancer: a meta-analysis of long-term follow-up. Journal of Cancer Research and Clinical Oncology 2014:epub.	Full-text not in English, published pre-2014 or irrelevant publication type
Huang RC, Auvinen A, Hakama M, et al. Effect of intervention on decision making of treatment for disease progression, prostate-specific antigen biochemical failure and prostate cancer death. Health expectations 2014;17:776-783.	Irrelevant patient population
Hussain M, Tangen CM, Thompson IM, et al. Phase III intergroup trial of adjuvant androgen deprivation with or without mitoxantrone plus prednisone in patients with high-risk prostate cancer after radical prostatectomy: SWOG S9921. Journal of Clinical Oncology 2018;36:1498-1504.	Irrelevant patient population
Ilic D, Evans SM, Allan CA, et al. Laparoscopic and robot-assisted vs open radical prostatectomy for the treatment of localized prostate cancer: a Cochrane systematic review. BJU International 2018;121:845-853.	Full-text not in English, published pre-2014 or irrelevant publication type
Ilic D, Evans SM, Allan CA, et al. Laparoscopic and robotic-assisted versus open radical prostatectomy for the treatment of localised prostate cancer. Cochrane Database of Systematic Reviews 2017.	Full-text not in English, published pre-2014 or irrelevant publication type
Incrocci L, Wortel RC, Alemayehu WG, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy	Included in the updated SLR or any other included SLR

Reference	Reason for exclusion
results from a randomised, multicentre, open-label, phase 3 trial. The Lancet Oncology 2016;17:1061-1069.	
Incrocci L, Wortel RC, Aluwini S, et al. Hypofractionated versus conventionally fractionated radiation therapy for prostate cancer: five-year oncologic outcomes of the Dutch randomized phase 3 HYPRO trial. International journal of radiation oncology biology physics 2016;94:1-2.	Full-text not in English, published pre-2014 or irrelevant publication type
Ishiyama H, Hirayama T, Jhaveri P, et al. Is there an increase in genitourinary toxicity in patients treated with transurethral resection of the prostate and radiotherapy? A systematic review. American Journal of Clinical Oncology 2014;37:297-304.	Full-text not in English, published pre-2014 or irrelevant publication type
Isrctn. Investigating the timing of high dose rate (HDR) brachytherapy with external beam radiation therapy (EBRT) in intermediate and high risk localised prostate cancer patients and its effects on toxicity and quality of life. Http://www.who.int/trialsearch/trial2.aspx? Trialid=isrctn15835424 2015.	Irrelevant patient population
Isrctn. SPCG-17 - when to treat men who are in active surveillance for prostate cancer, a randomized study comparing current practice with standardized triggers for initiation of curative treatment. Http://www.who.int/trialsearch/trial2.aspx? Trialid=isrctn64382660 2016.	Full-text not in English, published pre-2014 or irrelevant publication type
Joseph DJ, Lamb DS, Denham JW, et al. Ten year final results of the TROG 03.04 (RADAR) randomised phase 3 trial evaluating duration of androgen suppression ± zoledronate for locally advanced prostate cancer. Journal of clinical oncology 2018;36.	Full-text not in English, published pre-2014 or irrelevant publication type
Jprn U. A comparative study on the efficacies of gonadotropin-releasing hormone (GnRH) agonist and GnRH antagonist in neoadjuvant androgen deprivation therapy combined with transperineal prostate brachytherapy for localized prostate cancer. Http://www.who.int/trialsearch/trial2.aspx? Trialid=jprn-umin000015519 2014.	Full-text not in English, published pre-2014 or irrelevant publication type
Jprn U. A multi-institutional clinical trial of proton beam therapy for localized intermediate-risk prostate cancer. Http://www.who.int/trialsearch/trial2.aspx? Trialid=jprn-umin000025453 2017.	Irrelevant study type
Jprn U. efficacy of neoadjuvant androgen deprivation therapy fof high risk prostate cancer. Http://www.who.int/trialsearch/trial2.aspx? Trialid=jprn-umin000028874 2017.	Irrelevant study type
Jprn U. Study of the difference in clinical efficacy by the difference between the GnRH agonist and GnRH antagonist when adding short-term androgen deprivation therapy to definitive radiation therapy for localized intermediate-risk prostate cancer. Http://www.who.int/trialsearch/trial2.aspx? Trialid=jprn-umin000021806 2016.	Full-text not in English, published pre-2014 or irrelevant publication type
Jung JH, Risk MC, Goldfarb R, et al. Primary cryotherapy for localised or locally advanced prostate cancer. Cochrane Database of Systematic Reviews 2018;2018 (5) (no pagination).	Irrelevant patient population
Kass-Iliyya A, Jovic G, Murphy C, et al. Two-years Postradiotherapy Biopsies: Lessons from MRC RT01 Trial. European Urology 2018;73:968-976.	No relevant outcomes
Keane FK, Chen MH, Zhang D, et al. The likelihood of death from prostate cancer in men with favorable or unfavorable intermediate-risk disease. Cancer 2014;120:1787-1793.	No relevant outcomes
Klotz L, Miller K, Crawford ED, et al. Disease control outcomes from analysis of pooled individual patient data from five comparative randomised clinical trials of degarelix versus luteinising hormone-releasing hormone agonists. European Urology 2014;66:1101-1108.	Irrelevant patient population
Klotz L, Nabid A, Higano C, et al. Effect of dutasteride in men receiving intermittent androgen ablation therapy: The AVIAS trial. Canadian Urological Association Journal 2014;8:E789-94.	Irrelevant patient population
Koerber SA, Katayama S, Sander A, et al. Prostate bed irradiation with alternative radio-oncological approaches (PAROS) - A prospective, multicenter and randomized phase III trial. Radiation Oncology 2019;14 (1) (no pagination).	Full-text not in English, published pre-2014 or irrelevant publication type
Koontz BF, Bossi A, Cozzarini C, et al. A systematic review of hypofractionation for primary management of prostate cancer. European Urology 2014:epub.	Full-text not in English, published pre-2014 or irrelevant publication type
Krauss DJ, Hu C, Bahary JP, et al. Importance of local control in early-stage prostate cancer: Outcomes of patients with positive post-radiation therapy biopsy results treated in RTOG 9408. International Journal of Radiation Oncology Biology Physics 2015;92:863-873.	No relevant outcomes
Leslie T, Elliott D, Davies L, et al. A phase III study comparing partial prostate ablation versus radical prostatectomy (PART) in intermediate risk prostate cancer-initial data from the feasibility study. Journal of clinical urology 2018;11:61-62.	Full-text not in English, published pre-2014 or irrelevant publication type
Lestingi JFP, Guglielmetti G, Pontes J, et al. Extended versus limited pelvic lymphadenectomy during radical prostatectomy for intermediate- and high-risk prostate cancer: early outcomes from a randomized controlled phase III study. Journal of clinical oncology 2017;35.	Full-text not in English, published pre-2014 or irrelevant publication type
Linares-Espinos E, Carneiro A, Martinez-Salamanca JI, et al. New technologies and techniques for prostate cancer focal therapy. Minerva Urologica e Nefrologica 2018;70:252-263.	Full-text not in English, published pre-2014 or irrelevant publication type

Reference	Reason for exclusion
Loeb S, Bruinsma SM, Nicholson J, et al. Active surveillance for prostate cancer: A systematic review of clinicopathologic variables and biomarkers for risk stratification. European Urology 2015;67:619-626.	Full-text not in English, published pre-2014 or irrelevant publication type
Lukka H, Stephanie P, Bruner D, et al. Patient-reported outcomes in NRG Oncology/RTOG 0938, a randomized phase 2 study evaluating 2 ultrahypofractionated regimens (UHRs) for prostate cancer. International journal of radiation oncology biology physics 2016;94:2-.	Full-text not in English, published pre-2014 or irrelevant publication type
Mahal BA, Chen MH, Renshaw AA, et al. Early versus delayed initiation of salvage androgen deprivation therapy and risk of prostate cancer-specific mortality. JNCCN Journal of the National Comprehensive Cancer Network 2018;16:727-734.	No relevant outcomes
Majumder K, Nilsson S, Johansson H, et al. Higher sexual interest with androgen receptor inhibitor monotherapy than with castration plus an androgen receptor inhibitor in prostate cancer patients treated with curative radiotherapy, but otherwise small health-related quality of life differences: A randomised prospective 18-month follow-up study. European Journal of Cancer 2016;65:43-51.	Irrelevant patient population
Marandino L, De Luca E, Zichi C, et al. Quality-of-Life Assessment and Reporting in Prostate Cancer: Systematic Review of Phase 3 Trials Testing Anticancer Drugs Published Between 2012 and 2018. Clinical Genitourinary Cancer. 2019.	Irrelevant patient population
Marcello M, Ebert MA, Haworth A, et al. Association between measures of treatment quality and disease progression in prostate cancer radiotherapy: An exploratory analysis from the TROG 03.04 RADAR trial. Journal of Medical Imaging and Radiation Oncology 2018;62:248-255.	No relevant outcomes
Mason M, Richaud P, Bosnyak Z, et al. Degarelix Versus Goserelin Plus Bicalutamide in the Short-Term Relief of Lower Urinary Tract Symptoms in Prostate Cancer Patients: Results of a Pooled Analysis. LUTS: Lower Urinary Tract Symptoms 2017;9:82-88.	Irrelevant patient population
McKay RR, Xie W, Lis R, et al. Results of a phase II trial of neoadjuvant abiraterone + prednisone+ enzalutamide + leuprolide (APEL) versus enzalutamide + leuprolide (EL) for patients with high-risk localized prostate cancer (PC) undergoing radical prostatectomy (RP). Journal of clinical oncology 2018;36.	Full-text not in English, published pre-2014 or irrelevant publication type
McKay RR, Ye H, Xie W, et al. Evaluation of intense androgen deprivation before prostatectomy: A randomized Phase II trial of enzalutamide and leuprolide with or without abiraterone. Journal of Clinical Oncology 2019;37:923-931.	Irrelevant patient population
McKenzie M, Dearnaley D, Tombal B, et al. ATLAS: a randomized, double-blind, phase 3 study of ARN-509 in patients with high-risk localized or locally advanced prostate cancer receiving primary radiation therapy. Canadian urological association journal 2016;10:S73-S74.	Full-text not in English, published pre-2014 or irrelevant publication type
Menon M, Dalela D, Jamil M, et al. Functional Recovery, Oncologic Outcomes and Postoperative Complications after Robot-Assisted Radical Prostatectomy: An Evidence-Based Analysis Comparing the Retzius Sparing and Standard Approaches. Journal of Urology 2018;199:1210-1217.	Irrelevant patient population
Merrick GS, Wallner KE, Galbreath RW, et al. Is supplemental external beam radiation therapy necessary for patients with higher risk prostate cancer treated with ¹⁰³Pd? Results of two prospective randomized trials. Brachytherapy 2015;14:677-685.	Irrelevant patient population
Michalski JM, Moughan J, Purdy JA, et al. Initial results of a phase 3 randomized study of high dose 3DCRT/IMRT versus standard dose 3D-CRT/IMRT in patients treated for localized prostate cancer (RTOG 0126). International journal of radiation oncology biology physics. 2014;90:1263.	Full-text not in English, published pre-2014 or irrelevant publication type
Miki K, Sasaki H, Kido M, et al. A comparative study on the efficacies of gonadotropin-releasing hormone (GnRH) agonist and GnRH antagonist in neoadjuvant androgen deprivation therapy combined with transperineal prostate brachytherapy for localized prostate cancer. BMC cancer 2016;16.	No relevant outcomes
Mirhadi AJ, Zhang Q, Hanks GE, et al. Effect of Long-Term Hormonal Therapy (vs Short-Term Hormonal Therapy): A Secondary Analysis of Intermediate-Risk Prostate Cancer Patients Treated on NRG Oncology RTOG 9202. International Journal of Radiation Oncology Biology Physics 2017;97:511-515.	Irrelevant patient population
Moderate Hypofractionation in Intermediate- and High-Risk, Localized Prostate Cancer: health-Related Quality of Life From the Randomized, Phase 3 HYPRO Trial. International journal of radiation oncology biology physics 2019;103:823-833.	Irrelevant patient population
Monninkhof EM, van Loon JWL, van Vulpen M, et al. Standard whole prostate gland radiotherapy with and without lesion boost in prostate cancer: Toxicity in the FLAME randomized controlled trial. Radiotherapy and Oncology 2018;127:74-80.	Irrelevant patient population

Reference	Reason for exclusion
Montgomery B, Tretiakova MS, Joshua AM, et al. Neoadjuvant enzalutamide prior to prostatectomy. Clinical Cancer Research 2017;23:2169-2176.	Irrelevant patient population
Moore CM, Robertson NL, Jichi F, et al. The Effect of Dutasteride on Magnetic Resonance Imaging Defined Prostate Cancer: mAPPED-A Randomized, Placebo Controlled, Double-Blind Clinical Trial. Journal of urology 2017;197:1006-1013.	No relevant outcomes
Moore KL, Schmidt R, Moiseenko V, et al. Quantifying Unnecessary Normal Tissue Complication Risks due to Suboptimal Planning: a Secondary Study of RTOG 0126. International journal of radiation oncology, biology, physics 2015;92:228-235.	Irrelevant intervention or comparator
Moran BJ, Braccioforte MH. PSA outcomes in a single institution, prospective randomized 131CS/125I permanent prostate brachytherapy trial. Brachytherapy. 2014;13:S34-S35.	Full-text not in English, published pre-2014 or irrelevant publication type
Morgan SC, Hoffman K, Loblaw DA, et al. Hypofractionated Radiation Therapy for Localized Prostate Cancer: An ASTRO, ASCO, and AUA Evidence-Based Guideline. Journal of Urology 2018;09:09.	Full-text not in English, published pre-2014 or irrelevant publication type
Morgan SC, Hoffman K, Loblaw DA, et al. Hypofractionated Radiation Therapy for Localized Prostate Cancer: Executive Summary of an ASTRO, ASCO and AUA Evidence-Based Guideline. Journal of Urology 2019;201:528-534.	Full-text not in English, published pre-2014 or irrelevant publication type
Morgan SC, Hoffman K, Loblaw DA, et al. Hypofractionated Radiation Therapy for Localized Prostate Cancer: Executive Summary of an ASTRO, ASCO, and AUA Evidence-Based Guideline. Practical Radiation Oncology 2018;8:354-360.	Full-text not in English, published pre-2014 or irrelevant publication type
Morris WJ, Pickles T, Keyes M. Using a surgical prostate-specific antigen threshold of >0.2 ng/mL to define biochemical failure for intermediate- and high-risk prostate cancer patients treated with definitive radiation therapy in the ASCENDE-RT randomized control trial. Brachytherapy 2018;17:837-844.	Irrelevant patient population
Morton G, Chung H, McGuffin M, et al. Prostate hdr monotherapy: initial efficacy results from a randomized trial of one versus two fractions. Brachytherapy 2017;16:S19-S20.	Full-text not in English, published pre-2014 or irrelevant publication type
Moschini M, Carroll PR, Eggener SE, et al. Low-risk Prostate Cancer: Identification, Management, and Outcomes. European Urology 2017;72:238-249.	Full-text not in English, published pre-2014 or irrelevant publication type
Moteabbed M, Trofimov A, Khan FH, et al. Impact of interfractional motion on hypofractionated pencil beam scanning proton therapy and VMAT delivery for prostate cancer. Medical Physics 2018;45:4011-4019.	Full-text not in English, published pre-2014 or irrelevant publication type
Murray L, Henry A, Hoskin P, et al. Second primary cancers after radiation for prostate cancer: a systematic review of the clinical data and impact of treatment technique. Radiotherapy and Oncology 2014;110:213-228.	Full-text not in English, published pre-2014 or irrelevant publication type
Nabid A, Carrier N, Martin AG, et al. Duration of Androgen Deprivation Therapy in High-risk Prostate Cancer: A Randomized Phase III Trial. European Urology 2018;74:432-441.	Irrelevant patient population
Naismith OF, Griffin C, Syndikus I, et al. Forward- and Inverse-Planned Intensity-Modulated Radiotherapy in the CHHiP Trial: A Comparison of Dosimetry and Normal Tissue Toxicity. Clinical Oncology 2019;31:600-610.	No relevant outcomes
Nakai Y, Tanaka N, Anai S, et al. A Randomized Control Trial Comparing the Efficacy of Antiandrogen Monotherapy: flutamide vs. Bicalutamide. Hormones & cancer 2015;6:161-167.	No relevant outcomes
Nct. A Study of Apalutamide in Participants With High-Risk, Localized or Locally Advanced Prostate Cancer Who Are Candidates for Radical Prostatectomy. Https://clinicaltrials.gov/show/nct03767244 2018.	Full-text not in English, published pre-2014 or irrelevant publication type
Nct. A Study of Hormonal Therapy and Apalutamide With or Without Abiraterone Acetate and Prednisone in Newly Diagnosed Prostate Cancers. Https://clinicaltrials.gov/show/nct03436654 2018.	Irrelevant patient population
Nct. A Study to Evaluate the Safety, Tolerability and Efficacy of a Liproca® Depot Injection in Patients With Prostate Cancer. Https://clinicaltrials.gov/show/nct03348527 2017.	Full-text not in English, published pre-2014 or irrelevant publication type
Nct. An Efficacy and Safety Study of JNJ-56021927 (Apalutamide) in High-risk Prostate Cancer Subjects Receiving Primary Radiation Therapy: ATLAS. Https://clinicaltrials.gov/show/nct02531516 2015.	Full-text not in English, published pre-2014 or irrelevant publication type
Nct. Androgen Suppression With Stereotactic Body or External Beam Radiation Therapy (ASSERT). Https://clinicaltrials.gov/show/nct02594072 2015.	Irrelevant patient population

Reference	Reason for exclusion
Nct. Apalutamide With Radiotherapy and Androgen Deprivation Therapy in Prostate Cancer. Https://clinicaltrials.gov/show/nct03488810 2018.	Full-text not in English, published pre-2014 or irrelevant publication type
Nct. Comparison of Intermittent Androgen Deprivation Therapy With or Without Irradiation Recovery in Prostate Cancer Patients. Https://clinicaltrials.gov/show/nct03630666 2018.	Irrelevant patient population
Nct. Conventional or Hypofractionated Radiation Therapy in Treating Patients With Prostate Cancer. Https://clinicaltrials.gov/show/nct03987386 2019.	Full-text not in English, published pre-2014 or irrelevant publication type
Nct. Enzalutamide in Androgen Deprivation Therapy With Radiation Therapy for High Risk, Clinically Localised, Prostate Cancer. Https://clinicaltrials.gov/show/nct02446444 2015.	Full-text not in English, published pre-2014 or irrelevant publication type
Nct. Enzalutamide/Leuprolide +/- Abiraterone/Pred in Prostate. Https://clinicaltrials.gov/show/nct02268175 2014.	Full-text not in English, published pre-2014 or irrelevant publication type
Nct. Extended Pelvic Lymph Node Dissection vs. no Pelvic Lymph Node Dissection at Radical Prostatectomy for intermediate-and High-risk Prostate Cancer. Https://clinicaltrials.gov/show/nct03921996 2019.	Full-text not in English, published pre-2014 or irrelevant publication type
Nct. Feasibility Study of Stereotactic Body Radiotherapy (SBRT) for Localized Prostate Cancer: cyberknife vs. VMAT. Https://clinicaltrials.gov/show/nct02344667 2015.	Full-text not in English, published pre-2014 or irrelevant publication type
Nct. Hypofractionated Boost vs Conventionally Fractionated Boost for Localized High Risk Prostate Cancer. Https://clinicaltrials.gov/show/nct03526510 2018.	Full-text not in English, published pre-2014 or irrelevant publication type
Nct. Moderately Hypofractionated Radiotherapy for Prostate Cancer. Https://clinicaltrials.gov/show/nct03827616 2019.	Full-text not in English, published pre-2014 or irrelevant publication type
Nct. MRI Guided SBRT for Localized Prostate Cancer. Https://clinicaltrials.gov/show/nct03778112 2018.	Full-text not in English, published pre-2014 or irrelevant publication type
Nct. Neoadjuvant Androgen Deprivation Therapy Plus Abiraterone With or Without Apalutamide for High-Risk Prostate Cancer. Https://clinicaltrials.gov/show/nct02789878 2016.	Full-text not in English, published pre-2014 or irrelevant publication type
Nct. ODM-201 vs Androgen Deprivation Therapy in Hormone naïve Prostate Cancer. Https://clinicaltrials.gov/show/nct02972060 2016.	Irrelevant patient population
Nct. Open Anterograde Radical Prostatectomy Compared to Open Retrograde Technique. Https://clinicaltrials.gov/show/nct02687308 2016.	No relevant outcomes
Nct. Open- Label Trial of Sipuleucel-T Administered to Active Surveillance Patients for Newly Diagnosed Prostate Cancer. Https://clinicaltrials.gov/show/nct03686683 2018.	Irrelevant intervention or comparator
Nct. Optimal Prostate Study. Https://clinicaltrials.gov/show/nct03386045 2017.	Irrelevant patient population
Nct. Phase 3, Multicenter, Randomized Study, Evaluating the Efficacy and Tolerability of Focused HIFU (High Intensity Focused Ultrasound) Therapy Compared to Active Surveillance in Patients With Significant Low Risk Prostate Cancer. Https://clinicaltrials.gov/show/nct03531099 2018.	Full-text not in English, published pre-2014 or irrelevant publication type
Nct. Phase II Study of Ultra-high-dose Hypofractionated vs. Single-dose Image-Guided Radiotherapy for Prostate Cancer. Https://clinicaltrials.gov/show/nct02570919 2015.	Full-text not in English, published pre-2014 or irrelevant publication type
Nct. Prostate Boost Irradiation With Stereotactic Body RT (SBRT). Https://clinicaltrials.gov/show/nct03380806 2017.	Full-text not in English, published pre-2014 or irrelevant publication type
Nct. Prostate Radiotherapy Comparing Moderate and Extreme Hypo-fractionation (PRIME Trial). Https://clinicaltrials.gov/show/nct03561961 2018.	Full-text not in English, published pre-2014 or irrelevant publication type
Nct. Radical Retropubic Prostatectomy Versus Conventional External Beam Radiotherapy for Clinically Localized Prostate Cancer. Https://clinicaltrials.gov/show/nct02091661 2014.	Full-text not in English, published pre-2014 or irrelevant publication type
Nct. SPCG17: prostate Cancer Active Surveillance Trigger Trial. Https://clinicaltrials.gov/show/nct02914873 2016.	Full-text not in English, published pre-2014 or irrelevant publication type

Reference	Reason for exclusion
Nct. Study of Proscavax Vaccine in Patients With Localized Prostate Cancer vs Active Surveillance. Https://clinicaltrials.gov/show/nct03579654 2018.	Full-text not in English, published pre-2014 or irrelevant publication type
Nct. Timing of HDR With EBRT in Localised Prostate Cancer,Toxicity and Quality of Life Assessment. Https://clinicaltrials.gov/show/nct02618161 2015.	Irrelevant patient population
Nct. Trial Comparing Irradiation Plus Long Term Adjuvant Androgen Deprivation With GnRH Antagonist Versus GnRH Agonist Plus Flare Protection in Patients With Very High Risk Localized or Locally Advanced Prostate Cancer. Https://clinicaltrials.gov/show/nct02799706 2016.	Full-text not in English, published pre-2014 or irrelevant publication type
Nead KT, Boldbaatar N, Yang DD, et al. Association of Androgen Deprivation Therapy and Thromboembolic Events: A Systematic Review and Meta-analysis. Urology 2018;114:155-162.	Full-text not in English, published pre-2014 or irrelevant publication type
Nichols RC, Hu C, Bahary JP, et al. Serum testosterone changes in patients treated with radiation therapy alone for prostate cancer on NRG oncology RTOG 9408. Advances in Radiation Oncology 2017;2:608-614.	No relevant outcomes
Nouhi M, Mousavi SM, Olyaeemanesh A, et al. Long-Term Clinical Outcomes of Radical Prostatectomy versus Watchful Waiting in Localized Prostate Cancer Patients: A Systematic Review and Meta-Analysis. Iranian Journal of Public Health 2019;48:566-578.	Full-text not in English, published pre-2014 or irrelevant publication type
Parsons JK, Pierce JP, Mohler J, et al. Men's Eating and Living (MEAL) study (CALGB 70807 [Alliance]): recruitment feasibility and baseline demographics of a randomized trial of diet in men on active surveillance for prostate cancer. BJU international 2018;121:534-539.	Full-text not in English, published pre-2014 or irrelevant publication type
Pasalic D, Kuban DA, Allen PK, et al. Dose Escalation for Prostate Adenocarcinoma: A Long-Term Update on the Outcomes of a Phase 3, Single Institution Randomized Clinical Trial. International Journal of Radiation Oncology Biology Physics 2019;104:790-797.	No relevant outcomes
Petrelli F, Vavassori I, Coinu A, et al. Radical prostatectomy or radiotherapy in high-risk prostate cancer: a systematic review and metaanalysis. Clinical Genitourinary Cancer 2014;12:215-224.	Full-text not in English, published pre-2014 or irrelevant publication type
Pisansky TM, Hunt D, Gomella LG, et al. Duration of androgen suppression before radiotherapy for localized prostate cancer: Radiation therapy oncology group randomized clinical trial 9910. Journal of Clinical Oncology 2015;33:332-339.	No relevant outcomes
Qiu X, Xu L, Ma H, et al. Comparison of urinary continence between retziussparing robot-assisted radical prostatectomy and conventional robot-assisted radical prostatectomy: preliminary data from a prospective randomized controlled study. Journal of urology 2018;199:e568-.	Full-text not in English, published pre-2014 or irrelevant publication type
Ramsay CR, Adewuyi TE, Gray J, et al. Ablative therapy for people with localised prostate cancer: A systematic review and economic evaluation. Health Technology Assessment 2015;19:1-8.	Full-text not in English, published pre-2014 or irrelevant publication type
Reeves F, Preece P, Kapoor J, et al. Preservation of the neurovascular bundles is associated with improved time to continence after radical prostatectomy but not long-term continence rates: results of a systematic review and meta-analysis. European Urology 2014:epub.	Full-text not in English, published pre-2014 or irrelevant publication type
Roach M, Ceron Lizarraga TL, Lazar AA. Radical prostatectomy versus radiation and androgen deprivation therapy for clinically localized prostate cancer: How good is the evidence? International Journal of Radiation Oncology Biology Physics 2015;93:1064-1070.	Full-text not in English, published pre-2014 or irrelevant publication type
Roach M, Moughan J, Lawton CAF, et al. Sequence of hormonal therapy and radiotherapy field size in unfavourable, localised prostate cancer (NRG/RTOG 9413): long-term results of a randomised, phase 3 trial. The Lancet Oncology 2018;19:1504-1515.	No relevant outcomes
Roach M, Moughan J, Lawton CAF, et al. Sequence of hormonal therapy and radiotherapy field size in unfavourable, localised prostate cancer (NRG/RTOG 9413): long-term results of a randomised, phase 3 trial. The lancet. Oncology 2018;19:1504-1515.	Irrelevant patient population
Rodda S, Tyldesley S, Morris W. GU and GI toxicity in ASCENDE-RT*: a multicentre randomized trial of dose-escalated radiation for prostate cancer. Radiotherapy and oncology. 2015;115:S22-S23.	Full-text not in English, published pre-2014 or irrelevant publication type
Rosenthal SA, Hu C, Sartor O, et al. Effect of chemotherapy with docetaxel with androgen suppression and radiotherapy for localized high-risk prostate cancer: the randomized phase III NRG Oncology RTOG 0521 Trial. Journal of clinical oncology 2019;37:1159-1168.	No relevant outcomes
Rosenthal SA, Hunt D, Sartor AO, et al. A Phase 3 Trial of 2 Years of Androgen Suppression and Radiation Therapy With or Without Adjuvant Chemotherapy for High-Risk Prostate Cancer: final Results of Radiation Therapy Oncology Group Phase 3 Randomized Trial NRG Oncology RTOG 9902. International journal of radiation oncology, biology, physics 2015;93:294-302.	No relevant outcomes

Reference	Reason for exclusion
Royce TJ, Chen MH, Wu J, et al. A comparison of surrogate endpoints for all cause mortality in men with localized unfavorable-risk prostate cancer. Journal of clinical oncology 2017;35.	Full-text not in English, published pre-2014 or irrelevant publication type
Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Part II: Recommended Approaches and Details of Specific Care Options. Journal of Urology 2018;199:990-997.	Full-text not in English, published pre-2014 or irrelevant publication type
Sanford NN, Chen MH, Loffredo M, et al. Duration of the anti-androgen in men undergoing 6 months of an LHRH agonist and radiation therapy for unfavorable-risk prostate cancer and the risk of death. International journal of radiation oncology 2016;96:E226-E227.	Full-text not in English, published pre-2014 or irrelevant publication type
Sanguineti G, Giannarelli D, Petrongari MG, et al. Leukotoxicity after moderately Hypofractionated radiotherapy versus conventionally fractionated dose escalated radiotherapy for localized prostate Cancer: A secondary analysis from a randomized study. Radiation Oncology 2019;14 (1) (no pagination).	No relevant outcomes
Sasaki N, Yamazaki H, Shimizu D, et al. Long-term outcomes of a dose-reduction trial to decrease late gastrointestinal toxicity in patients with prostate cancer receiving soft tissue-matched image-guided intensity-modulated radiotherapy. Anticancer Research 2018;38:385-391.	Irrelevant patient population
Sayyid RK, Evans A, Hersey K, et al. A phase II, randomized, open-label study of neoadjuvant degarelix versus LHRH agonist in prostate cancer patients prior to radical prostatectomy. Clinical Cancer Research 2017;23:1974-1980.	Irrelevant patient population
Scheltema MJ, van den Bos W, de Bruin DM, et al. Focal vs extended ablation in localized prostate cancer with irreversible electroporation; a multi-center randomized controlled trial. BMC cancer 2016;16:299.	Full-text not in English, published pre-2014 or irrelevant publication type
Schmidt-Hansen M, Hoskin P, Kirkbride P, et al. Hormone and Radiotherapy versus Hormone or Radiotherapy Alone for Non-metastatic Prostate Cancer: A Systematic Review with Meta-analyses. Clinical Oncology 2014;26:21-46.	Full-text not in English, published pre-2014 or irrelevant publication type
Schmidt-Hansen M, Hoskin P, Kirkbride P, et al. Hormone and radiotherapy versus hormone or radiotherapy alone for non-metastatic prostate cancer: a systematic review with meta-analyses. Clinical Oncology 2014;26:e21-e46.	Full-text not in English, published pre-2014 or irrelevant publication type
Shah TT, Ahmed H, Kanthabalan A, et al. Focal cryotherapy of localized prostate cancer: a systematic review of the literature. Expert Review of Anticancer Therapy 2014;14:1337-1347.	Full-text not in English, published pre-2014 or irrelevant publication type
Shaikh T, Li T, Handorf EA, et al. Long-Term Patient-Reported Outcomes From a Phase 3 Randomized Prospective Trial of Conventional Versus Hypofractionated Radiation Therapy for Localized Prostate Cancer. International journal of radiation oncology, biology, physics 2017;97:722-731.	Irrelevant patient population
Shaikh T, Ruth K, Devarajan K, et al. Dosimetric and clinical predictors of long-term toxicity in patients undergoing hypofractionated prostate radiation therapy: results from a randomized phase 3 trial. International journal of radiation oncology 2016;96:S123-.	Full-text not in English, published pre-2014 or irrelevant publication type
Shimizu N, Minami T, Sugimoto K, et al. Efficacy of silodosin in patients undergoing brachytherapy: a randomized trial involving a pressure flow study. World journal of urology 2014;32:1423-1432.	Irrelevant intervention or comparator
Sierra Labarta CR, Sánchez Zalabardo D, de Pablo Cárdenas A. Quality of life in patients diagnosed of prostate cancer treated with continuous androgen deprivation therapy vs. intermittent therapy. Anales del sistema sanitario de navarra 2015;38:193-201.	Full-text not in English, published pre-2014 or irrelevant publication type
Simpkin AJ, Tilling K, Martin RM, et al. Systematic review and meta-analysis of factors determining change to radical treatment in active surveillance for localized prostate cancer. European Urology 2015;67:993-1005.	Full-text not in English, published pre-2014 or irrelevant publication type
Slovin SF, Melloni C, Mansor-Lefebvre S, et al. A multicenter, randomized, controlled trial comparing the occurrence of major adverse cardiovascular events (MACEs) in patients (PTS) with prostate cancer (pc) and cardiovascular disease (CVD) receiving degarelix (GnRH receptor antagonist) or leuprolide (GnRH receptor agonist). Journal of clinical oncology 2018;36.	Full-text not in English, published pre-2014 or irrelevant publication type
Sridharan K, Sivaramakrishnan G. Prostatectomies for localized prostate cancer: a mixed comparison network and cumulative meta-analysis. Journal of robotic surgery 2018;12:633-639.	Full-text not in English, published pre-2014 or irrelevant publication type
Sun F, Oyesanmi O, Fontanarosa J, et al. Agency for Healthcare Research and Quality 2014:12.	Full-text not in English, published pre-2014 or irrelevant publication type

Reference	Reason for exclusion
Sun F, Oyesanmi O, Fontanarosa J, et al. Therapies for clinically localized prostate cancer: update of a 2008 systematic review. 2014:1-137.	Full-text not in English, published pre-2014 or irrelevant publication type
Sun L, Zhu S, Zhao Y, et al. Who benefits from hypofractionated radiation therapy for clinically localized prostate cancer: evidence from meta-analysis. Tumor Biology 2014:epub.	Full-text not in English, published pre-2014 or irrelevant publication type
Taplin ME, Montgomery B, Logothetis CJ, et al. Intense androgen-deprivation therapy with abiraterone acetate plus leuprolide acetate in patients with localized high-risk prostate cancer: Results of a randomized phase II neoadjuvant study. Journal of Clinical Oncology 2014;32:3705-3715.	Irrelevant patient population
Taratkin M, Enikeev D, Rapoport L, et al. Comparative analysis of cryoablation, brachytherapy, HIFU and active surveillance: oncological outcomes in low-risk prostate cancer. European urology, supplements 2019;18:e1723-.	Full-text not in English, published pre-2014 or irrelevant publication type
Teo MY, Taplin ME, Eastham JA, et al. Metacure: multi-arm multimodality therapy for very high risk localized and low volume metastatic prostatic adenocarcinoma. Journal of clinical oncology 2019;37.	Full-text not in English, published pre-2014 or irrelevant publication type
Tian Z, Wang X, Wu P, et al. Comparison of radical prostatectomy versus conservative treatment in localized prostate cancer: systematic review and meta-analysis. Journal of B.U.ON 2019;: official journal of the Balkan Union of Oncology. 24:239-248.	Full-text not in English, published pre-2014 or irrelevant publication type
Tondel H, Lund J, Lydersen S, et al. Randomized controlled trial of Cone Beam CT IGRT in prostate cancer. Radiotherapy and oncology 2018;127:S258-.	Full-text not in English, published pre-2014 or irrelevant publication type
Tondel H, Lund JA, Lydersen S, et al. Radiotherapy for prostate cancer - Does daily image guidance with tighter margins improve patient reported outcomes compared to weekly orthogonal verified irradiation? Results from a randomized controlled trial. Radiotherapy and Oncology 2018;126:229-235.	Irrelevant intervention or comparator
Tosco L, Briganti A, D'Amico A V, et al. Systematic Review of Systemic Therapies and Therapeutic Combinations with Local Treatments for High-risk Localized Prostate Cancer. European Urology 2019;75:44-60.	Irrelevant patient population
Tosco L, Laenen A, Gevaert T, et al. Neoadjuvant degarelix with or without apalutamide followed by radical prostatectomy for intermediate and high-risk prostate cancer: ARNEO, a randomized, double blind, placebo-controlled trial. BMC Cancer 2018;18 (1) (no pagination).	Full-text not in English, published pre-2014 or irrelevant publication type
Valerio M, Ahmed HU, Emberton M, et al. The role of focal therapy in the management of localised prostate cancer: a systematic review. European Urology 2014;66:732-51.	Full-text not in English, published pre-2014 or irrelevant publication type
Van As NJ, Brand D, Tree A, et al. PACE: analysis of acute toxicity in PACE-B, an international phase III randomized controlled trial comparing stereotactic body radiotherapy (SBRT) to conventionally fractionated or moderately hypofractionated external beam radiotherapy (CFMHRT) for localized prostate cancer (LPCa). Journal of clinical oncology 2019;37.	Full-text not in English, published pre-2014 or irrelevant publication type
Vicier C, Faivre L, Lesaunier F, et al. Modelling relapse in patients with high-risk localised prostate cancer treated randomly in the GETUG 12 phase III trial reveals two populations of relapsing patients. Annals of oncology 2016;27.	Full-text not in English, published pre-2014 or irrelevant publication type
Wang T, Wang Q, Wang S. A meta-analysis of robot assisted laparoscopic radical prostatectomy versus laparoscopic radical prostatectomy. Open Medicine (Poland) 2019;14:485-490.	Full-text not in English, published pre-2014 or irrelevant publication type
Widmark A, Gunnlaugsson A, Beckman L, et al. Extreme hypofractionation versus conventionally fractionated radiotherapy for intermediate risk prostate cancer: early toxicity results from the scandinavian randomized phase III trial “HYPO-RT-PC”. International journal of radiation oncology biology physics 2016;96:938-939.	Full-text not in English, published pre-2014 or irrelevant publication type
Widmark A, Gunnlaugsson A, Beckman L, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. The Lancet 2019;394:385-395.	Irrelevant patient population
Wilkins A, Mossop H, Syndikus I, et al. Hypofractionated radiotherapy versus conventionally fractionated radiotherapy for patients with intermediate-risk localised prostate cancer: 2-year patient-reported outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. The Lancet Oncology 2015;16:1605-1616.	Included in the updated SLR or any other included SLR
Wilkins A, Stuttle C, Hassan S, et al. Methodology for tissue sample collection within a translational sub-study of the CHHiP trial (CRUK/06/016), a large randomised phase III trial in localised prostate cancer. Clinical and Translational Radiation Oncology 2018;10:1-6.	Full-text not in English, published pre-2014 or irrelevant publication type

Reference	Reason for exclusion
Williams S, Davis ID, Sweeney C, et al. Randomised phase 3 trial of enzalutamide in androgen deprivation therapy (ADT) with radiation therapy for high risk, clinically localized prostate cancer: ENZARAD (ANZUP 1303). Journal of clinical oncology 2018;36.	Full-text not in English, published pre-2014 or irrelevant publication type
Williams S, Davis ID, Sweeney C, et al. Randomised phase III trial of enzalutamide in androgen deprivation therapy (ADT) with radiation therapy for clinically localised, high risk, or node-positive prostate cancer: ENZARAD (ANZUP 1303). Journal of clinical oncology 2017;35.	Full-text not in English, published pre-2014 or irrelevant publication type
Williams SG, Davis ID, Sweeney C, et al. Randomised phase 3 trial of enzalutamide in androgen deprivation therapy (ADT) with radiation therapy for clinically localised high-risk or node-positive prostate cancer: ENZARAD (ANZUP 1303). Journal of clinical oncology 2016;34.	Full-text not in English, published pre-2014 or irrelevant publication type
Williams SG, Davis ID, Sweeney C, et al. Randomised phase 3 trial of enzalutamide in androgen deprivation therapy with radiation therapy for high risk, clinically localised, prostate cancer: enzarad (anzup 1303). Asia-pacific journal of clinical oncology. (var.pagings) 2015;11:149.	Full-text not in English, published pre-2014 or irrelevant publication type
Wilt T, Jones K, Barry M, et al. Radical prostatectomy versus observation for early prostate cancer: follow-up results of the prostate cancer intervention versus observation trial (PIVOT). Journal of urology 2017;197:e915-.	Full-text not in English, published pre-2014 or irrelevant publication type
Wirth M, Tammela T, Cicalese V, et al. Prevention of bone metastases in patients with high-risk nonmetastatic prostate cancer treated with zoledronic acid: efficacy and safety results of the Zometa European Study (ZEUS). European Urology 2015;67:482-91.	Irrelevant patient population
Wolff RF, Ryder S, Bossi A, et al. A systematic review of randomised controlled trials of radiotherapy for localised prostate cancer. European Journal of Cancer 2015;51:2345-2367.	Full-text not in English, published pre-2014 or irrelevant publication type
Wortel RC, De Vries K, Pos FJ, et al. Hyprofractionated vs conventionally fractionated radiotherapy for prostate cancer: 7-year outcome from the Dutch HYPRO trial. European urology, supplements 2019;18:e956-e957.	Full-text not in English, published pre-2014 or irrelevant publication type
Wortel RC, Pos FJ, Heemsbergen WD, et al. Sexual Function After Hypofractionated Versus Conventionally Fractionated Radiotherapy for Prostate Cancer: Results From the Randomized Phase III HYPRO Trial. Journal of Sexual Medicine 2016;13:1695-1703.	Included in the updated SLR or any other included SLR
Xiong T, Turner RM, Wei Y, et al. Comparative efficacy and safety of treatments for localised prostate cancer: An application of network meta-analysis. BMJ Open 2014;4 (5) (no pagination).	Full-text not in English, published pre-2014 or irrelevant publication type
Yuh B, Artibani W, Heidenreich A, et al. The role of robot-assisted radical prostatectomy and pelvic lymph node dissection in the management of high-risk prostate cancer: a systematic review. European Urology 2014;65:918-927.	Full-text not in English, published pre-2014 or irrelevant publication type
Zhu Z, Zhang J, Liu Y, et al. Efficacy and toxicity of external-beam radiation therapy for localised prostate cancer: A network meta-analysis. British Journal of Cancer 2014;110:2396-2404.	Full-text not in English, published pre-2014 or irrelevant publication type
Zilli T, Dal Pra A, Kountouri M, et al. Prognostic value of biochemical response to neoadjuvant androgen deprivation before external beam radiotherapy for prostate cancer: A systematic review of the literature. Cancer Treatment Reviews 2016;46:35-41.	Full-text not in English, published pre-2014 or irrelevant publication type

Appendix 3 — Summary and appraisal of individual studies

Data Extraction

Questions 1 and 2

Table 39a. CAP, Martin 2018

Study Reference	CAP (Martin 2018)
Study Design	Study name Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) Design Cluster randomised controlled trial Objective To determine the effects of a low-intensity, single invitation PSA test and standardised diagnostic pathway on prostate cancer-specific and all-cause mortality while minimising over-detection and overtreatment. Dates 2001–2009 Country UK Setting 911 primary care practices located near 8 hospital centres in England and Wales
Population Characteristics	Patient recruitment and eligibility NR **Inclusion** Men aged 50 to 69 years in each of the randomised primary care practices. **Exclusion** A history of prostate cancer on or before the randomisation date and patient registration with the practice on a temporary or emergency basis. **Other** NR Sample size N screened/invited = NR N eligible = 415,357 (intervention 195,912, control 219,445)

Study Reference	CAP (Martin 2018)

N enrolled = 408,825 (Intervention 189,386; control 219,439)
N excluded (with reason) = 4,225 men excluded from randomised practices (2026 in intervention group, 2199 in control group). Reasons: Diagnosed with prostate cancer prior to randomisation: intervention 1433, control 1688; no record of registration with NHS Digital Organisation: intervention 257, control 127; died prior to randomisation: intervention 176, control 286; unable to identify with NHS organisation: intervention 160; control 95; refused to participate: control 3.
6,532 men excluded from primary analysis at or before randomisation (6526 in intervention group; 6 in control group). Reasons: Refused to participate: intervention 6311, control 0; Did not give informed consent; intervention 198, control 0; Died or diagnosed with prostate cancer on randomisation date: intervention 8, control 3; No record of registration with NHS Digital Organisation on randomisation date: intervention 0; control 2; Date of birth missing: intervention 7, control 0; Record removed from NHS Digital Organisation per patient request; intervention 2; control 1.
N lost to follow-up = NR
N completed = 408,825 (Intervention 189,386; control 219,439)
N included in analysis = 408,825 (intervention 189,386; control 219,439)

Demographics

Parameter	Screening arm (n=189,386)	Control arm (n=219,439)
Individual		
Age at recruitment/randomisation, median (IQR), years	58.5 (54.3–63.5)	58.6 (54.3–63.5)
Ethnicity	NR	NR
Previous PSA test	NR	NR
Previous biopsy	NR	NR
Family history of prostate cancer	NR	NR
Socioeconomic status (e.g. education)	NR	NR
BMI	NR	NR
Weight	NR	NR
Comorbidity index	NR	NR
Diabetes	NR	NR
Primary Care Practice		
No. of practices	271	302
No. of individuals per practice, median (IQR)	6300 (4150–9107)	6300 (3793–9000)
Located in urban area, n (%)	244 (90)	267 (88)
Multiple partners within practice, n (%)	242 (89)	267 (88)
Quality and Outcomes Framework[a]		
No. of practices in England	224	266
Percentage of total points achieved, median (IQR)	98.9 (97.4–99.6)	99.0 (97.4–99.7)

Study Reference	CAP (Martin 2018)		
	Index of Multiple Deprivation[b]		
	No. of practice in England	231	271
	Median (IQR)	21.8 (12.7–44.1)	23.6 (13.3–46.7)
	No. of practices in Wales	40	31
	Median (IQR)	18.8 (11.9–22.9)	20.1 (7.6–34.5)
	Prevalence across practices, mean (SD), %[c]		
	All types of cancer	0.6 (0.3)	0.5 (0.2)
	Diabetes	3.6 (1.0)	3.7 (1.0)
	Obesity	8.0 (2.8)	7.8 (2.8)
	Coronary heart disease	4.1 (1.4)	3.9 (1.3)

[a] A system for the performance management and payment of primary care clinicians based on the quality of their care. [b] A measure of relative deprivation for small areas; a higher score indicates more deprivation (range, 0-100). English and Welsh scores are not directly comparable; therefore, they are reported separately. [c] Calculated as (No. of individuals registered with a health condition at each practice/total No. of individuals registered at each practice) × 100

Methods

Duration of follow-up
10 years

Randomisation
Primary care practices were randomised to the intervention and control groups prior to practice recruitment and obtaining consent. Randomisation was stratified within geographical groups and block sizes of 10 to 12 neighbouring practices using a computerized random number generator. Because randomisation preceded practices being invited to take part in the study and because the invitation was tailored to the group (intervention or control) to which the practice had been randomised, it was not possible to conceal randomisation while practices decided whether to participate. Characteristics of the practices that agreed to participate were compared.

Screening Arm
In the intervention group, men aged 50 to 69 years received a single invitation to a nurse-led clinic appointment. At the appointment, men were provided with information about PSA testing. After giving consent, men were offered the PSA test. Men with PSA levels of 3.0 ng/mL or greater were offered a standardised 10-core transrectal ultrasound–guided biopsy. Those diagnosed with clinically localised prostate cancer and who met the eligibility criteria were recruited to participate in the ProtecT trial to receive treatment.

Control Arm
The control practices provided standard National Health Service management, and information about PSA testing was provided only to men who requested it.

Data Collection
Cases of prostate cancer that were detected among men in the intervention group who did not attend the nurse-led PSA clinic appointment and among men in the control group were managed by the same clinicians as those who attended the PSA clinic in the intervention group. Men were linked to the National Health Service Digital Organisation and the Office for National Statistics for deaths and cancer registrations. There were only 639 men (0.15%) unable to be linked or who were not registered. Prostate cancer stage and Gleason grade at diagnosis were obtained from Public Health England and Public Health Wales, and supplemented with routine hospital data from the study centres. Study personnel were unable to abstract good quality data on metastases from routine records. Study data were collected using the REDCap (Research Electronic Data Capture) electronic data capture tool (a secure, web-based application designed to support data capture for research studies) hosted at the University of Bristol.

Study Reference **CAP (Martin 2018)**

Outcomes

- The primary outcome was definite, probable, or intervention-related prostate cancer mortality at a median follow-up of 10 years and was determined by an independent cause of death evaluation committee that was blinded to trial group assignment.
- The secondary outcomes were all-cause mortality, prostate cancer stage, and Gleason grade at prostate cancer diagnosis. Prostate cancer and all-cause mortality at 15 years, health-related quality of life, and cost-effectiveness also were prespecified secondary end points but are not reported in this article.
- Incidence was also reported in a secondary analysis

Statistical Analysis

- Primary analysis followed the intention-to-screen principle.
- Kaplan-Meier plots were used to display cumulative incidence of the primary and secondary outcomes. Estimated rate ratios (RRs) were used to compare prostate cancer incidence and mortality in intervention vs control practices using mixed-effects Poisson regression, which allows for clustering of men within primary care practices and of neighbouring primary care practices within randomization strata. Because the incidence of prostate cancer varies greatly by age, each man's follow-up was divided into periods defined by his age using a lexis diagram approach (≤59, 60-64, 65-69, 70-74 and ≥75 years; the youngest age stratum was larger to compensate for fewer events). With a separate mean baseline rate for each age group, the assumption of a constant baseline rate applies to each group separately.
- A prespecified secondary analysis was estimation (using random allocation as an instrumental variable) of the effect of the trial intervention in those accepting the PSA clinic invitation and attending the clinic, using a generalized method of moments estimator. Prespecified subgroup analyses investigated the effects of PSA testing on prostate cancer–specific mortality by baseline age group and socioeconomic status using a likelihood ratio test for interaction.
- The original power calculations were based on the estimated 10-year incidence of prostate cancer mortality using 1994 data for England and Wales, assuming a plausible between-practice coefficient of variation of 0.2. Calculations predicted that 209 men in each group would yield 1720 prostate cancer deaths during a median follow-up of 10 years, and allow a prostate cancer mortality RR of 0.87 to be detected with 80% power at a significance level of .05. Assuming an uptake in PSA testing of between 35% and 50%, this corresponds to RRs between 0.62 and 0.73 among men actually undergoing PSA testing. Estimates of the effect on power of ever undergoing PSA testing during follow-up in the control group suggested that the effect would be minimal unless reaching 20%.

Mortality and/or Morbidity Outcomes

Mortality during 10-year follow-up by trial arm

Outcome	Screening arm (n=189,386)[a]		Control arm (n=219,439)[b]		Rate Difference/1000 Person-Years (95% CI)	Rate Ratio (95% CI)[c]	p-value	Rate Ratio (95% CI)[d]	p-value
	No. of Deaths	Rate/1000 Person-Years (95% CI)	No. of Deaths	Rate/1000 Person-Years (95% CI)					
Prostate cancer mortality[e]	549	0.30 (0.27–0.32)	647	0.31 (0.29–0.33)	–0.013 (–0.047–0.002)	0.96 (0.85–1.08)	0.50	0.93 (0.67–1.29)	0.66
All-cause mortality	25,459	13.74 (13.57–13.91)	28,306	13.51 (13.35–13.67)	0.229 (–0.001–0.460)	0.99 (0.94–1.03)	0.49	1.07 (0.93–1.23)	0.35

Study Reference	CAP (Martin 2018)

[a] There were 1,853,167 person-years, calculated as the time until death or censoring. [b] There were 2,095,405 person-years, calculated as the time until death or censoring. [c] Likelihood ratio test of the null hypothesis (i.e. no difference in prostate cancer mortality between the groups), adjusted for randomisation cluster and age stratum. [d] Analysis to obtain the causal effect of screening among those attending the PSA testing clinic using a generalised method of moments estimator with random allocation as an instrumental variable. [e] Defined as definite, probable or intervention-related prostate cancer death as determined by an independent cause of death committee.

Prostate cancer mortality rate ratios were also reported according to age and deprivation scores.

Morbidity outcomes
NR

Characteristics of prostate cancer cases at diagnosis (including prostate cancer incidence) at median follow-up of 10 years

	Screening arm			Control arm (n=219,439)	Between-group difference (95% CI)
	Total (n=189,386)	Attended PSA clinic (n=75,707)	Did not attend PSA clinic (n=113,679)		
Prostate cancer, No. (%)	8054 (4.3)	4687 (6.2)	3367 (3.0)	7853 (3.6)	-
Person-years of follow-up[a]	1808031	750573	1057458	2063912	-
Incidence rate per 1,000 person-years	4.45 (4.36–4.55)	6.24 (6.07–6.43)	3.18 (3.08–3.29)	3.80 (3.72–3.89)	0.65 (0.52–0.78)[b] P<0.01
Age, median (IQR), y	66.3 (62.1–70.0)	65.3 (61.2–69.0)	67.9 (63.7–71.5)	67.7 (63.6–71.6)	–1.37 (–1.56 to –1.19)[c]
Time from randomisation to diagnosis, median (IQR), y	4.3 (0.8–7.9)	1.2 (0.5–7.0)	6.2 (3.4–8.7)	6.2 (3.6–8.4)	–1.49 (–1.61 to –1.37)[c]
Gleason grade recorded, No./total (%)	7276/8054 (90.3)	4388/4678 (93.6)	2888/3367 (85.8)	6899/7853 (87.9)	-
≤6	3263/189386 (1.7)	2297/75707 (3.0)	966/113679 (0.8)	2440/219439 (1.1)	6.11 (5.38–6.84)[d]
7	2710/189386 (1.4)	1526/75707 (2.0)	1184/113679 (1.0)	2823/219439 (1.3)	1.44 (0.73–2.16)[d]
≥8	1303/189386 (0.7)	565/75707 (0.7)	738/113679 (0.6)	1636/219439 (0.7)	–0.58 (–1.09 to –0.06)[d]
Cancer stage recorded, No./total (%)	7197/9054 (89.4)	4299/4687 (91.7)	2898/3367 (86.1)	7009/7853 (89.3)	-
T1 or T2	4938/189386 (2.6)	3308/75707 (4.4)	1630/113679 (1.4)	4192/219439 (1.9)	6.97 (6.05–7.89)[d]
T3	1329/189386 (0.7)	690/75707 (0.9)	639/113679 (0.6)	1540/219439 (0.7)	0 (–0.51 to 0.51)[d]
T4, N1 or M1	930/189386 (0.5)	301/75707 (0.4)	629/113679 (0.6)	1277/219439 (0.6)	–0.91 (–1.36 to –0.46)[d]

[a] Person-years of follow-up were calculated as the time until diagnosis, death or censoring. These figures are lower than those in the previous table because they exclude person-years after diagnosis. [b] Difference in incidence rate. [c] Difference in medians calculated using the generalised Hodges-Lehmann method. [d] Difference per 1,000 men.

Study Reference	CAP (Martin 2018)
Authors' Conclusions	Among practices randomised to a single PSA screening intervention vs standard practice without screening, there was no significant difference in prostate cancer mortality after a median follow-up of 10 years, but the detection of low-risk prostate cancer cases increased. Although longer-term follow-up is under way, the findings do not support single PSA testing for population-based screening.

Abbreviations: BMI, body mass index; CAP, Cluster Randomized Trial of PSA Testing for Prostate Cancer; CI: confidence interval; IQR, interquartile range; NR: not reported; PSA: prostate-specific antigen; RR: risk ratio; SD: standard deviation.

Table 39b. ERSPC Multiple Centres, Hugosson 2019/Auvinen 2016

Study Reference	ERSPC (Hugosson 2019/Auvinen 2016) Linked records: Carlsson 2019; Hakama 2017; Walter 2017; Buzzoni 2015; Schröder 2014
Study Design	Study name European Randomized study of Screening for Prostate Cancer (ERSPC) Design Randomised controlled trial Objective **Hugosson 2019** To determine whether PSA screening decreases PCa mortality for up to 16 years and to assess results following adjustment for nonparticipation and the number of screening rounds attended **Auvinen 2016** To relate indicators of mortality reduction and overdetection by centre within the ERSPC Dates Initiation/recruitment: 1991–1999 (France later in 2003) Maximum follow-up: 2014 (different for different centres) Country 8 European countries: Belgium, Finland, Italy, The Netherlands, Spain, Sweden, Switzerland, France (French centres excluded from this analysis due to inability to comply with quality criteria and short follow-up) Setting International multicentre
Population Characteristics	Patient recruitment and eligibility Eligible subjects were identified from population registries and individually randomised on the basis of random numbers (1:1 allocation, except from Finland where a fixed size of the screening arm led to a screening/control ratio of ~1:1.5) Men received regular screening invitations (most centres at a 4-year interval, Sweden and France at a 2-year interval and Belgium at a 7-year interval) **Inclusion** Men aged 55–69 years (the core age group which was common to all centres although note that age ranged from 50–74 across the different centres) **Exclusion** NR

Study Reference	**ERSPC (Hugosson 2019/Auvinen 2016)** Linked records: Carlsson 2019; Hakama 2017; Walter 2017; Buzzoni 2015; Schröder 2014

Other

The median follow-up for the two French centres, Herault and Tarn, was too short for their data to be included in this analysis and screening participation was <50% (uncompliant with a primary criterion)

Sample size

N screened/invited = NR
N eligible = NR
N enrolled (underwent randomisation) = 268,539 (all ages)
N excluded (with reason) = 86,379 (men from French centres excluded due to inability to comply with quality criteria/short follow-up); 19,771 ("outside core age group")
N in the intervention group = 72,890
N in the control group = 89,351
N lost to follow-up = NR
N completed = NR
N excluded from analysis = NR
N included in analysis = NR

Characteristics of the study overall and by centre at 16 year follow-up

Parameter	Belgium	Finland	Italy	The Netherlands	Spain	Sweden	Switzerland	Total
Age at randomisation, yr (IQR)	63 (60.2, 66.2)	59 (54.8, 62.7)	62 (58.4, 65.9)	62 (58.0, 65.6)	60 (57.4, 64.2)	60 (57.2, 62.4)	61 (57.8, 65.1)	60 (57.1, 64.2)
Randomised, n	8562	80379	14515	34833	2197	11852	9903	162241
Screening, n (%)	4307 (50)	31970 (40)	7265 (50)	17443 (50)	1056 (48)	5901 (50)	4948 (50)	72890 (45)
Control, n (%)	4255 (50)	48409 (60)	7250 (50)	17390 (50)	1141 (52)	5951 (50)	4955 (50)	89351 (55)
Follow-up, yr (IQR)	16 (11.1, 16.0)	16 (13.8, 16.0)	15 (13.2, 16.0)	16 (13.8, 16.0)	16 (15.1, 15.9)	16 (13.9, 16.0)	13 (11.6, 14.2)	16 (13.0, 16.0)
Screening rounds per man, mean n	1.5	1.6	1.8	2.3	1.7	2.6	2.4	1.9
Men with positive tests, n (%)	914 (21)	4635 (14)	1054 (15)	6793 (39)	326 (31)	1537 (26)	1729 (35)	16988 (23)
Biopsies, n	752	5404	902	8541	263	2509	2027	20398
Biopsies/positive tests, %	71.1	91.2	62.5	89.4	74.3	86.6	78.0	85.6
Prostate cancer cases – screening group								
Overall, n	482	3500	560	2376	92	814	620	8444
Screen-detected, n	188	1632	197	1868	60	576	436	4957
Interval and cancers among non-attendees, n	294	1868	363	508	32	238	184	3487
Screen-detected/biopsy, %	25.0	30.2	21.8	21.9	22.8	23.0	21.5	24.3
Cumulative incidence, %	11.2	11.0	8.0	13.6	8.7	13.8	12.6	11.7
Prostate cancer cases – control group								
Overall, n	393	4546	452	4325	60	592	364	7732
Cumulative incidence, %	9.2	9.4	6.5	7.6	5.3	9.9	7.4	8.7

Methods	Randomisation Across centre, two types of randomisation using computer-generated random numbers, were used: • Randomisation before consent (Zelen-type, effectiveness design) – Sweden, Finland, Italy

Study Reference	**ERSPC (Hugosson 2019/Auvinen 2016)** Linked records: Carlsson 2019; Hakama 2017; Walter 2017; Buzzoni 2015; Schröder 2014

- Randomisation after consent (efficacy design) – Belgium, The Netherlands, Spain, Switzerland

Duration of follow-up
Hugosson 2019 Maximum 16 years
Auvinen 216 Maximum of 13 years (e.g. Sweden truncated at 10 years follow-up)

Outcomes
Mortality/morbidity outcomes

- Primary extraction
  - Hugosson 2019: PCa mortality (also assessed with adjustment for nonparticipation and the number of screening rounds attended) – medical records evaluated by a cause of death committee using a standardised flowchart to establish the cause of death; PCa incidence; NNI; NND
- Linked studies: PCa mortality; incidence rate ratios; metastasis; PCa deaths by treatment allocation; efficacy and effectiveness of screening

Harms of PSA screening outcomes

- Primary extraction
  - Auvinen 2016: PCa mortality, overdiagnosis (as NNO)

Definitions of absolute measures of screening benefits:

- NNI, number needed to invite to avert one PCa death: calculated as the inverse of the absolute risk difference in PCa mortality between the arms to indicate the mortality reduction by screening (NNI = $1/(M_c–M_s)$)
- NNO, number needed for overdetection: represents the absolute risk of overdiagnosis (NNO = $1/(I_s – I_c)$)
- NND, number needed to detect: a measure of the overall impact (benefits and harms) as the ratio of the reduction in PCa mortality to the excess PCa incidence (NND = NNI/NNO)

Mortality and/or Morbidity Outcomes (Q1)

Outcomes from Hugosson 2019

Cumulative PCa-Specific Incidence

Outcome	Screening arm (n=72890)	Control arm (n=89351)	Rate or risk ratio (95% CI)	Rate or risk difference/1000 person-years or men (95% CI)
Years 1–9				
Prostate cancer, n	6172	4154	-	-
Person years	584776	735777	-	-
Rate/1000 person-years	10.55	5.65	1.90 (1.83–1.98)	5.00 (4.69–5.31)
Risk/1000 men	85.16	46.71	1.85 (1.78–1.93)	39.15 (36.65–41.65)
Years 1–11				
Prostate cancer, n	6852	5333	-	-
Person years	695850	877302	-	-
Rate/1000 person-years	9.85	6.08	1.65 (1.59–1.71)	3.86 (3.58–4.14)
Risk/1000 men	94.54	59.97	1.60 (1.54–1.66)	35.41 (32.71–38.12)
Years 1–13				
Prostate cancer, n	7655	6384	-	-
Person years	797774	1007337	-	-
Rate/1000 person-years	9.60	6.34	1.54 (1.49–1.59)	3.35 (3.09–3.61)
Risk/1000 men	105.62	71.79	1.49 (1.44–1.54)	34.82 (31.93–37.72)

Study Reference **ERSPC (Hugosson 2019/Auvinen 2016)**
Linked records: Carlsson 2019; Hakama 2017; Walter 2017; Buzzoni 2015; Schröder 2014

Years 1–16				
Prostate cancer, n	8444	7732	-	-
Person years	918300	1162062	-	-
Rate/1000 person-years	9.20	6.65	1.41 (1.36–1.45)	2.66 (2.42–2.90)
Risk/1000 men	116.51	86.95	1.36 (1.32–1.41)	31.15 (28.05–34.25)

Nelson-Aalen estimates of cumulative PCa-specific incidence at 16 years: screening arm: 13.3%; control arm: 10.3%

Mortality Outcomes

Outcome	Screening arm (n=72890)	Control arm (n=89351)	Rate or risk ratio (95% CI)	P value	Rate or risk difference/1000 person-years or men (95% CI)
Years 1–9					
Prostate cancer deaths, n	191	280	-	-	-
Person years	612723	749801	-	-	-
Rate/1000 person-years	0.31	0.37	Total: 0.84 (0.70–1.00) Attenders: 0.78 (0.63–0.96)	0.053 **0.022**	–0.06 (–0.12–0.00)
Risk/1000 men	2.64	3.15	0.84 (0.70–1.00)	-	–0.51 (–1.04–0.01)
NNI (95% CI)	1947 (963–inf)		-	-	-
NND	76		-	-	-
Years 1–11					
Prostate cancer deaths, n	268	419	-	-	-
Person years	735205	899370	-	-	-
Rate/1000 person-years	0.36	0.47	Total: 0.78 (0.67–0.91) Attenders: 0.72 (0.60–0.86)	**0.001** **<0.001**	–0.10 (–0.17– –0.04)
Risk/1000 men	3.70	4.71	0.78 (0.67–0.91)	-	–1.04 (–1.67– –0.41)
NNI (95% CI)	962 (598–2463)		-	-	-
NND	34		-	-	-
Years 1–13					
Prostate cancer deaths, n	371	570	-	-	-
Person years	848802	1038723	-	-	-
Rate/1000 person-years	0.44	0.55	Total:0.79 (0.69–0.90) Attenders: 0.73 (0.63–0.85)	**<0.001** **<0.001**	–0.12 (–0.18– –0.05)
Risk/1000 men	5.12	6.41	0.79 (0.70–0.90)	-	–1.35 (–2.09– –0.61)
NNI (95% CI)	742 (478–1650)		-	-	-
NND	26		-	-	-
Years 1–16					
Prostate cancer deaths, n	520	793	-		-
Person years	985382	1207411	-		-
Rate/1000 person-years	0.53	0.66	Total: 0.80 (0.72–0.89) Attenders: 0.75 (0.66–0.85)	**<0.001** **<0.001**	–0.13 (–0.20– –0.07)
Risk/1000 men	7.17	8.92	0.80 (0.72–0.90)	-	–1.76 (–2.63– –0.88)
NNI (95% CI)	570 (380–1137)		-	-	-
NND	18		-	-	-

Study Reference

ERSPC (Hugosson 2019/Auvinen 2016)
Linked records: Carlsson 2019; Hakama 2017; Walter 2017; Buzzoni 2015; Schröder 2014

Effectiveness of screening at 16 years by ERSPC centre

Centre	Prostate cancer incidence rate ratio (95% CI) (screening vs control)	p-value	Prostate cancer mortality rate ratio (95% CI) (screening vs control)	p-value	NNI	NND
Belgium	1.22 (1.07 - 1.40)	0.003	0.78 (0.44 - 1.34)	0.364	678 (209 -Inf)	13
Finland	1.19 (1.14 - 1.24)	0.000	0.91 (0.77 - 1.06)	0.210	1206 (471 -Inf)	19
Italy	1.24 (1.10 - 1.41)	0.001	0.99 (0.66 - 1.49)	0.958	44232 (369 -Inf)	673
Netherlands	1.89 (1.77 - 2.03)	0.000	0.67 (0.53 - 0.85)	0.001	303 (191 - 731)	18
Spain	1.72 (1.24 - 2.39)	0.001	0.65 (0.13 - 2.63)	0.550	647 (153 - Inf)	22
Sweden	1.44 (1.30 - 1.60)	0.000	0.63 (0.44 - 0.88)	0.008	189 (109 - 703)	7
Switzerland	1.78 (1.57 - 2.03)	0.000	0.84 (0.47 - 1.50)	0.556	1244 (285 -Inf)	65

Effectiveness of one single PSA test on PCa mortality (assuming various effects)

Assumed RR for men attending exactly once	RR for men attending at least twice (95% CI)
0.75	0.75 (0.60 - 0.92)
0.80	0.67 (0.55 - 0.82)
0.85	0.62 (0.50 - 0.75)
0.90	0.57 (0.47 - 0.70)
0.95	0.54 (0.44 - 0.66)
1.00	0.52 (0.42 - 0.63)

Harms of PSA-Based Screening (Q2)

Outcomes from Auvinen 2016

Prostate biopsy method (if applicable)
N/A

Cumulative incidence of PCa by arm, with excess incidence and NNO by ERSPC centre (13 year follow-up)

Centre	Cumulative PCa incidence, %		Excess incidence (I_s–I_c), %	**NNO (1/(I_s–I_c))[a]**
	Screening, I_s	Control, I_c		
Belgium	9.7	7.5	2.1	**47**
Finland	9.4	7.5	2.0	**51**
Italy	5.5	4.0	1.5	**69**
Netherlands	12.5	6.2	6.3	**16**
Spain	8.2	4.6	3.7	**28**

Study Reference

ERSPC (Hugosson 2019/Auvinen 2016)
Linked records: Carlsson 2019; Hakama 2017; Walter 2017; Buzzoni 2015; Schröder 2014

Sweden	12.5	7.9	4.6	**22**
Switzerland	11.6	6.0	5.6	**18**

[a]Expressed as an integer, with rounding upward

When patients treated with active surveillance were excluded, the extent of overdetection was strongly reduced in Sweden (NNO increased from 22 to 41), Finland (from 51 to 137), and Switzerland (from 18 to 34), where active surveillance was commonly used, and also to some extent in Belgium (from 47 to 62), but the difference was not substantial in the other centres (in the Netherlands from 16 to 19, Italian and Spanish results almost unaltered because of infrequent use of active surveillance).

PCa mortality by arm, with mortality reduction and NNI by ERSPC centre (13 year follow-up)

Centre	Cumulative PCa mortality, %		Mortality reduction (M_s–M_c), %	NNI ($1/M_s$–M_c))[a]	
	Screening, M_s	Control, M_c			NND (NNI/NNO)[b]
Belgium	0.42	0.54	0.12	816 (243–ND)	18
Finland	0.53	0.59	0.05	1821 (631–ND)	37
Italy	0.36	0.44	0.08	1198 (349–ND)	29
Netherlands	0.49	0.72	0.24	422 (253–1381)	27
Spain	0.19	0.35	0.16	621 (419–ND)	23
Sweden	0.64	1.04	0.40	252 (140–1534)	12
Switzerland	0.32	0.28	–0.04	ND[c]	ND[c]

[a]Expressed as an integer, with rounding upward
[b]NNI/NNO (1/mortality reduction : 1/excess incidence = excess incidence/mortality reduction)
[c]No mortality reduction, NNI not meaningful

The ratio the mortality reduction to excess incidence (mean NND, calculated as NNI/NNO) for the centres was 22, with a range of 12 to 36. It was smallest for Sweden (NND 12), indicating that the number of excess cases per averted PCa death was less than in other centres, and largest for Finland (NND 36), with both smaller mortality reduction and excess incidence.

Authors' Conclusions

Hugosson 2019

- This 16-year report from ERSPC shows that the absolute effect of screening on PCa mortality increases with longer follow-up.
- The excess PCa incidence among screened men is decreasing but is still rather high.
- The PCa mortality reduction seems to be related to the duration of screening, and a one-time screening test is suggested to have little or no effect on PCa mortality due to a prevalence pool of more advanced disease in which treatment is unlikely to provide major benefits.

Auvinen 2016

- At 13 years of follow-up, on average 12 to 36 excess PCa cases have to be detected to avert one death from the disease.
- In comparison between the ERSPC centres, a direct correlation was observed between screening benefit and harm. This suggests that with the current screening regimens, any efforts to increase the effectiveness of screening are likely accompanied by unavoidable increase in the harmful effects.
- A likely explanation is the largely overlapping PSA distribution among fatal and overdiagnosed prostate cancer cases, that is, PSA does not allow a sharp distinction of lethal and inconsequential prostate cancer in the early preclinical phase of the disease due to a long lead time (detection several years earlier—and at a younger age—compared with clinical diagnosis) and length bias (increased detection of slowly growing cancers with a long detectable preclinical phase by screening).

Study Reference

ERSPC (Hugosson 2019/Auvinen 2016)
Linked records: Carlsson 2019; Hakama 2017; Walter 2017; Buzzoni 2015; Schröder 2014

- The results indicate a strong interrelation between benefits and harms of PCa screening. Decision-making about PCa screening needs to involve judgement of the importance of averted PCa death relative to unnecessary diagnosis and harms of treatment, to gauge the trade-offs between benefits and harms.

Additional Results/ Conclusions from Linked Records

Buzzoni 2015

Cumulative incidence rate ratio (RaR) by risk category for the original data and after data imputation at **13 years of follow-up**

Risk category	Original data			After data imputation		
	Screening, n (%)	Control, n (%)	Rate ratio (95% CI)	Screening, %	Control, %	Rate ratio (95% CI)
Low risk	4442 (60)	2543 (42)	2.29 (2.18–2.42)	65	47	2.14 (2.03–2.25)
Intermediate risk	1625 (22)	1711 (28)	1.27 (1.18–1.37)	24	30	1.24 (1.16–1.34)
High risk	519 (7)	667 (11)	1.02 (0.90–1.15)	8	12	1.00 (0.89–1.13)
M1 and/or PSA 100+ risk	252 (3)	586 (10)	0.56 (0.48–0.65)	4	11	0.60 (0.52–0.70)
Missing values	570 (8)	600 (10)	1.01 (0.90–1.13)	-	-	-
Total	7408 (100)	6107 (100)	1.56 (1.50–1.62)	100	100	1.56 (1.51–1.62)

Author's conclusions
The present results confirm a stage migration in the screening arm with a 40% reduction in metastatic disease at diagnosis which preceded a mortality reduction by almost three years. These results strongly suggest that a decrease of metastatic disease at diagnosis is a major determinant of the reduction of PCa mortality in the ERSPC trial, although we cannot exclude additional contributions from other factors

Carlsson 2019

Contribution of treatment differences to the observed PC mortality reduction between the screening and control arm at **16 years of follow-up** in the Finland, Netherlands, Sweden and Switzerland centres

The difference in estimated and observed numbers of PCa deaths was very small (0.05% [95% CI 0.1%,0.2%] when applying the control arm model to the screening arm and 0.01% [95% CI 0.3%, 0.2%] when applying the screening arm model to the control arms, had the two groups received identical primary treatment, given their clinical characteristics). As the observed difference between trial arms was 4.2%, our findings suggest that differential treatment explains only a trivial proportion of the main findings of ERSPC. Similar findings were seen in a complete case-only analysis

Author's conclusions

Differences in the receipt of primary treatment between the screening and control arm were minimal, and the potential effect of these differences on PCa mortality was extremely small. These findings suggest that the effectiveness of PSA screening in reducing PCa mortality in the ERSPC trial was largely due to early detection, allowing for effective management, and was not attributable to differential treatment between trial arms

Hakama 2017

Design-corrected estimates of the effect of screening on PCa mortality by centre at **13 years of follow-up** in 6 centres (3 with pre-consent randomisation [effectiveness design], 3 with post-consent randomisation [efficacy design])

Centre	Prostate cancer mortality by arm		Attendance proportion	Effectiveness	Efficacy
	Rate per 1000 person-years				

Study Reference **ERSPC (Hugosson 2019/Auvinen 2016)**
Linked records: Carlsson 2019; Hakama 2017; Walter 2017; Buzzoni 2015; Schröder 2014

	Screening	Control	Rate Ratio (95% CI)		% mortality reduction	% mortality reduction (95% CI)
Pre-consent randomisation						
Finland	0.47	0.51	0.91 (0.75–1.10)	0.65	9	15 (–18– 37)
Italy	0.32	0.39	0.81 (0.48–1.35)	0.68	19	26 (–43– 56)
Sweden	0.55	0.89	0.62 (0.41–0.92)	0.62	38	52 (15–73)
Total			0.58 (0.72–0.99)		15	26 (2–43)*
Post-consent randomisation						
Belgium	0.38	0.50	0.77 (0.41–1.42)	0.88	n.e.	24 (–45– 56)
Netherlands	0.43	0.63	0.67 (0.51–0.88)	0.95	n.e.	35 (13–52)
Switzerland	0.33	0.29	1.14 (0.56–2.33)	0.96	n.e.	–14 (–135– 45)
Total			0.73 (0.57–0.92)		n.e.	29 (9–45)
Overall total	0.43	0.54	0.79 (0.69–0.91)	0.76		28 (13–40)*

*With adjustment for the control population in Finland
n.e. not estimable

Author's conclusions
The correction for study design did not reduce the variation between individual centres, suggesting that centre-specific variation in the mortality reduction could not be accounted for by the randomisation method

Schröder 2014

Prostate cancer incidence in the intervention and control arms during 3 time periods truncated – all centres, core age group, France excluded except for years 1–9

	Screening			Control			Rate ratio (95% CI)[1]	Rate difference per 1000 person-years (95% CI)[1]	Rate difference per 1000 men[1]
	Prostate cancer N	Person years	Rate /1000 person-years	Prostate cancer N	Person years	Rate /1000 person-years			
Years 1–9 (including France)	7902	835353	9.46	5726	984993	5.81	1.64 (1.58–1.69)	3.69 (3.42–3.95)	26.5
Years 1–9	6147	585627	10.50	4127	736688	5.60	1.91 (1.83–1.99)	5.00 (4.68–5.32)	39.0
Years 1–11	6797	692186	9.82	5262	873415	6.02	1.66 (1.60–.73)	3.90 (3.61–4.20)	35.5
Years 1–13	7408	775527	9.55	6107	980474	6.23	1.57 (1.51–1.62)	3.44 (3.16–3.72)	34.8

[1]Control group for Finland weighted by 1:1.5

Prostate cancer mortality in the intervention and control arms during 3 time periods truncated – all centres, core age group, France excluded except for years 1–9

	Screening	Control				

Study Reference

ERSPC (Hugosson 2019/Auvinen 2016)
Linked records: Carlsson 2019; Hakama 2017; Walter 2017; Buzzoni 2015; Schröder 2014

	Prostate cancer deaths N	Person years	Rate /1000 person-years	Prostate cancer deaths N	Person years	Rate /1000 person-years	Rate ratio (95% CI)[1]	Rate difference per 1000 person-years (95% CI)[1]	Rate difference per 1000 men[1]	Adjusted rate ratio in attenders
Years 1–9	193	614590	0.31	278	751777	0.37	0.85 (0.70–1.03) p=0.10	–0.06 (–0.12–+0.01)	–0.46	
Years 1–11	265	732133	0.35	415	896367	0.46	0.78 (0.66–0.91) p=0.002	–0.10 (–0.17––0.04)	–1.02	0.71 (0.58–0.88) p=0.001
Years 1–13	355	825018	0.43	545	1011192	0.54	0.79 (0.69–0.91) p=0.001	–0.11 (–0.18––0.05)	–1.28	0.73 (0.61–0.88) p<0.001

[1]Control group for Finland weighted by 1:1.5

NNI and NND per follow-up period: core age group

	11 years of follow-up		13 years of follow-up	
	NNI (95% CI)	NND (95% CI)	NNI (95% CI)	NND (95% CI)
Total excluding France	979 (594–2770)	35 (21–96)	781 (490–1929)	27 (17–66)

Also reports randomisation, participants and results of screening for all centres with data truncated at 13 years of follow-up and all cause and PCa mortality by age at randomisation (excluding France)

Author's conclusions

With data truncated at 13 years of follow-up, out study continues to demonstrate a significant 21% relative PCa mortality reduction in favour of screening, with one PCa death averted per 781 men invited and 27 excess cases detected. The relative risk reduction in men actually screened was 27% after adjustment for selected effects. In spite of these findings further quantification of harms and their reduction are still considered as pre-requirements for the introduction of population based screening

Walter 2017

Correcting for adjudication inaccuracies in 5 centres and assessing whether this modifies the study results

Country	Estimation method (odds ratios for prostate cancer death between screening and control arm)			
	Empirical [a]	Empirical, corrected using overall estimates of adjudicator accuracy [b]	Empirical, corrected using differential estimates of adjudicator accuracy by study arm [c]	Directly from latent class model [d]
Netherlands	0.342	0.35	0.337	0.328
Belgium	0.759	0.904	0.866	0.902
Sweden	0.355	0.381	0.395	0.368
Finland	0.52	0.575	0.568	0.556
Switzerland	0.625	0.5	0.259	0.437

[a] Estimated from cross-tabulation of adjudication consensus by study arm
[b] Estimated proportions of prostate cancer deaths in each study arm were corrected using estimated false positive and false negative adjudication ratees in latent class model 2. Odds ratios were then calculated from these corrected proportions
[c] Similar to approach (b), except that adjudicator accuracy was estimated from latent class model 3
[d] Based on latent class model 2 estimates of the association of study arm with the latent variable (prostate cancer death)

Author's conclusions

Study Reference	**ERSPC (Hugosson 2019/Auvinen 2016)** Linked records: Carlsson 2019; Hakama 2017; Walter 2017; Buzzoni 2015; Schröder 2014
	We can conclude that observer variation, while demonstrably present, was unlikely to have had a strong influence on the main study results. Hence, we conclude that the ERSPC results are not attributable to biased or unreliable cause of death adjudication, and one possible source of bias that could explain a mortality reduction associated with PCa screening can be effectively ruled out

Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer; I_c, incidence in control arm; IQR, interquartile range; I_s, incidence in screening arm; M_c, mortality in control arm; M_s, mortality in screening arm; ND, not detected; NND, number needed to detect; NNI, number needed to invite; NNO, number needed for overdiagnosis; NR, not reported; PCa, prostate cancer; PSA, prostate-specific antigen

Table 39c. Göteborg Screening Study (Swedish ERSPC), Arnsrud Godtman 2015

Study Reference	**Göteborg Screening Study (Swedish ERSPC) (Arnsrud Godtman 2015)** Linked records: Hugosson 2018
Study Design	Study name Göteborg Screening Study (Swedish ERSPC) Design Randomised controlled trial Objective To compare the ability to reduce PCa mortality and the risk of overdiagnosis between organised and opportunistic screening Dates Initiation/recruitment: 1995 Maximum follow-up: 2012 Country Sweden Setting NR
Population Characteristics	Patient recruitment and eligibility 20,000 of the men recorded in the population register as living in Gothenburg (born 1930–1944) were computer-randomised, 10,000 to a screening group and 10,000 to a control group. Men in the screening group received written information about PSA screening together with an invitation to participate every 2 years. Men with PSA above a threshold (2.5 ng/mL since 2005) were recommended further urological work-up including prostate biopsy. **Inclusion** At recruitment, men were aged 50–64 years. The upper age limit for invitation was 67–71 years (mean 69 years) **Exclusion** NR Sample size N screened/invited = N/A N eligible = 32,298 men in Göteborg

Study Reference

Göteborg Screening Study (Swedish ERSPC) (Arnsrud Godtman 2015)
Linked records: Hugosson 2018

N enrolled (underwent randomisation) = 20,000 (screening:control in 1:1 ratio)
N excluded (with reason) = screening: 50 (28 men with prevalent PCa, 22 men who had emigrated or died); control: 51 (27 men with prevalent PCa, 24 men who had emigrated, died or were excluded due to other reasons)
N in the intervention group = 9,950 (invited every 2 years for a PSA test)
N in the control group = 9,949 (not invited)
N lost to follow-up = NR
N completed = 7,647 (77%) attended at least one screening
N excluded from analysis = NR
N included in analysis = NR

Prostate cancers diagnosed in the study group

Parameter	Screening		Control	
Men randomised, n	10000		10000	
Men invited, n	9950		9949	
PCa cases, n	1396		962	
Median age at diagnosis, yr (IQR)	65.8 (62.2–68.3)		67.8 (64.2–71.3)	
Median PSA at diagnosis, ng/mL	4.9		8.7	
Prostate cancer cases, n (%)	Screen-detected	Not screen-detected	Screen-detected	Not screen-detected
Number	1022[a]	374	361	601[b]
Low risk[c]	613 (60)	84 (22)	128 (35)	125 (21)
Intermediate risk[d]	331 (32)	138 (37)	168 (47)	192 (32)
High risk[e]	63 (6.2)	73 (19)	42 (12)	127 (21)
Advanced[f]	12 (1.3)	54 (14)	10 (2.8)	107 (18)
Unknown	2 (0.2)	25 (6.7)	13 (3.6)	50 (8.3)
PCa deaths	79		122	

[a]Includes 9 cases detected as a results of erroneous investigation
[b]Includes 8 cases diagnosed at autopsy
[c]T1, not N1 or M1, Gleason score ≤6 and PSA <10 ng/mL
[d]T1–2, not N1 or M1, Gleason score ≤7 and/or PSA <20 ng/mL
[e]T1–4, not N1 or M1, Gleason score ≥8 and/or PSA <100 ng/mL
[f]N1 and/or M1 and/or PSA ≥100 ng/mL

Methods

Randomisation
Computer-randomised
- Randomisation before consent (Zelen-type, effectiveness design)

Duration of follow-up
18 years

Note that the control arm involved opportunistic screening.

Outcomes
Mortality/morbidity outcomes
- Primary extraction

Study Reference

Göteborg Screening Study (Swedish ERSPC) (Arnsrud Godtman 2015)
Linked records: Hugosson 2018

- Arnsrud Godtman 2015: PCa mortality rates and observed cumulative incidence rates (calculated using the actuarial method); expected PCa incidence and mortality rates in the absence of PSA testing (calculated using historical data from 1990–1994 [pre-PSA era])
- Linked studies: PCa mortality with respect to sociodemographic inequality

Harms of PSA screening outcomes

- Primary extraction
  - Arnsrud Godtman 2015: NNI and NND (calculated by comparing the expected versus observed incidence and mortality rates)

Mortality and/or Morbidity Outcomes (Q1)

Incidence (18 year follow-up)

Outcome	Screening arm (n=9950)	Control arm (n=9949)	P value
Median time from randomisation to diagnosis	8.6 yr	10.3 yr	<0.001
Observed cumulative incidence of PCa	16%	11%	
Expected PCa incidence	6.8%	6.9%	

Mortality (18 year follow-up)

Outcome	Screening arm (n=9950)	Control arm (n=9949)
Observed cumulative PCa mortality	0.98%	1.5%
Expected PCa mortality	1.7%	1.7%
Absolute mortality reduction (from screening)	0.72% (95% CI 0.50–0.94%)	
Relative risk reduction (from screening)	42% (95% CI 28–54%)	

Exposure to an increasing rate of opportunistic PSA screening, as documented in previous reports relevant to the control group, did not result in any significant difference between the observed and expected PCa mortality during any period of the follow-up (absolute reduction of 0.20% [95% CI –0.06% to 0.47%], relative risk reduction 12% [95% CI –5% to 26%]).

PCa incidence rate, mortality rate and rate ratio at different lengths of follow-up for the screening and control groups, stratified by age (Hugosson 2018)

	Rate per 1000 person-years (95% CI)		Rate ratio (screening vs control) (95% CI)			
	Screening arm	Control arm	All men	50–54 yr	55–59 yr	60–64 yr
14 year follow-up						
N PCa/person-years	1140/132199	722/136840	-	-	-	-
PCa incidence	8.6 (8.1–9.1)	5.3 (4.9–5.7)	1.63 (1.49–1.80)	1.85 (1.56–2.20)	1.67 (1.43–1.97)	1.43 (1.22–1.69)
N PCa deaths/person-years	44/125973	78/125914	-	-	-	-
PCa mortality	0.35 (0.26–0.47)	0.62 (0.50–0.77)	0.56 (0.38–0.83)	0.62 (0.16–2.15)	0.35 (0.16–0.68)	0.77 (0.45–1.31)
16 year follow-up						
N PCa/person-years	1288/131683	860/136317	-	-	-	-
PCa incidence	9.8 (9.3–10.3)	6.3 (5.9–6.7)	1.55 (1.42–1.69)	1.80 (1.55–2.10)	1.45 (1.25–1.69)	1.43 (1.22–1.67)
N PCa deaths/person-years	60/141118	98/141035	-	-	-	-
PCa mortality	0.43 (0.33–0.55)	0.69 (0.57–0.85)	0.61 (0.44–0.85)	0.54 (0.18–1.44)	0.35 (0.18–0.65)	0.90 (0.57–1.43)
18 year follow-up						

Study Reference

Göteborg Screening Study (Swedish ERSPC) (Arnsrud Godtman 2015)
Linked records: Hugosson 2018

N PCa/person-years	1396/143776	962/149129	-	-	-	-
PCa incidence	9.7 (9.2–10.2)	6.5 (6.1–6.9)	1.51 (1.39–1.64)	1.77 (1.54–2.04)	1.37 (1.19–1.59)	0.47 (0.28–0.79)
N PCa deaths/person-years	79/155374	122/155245	-	-	-	-
PCa mortality	0.51 (0.41–0.64)	0.79 (0.66–0.94)	0.65 (0.48–0.87)	0.50 (0.20–1.16)	0.47 (0.28–0.79)	0.85 (0.56–1.28)

Harms of PSA-Based Screening (Q2)

Prostate biopsy method (if applicable)
N/A

NNI and NND for different follow-up lengths

Follow-up length	Screening arm		Control arm	
	NNI	NND	NNI[a]	NND
12 years	461	36	-	-
13 years	400	34	-	-
14 years	261	22	-	-
15 years	216	19	1053	46
16 years	188	17	1190	55
17 years	164	15	820	39
18 years	139	13	493	23

[a]NNI could not be assessed before 15 years of follow-up because no mortality reduction was discernible before that point in time

Authors' Conclusions

- After 18 yr, PCa incidence in the control group had increased by almost 70% compared to the pre-screening era, indicating considerable uptake of opportunistic screening in the control group. This is further supported by the fact that almost 40% of the cancers in the control group were diagnosed through opportunistic screening in asymptomatic men. It is likely that many more men in the control group reporting modest micturition symptoms were also actually screen-detected. The increase in incidence was apparent by 3 yr after the study start
- In the screening group, NNI to prevent one PCa death was 139 at 18 years. The corresponding value in the control group was 493. This large discrepancy in NNI shows the difference in the ability to reduce PCa mortality between organised and opportunistic PSA screening.
- More important is the difference in NND as it reflects the rate of overdiagnosis. Almost twice the number of men needed to be diagnosed to save one man from dying from PC with opportunistic screening compared to men offered an organised biennial screening program (NND 23 vs 13).
- When the screening group was instead compared to the control group, NNI and NND were 190 and 9, respectively at 18 years. These data show that the background use of PSA testing in the control group results in underestimation of both the mortality reduction and the amount of overdiagnosis (as NND) when the screening group is compared to the control group. Our results also suggest that opportunistic screening detects tumours at a later stage when compared to organised screening, as the men in the control group were older at diagnosis and screen-detected tumours in the control group were more advanced than those in the screening group
- Results indicate that organised intense screening effectively reduces PCa mortality but is associated with considerable overdiagnosis; after 18 years of follow-up, 13 men must be diagnosed to prevent one PCa death compared to a situation with no PSA testing.
- Opportunistic PSA testing had little if any effect on PCa mortality, and was associated with greater overdiagnosis in comparison to organised screening, as estimated by NND.

Additional Results/ Conclusions

Hugosson 2018

Study Reference	**Göteborg Screening Study (Swedish ERSPC) (Arnsrud Godtman 2015)** Linked records: Hugosson 2018
from Linked Records	Reports PCa incidence and PCa-specific mortality among attendees in sociodemographic subgroups at 18-year follow-up. This data is not extracted because results are not compared between screening and control arms

Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer; IQR, interquartile range; N/A, not applicable; NND, number needed to detect; NNI, number needed to invite; NR, not reported; PCa, prostate cancer; PSA, prostate-specific antigen

Table 39d. ERSPC Rotterdam, Bokhorst 2015/Chiu 2017

Study Reference	**ERSPC Rotterdam (Bokhorst 2015/Chiu 2017)** Linked records: Bokhorst 2014
Study Design	Study name ERSPC Rotterdam Design Randomised controlled trial Objective **Bokhorst 2015:** To assess differences in treatment between the screening and control arms of ERSPC Rotterdam and study whether possible treatment differences could explain the positive study outcome **Chiu 2017:** To investigate biopsy complications and hospital admissions that could be reduced by the use of ERSPC risk calculators Dates Initiation/recruitment: 1993–1999 Maximum follow-up: 2010 for outcomes; 2015 for biopsy complications Country The Netherlands Setting NR
Population Characteristics	Patient recruitment and eligibility In the screening arm, men were invited for PSA testing every 4 years until age 75 years. In the first half of the first screening round men were offered prostate biopsy if PSA was ≥4 ng/mL or DRE was abnormal. After the first half of the first screening round PSA ≥3 ng/mL was the only indication for prostate biopsy in all subsequent screening rounds. **Inclusion** At recruitment, men were aged 55–74 years. **Exclusion** NR Sample size N screened/invited = N/A N eligible = NR N enrolled (underwent randomisation) = 42,376 (21,210 in the screening arm; 21,166 in the control arm [17,443 and 17,390 respectively in the core age group of 55–69])

Study Reference	**ERSPC Rotterdam (Bokhorst 2015/Chiu 2017)** Linked records: Bokhorst 2014

N excluded (with reason) = NR
N in the intervention group = NR
N in the control group = NR
N lost to follow-up = NR
N completed = NR
N excluded from analysis = NR
N included in analysis = NR

Prostate cancers diagnosed in the study group

Parameter	Screening	Control
Cases, n	2699	1444
Median age at diagnosis, yr (IQR)	68.7 (64.8–72.5)	72.1 (67.5–75.8)
Median PSA at diagnosis, ng/mL (IQR)	5.2 (3.5–9.1)	11.8 (7.2–27.5)
cT stage at diagnosis, n (%)		
1	1504 (55.7)	700 (48.5)
2	819 (30.3)	379 (26.2)
3	319 (11.8)	272 (18.8)
4	28 (1)	65 (4.5)
Missing	29 (1.1)	28 (1.9)
Gleason Score at diagnosis, n (%)		
≤6	1863 (69)	701 (48.5)
7	592 (21.9)	426 (29.5)
≥8	223 (8.3)	292 (20.2)
Missing	21 (0.8)	25 (1.7)
M stage at diagnosis, n (%)		
0/X	2643 (97.9)	1312 (90.9)
1	56 (2.1)	132 (9.1)
Risk group at diagnosis, n (%)		
Low	1386 (51.4)	350 (24.2)
Intermediate	553 (20.5)	371 (25.7)
High	647 (24)	512 (35.5)
Metastatic	73 (2.7)	182 (12.6)
Missing	40 (1.5)	29 (2)
Deaths, n (%)		
All causes	781 (28.9)	490 (33.9)
PCa-specific	151 (5.6)	188 (13)

[a]In 141 men in screening arm and 22 controls with missing Gleason Score (3.9% of all with PCa) tumour grades 1, 2 and 3 were recorded as Gleason Score groups of ≤6, 7 and ≥8, respectively, to enable more complete analysis while 46 had missing Gleason Score and tumour grade.

Methods	Randomisation Computer-randomised • Randomisation after consent (efficacy design) Duration of follow-up Median 12.8 years

Study Reference

ERSPC Rotterdam (Bokhorst 2015/Chiu 2017)
Linked records: Bokhorst 2014

Outcomes

Mortality/morbidity outcomes

- Primary extraction
  - Bokhorst 2015: PCa-specific mortality (analysed in entire cohort and core age group of 55–69 years), incidence
- Linked studies: PCa-specific mortality after adjustment for nonattendance and contamination

Harms of PSA screening outcomes

- Primary extraction
  - Chiu 2017: biopsy complications and hospital admissions (prospectively recorded in questionnaires that were completed 2 weeks after biopsy). All biopsies (N=10,970 from 7,422 men) performed between 1993 and 2015 were included. Complications after prostate biopsy included fever, haematuria, haematospermia, pain (persistent pain on 10–14th day after biopsy), and any hospital admission within the first 2 weeks; proportion of biopsies, complications and admissions that could be avoided by applying the ERSPC risk calculators to men with a PSA value ≥3.0 ng/mL at initial and repeat biopsy.

Mortality and/or Morbidity Outcomes (Q1)

Prostate cancer incidence and mortality in screening and control arms by risk group

Risk group	Overall incidence			Overall mortality			P value (RR incidence vs mortality)
	Screening, n (%)	Control, n (%)	RR	Screening, n (%)	Control, n (%)	RR	
Overall	2699 (12.7)	1444 (6.8)	1.87	151 (0.71)	188 (0.89)	0.80	<0.001
Missing	40 (0.2)	29 (0.1)	1.38	0	1 (0.005)	-	-
Low	1386 (6.5)	350 (1.7)	3.95	15 (0.07)	1 (0.005)	14.97	0.198
Intermediate	553 (2.6)	371 (1.8)	1.49	14 (0.07)	10 (0.05)	1.40	0.881
High	647 (3.1)	512 (2.4)	1.26	87 (0.41)	82 (0.39)	1.06	0.287
Metastatic	73 (0.3)	182 (0.9)	0.40	35 (0.17)	94 (0.44)	0.37	0.758

The slope of the regression line of ln(RR) PCa incidence on ln(RR) PCa mortality in the intermediate, high and metastatic risk group was 1.00 (95% CI 0.30–1.74, R^2=0.94). This means that incidence and mortality were 1:1 related in these groups and 94% of the changes in morality could be explained by differences in incidence. Adding the low risk group did not change the results (slope 1.06, 95% CI 0.44–1.68, R^2=0.91)

Harms of PSA-Based Screening (Q2)

Prostate biopsy method (if applicable)
Systemic sextant biopsy of the prostate with a TRUS-guided approach according to the ERSPC protocol

Biopsy complications and baseline characteristics of those with biopsies (N=10,747 with biopsy complication data available)

	Total biopsies (N=10747)
Median age, yr (IQR)	68.0 (64.0–71.5)
Median prostate volume, mL (IQR)	45.0 (34.0–59.4)
Fever in previous biopsy, n (%)	100 (0.9)
Diabetes, n (%)	692 (6.4)
Heart disease, n (%)	1883 (17.5)
Any complications, n (%)	7294 (67.9)
Fever, n (%)	424 (3.9)
Haematuria, n (%)	2733 (25.4)
Haematospermia, n (%)	5369 (50.0)

Study Reference

ERSPC Rotterdam (Bokhorst 2015/Chiu 2017)
Linked records: Bokhorst 2014

Pain, n (%)	490 (4.6)
Hospital admission, n (%)	92 (0.9)

Biopsies, complications and admissions that could be reduced by avoiding biopsies in applying ERSPC risk calculators 3 and 4 (RC4) (N=7,704)

Events reduced by avoiding biopsy if RC3 or RC4: PCa risk <12.5% and HGPCa risk <3%	Whole cohort (RC3 or RC4) N=7704, % (n/N)	RC3 for 1st round of screening and without previous biopsies N=3083 % (n/N)	RC4 for 2nd–5th rounds of screening and/or previous negative biopsy N=4621 % (n/N)
Biopsy	35.8 (2757/7704)	27.1 (837/3083)	41.5 (1920/4621)
Any complication	37.4 (1972/5268)	28.2 (564/2000)	43.1 (1408/3268)
Fever	39.4 (128/325)	31.5 (39/124)	44.3 (89/201)
Haematuria	43.3 (893/2063)	32.1 (224/698)	49.0 (669/1365)
Haematospermia	35.8 (1363/3810)	27.4 (407/1483)	41.1 (956/2327)
Pain	39.0 (141/362)	33.3 (48/144)	42.7 (93/218)
Hospital admissions	42.3 (30/71)	15.4 (2/13)	48.3 (25/58)

Authors' Conclusions

Bokhorst 2015

- A favourable stage shift with less metastatic disease at diagnosis was seen in ERSPC Rotterdam. The changes in mortality were consistent with the changes in PCa incidence per risk group initiated through screening. This observation supports a stage shift with subsequent earlier treatment as the main reason for lower PCa mortality in the screening arm or ERSPC Rotterdam, excluding a large effect on the primary outcome of observed differences in treatment between the arms.

Chiu 2017

- A significant proportion of biopsy complications, hospital admissions and associated costs could be reduced if biopsy decisions were carried out on the basis of an individual multivariate risk assessment using the ERSPC risk calculators. This effect was most prominent in men who had undergone multiple biopsy sessions.

Additional Results/ Conclusions from Linked Records

Bokhorst 2014

Reduction of PCa-specific mortality from screening (for the intention to screen analysis, correction for nonattendance and correction for contamination*)

	RR	95% CI	P value
Intention to screen	0.68	0.53–0.89	0.004
Correction for nonattenders	0.67	0.51–0.88	0.004
Correction for PSA contamination	0.61	0.42–0.88	0.008
Correction for biopsy contamination	0.53	0.32–0.88	0.014
Correction for nonattenders plus PSA	0.58	0.39–0.86	0.007
Correction for nonattenders plus biopsy	0.49	0.27–0.87	0.015

*Mortality follow-up until the end of 2010

The correction for nonattendance and biopsy contamination resulted in a reduction of the PCa-specific mortality of 51% in favour of screening. Correction for nonattendance alone had a small effect (RR for intention to screen: 0.68, RR with correction: 0.67).

Abbreviations: DRE, digital rectal examination; ERSPC, European Randomized Study of Screening for Prostate Cancer; HGPCa, high-grade prostate cancer; IQR, interquartile range; N/A, not applicable; PCa, prostate cancer; PSA, prostate-specific antigen; RR, risk reduction; TRUS, transrectal ultrasound

Table 39e. FinRSPC (Finnish ERSPC), Neupane 2018/Pashayan 2015/Booth 2014

Study Reference	**FinRSPC (Finnish ERSPC) (Neupane 2018/Pashayan 2015/Booth 2014)** Linked records: Kilpeläinen 2017; Kilpeläinen 2016; Kilpeläinen 2015; Lindberg 2019; Pakarainen 2019; Pakarainen 2016
Study Design	Study name FinRSPC Design Randomised controlled trial Objective **Neupane 2018:** To identify the prognostic factors of prostate cancer death among patients enrolled in a Finnish prostate cancer screening trial **Pashayan 2015:** To estimate mean sojourn time and sensitivity and then use these estimates to derive the probability of overdiagnosis by polygenic risk **Booth 2014:** To quantify the long-term HRQoL impact associated with screening for PCa Dates Initiation/recruitment: 1996–1999 Maximum follow-up: 2013 Country Finland Setting 2 study centres in Helsinki and Tampere
Population Characteristics	Patient recruitment and eligibility Men were identified from the Finnish Population Registry. A random sample of 8,000 men was annually allocated to the screening arm, and the remaining men formed the control arm without any intervention. **Inclusion** At recruitment, men were aged 55–67 years **Exclusion** Men aged >71 years, those diagnosed with PCa and men who had emigrated from the study area were no longer invited. Sample size N screened/invited = N/A N eligible = NR N enrolled (underwent randomisation) = 80,176 (screening arm: 31,866; control arm: 48,278) N excluded (with reason) = NR N in the intervention group = NR N in the control group = NR N lost to follow-up = NR N completed = NR

Study Reference **FinRSPC (Finnish ERSPC) (Neupane 2018/Pashayan 2015/Booth 2014)**
Linked records: Kilpeläinen 2017; Kilpeläinen 2016; Kilpeläinen 2015; Lindberg 2019; Pakarainen 2019; Pakarainen 2016

N excluded from analysis = NR
N included in analysis = NR

Characteristics of the PCa cases and PCa deaths by trial arm

Parameter	PCa cases			PCa death		
	Screening (n=3473)	Control (n=4475)	P value	Screening (n=456)	Control (n=278)	P value
Age at randomisation, n (%)			0.35			0.93
55 years	829 (23.9)	1035 (23.1)		41 (14.8)	67 (14.7)	
59 years	897 (25.8)	1154 (25.8)		65 (23.4)	102 (22.4)	
63 years	925 (26.6)	1152 (25.7)		76 (27.3)	119 (26.1)	
67 years	822 (23.7)	1134 (25.7)		96 (34.5)	168 (36.8)	
Median age at diagnosis, yr (IQR)	67 (55–83)	69 (55–83)		67 (55–81)	68 (55–81)	
Median PSA at diagnosis, ng/mL (IQR)	8.0 (0.5–2700)	9.8 (0.4–8930)		32.8 (2.1–2370)	40.3 (1.2–8430)	
Biopsy Gleason sum, n (%)			<0.001			0.12
2–6	2071 (59.6)	2034 (45.5)		64 (23.0)	78 (17.1)	
7	877 (25.3)	1478 (33.0)		75 (27.0)	113 (24.8)	
8–10	464 (13.4)	836 (18.7)		126 (45.3)	230 (50.4)	
Missing	61 (1.8)	127 (2.8)		13 (4.7)	35 (7.7)	
Risk group, n (%)			<0.001			0.07
Low	995 (28.6)	1160 (25.9)		9 (3.2)	17 (3.7)	
Intermediate	764 (22.0)	1398 (31.2)		33 (11.9)	40 (8.8)	
High	651 (18.8)	1155 (25.8)		80 (28.8)	121 (26.5)	
Advanced	238 (6.9)	520 (11.6)		121 (43.5)	262 (57.5)	
Missing	825 (23.7)	242 (5.3)		35 (12.6)	16 (3.5)	

Characteristics of the PCa cases and PCa deaths by method of detection in the screening arm (compared to control)

Parameter	PCa cases				PCa death			
	Screen-detected (n=1633)	Not screen-detected (n=1840)	Control (n=4475)	P value	Screen-detected (n=93)	Not screen-detected (n=185)	Control (n=278)	P value
Age at randomisation, n (%)				0.001; 0.10				0.90; 0.78
55 years	358 (21.9)	471 (25.6)	1035 (23.1)		13 (14.0)	28 (15.1)	67 (14.7)	
59 years	458 (28.1)	439 (23.9)	1154 (25.8)		18 (19.4)	47 (25.4)	102 (22.4)	
63 years	474 (29.0)	451 (24.5)	1152 (25.7)		27 (29.0)	49 (26.5)	119 (26.1)	
67 years	343 (21.0)	479 (26.0)	1134 (25.7)		35 (37.6)	61 (33.0)	168 (36.8)	
Median age at diagnosis, yr (IQR)	67 (55–72)	69 (55–83)	69 (55–83)		67 (55–72)	68 (58–81)	68 (55–81)	
Median PSA at diagnosis, ng/mL (IQR)	5.6 (2–123)	9.6 (0.5–2700)	9.8 (0.4–8930)		9.1 (3.6–1185)	37.9 (4.7–2370)	40.3 (1.2–8430)	
Biopsy Gleason sum, n (%)				<0.001; 0.12				<0.001; 0.51
2–6	1195 (73.2)	876 (47.6)	2034 (45.5)		38 (40.9)	26 (14.1)	78 (17.1)	

Study Reference	**FinRSPC (Finnish ERSPC) (Neupane 2018/Pashayan 2015/Booth 2014)** Linked records: Kilpeläinen 2017; Kilpeläinen 2016; Kilpeläinen 2015; Lindberg 2019; Pakarainen 2019; Pakarainen 2016							
	7	318 (19.5)	559 (30.4)	1478 (33.0)		31 (33.3)	44 (23.8)	113 (24.8)	
	8–10	117 (7.2)	347 (18.9)	836 (18.7)		24 (25.8)	102 (55.1)	230 (50.4)	
	Missing	3 (0.2)	58 (3.2)	127 (2.8)		0	13 (7.0)	35 (7.7)	
	Risk group, n (%)				<0.001; 0.74				<0.001; 0.53
	Low	520 (31.8)	475 (25.8)	1160 (25.9)		6 (6.5)	3 (1.6)	17 (3.7)	
	Intermediate	200 (12.3)	564 (30.7)	1398 (31.2)		14 (15.1)	19 (10.3)	40 (8.8)	
	High	215 (13.2)	436 (23.7)	1155 (25.8)		31 (33.3)	49 (26.5)	121 (26.5)	
	Advanced	35 (2.1)	203 (11.0)	520 (11.6)		15 (16.1)	106 (57.3)	262 (57.5)	
	Missing	663 (40.6)	162 (8.8)	242 (5.3)		27 (29.0)	8 (4.3)	16 (3.5)	
Methods	Randomisation Computer-randomised • Randomisation before consent (Zelen-type, effectiveness design) Duration of follow-up 16 years (Neupane 2018) 13 years (Pashayan 2015; Booth 2014) Outcomes **Mortality/morbidity outcomes** • Primary extraction o Neupane 2018: PCa-specific mortality (causes of death obtained from Statistics Finland). Method of PCa detection was divided into screen-detected and other cases, where other cases included those in the control arm, as well as interval cases and cancers among non-participants from the screening arm. **Harms of PSA screening outcomes** • Primary extraction o Pashayan 2015: overdiagnosis (probability derived by polygenic risk) ▪ Polygenic risk score (PRS) was calculated based on the genotypes of 66 known PCa loci for 4,967 men from the Finnish section of the ERSPC and the 72,072 men in the trial were stratified into those with polygenic risk above and below the median ▪ Mean sojourn time and sensitivity of PSA were estimated by the Walter and Day (1993) method ▪ For each polygenic risk group, the proportion of screen-detected cancers that are likely to be overdiagnosed were estimated from the difference between the observed and expected number of screen-detected cancers o Booth 2014: HRQoL, ascertained by postal questionnaire surveys (conducted in 1998, 2000, 2004 and 2011) (RAND 36-Item Short Form Health Survey, which can be used to produce SF-6D; 15D health state description system and EQ-5D instrument) among men in FinRSPC diagnosed with PCa (total n=7,011) and among a random subsample of the trial population (n=2,200).								
Mortality and/or Morbidity Outcomes (Q1)	Cause-specific survival from randomisation **Screening vs control arm** • Higher among the cases in the screening arm compared with the control arm (Kaplan-Meier survival estimates 0.96 vs 0.95 at wo years, 0.92 vs 0.90 at 15 years; age-adjusted HR 0.79 [95% CI 0.74–0.84]) • PCa mortality in the two arms began to diverge after 7–8 years and the difference increased over time **Screening arm: screen-detected vs other cases**								

Study Reference — **FinRSPC (Finnish ERSPC) (Neupane 2018/Pashayan 2015/Booth 2014)**
Linked records: Kilpeläinen 2017; Kilpeläinen 2016; Kilpeläinen 2015; Lindberg 2019; Pakarainen 2019; Pakarainen 2016

- A survival advantage was also seen for screen-detected cases compared with other cancers (Kaplan–Meier mortality estimates 0.03 vs 0.05 at 10 years and 0.06 vs 0.09 at 15 years; HR 0.58, 95% CI 0.53–0.64 for the entire follow up) with 33% lower risk of PCa mortality among screen detected cases

Impact of prognostic factors

Screening vs control arm

- Most prognostic factors had a comparable effect in both arms
- PSA 6–10 carried a poorer prognosis than PSA <6 in the screening arm (HR 1.65, 95% CI 0.86 to 3.17), but not in the control arm (HR 1.08, 95% CI 0.69 to 1.68)
- Gleason score of 8–10 had a stronger effect in the screening arm (HR 9.10, 95% CI 6.76 to 12.25) compared with the control (HR 7.39, 95% CI 5.70 to 9.58)
- Presence of comorbidity was associated with poorer survival in the screening arm (HR 1.52, 95% CI 1.05 to 2.21) compared with the control (HR 1.25, 95% CI 0.93 to 1.66) – the difference between the arms was not significant (P=0.41)
- Risk group was a strong prognostic determinant in both arms, with some suggestion of poorer outcome for advanced disease in the control arm (survival proportion at 15 years in the screening arm 0.60 vs 0.51 in the control arm)

Harms of PSA-Based Screening (Q2)

Prostate biopsy method (if applicable)
N/A

Overdiagnosis (Pashayan 2015)

Proportion of the study population with PRS and of those in the higher risk group

	N (%) with PRS	N (%) with PRS in the higher risk group
Screening arm		
Men with no PCa (N=21,030)	3877 (18.4)	1930 (49.8)
Screen-detected cancer at first round of screening (N=686)	173 (25.2)	131 (75.7)
Screen-detected cancer at subsequent rounds of screening (N=960)	406 (42.3)	285 (70.2)
Interval cancer (N=525)	115 (21.9)	92 (80.0)
Clinically diagnosed cancer >4 years after last screen (N=565)	34 (6.0)	25 (73.5)
Non-participants with clinically diagnosed cancer (N=562)	22 (3.9)	17 (77.3)
Non-participants with no cancer diagnosis (N=7,542)	0 (0.0)	0 (0.0)
Control arm		
Clinically diagnosed cancer	339 (8.2)	250 (73.8)
No cancer	1 (0.0)	1 (100.0)

Proportion of screen-detected cancers which are likely to be overdiagnosed by polygenic risk

Screening round	N screening episodes	N screen-detected cancer	Expected N of non-overdiagnosed screen-detected cancer	% overdiagnosis (95% CI)
Overall				
Screening round 1	23771	686	504	42 (37–52)
Screening round 2	18044	596	272	

Study Reference **FinRSPC (Finnish ERSPC) (Neupane 2018/Pashayan 2015/Booth 2014)**
Linked records: Kilpeläinen 2017; Kilpeläinen 2016; Kilpeläinen 2015; Lindberg 2019; Pakarainen 2019; Pakarainen 2016

Screening round 3	10328	364	173	
Total	52143	1646	949	
PRS risk groups				
Lower risk group				
Screening round 1	11938	167	101	58 (54–65)
Screening round 2	9062	178	55	
Screening round 3	5187	108	35	
Total	26186	453	191	
Higher risk group				
Screening round 1	11833	519	402	37 (31–47)
Screening round 2	8982	418	217	
Screening round 3	5141	256	139	
Total	25957	1193	758	

HRQoL (Booth 2014)

Response to questionnaires

	Screening arm				Control arm			
	1998	1999	2003	2011	1998	1999	2003	2011
Men diagnosed with PCa (recruited over the course of the trial)								
Unit response	148	272	891	1587	36	97	536	1706
Unit nonresponse	12	20	86	430	3	6	80	613
No address or dead	4	14	89	145	1	3	55	177
15D responses	144	260	879	1539	34	94	530	1644
EQ-5D responses	N/A	N/A	N/A	1536	N/A	N/A	N/A	1632
SF-6D responses	142	245	828	1423	32	88	486	1521
Random sample of 1,100 men drawn from each trial arm (in 1998)								
Unit response	740	748	683	549	733	752	690	539
Unit nonresponse	354	326	328	279	361	326	316	301
No address or dead	6	26	89	272	6	22	94	260
15D responses	735	736	682	534	729	742	688	522
EQ-5D responses	N/A	N/A	N/A	519	N/A	N/A	N/A	514
SF-6D responses	700	697	653	486	688	697	656	483

Cross-sectional analysis (2011 survey)

Men diagnosed with PCa (screening vs control arm)

- 15D: 0.872 vs 0.866 (p=0.14)
- EQ-5D: 0.852 vs 0.831 (p=0.03)
- SF-6D: 0.763 vs 0.756 (p=0.06)

Men from trial subsample

- 15D: 0.889 vs 0.892 (p=0.62)

Study Reference	**FinRSPC (Finnish ERSPC) (Neupane 2018/Pashayan 2015/Booth 2014)** Linked records: Kilpeläinen 2017; Kilpeläinen 2016; Kilpeläinen 2015; Lindberg 2019; Pakarainen 2019; Pakarainen 2016
	• EQ-5D: 0.831 vs 0.852 (p=0.08) • SF-6D: 0.775 vs 0.777 (p=0.88) *Comparison of both* • The decrement in the mean HRQoL scores of men with PCa relative to the trial subsample was slightly more pronounced in the control arm than in the screening arm o Control arm: mean scores of all HRQoL measures were lower for men with PCa than trial subsample (not PCa) o Screening arm: men with stage T1 or T2 PCa had higher or similar mean HRQoL scores than men in trial subsample (but lower for T3 or T4) Longitudinal analysis (1998 to 2011 surveys) *Men from trial subsample* • Age and socioeconomic status were statistically significant determinants of the 15D score (no differences between trial arms or localities) *Men with PCa* • Mean 15D scores in all surveys were higher in the screening arm (by increment of 0.01) than in control arm after adjustment for age, domicile and socioeconomic status
Authors' Conclusions	**Neupane 2018** • Screen-detected cancers have a better prognosis than cases detected outside screening. • The screening arm had a 20% reduced risk of PCa mortality compared with the controls. • Advanced disease is associated with poorer outcomes in cases outside of screening than screen-detected cancers, even when lead-time is eliminated. • Minor differences were found for specific prognostic factors. • A high diagnostic PSA was related to poor outcome, especially among the cases detected outside of screening. This indicates that the screening resulted in earlier treatment among the cases in the screening arm. Nevertheless, the prognostic risk group based on stage, Gleason score and PSA at diagnosis remains the major prognostic determinant for PCa detected by screening and other means. **Pashayan 2015** • Targeting screening to men at higher polygenic risk could reduce the proportion of cancers overdiagnosed **Booth 2014** • This study shows a small advantage in the mean HRQoL scores for the screening arm over the control arm for men diagnosed with PCa. These differences were small and not detected by all of the generic indicators at all times in the course of the 13-year follow-up. • Using these HRQoL measures, this study provides little evidence than mean health-state utility value scores differed markedly between the trial arms for the trial population overall
Additional Results/ Conclusions from Linked Records	**Kilpeläinen 2016** Crosstabulations of causes of death by official Statistics Finland registry and evaluation of cause of death committee (the gold standard) in the Finnish Randomized Study of Screening for Prostate Cancer (1996–2014) at **16 years of follow up**

Statistics Finland	Cause of death committee		
	PCa death	Other cause of death	Total
Screening arm			
PCa death	61	7	68
Other cause of death	4	133	137

Study Reference **FinRSPC (Finnish ERSPC) (Neupane 2018/Pashayan 2015/Booth 2014)**
Linked records: Kilpeläinen 2017; Kilpeläinen 2016; Kilpeläinen 2015; Lindberg 2019; Pakarainen 2019; Pakarainen 2016

Total death	65	140	205
Sensitivity (=61/(61+4))		0.94 (95% CI 0.84–0.98)	
Specificity (+133/(133+7))		0.95 (95% CI 0.90–0.98)	
PPV (=61/(61+7))		0.90 (95% CI 0.79–0.95)	
NPV (=133/(133+4))		0.97 (95% CI 0.92–0.99)	
Agreement		94.6%	
Expected agreement		56.2%	
Kappa		0.88 (95% CI 0.82–0.94)	
Correcting factor		0.956	
Control arm			
PCa death	105	7	112
Other cause of death	4	121	125
Total death	109	128	237
Sensitivity (=61/(61+4))		0.96 (95% CI 0.90–0.99)	
Specificity (+133/(133+7))		0.95 (95% CI 0.89–0.98)	
PPV (=61/(61+7))		0.94 (95% CI 0.87–0.97)	
NPV (=133/(133+4))		0.97 (95% CI 0.92–0.99)	
Agreement		95.4%	
Expected agreement		50.2%	
Kappa		0.91 (95% CI0.86–0.95)	
Correcting factor		0.973	

Author's conclusions

There appears to be a small but real differential misclassification bias in the FinRSPC. This is probably caused by attribution bias as the screened men are more likely to be diagnosed with PCa. The PCa diagnosis can eventually be recorded as an official underlying cause of death, even when the chain of events leading to death is ultimately caused by another disease. In any screening trial with disease-specific mortality as an endpoint, this attribution bias should preferably be controlled with reviewing all deaths in those disease to maximize precision, although the benefit may remain minimal

Kilpeläinen 2017

By the first 4, 8 and 12 years of follow-up, 18.1%, 47.7% and 62.7% of men in the control arm had undergone PSA testing at least once and in the screening arm the proportions were 69.8%, 81.1% and 85.2%, respectively. The cumulative incidence of T1c PCa was 6.1% in the screening arm and 4.5% in the control arm (RR 1.21, 95% CI 1.13, 1.30)

A large proportion of men in the control arm had undergone a PSA test during the 15-year follow-up. Contamination is likely to dilute differences in PCa mortality between the arms in the Finnish screening trial

Kilpeläinen 2015

Investigating which had the largest impact on PCa deaths in the screening arm: non-participation, interval cancers or PSA threshold with **15 years of follow-up**

Hazard ratios after exclusion of specific subgroups from the screening arm

Study Reference **FinRSPC (Finnish ERSPC) (Neupane 2018/Pashayan 2015/Booth 2014)**
Linked records: Kilpeläinen 2017; Kilpeläinen 2016; Kilpeläinen 2015; Lindberg 2019; Pakarainen 2019; Pakarainen 2016

	Screening arm			Control arm			HR (95% CI)
	N of men	Person-years	N of PCa deaths (%)	N of men	Person-years	N of PCa deaths (%)	
All men (ITS analysis)	31866	426827	241 (0.76)	48278	646118	410 (0.85)	0.89 (0.76–1.04)
Correcting only the screening arm							
Excluding the non-participants	23771	334115	153 (0.64)	48278	646118	410 (0.85)	0.71 (0.59–0.86)
Excluding men with							
PSA 3.0–3.99 ng/mL and PC	31378	419532	218 (0.69)	48278	646118	410 (0.85)	0.85 (0.72–1.00)
Interval cancers	31630	423482	218 (0.69)	48278	646118	410 (0.85)	0.81 (0.69–0.96)
Correcting both screening arm and control arm							
Excluding the non-participants	23771	334115	153 (0.64)	36014	482181	277 (0.77)	0.78 (0.64–0.96)
Excluding men with							
PSA 3.0–3.99 ng/mL and PC	31378	419532	218 (0.69)	47539	635410	375 (0.79)	0.88 (0.74–1.04)
Interval cancers	31630	423482	218 (0.69)	47920	640974	375 (0.78)	0.88 (0.74–1.04)

Author's conclusions

Of the relevant subgroups in the SA, especially the nonparticipant population in the screening arm had a substantial impact on PC mortality. Avoidance of interval cancers and lower screening threshold would have also enhanced the relative mortality effect, but to a lesser extent. Despite the acceptable participation proportion achieved in the Finnish trial, special attention needs to be given to the high-risk men who tend to opt out from population-based screening programs.

Lindberg 2019

Correcting for noncompliance and contamination – cumulative incidence with **15 years of follow-up**

	Corrected screening arm			Control arm			Difference in cases per 1000 men (95% CI)	Risk ratio (95% CI)
	N [1]	Cases	Cases per 1000 men (95% CI [2])	N [1]	Cases	Cases per 1000 men (95% CI)		
Stage								
Local	16284	1738	406.7 (101.9–111.3)	24672	1568	63.6 (60.5–66.7)	43.2 (37.5–48.8)	1.68 (1.57–1.79)
Progressed	16284	126	7.7 (6.5–9.2)	24672	364	14.8 (13.3–16.3)	–7.0 (–9.0– –5.0)	0.52 (0.43–0.64)
Metastatic [1]	16284	41	2.5 (1.7–3.3)	24672	155	6.3 (5.4–7.3)	–3.8 (–5.0– –2.5)	0.40 (0.28–0.56)
Gleason score								
≤6	16273	1361	83.6 (79.5–87.9)	24636	952	38.6 (36.4–41.2)	45.0 (40.0–50.0)	2.16 (2.00–2.34)
3 + 4	16273	223	13.7 (11.9–15.5)	24636	441	17.9 (16.4–19.7)	–4.2 (–6.7– –1.7)	0.77 (0.65–0.90)
4 + 3	16273	167	10.3 (8.8–12.0)	24636	312	12.7 (11.3–14.2)	–2.4 (–4.5– –0.3)	0.81 (0.67–0.98)
4 + 4	16273	90	5.5 (4.5–6.8)	24636	189	7.7 (6.6–8.8)	–2.1 (–3.8– –0.5)	0.72 (0.55–0.92)
>8	16273	91	5.6 (4.5–6.8)	24636	208	8.4 (7.3–9.6)	–2.9 (–4.5– –1.2)	0.66 (0.51–0.84)
Risk group [3]								
Low	16264	1117	68.7 (64.9–72.6)	24593	539	21.9 (20.2–23.9)	46.8 (42.4–51.1)	3.13 (2.83–3.47)
Intermediate	16264	458	28.2 (25.6–30.7)	24593	691	28.1 (26.1–30.2)	0.1 (–3.2–3.4)	1.00 (0.89–1.13)

Study Reference **FinRSPC (Finnish ERSPC) (Neupane 2018/Pashayan 2015/Booth 2014)**
Linked records: Kilpeläinen 2017; Kilpeläinen 2016; Kilpeläinen 2015; Lindberg 2019; Pakarainen 2019; Pakarainen 2016

High	16264	293	18.0 (16.0–20.1)	24593	566	23.0 (21.3–25.0)	–5.0 (–7.8– –2.1)	0.78 (0.68–0.90)
Metastatic [1]	16264	62	3.8 (2.9–4.7)	24593	239	9.7 (8.6–11.1)	–5.9 (–7.4– –4.2)	0.39 (0.29–0.52)

[1] The TNM stage metastatic only includes M1 cases but the risk group metastatic has wider definition
[2] 95% CI = 95% bias-corrected CI based on 5000 bootstrap samples
[3] ERSPC prognostic risk group based on TNM stage, PSA and Gleason

Correcting for noncompliance and contamination – PCa mortality with **15 years of follow-up**

Age group	Corrected screening arm			Control arm			Difference in cases per 1000 men (95% CI)	Risk ratio (95% CI)
	N [1]	Cases	Cases per 1000 men (95% CI [2])	N [1]	Cases	Cases per 1000 men (95% CI)		
Total	16287	77	4.7 (3.8–5.9)	24677	152	6.2 (5.3–7.2)	–1.4 (–2.8–0.0)	0.77 (0.58–1.01)
55	5656	13	2.3 (1.4–3.9)	8589	25	2.9 (1.7–4.0)	–0.6 (–2.3–1.1)	0.79 (0.37–1.51)
59	4437	14	3.2 (1.6–4.7)	6750	26	3.9 (2.4–5.3)	–0.7 (–2.9–1.6)	0.82 (0.39–1.58)
63	3446	24	7.0 (4.1–9.6)	5192	36	6.9 (4.6–9.2)	0.0 (–3.5–3.7)	1.00 (0.58–1.69)
67	2742	26	9.5 (5.8–13.1)	4142	66	15.9 (12.6–20.0)	–6.5 (–11.9– –1.1)	0.60 (0.35–0.92)

Author's conclusions
Undergoing screening in accordance with the Finnish trial protocol is associated with an overall increase in risk of PCa by 3%, a 1% reduction in risk of advanced PCa, and a 0.1–0.2% reduction in risk of PCa death at 15 years

Pakarainen 2019

Incidence by number of screening rounds attended

Screening round	Prostate cancer cases	Incidence	HR (95% CI)
Screening round 0	563	499	0.75 (0.69–0.82)
Screening round 1	1125	960	1.57 (1.47–1.68)
Screening round 2	1038	1058	1.22 (1.14–1.31)
Screening round 3	615	987	1.38 (1.26–1.51)
Control arm	4264	706	1 (reference)

Mortality by number of screening rounds attended – age-adjusted HR for PCa-related death (95% CI)

Screening round	HR for PCa-related death (95% CI)			
	0–4 years	4–8 years	8–15 years	Overall
Screening round 0	1.25 (0.60–2.60)	1.68 (1.06–2.67)	1.57 (1.17–2.11)	1.58 (1.25–2.00)
Screening round 1	0.52 (0.24–1.13)	2.06 (1.33–3.18)	1.95 (1.46–2.61)	1.68 (1.33–2.12)
Screening round 2	-[a]	0.23 (0.10–0.49)	0.64 (0.45–0.90)	0.48 (0.35–0.66)
Screening round 3	-[a]	-[a]	0.17 (0.09–0.33)	0.17 (0.09–0.33)
Overall	0.75 (0.42–1.35)	0.99 (0.71–1.38)	0.89 (0.73–1.09)	0.90 (0.77–1.06)
Control arm	1	1	1	1

[a] Not estimable, due to lack of follow-up prior to 4 years for the second round and 8 years for the third round

Study Reference	**FinRSPC (Finnish ERSPC) (Neupane 2018/Pashayan 2015/Booth 2014)** Linked records: Kilpeläinen 2017; Kilpeläinen 2016; Kilpeläinen 2015; Lindberg 2019; Pakarainen 2019; Pakarainen 2016
	Author's conclusions Our findings indicate that repeated PSA-based screening is associated with diminished prostate cancer mortality. However, a single screening round is insufficient to achieve it and a minimum of two rounds is required. Excess incidence was comparable for men screened 1–3 times when the age difference was taken into account. This suggests a more favourable balance of benefits-to harms with continued screening **Pakarainen 2016** Further screening round outcomes from 2016. The main conclusions were that the post screening PC incidence is reduced after attending three screening rounds, but not after only one or two rounds. Thus, the increased cancer detection at screening is compensated by a subsequent risk reduction only after repeated screening cycles.

Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer; HRQoL, health-related quality of life; IQR, interquartile range; ITS, intention-to-screen; N/A, not applicable; NPV, negative predictive value; PCa, prostate cancer; PPV, positive predictive value; PRS, polygenic risk score; PSA, prostate-specific antigen

Table 39f. Spanish ERSPC, Luján 2015

Study Reference	**Spanish ERSPC (Luján 2015)** Linked records: Luján 2014
Study Design	Study name Spanish ERSPC Design Randomised controlled trial Objective To present the long-term results of the Spanish branch of the ERPSC Dates Initiation/recruitment: 1996–1999 Maximum follow-up: 2013 (mortality data until and including 2011) Country Spain Setting Getafe and Parla (two cities in the industrial belt of Madrid)
Population Characteristics	Patient recruitment and eligibility 18,612 males between 45 and 70 years old and registered in the census of the municipalities of Getafe and Parla were invited (by mailed invitation) to participate in the study **Inclusion** At recruitment, men were aged 45–70 years **Exclusion**

Study Reference	**Spanish ERSPC (Luján 2015)** Linked records: Luján 2014
	Men with a life expectancy of <10 years Sample size N invited = 18,612 N eligible = 18,612 invited from registry lists N excluded prior to randomisation = 993 (life expectancy <10 years) N enrolled (underwent randomisation) = NR N excluded after randomisation (with reason) = 2 (PCa detected prior to randomisation); 5,200 (men randomised before invitation [early phase]) N in the intervention group = 2,415 N in the control group = 1,861 N lost to follow-up = NR N completed = NR N excluded from analysis = NR N included in analysis = NR Characteristics of men included: age, PSA level and follow-up time

Parameter	N	Minimum	Maximum	Mean	SE of mean	Median	P value
Age, years							
Screening	2415	45.48	71.02	57.72	0.11	56.90	0.522
Control	1861	45.38	70.79	57.88	0.14	57.12	
Total	4276	45.38	71.02	57.79	0.09	56.98	
PSA, ng/mL							
Screening	2415	0.00	68.90	1.59	0.06	0.90	N/A
Control	0						
Total	2415	0.00	68.90	1.59	0.06	0.90	
Follow-up time, years							
Screening	2415	0.58	18.12	15.16	0.06	15.92	<0.001
Control	1861	0.03	17.94	14.94	0.07	15.75	
Total	4276	0.03	18.12	15.06	0.05	15.83	

Methods

Randomisation
Computer-randomised
- Randomisation after consent (efficacy design)

Duration of follow-up
Median 15.8 years

Outcomes
Mortality/morbidity outcomes
- Primary extraction
  - Lujan 2015: incidence, mortality (including cause of death) – identification and follow-up of PCa detected cases were performed with crossing of databases with the Patologic Anatomy departments of the University Hospital of Getafe and the University Hospital Infanta Cristina (Parla). The date and main cause of death were obtained from the registered data of the death certificates, through agreement with the Statistics National Institute. The cause of death in PCa-diagnosed

Study Reference	Spanish ERSPC (Luján 2015) Linked records: Luján 2014

patients was contrasted with the clinical history data and was assigned by consensus of a local committee of causes of death created for such purpose, according to the guidelines of the main ERSPC study.

- Linked studies: PCa incidence and disease-specific mortality

Harms of PSA screening outcomes

- No outcomes

Mortality and/or Morbidity Outcomes (Q1)

Incidence (median 15.8 year follow-up)

- Total diagnosed cases: 242 cases of PCa were diagnosed throughout monitoring (5.7% of males in the study)
  - Screening arm: 162 (6.7%); control arm: 80 (4.3%) (p<0.001)
- Probability of remaining PCa-diagnosis free in 15 years
  - Screening arm: 93%; control arm: 95.4%

Clinical stage at diagnosis of detected tumours (Chi-square test p=0.024)

Outcome	Screening arm (n=162)	Control arm (n=80)	Total
Clinical stage, n (%)			
Organ confined	148 (91.4)	66 (82.5)	214 (88.4)
Extracapsular	6 (3.7)	8 (10.0)	14 (5.8)
Regional (N+)	4 (2.5)	0 (0.0)	4 (1.7)
Metastatic (M+)	4 (2.5)	4 (5.0)	8 (3.3)
Unknown	0 (0.0)	2 (2.5)	2 (0.8)

Out of the 242 diagnosed PCa cases, 18 evolved to advanced disease (10 screening arm, 8 control arm; p=0.938)

Mortality (12 years of available mortality data)

- Total mortality: 618 (14.5%) deaths
  - Screening arm: 340 (14.1%); control arm: 278 (14.9%) (no significant difference)
- Main causes of death: neoplasm (54.0%); cardiovascular (17.6%); respiratory (8.7%); digestive (4.0%) – no significant difference between arms
- Probability of dying from prostate cancer log-rank test p=0.907

Causes of cancer-related death (n=334) (Chi-square test p=0.741)

Outcome	Screening arm (n=185)	Control arm (n=149)	Total (n=334)
Lung and bronchi, n (%)	63 (34.1)	44 (29.5)	107 (32.0)
Colon and rectum, n (%)	27 (14.6)	25 (16.8)	52 (15.6)
Pancreas, n (%)	9 (4.9)	8 (5.4)	17 (5.1)
Liver, n (%)	7 (3.8)	6 (4.0)	13 (3.9)
Stomach, n (%)	11 (5.9)	17 (11.4)	28 (8.4)
Oesophagus, n (%)	2 (1.1)	4 (2.7)	6 (1.8)
Urinary bladder, n (%)	6 (3.2)	8 (5.4)	14 (4.2)
Haematological, n (%)	18 (9.7)	8 (5.4)	26 (7.8)
Kidney and renal pelvis, n (%)	5 (2.7)	3 (2.0)	8 (2.4)
Brain, n (%)	9 (4.9)	5 (3.4)	14 (4.2)
Head and neck, n (%)	5 (2.7)	4 (2.7)	9 (2.7)

Study Reference	**Spanish ERSPC (Luján 2015)** Linked records: Luján 2014			
	Prostate, n (%)	**7 (3.8)**	**5 (3.4)**	**12 (3.6)**
	Other, n (%)	16 (8.6)	12 (8.1)	28 (8.4)
Harms of PSA-Based Screening (Q2)	No outcomes			
Authors' Conclusions	• Although we have verified that PCa screening produces a migration of the diagnosis of the disease to earlier stages, in our experience it has not produced a benefit in terms of global or cancer-specific survival after more than 15 years of monitoring. The low mortality for this disease in our environment could be one of the main factors to explain the results			
Additional Results/ Conclusions from Linked Records	No additional results			

Abbreviations: ERSPC, European Randomized Study of Screening for Prostate Cancer; N/A, not applicable; NR, not reported; PCa, prostate cancer; PSA, prostate-specific antigen; SE, standard error

Table 39g. PLCO, Pinsky 2019/Pinsky 2014

Study Reference	**PLCO, Pinsky 2019a/Pinsky 2014** Linked records; Pinsky 2019b, Pinsky 2017, Miller 2018, Kelly 2017, Lewicki 2017, Shoag 2016, Boniol 2015
Study Design	Study name Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial Design Randomised, population-based trial Objective **Pinsky 2019a:** To examine prostate cancer incidence and mortality by arm in the randomised PLCO screening trial **Pinsky 2014**: To examined mortality after prostate biopsy and compare rates with those of men with negative prostate screens. To also analyse complication rates, and examine factors associated with complications. Dates 1993–2001 Country US Setting 10 screening centres
Population Characteristics	Patient recruitment and eligibility Patients were recruited from 10 institutions and randomised to either screening or usual care. **Inclusion**

Study Reference	**PLCO, Pinsky 2019a/Pinsky 2014** Linked records; Pinsky 2019b, Pinsky 2017, Miller 2018, Kelly 2017, Lewicki 2017, Shoag 2016, Boniol 2015

Men aged 55–74 years at baseline with no previous reports of a PLCO cancer or current treatment

Exclusion
History of a PLCO cancer or current cancer treatment. From 1995, having had more than one PSA blood test in the prior 3 years was also an exclusion criterion.

Other
NR

Sample size
N randomised: intervention: 38340; usual care: 38343

Demographics

Parameter	Screening arm (n=38,340)	Usual care (n=38,343)
Age at baseline, n (%)		
55–59 years	12,387 (32.3)	12,372 (32.3)
60–64 years	12,012 (31.3)	12,015 (31.3)
65–69 years	8,877 (23.2)	8,885 (23.2)
70–74 years	5,064 (13.2)	5,071 (13.2)
Race/ethnicity, n (%)		
Non-Hispanic white	33,043 (88.3)	32,136 (88.3)
Non-Hispanic black	1,713 (4.6)	1,657 (4.6)
Hispanic	816 (2.2)	787 (2.2)
Asian	1,532 (4.1)	1,476 (4.1)
Other	322 (0.9)	329 (0.9)
Previous PSA test		
Once	13,252 (38.8)	13,135 (39.5)
More than once	3,588 (10.5)	3,760 (11.3)
Previous biopsy	NR	NR
Family history of prostate cancer, n (%)	2,737 (7.5)	2,589 (7.3)
Education, n (%)		
College graduate	15,294 (40.9)	14,656 (40.5)
BMI	NR	NR
Weight	NR	NR
Comorbidity index	NR	NR
Diabetes	NR	NR

Study Reference	**PLCO, Pinsky 2019a/Pinsky 2014** Linked records; Pinsky 2019b, Pinsky 2017, Miller 2018, Kelly 2017, Lewicki 2017, Shoag 2016, Boniol 2015
Methods	Randomisation Screening arm: Men randomised to the screening arm had their PSA levels measured at baseline and annually for the following 5 years. The trial also included an annual DRE at baseline and for the following 3 years. Men with PSA levels >4 ng/mL or had an abnormality identified by DRE were considered to have a positive test and referred for follow-up with their primary physician. Usual care: Men were not part of an organised screening regimen but could be screened through usual care under their physician. To assess screening in the usual care arm, a Health Status Questionnaire (HSQ) was administered to a sample of men during the active screening period of the trial. The HSQ was also administered to a sample of men from body study arms during the post-screening period. Duration of follow-up Median follow-up for mortality was 16.9 (intervention) and 16.7 years (usual care) Outcomes • The primary endpoint was PCa-specific mortality. • Secondary outcomes: o Overall mortality: Ascertainment of deaths changed during the study. During the original analysis period (through 2010), participant deaths were identified either through reports from next-of-kin, which were confirmed with a death certificate, or through linkages with the National Death Index (NDI). In 2011, participants were re-consented in the study and could choose to be actively or passively followed or refuse further follow-up. For participants choosing to be followed passively (approximately 18%), deaths after the original analysis period were ascertained only through linkage with the NDI. o PCa incidence: Incidence cases of PCa were primarily ascertained through annual study update questionnaires or follow-up of positive screening tests. o PCa characteristics: Diagnostic confirmation and tumour characteristics were determined through review of medical records by trained medical record abstractors.
Mortality and/or Morbidity Outcomes	Mortality Prostate cancer mortality rate and incidence, over a median follow-up of 17 years, as reported by Pinsky 2019. Pinsky 2017 reports on these outcomes at a follow-up of 12 years.

Outcome	Follow-up	Screening arm (533,014 person-years)	Control arm (529,860 person-years)	Rate Ratio (RR) (95% CI)	p-value	HR (95% CI)	p-value
Prostate cancer deaths N (rate/100,00 person-years)	Years 0–8	72 (22.8)	70 (21.3)	1.07 (0.78–1.48)	0.68	1.07 (0.77–1.48)	0.69
	Years 0–10	113 (28.6)	114 (28.9)	0.99 (0.77–1.29)	0.93	0.99 (0.76–1.28)	0.99
	Years 0–12	165 (36.2)	164 (36.1)	1.003 (0.81–1.25)	0.98	1.001 (0.80–1.25)	0.99
	15 years	255 (47.8)	244 (46.0)	1.04 (0.87–1.24)	0.67	1.03 (0.87–1.23)	0.72
All-cause deaths N (rate/100,00 person-years)100,000 person-years	15 years	9212 (1728.3)	9369 (1769.3)	0.977 (0.950–1.004)	0.11	0.973 (0.945–1.001)	0.06
Outcome	Follow-up	Screening arm (N=38,340)	Control arm (N=38,343)	RR (95% CI)	p-value	HR (95% CI)	p-value

Study Reference **PLCO, Pinsky 2019a/Pinsky 2014**
Linked records; Pinsky 2019b, Pinsky 2017, Miller 2018, Kelly 2017, Lewicki 2017, Shoag 2016, Boniol 2015

Prostate cancer deaths N (rate/100,00 person-years)	17 years	333 (5.5)	352 (5.9)	0.93 (0.81–1.08)	0.38	NR	NR

Causes of death by arm at 15-year follow-up (Pinksy 2017)

Outcome	Screening arm, n (%)	Control arm, n (%)
Prostate cancer	255 (2.8)	244 (2.6)
Other cancer (excluding lung and colorectal cancer)	1,933 (21.0)	1,882 (20.1)
Ischaemic heart disease	1,699 (18.4)	1,650 (17.6)
Cerebrovascular accident	454 (4.9)	513 (5.5)
Other circulatory disease	1,317 (14.3)	1,364 (14.6)
Respiratory disease	1,028 (11.2)	1,069 (11.4)
Digestive disease	302 (3.3)	303 (3.2)
Infectious disease	187 (2.0)	175 (1.9)
Endocrine and metabolic	334 (3.6)	371 (4.0)
Nervous system	438 (4.8)	470 (5.0)
Accidental	463 (5.0)	482 (5.1)
Other	802 (8.7)	852 (9.1)
Total (excluding lung and colorectal cancer)	9,212	9,375

Incidence Outcomes

Outcome	Screening arm (38,340)	Control arm (38,343)	RR (95% CI)	**p-value**
Follow-up: 15 years (Pinsky 2017)				
Total person-years	466,079	463,950	-	-
N (rate/10,000 person-years)	-	-	-	-
Metastatic disease at diagnosis	115 (2.47)	126 (2.72)	0.91 (0.70–1.17)	NR
Progression to metastatic disease	105 (2.25)	98 (2.11)	1.07 (0.81–1.41)	NR
Total metastatic disease	220 (4.72)	224 (4.83)	0.98 (0.81–1.18)	NR
Follow-up: 17 years (Pinsky 2019)				
N (rate/10,000 person-years)	-	-	-	-
All prostate cancer	5574 (106.4)	5287 (101.2)	1.05 (1.01–1.09)	<0.001
Gleason 2–6 (biopsy)	3,095 (59.0)	2,648 (50.6)	1.17 (1.11–1.23)	<0.001
Gleason 7 (biopsy)	1,510 (28.8)	1,511 (28.9)	1.00 (0.93–1.07)	0.92

Study Reference

PLCO, Pinsky 2019a/Pinsky 2014
Linked records; Pinsky 2019b, Pinsky 2017, Miller 2018, Kelly 2017, Lewicki 2017, Shoag 2016, Boniol 2015

Gleason 8–10 (biopsy)	630 (12.0)	708 (13.6)	0.89 (0.80–0.99)	0.03
Gleason 8–10 (best)	654 (12.5)	749 (14.3)	0.87 (0.78–0.97)	0.01
Metastatic (at diagnosis)	134 (2.6)	158 (3.0)	0.85 (0.67–1.06)	0.15

Incidence of prostate cancer: aggression (Kelly 2017)

Disease Incidence	Screening arm (n=34,207)	Usual care (n=35,666)	Rate Ratio (RR) (95% CI)
Incident prostate cancer (n=7,822)	3,649 (46.7)	4,173 (53.3)	
Non-aggressive PCa (n=4,587)	2,031 (44.3)	2,556 (55.7)	
Aggressive PCa (n=3,078)	1,548 (50.3)	1,530 (49.7)	0.91 (0.70–1.17)

Distribution of prostate cancer cases according to PSA levels were also reported by Boniol 2015.

Shoag 2016 analysed 13-year screening and outcomes data from the 151 participants who died of prostate cancer in the screening arm of the trial only, in order to better understand how randomisation to screening failed to prevent prostate cancer in these men.

Morbidity Outcomes
NR

Harms of PSA-Based Screening (Q2)

Prostate biopsy method (if applicable)
NR

Mortality after biopsy

	Biopsy group	No biopsy (negative screen)	Relative Risk (RR) (95% CI)	
			Univariate analysis	Multivariate analysis[b]
120 days				
Number of biopsies/number of negative screens	6295	139,931	-	-
Number of deaths	6[a]	255[a]	-	-
Rate per 1000 biopsies/rate per 1000 negative screens	0.95	1.8	0.52 (0.2–1.2)	0.49 (0.2–1.1)
180 days				
Number of biopsies/number of negative screens	6295	139,931	-	-
Number of deaths	14	411	-	-
Rate per 1000 biopsies/1000 negative screens	2.2	2.9	0.76 (0.4–1.3)	0.70 (0.4–1.2)

[a] The six deaths within 120 days were from pancreatic cancer, ischaemic heart disease, other heart disease and chronic airway obstruction. Eight additional deaths in the 120–180 day period were from other heart disease, other respiratory disease, lung cancers, pneumonia and accidents/injury. Deaths from prostate cancer were excluded. [b] Model included age (5-year groups), marital status, black race, college education, smoking status, modified CCI score and study year.

Complications

- Of 3706 positive screens with a single follow-up biopsy and no accompanying prostate cancer diagnosis during that study year, a total of 75 biopsies had reported complications, 63 (84%) of which occurred within 30 days of biopsy.

Study Reference **PLCO, Pinsky 2019a/Pinsky 2014**
Linked records; Pinsky 2019b, Pinsky 2017, Miller 2018, Kelly 2017, Lewicki 2017, Shoag 2016, Boniol 2015

- Of the 48 biopsies with non-infectious complications, 19 had urinary-related complications and 14 had bleeding-related complications

	Total biopsies[a]	All complications, N=75		Infectious complications, N=29		Non-infectious complications, N=48	
		Rate (per 1000)	p-value	Rate (per 1000)	p-value	Rate (per 1000)	p-value
All	3,706	20.2	-	7.8	-	13.0	-
Covariate							
Under age 70 years[b]	2821	17.7	0.06	6.4	0.09	11.7	0.23
Age ≥70 years[b]	885	28.2		12.4		16.9	
Year 1994–1998[b]	1965	25.4	0.02	7.6	0.88	18.3	0.003
Year 1999–2006[b]	1741	13.5		8.0		6.9	
Non-black race	3564	19.1	0.02	6.5	<0.001	13.2	0.53
Black race	142	49.3		42.3		7.0	
CCI score=0[c]	2753	17.8	0.08	7.6	0.82	10.9	0.06
CCI score ≥1[c]	953	27.3		8.4		18.9	
No prostate inflammation or enlargement[d]	2325	12.5	<0.001	3.9	0.001	8.6	0.003
Prostate inflammation or enlargement[d]	1381	33.3		14.5		20.3	
First biopsy	2969	22.6	0.07	7.7	0.91	15.2	0.03
Repeat biopsy	737	10.9		8.1		4.1	

[a] Restricted to subjects with a single biopsy in the study year and no corresponding prostate cancer diagnosis in that study year. [b] Age/year at time of biopsy. [c] Modified CCI score, assessed at baseline. [d] Assessed at baseline. P values are for null hypotheses of equal rates across covariate categories.

Overdiagnosis

Incidence	Black	White	RR (95% CI)
Overall	494	7314	NA
Screening arm	252	3891	NA
Usual care arm	242	3423	NA
Overdiagnosis rate (screen-detected)	1.3%	20.6%	19.3 (−11.1–3.36)
Overdiagnosis rate (screened population)	0.1%	1.2%	1.1 (−6.3–8.2)

Distribution of false-positive test results by race in the screening arm of the PLCO trial, at a follow-up of up to 19 years from randomisation

Study Reference	**PLCO, Pinsky 2019a/Pinsky 2014** Linked records; Pinsky 2019b, Pinsky 2017, Miller 2018, Kelly 2017, Lewicki 2017, Shoag 2016, Boniol 2015

Outcome	Black	White	p-value
False positive test (first positive result), n (%)			
PSA+(any DRE result)	228 (14.5)	3,915 (12.4)	0.02
PSA+/DRE−[a]	215 (13.6)	3,508 (11.1)	0.002
DRE+(any PSA result)	172 (10.9)	4,462 (14.2)	<0.001
DRE+/PSA−	162 (10.3)	4,195 (13.3)	<0.001
PSA+ or DRE+	377 (23.9)	7,703 (24.5)	0.60

[a] Denominator excludes men with positive DRE or PSA tests, respectively

Authors' Conclusions	• After almost 17 years of median follow-up, there was no significant reduction in PCa mortality in the intervention compared with the usual care arm. There was a significant increase in Gleason 2–6 disease and a significant reduction in Gleason 8–10 disease in the intervention compared with the usual care arm. • Mortality rates were not found to be higher after prostate biopsy in the PLCO trial and complications were relatively infrequent, with several risk factors identified. • There was evidence that false-positive test results differed by race and screening test. Consistent with previous studies, cancer outcomes, and tumour characteristics were all more unfavourable in black men. Given the disproportionate prostate cancer burden and mortality among black men, along with shifting recommendations to discuss the benefits and harms of screening with patients, it is essential that black men receive sufficient evidence to make an informed decision.

Abbreviations: CCI, Charlson comorbidity index; CI, confidence interval; BMI, body mass index; DRE, digital rectal examination; HR, hazard ratio; HSQ, Health Status Questionnaire; NDI, National Death Index; NR, not reported; PCa, prostate cancer; PLCO, Prostate, Lung, Colorectal and Ovarian cancer screening trial; PSA, prostate-specific antigen; RR, relative risk/rate ratio

Table 39h. Tsodikov 2017 (Analysis of ERSPC and PLCO)

Study Reference	**Tsodikov 2017** (Analysis of ERSPC and PLCO) Linked records: no linked records
Study Design	Study name ERSPC and PLCO (analysis) Design Randomised controlled trials Objective To evaluate whether effects of screening on PC mortality relative to no screening differed between the ERSPC and PLCO Dates NR Country Europe and the US

Study Reference

Tsodikov 2017 (Analysis of ERSPC and PLCO)
Linked records: no linked records

Setting
Multicentre

Population Characteristics

Patient recruitment and eligibility
NR, but see eligibility criteria from PLCO and ERSPC extractions

Sample size
N randomised to the intervention group = **ERSPC:** 72,473; **PLCO**: 38,340
N randomised to the control group = **ERSPC:** 88,921; **PLCO:** 38,343
N lost to follow-up = NR
N completed = NR
N excluded from analysis = NR
N included in analysis = NR

Characteristics of men included

Parameter	ERSPC		PLCO	
	Control	Screening	Control	Screening
N participants	88921	72473	38343	38340
Age at randomisation, yrs, median (range)	59 (55–69)	60 (55–69)	62 (55–74)	62 (55–74)
All available follow-up				
Follow-up from randomisation, yrs, median (range)	11.0 (0.4–17.5)	11.1 (0.4–17.3)	12.5 (0.0–13.0)	12.5 (0.0–13.0)
N prostate cancer cases	5398	6967	4040	4430
Person-years of follow-up for incidence	933854	740775	403955	400008
N deaths total	17019	13652	7149	6940
N deaths due to other causes	16557	13353	7003	6788
N deaths due to PCa	462	299	146	152
Person-years of follow-up for mortality	990678	827148	426720	427824
Restricted to 11 years of follow-up				
Follow-up from randomisation, yrs, median (range)	11.0 (0.4–11.0)	11.0 (0.4–11.0)	11.0 (0.0–11.0)	11.0 (0.0–11.0)
N prostate cancer cases	4961	6586	3641	4038
Person-years of follow-up for incidence	868834	686766	368844	365129
N deaths total	13207	10397	5880	5798
N deaths due to other causes	12822	10150	5771	5687
N deaths due to PCa	385	247	109	111
Person-years of follow-up for mortality	890581	725997	387027	387861

Methods

Randomisation
See extractions for PLCO and ERSPC trials

Duration of follow-up
Cut off at 11 years

Outcomes (and methods of analysis)
Mortality/morbidity outcomes

Study Reference

Tsodikov 2017 (Analysis of ERSPC and PLCO)
Linked records: no linked records

- Traditional statistical analysis that combined data from both trials and compared hazards or PCa death in the intervention versus control arms adjusting for participant age and trial setting. Questionable analysis due to remaining differences in implementation between trials
- Extended analyses conducted to overcome this limitation (accounted for variable screening and diagnostic workup ["screening intensity"] in each trial arm, which was operationalised using MLTs)
  - MLTs reflect the magnitude of increased PCa incidence relative to a baseline level expected in the absence of screening, thus capturing differences in both design and adherence.
  - MLTs were estimated both empirically and using analytic or microsimulation models; using multiple approaches allowed assessment of robustness of results to this uncertain quantity

Mortality and/or Morbidity Outcomes (Q1)

Cox regression analysis results and estimated mortality reductions

Cox regression analysis				Estimated mortality reduction relative to no screening			
				Setting of ERSPC intervention arm		Setting of PLCO intervention arm	
Covariate		HR (95% CI)	P value	MLT	Reduction (95% CI)	MLT	Reduction (95% CI)
Traditional analysis							
PLCO setting[1]		0.53 (0.45–0.62)	<0.0001				
Age[2]		1.13 (1.11–1.14)	<0.0001				
Intervention arm[3]		0.84 (0.73–0.96)	0.0099	N/A	16% (4–27)	N/A	16% (4–27)
Extended analyses							
Empirical	PLCO setting	0.57 (0.48–0.67)	<0.0001	3.96	29% (11–43)	4.02	29% (11–44)
	Age	1.13 (1.11–1.14)	<0.0001				
	Intervention arm	0.92 (0.87–0.97)	0.0027				
FHCRC	PLCO setting	0.58 (0.49–0.69)	<0.0001	4.00	27% (10-40)	4.10	27% (10–41)
	Age	1.13 (1.11–1.14)	<0.0001				
	Intervention arm	0.93 (0.88–0.97)	0.0029				
MISCAN	PLCO setting	0.63 (0.51–0.77)	<0.0001	3.49	25% (9–38)	4.62	32% (12–47)
	Age	1.13 (1.11–1.14)	<0.0001				
	Intervention arm	0.92 (0.87–0.97)	0.0032				
UMICH	PLCO setting	0.57 (0.48–0.68)	<0.0001	3.83	31% (12–45)	4.01	32% (12–47)
	Age	1.13 (1.11–1.14)	<0.0001				
	Intervention arm	0.91 (0.85–0.97)	0.0029				

[1] PLCO setting = indicator of PLCO setting relative to the ERSPC setting to account for differential baseline risk of PCa death
[2] Age = participant age at randomisation (continuous)
[3] Intervention arm = indicator of randomisation to intervention arm

Harms of PSA-Based Screening (Q2)

No outcomes

Authors' Conclusions

- Taken together, the data from the two screening trials do not provide evidence that screening efficacy (relative to no screening) differed between the ERSPC and PLCO after accounting for differences in implementation and setting.

Study Reference	**Tsodikov 2017** (Analysis of ERSPC and PLCO) Linked records: no linked records
	• Out estimation results of the common effect of screening suggest that screening can significantly reduce the risk of PCa death. However, as for all interventions, the benefit of screening must be weighed against its potential harms for informed clinical and shared decision making
Additional Results/ Conclusions from Linked Records	No additional results

Abbreviations: CI, confidence interval; ERSPC, European Randomised Study of Screening for Prostate Cancer; FHCRC, Fred Hutchinson Cancer Research Center; HR, hazard ratio; MISCAN, Erasmus University Medical Center MIcrosimulation SCreening ANalysis; MLT, mean lead time; PLCO, Prostate, Lung, Colorectal and Ovarian cancer screening trial; UMICH, University of Michigan

Question 3

Table 40a. SABOR Cohort Study, Ankerst 2016

Study Reference	San Antonio Biomarkers Of Risk (SABOR) Cohort Study (Ankerst 2016)
Study Design	Study name San Antonio Biomarkers Of Risk (SABOR) Cohort Study Design Prospective cohort study Objective To characterise the diagnostic properties of serial percent-free PSA in relation to PSA in a multi-ethnic, multi-racial cohort of healthy men Dates 2007–2010 Country USA Setting National Cancer Institute (NCI) sponsored clinical validation centre recruiting men from San Antonio and South Texas
Population Characteristics	Patient recruitment and eligibility Men in the San Antonio and South Texas area without a prior diagnosis of prostate cancer **Inclusion** Not reported **Exclusion** Prior diagnosis of prostate cancer **Other** N/A Sample size 2,183 (1,625 men who never underwent biopsy, 497 who underwent one or more biopsies negative for prostate cancer, and 61 diagnosed with prostate cancer) Demographics

Parameter	No biopsy (n=1,625)	Negative biopsy (n=497)	Prostate cancer (n=61)
Age at entry (median, min, max)	61.7 (45.1, 84.7)	67.9 (45.5, 84.9)	65.5 (53.8, 78.6)
Race (n, %)			
White	1443 (88.8)	445 (89.5)	49 (80.3)
Black	179 (11)	52 (10.5)	12 (19.7)
Other	3 (0.2)	0 (0)	0 (0)
Ethnicity (n, %)			
Non-Hispanic	1017 (62.6)	361 (72.6)	51 (83.6)

Study Reference	**San Antonio Biomarkers Of Risk (SABOR) Cohort Study (Ankerst 2016)**			
	Hispanic Mexican Hispanic Other	570 (35.1) 38 (2.3)	125 (25.2) 11 (2.2)	9 (14.8) 1 (1.6)
	Previous PSA test	NR	NR	NR
	Previous biopsy (n, %) 0 1 ≥2	 1625 (100) 0 (0) 0 (0)	 1 (0.2) 335 (67.4) 161 (32.4)	 36 (59) 12 (19.7) 13 (21.3)
	Family history of prostate cancer (n, %)	300 (18.5)	146 (29.4)	23 (37.7)
	Socioeconomic status (e.g. education)	NR	NR	NR
	BMI	NR	NR	NR
	Weight	NR	NR	NR
	Comorbidity index	NR	NR	NR
	Diabetes	NR	NR	NR
Methods	Index test Percent-free PSA test (no details of procedure reported). A measurement of <25% was considered indicative of abnormal percent-free PSA. A more conservative threshold of 15% was also used for comparison Reference standard Prostate biopsy (no details of procedure reported). Prostate biopsy was recommended for men with PSA >2.5 ng/mL or an abnormal DRE Comparator PSA test (no details of procedure reported) Measures of test accuracy Computed the number of cases for which percent-free PSA would have spared a biopsy by testing negative in the presence of a positive PSA test, as well as the number of instances of cancer that would have been detected by percent-free PSA but not PSA. For the purposes of analysis, a measurement of ≥4 ng/mL was considered indicative of abnormal PSA Disease-related outcomes NR			
Test Accuracy	Would percent-free PSA have prevented a negative biopsy prompted by PSA? 417 men had one or more biopsies performed that proved to be negative. For the 79 men who had a PSA ≥4 ng/mL, 25 (31.6%) and 52 (65.8%) would have tested negative by the percent-free PSA test by exceeding the thresholds 25% and 15%, respectively. These numbers were 58 (45.7%) and 110 (86.6%), respectively, among the 127 men with PSA 2–4 ng/mL, and 142 (67.3%) and 195 (92.4%), respectively, among the 211 men with PSA <2 ng/mL Would percent-free PSA have caught a cancer missed by PSA? Among the 41 cancer cases that had a PSA <4 ng/mL, 35 (85.4%) had a percent-free PSA <25%, while 18 (43.9%) had a percent-free PSA <15%			
Authors' Conclusions	Percent-free PSA as a stand-alone biomarker has a very high false-positive rate and cannot substitute for PSA. However, percent-free PSA as a reflex marker in the setting of PSA testing demonstrated quite high levels of performance in this study, with the capability to spare 65.8% of unnecessary biopsies, which compares very well with other candidate reflex biomarkers that incur far greater cost. Percent-free			

Study Reference	San Antonio Biomarkers Of Risk (SABOR) Cohort Study (Ankerst 2016)
	PSA should accompany PSA testing in order to potentially spare unnecessary biopsies or detect cancer earlier. When near the threshold, both tests should be repeated due to commonly observed fluctuation

Abbreviations: BMI, body mass index; DRE, digital rectal examination; N/A, not applicable; NCI, National Cancer Institute; NR, not reported; PSA, prostate-specific antigen; SABOR, San Antonio Biomarkers Of Risk cohort study

Table 40b. Nam 2016

Study Reference	Nam 2016
Study Design	Study name NR Design Screening pilot study Objective The role of MRI as a first line screening test for prostate cancer is unknown. A pilot study to was performed to evaluate the feasibility of prostate MRI as the primary screening test for prostate cancer Dates Not reported Country Canada Setting Sunnybrook Health Sciences Centre, Sunnybrook Research Institute, University of Toronto
Population Characteristics	Patient recruitment and eligibility Unselected men were recruited from the general population using a news advertisement in a large local newspaper in the Greater Toronto Area for one week. Volunteers were solicited to undergo MRI for biopsy irrespective of PSA level. **Inclusion** 1) age between 50 and 75 years, 2) no family history of prostate cancer, 3) no history of previous prostate biopsy **Exclusion** 1) previous history of any cancer other than non-melanomatous cutaneous cancer, 2) unable to speak English **Other** There were no incentives for patients to participate Sample size N screened/invited = 319 N eligible = 120 N enrolled = 50 N completed = 47

<table>
<tr><td><u>Study Reference</u></td><td>Nam 2016</td></tr>
<tr><td></td><td>N included in analysis = 47

<u>Demographics</u>
<table>
<tr><th>Parameter</th><th>Underwent MRI and prostate biopsy (n=47)</th></tr>
<tr><td>Age at recruitment (median, IQR)</td><td>61 (55–68)</td></tr>
<tr><td>Ethnicity</td><td>NR</td></tr>
<tr><td>Previous PSA test</td><td>NR</td></tr>
<tr><td>Previous biopsy (%)</td><td>0</td></tr>
<tr><td>Family history of prostate cancer (%)</td><td>0</td></tr>
<tr><td>Socioeconomic status (e.g. education)</td><td>NR</td></tr>
<tr><td>BMI</td><td>NR</td></tr>
<tr><td>Weight</td><td>NR</td></tr>
<tr><td>Comorbidity index</td><td>NR</td></tr>
<tr><td>Diabetes</td><td>NR</td></tr>
</table></td></tr>
<tr><td>Methods</td><td><u>Index test</u>
Multiparametric MRI II imaging was performed on a 3 Tesla Achieva MRI system (Philips Healthcare, Best, The Netherlands) without an endorectal coil. A 6-channel SENSE cardiac surface coil (Philips Healthcare) was positioned over the pelvis. One uroradiologist with extensive MRI experience identified all lesions. The presence or absence of up to 4 cancer targets was scored on a 5-point scale according to recent European Consensus Guidelines

<u>Reference standard</u>
Prostate biopsy. Patients with no identifiable lesion on prostate MRI underwent transrectal ultrasound guided prostate biopsy using a random 12-core pattern in the lateral and medial zones of the prostate gland. Patients in whom a prostate lesion was found on MRI underwent targeted biopsy using cognitive co-registration, in addition to random 12-core biopsy. A maximum of 4 cores was allowed for the primary target. All biopsies were performed using an 18 gauge, spring loaded, needle core biopsy gun

<u>Comparator</u>
At the time of evaluation a blood sample was drawn to determine PSA (no details of procedure reported). A measurement of ≥4 ng/mL was considered indicative of abnormal PSA

<u>Measures of test accuracy</u>
Prostate cancer PPV and NPV were calculated based on MRI scores. ROC curves were constructed and AUC analysis was done between MRI and PSA tests for prostate cancer detection

<u>Disease-related outcomes</u>
Not reported</td></tr>
<tr><td>Test Accuracy</td><td><u>Area under the curve (AUC)</u>
When comparing the performance of MRI and PSA to predict prostate cancer, MRI score had a higher AUC than PSA (0.81, 95% CI 0.67–0.94 vs 0.67, 95% CI 0.52–0.84). Compared to PSA, the ROC curves showed better performance at all MRI scores</td></tr>
</table>

Study Reference	Nam 2016
	Positive predictive value (PPV) and Negative predictive value (NPV) Prostate cancer was diagnosed in 9 of the 30 men (30.0%) with normal PSA. The PPV in patients with a MRI score of 4 or more was 66.7% (6 of 9) and the NPV in patients with a MRI score of 3 or less was 85.7% (18 of 21, chi-square test p = 0.004). Nine of the 17 patients (52.9%) with PSA 4.0 ng/ml or greater had prostate cancer. The PPV in patients with a MRI score of 4 or greater was 75.0% (6 of 8) and the NPV in patients with a MRI score of 3 or less was 66.7% (6 of 9, chi-square test p = 0.08).
Authors' Conclusions	This pilot study determined the feasibility of using multiparametric prostate MRI as the primary screening test for prostate cancer. Initial results showed that prostate MRI was better at predicting prostate cancer than PSA in an unselected sample of the general population. Prostate MRI should be further evaluated in a larger prostate cancer screening study

Abbreviations: AUC, area under the curve; BMI, body mass index; IQR, interquartile range; MRI, magnetic resonance imaging; NPV, negative predictive value; NR, not reported; PPV, positive predictive value; PSA, prostate-specific antigen; ROC, receiver operating characteristic

Table 40c. Rubio-Briones 2014

Study Reference	Rubio-Briones 2014
Study Design	Study name Not reported Design Prospective randomised controlled study Objective To evaluate the use of PCA3 as a second-line biomarker after PSA and rectal examination (DRE) performed by a urologist. The primary objective was to assess the potential reduction in the number of biopsies. The secondary objectives were to evaluate the false negative rates for PCA3 and their prognostic value within opportunistic screening Dates September 2010–September 2012 Country Spain Setting Valencian Foundation Institute of Oncology, Valencia
Population Characteristics	Patient recruitment and eligibility Opportunistic screening program **Inclusion** Healthy men aged 40–75 years, with more than 10 years of life expectancy, with no prior biopsy, who freely committed to the protocol and signed the informed consent form **Exclusion** Men who had already been biopsied or who had a history of prostatitis or urinary infections during the previous year were excluded **Other**

Study Reference	**Rubio-Briones 2014**

E.g. N/A

Sample size
N screened/invited = 2,422
N eligible = 2,366
N included = 2,366
N excluded (did not meet eligibility criteria) = 56
N included in analysis = 2,366

Demographics

Parameter	Included participants (n=2,366)
Age at recruitment (mean, SD)	57.5 (6.2)
Age at recruitment (median, range)	57 (40–74)
Ethnicity	NR
Previous PSA test	NR
Previous biopsy (%)	0
Family history of prostate cancer	NR
Socioeconomic status (e.g. education)	NR
BMI	NR
Weight	NR
Comorbidity index	NR
Diabetes	NR

Methods

Trial design
During the initial visit, a specialist nurse obtained the PSA, after which a urologist performed the DRE. Participants with PSA ≥3 ng/mL and/or abnormal DRE results had their PCA3 levels determined. Men with normal DRE and PSA results (<3 ng/mL) proceeded to repeat PSA and DRE monitoring at 1, 2, 3 or 4 years if their PSA level was 2–3, 1–2, 0.5–1 or <0.5 ng/mL, respectively. At repeat visits, participants with PSA ≥3 ng/mL and/or abnormal DRE results had their PCA3 levels determined. At initial or repeat visits, men with PCA3 levels ≥35 were recommended to undergo a 12-core initial biopsy. Participants with PCA3 levels <35 were blindly randomized 1:1 to 12-core initial biopsy or observation

Index test
PCA3 levels determined with the ProgensaTMPCA3 test (Genetics Probe-Hologic, San Diego, USA)

Reference standard
12-core initial biopsy (no details of procedure reported)

Comparator
PSA test alone (no details of procedure reported). It is implied (although not explicitly stated) that a measurement of ≥3 ng/mL was considered indicative of abnormal PSA

<table>
<tr><td><u>Study Reference</u></td><td>Rubio-Briones 2014</td></tr>
<tr><td></td><td><u>Measures of test accuracy</u>
The areas under the curve (AUC) of the receiver operating characteristic (ROC) for PCA3 and PSA were compared with the De Long test. A two-sided test was used and a p-value ≤ 0.05 was considered statistically significant. Sensitivity and specificity were calculated for PCA3 at multiple cut-offs

<u>Disease-related outcomes</u>
Not reported</td></tr>
<tr><td>Test Accuracy</td><td><u>True positives and false negatives</u>
289 (12.2%) men had their PCA3 levels determined due to abnormal PSA and/or DRE at the initial visit. 32 more had a PCA3 test due to abnormal PSA and/or DRE at a repeat visit. Hence, 321 (13.6%) men were tested for PCA3. Of these, 110 (34.3%) men had PCA3 levels ≥35 and underwent prostate biopsy, of which 43 (39.1%) had prostate cancer. Of the 211 (65.7%) men with PCA3 levels <35, 101 were randomised to prostate biopsy, of which 12 (11.9%) had prostate cancer

<u>Area under the curve (AUC), sensitivity and specificity</u>
The AUC was 0.601 for PSA (95% CI: 0.514–0.689) and 0.748 for PCA3 (95% CI: 0.677–0.819), showing a statistically significant difference (p = <0.008). The cut-off of 35 for PCA3 achieved 78.2% sensitivity and 57.1% specificity

<table>
<tr><th>PCA3 cut-off</th><th>Sensitivity (%)</th><th>Specificity (%)</th></tr>
<tr><td>≥10</td><td>100.0</td><td>26.9</td></tr>
<tr><td>≥15</td><td>94.5</td><td>33.3</td></tr>
<tr><td>≥20</td><td>87.3</td><td>41.0</td></tr>
<tr><td>≥25</td><td>83.6</td><td>47.4</td></tr>
<tr><td>≥30</td><td>80.0</td><td>53.2</td></tr>
<tr><td>≥35</td><td>78.2</td><td>57.1</td></tr>
<tr><td>≥40</td><td>70.9</td><td>63.5</td></tr>
<tr><td>≥45</td><td>63.6</td><td>70.5</td></tr>
<tr><td>≥50</td><td>56.4</td><td>74.4</td></tr>
</table></td></tr>
<tr><td>Authors' Conclusions</td><td>The use of PCA3 at a cut-off of 35 as a second-line biomarker could reduce initial biopsies by 65.7%, with a false negative rate of approximately 12%. A longer follow-up is needed to understand its true value as a diagnostic and prognostic tool and thereby weigh the rate of biopsy savings and its cost</td></tr>
</table>

Abbreviations: AUC, area under the curve; BMI, body mass index; DRE, digital rectal examination; N/A, not applicable; NR, not reported; PCA3, prostate cancer antigen 3; PSA, prostate-specific antigen; ROC, receiver operating characteristic; SD, standard deviation

Table 40d. Göteborg Randomised Screening Trial, Grenabo Bergdahl 2016

Study Reference	**Göteborg Randomised Screening Trial (Grenabo Bergdahl 2016)**
Study Design	Study name Göteborg Randomised Screening Trial

Study Reference	**Göteborg Randomised Screening Trial (Grenabo Bergdahl 2016)**
	Design Pilot study nested within the Göteborg Randomised Screening Trial Objective To compare the efficacy of sequential screening (PSA + MRI) with conventional PSA screening for prostate cancer Dates 2013–14 Country Sweden Setting Not reported
Population Characteristics	Patient recruitment and eligibility The pilot study was nested within the 10th and last screening round of the Göteborg randomised screening trial, in which 20,000 men aged 50–64 years were randomised to a screening and a control group in 1995. Men in the screening group received invitations to PSA-screening biennially until an upper age limit (average 69 years) **Inclusion** Not reported **Exclusion** Not reported **Other** E.g. N/A Sample size N invited = 596 N attended = 384 Demographics

Parameter	Included participants (n=384)
Age at recruitment (median, IQR)	69.3 (69.0–69.6)
Ethnicity	NR
Previous PSA test (%)	98
Previous biopsy	NR
Family history of prostate cancer	NR
Socioeconomic status (e.g. education)	NR
BMI	NR
Weight	NR
Comorbidity index	NR

Study Reference	**Göteborg Randomised Screening Trial (Grenabo Bergdahl 2016)**
	Diabetes: NR

Methods

Trial design
Men with PSA <1.8ng/mL underwent no further screening. Men with PSA ≥1.8 ng/ml were referred for evaluation with MRI. Men with a positive MRI and/or those with PSA of ≥3.0 ng/ml were referred for biopsy. A TRUS-guided systematic biopsy was sampled first, blinded to MRI results. The MRI results were then revealed, and MRI-targeted biopsy was performed on men with cancer-suspicious findings on MRI. In the final analysis, three different screening strategies were compared (1) PSA ≥3.0ng/mL and systematic biopsy; (2) PSA ≥3.0ng/mL, MRI scan, and targeted prostate biopsy in the event of a positive MRI scan; and (3) PSA ≥1.8ng/mL, MRI scan, and targeted prostate biopsy in the event of a positive MRI scan

Index test
All MRI examinations were performed using a 3Tesla system (Philips Achieva 3.0, Philips Healthcare, Best, the Netherlands). During the first part of the study, a SENSE Cardiovascular Array Coil with 32 overlapping elements was used. During the study period the system was upgraded and a digital coil system (dStream Torso with integrated anterior and posterior coils) was used (no endorectal coil). Suspicious lesions were according to the validated Prostate Imaging Reporting and Data System for each sequence, ranging from 1 to 5 according to the likelihood of significant prostate cancer presence. A score in any sequence of ≥3 (equivocal) was regarded as positive. All images were read in consensus by three radiologists of whom two had several years' experience of MRI-reading

Reference standard
TRUS-guided biopsy was performed first, blinded to MRI results, before an MRI-targeted biopsy was performed in all participants with a positive MRI result. The systematic prostate biopsy was a 10-core TRUS-guided systematic biopsy using a scheme with 12 anterior and 12 posterior sectors of which 10 posterior were sampled routinely. The targeted prostate biopsy was an MRI-targeted biopsy performed on men with cancer-suspicious findings on MRI through three additional cores sampled per suspicious region by means of "cognitive" targeting

Comparator
Strategy 1 (PSA ≥3.0ng/mL and systematic prostate biopsy) was considered the 'reference strategy'

Measures of test accuracy
Point estimates for the statistics sensitivity, specificity, and positive and negative predictive values were calculated as row or column percentages of the two-by-two tables. A p-value for comparing positive predictive value and negative predictive value were calculated using the method described by Moskowitz and Pepe

Disease-related outcomes
Not reported

Test Accuracy

Estimated test performance for prostate cancer detection of three different screening strategies

Parameter	Strategy 1: PSA ≥3.0 + systematic biopsy		Strategy 2: PSA ≥3.0 + MRI + targeted biopsy		Strategy 3: PSA ≥1.8 + MRI + targeted biopsy	
	%	95% CI	%	95% CI	%	95% CI
Sensitivity	0.64	0.47–0.82	0.46	0.27–0.65	0.73	0.56–0.90
Specificity	0.52	0.43–0.62	0.92	0.86–0.97	0.79	0.70–0.87
PPV	0.27	0.16–0.37	0.60	0.39–0.81	0.48	0.32–0.63
NPV	0.84	0.75–0.93	0.87	0.80–0.93	0.92	0.86–0.98

Study Reference	**Göteborg Randomised Screening Trial (Grenabo Bergdahl 2016)**

Comparison between screening strategies for significant differences (p-values)

Parameter	Strategy 1 vs. 2	Strategy 1 vs. 3	Strategy 2 vs. 3
Sensitivity	0.21	0.47	0.008
Specificity	<0.001	0.001	<0.001
PPV	<0.001	0.006	0.09
NPV	0.55	0.17	0.03

Authors' Conclusions	A screening strategy with a lowered PSA cut-off followed by targeted prostate biopsy in MRI-positive men seems to increase the detection of significant cancers while improving specificity. If replicated, these results may contribute to a paradigm shift in future screening

Abbreviations: BMI, body mass index; IQR, interquartile range; MRI, magnetic resonance imaging; N/A, not applicable; NPV, negative predictive value; NR, not reported; PPV, positive predictive value; TRUS, transrectal ultrasound

Table 40e. PLCO Trial, Halpern 2017

Study Reference	**Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (Halpern 2017)**
Study Design	Study name Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial Design Randomised controlled trial Objective The absence of definitive data or explicit guidelines regarding the use of DRE for prostate cancer screening may lead to confusion for physicians and patients alike. This study evaluated the prognostic value of abnormal DRE and PSA following the widespread dissemination of PSA testing in the USA Dates Randomisation in 1993–2001, with up to 13 years of follow-up Country USA Setting NR
Population Characteristics	Patient recruitment and eligibility The PLCO Cancer Screening Trial was a national, randomised controlled trial of prostate cancer screening that has been described previously **Inclusion** Men 55 to 74 years old **Exclusion**

Study Reference	**Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (Halpern 2017)**

Men with a history of prostate cancer or prostatectomy, ongoing treatment for malignancy, use of finasteride within 6 months or more than 1 PSA test in the last 3 years were excluded from analysis

Other
N/A

Sample size
N randomised to the screening arm = 38,340
N died before screening = 6
N excluded (did not undergo DRE despite randomisation to screening) = 2,984
N included in analysis = 35,350

Demographics

Parameter	Suspicious DRE (n=3,265)	Normal DRE (n=32,085)
Age at baseline (median, IQR)	64 (60–68)	62 (58–66)
Ethnicity	NR	NR
Previous PSA test (n, %)	1,589 (53.5)	14,287 (49.3)
Previous biopsy	NR	NR
Family history of prostate cancer	NR	NR
Socioeconomic status (e.g. education)	NR	NR
BMI	NR	NR
Weight	NR	NR
Comorbidity index	NR	NR
Diabetes	NR	NR

Methods

Trial design
Participants were randomised to routine prostate cancer screening with DRE and PSA or usual care. Men in the screening arm underwent annual DRE and PSA for the first 4 and 6 years of the trial, respectively. As men in the usual care arm did not undergo routine DRE, these men were excluded from the analysis. Following a positive screening encounter, the subsequent diagnostic and therapeutic course of each man was determined by his individual physician. Follow-up was obtained for 13 years after trial initiation, throughout which study coordinators actively tracked trial participants' screening test results, medical record, diagnostic evaluations, treatments and oncologic end points

Index test
The presence or absence of suspicious abnormality on DRE was determined by the screening clinician (physician, physician assistant or nurse). Non-physician examiners were trained and supervised by a licensed physician, typically a urologist. DRE was considered positive or suspicious in the presence of induration, nodularity, significant asymmetry or loss of anatomical landmarks as determined by the examiner

Reference standard
Prostate biopsy (no details of procedure reported)

Comparator
PSA test (no details of procedure reported). A measurement of ≥4 ng/mL was considered indicative of abnormal PSA

Study Reference	**Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (Halpern 2017)**
	Measures of test accuracy Not reported Disease-related outcomes Prostate cancer specific mortality was a primary endpoint. The occurrence of death was determined via routine follow-up and cause of death, when applicable, was determined by death certificate with confirmation via study specific adjudication process. Median follow-up was 10.5 years. Univariable and multivariable competing risks regression models were used to identify the role of DRE as a prognostic tool of prostate cancer specific mortality
Test Accuracy	Prostate cancer specific mortality During follow-up there were 64 prostate cancer specific deaths. On univariable analysis, suspicious DRE was associated with prostate cancer specific mortality (HR 3.49, 95% CI 1.96–6.23, p <0.001). On multivariable analysis, adjusting for age and intra-study PSA, suspicious DRE remained associated with prostate cancer specific mortality (HR 2.54, 95% CI 1.41–4.58, p = 0.002). On multivariable analysis, abnormal PSA was associated with prostate cancer specific mortality (HR 5.23, 95% CI 3.08–8.88, p <0.001). Multivariable hazard regression

Parameter	Suspicious DRE			Abnormal PSA		
	HR	95% CI	p-value	HR	95% CI	p-value
Prostate cancer specific mortality	2.54	1.41, 4.58	0.002	5.23	3.08, 8.88	<0.001

Authors' Conclusions	Suspicious DRE and abnormal PSA on routine screening are associated with clinically significant prostate cancer and prostate cancer specific mortality. These findings support a continued role for DRE and PSA in the context of shared decision making and individualised screening regimens. However, additional research is needed to optimise screening protocols and further evaluate the synergistic relationship between these two tests

Abbreviations: BMI, body mass index; CI, confidence interval; DRE, digital rectal examination; HR, hazard ratio; IQR, interquartile range; N/A, not applicable; NR, not reported; PLCO, Prostate, Lung, Colorectal and Ovarian cancer screening trial; PSA, prostate-specific antigen

Table 40f. Stockholm 3 (STHLM3) Study, Grönberg 2015

Study Reference	**Stockholm 3 (STHLM3) Study (Grönberg 2015)** Linked records: Strom 2018
Study Design	Study name Stockholm 3 (STHLM3) Study Design Prospective, diagnostic study following a paired, screen-positive design Objective To develop and validate a model to identify high-risk prostate cancer (with a Gleason score of at least 7) with better test characteristics than that provided by PSA screening alone Dates

Study Reference	**Stockholm 3 (STHLM3) Study (Grönberg 2015)** Linked records: Strom 2018
	Training cohort was recruited in May 2012 to May 2013. Validation cohort was recruited in August 2013 to December 2014 Country Sweden Setting Community-based/primary care/records
Population Characteristics	Patient recruitment and eligibility The study recruited men aged 50–69 years from Stockholm, Sweden. Men, irrespective of any comorbidity except prostate cancer, were randomly selected by date of birth from the Swedish Population Register kept by the Swedish Tax Agency and invitations were posted to them **Inclusion** Aged 50–69 years with a residential address in Stockholm **Exclusion** Previous prostate cancer diagnosis **Other** The study consisted of a training cohort and a validation cohort. The training cohort was used to train and predefine the STHLM3 model algorithm. The validation cohort was used to prospectively test the STHLM3 algorithm Sample size N invited to participate in training cohort = 145,905 N excluded from training cohort (prevalent prostate cancer) = 1,633 N recruited to training cohort = 11,130 N invited to participate in validation cohort = 113,082 N excluded from validation cohort (prevalent prostate cancer) = 1,263 N recruited to validation cohort = 47,688 Demographics

Parameter	Validation cohort (n=47,688)
Age at recruitment (n, %) 50–54 55–59 60–64 65–69	 11,723 (25) 10,924 (23) 11,159 (23) 13,882 (29)
Ethnicity	NR
Previous PSA test within 10 years of inclusion (n, %)	31,435 (66)
Previous negative biopsy within 10 years of inclusion (n, %)	1,739 (4)
First-degree relative with prostate cancer (n, %)	5,872 (12)
Socioeconomic status (e.g. education)	NR
BMI	NR
Weight	NR

Study Reference	**Stockholm 3 (STHLM3) Study (Grönberg 2015)** Linked records: Strom 2018

Comorbidity index	NR
Diabetes	NR

Methods

Index test
The STHLM3 model is a test consisting of a combination of plasma protein biomarkers (PSA, free PSA, intact PSA, hK2, MSMB, and MIC1), genetic markers (232 SNPs), clinical variables (age, family history, previous prostate biopsy) and a prostate exam (DRE and prostate volume).

PSA levels were analysed in all participants and in those with a PSA concentration of ≥1 ng/mL, genetic and plasma protein biomarkers were analysed. A genetic score was computed for each participant by summing the number of risk alleles at each of the 232 SNPs multiplied by the logarithm of each SNP's odds ratio estimated from published studies. The biomarker score was computed for each participant by combining the genetic score and five plasma biomarkers (MSMB, MIC1, free PSA, intact PSA and hK2) using logistic regression. If the STHLM3 model indicated ≥10% risk of high-grade prostate cancer, patients were referred to a urologist, who performed DREs, prostate volume measurements, and transrectal prostate biopsy

Reference standard
According to a standardised biopsy protocol, 10 core biopsies were taken if the prostate volume was less than 35 cm and 12 core biopsies were taken if the volume was greater or equal to 35 cm. A single pathologist blinded to the results of PSA concentration and biomarker levels assessed all biopsies to reduce inter-observer variance

Comparator
PSA test alone. A measurement of ≥3 ng/mL was considered indicative of abnormal PSA. Men with PSA ≥3 ng/ml were biopsied regardless of STHLM3 results

Measures of test accuracy
For model comparisons, the area under the curve (AUC) was determined with 95% CI calculated using the bootstrap method. The p-value from DeLong's test was used for differences in AUC. Men with PSA ≥10, 5-α-reductase inhibitor use or incomplete data were excluded from the analyses

Disease-related outcomes
Not reported

Test Accuracy

Performance of the STHLM3 model for prediction of prostate cancers with a Gleason score ≥7
These results are based on the STHLM3 validation cohort including 4,947 biopsies done in men aged 50–69 years

Parameter	AUC (univariate)		AUC (stepwise multivariate)		Cumulative AUC		p-value
	AUC	95% CI	AUC	95% CI	AUC	95% CI	
Total PSA	0.56	0.54–0.59	0.56	0.54–0.59	0.56	0.55–0.60	Reference
Risk factors	-	-	-	-	0.58	0.56-0.60	<0.0001
Age	0.54	0.52–0.56	0.57	0.55–0.59	-	-	-
Family history	0.52	0.51–0.54	0.58	0.55–0.60	-	-	-
Previous biopsies	0.51	0.50–0.52	0.58	0.56–0.60	-	-	-
Biomarkers	-	-	-	-	0.70	0.68–0.72	<0.0001
Genetic score	0.54	0.52–0.56	0.60	0.58–0.62	-	-	-

Study Reference **Stockholm 3 (STHLM3) Study (Grönberg 2015)**
Linked records: Strom 2018

MSMB	0.54	0.52–0.56	0.61	0.59–0.63	-	-	-
MIC1	0.53	0.51–0.56	0.62	0.60–0.64	-	-	-
Free PSA	0.55	0.53–0.57	0.66	0.64–0.68	-	-	-
Intact PSA	0.52	0.50–0.55	0.69	0.67–0.71	-	-	-
hK2	0.55	0.53–0.57	0.70	0.68–0.72	-	-	-
Prostate exam[a]	-	-	-	-	0.74	0.72–0.75	<0.0001
DRE	0.57	0.56–0.59	0.72	0.70–0.74	-	-	-
Prostate volume	0.62	0.60–0.64	0.74	0.72–0.75	-	-	-

[a]Because all blood-based markers are used to refer men to a urological assessment (DRE and transrectal ultrasound), they are added to the model before adding DRE and prostate volume as predictors. Prostate volume and DRE were only assessed in men who had biopsy samples taken

Comparison of the STHLM3 model and PSA test using different endpoints
These results are based on the STHLM3 validation cohort including 4,947 biopsies done in men aged 50–69 years

Endpoint	PSA test		STHLM3 model	
	AUC	95% CI	AUC	95% CI
All prostate cancers	0.52	0.50–0.53	0.69	0.68–0.71
Cancers with a Gleason score ≥7	0.56	0.54–0.59	0.74	0.72–0.75
Excluding very low-risk cancer (CAPRA score 0–2)	0.64	0.62–0.67	0.78	0.76–0.80
Cancers with a Gleason score ≥(4 + 3)	0.60	0.56–0.64	0.74	0.71–0.77

Performance of an *updated* STHLM3 model for prediction of prostate cancers with a Gleason score ≥7
The original version of the STHLM3 model included intact PSA, but it was subsequently removed. In addition, a new biomarker was included, the *HOXB13* SNP, a rare germline mutation of the *HOXB13* gene with a large effect on the risk of prostate cancer. These analyses included all biopsied participants from the pilot study and the validation study, and all additional participants who had not had a blood test before the database of the STHLM3 study was locked

Parameter	Bivariate AUC[a]		Cumulative AUC[b]		Remove AUC[c]	
	AUC	95% CI	AUC	95% CI	AUC	95% CI
Age	0.59	0.57–0.61	0.59	0.57–0.61	0.75	0.74–0.77
DRE	0.63	0.61–0.64	0.63	0.61–0.65	0.75	0.73–0.76
Previous biopsies	0.61	0.59–0.63	0.65	0.63–0.66	0.75	0.74–0.77
Prostate volume	0.67	0.66–0.69	0.71	0.69–0.73	0.74	0.73–0.76
Family history	0.59	0.57–0.61	0.71	0.70–0.73	0.76	0.74–0.77

Study Reference **Stockholm 3 (STHLM3) Study (Grönberg 2015)**
Linked records: Strom 2018

Free PSA	0.65	0.63–0.67	0.72	0.71–0.74	0.76	0.74–0.78
Free/total PSA ratio	0.65	0.63–0.67	0.73	0.71–0.74	0.76	0.74–0.77
Intact PSA[d]	0.58	0.56–0.60	0.74	0.72–0.75	0.75	0.73–0.77
hK2	0.59	0.57–0.61	0.75	0.74–0.77	0.75	0.73–0.76
MIC1	0.59	0.57–0.61	0.75	0.74–0.77	0.76	0.74–0.77
MSMB	0.60	0.58–0.62	0.76	0.74–0.77	0.76	0.74–0.77
HOXB13	0.59	0.56–0.60	0.76	0.74–0.77	0.76	0.74–0.77
Genetic score	0.61	0.59–0.63	0.76	0.74–0.77	0.76	0.74–0.77

[a]Individual STHLM3 biomarkers in combination with PSA (including intact PSA). [b]The cumulative performance for inclusion of each biomarker in the order presented (including intact PSA). [c]The remaining value after removing the biomarker from the full set of predictors (including intact PSA). [d]Intact PSA is no longer part of STHLM3 but was evaluated among the set of individual predictors

Test	AUC	
	AUC	95% CI
Updated STHLM3 model	0.75	0.73–0.77
PSA test	0.58	0.57–0.60

Performance of an *updated* STHLM3 model for prediction of prostate cancers with a Gleason score ≥7, if used as a reflex test in patients with PSA ≥3 ng/mL **(Strom 2018)**
These analyses consider the use of the updated STHLM3 model as a reflex test in participants with a PSA concentration of ≥3 ng/mL

Parameter	Bivariate AUC[a]		Cumulative AUC[b]	
	AUC	95% CI	AUC	95% CI
Age	0.59	0.56–0.61	0.59	0.56–0.61
DRE	0.63	0.60–0.65	0.62	0.60–0.65
Previous biopsies	0.61	0.59–0.63	0.65	0.62–0.67
Prostate volume	0.69	0.67–0.70	0.72	0.70–0.74
Family history	0.59	0.57–0.61	0.72	0.70–0.74
Free PSA	0.65	0.63–0.67	0.73	0.71–0.75
Free/total PSA ratio	0.65	0.63–0.67	0.73	0.71–0.75
Intact PSA[c]	0.58	0.56–0.61	0.75	0.73–0.76
hK2	0.59	0.56–0.61	0.76	0.74–0.78
MIC1	0.59	0.57–0.61	0.76	0.74–0.78
MSMB	0.60	0.58–0.62	0.77	0.75–0.78
HOXB13	0.59	0.57–0.61	0.77	0.75–0.79
Genetic score	0.61	0.59–0.63	0.77	0.75–0.79

Study Reference	**Stockholm 3 (STHLM3) Study (Grönberg 2015)** Linked records: Strom 2018

[a]Individual STHLM3 biomarkers in combination with PSA (including intact PSA). [b]The cumulative performance by including each biomarker in the order presented (including intact PSA). [c]Intact PSA is no longer part of STHLM3 but was evaluated among the set of individual predictors

Test	AUC	
	AUC	95% CI
Updated STHLM3 model	0.76	0.74–0.77
PSA test	0.58	0.56–0.60
Free/total PSA ratio	0.64	0.62–0.67
PSA density[a]	0.69	0.67–0.70
Clinical model[b]	0.71	0.69–0.73
Age + four kallikreins[c]	0.70	0.68–0.72

[a]PSA/prostate volume; the referral value is the actual value for the density, not a probability of Gleason score ≥7 cancer. [b]PSA, age, DRE and prostate volume. [c]Age, PSA, free PSA, free/total PSA ratio, hK2 and intact PSA

Authors' Conclusions	The STHLM3 model could reduce unnecessary biopsies without compromising the ability to diagnose prostate cancer with a Gleason score of at least 7, and could be a step towards personalised risk-based prostate cancer diagnostic programmes. The STHLM3 model, a combination of plasma protein biomarkers, genetic polymorphisms, and clinical variables, can significantly improve prostate cancer screening specificity with the same sensitivity compared with PSA testing

Abbreviations: AUC, area under the curve; BMI, body mass index; CAPRA, Cancer of the Prostate Risk Assessment; CI, confidence interval; DRE, digital rectal examination; hK2, hexokinase 2; MSMB, Microseminoprotein Beta; PSA, prostate-specific antigen; SNP, single nucleotide polymorphism; STHLM3, Stockholm-3

Question 4

Table 41a. NG131 [C] (NICE 2019): Radical radiotherapy

Study Reference	**NG131 [C] (NICE 2019)** Linked records: Hoffman 2018; Wilkins 2015 (CHHiP) Yin 2019 is an SLR that includes some of the same trials
Study Design	Study name N/A Design Systematic literature review Objective To determine the optimal dose of radiotherapy for people with localised PCa To determine the effectiveness of 1) hypofractionated external beam radiotherapy versus conventional external beam radiotherapy and 2) brachytherapy, as a monotherapy or as a boost in combination with external beam radiotherapy, versus conventional external beam radiotherapy Search dates 2008–2017, up to August 2018 with update Country N/A Setting N/A
Population Characteristics	Study eligibility **Inclusion (PICOS)** Population: People with localised PCa (T1b–T3a N0 M0) Intervention: Hypofractionated RT to the prostate; Brachytherapy plus external beam RT; Brachytherapy alone Comparator: Conventional fractionation with external beam therapy Outcomes: PCa-specific mortality; OS; Metastasis-free survival; Treatment-related morbidity e.g. late effects of radiation therapy, biochemical relapse-free survival, toxicity; HRQoL (including separate reporting of psychological aspects) Study design: RCTs; Systematic reviews of RCTs **Exclusion (reasons given in excluded study list)** • Conference abstract • Non-systematic review article

Study Reference	**NG131 [C] (NICE 2019)** Linked records: Hoffman 2018; Wilkins 2015 (CHHiP) Yin 2019 is an SLR that includes some of the same trials

- Dose-escalation or high versus low dose
- Hypo boost versus conventional
- Comparison of differing brachytherapy doses
- Brachytherapy plus hypofractionated external beam RT vs hypofractionated external beam RT alone
- Not a relevant study design (e.g. non-randomised or retrospective)
- Full text not available
- Data not reported in an extractable format
- Study did not report outcomes of interest
- Comparator did not match that specified in the protocol
- Study not reported in English language
- Study did not contain relevant interventions
- Study published pre-2008

Other
The review was conducted as part of a larger update of the NICE Prostate Cancer guideline (CG175)

Flow of Studies (PRISMA)
Titles/abstracts reviewed = 2,688
Full texts reviewed = 163
Articles included = 24 articles* on 11 unique RCTs (after update)

- Conventional versus hypofractionated RT = 22 articles on 10 RCTs
- ERBT alone versus ERBT + low-dose-rate brachytherapy boost = 2 articles on 1 RCT
- Brachytherapy alone = 0 articles

* Only 20 publications are accounted for in the evidence table for the included studies

Included study characteristics

Short title and related studies	Study type	Location and setting	Dates and duration of follow-up	Inclusion criteria	Exclusion criteria	Sample characteristics	Interventions	Outcomes
Conventional versus hypofractionated RT								
Alwuni 2016 (HYPRO) Alwuni 2015 Alwuni 2015 Incrocci 2016 Wortel 2017	RCT	Country: The Netherlands Setting: 7 RT centres	Mar 2007–Dec 2010 Follow-up: 60 months	Intermediate to high risk PCa (T1b–T4 NX–0 MX–0, SPSA ≤60 ng/mL, WHO PS 0–2) Age 44–85 years	Prior radical prostatectomy, pelvis irradiation Low risk PCa (T1b–T2a, Gleason score ≤6, PSA ≤10 ng/mL Evidence of pelvic nodal disease or distant metastasis	N: 820 (410 in each arm), 795 in ITT LTFU: 38/820 Median age (IQR): Arm 1: 70 (66–74), Arm 2: 71 (67–75)	Arm 1: hypofractionated RT (63.6 gy in 19 x 3.4 fr) Arm 2: conventional RT (78 gy in 39 x 2 gy fr)	Toxicity: Long-term toxicity Survival: 5-year relapse free survival

Study Reference	**NG131 [C] (NICE 2019)** Linked records: Hoffman 2018; Wilkins 2015 (CHHiP) Yin 2019 is an SLR that includes some of the same trials								
	Catton 2017 (PROFIT)	RCT	Country: Canada, Australia, France Setting: 27 centres	2006–2016 Follow-up: 5 years	Intermediate risk PCa (T1–T2a, Gleason score ≤6 and PSA 10.1–20; T2b–T2c, Gleason score ≤6 and PSA ≤20 ng/mL; or T1–2, Gleason score 7 and PSA ≤20 ng/mL) without evidence of lymph node or bone metastasis	Prior radiology or PCa therapy other than biopsy or transurethral resection Malignancy diagnosed within 5 years of entry other than non-melanoma skin cancer or IBD, PCa diagnosis ≥6 months before study entry	N: 1,206 (608 Arm 1, 598 Arm 2), 1,192 completed treatment, 1116 analysed LTFU: 76 Median age (IQR): Arm 1: 71 (67–75), Arm 2: 72 (68–75)	Arm 1: hypofractionated RT (60 gy in 20 x 3 gy fr over 4 weeks) Arm 2: conventional RT (78 gy in 39 x 2 gy fr over 8 weeks) Type of RT: IMRT encouraged however 3D-CRT permitted if dose constraints met	Toxicity: Acute (14-week) and late (5-year) toxicity Survival: OS and freedom from PCa-related death Biochemical failure: Biochemical clinical failure
	Dearnaley 2016 (CHHiP) Dearnaley 2012 Wilkins 2015	RCT	Country: UK Setting: 71 centres	Oct 2002–Jun 2016 Follow-up: 5 years	PCa (T1b–T3a N0 M0 and WHO PS 0–1) Until Aug 1 2006, PSA <40 ng/mL and <30% risk of lymph node involvement; after Aug 1 2006, PSA <30 ng/mL and <30% risk of senubak vesicle involvement Age >16 years	Prior radical prostatectomy or pelvis RT or androgen suppression Another active malignancy in the past 5 years (other than cutaneous basal-cell carcinoma), comorbid conditions precluding radical radiotherapy, hip prosthesis, full anticoagulation treatment T3 tumours and Gleason score ≥8 Life expectancy <10 years	N: 3,216 (Arm 1: 1,065, Arm 2: 1,074, Arm 3: 1,077), 3,133 received at least one dose of treatment LTFU: 35 (64 did not receive treatment due to ineligibility/ technical unsuitability) Median age (IQR): Arm 1: 68 (48–85), Arm 2: 69 (48–84), Arm 3: 69 (44–83) Short course ADT was given for 3–6 months before and during RT, this was optional for patients with low risk disease	Arm 1: conventional RT (74 gy in 37 x 2 gy fr) Arm 2: hypofractionated RT (60 gy in 20 x 3 gy fr) Arm 3: hypofractionated RT (57 gy in 19 x 3 gy fr) Type of RT: Forward or inverse 3D methods	Toxicity: Acute (18-week) and late toxicity Survival: DFS and OS Biochemical failure: Biochemical clinical failure
	Lee 2016 (RTOG 0415)	RCT	Country: NR Setting: NR	2006–2014 Follow-up: Minimum 5 years, median 5.8 years	Low-risk PCa (T1b–T2c, Gleason score 2–6, PSA <10, Zubrod PS <2) Age >18 years Male	Prior bilateral orchiectomy, cryosurgery or definitive surgery for PCa, prior chemotherapy or RT	N: 1,115 (Arm 1: 558 [randomised] 542 [received treatment], Arm 2: 557 [randomised] 557 [received	Arm 1: conventional RT (73.8 gy in 41 x 1.8 gy fr over 8.2 weeks) Arm 2: hypofractionated	Toxicity: Acute and late GI and GU Survival: DFS and OS PSA levels:

Study Reference	**NG131 [C] (NICE 2019)** Linked records: Hoffman 2018; Wilkins 2015 (CHHiP) Yin 2019 is an SLR that includes some of the same trials								
						Other invasive cancer (other than localised basal or squamous cell skin carcinoma) unless continually cancer-free for ≥5 years	treatments]), 1,092 analysed LTFU: 33 Median age (IQR): NR	RT (70 gy in 28 x 2.5 gy fr over 5.6 weeks) Type of RT: Randomised to 3D-CRT or IMRT	PSA measured every 3 months for the first 2 years, every 6 months for next 3 years and annually thereafter
	Marzi 2009	RCT	Country: Italy Setting: Single institution	Mar 2003–Jun 2008 Follow-up: Median 30 months	High-risk PCa with 2 of the following: T2c–T4, PSA >10 ng/mL, Gleason score 7–10 Age <85 years	Prior prostatectomy or radiology No node involvement or other malignant disease (except for basal cell carcinoma) or other tumours in past 5 years	N: 162, 114 analysed (57 in each arm) (those with follow-up of >6 months) LTFU: 48 Median age (IQR): NR	Arm 1: Hypofractionated RT (62 gy in 20 x 3.1 fr over 5 weeks) Arm 2: Conventional RT (80 gy in 40 x 2 gy fr over 8 weeks) Type of RT: 3D-CRT	Toxicity: Late rectal toxicity using RTOG scale
	Norkus 2009	RCT	Country: Lithuania Setting: NR	NR Follow-up: Minimum 12 months	NR	NR	N: NR LTFU: 7 Median age (IQR): NR	NR	Toxicity Weekly evaluations for 12 weeks, 3-month during 1st year and 6-monthly thereafter
	Norkus 2013	RCT	Country: Lithuania Setting: Vilnius University	2004 Follow-up: Minimum of 3 months	Low-to-intermediate risk PCa with <15% risk of seminal vesicle and/or lymph node involvement	Surgical castration before RT Hormonal therapy before RT Androgen suppression	N: 91 (Arm 1: 44, Arm 2: 47) LTFU: 0 Median age (IQR): Arm 1: 65 (50–78), Arm 2: 63 (53–75)	Arm 1: Conventional RT (74 gy in 37 x 2 gy fr over 7.5 weeks) Arm 2: Hypofractionated RT (57 gy in 13 x 3 gy fr over 3.5 weeks + 4 x 4.5 gy fr) Type of RT: 3D-CRT	Toxicity: GI + GU measured using RTOG/EORTC scale
	Pollack 2013 (FCCC) Pollack 2006 Shaikh 2017	RCT	Country: USA Setting: Fox Chase Cancer Centre and	2002–2013 Follow-up: Median 69 months (range 7–	PCa (T1–T3, Gleason score ≥5 if they had intermediate/high-risk features)	High-risk patients were planned to receive 24 months of ADT; less than high-risk patients were	N: 307 (Arm 1: 152, Arm 2: 151), 303 analysed LTFU: 0	Arm 1: Conventional RT (76 gy in 2 gy x 38 fr) Arm 2: Hypofractionated	Toxicity: Protocol toxicity measured using modified

Study Reference	**NG131 [C] (NICE 2019)** Linked records: Hoffman 2018; Wilkins 2015 (CHHiP) Yin 2019 is an SLR that includes some of the same trials								
			University of Miami	136 months)		planned to receive 4 months ADT, beginning ≤4 months before random assignment	Median age (IQR): Arm 1: 67 (45–86), Arm 2: 67 (49–86)	RT (70.2 gy in 2.7 gy x 27 fr) Type of RT: IMRT	LENT/RTOG criteria QoL: QoL measured using EPIC, IPSS and EQ-5D
	Arcangeli 2010 (RENCI)	Not included in evidence table							
	Hoffman 2014	Not included in evidence table							
	ERBT alone versus ERBT + low-dose-rate brachytherapy boost								
	Morris 2017 (ASCENDE-RT) Rodda 2017	RCT	Country: Canada Setting: NR	2002–2014 Follow-up: Median 6.5 years	Intermediate-to-high-risk PCa	NR	N: 398 (Arm 1: 200, Arm 2: 198), all in ITT, 15 not included in toxicity assessment LTFU: 1 (29 did not receive allocated intervention) Median age (IQR): 68 (45–86) All patients received 8 months of ADT prior to RT	Arm 1: EBRT (dose-escalated 46 gy in 23 fr + 32 gy boost in 16 fr) Arm 2: External beam + LDR-BT (46 gy in 20 fr + LDR-BT boost of I125 brachytherapy implant of 116 gy) Type of RT: 3DCRT	Toxicity: Acute (within 6 months) and late (after 6 months) Survival: OS and freedom from prostate-related death Biochemical failure: Biochemical failure

Methods

Searches
Sources searched:

- CDSR (Wiley), CENTRAL (Wiley), DARE (Wiley), EMBASE (Ovid), MEDLINE (Ovid), MEDLINE In-Process (Ovid)

Screening and selection process
10% of the abstracts were reviewed by 2 reviewers with any disagreements resolved by discussion or a 3rd independent reviewer if necessary. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by 2 reviewers; this process was continued until agreement was achieved between the 2 reviewers and the remaining abstracts screened by a single reviewer

Study quality assessment
Cochrane Risk of Bias Tool

Methods for combining intervention evidence
MAs of the interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins *et al.*, 2011)

Study Reference

NG131 [C] (NICE 2019)
Linked records: Hoffman 2018; Wilkins 2015 (CHHiP)
Yin 2019 is an SLR that includes some of the same trials

- Continuous data: MA conducted on the mean difference (first converted to the same scale if necessary or using standardised mean differences if outcomes were measured using different instruments/metrics)
- Dichotomous data: pooled RR and AR (by applying the RR to the pooled risk in the comparator arm of the MA)
- Fixed and random-effects (der Simonian and Laird) models were fitted for all syntheses
- Significant heterogeneity between studies was identified and recorded by the reviewer in advance of conducting the analysis
- In any MA where some data came from studies at high RoB, sensitivity analyses were conducted to exclude those studies from the analysis
- GRADE was used to assess the quality of evidence for the selected outcomes

Harms and Benefits of Interventions and Quality Assessment of Included Studies

Forest plot data

Conventional RT vs hypofractionated RT

Outcome	Study or subgroup	Hypofractionated RT		Conventional RT		Weight (%)	Effect size (95% CI)	Heterogeneity	Z score
		Total N	Events (n)	Total N	Events (n)		RR		
Freedom from biochemical failure	Arcangeli 2017 (IRE)	83	65	85	60	4.3	1.11 (0.93, 1.33)	Chi^2=1.44	1.83
	Catton 2017 (PROFIT)	608	511	598	498	36.5	1.01 (0.96, 1.06)	df=3 (P=0.70)	(P=0.07)
	Incrocci 2016 (HYPRO)	407	337	397	315	23.2	1.04 (0.98, 1.12)	I^2=0%	
	Lee 2016 (RTOG 0415)	550	511	542	492	36.0	1.02 (0.99, 1.06)		
	Total	1648	1424	1622	1365	100.0	1.03 (1.00, 1.06)		
Freedom from biochemical-clinical failure	Catton 2017 (PROFIT)	608	499	598	481	18.3	1.02 (0.97, 1.08)	Chi^2=6.81	1.11
	Dearnaley 2016 (CHHiP 57 gy)	1077	945	532	477	24.1	0.98 (0.94, 1.01)	df=5 (P=0.24)	(P=0.27)
	Dearnaley 2016 (CHHiP 60 gy)	1074	986	533	477	24.0	1.03 (0.99, 1.06)	I^2=27%	
	Incrocci 2016 (HYPRO)	407	327	397	308	11.8	1.04 (0.96, 1.11)		
	Lee 2016 (RTOG 0415)	550	464	542	443	16.8	1.03 (0.98, 1.09)		
	Pollack 2013 (FCCC)	151	125	152	133	5.0	0.95 (0.86, 1.04)		
	Total	3867	3346	2754	2319	100.0	1.01 (0.99, 1.03)		
Overall survival	Arcangeli 2017 (IRE)	83	64	85	59	2.0	1.11 (0.92, 1.33)	Chi^2=3.35	0.98
	Catton 2017 (PROFIT)	608	532	598	520	18.3	1.01 (0.96, 1.05)	df=6 (P=0.76)	(P=0.33)
	Dearnaley 2016 (CHHiP 57 gy)	1077	990	532	486	22.7	1.01 (0.97, 1.04)	I^2=0%	
	Dearnaley 2016 (CHHiP 60 gy)	1074	1001	533	487	22.7	1.02 (0.99, 1.05)		
	Incrocci 2016 (HYPRO)	407	346	397	338	12.0	1.00 (0.94, 1.06)		
	Lee 2016 (RTOG 0415)	550	501	542	491	17.3	1.01 (0.97, 1.04)		
	Pollack 2013 (FCCC)	151	135	152	141	4.9	0.96 (0.90, 1.03)		
	Total	3950	3569	2839	2522	100.0	1.01 (0.99, 1.03)		
Freedom from prostate-cancer related death	Arcangeli 2017 (IRE)	83	80	85	76	4.3	1.08 (0.99, 1.17)	Chi^2=4.34	0.76
	Catton 2017 (PROFIT)	608	598	598	586	33.8	1.00 (0.99, 1.02)	df=4 (P=0.36)	(P=0.45)
	Incrocci 2016 (HYPRO)	407	391	397	382	22.1	1.00 (0.97, 1.03)	I^2=8%	
	Lee 2016 (RTOG 0415)	550	549	542	540	31.2	1.00 (1.00, 1.01)		
	Pollack 2013 (FCCC)	151	147	152	150	8.6	0.99 (0.96, 1.02)		
	Total	1799	1765	1774	1734	100.0	1.00 (0.99, 1.01)		
Genitourinary acute toxicity	Aluwini 2015 (HYPRO)	403	244	391	226	20.8	1.05 (0.93, 1.18)	Chi^2=10.47	0.23
	Arcangeli 2011 (IRE)	83	39	85	34	3.0	1.17 (0.83, 1.66)	df=8	(P=0.82)

Study Reference **NG131 [C] (NICE 2019)**
Linked records: Hoffman 2018; Wilkins 2015 (CHHiP)
Yin 2019 is an SLR that includes some of the same trials

	Catton 2017 (PROFIT)	608	185	598	183	16.7	0.99 (0.84, 1.18)	(P=0.23)	
	Dearnaley 2016 (CHHiP 57 gy)	713	327	358	166	20.0	0.99 (0.86, 1.13)	I^2=24%	
	Dearnaley 2016 (CHHiP 60 gy)	720	356	357	165	20.0	1.07 (0.94, 1.22)		
	Lee 2016 (RTOG 0415)	545	147	534	145	13.3	0.99 (0.82, 1.21)		
	Norkus 2009	47	9	44	21	2.0	0.40 (0.21, 0.78)		
	Norkus 2013	67	16	57	16	1.6	0.85 (0.47, 1.54)		
	Pollack 2006 (FCCC)	50	24	50	28	2.5	0.86 (0.59, 1.25)		
	Total	3236	1347	2474	984	100.0	1.01 (0.95, 1.07)		
Gastrointestinal acute toxicity	Aluwini 2015 (HYPRO)	402	169	391	122	23.2	1.35 (1.12, 1.62)	Chi^2=11.70	7.08
	Arcangeli 2011 (IRE)	83	29	85	18	3.3	1.65 (1.00, 2.73)	df=8	(P<0.00001)
	Catton 2017 (PROFIT)	608	99	598	62	11.7	1.57 (1.17, 2.11)	(P=0.17)	
	Dearnaley 2016 (CHHiP 57 gy)	713	270	358	88	22.0	1.54 (1.26, 1.89)	I^2=32%	
	Dearnaley 2016 (CHHiP 60 gy)	720	277	357	88	22.1	1.56 (1.27, 1.91)		
	Lee 2016 (RTOG 0415)	545	58	534	55	10.4	1.03 (0.73, 1.46)		
	Norkus 2009	47	8	44	10	1.9	0.75 (0.33, 1.72)		
	Norkus 2013	67	26	57	23	4.7	0.96 (0.62, 1.49)		
	Pollack 2006 (FCCC)	50	9	50	4	0.7	2.25 (0.74, 6.83)		
	Total	3235	945	2474	470	100.0	1.42 (1.29, 1.56)		
Genitourinary late toxicity	Aluwini 2016 (HYPRO)	395	163	387	151	25.3	1.06 (0.89, 1.26)	Chi^2=9.52	1.40
	Arcangeli 2017 (IRE)	83	11	85	17	2.8	0.66 (0.33, 1.33)	df=7	(P=0.16)
	Catton 2017 (PROFIT)	608	136	598	134	22.4	1.00 (0.81, 1.23)	(P=0.22)	
	Dearnaley 2016 (CHHiP 57 gy)	1057	57	520	33	7.3	0.85 (0.56, 1.29)	I^2=26%	
	Dearnaley 2016 (CHHiP 60 gy)	1049	88	520	33	7.3	1.32 (0.90, 1.94)		
	Hoffman 2014	102	15	102	16	2.6	0.94 (0.49, 1.79)		
	Lee 2016 (RTOG 0415)	545	161	534	121	20.2	1.30 (1.06, 1.60)		
	Pollack 2006 (FCCC)	151	68	152	73	12.1	0.94 (0.74, 1.19)		
	Total	3990	699	2898	578	100.0	1.07 (0.97, 1.18)		
Gastrointestinal late toxicity	Aluwini 2016 (HYPRO)	395	87	387	68	15.8	1.25 (0.94, 1.67)	Chi^2=25.76	0.45
	Arcangeli 2017 (IRE)	83	11	85	12	2.7	0.94 (0.44, 2.01)	df=8	(P=0.65)
	Catton 2017 (PROFIT)	608	54	598	83	19.2	0.64 (0.46, 0.88)	(P=0.001)	
	Dearnaley 2016 (CHHiP 57 gy)	1057	95	520	55	16.9	0.85 (0.62, 1.16)	I^2=69%	
	Dearnaley 2016 (CHHiP 60 gy)	1049	105	520	56	17.2	0.93 (0.68, 1.26)		
	Hoffman 2014	102	11	102	5	1.1	2.20 (0.79, 6.11)		
	Lee 2016 (RTOG 0415)	545	121	534	75	17.4	1.58 (1.22, 2.05)		
	Marzi 2009	81	7	81	8	1.8	0.88 (0.33, 2.30)		
	Pollack 2013 (FCCC)	151	27	152	34	7.8	0.80 (0.51, 1.26)		
	Total	4071	518	2979	396	100.0	1.03 (0.91, 1.16)		
		log[HR] (SE)					HR		
Time to biochemical failure	Arcangeli 2017 (IRE)	0.48243 (0.310305)				31.8	1.62 (0.88, 2.98)	Chi^2=0.35	1.90 (P=0.06)
	Lee 2016 (RTOG 0415)	0.26136 (0.211824)				68.2	1.30 (0.86, 1.97)	df=1 (P=0.56)	
	Total					100.0	1.39 (0.99, 1.96)	I^2=0%	
Time to biochemical-clinical failure	Pollack 2013 (FCCC)	–0.3581 (0.297786)				3.1	0.70 (0.39, 1.25)	Chi^2=9.56	0.51 (P=0.61)
	Incrocci 2016 (HYPRO)	0.15082 (0.155728)				11.2	1.16 (0.86, 1.58)	df=5 (P=0.09)	
	Lee 2016 (RTOG 0415)	0.16252 (0.147274)				12.5	1.18 (0.88, 1.57)	I^2=48%	
	Catton 2017 (PROFIT)	0.040822 (0.11319)				21.2	1.04 (0.83, 1.30)		
	Dearnaley 2016 (CHHiP 60 gy)	0.17435 (0.105924)				24.2	1.19 (0.97, 1.47)		
	Dearnaley 2016 (CHHiP 57 gy)	–0.182322 (0.099104)				27.7	0.83 (0.69, 1.01)		
	Total					100.0	1.03 (0.93, 1.14)		

Study Reference

NG131 [C] (NICE 2019)
Linked records: Hoffman 2018; Wilkins 2015 (CHHiP)
Yin 2019 is an SLR that includes some of the same trials

Time to death from any cause	Arcangeli 2017 (IRE) Dearnaley 2016 (CHHiP 57 gy) Dearnaley 2016 (CHHiP 60 gy) Incrocci 2016 (HYPRO) Lee 2016 (RTOG 0415) *Total*	0.37106 (0.299761) 0.08338 (0.151193) 0.24846 (0.155844) –0.019803 (0.18391) 0.05129 (0.201499)	7.4 29.1 27.4 19.7 16.4 100.0	1.45 (0.81, 2.61) 1.09 (0.81, 1.46) 1.28 (0.94, 1.74) 0.98 (0.68, 1.41) 1.05 (0.71, 1.56) 1.13 (0.97, 1.33)	Chi^2=2.13 df=4 (P=0.71) I^2=0%	1.52 (P=0.13)
Time to prostate cancer-related death	Arcangeli 2017 (IRE) Lee 2016 (RTOG 0415) *Total*	0.875469 (0.557182) 0.274436 (0.443436)	38.8 61.2 100.0	2.40 (0.81, 7.15) 1.32 (0.55, 3.14) 1.66 (0.84, 3.28)	Chi^2=0.71 df=1 (P=0.40) I^2=0%	1.46 (P=0.14)

GRADE Tables

Conventional versus hypofractionated RT: survival and AE outcomes – GRADE Table

N of studies	Sample size	Effect size (95% CI)	Absolute risk per 1,000 people		RoB	Inconsistency	Indirectness	Imprecision	Quality
			Control	Intervention (95% CI)					
Overall freedom from biochemical failure – RR >1 favours hypofractionated									
4	3,270	RR **1.03** (1.00, 1.06)	840[6]	866 (–26 to +25)[6]	Not serious	Not serious	Not serious	Not serious	High
Time to biochemical failure – HR >1 favours hypofractionated									
2	1,260	HR **1.39** (0.99, 1.96)	-	-	Not serious	Serious[4]	Not serious	Serious[2]	Low
Overall freedom from biochemical clinical failure – RR >1 favours hypofractionated									
6	6,621	RR **1.01** (0.99, 1.03)	896[5]	905 (887–923)[5]	Not serious	Not serious	Not serious	Serious[2]	Moderate
Time to biochemical clinical failure – HR <1 favours hypofractionated									
6	6,621	HR **1.03** (0.93, 1.14)	-	-	Not serious	Not serious	Not serious	Serious[2]	Moderate
OS (5–10 years) – RR >1 favours hypofractionated									
7	6,789	RR **1.01** (0.99, 1.03)	922[5]	932 (–18 to +18)[5]	Not serious	Not serious	Not serious	Not serious	High
Time to any-cause death – HR >1 favours hypofractionated									
6	6,486	HR **1.13** (0.97, 1.33)	-	-	Not serious	Not serious	Not serious	Serious[2]	Moderate
Freedom from PCa-related death – RR >1 favours hypofractionated									
5	3,553	RR **1.00** (0.99, 1.01)	984[6]	984 (–10 to +10)[6]	Not serious	Not serious	Not serious	Not serious	High
Time to PCa-related death – HR >1 favours hypofractionated									
2	1,374	HR **1.66** (0.84, 3.28)	-	-	Not serious	Not serious	Not serious	Serious[2]	Moderate
Acute GU toxicity – RR <1 favours hypofractionated									
9	5,710	RR **1.01** (0.95, 1.07)	398	402 (–24 to +24)	Serious[1]	Not serious	Not serious	Not serious	Moderate
Acute GI toxicity – RR <1 favours hypofractionated									
9	5,709	RR **1.42** (1.29, 1.56)	190	270 (–25 to +26)	Serious[1]	Not serious	Not serious	Not serious	Moderate
Late GU toxicity – RR <1 favours hypofractionated									
8	6,888	RR **1.07** (0.97, 1.18)	199	213 (–20 to +22)	Serious[1]	Not serious	Not serious	Not serious	Moderate
Late GI toxicity – RR <1 favours hypofractionated									

Study Reference

NG131 [C] (NICE 2019)
Linked records: Hoffman 2018; Wilkins 2015 (CHHiP)
Yin 2019 is an SLR that includes some of the same trials

9	7,050	RR **1.03** (0.91, 1.16)	133	137 (–16 to +17)	Serious[1]	Serious[4]	Not serious	Not serious	Low

[1] Blinding procedures were not possible/attempted and this may have affected the reporting and/or scoring of this outcome
[2] 95% confidence intervals for the effect size crossed the line of no effect – downgraded once
[3] 95% confidence intervals for the effect size crossed one line of the MID – downgraded once
[4] I^2 > 33.3%
[5] Follow-up length 5 years with exception of one study (RENCI: 10-years). A 5-year estimate was calculated using CHHiP study as a control
[6] Follow-up length 5 years with exception of one study (RENCI: 10-years). A 5-year estimate was calculated using PROFIT study as a control

Conventional versus hypofractionated RT: QoL outcomes over time – GRADE Table

N of studies	Sample size	Effect size (95% CI)	Absolute risk per 1,000 people		RoB	Inconsistency	Indirectness	Imprecision	Quality
			Control	Intervention (95% CI)					
Time to worsening of IPSS overall – HR <1 favours better outcomes associated with hypofractionated over time									
1	303	HR **0.90** (0.46, 1.78)	-	-	Very serious[1]	N/A	Not serious	Serious[2]	Very low
Time to worsening of IPSS Quality of life – HR <1 favours better outcomes associated with hypofractionated over time									
1	303	HR **1.47** (0.62, 3.48)	-	-	Very serious[1]	N/A	Not serious	Serious[2]	Very low
Time to worsening of urinary incontinence (EPIC) – HR<1 favours better outcomes associated with hypofractionated over time									
1	225	HR **1.91** (0.97, 3.76)	-	-	Very serious[1]	N/A	Not serious	Serious[2]	Very low
Time to worsening urinary irritative/obstructive (EPIC) – HR <1 favours better outcomes associated with hypofractionated over time									
1	225	HR **0.40** (0.10, 1.55)	-	-	Very serious[1]	N/A	Not serious	Serious[2]	Very low
Time to worsening sexual bother (EPIC) – HR <1 favours better outcomes associated with hypofractionated over time									
1	225	HR **2.27** (0.68, 4.91)	-	-	Very serious[1]	N/A	Not serious	Serious[2]	Very low
Time to worsening hormonal bother (EPIC) – HR <1 favours better outcomes associated with hypofractionated over time									
1	225	HR **1.22** (0.59, 2.55	-	-	Very serious[1]	N/A	Not serious	Serious[2]	Very low
Time to worsening bowel bother (EPIC) – HR <1 favours better outcomes associated with hypofractionated over time									
1	225	HR **0.77** (0.25, 2.36)	-	-	Very serious[1]	N/A	Not serious	Serious[2]	Very low
Time to worsening visual analogue scale scores (EQ5D) – HR <1 favours better outcomes associated with hypofractionated over time									
1	215	HR **1.61** (0.42, 6.18)	-	-	Very serious[1]	N/A	Not serious	Serious[2]	Very low
Time to worsening EQ5D Index scores – HR <1 favours better outcomes associated with hypofractionated over time									
1	215	HR **2.13** (0.60, 7.56)	-	-	Very serious[1]	N/A	Not serious	Serious[2]	Very low
Time to worsening of overall urinary bother – HR <1 favours better outcomes associated with hypofractionated over time									
1	1560 across all 3 arms	HR **1.03** (0.72, 1.48	-	-	Very serious[1,4]	N/A	Not serious	Serious[2]	Very low
		HR **0.85** (0.58, 1.24)	-	-	Very serious[1,4]	N/A	Not serious	Serious[2]	Very low
Time to worsening of overall bowel bother – HR <1 favours better outcomes associated with hypofractionated over time									
1	1762 across all 3 arms	HR **1.10** (0.80, 1.48)	-	-	Very serious[1,4]	N/A	Not serious	Serious[2]	Very low
		HR **0.90** (0.65, 1.24)	-	-	Very serious[1,4]	N/A	Not serious	Serious[2]	Very low
Time to worsening of overall sexual bother – HR <1 favours better outcomes associated with hypofractionated over time									

Study Reference

NG131 [C] (NICE 2019)
Linked records: Hoffman 2018; Wilkins 2015 (CHHiP)
Yin 2019 is an SLR that includes some of the same trials

1	997 across all 3 arms	HR **1.19** (0.92, 1.55)	-	-	Very serious[1,4]	N/A	Not serious	Serious[2]	Very low
		HR **1.14** (0.88, 1.48)	-	-	Very serious[1,4]	N/A	Not serious	Serious[2]	Very low

[1] Blinding was not attempted/possible and this had a high risk of biasing the outcome, there is also variability between questionnaires in response rate.
[2] 95% confidence intervals for the effect size crossed the line of no effect – downgraded once

EBRT alone vs EBRT plus LDR-BT: survival and AE outcomes – GRADE Table

N of studies	Sample size	Effect size (95% CI)	Absolute risk per 1,000 people		RoB	Inconsistency	Indirectness	Imprecision	Quality
			Control	Intervention (95% CI)					
Time to biochemical failure – HR >1 favours brachytherapy									
1	398	HR **2.04*** (1.25, 3.33)	-	-	Not serious	N/A	Not serious	Not serious	High
Time to any-cause death – HR >1 favours brachytherapy									
1	398	HR **1.13**** (0.69, 1.85)	-	-	Not serious	N/A	Not serious	Serious[2]	Moderate
Freedom from prostate cancer-related death – RR >1 favours brachytherapy									
1	398	RR **1.02** (0.98, 1.06)	945	948 (–7 to +5)	Not serious	N/A	Not serious	Not serious	High
Acute GU toxicity – RR <1 favours brachytherapy									
1	383	RR **2.24** (1.55, 3.23)	164	368 (–114 to +162)	Serious[1]	N/A	Not serious	Not serious	Moderate
Acute GI toxicity – RR <1 favours brachytherapy									
1	383	RR **1.01** (0.82, 1.25)	143	145 (–26 to +35)	Serious[1]	N/A	Not serious	Not serious	Moderate
5-year urinary toxicity: Usage of pads – RR < favours brachytherapy									
1	383	RR **2.95** (1.58, 5.51)	60	177 (–82 to +153)	Serious[1]	N/A	Not serious	Not serious	Moderate
5-year catheterization – RR <1 favours brachytherapy									
1	383	RR **3.70** (1.53, 8.94)	30	111 (–65 to +157)	Serious[1]	N/A	Not serious	Not serious	Moderate
Time to grade 2 late GU toxicity – HR >1 favours brachytherapy									
1	383	HR **0.51** (0.33, 0.77)	-	-	Serious[1]	N/A	Not serious	Not serious	Moderate
Time to grade 2 late GI toxicity – HR >1 favours brachytherapy									
1	383	HR **0.75** (0.48, 1.17)	-	-	Serious[1]	N/A	Not serious	Serious[2]	Low

[1] Blinding procedures were not possible/attempted and this had the potential to impact on the reporting and/or scoring of this outcome
[2] 95% confidence intervals crosses the line of no effect – downgraded once
*Taken from multivariate analysis controlling for log pre-treatment PSA, percentage of positive cores, clinical T stage, and Gleason sum: HR 2.17 in univariate analysis.
**Taken from multivariate analysis controlling for age, disease status (relapse vs. no relapse) and log pre-treatment PSA: HR 1.29 in univariate analysis.

Quality Assessment

Quality assessment of included studies (risk of bias)

Short title	Randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias	Overall risk of bias	Directness

Study Reference

NG131 [C] (NICE 2019)
Linked records: Hoffman 2018; Wilkins 2015 (CHHiP)
Yin 2019 is an SLR that includes some of the same trials

Alwuni 2016	Low	Unclear	High	Unclear	Low	Low	Low	Moderate	Directly applicable
Catton 2017	Low	Unclear	Unclear	Unclear	Low	Low	Low	Moderate	Directly applicable
Dearnaley 2016	Low	High	High	Unclear	Low	Low	Low	Moderate	Directly applicable
Lee 2016	Low	Unclear	Unclear	Unclear	Low	Low	Low	Moderate	Directly applicable
Marzi 2009	Low	Unclear	Unclear	Unclear	Low	Low	High	High*	Partially directly applicable
Morris 2017	Low	Unclear	Unclear	Unclear	Low	Low	Low	Moderate	Directly applicable
Norkus 2009	Low	Unclear	Unclear	Unclear	Low	Low	Low	Moderate	Directly applicable
Norkus 2013	Low	Unclear	Unclear	High	Low	Low	Low	High*	Partially directly applicable
Pollack 2013	Low	Unclear	Unclear	Unclear	High	Low	Low	High*	Directly applicable
Arcangeli 2010	Not included in evidence table								
Hoffman 2014	Not included in evidence table								

*The three studies at an overall high risk of bias were graded as such because it was judged that there was potential for all outcomes of interest to be impacted by lack of blinding procedures

Authors' Conclusions

Evidence Statements

Conventional vs hypofractionated RT

- Low- to high-quality evidence from up to 10 RCTs reporting data on up to 7,050 people with localised PCa shows there is no difference in overall freedom from biochemical or biochemical–clinical failure, overall freedom from PCa-related death, OS, late GU and GI toxicity, and acute GU toxicity between people receiving hypofractionated RT and those receiving conventional RT.
- Low- to moderate-quality evidence from up to 6 RCTs reporting data on up to 6,621 people with localised PCa could not differentiate time to biochemical or biochemical–clinical failure, time to death from any causes or time to PCa-related death between people receiving hypofractionated RT and those receiving conventional RT.
- Moderate-quality evidence from 9 RCTs reporting data on 5,709 people with localised PCa found higher rates of people reporting grade 2 or worse acute GI toxicity in people receiving hypofractionated RT than those receiving conventional RT.
- Very low-quality evidence from up to 5 RCTs reporting data on up to 303 people with localised PCa could not differentiate time to worsening of QoL (on any sub-domain), or rates of worsening QoL (on any sub-domain) between hypofractionated and conventional RT.

EBRT vs EBRT plus LDR-BT

- High-quality evidence from 1 RCT reporting data on 398 people with localised PCa found a greater length of time to biochemical failure in people given EBRT with a LDR-BT boost than those given EBRT alone.
- Moderate-quality evidence from 1 RCT reporting data on 398 people with localised PCa found a greater length of time to grade 2 late GU toxicity and lower rates of acute GU toxicity, 5-year catheterization and 5-year usage of pads for urinary incontinence in people given EBRT alone than in those people given EBRT with a LDR-BT boost.

Study Reference	**NG131 [C] (NICE 2019)** Linked records: Hoffman 2018; Wilkins 2015 (CHHiP) Yin 2019 is an SLR that includes some of the same trials
	• Moderate- to high- quality evidence from 1 RCT reporting data on 398 people with localised PCa found no difference in acute GU toxicity or freedom-from PCa-related death between those given EBRT alone and those given EBRT with a LDR-BT boost. • Low- to moderate- quality evidence from 1 RCT reporting data on 398 people with localised PCa could not differentiate time to grade 2 late GI toxicity or death from any cause between those given EBRT alone and those given EBRT with a LDR-BT boost. NG131 Recommendations for Treatment **Low-risk localised PCa:** AS, radical prostatectomy or radical RT **Intermediate-risk localised PCa:** radical prostatectomy or radical RT (consider AS for people who do not choose to have immediate radical treatment) **High-risk localised PCa:** radical prostatectomy or radical RT (do not offer AS)
Additional results/ conclusions published after NG131 or not included in NG131	**Hoffman 2018** Follow up Results reported up to 5 years of follow-up Results (summary) No significant results were reported for the comparison of conventional (n=101) and hypofractionated (n=101) RT for comparison of urinary, bowel and sexual function and change in urinary, bowel and sexual function from baseline, at any follow-up points (2, 3, 4, 5 years) Author's conclusions • In conclusion, it seems that dose-escalated IMRT using a moderate hypofractionation regimen (72.0 Gy in 2.4 Gy fractions) can be delivered safely without adversely impacting urinary or bowel function from the patient's perspective. However, it is possible that insufficient data were collected to detect clinically meaningful differences between the treatment groups. • Patient-reported function provided more detail and insight about patient experience after prostate radiation than the physician-assigned numeric toxicity score. • Additional research is needed to determine whether hypofractionated radiation adversely impacts long-term sexual function from the patient's perspective relative to conventional fractionation.

Abbreviations: 3DCRT, 3-dimensional conformal radiation therapy; ADT, androgen deprivation therapy; AE, adverse event; AR, absolute risk; AS, active surveillance; CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CI, confidence interval; DARE, Database of Abstracts of Reviews of Effects; DFS, disease-free survival; EBRT, external beam radiation therapy; EORTC, European Organisation for Research and Treatment of Cancer; EPIC, Expanded Prostate Cancer Index Composite; EQ-5D, EuroQol 5 Dimension; fr, fractions; GI, gastrointestinal; GRADE, Grading of Recommendations Assessment, Development and Evaluation; GU, genitourinary; HR, hazard ratio; HRQoL, health-related quality of life; HTA, Health Technology Assessment; IMRT, intensity-modulated radiation therapy; IPSS, International Prostate Symptom Score; IQR, interquartile range; ITT, intention-to-treat; LDR-BT, low dose rate brachytherapy; LENT, Late Effects Normal Tissue; LTFU, loss-to-follow-up; MA, meta-analysis; N/A, not applicable; OS, overall survival; PCa, prostate cancer; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PS, performance score; PSA, prostate-specific antigen; QoL, quality of life; RCT, randomised controlled trial; RoB, risk of bias; RR, risk ratio; RT, radiotherapy/radiation therapy; RTOG, Radiation Therapy Oncology Group; WHO, World Health Organization.

Table 41b. NG131 [G] (NICE 2019): Observation, radical prostatectomy or radical radiotherapy

Study Reference

NG131 [G] (NICE 2019)
Linked records: Bill-Axelson 2018 (SPCG04 trial); Johansson 2018 (SPCG-4 trial); Lane 2016 (ProtecT trial); Lane 2014 (ProtecT trial)
Ng 2019 is an SLR that includes the same trials

Study Design

Study name
Included in SLR: PIVOT, SPCG-4, ProtecT

Design
Systematic literature review

Objective
To determine the clinical and cost-effectiveness of AS, radical prostatectomy or radical RT compared to each other for people with localised PCa

Search dates
2007–March 2018

Country
N/A

Setting
N/A

Population Characteristics

Study eligibility

Inclusion (PICOS)

Population	People with localised PCa
Intervention	AS (also referred to as observation) Radical RT (alone or in combination with brachytherapy) Radical prostatectomy
Comparator	Relevant interventions compared to each other Alternative protocols within the intervention class (e.g. different AS approaches compared to each other)
Outcomes	PCa-specific mortality Treatment-related mortality Metastasis-free survival HRQoL (including separate reporting of psychological aspects) Treatment-related morbidity e.g. late effects of radiation therapy, toxicity Number of severe AEs (incontinence, erectile dysfunction) Number of treatment discontinuations due to AEs
Study design	RCTs Systematic reviews of RCTs

Exclusion (reasons given in excluded study list)

- Study did not contain relevant interventions
- Study did not contain a population of localised PCa
- Comparator did not match that specified in the protocol
- Conference abstract
- Data not reported in an extractable format
- Not a relevant study design (e.g. discussion of one of the included trials, protocol, commentary)

Study Reference

NG131 [G] (NICE 2019)
Linked records: Bill-Axelson 2018 (SPCG04 trial); Johansson 2018 (SPCG-4 trial); Lane 2016 (ProtecT trial); Lane 2014 (ProtecT trial)
Ng 2019 is an SLR that includes the same trials

- Duplicate reference
- Non-systematic review article
- Study did not report outcomes of interest

Other
The review was conducted as part of a larger update of the NICE Prostate Cancer guideline (CG175)

Flow of Studies (PRISMA)
Titles/abstracts reviewed = 8,337
Full texts reviewed = 144
Articles included = 13 articles on 3 unique RCTs

Included study characteristics

Short title and related studies	Study type	Location and setting	Dates and duration of follow-up	Inclusion criteria	Exclusion criteria	Sample characteristics	Interventions	Outcomes
Observation (active surveillance) vs radical RT vs radical prostatectomy								
Donovan 2016 (ProtecT) Hamdy 2016	RCT	Country: UK Setting: Primary care centres in 9 cities	Oct 2001–Jan 2009 Follow-up: Median 10 years	Estimated life expectancy >10 years Localised PCa Negative results for metastatic disease Age 50–69	Any previous malignancy apart from skin cancer Previous renal transplant or on renal dialysis Major CV or respiratory comorbidities Bilateral hip replacement PSA >20 ng/mL	N: 2,664 (1,634 randomised; Arm1: 545, Arm 2: 545, Arm 3: 553) LTFU: 55 (3.3%) Median age (IQR): Arm 1: 62 (50–69) Arm 2: 62 (49–69) Arm 3: 62 (50–69) Median PSA (range) Arm 1: 4.6 (3.0–20.9) ng/mL Arm 2: 4.6 (3.0–18.8) ng/mL Arm 3: 4.7 (3.0–18.4) Tumour stage, n (%) Arm 1: T1c = 410 (75%), T2 = 135 (25%) Arm 2: T1c = 429 (79%), T2 = 116 (21%) Arm 3: T1c = 410 (74%), T2 = 143 (26%)	Arm 1: active monitoring Arm 2: RT Arm 3: radical prostatectomy	Overall mortality PCa-specific mortality Distant metastases Urinary incontinence Erectile and sexual dysfunction Lower urinary tract symptoms Effect of urinary function on QoL Effect of sexual function on QoL Bowel function Effect of bowel function on QoL General health status Anxiety and depression Cancer-related QoL
Prostatectomy vs observation (watchful waiting)								
Holmberg 2002 (SPCG-4)	RCT	Country: Sweden, Finland, Iceland	Oct 1989–Feb 1999 Follow-up:	Age <75 Primary, previously untreated	NR	N: 695 (Arm 1: 347, Arm 2: 348) LTFU: 0 Mean age (SD):	Arm 1: radical prostatectomy	Overall mortality PCa-specific mortality Distant metastases

Study Reference	**NG131 [G] (NICE 2019)** Linked records: Bill-Axelson 2018 (SPCG04 trial); Johansson 2018 (SPCG-4 trial); Lane 2016 (ProtecT trial); Lane 2014 (ProtecT trial) Ng 2019 is an SLR that includes the same trials								
	Bill-Axelson 2008 Bill-Axelson 2011 Bill-Axelson 2013 Bill-Axelson 2014 Bill-Axelson 2009 Johansson 2011 Steineck 2002 Bill-Axelson 2005		Setting: 14 centres	18 years (across multiple publications)	adenocarcinoma of the prostate Stage T0d, T1 or T2 (T1c after 1994) Estimated life expectancy <10 years Localised PCa PSA <50 ng/mL Negative results for metastatic disease		Arm 1: 64.7 (5.1) Arm 2: 64.7 (5.1) Mean PSA Arm 1: 13.5 ng/mL Arm 2: 12.3 ng/mL Tumour stage, n (%) Arm 1: T1b = 33 (9.5), T1c = 43 (12.4), T2 = 270 (77.8), unknown = 1 (0.3) Arm 2: T1b = 50 (14.4), T1c = 38 (10.9), T2 = 259 (74.4), unknown = 1 (0.3)	Arm 2: watchful waiting	Urinary incontinence Erectile and sexual dysfunction Weak urinary system Nocturia QoL
	Wilt 2012 (PIVOT) Wilt 2017	RCT	Country: USA Setting: Department of Veterans Affairs and National Cancer Institute medical centres	Nov 1994–Jan 2002 Follow-up: 12–19.5 years (in most recent study)	Age <75 Estimated life expectancy >10 years Localised PCa Diagnosed within previous 12 months PSA <50 ng/mL Negative results for metastatic disease	NR	N: 731 (Arm 1: 367, Arm 2: 364) LTFU: NR Mean age (SD): 67 Mean PSA: 7.8 ng/mL	Arm 1: radical prostatectomy Arm 2: observation	Overall mortality PCa-specific mortality Distant metastases PSA progression AEs requiring treatment Urinary incontinence Erectile and sexual dysfunction Worry about health 'Bother' due to PCa Physical discomfort Functional limitations Bowel function
Methods	Searches Sources searched: • CDSR (Wiley), CENTRAL (Wiley), DARE (Wiley), EMBASE (Ovid), MEDLINE (Ovid), MEDLINE In-Process (Ovid) Screening and selection process NR								

Study Reference

NG131 [G] (NICE 2019)
Linked records: Bill-Axelson 2018 (SPCG04 trial); Johansson 2018 (SPCG-4 trial); Lane 2016 (ProtecT trial); Lane 2014 (ProtecT trial)
Ng 2019 is an SLR that includes the same trials

Study quality assessment
Cochrane Risk of Bias Tool

Methods for combining intervention evidence
MAs of the interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins *et al.*, 2011)

- Continuous data: MA conducted on the mean difference (first converted to the same scale if necessary or using standardised mean differences if outcomes were measured using different instruments/metrics)
- Dichotomous data: pooled RR and AR (by applying the RR to the pooled risk in the comparator arm of the MA)
- Fixed and random-effects (der Simonian and Laird) models were fitted for all syntheses
- Significant heterogeneity between studies was identified and recorded by the reviewer in advance of conducting the analysis
- In any MA where some data came from studies at high RoB, sensitivity analyses were conducted to exclude those studies from the analysis
- GRADE was used to assess the quality of evidence for the selected outcomes

Harms and Benefits of Interventions and Quality Assessment of Included Studies

Forest plot data

Radical prostatectomy vs AS

RR/HR >0 or MD >1 favours observation (AS)

Outcome	Follow-up length	Study	Radical prostatectomy		AS/observation		Weight (%)	Effect size (95% CI)	Heterogeneity	Z score
			Total N	Events (n)	Total N	Events (n)		RR		
Number of severe AEs for **incontinence**	6 months	ProtecT	476	338	459	179	100.0	1.82 (1.60, 2.07)	N/A	9.18 (P<0.00001)
	2 years		468	313	453	204	100.0	1.49 (1.32, 1.67)	N/A	6.46 (P<0.00001)
	4 years		462	332	463	227	100.0	1.47 (1.31, 1.63)	N/A	6.87 (P<0.00001)
	6 years		463	318	451	226	100.0	1.37 (1.23, 1.53)	N/A	5.58 (P<0.0001)
Number of severe AEs for **erectile dysfunction**	6 months	ProtecT	359	316	375	202	100.0	1.63 (1.48, 1.81)	N/A	9.52 (P<0.00001)
	2 years		391	317	378	200	100.0	1.53 (1.38, 1.70)	N/A	7.86 (P<0.00001)
	4–5 years		447	357	442	309	100.0	1.14 (1.06, 1.23)	N/A	3.40 (P=0.0007)
	6–8 years		461	385	452	318	100.0	1.19 (1.10, 1.28)	N/A	4.65 (P<0.00001)
Moderate/severe impact on QoL	6 months	ProtecT	573	93	464	18	100.0	4.18 (2.56, 6.83)	N/A	5.73 (P<0.0001)
	3 years		465	56	473	32	100.0	1.78 (1.18, 2.70)	N/A	2.72 (P=0.006)

Study Reference

NG131 [G] (NICE 2019)
Linked records: Bill-Axelson 2018 (SPCG04 trial); Johansson 2018 (SPCG-4 trial); Lane 2016 (ProtecT trial); Lane 2014 (ProtecT trial)
Ng 2019 is an SLR that includes the same trials

for **incontinence**	6 years		464	58	455	38	100.0	1.50 (1.02, 2.21)	N/A	2.04 (P=0.04)
Moderate/severe impact on QoL for **sexual dysfunction**	6 months	ProtecT	355	226	328	91	100.0	2.29 (1.89, 2.78)	N/A	8.50 (P<0.00001)
	3 years		417	188	414	140	100.0	1.33 (1.12, 1.58)	N/A	3.29 (P=0.001)
	6 years		457	190	438	164	100.0	1.11 (0.94, 1.31)	N/A	1.26 (P=0.21)
Moderate/severe impact on QoL for **bowel habits**	6 months	ProtecT	362	12	348	11	100.0	1.05 (0.47, 2.35)	N/A	0.12 (P=0.91)
	3 years		439	9	439	11	100.0	0.82 (0.34, 1.95)	N/A	0.45 (P=0.65)
	6 years		467	12	463	16	100.0	0.74 (0.36, 1.55)	N/A	0.79 (P=0.43)
			Total N	Mean (SD)	Total N	Mean (SD)		Mean difference		
Treatment-related morbidity (EPIC scores) for **urinary function**	6 months	ProtecT	364	80.1 (16.6)	347	90.6 (10.7)	100.0	10.50 (8.46, 12.54)	N/A	10.07 (P<0.00001)
	3 years		433	87.9 (12.1)	433	89.3 (11.5)	100.0	1.40 (–0.17, 2.97)	N/A	1.75 (P=0.08)
	6 years		455	88.7 (11.3)	454	89 (12.5)	100.0	0.30 (–1.25, 1.85)	N/A	0.38 (P=0.70)
Treatment-related morbidity (EPIC scores) for **sexual dysfunction**	6 months	ProtecT	352	25.7 (23.9)	327	51.9 (27.9)	100.0	26.20 (22.30, 30.10)	N/A	13.18 (P<0.00001)
	3 years		413	33.9 (23.9)	413	45.9 (28.4)	100.0	12.00 (8.42, 15.58)	N/A	6.57 (P<0.00001)
	6 years		454	32.3 (23.2)	437	40.6 (26.7)	100.0	8.30 (5.01, 11.59)	N/A	4.95 (P<0.00001)
Treatment-related morbidity (EPIC scores) for **bowel function**	6 months	ProtecT	363	92.9 (9)	348	92.8 (9.1)	100.0	–0.10 (–1.43, 1.23)	N/A	0.15 (P=0.88)
	3 years		436	93.8 (8)	433	92.8 (10.8)	100.0	–1.00 (–2.26, 0.26)	N/A	1.55 (P=0.12)
	6 years		463	93.2 (8.7)	457	93 (9.8)	100.0	–0.20 (–1.40, 1.00)	N/A	0.33 (0.74)
Psychological aspects on QoL (HADS) for **anxiety**	1 year	ProtecT	485	4 (3.6)	467	3.9 (3.7)	100.0	–0.10 (–0.56, 0.36)	N/A	0.42 (P=0.67)
	3 years		470	3.7 (3.4)	474	3.9 (3.8)	100.0	0.20 (–0.26, 0.66)	N/A	0.85 (P=0.39)
	6 years		465	3.7 (3.5)	458	4.1 (3.9)	100.0	0.40 (–0.08, 0.88)	N/A	1.64 (P=0.10)
Psychological aspects on QoL (HADS) for **depression**	6 months	ProtecT	487	2.8 (3)	470	2.4 (3)	100.0	–0.40 (–0.78, –0.02)	N/A	2.06 (P=0.04)
	3 years		471	2.5 (2.8)	476	2.7 (3.2)	100.0	0.20 (–0.18, 0.58)	N/A	1.02 (P=0.31)
	6 years		459	2.7 (3.1)	464	3.1 (3.4)	100.0	0.40 (–0.02, 0.82)	N/A	1.87 (P=0.06)

Radical prostatectomy vs watchful waiting

RR/HR >0 or MD >1 favours observation (watchful waiting)

Study Reference

NG131 [G] (NICE 2019)
Linked records: Bill-Axelson 2018 (SPCG04 trial); Johansson 2018 (SPCG-4 trial); Lane 2016 (ProtecT trial); Lane 2014 (ProtecT trial)
Ng 2019 is an SLR that includes the same trials

Outcome	Follow-up length	Study	Radical prostatectomy		Watchful waiting		Weight (%)	Effect size (95% CI)	Heterogeneity	Z score*
			Total N	Events (n)	Total N	Events (n)		RR		
Number of people who developed **distant metastases**	6 years	SPCG-4	347	35	348	54	100.0	0.65 (0.44, 0.97)	N/A	2.12 (P=0.03)
	10 years		364	17	367	39	100.0	0.44 (0.25, 0.76)	N/A	2.93 (P=0.003)
	18 years		347	89	348	138	100.0	0.65 (0.52, 0.81)	N/A	3.86 (P=0.0001)
Number of severe AEs for **incontinence**	2–3 years	PIVOT SPCG-4 *Total*	287 52 339	49 22 71	284 53 337	18 6 24	75.3 24.7 100.0	2.69 (1.61, 4.51) 3.74 (1.65, 8.47) 2.95 (1.91, 4.56)	Chi^2=0.44 df=1 (P= 0.51) I^2=0%	4.88 (P<0.00001)
	4–5 years	SOCG-4	164	80	155	33	100.0	2.29 (1.63, 3.22)	N/A	4.77 (P<0.00001)
	6–8 years	SPCG-4	55	31	48	12	100.0	2.25 (1.31, 3.88)	N/A	2.94 (P=0.003)
	12+ years	PIVOT SPCG-4 *Total*	364 173 537	63 93 156	367 164 531	16 36 52	40.5 59.5 100.0	3.97 (2.34, 6.74) 2.45 (1.78, 3.37) 2.98 (1.85, 4.78)	Chi^2=2.44 df=1 (P= 0.12) I^2=59%	4.51 (P<0.00001)
Number of severe AEs for **erectile dysfunction**	2 years	SPCG-4 PIVOT *Total*	51 285 336	41 231 272	51 281 332	19 124 143	13.2 86.8 100.0	2.16 (1.47, 3.16) 1.84 (1.59, 2.12) 1.88 (1.64, 2.15)	Chi^2=0.60 df=1 (P= 0.44) I^2=0%	9.22 (P<0.00001)
	4–5 years	SPCG-4	161	129	158	71	100.0	1.78 (1.48, 2.15)	N/A	6.00 (P<0.00001)
	6–8 years	SPCG-4	54	45	53	29	100.0	1.52 (1.16, 2.00)	N/A	3.03 (P=0.002)
	12–18 years	SPCG-4 PIVOT *Total*	173 364 537	146 53 199	153 387 540	122 20 142	51.9 48.1 100.0	1.06 (0.96, 1.17) 2.82 (1.72, 4.62) 1.69 (0.50, 5.78)	Chi^2=23.72 df=1 (P<0.00001) I^2=96%	0.84 (P=0.40)
			log[HR] (SE)					HR		
Overall mortality	4 years	PIVOT	–0.3857 (0.2106)				100.0	0.68 (0.45, 1.03)	N/A	1.83 (P=0.07)
	6 years	SPCG-4	–0.1863 (0.1917)				100.0	0.83 (0.57, 1.21)	N/A	0.97 (P=0.33)
	8 years	PIVOT SPCG-4 *Total*	–0.1054 (0.121) –0.3011 (0.1422)				58.0 42.0 100.0	0.90 (0.71, 1.14) 0.74 (0.56, 0.98) 0.83 (0.69, 0.99)	Chi^2=1,10 df=1 (P= 0.29) I^2=9%	2.04 (P=0.04)
	10 years	PIVOT SPCG-4 *Total*	–0.1278 (0.1095) –0.1985 (0.1185)				53.9 46.1 100.0	0.88 (0.71, 1.09) 0.82 (0.65, 1.03) 0.85 (0.73, 1.00)	Chi^2=0.19 df=1 (P= 0.66) I^2=0%	1.99 (P=0.05)
	12–14 years	PIVOT SPCG-4 *Total*	–0.1278 (0.0816) –0.3425 (0.0945)				57.3 42.7 100.0	0.88 (0.75, 1.03) 0.71 (0.59, 0.85) 0.80 (0.71, 0.91)	Chi^2=2.96 df=1 (P=0.09) I^2=66%	3.55 (P=0.0004)
	16 years	PIVOT	–0.1165 (0.0608)				100.0	0.89 (0.79, 1.00)	N/A	1.92 (P=0.06)

Study Reference

NG131 [G] (NICE 2019)
Linked records: Bill-Axelson 2018 (SPCG04 trial); Johansson 2018 (SPCG-4 trial); Lane 2016 (ProtecT trial); Lane 2014 (ProtecT trial)
Ng 2019 is an SLR that includes the same trials

	18 years	SPCG-4	–0.3425 (0.0945)	100.0	0.71 (0.59, 0.85)	N/A	3.62 (P=0.0003)
PCa-specific mortality	4 years	PIVOT	0.01 (0.5707)	100.0	1.01 (0.33, 3.09)	N/A	0.02 (P=0.99)
	6 years	SPCG-4	–0.6931 (0.3144)	100.0	0.50 (0.27, 0.93)	N/A	2.20 (P=0.03)
	8 years	PIVOT SPCG-4 *Total*	–0.478 (0.3704) –0.5798 (0.2254)	27.0 73.0 100.0	0.62 (0.30, 1.28) 0.56 (0.36, 0.87) 0.58 (0.39, 0.84)	Chi^2=0.06 df=1 (P=0.81) $I^{2=0}$%	2.87 (P=0.004)
	12 years	PIVOT SPCG-4 *Total*	–0.6539 (0.2979) –0.4308 (0.1876)	28.4 71.6 100.0	0.52 (0.29, 0.93) 0.65 (0.45, 0.94) 0.61 (0.45, 0.83)	Chi^2=0.40 df=1 (P=0.53) I^2=0%	3.11 (P=0.002)
	16 years	PIVOT	–0.5108 (0.2467)	100.0	0.60 (0.37, 0.97)	N/A	2.07 (P=0.04)
	18 years	SPCG-4	–0.5798 (0.1591)	100.0	0.56 (0.41, 0.76)	N/A	3.64 (P=0.0003)
Disease progression	6.2 years 12–19.5 years	SPCG-4 PIVOT *Total*	–1.1712 (0.175) –0.821 (0.1787)	51.0 49.0 100.0	0.31 (0.22, 0.44) 0.44 (0.31, 0.62) 0.37 (0.29, 0.47)	Chi^2=1.96 df=1 (P=0.16) I^2=49%	8.00 (P<0.00001)

Radical RT vs AS

RR/HR >0 or MD >1 favours observation (AS)

Outcome	Follow-up length	Study	RT		AS		Weight (%)	Effect size (95% CI)	Heterogeneity	Z score*
			Total N	Events (n)	Total N	Events (n)		RR		
Number of severe AEs for **erectile dysfunction**	1 year	ProtecT	338	263	375	202	100.0	1.44 (1.29, 1.61)	N/A	6.58 (P<0.00001)
	3 years		420	277	421	248	100.0	1.12 (1.01, 1.24)	N/A	2.10 (P=0.04)
	6 years		456	331	452	318	100.0	1.03 (0.95, 1.12)	N/A	0.74 (P=0.46)
Moderate/severe impact on QoL for **incontinence**	6 months	ProtecT	474	27	464	18	100.0	1.47 (0.82, 2.63)	N/A	1.29 (P=0.20)
	3 years		460	17	473	32	100.0	0.55 (0.31, 0.97)	N/A	2.06 (P=0.04)
	6 years		458	21	455	38	100.0	0.55 (0.33, 0.92)	N/A	2.27 (P=0.02)
Moderate/severe impact on QoL for **sexual dysfunction**	6 months	ProtecT	334	152	328	91	100.0	1.64 (1.33, 2.02)	N/A	4.61 (P<0.00001)
	3 years		418	153	414	140	100.0	1.08 (0.90, 1.30)	N/A	0.84 (P=0.40)
	6 years		448	150	438	164	100.0	0.89 (0.75, 1.07)	N/A	1.23 (P=0.22)
Moderate/severe impact on QoL for **bowel habits**	6 months	ProtecT	345	36	348	11	100.0	3.30 (1.71, 6.38)	N/A	3.55 (P=0.0004)
	3 years		432	20	439	11	100.0	1.85 (0.90, 3.81)	N/A	1.66 (P=0.10)
	6 years		472	10	463	16	100.0	0.61 (0.28, 1.34)	N/A	1.23 (P=0.22)
			Total N	Mean (SD)	Total N	Mean (SD)		Mean difference		
Treatment-related morbidity (EPIC scores) for **urinary function**	6 months	ProtecT	343	84.7 (13.8)	347	90.6 (10.7)	100.0	5.90 (4.06, 7.74)	N/A	6.27 (P<0.00001)
	3 years		425	91.7 (9.2)	433	89.3 (11.5)	100.0	–2.40 (–3.79, –1.01)	N/A	3.38 (P=0.0007)
	6 years		452	91.4 (9.2)	454	89 (12.5)	100.0	–2.40 (–3.83, –0.97)	N/A	3.29 (P=0.001)

Study Reference

NG131 [G] (NICE 2019)
Linked records: Bill-Axelson 2018 (SPCG04 trial); Johansson 2018 (SPCG-4 trial); Lane 2016 (ProtecT trial); Lane 2014 (ProtecT trial)
Ng 2019 is an SLR that includes the same trials

Treatment-related morbidity (EPIC scores) for **sexual dysfunction**	6 months	ProtecT	329	31.9 (27.1)	327	51.9 (27.9)	100.0	20.00 (15.79, 24.21)	N/A	9.31 (P<0.00001)
	3 years		414	42.5 (25.9)	413	45.9 (28.4)	100.0	3.40 (–0.30, 7.10)	N/A	1.80 (P=0.07)
	6 years		440	41.3 (24.9)	437	40.6 (26.7)	100.0	–0.70 (–4.12, 2.72)	N/A	0.40 (P=0.69)
Treatment-related morbidity (EPIC scores) for **bowel function**	6 months	ProtecT	345	86.3 (16)	348	92.8 (9.1)	100.0	6.50 (4.56, 8.44)	N/A	6.57 (P<0.00001)
	3 years		430	90.8 (11.2)	433	92.8 (10.8)	100.0	2.00 (0.53, 3.47)	N/A	2.67 (P=0.008)
	6 years		466	91.2 (10.9)	457	93 (9.8)	100.0	1.80 (0.46, 3.14)	N/A	2.64 (P=0.008)
Psychological aspects on QoL (HADS) for **anxiety**	6 months	ProtecT	467	3.9 (3.7)	476	4 (3.6)	100.0	–0.10 (–0.57, 0.37)	N/A	0.42 (P=0.67)
	3 years		474	3.9 (3.8)	466	3.7 (3.5)	100.0	0.20 (–0.27, 0.67)	N/A	0.84 (P=0.40)
	6 years		458	4.1 (3.9)	465	3.4 (3.2)	100.0	0.70 (0.24, 1.16)	N/A	2.98 (P=0.003)
Psychological aspects on QoL (HADS) for **depression**	6 months	ProtecT	478	2.7 (3)	470	2.4 (3)	100.0	–0.30 (–0.68, 0.08)	N/A	1.54 (P=0.12)
	3 years		467	2.7 (3)	476	2.7 (3.2)	100.0	0.00 (–0.40, 0.40)	N/A	0.00 (P=1.00)
	6 years		464	2.7 (2.9)	464	3.1 (3.4)	100.0	0.40 (–0.01, 0.81)	N/A	1.93 (P=0.05)

Radical prostatectomy vs radical RT

RR/HR >0 or MD >1 favours RT

Outcome	Follow-up length	Study	Prostatectomy		RT		Weight (%)	Effect size (95% CI)	Heterogeneity	Z score*
			Total N	Events (n)	Total N	Events (n)		RR		
Number of severe AEs for **erectile dysfunction**	1 year	ProtecT	356	304	351	219	100.0	1.37 (1.25, 1.50)	N/A	6.69 (P<0.00001)
	3 years		427	338	420	277	100.0	1.20 (1.10, 1.31)	N/A	4.25 (P<0.0001)
	6 years		461	385	456	331	100.0	1.15 (1.07, 1.23)	N/A	3.96 (P<0.0001)
Moderate/severe impact on QoL for **incontinence**	3 months	ProtecT	573	93	460	17	100.0	4.39 (2.66, 7.26)	N/A	5.77 (P<0.00001)
	3 years		465	56	458	21	100.0	2.63 (1.62, 4.26)	N/A	3.91 (P<0.0001)
	6 years		464	58	464	58	100.0	1.00 (0.71, 1.41)	N/A	0.00 (P=1.00)
Moderate/severe impact on QoL for **sexual dysfunction**	6 months	ProtecT	355	226	418	153	100.0	1.74 (1.50, 2.02)	N/A	7.30 (P<0.00001)
	3 years		417	188	448	150	100.0	1.35 (1.14, 1.59)	N/A	3.47 (P=0.0005)
	6 years		457	190	457	190	100.0	1.00 (0.86, 1.17)	N/A	0.00 (P=1.00)
Moderate/severe impact on QoL for **bowel habits**	6 months	ProtecT	362	12	432	20	100.0	0.72 (0.35, 1.44)	N/A	0.93 (P=0.35)
	3 years		439	9	472	10	100.0	0.97 (0.40, 2.36)	N/A	0.07 (P=0.94)
	6 years		467	12	467	12	100.0	1.00 (0.45, 2.20)	N/A	0.00 (P=1.00)
			Total N	Mean (SD)	Total N	Mean (SD)		Mean difference		
Treatment-related morbidity	6 months	ProtecT	364	80.1 (16.6)	343	84.7 (13.8)	100.0	4.60 (2.35, 6.85)	N/A	4.02 (P<0.0001)

Study Reference

NG131 [G] (NICE 2019)
Linked records: Bill-Axelson 2018 (SPCG04 trial); Johansson 2018 (SPCG-4 trial); Lane 2016 (ProtecT trial); Lane 2014 (ProtecT trial)
Ng 2019 is an SLR that includes the same trials

(EPIC scores) for **urinary function**	3 years		433	87.9 (12.1)	425	91.7 (9.2)	100.0	3.80 (2.36, 5.24)	N/A	5.18 (P<0.00001)
	6 years		455	88.7 (11.3)	452	91.4 (9.2)	100.0	2.70 (1.36, 4.04)	N/A	3.95 (P<0.0001)
Treatment-related morbidity (EPIC scores) for **sexual dysfunction**	6 months	ProtecT	352	25.7 (23.5)	329	31.9 (27.1)	100.0	6.20 (2.38, 10.02)	N/A	3.18 (P=0.001)
	3 years		413	33.9 (23.9)	414	42.5 (25.9)	100.0	8.60 (5.20, 12.00)	N/A	4.96 (P<0.00001)
	6 years		454	32.3 (23.2)	440	41.3 (24.9)	100.0	9.00 (5.84, 12.16)	N/A	5.59 (P<0.00001)
Treatment-related morbidity (EPIC scores) for **bowel function**	6 months	ProtecT	363	92.9 (9)	345	86.3 (16)	100.0	–6.60 (–8.53, –4.67)	N/A	6.72 (P<0.00001)
	3 years		436	93.8 (8)	430	90.8 (11.2)	100.0	–3.00 (–4.30, –1.70)	N/A	4.53 (P<0.00001)
	6 years		463	93.2 (8.7)	466	91.2 (10.9)	100.0	–2.00 (–3.27, –0.73)	N/A	3.09 (P=0.002)
Psychological aspects on QoL (HADS) for **anxiety**	6 months	ProtecT	485	4 (3.6)	476	4 (3.6)	100.0	0.00 (–0.46, 0.46)	N/A	0.00 (P=1.00)
	3 years		470	3.7 (3.4)	466	3.7 (3.5)	100.0	0.00 (–0.44, 0.44)	N/A	0.00 (P=1.00)
	6 years		465	3.7 (3.5)	465	3.4 (3.2)	100.0	0.30 (–0.13, 0.73)	N/A	1.36 (P=0.17)
Psychological aspects on QoL (HADS) for **depression**	6 months	ProtecT	487	2.8 (3)	478	2.7 (3)	100.0	0.10 (–0.28, 0.48)	N/A	0.52 (P=0.60)
	3 years		471	2.5 (2.8)	467	2.7 (3)	100.0	–0.20 (–0.57, 0.17)	N/A	1.06 (P=0.29)
	6 years		459	2.7 (3.1)	464	2.7 (2.9)	100.0	0.00 (–0.39, 0.39)	N/A	0.00 (P=1.00)

GRADE Tables

Radical prostatectomy vs AS

N of studies	Sample size	Effect size (95% CI)	Absolute risk per 100 people		RoB	Inconsistency	Indirectness	Imprecision	Quality
			AS	Prostatectomy (95% CI)					
Overall survival – HR <1 favours radical prostatectomy group (10 year follow up)									
1	1643	HR 0.93 (0.65, 1.33)	-	-	Not serious	Not serious	N/A	Serious[1]	Moderate
Prostate cancer-specific survival – HR <1 favours radical prostatectomy group (10 year follow up)									
1	1643	HR 0.63 (0.21, 1.89)	-	-	Not serious	N/A	Not serious	Serious[1]	Moderate
Number of people who developed distant metastasis – RR <1 favours radical prostatectomy group (10 year follow up)									
1	1643	RR 0.39 (0.21, 0.73)	6.1 per 100	2.4 per 100 (1.3, 4.4)	Not serious	N/A	Not serious	Not serious	High
Disease Progression – HR <1 favours radical prostatectomy group									
1	1643	HR 0.39 (0.27, 0.56)	-	-	Not serious	N/A	Not serious	Not serious	High
Number of Severe Adverse Events: Incontinence – RR <1 favours radical prostatectomy group Subgroup analysis – 6 month, 2 year, 4 year, 6 year follow up									
1 	935 921	RR 1.82 (1.60, 2.07) RR 1.49 (1.32, 1.67)	38.9 45.0	71.0 (18.1, 46.8) 67.1 (59.4, 75.2)	Serious[2] Serious[2]	N/A N/A	Not serious Not serious	Not serious Not serious	Moderate Moderate

Study Reference

NG131 [G] (NICE 2019)
Linked records: Bill-Axelson 2018 (SPCG04 trial); Johansson 2018 (SPCG-4 trial); Lane 2016 (ProtecT trial); Lane 2014 (ProtecT trial)
Ng 2019 is an SLR that includes the same trials

	925	RR 1.47 (1.31, 1.63)	49.0	72.1 (64.2, 79.9)	Serious[2]	N/A	Not serious	Not serious	Moderate
	914	RR 1.37 (1.23, 1.53)	50.1	68.7 (61.6, 76.7)	Serious[2]	N/A	Not serious	Serious[3]	Low
Number of Severe Adverse Events: Erectile dysfunction – RR <1 favours radical prostatectomy group Subgroup analysis – 1 year, 2 year, 4 year, 6 year follow up									
1	1643	RR 1.63 (1.48, 1.81)	53.9	87.8 (79.7, 97.4)	Serious[2]	N/A	Not serious	Not serious	Moderate
	1643	RR 1.53 (1.38, 1.70)	52.9	81.0 (73.0, 89.9)	Serious[2]	N/A	Not serious	Not serious	Moderate
	1643	RR 1.14 (1.06, 1.23)	69.9	79.7 (74.1, 86.0)	Serious[2]	N/A	Not serious	Not serious	Moderate
	1643	RR 1.19 (1.10, 1.28)	70.4	83.7 (77.4, 90.1)	Serious[2]	N/A	Not serious	Serious[3]	Low
Treatment-related morbidity (EPIC summary scores): Urinary function – MD <0 favours radical prostatectomy group Subgroup analysis – 6 month, 3 year, 6 year follow up									
1	711	MD 10.50 (8.46, 12.54)	-	-	Serious[2]	N/A	Not serious	Not serious	Moderate
	866	MD 1.40 (-0.17, 2.97)	-	-	Serious[2]	N/A	Not serious	Not serious	Moderate
	909	MD 0.30 (-1.25, 1.85)	-	-	Serious[2]	N/A	Not serious	Not serious	Moderate
Treatment-related morbidity (EPIC summary scores): Erectile dysfunction – MD <0 favours radical prostatectomy group Subgroup analysis – 6 month, 3 year, 6 year follow up									
1	679	MD 26.20 (22.30, 30.10)	-	-	Serious[2]	N/A	Not serious	Not serious	Moderate
	826	MD 12.00 (8.42, 15.58)	-	-	Serious[2]	N/A	Not serious	Serious[3]	Low
	891	MD 8.30 (5.01, 11.59)	-	-	Serious[2]	N/A	Not serious	Serious[3]	Low
Treatment-related morbidity (EPIC summary scores): Bowel function – MD <0 favours radical prostatectomy group Subgroup analysis – 6 month, 3 year, 6 year follow up									
1	711	MD 0.10 (-1.43, 1.23)	-	-	Serious[2]	N/A	Not serious	Not serious	Moderate
	869	MD -1.00 (-2.26, 0.26)	-	-	Serious[2]	N/A	Not serious	Not serious	Moderate
	920	MD -0.20 (-1.40, 1.00)	-	-	Serious[2]	N/A	Not serious	Not serious	Moderate
Moderate/severe impact of treatment on QoL (incontinence) – RR >1 favours radical prostatectomy group Subgroup analysis – 6 month, 3 year, 6 year follow up									
1	1037	RR 4.18 (2.56, 6.83)	3.8	16.2 (9.9, 26.5)	Serious[2]	N/A	Not serious	Not serious	Moderate
	938	RR 1.78 (1.18, 2.70)	6.8	12.0 (7.9, 18.2)	Serious[2]	N/A	Not serious	Serious[3]	Low
	919	RR 1.50 (1.02, 2.21)	12.5	18.8 (12.8, 27.6)	Serious[2]	N/A	Not serious	Serious[3]	Low
Moderate/severe impact of treatment on quality of life (erectile dysfunction) – RR >1 favours radical prostatectomy group Subgroup analysis – 6 month, 3 year, 6 year follow up									
1	683	RR 2.29 (1.89, 2.78)	27.7	63.5 (52.4, 77.1)	Serious[2]	N/A	Not serious	Not serious	Moderate
	831	RR 1.33 (1.12, 1.58)	33.8	44.9 (37.9, 53.4)	Serious[2]	N/A	Not serious	Serious[3]	Low
	895	RR 1.11 (0.94, 1.31)	37.4	41.6 (35.1, 49.1)	Serious[2]	N/A	Not serious	Serious[3]	Low
Moderate/severe impact of treatment on quality of life (bowel habits) – RR >1 favours radical prostatectomy group Subgroup analysis – 6 month, 3 year, 6 year follow up									
1	710	RR 1.05 (0.47, 2.35)	3.16	3.32 (1.49, 7.43)	Serious[2]	N/A	Not serious	Very serious[4]	Very low
	878	RR 0.82 (0.34, 1.95)	2.51	2.05 (8.52, 4.89)	Serious[2]	N/A	Not serious	Very serious[4]	Very low
	930	RR 0.74 (0.36, 1.55)	2.57	1.90 (0.92, 3.98)	Serious[2]	N/A	Not serious	Serious[3]	Low
Cancer-specific quality of life: Global health status – MD <0 favours radical prostatectomy group									
1	1643	MD -1.60 (-4.08, 0.88)	-	-	Serious[2]	N/A	Not serious	Very serious[4]	Very low
HADS Score: Anxiety – MD >0 favours radical prostatectomy group Subgroup analysis – 1 year, 3 year, 6 year follow up									
1	952	MD -0.10 (-0.56, 0.36)	-	-	Serious[2]	N/A	Not serious	Very serious[4]	Very low
	944	MD 0.20 (-0.26, 0.66)	-	-	Serious[2]	N/A	Not serious	Very serious[4]	Very low
	923	MD -0.40 (-0.08, 0.88)	-	-	Serious[2]	N/A	Not serious	Very serious[4]	Very low
HADS Score: Depression – MD >0 favours radical prostatectomy group Subgroup analysis – 1 year, 3 year, 6 year follow up									

Study Reference

NG131 [G] (NICE 2019)
Linked records: Bill-Axelson 2018 (SPCG04 trial); Johansson 2018 (SPCG-4 trial); Lane 2016 (ProtecT trial); Lane 2014 (ProtecT trial)
Ng 2019 is an SLR that includes the same trials

1	957	MD-0.40 (-0.78, -0.02)	-	-	Serious[2]	N/A	Not serious	Serious[3]	Low
	947	MD 0.20 (-0.18, 0.58)	-	-	Serious[2]	N/A	Not serious	Serious[3]	Low
	923	MD 0.40 (-0.02, 0.82)	-	-	Serious[2]	N/A	Not serious	Serious[3]	Low

[1] 95% confidence intervals crosses the line of no effect, downgraded once
[2] Moderate risk of bias – due to lack of participant blinding for patient-reported outcomes, downgraded once
[3] 95% confidence interval for the effect size crossed one line of the MID, downgraded once
[4] 95% confidence interval for the effect size crossed both lines of the MID, downgraded twice

Radical prostatectomy vs watchful waiting

N of studies	Sample size	Effect size (95% CI)	Absolute risk per 1,000 people		RoB	Inconsistency	Indirectness	Imprecision	Quality
			Watchful waiting	Prostatectomy (95% CI)					
Overall mortality – HR <1 favours radical prostatectomy group Subgroup analysis – 4 year, 6 year, 8 year, 12 year, 16 year, 18 year follow up									
1	731	HR 0.68 (0.45, 1.03)	-	-	Serious[1]	N/A	Not serious	Serious[2]	Low
1	698	HR 0.83 (0.57, 1.21)	-	-	Not serious	N/A	Not serious	Serious[2]	Moderate
2	1429	HR 0.83 (0.69, 0.99)	-	-	Serious[3]	Not serious	Not serious	Not serious	Moderate
2	1429	HR 0.86 (0.75, 0.98)	-	-	Serious[3]	Serious[4]	Not serious	Not serious	Low
1	731	HR 0.89 (0.79, 1.00)	-	-	Serious[1]	N/A	Not serious	Serious[2]	Low
1	698	HR 0.71 (0.59, 0.85)	-	-	Not serious	N/A	Not serious	Not serious	High
Prostate cancer-specific mortality – HR <1 favours radical prostatectomy group Subgroup analysis – 4 year, 6 year, 8 year, 12 year, 16 year, 18 year follow up									
1	731	HR 1.01 (0.33, 3.09)	-	-	Serious[1]	N/A	Not serious	Serious[2]	Low
1	698	HR 0.50 (0.27, 0.93)	-	-	Not serious	N/A	Not serious	Not serious	High
2	1429	HR 0.58 (0.39, 0.84)	-	-	Serious[1]	Not serious	Not serious	Not serious	Moderate
2	1429	HR 0.61 (0.45, 0.83)	-	-	Serious[1]	N/A	Not serious	Not serious	Moderate
1	731	HR 0.60 (0.37, 0.97)	-	-	Serious[1]	N/A	Not serious	Not serious	Moderate
1	698	HR 0.56 (0.41, 0.76)	-	-	Not serious	N/A	Not serious	Not serious	High
Number of people who developed distant metastasis – RR <1 favours radical prostatectomy group Subgroup analysis – 6 year, 10 year, 18 year follow up									
1	698	RR 0.65 (0.44, 0.97)	15.5	10.0 (6.8, 15.1)	Not serious	N/A	Not serious	Serious[4]	Moderate
1	731	RR 0.44 (0.25, 0.76)	10.6	4.7 (2.7, 8.1)	Serious[1]	N/A	Not serious	Not serious	Moderate
1	698	RR 0.65 (0.52, 0.81)	39.6	25.8 (20.6, 32.1)	Not serious	N/A	Not serious	Serious[4]	Moderate
Disease Progression – HR <1 favours radical prostatectomy group									
2	1429	HR 0.37 (0.29, 0.47)	-	-	Serious[1]	Not serious	Not serious	Not serious	Moderate
Number of Severe Adverse Events: Incontinence – RR <1 favours radical prostatectomy group Subgroup analysis – 2-3 year, 4-5 year, 6-8 year, 12 year follow up									
2	696	RR 2.95 (1.91, 4.56)	7.1	21.0 (13.6, 32.4)	Serious[1]	Not serious	Not serious	Not serious	Moderate
1	319	RR 2.29 (1.63, 3.22)	21.3	48.8 (34.7, 68.5)	Not serious	N/A	Not serious	Not serious	High
1	698	RR 2.25 (1.31, 3.88)	25	56.2 (32.7, 97.0)	Not serious	N/A	Not serious	Not serious	High
2	103	RR 2.98 (1.85, 4.78)	9.8	29.1 (18.1, 46.8)	Serious[1]	Serious[3]	Not serious	Not serious	Low
Number of Severe Adverse Events: Erectile dysfunction – RR <1 favours radical prostatectomy group Subgroup analysis – 2 year, 4-5 year, 6-8 year, 18 year follow up									

Study Reference

NG131 [G] (NICE 2019)
Linked records: Bill-Axelson 2018 (SPCG04 trial); Johansson 2018 (SPCG-4 trial); Lane 2016 (ProtecT trial); Lane 2014 (ProtecT trial)
Ng 2019 is an SLR that includes the same trials

2	668	RR 1.88 (1.64, 2.15)	48.3	83.6 (70.5, 99.5)	Serious[1]	Not serious	Not serious	Not serious	Moderate
1	319	RR 1.78 (1.48, 2.15)	45.0	80.0 (66.5, 96.6)	Not serious	N/A	Not serious	Not serious	High
1	108	RR 1.52 (1.16, 2.00)	68.7	89.3 (70.7, 100)	Not serious	N/A	Not serious	Serious[4]	Moderate
2	1097	RR 1.69 (0.50, 5.78)	26.3	44.4 (13.1, 100)	Serious[1]	Very serious	Not serious	Not serious	Very low
Number of people with moderate/high anxiety – RR <1 favours radical prostatectomy group Subgroup analysis – 4 year, 12 year follow up									
1	698	RR 0.74 (0.51, 1.07)	30.5	22.6 (15.6, 32.7)	Serious[5]	N/A	Not serious	Serious[4]	Very low
1	698	RR 1.01 (0.79, 1.10)	42.9	43.3 (33.9, 47.1)	Serious[5]	N/A	Not serious	Serious[4]	Very low
Number of people with moderate/high depression – RR <1 favours radical prostatectomy group Subgroup analysis – 4 year, 12 year follow up									
1	698	RR 0.91 (0.68, 1.21)	38.2	34.8 (25.9, 46.2)	Serious[5]	N/A	Not serious	Very serious[4]	Very low
1	698	RR 0.92 (0.74, 1.14)	51.6	47.4 (38.2, 58.8)	Serious[5]	N/A	Not serious	Serious[4]	Very low

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[3] 95% confidence interval for the effect size crossed one line of the MID, downgraded once
[4] 95% confidence interval for the effect size crossed both lines of the MID, downgraded twice

Radical RT vs AS

N of studies	Sample size	Effect size (95% CI)	Absolute risk per 1,000 people		RoB	Inconsistency	Indirectness	Imprecision	Quality
			AS	RT (95% CI)					
Overall mortality – HR <1 favours radical RT group									
1	1643	HR 0.94 (0.65, 1.36)	-	-	Not serious	N/A	Not serious	Serious[1]	Moderate
PCa-specific mortality – HR <1 favours radical RT group									
1	1643	HR 0.51 (0.15, 1.73)	-	-	Not serious	N/A	Not serious	Serious[1]	Moderate
Number of people who developed distant metastasis – RR <1 favours radical RT group									
1	1643	RR 0.48 (0.27, 0.87)	6.1	2.9 (1.6, 5.3)	Not serious	N/A	Not serious	Serious[3]	Moderate
Disease Progression – HR <1 favours radical RT group									
1	1643	HR 0.39 (0.27, 0.56)	-	-	Not serious	N/A	Not serious	Not serious	High
Number of Severe Adverse Events: Erectile dysfunction – RR <1 favours radical RT group Subgroup analysis – 6 month, 3 year, 6 year follow up									
1	713	RR 1.44 (1.29, 1.61)	53.8	77.6 (69.5, 86.7)	Not serious	N/A	Not serious	Not serious	High
1	841	RR 1.12 (1.01, 1.24)	58.9	65.9 (59.5, 73.0)	Not serious	N/A	Not serious	Not serious	High
1	908	RR 1.03 (0.95, 1.12)	70.3	72.5 (66.8, 78.8)	Not serious	N/A	Not serious	Not serious	High
Treatment-related morbidity (EPIC summary scores): Urinary function – MD <0 favours radical RT group Subgroup analysis – 6 month, 3 year, 6 year follow up									
1	690	MD 5.90 (7.74, 4.06)	-	-	Serious[4]	N/A	Not serious	Serious[6]	Very low
1	858	MD -2.40 (-1.01,-3.79)	-	-	Serious[4]	N/A	Not serious	Not serious	Low
1	906	MD -2.40 (-0.97,-3.83)	-	-	Serious[4]	N/A	Not serious	Not serious	Low
Treatment-related morbidity (EPIC summary scores): Sexual dysfunction – MD <0 favours radical RT group Subgroup analysis – 6 month, 3 year, 6 year follow up									

Study Reference

NG131 [G] (NICE 2019)
Linked records: Bill-Axelson 2018 (SPCG04 trial); Johansson 2018 (SPCG-4 trial); Lane 2016 (ProtecT trial); Lane 2014 (ProtecT trial)
Ng 2019 is an SLR that includes the same trials

1 1 1	656 827 877	MD 20.00 (24.21, 15.79) MD 3.40 (-0.30, 7.10) MD -0.70 (-4.12, 2.72)	- - -	- - -	Serious[4] Serious[4] Serious[4]	N/A N/A N/A	Not serious Not serious Not serious	Not serious Not serious Not serious	Low Low Low
Treatment-related morbidity (EPIC summary scores): Bowel function – MD <0 favours radical RT group Subgroup analysis – 6 month, 3 year, 6 year follow up									
1 1 1	693 863 923	MD 6.50 (4.56, 8.44) MD 2.00 (0.53, 3.47) MD 1.80 (0.46, 3.14)	- - -	- - -	Serious[4] Serious[4] Serious[4]	N/A N/A N/A	Not serious Not serious Not serious	Serious[7] Not serious Not serious	Very low Low Low
Moderate/severe impact of treatment on QoL (incontinence) – RR <1 favours radical RT group Subgroup analysis – 6 month, 3 year, 6 year follow up									
1 1 1	938 933 913	RR 1.47 (0.82, 2.63) RR 0.55 (0.31, 0.97) RR 0.55 (0.33, 0.92)	3.9 6.8 8.4	5.7 (3.2, 10.2) 3.7 (2.1, 6.6) 4.6 (2.8, 7.7)	Serious[4] Serious[4] Serious[4]	N/A N/A N/A	Not serious Not serious Not serious	Very serious[5] Serious[3] Serious[3]	Very low Very low Very low
Moderate/severe impact of treatment on QoL (sexual dysfunction) – RR >1 favours radical RT group Subgroup analysis – 6 month, 3 year, 6 year follow up									
1 1 1	662 432 936	RR 1.61 (1.33, 2.02) RR 1.08 (0.90, 1.30) RR 0.89 (0.75, 1.07)	27.7 33.8 37.4	45.5 (36.8, 56.0) 36.5 (30.4, 44.0) 33.3 (28.0, 40.1)	Serious[4] Serious[4] Serious[4]	N/A N/A N/A	Not serious Not serious Not serious	Not serious Serious[3] Serious[3]	Low Very low Very low
Moderate/severe impact of treatment on QoL (bowel function) – RR <1 favours radical RT group Subgroup analysis – 6 month, 3 year, 6 year follow up									
1 1 1	693 871 935	RR 3.30 (1.71, 6.38) RR 1.85 (0.90, 3.81) RR 0.61 (0.28, 1.34)	3.2 2.5 3.5	10.4 (5.4, 20.1) 4.6 (2.3, 9.6) 2.1 (0.97, 4.6)	Serious[4] Serious[4] Serious[4]	N/A N/A N/A	Not serious Not serious Not serious	Not serious Serious[3] Very serious[5]	Low Very low Very low
Cancer-specific QoL: Global health status – MD >0 favours radical RT group									
1	1643	MD 0.60 (-1.95, 3.15)	-	-	Serious[4]	N/A	Not serious	Very serious[5]	Very low
Psychological aspects of QoL (Hospital Anxiety & Depression Scores): Anxiety – MD >0 favours radical RT group Subgroup analysis – 6 month, 3 year, 6 year follow up									
1 1 1	943 940 923	MD -0.10 (-0.57, 0.37) MD 0.20 (-0.27, 0.67) MD 0.70 (-0.24, 1.16)	- - -	- - -	Serious[4] Serious[4] Serious[4]	N/A N/A N/A	Not serious Not serious Not serious	Very serious[5] Very serious[5] Very serious[5]	Very low Very low Very low
Psychological aspects of QoL (Hospital Anxiety & Depression Scores): Depression – MD >0 favours radical RT group Subgroup analysis – 6 month, 3 year, 6 year follow up									
1 1 1	948 943 928	MD -0.30 (-0.68,0.08) MD 0.00 (-0.40, 0.40) MD 0.40 (0.01, 0.81)	- - -	- - -	Serious[4] Serious[4] Serious[4]	N/A N/A N/A	Not serious Not serious Not serious	Serious[3] Very serious[5] Serious[3]	Very low Very low Very low

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[3] 95% confidence interval for the effect size crossed one line of the MID, downgraded once
[4] 95% confidence interval for the effect size crossed both lines of the MID, downgraded twice

Radical RT vs radical prostatectomy

N of studies	Sample size	Effect size (95% CI)	Absolute risk per 1,000 people		RoB	Inconsistency	Indirectness	Imprecision	Quality
			RT	Prostatectomy (95% CI)					

Study Reference

NG131 [G] (NICE 2019)
Linked records: Bill-Axelson 2018 (SPCG04 trial); Johansson 2018 (SPCG-4 trial); Lane 2016 (ProtecT trial); Lane 2014 (ProtecT trial)
Ng 2019 is an SLR that includes the same trials

PCa-specific mortality – HR <1 favours radical prostatectomy group									
1	1643	HR 0.80 (0.22, 2.91)	-	-	Not serious	N/A	Not serious	Serious[1]	Moderate
Number of people who developed distant metastasis – RR <1 favours radical prostatectomy group									
1	1643	RR 1.25 (0.61, 2.57)	2.9	3.7 (1.4, 6.0)	Not serious	N/A	Not serious	Very serious[4]	Low
Disease Progression – HR <1 favours radical prostatectomy group									
1	1643	HR 0.99 (0.67, 1.46)	8.4	8.3 (5.7, 12.3)	Not serious	N/A	Not serious	Very serious[4]	Low
Number of Severe Adverse Events: Erectile dysfunction – RR <1 favours radical prostatectomy group Subgroup analysis – 6 month, 3 year, 6 year follow up									
1	707	RR 1.37 (1.25, 1.50)	62.4.	85.5 (77.9, 93.6)	Not serious	N/A	Not serious	Serious[2]	Moderate
1	847	RR 1.20 (1.10, 1.31)	65.9	79.1 (72.5, 86.4)	Not serious	N/A	Not serious	Serious[2]	Moderate
1	918	RR 1.15 (1.07, 1.23)	72.6	83.5 (77.7, 89.2)	Not serious	N/A	Not serious	Not serious	High
Treatment-related morbidity (EPIC summary scores): Urinary function – MD <0 favours radical prostatectomy group Subgroup analysis – 6 month, 3 year, 6 year follow up									
1	709	MD 4.60 (2.35, 6.85)	-	-	Serious3	N/A	Not serious	Not serious	Moderate
1	878	MD 3.80 (2.36, 5.24)	-	-	Serious3	N/A	Not serious	Not serious	Moderate
1	907	MD 2.70 (1.36, 4.04)	-	-	Serious3	N/A	Not serious	Not serious	Moderate
Treatment-related morbidity (EPIC summary scores): Sexual dysfunction – MD <0 favours radical prostatectomy group Subgroup analysis – 6 month, 3 year, 6 year follow up									
1	681	MD 6.20 (2.38, 10.02)	-	-	Serious3	N/A	Not serious	Not serious	Moderate
1	827	MD 8.60 (5.20, 12.00)	-	-	Serious3	N/A	Not serious	Serious[5]	Moderate
1	894	MD 9.00 (5.84, 12.16)	-	-	Serious3	N/A	Not serious	Serious[5]	Moderate
Treatment-related morbidity (EPIC summary scores): Bowel function – MD <0 favours radical prostatectomy group Subgroup analysis – 6 month, 3 year, 6 year follow up									
1	698	MD -6.60 (-8.53,-4.67)	-	-	Serious3	N/A	Not serious	Serious[6]	Low
1	866	MD -3.00 (-4.30,-1.70)	-	-	Serious3	N/A	Not serious	Not serious	Moderate
1	929	MD -2.00 (-3.27,-0.73)	-	-	Serious3	N/A	Not serious	Not serious	Moderate
Moderate/severe impact of treatment on QoL (incontinence) – RR <1 favours radical prostatectomy group Subgroup analysis – 6 month, 3 year, 6 year follow up									
1	1033	RR 4.39 (2.66, 7.26)	3.7	16.2 (9.7, 26.8)	Serious3	N/A	Not serious	Not serious	Moderate
1	923	RR 2.63 (1.62, 4.26)	4.6	12.1 (7.43, 19.5)	Serious3	N/A	Not serious	Not serious	Moderate
1	1643	RR 1.00 (0.71, 1.41)	12.5	12.5 (8.8, 14.6)	Serious3	N/A	Not serious	Not serious	Moderate
Moderate/severe impact of treatment on QoL (sexual dysfunction) – RR >1 favours radical prostatectomy group Subgroup analysis – 6 month, 3 year, 6 year follow up									
1	928	RR 1.74 (1.50, 2.02)	36.6	63.7 (54.9, 80.5)	Serious3	N/A	Not serious	Not serious	Moderate
1	773	RR 1.35 (1.14, 1.59)	33.5	45.2 (38.2, 53.2)	Serious3	N/A	Not serious	Serious[2]	Low
1	914	RR 1.00 (0.86, 1.17)	41.6	41.6 (35.8, 48.6)	Serious3	N/A	Not serious	Not serious	Moderate
Moderate/severe impact of treatment on QoL (bowel function) – RR <1 favours radical prostatectomy group Subgroup analysis – 6 month, 3 year, 6 year follow up									
1	794	RR 0.72 (0.35, 1.44)	4.6	3.3 (1.6, 6.7)	Serious3	N/A	Not serious	Very serious[4]	Very low
1	911	RR 0.97 (0.40, 2.36)	2.1	2.0 (0.9, 0.5)	Serious3	N/A	Not serious	Very serious[4]	Very low
1	934	RR 1.00 (0.45, 2.20)	2.6	2.6 (1.2, 5.7)	Serious3	N/A	Not serious	Very serious[4]	Very low
Cancer-specific QoL: Global health status – MD >0 favours radical prostatectomy group									
1	1643	MD -1.00 (-3.57, 1.57)	-	-	Serious3	N/A	Not serious	Very serious[4]	Very low
Psychological aspects of QoL (Hospital Anxiety & Depression Scores): Anxiety – MD >0 favours radical prostatectomy group Subgroup analysis – 6 month, 3 year, 6 year follow up									

Study Reference

NG131 [G] (NICE 2019)
Linked records: Bill-Axelson 2018 (SPCG04 trial); Johansson 2018 (SPCG-4 trial); Lane 2016 (ProtecT trial); Lane 2014 (ProtecT trial)
Ng 2019 is an SLR that includes the same trials

1	961	MD 0.00 (-0.46, 0.46)	-	-	Serious3	N/A	Not serious	Very serious[4]	Very low
1	936	MD 0.00 (-0.44, 0.44)	-	-	Serious3	N/A	Not serious	Very serious[4]	Very low
1	930	MD 0.30 (-0.13, -0.73)	-	-	Serious3	N/A	Not serious	Serious[3]	Low
Psychological aspects of QoL (Hospital Anxiety & Depression Scores): Depression – MD >0 favours radical prostatectomy group Subgroup analysis – 6 month, 3 year, 6 year follow up									
1	965	0.10 (-0.28, 0.48)	-	-	Serious3	N/A	Not serious	Very serious[4]	Very low
1	938	-0.20 (-0.57, 0.17)	-	-	Serious3	N/A	Not serious	Serious[2]	Low
1	923	0.00 (-0.39, 0.39)	-	-	Serious3	N/A	Not serious	Very serious[4]	Very low

[1] 95% confidence intervals crosses the line of no effect, downgraded once
[2] Moderate risk of bias – due to lack of participant blinding for patient-reported outcomes, downgraded once
[3] 95% confidence interval for the effect size crossed one line of the MID, downgraded once
[4] 95% confidence interval for the effect size crossed both lines of the MID, downgraded twice

Quality assessment

Quality assessment of included studies (risk of bias)

Short title	Randomisation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias	Overall risk of bias	Directness
Donovan 2016 (ProtecT)	Low	Low	Unclear	Unclear	Low	Low	Low	Moderate	Directly applicable
Holmberg 2002 (SPCG-4)	Low	Low	Low	Unclear	Low	Low	Low	Moderate	Directly applicable
Wilt 2012 (PIVOT)	Unclear	Low	Low	Unclear	Low	Low	Low	Moderate	Directly applicable

Authors' Conclusions

Evidence Statements

Radical prostatectomy vs AS

- Moderate to high-quality evidence from 1 RCT (ProtecT) reporting data on 1,643 people with localised PCa found there was reduced time to disease progression and fewer people developing distant metastases but a greater number of people reporting issues with urinary incontinence in those offered prostatectomy compared to those offered active surveillance. Subgroup analysis found that there were more people reporting urinary and sexual dysfunction at up to 3 years follow-up in those people who were offered prostatectomy compared to those who were offered active surveillance.
- Very-low to moderate-quality evidence from 1 RCT (ProtecT) reporting data on 1,643 people with localised PCa could not differentiate overall survival, PCa-specific survival, erectile dysfunction, issues with bowel function, the effects of bowel function issues on quality of life, cancer-specific quality of life, anxiety or depression between people offered prostatectomy compared to those offered active surveillance.
- Very-low to low-quality evidence from 1 RCT (ProtecT) reporting data on 1,643 people with localised PCa demonstrated there is no difference in urinary function (at 3 years and 6 years follow-up) or bowel function at 6 months, 3 years and 6 years follow-up between people offered active surveillance and those offered prostatectomy.
- Low to moderate-quality evidence from 1 RCT (ProtecT) reporting data on 1,643 people with localised PCa found no meaningful difference in erectile dysfunction at 4 and 6 years follow-up between people offered active surveillance and those offered prostatectomy.

Radical prostatectomy vs watchful waiting

Study Reference	NG131 [G] (NICE 2019) Linked records: Bill-Axelson 2018 (SPCG04 trial); Johansson 2018 (SPCG-4 trial); Lane 2016 (ProtecT trial); Lane 2014 (ProtecT trial) Ng 2019 is an SLR that includes the same trials

- Very-low to high-quality evidence from 2 RCTs (SPCG-4 and PIVOT) reporting data on 1,429 people with localised PCa found improved overall survival at 8 years follow-up, improved PCa-specific survival at 6 years follow-up, fewer signs of disease progression and fewer people developing distant metastases for people offered prostatectomy compared to those offered watchful waiting. More people offered prostatectomy experienced issues with urinary incontinence and erectile dysfunction up to 8 years.
- Moderate to high-quality evidence from 2 RCTs (SPCG-4 and PIVOT) reporting data on 1,429 people with localised PCa could not differentiate overall mortality up to 6 years, PCa-specific mortality up to 4 years or erectile dysfunction at 18 years between people offered prostatectomy or watchful waiting.

Radical RT vs AS

- Very-low to high-quality evidence from 1 RCT (ProtecT) reporting data on 1,643 people found there was no meaningful difference in urinary function or in erectile dysfunction from 3 years onwards between people offered active surveillance and those offered radiotherapy.
- Very-low to high-quality evidence from 1 RCT (ProtecT) reporting data on 1,643 people found fewer signs of disease progression, fewer people developing distant metastases and lower anxiety and depression (at 6 years) for people offered radiotherapy compared to those offered active surveillance. Subgroup analysis found that at 6 months, there were more issues with erectile dysfunction, greater sexual and bowel function issues and a greater impact of sexual function issues on quality of life for people offered radiotherapy compared to those offered active surveillance.
- Very-low to high-quality evidence from 1 RCT (ProtecT) reporting data on 1,643 people could not differentiate overall survival, PCa-specific survival, cancer-related quality of life or the effects of urinary or bowel function issues on quality of life between people offered radiotherapy compared to those offered active surveillance. From 3 years onwards evidence could not differentiate between the two groups for sexual function issues or impact of sexual function issues on quality of life.
- Very-low to high-quality evidence from 1 RCT (ProtecT) reporting data on 1,643 people demonstrates that, from 3 years onwards, there is no difference in sexual function or bowel function between people offered active surveillance or radiotherapy.

Radical RT vs radical prostatectomy

- Moderate to high-quality evidence from 1 RCT (ProtecT) reporting data on up to 1,643 people with localised PCa found that there was no meaningful difference for urinary function, erectile dysfunction or bowel function (from 3 years) between people offered radiotherapy and those offered prostatectomy.
- Very-low to high-quality evidence from 1 RCT (ProtecT) reporting data on up to 1,643 people with localised PCa found more issues with bowel function at 6 months for people offered radiotherapy compared to those offered prostatectomy. Urinary function issues and sexual function issues (up to 3 years) had a greater impact on quality of life for people offered prostatectomy compared to those offered radiotherapy.
- Very-low to high-quality evidence from 1 RCT (ProtecT) reporting data on up to 1,643 people could not differentiate overall survival, PCa-specific survival, the number of people developing distant metastases, disease progression, cancer-related quality of life, anxiety or depression between people offered radiotherapy compared to those offered prostatectomy. Subgroup analysis found that, from 3 years onwards, evidence could not differentiate between the two groups for the impact of sexual function issues on quality of life.

NG131 Recommendations for Treatment
Low-risk localised PCa: AS, radical prostatectomy or radical RT
Intermediate-risk localised PCa: radical prostatectomy or radical RT (consider AS for people who do not choose to have immediate radical treatment)
High-risk localised PCa: radical prostatectomy or radical RT (do not offer AS)

Study Reference

NG131 [G] (NICE 2019)
Linked records: Bill-Axelson 2018 (SPCG04 trial); Johansson 2018 (SPCG-4 trial); Lane 2016 (ProtecT trial); Lane 2014 (ProtecT trial)
Ng 2019 is an SLR that includes the same trials

Additional results/ conclusions published after NG131 or not included in NG131

SPCG-4 (Bill-Axelson 2018)

Follow-up
29 years

Outcomes
Death from any cause, death from PCa, metastasis

Endpoint estimates at 23 years and RR over the 29 year trial period

Endpoint	Radical prostatectomy		Watchful waiting		Absolute difference in risk at 23 years (95% CI)	No. needed to treat to prevent endpoint at 23 years (95% CI)	RR (RP vs WW) (95% CI)	P value
	n events/ Total N	Cumulative incidence at 23 years (%)	n events/ Total N	Cumulative incidence at 23 years (%)				
Death from any cause								
All patients	261/347	71.9 (67.0–77.0)	292/348	83.8 (79.8–88.1)	12.0 (5.5–18.4)	8.4 (5.4–18.2)	0.74 (0.62–0.87)	<0.001
<65 year olds	105/157	62.6 (55.1–71.2)	129/166	77.6 (71.1–84.7)	15.0 (4.4–25.5)	6.7 (3.9–22.6)	0.62 (0.48–0.80)	
≥65 year olds	156/190	79.2 (73.4–85.4)	163/182	89.3 (84.6–94.3)	10.1 (2.4–17.8)	9.9 (5.6–41.4)	0.86 (0.69–1.07)	
Death from PCa								
All patients	71/347	19.6 (15.8–24.4)	110/348	31.3 (26.8–36.6)	11.7 (5.2–18.2)	8.6 (5.5–19.3)	0.55 (0.41–0.74)	<0.001
<65 year olds	39/157	22.8 (17.0–30.6)	63/166	37.9 (31.1–46.3)	15.1 (5.0–25.2)	6.6 (4.0–20.0)	0.50 (0.34–0.75)	
≥65 year olds	32/190	16.9 (12.3–23.1)	47/182	25.3 (19.7–32.6)	8.5 (0.2–16.8)	11.8 (6.0–601.0)	0.63 (0.40–0.99)	
Distant metastasis								
All patients	92/347	26.6 (22.3–31.7)	150/348	43.3 (38.3–48.9)	16.7 (9.6–23.7)	6.0 (4.2–10.4)	0.54 (0.42–0.70)	<0.001
<65 year olds	48/157	30.8 (24.3–39.0)	81/166	49.4 (42.2–57.8)	18.6 (7.9–29.2)	5.4 (3.4–12.7)	0.49 (0.34–0.70)	
≥65 year olds	44/190	23.2 (17.9–30.0)	69/182	37.7 (31.2–45.6)	14.6 (5.2–23.9)	6.9 (4.2–19.2)	0.59 (0.41–0.86)	

Mean life years gained in the radical prostatectomy group at 23 years of follow-up was 2.9 years

Author's conclusions

- After 29 years of follow-up, at a time when 80% of all the participants had died, lower overall mortality, lower mortality due to prostate cancer, and a lower risk of metastasis prevailed in the radical prostatectomy group
- The absolute benefit associated with radical prostatectomy increased by a factor of more than 2 between 10 and 23 years of follow-up for both overall mortality (from 5.0 to 12.0 percentage points) and disease-specific mortality (from 5.5 to 11.7 percentage points), whereas the relative risks remained stable during this period for both overall mortality (0.75 to 0.74) and disease-specific mortality (0.56 to 0.54)
- In clinically detected prostate cancer, the benefit of radical prostatectomy in otherwise healthy men can be substantial, with a mean gain of almost 3 years of life after 23 years of follow-up. The remaining expected lifetime is important in decision making, with the reservation that it is hard to predict. When our results are applied to inform current practice, several issues have to be considered: the lead time induced by screening, the addition to modern cohorts of overdiagnosed nonlethal cancers, and the influence of modern diagnostics on the definition of risk groups. Furthermore, even if the relative risks in our trial were fully applicable to modern studies, the amount of absolute benefit is highly dependent on baseline risk.

SPCG-4 (Johansson 2018)

Follow-up

Study Reference	**NG131 [G] (NICE 2019)** Linked records: Bill-Axelson 2018 (SPCG04 trial); Johansson 2018 (SPCG-4 trial); Lane 2016 (ProtecT trial); Lane 2014 (ProtecT trial) Ng 2019 is an SLR that includes the same trials

Median: 12.2 years

Outcomes
Self-assessed QoL, worry at clinical check-ups, amount of information received

ADT and psychological factors according to an ITT analysis using self-assessed and self-reported variables

Category and group	RR (RP vs RP_{ADT}) (95% CI)	RR (WW vs WW_{ADT}) (95% CI)	RR (WW vs control) (95% CI)	RR (RP_{ADT} vs WW_{ADT}) (95% CI)	RR (RP vs WW) (95% CI)
High QoL	1.22 (0.75–2.0)	2.21 (1.29–3.78)*	0.99 (0.75–1.30)	1.49 (0.77–2.87)	0.82 (0.6–1.13)
High sense of meaningfulness	0.99 (0.69–1.41)	1.89 (1.28–2.78)*	1.03 (0.85–1.26)	1.45 (0.91–2.31)	0.76 (0.59–0.97)*
High sense of energy	1.01 (0.59–1.73)	1.65 (0.91–3.0)	1.30 (0.88–1.91)	1.50 (0.75–2.98)	0.92 (0.61–1.38)
Moderate/high depressed mood	0.99 (0.72–1.35)	0.60 (0.44–0.80)*	1.00 (0.74–1.34)	0.69 (0.49–0.98)*	1.17 (0.86–1.59)
Moderate/high anxiety	0.84 (0.59–1.20)	0.66 (0.46–0.93)*	1.08 (0.78–1.51)	0.91 (0.63–1.31)	1.16 (0.83–1.63)
High wellbeing	1.17 (0.76–1.80)	1.61 (1.08–2.41)*	1.00 (0.80–1.27)	1.12 (0.67–1.88)	0.81 (0.62–1.07)
High physical health	1.00 (0.61–1.62)	1.84 (1.09–3.11)*	1.10 (0.81–1.49)	1.48 (0.79–2.77)	0.80 (0.57–1.14)
High self-esteem	1.16 (0.79–1.72)	1.38 (0.94–2.04)	1.03 (0.80–1.32)	1.14 (0.71–1.84)	0.96 (0.73–1.26)

*Statistically significant

Author's conclusions

- It is possible to live with untreated prostate cancer and maintain the same QoL as the background population. However, if faced with disease progression and bone metastases requiring ADT, QoL can be lower than for men progressing after RP.

ProtecT (Lane 2014)

Protocol for ProtecT with additional details on baseline characteristics and methods

ProtecT (Lane 2016)

Patient-reported outcomes (baseline urinary, bowel and sexual function and QoL). Less detailed than those included in the NG131 extraction so nothing additional to add.

Abbreviations: AE, adverse event; AR, absolute risk; AS, active surveillance; CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; CI, confidence interval; CV, cardiovascular; DARE, Database of Abstracts of Reviews of Effects; EPIC, Expanded Prostate Cancer Index Composite; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HADS, Hospital Anxiety and Depression Scale; HR, hazard ratio; HTA, Health Technology Assessment; IQR, interquartile range; LTFU, loss-to-follow-up; MA, meta-analysis; MD, mean difference; MID, minimal clinically important difference; N/A, not applicable; OS, overall survival; PCa, prostate cancer; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PSA, prostate-specific antigen; QoL, quality of life; RCT, randomised controlled trial; RoB, risk of bias; RR, risk ratio; RT, radiotherapy/radiation therapy; SD, standard deviation; SPCG-4, Randomised Scandinavian Prostate Cancer Group Study Number 4.

Table 41c. Chin 2017

Study Reference	**Chin 2017**
Study Design	Design Systematic literature review

Study Reference	**Chin 2017**
	Objective To provide oncologists, other health care practitioners, patients, and caregivers with recommendations regarding the use of brachytherapy for patients with prostate cancer that includes the most recent evidence Included study names Radiation Therapy Oncology Group (RTOG) 0232 Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT) Included study designs Randomised, open-label, phase III studies Dates RTOG 0232: 2003–2012 ASCENDE-RT: 2002–2011 Country RTOG 0232: NR ASCENDE-RT: NR Setting NR
Population Characteristics	Patient recruitment and eligibility **Inclusion** RTOG 0232: Patients with low-intermediate risk prostate cancer (Gleason 6, PSA 10 to 20 ng/mL or Gleason 7, PSA < 10 ng/mL) ASCENDE-RT: Patients with intermediate- and high-risk prostate cancer **Exclusion** NR **Other** NR Sample size RTOG 0232: 588 patients underwent randomisation ASCENDE-RT: 398 patients underwent randomisation Demographics

Parameter	RTOG 0232	ASCENDE-RT
Median age (years)	NR	68
Ethnicity	NR	NR
BMI	NR	NR
PSA level	NR	NR
Prostate volume	NR	NR

Study Reference	Chin 2017		
	Number of positive biopsy samples	NR	NR
	T stage	NR	NR
	M stage	NR	NR
	N stage	NR	NR
	Gleason score	NR	NR
	Risk group (n) *Low-intermediate risk* *High-intermediate risk* *High risk*	 588 0 0	 2 120 276
Methods	Systematic literature review Evidence was collected through a systematic review of the medical literature. Publications were included if they were phase III randomised clinical trials of brachytherapy compared with either EBRT or RP in men with prostate cancer. These publications were identified by running database searches in MEDLINE, EMBASE, and the Cochrane database of systematic reviews, from 2011 through to the end of August 2015. A final search for important papers was made in December 2016 Randomisation RTOG 0232: 588 patients randomly assigned 1:1 to arms 1 and 2 ASCENDE-RT: 398 patients randomly assigned to arms 1 and 2. Patients were stratified by risk category (intermediate v high risk) Study arms RTOG 0232 Arm 1: LDR-B alone (interstitial brachytherapy alone (145 Gy ^{125}I or 125 Gy ^{103}Pd given as interstitial seeds)) RTOG 0232 Arm 2: EBRT + LDR-B (EBRT (3DCRT or IMRT) 45 Gy, 25 fractions (5 days a week for 5 weeks) mini-pelvis + interstitial brachytherapy (110 Gy ^{125}I or 100Gy ^{103}Pd given as interstitial seeds)) ASCENDE-RT Arm 1: EBRT + LDR-B + ADT (whole pelvis EBRT: 46 Gy, 23 fractions followed by an ^{125}I boost to a minimum dose of 115 Gy to prostate; twelve months (8 months neoadjuvant, 2 months concurrent, 2 months adjuvant) of ADT) ASCENDE-RT Arm 2: EBRT + ADT (whole pelvis EBRT: 46 Gy, 23 fractions followed by conformal EBRT to prostate: 32 Gy, 16 fractions; twelve months (8 months neoadjuvant, 2 months concurrent, 2 months adjuvant) of ADT) Duration of follow-up RTOG 0232: 80.4 months (median) ASCENDE-RT: 78 months (median) Outcomes **Primary endpoint** RTOG 0232: 5-year progression-free survival (PFS; American Society for Radiation Oncology nadir + 2 biochemical failure, clinical failure, or death from any cause) ASCENDE-RT: 3-, 5-, 7- and 9-year biochemical disease-free survival (bDFS) as defined by biochemical criteria using the Phoenix (nadir + 2 ng/mL) threshold **Secondary endpoints** RTOG 0232: Grade 3 genitourinary (GU) toxicity; grade 3 gastrointestinal (GI) toxicity		

Study Reference **Chin 2017**

ASCENDE-RT: 3-, 5- and 7-year overall survival (OS) rate; prostate cancer–specific mortality (PCSM); metastasis-free survival rate (MFSR); Grade 3 and 4 GU toxicity; grade 3 and 4 GI toxicity. Quality-of-life was prospectively collected using the Short Form-36 instrument, which assessed physical function, role physical, bodily pain, general health, vitality, social functioning, and emotional and mental health. Additional items to gather data on urinary function, bowel function, and sexual function were added. All items were scored on a scale from 0 to 100

Harms and Benefits of Interventions

Efficacy outcomes

RCT	Treatment	No. patients	Primary outcome	OS rate	PCSM (No., %)	MFSR (No., %)
RTOG 0232	LDR-B alone	292	5-yr PFS: 86% (95% CI, 81% to 90%)	NR	NR	NR
	EBRT + LDR-B	287	5-yr PFS: 85% (95% CI, 80% to 89%) *HR, 1.02; P < .001 for futility*	NR	NR	NR
ASCENDE-RT	EBRT + LDR-B + ADT	198	bDFS: 3-yr, 94% 5-yr, 89% 7-yr, 86% 9-yr, 83%	3-yr, 91% 5-yr, 86% 7-yr, 78%	7 (3.5)	17 (8.5)
	EBRT + ADT	200	bDFS: 3-yr, 94%; 5-yr, 84%; 7-yr, 75%; 9-yr, 62% *Log-rank P < .001*	3-yr, 89% 5-yr, 82% 7-yr, 74% *P = .29*	11 (5.5) *P = .32*	18 (9) *P = .83*

Adverse effects

RCT	Treatment	No. patients	GU Toxicity		GI toxicity	
			Grade 3 (%)	Grade 4 (%)	Grade 3 (%)	Grade 4 (%)
RTOG 0232	LDR-B alone	292	3	NR	3	NR
	EBRT + LDR-B	287	7 *P = NR*	NR	2 *P = NR*	NR
ASCENDE-RT	EBRT + LDR-B + ADT	198	19[a]	1[a]	9[a]	1[a]
	EBRT + ADT	200	5[a] *P < .001*	1[a] *P = .547*	4[a] *P = .12*	0[a] *P = NR*

[a]5-year cumulative incidence (worst grade recorded)

ASCENDE-RT: area under the curve differences were detected for bodily pain (P = .04), general health (P = .01), sexual function (P = .02), and urinary function (P = .006) in favour of treatment with EBRT + ADT over EBRT + LDR-B + ADT. No health-related quality-of-life differences were detected for any other domains

Study Reference	**Chin 2017**
Authors' Conclusions	For patients with low-risk prostate cancer who require or choose active treatment, low–dose rate brachytherapy (LDR-B) alone, EBRT alone, and/or radical prostatectomy (RP) should be offered to eligible patients. For patients with intermediate-risk prostate cancer choosing EBRT with or without androgen-deprivation therapy, brachytherapy boost (LDR or high–dose rate [HDR]) should be offered to eligible patients. For low-intermediate risk prostate cancer (Gleason 7, prostate-specific antigen < 10 ng/mL or Gleason 6, prostate-specific antigen, 10 to 20 ng/mL), LDR brachytherapy alone may be offered as monotherapy. For patients with high-risk prostate cancer receiving EBRT and androgen-deprivation therapy, brachytherapy boost (LDR or HDR) should be offered to eligible patients. Iodine-125 and palladium-103 are each reasonable isotope options for patients receiving LDR brachytherapy; no recommendation can be made for or against using cesium-131 or HDR monotherapy

Abbreviations: 3DCRT, three-dimensional conformal radiotherapy; ADT, androgen deprivation therapy; ASCENDE-RT, Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy; bDFS, biochemical disease-free survival; BMI, body mass index; EBRT, external beam radiotherapy; GI, gastrointestinal; GU, genitourinary; HDR, high-dose rate; IMRT, intensity modulated radiotherapy; LDR, low-dose rate; LDR-B, low-dose rate brachytherapy; MFSR, metastasis-free survival rate; NR, not reported; OS, overall survival; PCSM, prostate cancer–specific mortality; PFS, progression-free survival; PSA, prostate-specific antigen; RP, radical prostatectomy; RTOG, Radiation Therapy Oncology Group

Table 41d. Ng 2019

Study Reference	Ng 2019
Study Design	Design Systematic literature review and meta-analysis Objective The primary aim of the study was to determine all-cause mortality and prostate cancer-related mortality between conservative management and radical treatment for localised prostate cancer. Secondary aims were to examine the incidence of distant metastases and quality of life measures (patient-reported erectile dysfunction and urinary incontinence) in these treatments Included study names Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4) Prostate Cancer Intervention versus Observation Trial (PIVOT) Prostate testing for cancer and Treatment (ProtecT) Included study designs Multi-centre randomised controlled trials Dates NR Country SPCG-4: Sweden, Finland, Iceland PIVOT: USA ProtecT: UK Setting NR
Population Characteristics	Study eligibility **Inclusion** The inclusion criteria set for the subjects were: (a) adults (≥ 18 years old), (b) diagnosed with localised prostate cancer (either PSA-diagnosed or clinically diagnosed), (c) radical treatment (prostatectomy or radiotherapy), (d) conservative measures (active monitoring, watchful waiting or observation) **Exclusion** NR **Other** NR Sample size See ‘n’ column of table below

Study Reference **Ng 2019**

Included study characteristics

Author (trial name)	Study type	Country	Median duration of follow-up (years)	Control	Comparator	n	Outcomes used in meta-analysis
Bill-Axelson 2014 (SPCG-4)	Multi-centre RCT	Sweden Finland Iceland	13.4	Watchful waiting	Prostatectomy	695	All-cause mortality PCa-related mortality Incidence of distant metastases Incidence of patient-reported erectile dysfunction Incidence of patient-reported use of pads for urinary incontinence
Wilt 2017 (PIVOT)	Multi-centre RCT	USA	12.7	Observation	Prostatectomy	731	All-cause mortality PCa-related mortality Incidence of distant metastases Incidence of patient-reported erectile dysfunction Incidence of patient-reported use of pads for urinary incontinence
Hamdy 2016; Donovan 2016 (ProtecT)	Multi-centre RCT	UK	10	Active monitoring	Prostatectomy, RT	1643	All-cause mortality PCa-related mortality Incidence of distant metastases Incidence of patient-reported erectile dysfunction Incidence of patient-reported use of pads for urinary incontinence

Methods

Systematic literature review

The research questions were formulated using a population (localised prostate cancer), intervention (radical treatments- prostatectomy or radiotherapy), control (conservative management/active monitoring, watchful waiting or observation) and outcomes approach. The MEDLINE, EMBASE, PubMed and CENTRAL databases were systematically searched from the study's inception until September 2018. Trial registers (ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform and the International Standard Randomised Controlled Trial Number Registry) were searched to identify any unpublished and ongoing studies. Only RCTs were included. Observational studies, case reports, case series, systematic reviews, trials published as abstracts and studies comparing different regimes of radiotherapy were excluded. No language restriction was applied to the search. The bibliographies of the included papers and relevant systematic reviews were scrutinised to find more papers for inclusion in this study.

Randomisation

NR

Study arms

See 'control' and 'comparator' columns in the table above

Study Reference	Ng 2019

Duration of follow-up
See 'duration of follow-up' column in the table above

Outcomes
Primary endpoint

The co-primary outcomes were all-cause mortality and prostate cancer-related mortality based on the analysis of the longest follow-up data

Secondary endpoints

Secondary outcomes were incidence of distant metastases, incidence of patient-reported erectile dysfunction and incidence of patient-reported use of pads for urinary incontinence

Harms and Benefits of Interventions

All-cause mortality

Study	Conservative		Radical		Weight (%)	Odds ratio M-H, Fixed, 95% CI	Year
	Events	Total	Events	Total			
SPCG-4	247	348	200	347	29.4	1.80 [1.31, 2.46]	2014
ProtecT	59	545	110	1098	32.9	1.09 [0.78, 1.52]	2016
PIVOT	245	367	223	364	37.7	1.27 [0.94, 1.72]	2017
Total (95% CI)		1260		1809	100.0	1.37 [1.14, 1.64]	
Total events	551		533				

Heterogeneity: $Chi^2 = 4.89$, df = 2 (P = 0.09), $I^2 = 59\%$
Test of overall effect: Z = 3.37 (P = 0.0008)

Prostate cancer-related mortality

Study	Conservative		Radical		Weight (%)	Odds ratio M-H, Fixed, 95% CI	Year
	Events	Total	Events	Total			
SPCG-4	99	348	63	347	60.2	1.79 [1.25, 2.57]	2014
ProtecT	8	545	9	1098	7.8	1.80 [0.69, 4.70]	2016
PIVOT	42	367	27	364	32.0	1.61 [0.97, 2.68]	2017
Total (95% CI)		1260		1809	100.0	1.74 [1.31, 2.30]	
Total events	149		99				

Heterogeneity: $Chi^2 = 0.12$, df = 2 (P = 0.94), $I^2 = 0\%$
Test of overall effect: Z = 3.86 (P = 0.0001)

Incidence of distant metastases

Study Reference **Ng 2019**

Study	Conservative		Radical		Weight (%)	Odds ratio M-H, Fixed, 95% CI	Year
	Events	Total	Events	Total			
SPCG-4	138	348	89	347	51.9	1.90 [1.38, 2.63]	2014
ProtecT	33	545	29	1098	17.5	2.38 [1.43, 3.96]	2016
PIVOT	54	367	37	364	30.6	1.52 [0.98, 2.38]	2017
Total (95% CI)		1260		1809	100.0	1.87 [1.48, 2.36]	
Total events	225		155				

Heterogeneity: $Chi^2 = 1.66$, df = 2 (P = 0.44), $I^2 = 0\%$
Test of overall effect: Z = 5.27 (P = < 0.00001)

Erectile dysfunction

Study	Conservative		Radical		Weight (%)	Odds ratio M-H, Fixed, 95% CI	Year
	Events	Total	Events	Total			
SPCG-4	80	367	84	364	34.7	0.93 [0.66, 1.32]	2014
ProtecT	318	452	718	917	38.1	0.66 [0.51, 0.85]	2016
PIVOT	20	367	53	364	27.3	0.34 [0.20, 0.58]	2017
Total (95% CI)		1186		1645	100.0	0.62 [0.39, 0.98]	
Total events	418		855				

Heterogeneity: $Tau^2 = 0.13$, $Chi^2 = 9.66$, df = 2 (P = 0.008), $I^2 = 79\%$
Test of overall effect: Z = 2.04 (P = 0.04)

Urinary incontinence

Study	Conservative		Radical		Weight (%)	Odds ratio M-H, Fixed, 95% CI	Year
	Events	Total	Events	Total			
SPCG-4	25	348	54	347	33.1	0.42 [0.25, 0.69]	2014
ProtecT	38	453	97	907	35.3	0.76 [0.52, 1.13]	2016
PIVOT	16	367	63	364	31.6	0.22 [0.12, 0.39]	2017
Total (95% CI)		1168		1618	100.0	0.42 [0.21, 0.86]	
Total events	79		214				

Heterogeneity: $Tau^2 = 0.34$, $Chi^2 = 13.09$, df = 2 (P = 0.001), $I^2 = 85\%$

Study Reference	**Ng 2019**

Test of overall effect: Z = 2.37 (P = 0.02)

Risk of bias

Trial	Cochrane Risk of Bias Tool								Funding
	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall risk of bias	
SPCG-4	Low	Low	Low*	Low*	Low	Low	Low	Low	The Swedish Cancer Society, the National Institutes of Health, the Karolinska Institute, the Prostate Cancer Foundation and Percy Falk Foundation
PIVOT	Low	Low	Low*	Low*	Low	Low	Low	Low	The Department of Veterans Affairs, the Agency for Healthcare Quality and Research, and the National Cancer Institute
ProtecT	Low	Low	Low*	Low*	Low	Low	Low	Low	The UK National Institute for Health Research Health Technology Assessment Programme (University of Oxford)

*No blinding was performed, but the review authors judged that the outcomes were not likely to be influenced by lack of blinding

Authors' Conclusions	Radical treatments (prostatectomy/radiotherapy) were found to reduce all-cause mortality, prostate cancer-related mortality and the incidence of distant metastases, at the expense of higher incidence of patient-reported erectile dysfunction and urinary incontinence. The clinical management of localised prostate cancer needs to be individualised based on each patient's age and PSA level, Gleason score and clinical stage at diagnosis, along with the patient's wishes

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel; NR, not reported; PCa, prostate cancer; PIVOT, Prostate Cancer Intervention versus Observation Trial; ProtecT, Prostate testing for cancer and Treatment; PSA, prostate-specific antigen; RCT, randomised controlled trial; SPCG-4, Scandinavian Prostate Cancer Group Study Number 4

Table 41e. Yin 2019

Study Reference	**Yin 2019**
Study Design	Design Systematic literature review and meta-analysis Objective To determine the efficacy and late toxicities of moderate (2.5–4 Gy) hypofractionated radiotherapy (H-RT) in localised prostate cancer, a meta-analysis of published randomised clinical trials comparing moderate H-RT with conventional fractionated RT (C-RT) was performed Included study names A Phase III Intensity Radiotherapy Dose Escalation for Prostate Cancer Using Hypofractionation (Hoffman et al, 2014; 2018) PROstate Fractionated Irradiation Trial (PROFIT) (Catton et al, 2017) Radiation Therapy Oncology Group (RTOG) 0415 (Lee et al, 2016) Conventional or Hypofractionated High dose intensity modulated radiotherapy for Prostate cancer (CHHiP) (Dearnaley et al, 2016) HYpofractionated irradiation for PROstate cancer (HYPRO) trial (Incrocci et al, 2016) Included study designs Phase III randomised trials Dates NR Country NR Setting NR
Population Characteristics	Patient recruitment and eligibility **Inclusion** See ‘patients’ column in table below **Exclusion** NR **Other** NR Sample size See ‘N’ column in table below Demographics NR
Methods	Systematic literature review Published randomised controlled trials comparing H-RT and C-RT for localised prostate cancer were included. PubMed, Embase, Science Direct, Wiley online library, the Cochrane Library, and CENTRAL were searched from the date of their inception until August 22nd 2018 for relevant articles. Abstracts were searched from the most important international meetings: ASTRO, ESTRO, ASCO. The three search terms

Study Reference	**Yin 2019**

were “prostate cancer” AND “hypofractionation” AND “radiotherapy”. Searches were restricted to reports published in English. To be eligible for inclusion, studies had to be randomised Phase III clinical trials comparing H-RT with C-RT in patients with localised prostate cancer without surgery. Observational and retrospective studies were excluded.

Randomisation
NR

Study arms
See ‘comparison’ column in table below

Duration of follow-up
See ‘follow-up’ column in table below

Outcomes
Primary endpoint

The primary endpoint of interest in the systematic literature review was biochemical and clinical disease failure (BCDF) rate. See table below for the primary endpoint of each study

Secondary endpoints

Secondary endpoints of interest in the systematic literature review were biochemical failure (BF) rate, overall survival (OS), and late GI and GU toxicities. See table below for the secondary endpoints reported in each study

Harms and Benefits of Interventions

Characteristics of randomised studies comparing H-RT with C-RT for localised prostate cancer

Study	Patients	Comparison	N	BCDF	BF	OS	GI	GU	Primary endpoint	Follow-up (months)
Hoffman et al, 2018	Low–high risk (T1b–2 N0)	H-RT: 72/2.4 Gy C-RT: 75.6/1.8 Gy	222	10 21	NR NR	19 24	11 5	15 15	Toxicity	102
Catton et al, 2017	Intermediate risk (T1–2c N0)	H-RT: 60/3.0 Gy C-RT: 78 Gy/2.0 Gy	1,206	109 117	97 100	76 78	54 82	135 133	BCDF	72
Lee et al, 2016	Low risk (T1–2 N0)	H-RT: 70/2.5 Gy C-RT: 73.8/1.8 Gy	1,092	86 99	39 50	49 51	121 75	161 121	BCDF	69.6
Dearnaley et al, 2016	Low–high risk (T1–T3a N0)	H-RT1: 60/3.0 Gy H-RT2: 57/3.0 Gy C-RT: 74/2.0 Gy	3,216	88 132 111	NR NR NR	87 73 92	105 95 111	88 57 66	BCDF	62
Incrocci et al, 2016	Intermediate–high risk (T1b–4 NX–0)	H-RT: 64.6/3.4 Gy C-RT: 78/2.0 Gy	804	80 89	70 82	61 59	NR NR	NR NR	BCDF (relapse-free survival)	60

Study Reference **Yin 2019**

Pollack et al, 2013	Intermediate–high risk (T1–3 N0)	H-RT: 70.2/2.6 Gy C-RT: 76/2.0 Gy	303	35 33	NR NR	NR NR	16 22	13 14	BCDF	68.4
Arcangeli et al, 2012	Predominately high risk (T1–3 N0)	H-RT: 62/3.1 Gy C-RT: 80/2.0 Gy	168	NR NR	13 22	7 15	NR NR	NR NR	FFBF	70

Biochemical and clinical disease failure

Study	H-RT		C-RT		Weight (%)	Odds ratio M-H, Fixed, 95% CI	Year
	Events	Total	Events	Total			
Pollack et al, 2013	35	151	33	152	5.6	1.07 (0.70, 1.62)	2013
Lee et al, 2016	86	550	99	542	17.1	0.86 (0.66, 1.11)	2016
Dearnaley et al, 2016	88	1,074	111	1,065	19.1	0.79 (0.60, 1.03)	2016
Dearnaley* et al, 2016	132	1,077	111	1,065	19.1	1.18 (0.93, 1.49)	2016
Incrocci et al, 2016	80	407	89	397	15.4	0.88 (0.67, 1.15)	2016
Catton et al, 2017	109	608	117	598	20.2	0.92 (0.72, 1.16)	2017
Hoffman et al, 2018	10	111	21	111	3.6	0.48 (0.24, 0.96)	2018
Total (95% CI)		3,978		3,930	100	0.92 (0.82, 1.02)	
Total events	540		581				

*Indicates that another comparison from the trial conducted by Dearnaley et al was in order to differentiate from the first comparison
Heterogeneity: Chi^2=9.67, df=6 (P=0.14), I^2=38%
Test of overall effect: Z=1.57 (P=0.12)

Biochemical failure

Study	H-RT		C-RT		Weight (%)	Odds ratio M-H, Fixed, 95% CI	Year
	Events	Total	Events	Total			
Arcangeli et al, 2012	13	83	22	85	8.3	0.61 (0.33, 1.12)	2012
Lee et al, 2016	39	550	50	542	19.2	0.77 (0.51, 1.15)	2016

Study Reference **Yin 2019**

Incrocci et al, 2016	70	407	82	397	31.6	0.83 (0.62, 1.11)	2016
Catton et al, 2017	97	698	100	598	41.0	0.83 (0.64, 1.07)	2017
Total (95% CI)		1,738		1,622	100	0.80 (0.68, 0.95)	
Total events	219		254				

Heterogeneity: Chi^2=0.99, df=3 (P=0.80), I^2=0%
Test of overall effect: Z=2.61 (P=0.009)

Overall survival

Study	H-RT		C-RT		Weight (%)	Odds ratio M-H, Fixed, 95% CI	Year
	Events	Total	Events	Total			
Arcangeli et al, 2012	7	83	15	85	3.6	0.48 (0.21, 1.11)	2012
Lee et al, 2016	49	550	51	542	12.4	0.95 (0.65, 1.38)	2016
Incrocci et al, 2016	61	407	59	397	14.4	1.01 (0.72, 1.40)	2016
Dearnaley* et al, 2016	87	1,077	92	1,065	22.4	0.94 (0.71, 1.24)	2016
Dearnaley et al, 2016	73	1,074	92	1,065	22.3	0.79 (0.59, 1.06)	2016
Catton et al, 2017	76	608	78	598	19.0	0.96 (0.71, 1.29)	2017
Hoffman et al, 2018	19	111	24	111	5.8	0.79 (0.46, 1.36)	2018
Total (95% CI)		3,910		3,863	100	0.89 (0.78, 1.02)	
Total events	372		411				

*Indicates that another comparison from the trial conducted by Dearnaley et al was in order to differentiate from the first comparison
Heterogeneity: Chi^2=3.94, df=6 (P=0.68), I^2=0%
Test of overall effect: Z=1.66 (P=0.10)

Gastrointestinal toxicity

Study	H-RT		C-RT		Weight (%)	Odds ratio M-H, Fixed, 95% CI	Year
	Events	Total	Events	Total			
Pollack et al, 2013	16	85	22	96	13.2	0.82 (0.46, 1.46)	2013

Study Reference **Yin 2019**

Hoffman et al, 2014	11	102	5	101	6.8	2.18 (0.78, 6.05)	2014
Dearnaley et al, 2016	105	882	111	810	20.5	0.87 (0.68, 1.11)	2016
Lee et al, 2016	121	542	75	533	20.2	1.59 (1.22, 2.06)	2016
Dearnaley* et al, 2016	95	841	111	810	20.4	0.82 (0.64, 1.07)	2016
Catton et al, 2017	54	608	82	598	18.8	0.65 (0.47, 0.90)	2017
Total (95% CI)		3,060		2,948	100	0.97 (0.71, 1.33)	
Total events	402		406				

*Indicates that another comparison from the trial conducted by Dearnaley et al was in order to differentiate from the first comparison
Heterogeneity: Tau^2=0.11, Chi^2=24.50, df=5 (P=0.0002), I^2=80%
Test of overall effect: Z=0.18 (P=0.85)

Genitourinary toxicity

Study	H-RT		C-RT		Weight (%)	Odds ratio M-H, Fixed, 95% CI	Year
	Events	Total	Events	Total			
Pollack et al, 2013	13	85	14	96	5.8	1.05 (0.52, 2.10)	2013
Hoffman et al, 2014	15	102	15	101	6.3	0.99 (0.51, 1.92)	2014
Dearnaley* et al, 2016	57	863	66	725	16.6	0.73 (0.52, 1.02)	2016
Lee et al, 2016	161	542	121	533	26.6	1.31 (1.07, 1.60)	2016
Dearnaley et al, 2016	88	882	66	725	18.8	1.10 (0.81, 1.48)	2016
Catton et al, 2017	135	608	133	598	25.9	1.00 (0.81, 1.23)	2017
Total (95% CI)		3,082		2,778	100	1.04 (0.87, 1.24)	
Total events	469		415				

*Indicates that another comparison from the trial conducted by Dearnaley et al was in order to differentiate from the first comparison
Heterogeneity: Tau^2=0.02, Chi^2=9.29, df=5 (P=0.10), I^2=46%
Test of overall effect: Z=0.40 (P=0.69)

Biological effective dose recalculated with α/β ratio as 1.5 Gy for prostate tumour and 5 Gy for GI and GU toxicities

Study Reference	Yin 2019

Study	N	$BED_{1.5}$	BED_5
Lee et al, 2016	1,092	H-RT: 187 Gy C-RT: 162 Gy	H-RT: 105 Gy C-RT: 100 Gy
Dearnaley et al, 2016	3,216	H-RT1: 180 Gy H-RT2: 171 Gy C-RT: 173 Gy	H-RT1: 96 Gy H-RT2: 91 Gy C-RT: 104 Gy
Incrocci et al, 2016	804	H-RT: 211 Gy C-RT: 182 Gy	H-RT: 109 Gy C-RT: 109 Gy
Hoffman et al, 2014	203	H-RT: 187 Gy C-RT: 166 Gy	H-RT: 107 Gy C-RT: 103 Gy

Risk of bias
NR

Authors' Conclusions	This meta-analysis provides reliable evidence that moderate H-RT decreases BF rate, while it does not improve OS. Compared with C-RT, H-RT with an increase in $BED_{1.5}$ improved BCDF rates significantly, and accordingly, an increase in BED_5 will result in elevated late GI and GU toxicities

Abbreviations: BCDF, biochemical and clinical disease failure; BED, biologically effective dose; BF, biochemical failure; CHHiP, Conventional or Hypofractionated High dose intensity modulated radiotherapy for Prostate cancer; CI, confidence interval; C-RT, conventional fractionated radiotherapy; FFBF, freedom from biochemical failure; GI, gastrointestinal; GU, genitourinary; H-RT, hypofractionated radiotherapy; M-H, Mantel-Haenszel; NR, not reported; OS, overall survival; PROFIT, PROstate Fractionated Irradiation Trial; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group

Table 41f. EORTC Trial 22991 (Bolla 2016)

Study Reference	EORTC Trial 22991 (Bolla 2016)
Study Design	Study name EORTC Trial 22991 Design Randomised controlled trial Objective To assess if biochemical DFS is improved by adding 6 months of androgen suppression to primary RT for intermediate- or high-risk localised PCa Dates September 2001 – April 2008 Country Various (Belgium, Cyprus, Czech Republic, France, Ireland, Italy, Luxembourg, Netherlands, Poland, Spain, United Kingdom)

Study Reference	**EORTC Trial 22991 (Bolla 2016)**
	Setting 37 centres from 14 countries
Population Characteristics	Patient recruitment and eligibility NR **Inclusion** Histologically confirmed prostate adenocarcinoma T1b to T2a (International Union Against Cancer 1997 staging criteria) PSA >10 ng/mL or Gleason ≥7 No involvement of pelvic lymph nodes as assessed by computed tomography scan, magnetic resonance imaging, or laparoscopic surgery No clinical evidence of metastatic spread No clinical tumour stages T2b to T4 and a PSA level of up to 12.5 times the UNL WHO performance status ≤2 No previous pelvic irradiation or radical prostatectomy No previous hormonal therapy No other malignancy except adequately treated basal cell carcinoma of the skin or another malignancy cured for at least 5 years **Exclusion** NR **Other** NR Sample size N invited = NR N assigned to intervention = 819 (total), 409 (Arm 1: RT alone), 410 (Arm 2: RT + androgen suppression) N eligible = NR N excluded (with reason) = 2 (Arm 1; metastatic not treated = 1, refused treatment = 1), 7 (Arm 2; received RT alone = 3, metastatic patient not treated = 1, refused all treatment = 3) N receiving treatment = 407 (Arm 1), 403 (Arm 2) N lost to follow-up = 17 (Arm 1), 24 (Arm 2) N completed = NR N excluded from analysis = NR included in analysis = • ITT = 409 (Arm 1), 410 (Arm 2) • Per protocol = 388 (Arm 1), 385 (Arm 2) • Safety set = 407 (Arm 1), 406 (Arm 2) Demographics

Parameter, n (%) [*unless otherwise stated*]	RT only (N=409)	RT + androgen suppression (N=410)
Age, y, median (range, IQR)	70 (43–80, 66–74)	71 (47–80, 66–74)
Ethnicity	NR	NR
BMI	NR	NR
Baseline PSA, ng/mL		

Study Reference	EORTC Trial 22991 (Bolla 2016)		
	Median (range, IQR)	10.3 (0.4–97.9, 7.0–15.9)	10.4 (0.3–50.7, 6.8–15.7)
	≤2.5 x UNL	198 (48.4)	199 (48.5)
	>2.5 x UNL to ≤ 4 x UNL	143 (35.0)	152 (37.1)
	>4 x UNL	68 (16.6)	59 (14.4)
	Prostate volume	NR	NR
	Number of positive biopsy samples	NR	NR
	Clinical T category		
	T1a (ineligible)	1 (0.2)	0 (0.0)
	T1b	16 (3.9)	11 (2.7)
	T1c	180 (44.0)	187 (45.6)
	T2a	207 (50.6)	210 (51.2)
	T2b (ineligible	5 (1.2)	2 (0.4)
	Clinical N category		
	N0	407 (99.5)	409 (99.8)
	Unknown	2 (0.5)	1 (0.2)
	Pathology N category		
	pN0	55 (13.4)	46 (11.2)
	Clinical M category		
	M0	408 (99.8)	409 (99.8)
	M1 (ineligible)	1 (0.2)	1 (0.2)
	Gleason sum		
	<6	46 (11.2)	46 (11.2)
	6	155 (37.9)	155 (37.8)
	7	171 (41.8)	164 (40.0)
	8–10	37 (9.0)	45 (11.0)
	WHO PS		
	0	349 (85.3)	372 (90.7)
	1	59 (14.4)	37 (9.0)
	2	1 (0.2)	1 (0.2)
	NCCN risk group*		
	Low (ineligible)	2 (0.5)	1 (0.2)
	Intermediate	174 (42.5)	187 (45.6)
	T2a (1997) with one other intermediate risk factor	80 (19.6)	84 (20.5)
	High	153 (37.4)	138 (33.7)
	D'Amico risk group		
	Low (ineligible)	2 (0.5)	1 (0.2)
	Intermediate	301 (73.6)	312 (76.1)
	High	106 (25.9)	97 (23.7)

* The NCCN risk groups are defined as: low risk if TNM 2002 stage T1c or T2a with PSA <10 ng/mL and Gleason ≤6; intermediate risk if TNM 2002 stage T2b to T2c, or Gleason = 7, or PSA ≥10 and <20 ng/mL and high risk if TNM 2002 stage T3a or PSA ≥20 ng/mL or Gleason >7 or two high-risk features.

Study Reference

EORTC Trial 22991 (Bolla 2016)

Methods

Randomisation

Random assignment performed at the EORTC headquarters according to a minimisation algorithm (variance method) with factors institution, clinical tumour stage (T1b–c vs T2a), Gleason sum (2–6 vs 7–10), PSA (2.5 x UNL, 2.5–4.0 x UNL and >4.0 x UNL). There was no blinding. The minimisation method was stratified by the radiation dose level because the dose was a centre-chosen characteristic.

Arm 1

RT alone

- 3DCRT or IMRT was performed with an isocentric beam arrangement, based on a computed tomographic definition of 3D PTV. Centres opted for one dose (70, 74 or 78 Gy)

Arm 2

RT + androgen suppression

- RT as above
- Androgen suppression consisted of 2 subcutaneous injections of every-3-months depot of LHRH analog (goserelin), given the first day of RT then 3 months later. Flare protection consisted of 1 month of antiandrogen (bicalutamide, 50 mg/d) started 1 week before the first LHRH injection

Duration of follow-up

Median follow-up 7.2 years, similar in the two treatment arms (p=0.475). Data cut-off October 20 2013. Censoring was applied to the last follow-up visit

Outcomes

Primary endpoint

- Biochemical DFS – defined from study entry until PSA relapse and clinical relapse by imaging or death or any cause to the first event of biochemical relapse. In the analysis, patients who started second-line treatment in the absence of pre-protocol progression were counted as biochemical failure when starting the treatment.
  - Clinical relapse was (1) palpable enlargement of an existing abnormality or regrowth by ≥25% of a previously regressed prostate gland, (2) urethral obstruction, (3) regional and distant metastases documented by imaging

Secondary endpoints

- Clinical DFS – defined from randomisation to clinical relapse
- OS – defined from randomisation to death

Harms and Benefits of Interventions

Biochemical DFS, OS, clinical DFS and other progression outcomes

Outcome	Number of events, n (%)			Rate at 5 years follow up, % (95% CI)				
	RT alone	RT + androgen suppression	P value	RT alone	RT + androgen suppression	P value	HR (95% CI) (Arm 2 vs Arm 1)	P value
Biochemical DFS	201 (49.1)	118 (410)	NR	69.8 (64.9–74.2)	82.6 (78.4–86.1)	NR	0.52 (0.41–0.66)	<0.001
Deaths in the absence of disease progression	54	54	NR	-	-	-	-	-
Deaths overall	83	69	NR	-	-	-	-	-
OS	-	-	-	88.4 (84.7–91.3)	91.3 (88.0–93.7)	NR	NR	NR
Clinical DFS	-	-	-	80.8 (76.5–84.3)	88.7 (85.2–82.1)	NR	0.63 (0.48–0.84)	0.001

Study Reference **EORTC Trial 22991 (Bolla 2016)**

Cumulative local relapse rate	-	-	-	6.6 (4.1–9.1)	2.1 (0.7–3.6)	NR	0.37 (0.21–0.68)	0.001
Distant metastases	31 (7.6)	18 (4.4)	0.05	-	-	-	-	-

Exploratory heterogeneity tests indicated no statistically significant impact of the radiation dose or the risk group on the unadjusted treatment effect (P>0.1)

Treatment discontinuations and adverse effects

Treatment discontinuation

- RT: n=7 (death = 2, toxicity = 3, intestinal occlusion = 1, lymphocele sepsis = 1)
- LHRH (receiving 1 injection instead of 2): n=11 (toxicity = 6, patient declined treatment = 4, other reasons = 1)

Adverse effects

- 6 month androgen suppression (n=403), n (%):
  - Hot flushes > once per day = 127 (31.5)
  - Gynecomastia = 27 (6.7)
  - Diarrhoea of ≥ grade 3 = 2 (0.5)
  - Elevation of ALT/AST = 20 (5.0)
- RT alone vs RT + androgen suppression, %:
  - Late grade 3–4 GU toxicity: 3.6% vs 5.9% (P=0.14)
  - Severe impairment of sexual function: 19.4% vs 27.0% (P=0.010)

Mean scores and mean score change from baseline for the primary HRQoL scales

Characteristic	Score		Score change from baseline	
	RT alone (N=364)	RT + androgen suppression (N=351)	RT alone (N=364)	RT + androgen suppression (N=351)
Global health status/QoL				
Baseline				
Median (range, IQR)	83.3 (0.0–100.0, 66.7–91.7)	83.3 (0.0–100.0, 66.7–91.7)	-	-
Mean (SD)	77.04 (18.72)	78.15 (17.71)	-	-
n	359	347	-	-
Month 6				
Median (range, IQR)	83.3 (0.0–100.0, 66.7–91.7)	83.3 (0.0–100.0, 66.7–91.7)	0.0 (283.3–75.0. 28.3–8.3)	0.0 (266.7–58.3, 28.3–8.3)
Mean (SD)	78.54 (18.17)	76.97 (18.32)	0.66 (18.39)	–2.36 (17.33)
n	271	305	239	261
Year 1				
Median (range, IQR)	83.3 (0.0–100.0, 66.7–91.7)	83.3 (16.7–100.0, 66.7–91.7)	0.0	0.0
Mean (SD)	77.65 (18.65)	78.52 (16.43)	0.52 (20.61)	–20.68 (17.91)
n	289	315	255	270
Year 2				
Median (range, IQR)	83.3 (0.0–100.0, 66.7–91.7)	83.3 (8.3–100.0, 66.7–91.7)	0.0	0.0

Study Reference	EORTC Trial 22991 (Bolla 2016)				
	Mean (SD)	66.7-91.7	66.7-91.7		
	n	321	322	286	275
	Year 3				
	Median (range, IQR)	83.3 (0.0–100.0, 66.7–91.7)	83.3 (0.0–100.0, 66.7–91.7)	0.0	0.0
	Mean (SD)	75.58 (19.47)	77.20 (18.85)	–2.91 (21.08)	–2.29 (19.60)
	n	301	307	269	262
	Hormonal symptoms				
	Baseline				
	Median (range, IQR)	5.6 (0.0–50.0, 0.0–11.1)	0.0 (0.0–5.3, 0.0–11.1)	-	-
	Mean (SD)	7.58 (10.32)	6.67 (9.59)	-	-
	n	308	306	-	-
	Month 6				
	Median (range, IQR)	5.6 (0.0–55.6, 0.0–11.1)	16.7 (0.0–83.3, 11.1–27.8)	0.0 (–38.9–55.6, 0.0–5.6)	11.1 (–11.1–66.7, 5.6–22.2)
	Mean (SD)	9.47 (11.66)	19.32 (13.65)	2.23 (10.62)	13.95 (12.01)
	n	235	264	193	219
	Year 1				
	Median (range, IQR)	8.3 (0.0–53.3, 0.0–16.7)	16.7 (0.0–61.1, 5.6–27.8)	0.0 (–33.3–42.2, 0.0–6.7)	11.1 (–27.8–46.7, 0.0–22.2)
	Mean (SD)	10.85 (11.99)	18.07 (14.11)	2.83 (10.54)	11.66 (12.68)
	n	257	274	216	230
	Year 2				
	Median (range, IQR)	6.7 (0.0–58.3, 0.0–16.7)	11.1 (0.0–0.60, 5.6–22.2)	0.0 (–44.4–44.4, 0.0–11.1)	5.6 (–33.3–54.4, 0.0–11.1)
	Mean (SD)	11.21 (11.99)	13.67 (12.89)	4.40 (11.33)	7.89 (12.58)
	n	281	279	237	231
	Year 3				
	Median (range, IQR)	8.3 (0.0–66.7, 0.0–16.7)	11.1 (0.0–66.7, 0.0–22.2)	0.0 (–44.4–55.6, 0.0–11.1)	5.6 (–22.2–46.7, 0.0–11.1)
	Mean (SD)	11.68 (12.87)	12.79 (12.83)	4.42 (13.38)	7.13 (11.53)
	n	263	262	221	218
	Sexual activity				
	Baseline				
	Median (range, IQR)	33.3 (0.0–100.0, 0.0–33.3)	33.3 (0.0–100.0, 0.0–33.3)	-	-
	Mean (SD)	27.99 (24.71)	27.43 (22.63)	-	-
	n	309	302	-	-
	Month 6				
	Median (range, IQR)	33.3 (0.0–100.0, 0.0–33.3)	0.0 (0.0–100.0, 0.0–33.3)	0.0 (–50.0–66.7, 0.0–16.7)	–16.7 (–100.0–100.0, –33.0–0.0)
	Mean (SD)	27.09 (22.41)	10.84 (19.22)	0.43 (20.22)	–15.67 (25.66)
	n	235	266	196	218
	Year 1				
	Median (range, IQR)	33.3 (0.0–100.0, 0.0–41.7)	0.0 (0.0–100.0, 0.0–33.3)	0.0 (–66.7–100.0, –16.7–16.7)	–16.7 (–100.0–100.0, –33.0–0.0)
	Mean (SD)	27.60 (24.87)	14.96 (21.93)	0.62 (25.41)	–13.54 (26.60)
	n	256	273	216	229
	Year 2				

Study Reference	EORTC Trial 22991 (Bolla 2016)				
	Median (range, IQR)	33.3 (0.0–100.0, 0.0–33.3)	16.7 (0.0–100.0, 0.0–33.3)	0.0 (–66.7–100.0)	0.0 (–100.0–100.0, –16.7–0.0)
	Mean (SD)	25.73 (22.42)	24.29 (23.30)	–2.35 (24.52)	–4.08 (24.88)
	n	274	280	234	233
	Year 3				
	Median (range, IQR)	33.3 (0.0–100.0, 0.0–33.3)	16.7 (0.0–100.0, 0.0–33.3)	0.0 (–83.3–100.0, 16.7–16.7)	0.0 (–83.3–100.0, 16.7–0.0)
	Mean (SD)	26.88 (24.11)	24.08 (23.32)	–1.98 (24.34)	–4.19 (23.96)
	n	261	263	219	215
	Sexual function (assigned a score of 0 in absence of activity)				
	Baseline				
	Median (range, IQR)	50.0 (0.0–100.0, 0.0–75.0)	56.9 (0.0–100.0, 0.0–8.3)	-	-
	Mean (SD)	40.49 (37.50)	43.91 (38.96)	-	-
	n	253	230	-	-
	Month 6				
	Median (range, IQR)	33.3 (0.0–100.0, 0.0–66.7)	0.0 (0.0–100.0, 0.0–0.0)	0.0 (–91.7–83.3, –16.7–0.0)	–8.3 (–100.0–75.0, –75.0–0.0)
	Mean (SD)	35.33 (34.67)	5.85 (17.76)	–4.34 (33.44)	–32.05 (39.79)
	n	181	211	142	132
	Year 1				
	Median (range, IQR)	25.0 (0.0–100.0, 0.0–66.7)	0.0 (0.0–100.0, 0.0–0.0)	0.0 (–100.0–75.0, –22.2–0.0)	–16.7 (–100.0–83.3, –61.1–0.0)
	Mean (SD)	33.11 (34.76)	12.65 (25.14)	–7.14 (31.98)	–29.24 (38.45)
	n	189	208	142	143
	Year 2				
	Median (range, IQR)	20.8 (0.0–100.0, 0.0–58.3)	13.9 (0.0–100.0, 0.0–58.3)	–8.3 (–91.7–83.3, –33.3–0.0)	–8.3 (–100.0–83.3, –33.0–0.0)
	Mean (SD)	30.63 (32.55)	28.18 (31.90)	–12.55 (33.30)	–17.03 (35.02)
	n	210	202	170	146
	Year 3				
	Median (range, IQR)	25.0 (0.0–100.0, 0.0–58.3)	8.3 (0.0–100.0, 0.0–58.3)	0.0 (–91.7–91.7, –33.3–0.0)	–8.3 (–100.0–100.0, –33.3–0.0)
	Mean (SD)	31.25 (32.96)	27.95 (31.64)	–13.96 (34.64)	–15.56 (34.95)
	n	197	195	157	131
	No clinically relevant difference in HRQoL was found between the groups. Hormonal treatment symptoms, as well as sexual activity and functioning scales, were clinically significantly impacted by androgen suppression at month 6 and year 1. However, no marked difference was seen between the arms from year 2 onward.				
Authors' Conclusions	• This study showed that 6 months of androgen suppression combined with RT significantly improved biochemical DFS and clinical DFS of patients with intermediate or high-risk (D'Amico) localised PCa, as compared with RT alone, irrespective of the radiation dose level. • Results suggest that adding 6 month androgen suppression as a concomitant and adjuvant modality improves biochemical DFS even at a dose of 78 Gy, with acceptable adverse effects. Furthermore for patients with low-volume high-risk localised PCa, the results pave the way to using a combination approach with 78 Gy RT plus a short androgen suppression duration. Such an approach should be formally compared with long-term or intermediate duration of androgen suppression.				

Abbreviations: 3DCRT, 3-dimentional conformal radiation therapy; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; DFS, disease-free survival; EORTC, European Organisation for Research and Treatment of Cancer; GU, genitourinary; HR, hazard ratio; HRQoL, health-related quality of life; IMRT, intensity-modulated radiation therapy; IQR, interquartile range; LHRH, luteinising hormone releasing hormone; N/A, not applicable; NR, not reported; OS, overall survival; PCa, prostate cancer; PS, performance status; PSA, prostate-specific antigen; PTV, prostate tumour volume; QoL, quality of life; RCT, randomised controlled trial; UNL, upper limit of normal; WHO, World Health Organization

Table 41g. NCT02668718, Hackman 2019

Study Reference	**NCT02668718**, Hackman 2019
Study Design	Study name NCT02668718 Design Randomised, open-label, parallel-group, multicentre trial Objective To compare the effectiveness and tolerability of adjuvant radiotherapy following radical prostatectomy Dates April 2004–October 2012 Country Finland Setting Multicentre
Population Characteristics	Patient recruitment and eligibility NR **Inclusion** Written informed consent, pT2N0M0 with a positive margin or pT3aN0M0 (with/without positive margins) prostate cancer, Gleason score 2–10, preoperative PSA 20 mg/l, and post-operative PSA 0.5 µg/l **Exclusion** Concurrent cancer therapy including systemic endocrine therapy, more than 12 weeks since radical prostatectomy, metastatic disease (N+ or M1), and invasion of seminal vesicles. **Other** NR Sample size N invited = 206 N eligible = 206 N enrolled = 206 N excluded (with reason) = 0 N lost to follow-up = 0 N completed = 157 N excluded from analysis = 54

Study Reference **NCT02668718**, Hackman 2019

N included in analysis = 157

Demographics

Parameter	Adjuvant (N=126)	Observation (N=124)
Age at recruitment/randomisation, median (IQR), years	61 (57–65)	62 (59–65)
Ethnicity	NR	NR
BMI	NR	NR
Preoperative PSA level		
<20	125	123
>20[a]	1	1
Median (IQR)	7.2 (5.2–10.1)	7.5 (5.5–10.2)
Postoperative PSA		
<0.05	24	35
<0.1	14	9
<0.2	20	20
<0.4	33	22
<0.5	35	37
0.5	0	1
Prostate volume	NR	NR
Number of positive biopsy samples	NR	NR
Clinical T stage		
1	4	2
1a	2	1
1c	62	66
2	17	26
2a	2	1
2b	2	0
3	1	3
3a	1	0
Unavailable	35	25
Pathological T stage		
2	1	0
2a	10	13
2b	10	11
2c	52	39
3a	53	59
4	0	1
Unavailable	0	1
M stage	NR	NR
N stage	NR	NR
Gleason score		

Study Reference	**NCT02668718**, Hackman 2019		
	5	9	8
	6	29	25
	7	81	83
	8	4	4
	9	3	4
	Other risk classification (e.g. D'Amico or CAPRA)	NR	NR

Methods

Randomisation
Following the patient's informed consent, the urologist called Finnish Cancer Registry (Helsinki, Finland), which conducted stratification into three groups by Gleason score (Gleason scores 2–6, 7, and 8–10) and randomisation; 250 patients were randomised 1:1, with the hypothesis that 80% in the adjuvant group and 60% in the observation group will remain biochemical progression free after 2 yr of follow-up, giving a power of >80% and significance level of 5%. As calculated by Fischer's exact test, the required sample size for two independent groups was 90 patients/ group. To avoid loss of power due to possible loss in follow-up, investigators writing the protocol decided to increase the sample size to patients/group (39% safety margin) based on clinical judgement and experience from previous prostate cancer trials. Following the patient's informed consent, the urologist called Finnish Cancer Registry (Helsinki, Finland), which conducted stratification into three groups by Gleason score (Gleason scores 2–6, 7, and 8–10) and randomisation.

Arm 1
Adjuvant radiotherapy

The radiation dose consisted of 66.6 Gy given in 37 fractions of 1.8 Gy/d, 5 d per week. Patients received three-dimensional conformal radiation therapy (with linear accelerator >10 MV) without pelvic lymph node irradiation.

Arm 2
Observation

In the observation group, salvage radiotherapy could be offered upon disease progression. The protocol defined progression as (1) PSA >0.4 mg/l in two successive measurements at least 4 weeks apart, (2) metastatic prostate cancer, or (3) recurrent prostate cancer in imaging regardless of PSA.

Duration of follow-up
Median of 9.3 years in the adjuvant RT group and 8.6 years in the observation group. Outcomes were reported as 10-year time points.

Outcomes
Primary, secondary and any other relevant outcomes (e.g. mortality, metastasis-free survival, quality of life, functioning, bowel, urinary and sexual dysfunction, psychological effects, endocrinological effects, surgical complications, rates of disease recurrence, treatment-related complications etc) reported in the study, in addition to the methods used to investigate these outcomes.

Primary endpoint

- Biochemical recurrence-free survival. Progression was defined as: (1) PSA >0.4 mg/l in two successive measurements at least 4 weeks apart, (2) metastatic prostate cancer, or (3) recurrent prostate cancer in imaging regardless of PSA. In the observation group, salvage radiotherapy could be offered upon disease progression.
- Overall survival
- Prostate-cancer specific survival

Study Reference **NCT02668718**, Hackman 2019

- Metastatic survival
- Castration-resistance prostate cancer-free survival
- All survival outcomes were calculated as 10-year survival rates

Secondary endpoints

- Adverse events, graded from patients' individual medical records from randomisation to progression or until the last follow-up if the patient was progression free.
- Patients filled out three questionnaires, and results were reported as predicted probabilities using a generalised mixed model (GLMM):
  - International Index of Erectile Function (IIEF-5). IIEF-5 score was modelled as binomially distributed scores 1–7 vs 8–25) over continuous time (months) according to GLMM. IIEF-5 score: 1–7 = severe erectile dysfunction, 8–21 = mild–moderate erectile dysfunction, and 22–25 = no erectile dysfunction.
  - International Prostate Symptom Score (IPSS). IPSS score was modelled as binomially distributed scores 20–35 vs 0–19) over continuous time (months) according to GLMM. IPSS score: 0–7 = mild urinary symptoms, 8–19 = moderate urinary symptoms, and 20–35 = severe urinary symptoms.
  - Late Effects Normal Tissue Task Force–Subjective, Objective, Management, Analytic (LENT-SOMA) questionnaire with intestinal and urinary questions from the subjective, objective, and management parts of the LENT-SOMA parameters. LENT- SOMA modelled as binomially distributed grades 3–4 vs 0–2) over continuous time (months) according to GLMM. The LENT-SOMA toxicities were graded according to the patients' answers from 0 to 4, where grade 0 stands for no toxicity and grade 4 stands for the most severe toxicity. For one LENT-SOMA question regarding the management of dysuria, the answer option for surgical intervention (grade 4 toxicity) was unavailable; therefore, the answers for this question were graded from 1 to 3. Urinary toxicities were modelled as binomially distributed grades 3–4 vs 0–2) over continuous time (months) according to GLMM.

Harms and Benefits of Interventions

Outcome	Number of events		HR (%, 95% CI)	p-value
	Adjuvant therapy (N=126)	Observation (N=124)		
Biochemical recurrence	15	43	0.30 (0.16–0.53)	<0.001
Metastatic	2	4	0.49 (0.09–2.68)	0.4
Castration resistant	3	6	0.47 (0.12–1.88)	0.3
Prostate cancer death	1	1	1.00 (0.06–15.91)	1
Death from any cause	10	13	0.76 (0.33–1.72)	0.5

Outcome	Number of events, %		OR (%, 95% CI)	p-value
	Adjuvant therapy (N=126)	Observation (N=124)		

Study Reference **NCT02668718**, Hackman 2019

Number of patients experiencing adverse event			0.71 (0.55–0.92)	0.009
Grade 1	121 (96)	105 (85)	–	–
Grade 2	115 (91)	107 (87)	–	–
Grade 3	70 (56)	50 (40)	–	–
Grade 4	1 (1)	0 (0)	–	–
Number of patients experiencing gastrointestinal disorders			0.12 (0.07–0.19)	<0.001
Grade 1	97 (77)	16 (13)	–	–
Grade 2	29 (23)	4 (3)	–	–
Grade 3	1 (1)	1 (1)	–	–
Grade 4	0 (0)	0 (0)	–	–
Number of patients experiencing urinary disorders			0.48 (0.36–0.64)	<0.001
Grade 1	111 (88)	77 (62)	–	–
Grade 2	72 (57)	47 (38)	–	–
Grade 3	18 (14)	7 (6)	–	–
Grade 4	0 (0)	0 (0)	–	–
Number of patients experiencing erectile dysfunction			0.75 (0.56–1.00)	0.050
Grade 1	71 (56)	52 (42)	–	–
Grade 2	94 (75)	95 (77)	–	–
Grade 3	47 (37)	35 (28)	–	–
Grade 4	0 (0)	0 (0)	–	–
Total number of adverse events			–	<0.001
Grade 1	733	259	–	–
Grade 2	298	165	–	–
Grade 3	105	62	–	–
Grade 4	1	0	–	–
Total	1137	486	–	–
Median and range of adverse events per patient			–	–
Grade 1	6 (0–17)	1.5 (0–11)	–	–
Grade 2	2 (0–14)	1 (0–4)	–	–
Grade 3	1 (0–6)	0 (0–3)	–	–
Grade 4	0 (0–1)	–	–	–

Predicted probabilities of toxicity grades

	Predicted probability of severe toxicity	
Toxicity	Observation vs adjuvant RT, OR (95% CI)	p-value

Study Reference	**NCT02668718**, Hackman 2019

Erectile dysfunction (IIEF-5)	0.70 (0.29–1.68	0.4
Urinary dysfunction (IPSS)	0.51 (0.25–1.03	0.061
Urinary toxicity (LENT-SOMA)	0.76 (0.40–1.42)	0.4
Intestinal toxicity (LENT-SOMA)	0.04 (0.00–0.43)	0.008

- The most common LENT-SOMA toxicities were urinary frequency (93% of the patients in the adjuvant group and 92% in the observation group filled the questionnaire), urinary incontinence (70% and 62%, respectively), decreased urinary stream (61% and 56%, respectively), and rectal tenesmus (64% and 42%, respectively).
- The most common grade 4 toxicities were kidney-related toxicity (18 patients in the adjuvant group and 15 in the observation group), urinary incontinence (seven and five patients, respectively), and urinary frequency (five and two patients, respectively). The most common grade 4 kidney-related toxicity was based on two questions: answering “yes” to “do you suffer from tiredness and headache?” led to grade 3, and “yes” to “are you passing less urine than you usually do/are your feet swollen?” led to grade toxicity.

Authors’ Conclusions

- In summary, adjuvant radiotherapy prolongs the time from radical prostatectomy to biochemical recurrence with the strongest impact on pT2 disease with positive margins and Gleason score 5–7. However, adjuvant radiotherapy causes more adverse effects compared with observation, and salvage therapy upon biochemical recurrence appears as effective as adjuvant therapy with regard to overall survival.
- In the observation arm, 37 of 124 patients received salvage radiotherapy for protocol-defined progression, after which remained recurrence free, while 121 of 126 patients in the adjuvant arm received radiotherapy following radical prostatectomy (five declined radiation despite randomisation into this arm). Of note, more cases of metastatic disease and CRPC occurred in the observation (“salvage”) arm, suggesting that high-risk patients should be offered the possibility to consider adjuvant radiotherapy following radical prostatectomy.
- Only the patient can balance the subjective questions of radiation-related adverse events to a lower risk of biochemical recurrence, cancer progression, and its consequences.

Abbreviations: CI: confidence interval; CRPC: castration-resistant prostate cancer; cT: clinical T stage; GLMM: generalised linear mixed model; IIEF: International Index of Erectile Function; IPSS: International Prostate Symptom Score; LENT-SOMA: Late Effects Normal Tissue Task Force (LENT)-Subjective, Objective, Management Analytic (SOMA); OR: odds ratio; PSA: prostate-specific antigen; pT: Pathological T stage; RT: radiotherapy.

Table 41h. Lennernäs 2015

Study Reference	**Lennernäs 2015**
Study Design	Study name NR Design Multicentre randomised, parallel and open trial Objective This paper is the first report on a study, performed in Sweden in 1996–2001, in which patients with localised/locally advanced PC were randomised to HDR brachytherapy (the RT group) (2 x 10 Gy) combined with external beam RT (EBRT, 25 x 2 Gy) or to an open surgery

Study Reference	Lennernäs 2015
	procedure (the RP group). The aim was to assess differences between the two treatment arms with regard to patient-reported outcomes, such as complications and HRQoL. Dates 1996–2001 Country Sweden Setting Hospitals in Gothenburg, Uppsala, Linköping, Eskilstuna and Stockholm
	Patient recruitment and eligibility **Inclusion** Men with localised/locally advanced PC clinical category T1b – T3a, N0, M0 and a PSA value ≤ 50 ng/ml were included. Patients should have accepted RP or RT **Exclusion** Patients should not have gone through myocardial infarction within the last six months; serum bilirubin, ASAT/ALAT should not exceed 1.2 times the normal highest reference limit. Other malignant disease, excluding basal cell carcinoma, was an exclusion criteria **Other** PC was proven histopathologically by ultrasound-guided transrectal core-needle biopsy, mapping a total of six biopsies from all four quadrants and at least two biopsies from the base of the seminal vesicles. Bone scans were performed on all patients with a PSA level ≥ 10 ng/ml and not older than three months at randomisation Sample size A total of 89 patients were included in the study and randomised
Population Characteristics	Demographics

Parameter	Randomised to prostatectomy (n=45)	Randomised to irradiation (n=44)
Median age (years)	64	66
Ethnicity	NR	NR
BMI	NR	NR
PSA level	NR	NR
Prostate volume	NR	NR
Number of positive biopsy samples	NR	NR
T stage, n (%) *T1* *T2* *T3* *Unknown*	 18 (40) 17 (38) 4 (9) 6 (13)	 17 (39) 16 (36) 3 (7) 8 (18)
Gleason score	NR	NR

Study Reference	Lennernäs 2015			
	Other risk classification (e.g. D'Amico or CAPRA)	NR	NR	
Methods	Randomisation The patients were randomised to HDR brachytherapy (2 x 10 Gy) combined with EBRT (25 x 2 Gy) (the RT group) or to an open surgery procedure (the RP group). Randomisation was performed by telephone and recorded at a central registration office at the Regional Oncology Centre, Sahlgrenska Hospital, Gothenburg. The patients were stratified according to the following: treating centre; G1 – G2 or G3, and T1 – T2 or T3; age < 70 years or ≥ 70 years; PSA < 20 or ≥ 20 ng/ml Arm 1 (RP group) **Prostatectomy** Patients randomised to RP underwent lymph node evaluation in connection to surgery. Only node-negative patients proceeded to a nerve sparing RP, which was performed within 3–4 months after randomisation. Lymphadenectomy was conducted in patients with stage T1b-T2 PC and PSA ≥ 20 ng/ml and in all those with either T3 tumours, irrespective of grades, or grade 3 tumours irrespective of stages. Bilateral lymph node dissection was done with laparoscopic technique with bilateral node dissection including obturator nodes. The RP procedure was the nerve sparing method. The surgeon aimed to conduct a radical operation and sacrificed the neurovascular bundles on the tumour side. If the patient was found to have more extensive disease than presumed preoperatively, surgery was still performed if technically feasible **Total androgen blockade** All patients were treated with total androgen blockade (TAB), consisting of a combination of antiandrogen and gonadotropin releasing hormone (GnRh) analogue in the neo-adjuvant setting. The TAB included leuprorelin (s.c. 3.75 mg every 4th week) and flutamide (250 mg orally three times a day) that continued for six months Arm 2 (RT group) Irradiation given as a combination of EBRT and HDR brachytherapy was initiated within 3 – 4 months after randomization. Before that, they all had lymph node dissection according to above described criteria. **EBRT** The clinical target volume (CTV) comprised the tumour and the entire prostate gland with a margin of 0.5 cm. The planning target volume (PTV) included CTV with a margin of 1.5 cm. If the posterior extension of this margin included more than half of the rectal lumen, the margin in this direction was restricted to encompass less than half of that area. RT was planned with a three-dimensional (3D) dose planning system (Dosetech or Helax), delivered with at least 8 MV photon beams. **HDR brachytherapy** CTV comprised the entire prostate including the tumour. PTV included an additional 3-mm margin. The minimum radiation dose was 10 Gy. The recommended rectal dose was not to be given in excess of 6 Gy, defined as the dose to the rectal volume outside a 3-cm long line drawn parallel to the dorsal limitation of the prostate. Two brachytherapy treatments given at a two-week intervals were planned for each patient. If the first brachytherapy session caused toxicity, or if the patient did not participate in a second session for any reason, the second treatment session was replaced with additional external RT of 14 Gy. All patients were evaluated according to the intention-to-treat principle. **Total androgen blockade** As above Duration of follow-up 10 years			

Study Reference	Lennernäs 2015
Harms and Benefits of Interventions	Outcomes HRQoL was assessed on three occasions: before randomisation to therapy and 12 and 24 months after randomisation. HRQoL was measured with the European Organization of Research and Treatment of Cancer Quality of Life Questionnaire C33 (EORTC QLQ-C33). A PC-specific HRQoL questionnaire consisting of 20 items (developed in Gothenburg, Sweden) was used to gather information on specific problems experienced by PC patients with respect to bowel, urinary tract, and sexual function. Survival rate, prostate cancer mortality and all-cause mortality were also recorded.

Mean scores and standard deviations (SD) for the EORTC QLQ-C33 subscales and single items

Variable	Randomisation arm	Assessment points		
		Randomisation Mean (SD)	12 months Mean (SD)	24 months Mean (SD)
Physical functioning[1]	Irradiation (n = 25) Prostatectomy (n = 33)	95 (13) 97 (11)	94 (14) 96 (9)	94 (17) 96 (12)
Role functioning[1]	Irradiation (n = 26) Prostatectomy (n = 33)	96 (14) 92 (25)	96 (14) 94 (24)	96 (14) 97 (17)
Emotional functioning[1]	Irradiation (n = 25) Prostatectomy (n = 33)	78 (19) 81 (21)	86 (19) 89 (15)	87 (17) 88 (16)
Cognitive functioning[1]	Irradiation (n = 25) Prostatectomy (n = 31)	89 (16) 88 (12)	88 (16) 89 (10)	88 (18) 87 (13)
Social functioning[1]	Irradiation (n = 26) Prostatectomy (n = 33)	92 (13) 92 (20)	83 (21) 82 (20)	83 (24) 90 (20)
Global quality of life[1]	Irradiation (n = 24) Prostatectomy (n = 31)	80 (18) 82 (20)	76 (22) 77 (16)	75 (20) 77 (21)
Fatigue[2]	Irradiation (n = 25) Prostatectomy (n = 32)	11 (18) 14 (18)	14 (17) 16 (15)	12 (14) 13 (16)
Pain[2]	Irradiation (n = 26) Prostatectomy (n = 33)	10 (16) 7 (13)	15 (18) 10 (18)	14 (24) 8 (14)
Insomnia[2]	Irradiation (n = 25) Prostatectomy (n = 33)	13 (26) 7 (14)	12 (23) 17 (24)	8 (14) 9 (15)
Constipation[2]	Irradiation (n = 26) Prostatectomy (n = 33)	4 (11) 1 (6)	5 (20) 4 (14)	3 (9) 3 (10)
Diarrhea[2]	Irradiation (n = 26) Prostatectomy (n = 33)	6 (16) 2 (8)	14 (23) 5 (12)	9 (15) 3 (10)
Financial difficulties[2]	Irradiation (n = 26) Prostatectomy (n = 33)	10 (16) 8 (20)	23 (31) 24 (29)	22 (31) 11 (23)

[1]Range 0–100, high values indicate high levels of functioning and quality of life; [2]Range 0–100, high levels indicate pronounced symptoms and problems

No statistically significant differences between the two randomization groups were found for any of the HRQoL variables. There was a statistically significant improvement in emotional functioning over time (df = 2.57, F = 8.227, p = 0.0005). Also, social functioning decreased

Study Reference **Lennernäs 2015**

with time (df = 2.57, F = 5.540, p = 0.0051), and financial difficulties increased (df = 2.57, F = 7.225, p = 0.0011). There were no statistically significant group-by-time interactions

Frequencies of prostate cancer-specific problems

Assessments	Randomisation		12 months		24 months	
	RT%	RP%	RT%	RP%	RT%	RP%
*Urinary urgency						
1	47	58	54	59	39	58
2	37	42	32	26	32	21
3	13	0	11	10	26	18
4	3	0	3	5	3	3
*Urinary incontinence						
1	76	83	76	46	61	45
2	17	14	19	41	29	39
3	7	0	5	5	5	11
4	0	3	0	8	5	5
*Bowel incontinence						
1	93	92	81	90	76	92
2	7	8	14	10	24	8
3	0	0	5	0	0	0
4	0	0	0	0	0	0
*Bowel blood						
1	90	10	89	92	79	94
2	10	0	8	8	15	3
3	0	0	3	0	3	3
4	0	0	0	0	3	0
*Hot flushes						
1	87	78	65	65	79	71
2	10	14	27	18	16	21
3	0	8	5	8	5	5
4	3	0	3	5	0	3
#Erectile problems						
1	21	31	5	3	3	5
2	32	36	19	5	11	5
3	32	22	19	11	27	16
4	15	11	57	81	59	74
#Sexual interest						
1	32	39	19	15	21	21
2	32	33	22	18	10	13
3	21	25	24	26	32	37
4	15	3	35	41	37	29

Study Reference	Lennernäs 2015
	Response categories: 1 = Not at all; 2 = Little; 3 = Quite a bit; 4 = Very much. *30 – 38 patients (RT), 36 – 39 patients (RP); #28 – 37 patients (RT), 36 – 38 patients (RP). No statistically significant differences were found between the groups in terms of prostate cancer-specific complications. However, a statistically significant group-by-time interaction was found for urinary incontinence (df = 55,2; F = 7.304; p = 0.0011). Grade 4 urinary incontinence was not reported in the RT group at the one-year assessment, whereas 8% (n = 3) had this problem in the RP group. At the two-year assessment, grade 3 – 4 urinary incontinence was reported by 10% (n = 3) in the RT group compared to 16% (n = 4) in the RP group. Both groups reported diminished sexual interest (df = 53,2; F = 11.789; p = 0.0001) and erectile dysfunction (df = 52,2; F = 49.77; p = 0.0001) Survival A total of 68 patients (76%) were still alive in 2011, 10 years after the last patient was randomised into the trial. Eight patients (9%) (n = 6 in RP-group and n = 2 in RT-group) died of PC, and 13 patients died (n = 6 in RP-group and 7 in RT-group) of other causes
Authors' Conclusions	This randomised study showed no statistically significant differences in HRQoL and complications between patients subjected to RP and those given high-dose rate brachytherapy combined with external beam radiation therapy. Few patients died during the 10-year follow-up, but no conclusions can be drawn regarding differences in survival as the study was underpowered

Abbreviations: ASAT/ALAT, aspartate transaminase/alanine transaminase ratio; BMI, body mass index; CAPRA, cancer of the prostate risk assessment; CTV, clinical target volume; EBRT, external beam radiotherapy; EORTC QLQ-C33, European Organization of Research and Treatment of Cancer Quality of Life Questionnaire C33; GnRh, gonadotropin releasing hormone; HDR, high dose-rate; HRQoL, health-related quality-of-life; NR, not reported; PC, prostate cancer; PSA, prostate-specific antigen; PTV, planning target volume; RP, radical prostatectomy; RT, radiotherapy; SD, standard deviation; TAB, total androgen blockade

Table 41i. PMH 9907 (McPartlin 2016)

Study Reference	PMH 9907 (McPartlin 2016)
Study Design	Study name PMH 9907 Design Randomised controlled trial (phase 3) Objective To assess the benefit of hormone therapy with DE-EBRT for patients with localised PCa Dates Recruitment: 1999–2006 (closed early in 2005 due to concerns over data indicating a survival deficit from the addition of bicalutamide therapy to watchful waiting) Country Canada Setting NR

Study Reference	PMH 9907 (McPartlin 2016)

Population Characteristics

Patient recruitment and eligibility
NR

Inclusion
Prostate carcinoma with stage T1b–T2 tumours
Gleason scores 6–8
PSA levels ≤20 ng/mL
Patients with clinical T1b/T2a tumours and a Gleason score of 6 were required to have PSA levels from 10–20 ng/mL
No previous hormone or cytotoxic therapy

Exclusion
NR

Other
All patients had an ECOG PS ≤2, were aged ≤80 years and had no contraindication to DE-EBRT

Sample size
N invited = 252
N assigned to intervention = 123 (Arm 1: bicalutamide + RT), 129 (Arm 2: RT alone)
N eligible and available for evaluation = 119 (Arm 1), 122 (Arm 2)
N excluded (with reason) = 4 (Arm 1; 3 did not meet inclusion criteria, 1 had no follow up), 7 (Arm 2; 5 did not meet inclusion criteria, 1 withdrew consent, 1 had no follow up)
N lost to follow-up = 1 (Arm 1), 1 (Arm 2)
N completed = 111 (Arm 1), 116 (Arm 2)
N excluded from per protocol analysis = 8 (Arm 1; 4 did not receive bicalutamide, 2 received <75.6 Gy, 2 did not receive bicalutamide and received <75.6 Gy), 6 (Arm 2; 5 received <75.6 Gy, 1 received <75.6 Gy and received bicalutamide)
N included in analysis =

- Per protocol = 111 (Arm 1), 116 (Arm 2)
- ITT = 119 (Arm 1), 122 (Arm 2)

Demographics

Parameter	RT + bicalutamide (N=119)	RT alone (N=122)	p value[a]
Age, y, median (range)	71.4 [57.6-79.4]	70.9 [55.3-79.5]	0.41[b]
Ethnicity	NR	NR	NR
BMI	NR	NR	NR
PSA level, ng/mL, median (range)			
At randomisation	8.3 (1.2–19.6)	7.6 (1.1–20)	0.49[b]
At RT	2.6 (0.1–20.4)	7.6 (0.4–22.3)	<0.001[b]
Prostate volume	NR	NR	NR
% positive cores			
Median (range)	50 (8–100)	50 (7–100)	0.36[b]
Number missing	6	5	
T stage			
T1b–T2a	96 (80.7)	91 (74.6)	0.28
T2b–T2c	23 (19.3)	31 (25.4)	

Study Reference	PMH 9907 (McPartlin 2016)			
	M stage	NR	NR	NR
	N stage	NR	NR	NR
	Gleason score			
	3 + 3	13 (10.9)	17 (13.9)	0.51
	3 + 4	67 (56.3)	71 (58.2)	
	4 + 3	34 (28.6)	26 (21.3)	
	3 + 5	1 (0.8)	2 (1.6)	
	4 + 4	4 (3.4)	5 (4.1)	
	5 + 3	0 (0)	1 (0.8)	
	Risk group			
	Unclassified intermediate	1 (0.8)	3 (2.5)	>0.99[d]
	Favourable intermediate	29 (24.4)	28 (23)	
	Unfavourable intermediate	84 (70.6)	83 (68)	
	High	5 (4.2)	8 (6.5)	
	RT dose, Gy			
	75.6	40 (33)	36 (29.5)	0.58[c]
	78–79.8	75 (63)	80 (66.4)	
	<75.6	4 (3.4)	6 (4.9)	

[a] Calculated by the Fisher exact test unless otherwise indicated
[b] P values determined using the Mann-Whitney test
[c] P value is for 75.6 Gy vs 78.0–79.8 Gy
[d] Favourable vs unfavourable

Methods

Randomisation
Stratified randomisation carried out according to initial PSA level (<10 vs ≥10 ng/mL), Gleason score (<7 vs 7 or 8) and tumour stage (T1 vs T2)

Arm 1 (n=119)
Bicalutamide + DE-EBRT

- 5 months of neoadjuvant and adjuvant bicalutamide (**150 mg once daily**) starting 3 months before RT
- Patients received RT using 6-coplanar, equally weighted 18 MV beams or IMRT with daily imaging using an electronic portal imaging device and setup verification using fiducial markers. From 1999–2001, patients received **75.6 Gy in 42 fr over 8.5 weeks**, subsequently, the dose was increased to **79.8 Gy in 42 fr** and then **78 Gy in 39 fr** as experience with DE-EBRT increased

Arm 2 (n=122)
DE-EBRT

- RT as above

Duration of follow-up
Median follow-up for surviving patients = 9.1 years (0.1–14.8 years)

Outcomes
Primary endpoint

- Biochemical failure – defined using the Phoenix criteria as a rise ≥2 ng/mL above the PSA nadir

Secondary endpoints

Study Reference | **PMH 9907 (McPartlin 2016)**

- Local tumour control – assessed by repeat transrectal prostate biopsy 2 years after the completion of RT
- QoL – measured using the EORTC QLQ-C30 v +3 and IIEF checklist
- OS
- Acute and late toxicity – measured using the RTOG acute and late toxicity scales

Harms and Benefits of Interventions

Biochemical failure and OS

Outcome	Rate at 5 years follow up, % (95% CI)			Rate at 9 years follow up, % (95% CI)		
	Bicalutamide + RT	RT alone	P value	Bicalutamide + RT	RT alone	P value
Biochemical failure	17 (11–25)	24 (17–33)	NR	40 (31–51)	47 (37–58)	0.32
OS				82 (75–90)	86 (80–94)	0.37

Biochemical failure: Bicalutamide + RT vs RT, HR = 0.82 (95% CI 0.55–1.21) (9 year follow up)
OS: Bicalutamide + RT vs RT, HR = 1.33 (95% CI, 0.72–2.47) (9-year follow up)

Multivariate analysis for biochemical failure (N=215)

Variable	HR	95% CI	P value
RT + bicalutamide vs RT alone	0.78	0.51–1.19	0.25
Unfavourable vs favourable risk group	1.89	1.09–3.25	0.022
High-dose vs low-dose RT	0.56	0.37–0.86	0.0082

RTOG acute and late toxicity

Toxicity	By treatment, n (%)			By RT dose, n (%)		
	Bicalutamide + RT (n=119)	RT alone (n=122)	P value[a]	75.6 Gy	78–79.8 Gy	P value[a]
Acute GI Grade 2	11 (9.6)	11 (8.7)	0.83	5 (6.6)	16 (10.3)	0.47
Acute GI Grade 3	0 (0)	0 (0)		0 (0)	0 (0)	
Acute GU Grade 2	33 (28.9)	38 (29.9)	>0.99	11 (14.5)	60 (38.7)	0.00027
Acute GU Grade 3	2 (1.8)	0 (0)		1 (1.3)	1 (0.6)	
Late GI Grade 2	4 (3.5)	6 (4.7)	0.55	0 (0)	9 (5.8)	0.033
Late GI Grade 3	0 (0)	1 (0.8)		0 (0)	1 (0.6)	
Late GU Grade 2	11 (9.6)	7 (5.5)	0.41	5 (6.6)	13 (8.4)	>0.99
Late GU Grade 3	13 (11.4)	14 (11)		9 (11.8)	15 (9.7)	

[a] Fisher exact tests reflect the association between grade 2 and 3 vs grade 0 and 1 toxicities and the treatment received (bicalutamide or RT dose)

Bicalutamide therapy was stopped prematurely in 5 patients (4.3%) due to gynecomastia (n=3), periorbital pain of unclear aetiology (n=1) and unspecified reasons (n=1).

QoL

There was almost no long-term change in erectile dysfunction in either group, although there were marked levels of impairment at baseline. There was deterioration in intercourse satisfaction and sexual desire in both arms during follow-up, but no clear change from baseline in overall satisfaction was observed 4 years after treatment in either group. The EORTC-30 questionnaire similarly identified no marked effect of the addition of bicalutamide, with stable overall QoL reported in both groups through the treatment period.

Study Reference	PMH 9907 (McPartlin 2016)
Authors' Conclusions	• The PMH 9907 study failed to demonstrate a significant benefit from the addition of bicalutamide to DE-EBRT for a group of patients with predominantly intermediate risk PCa. A trend toward a reduction in the biochemical failure rate after combination therapy was observed, and the conclusions were limited by failure to complete accrual. • Bicalutamide was well tolerated and, in this cohort, appeared to have no significant adverse effect on sexual function.

Abbreviations: CI, confidence interval; DE-EBRT, dose-escalated external beam radiotherapy; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; fr, fractions; GI, gastrointestinal; GU, genitourinary; HR, hazard ratio; IIEF, International Index or Erectile Function; IMRT, intensity-modulated radiation therapy; N/A, not applicable; MV, megavolt; OS, overall survival; NR, not reported; PCa, prostate cancer; PS, performance status; PSA, prostate-specific antigen; QLQ-C30, Quality-of-Life Questionnaire C30; QoL, quality of life; RCT, randomised controlled trial; RTOG, Radiation Therapy Oncology Group

Table 41j. NCT00116220, Sanford 2017/Royce 2017

Study Reference	NCT00116220**, Sanford 2017/Royce 2017**
Study Design	Study name NCT00116220 Design Randomised controlled trial Objective To evaluate whether the extent of anti-androgen received impacted the risk of all-cause mortality and prostate cancer-specific mortality within comorbidity subgroups adjusting for age and prostate cancer prognostic factors. Dates December 1995 to April 2001 Country United States Setting Academic and community based centres in Massachusetts
Population Characteristics	Patient recruitment and eligibility NR **Inclusion** Patients with clinical stage T1b–T2bN0M0 unfavourable-risk, including a PSA level >10 ng/mL (maximum 40 ng/mL), biopsy Gleason score 7–10, or radiographic evidence of extracapsular extension and/or seminal vesicle invasion by using endorectal MRI. **Exclusion** NR **Other** NR Sample size – Sanford 2017

Study Reference	NCT00116220**, Sanford 2017/Royce 2017**

N invited = 206
N eligible = 206
N enrolled = 2016
N excluded (with reason) = 0
N lost to follow-up = 0
N completed = 206
N excluded from analysis = 0
N included in analysis = 206

Sample size – Royce 2017
N invited = 206
N eligible = 206
N enrolled = 2016
N excluded (with reason) = 0
N lost to follow-up = 0
N completed = 157
N excluded from analysis = 54
N included in analysis = 157

Demographics

Parameter	Full ADT (N=73)	Partial ADT (N=29)	No ADT (N=104)
Age at recruitment/randomisation, median (IQR), years	71.97 (68.75, 75.38)	71.76 (70.17, 73.62)	73.21 (68.90, 76.30)
Ethnicity	NR	NR	NR
BMI	NR	NR	NR
PSA level			
Median (IQR)	11.0 (7.50, 14.84)	11.2 (7.85, 17.33)	11.0 (7.52, 16.35)
≤4, n (%)	4 (5.48)	4 (13.79)	6 (5.77)
>4–10, n (%)	27 (36.99)	9 (31.03)	38 (36.54)
>10–20, n (%)	36 (49.32)	9 (31.03)	43 (41.35)
>20, n (%)	6 (8.22)	7 (24.14)	17 (16.35)
Prostate volume	NR	NR	NR
Number of positive biopsy samples	NR	NR	NR
T stage			
T1	43 (58.90)	12 (41.38)	43 (41.35)
T2a	13 (17.81)	6 (20.69)	26 (25.00)
T2b	17 (23.29)	11 (37.93)	35 (33.65)
M stage	NR	NR	NR
N stage	NR	NR	NR
Gleason score			
9–10	4 (5.48)	2 (6.90)	11 (10.58)

Study Reference	NCT00116220**, Sanford 2017/Royce 2017**

8 or 4+3	22 (30.14)	6 (20.69)	31 (29.81)
3+4 or less	47 (64.38)	21 (72.41)	62 (59.62)
Other risk classification (e.g. D'Amico or CAPRA)	NR	NR	NR

Methods

Randomisation
E.g. The research coordinator assigned eligible patients 1:1 using a randomisation schedule generated by means of the SAS programme (version 9.1) and an interactive web response system. Neither the participants nor the investigators were masked to treatment allocation, because blinding was not feasible.

Arm 1: **RT + full ADT** vs RT + partial ADT vs **RT + no ADT**
ADT consisted of 6 months of an LHRH agonist (leuprolide or goserelin acetate) in combination with 6 months of the nonsteroidal AA flutamide. The prescription dose of flutamide was 250 mg three times a day. Liver function tests (LFTs) including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphate and total bilirubin levels were obtained at regular intervals. Flutamide was discontinued if the ALT or AST level exceeded twice the upper limit of normal and then resumed once these levels normalized. If AST or ALT levels were elevated to twice the upper limit of normal again, flutamide was permanently discontinued. Flutamide was also held if the patient experienced gastrointestinal side effects including cramping, diarrhoea, or uncontrolled nausea and was reintroduced once these symptoms resolved. If the patient could not tolerate the full dose of resumed flutamide, then a half dose was attempted. If the half dose could not be tolerated, then flutamide was discontinued permanently. The number of days each patient took flutamide was recorded. All patients received 6 months of LHRH antagonist. In the men receiving partial ADT, the median duration of flutamide was 4.2 months (interquartile range, 3.3 to 5.5 months).

No detail on radiation received.

Duration of follow-up
Median follow-up 16.62 years

Outcomes
Primary endpoint(s)
- All-cause mortality, adjusted for age and prostate cancer prognostic factors (PSA level, clinical T category, biopsy Gleason score). The oncologist following the patient determined the cause of death.
- Prostate cancer-specific mortality, adjusted for age and prostate cancer prognostic factors (PSA level, clinical T category, biopsy Gleason score). The oncologist following the patient determined the cause of death. For PC to be the cause of death, the following criteria had to be met: castrate-resistant metastatic PC, a rising PSA despite multiple salvage ADT regiments, and usually chemotherapy before death.

Secondary endpoints
- No secondary outcomes reported by Sanford 2017
- PSA failure (Royce 2017)

Harms and Benefits of Interventions

Royce 2017: PSA failure compared by RT+ADT and RT groups

Outcome	Events		p-value
	RT+ADT (N=78)	RT (N=79)	
PSA failure			
Yes	25 (32.05)	60 (75.95)	<0.001

Study Reference NCT00116220**, Sanford 2017/Royce 2017**

No	60 (75.95)	19 (24.05)	

Sanford 2017: All-cause and prostate-cancer-specific mortality by comorbidity/intervention groups

Outcome	All-cause mortality					Prostate cancer specific mortality				
	Number of all-cause deaths	Univariate HR (95% CI)	p-value	Multivariate adjusted HR (95% CI)	p-value	Number of prostate-cancer deaths	Univariate HR (95% CI), p-value	p-value	Multivariate adjusted HR (95% CI), p-value	p-value
No/minimal comorbidity group										
RT + full ADT (N=60)	42	1.03 (0.53–2.01)	0.93	0.97 (0.49–1.91)	0.92	3	0.35 (0.07–1.62)	0.18	0.39 (0.07–2.18)	0.28
RT (N=79)	57	1.56 (0.81–2.97)	0.18	1.54 (0.80–2.98)	0.20	20	2.41 (0.70–8.29)	0.16	3.08 (0.93–10.21)	0.07
RT + partial ADT (N=18)	11	1 (Ref)	NA	1 (Ref)	2	2	1 (Ref)	NA	1 (Ref)	NA
Moderate/severe comorbidity										
RT + full ADT (N=13)	13	2.55 (1.10–5.87)	0.03	2.25 (0.94–5.41)	0.07	0	NA[a]	NA[a]	NA[a]	NA[a]
RT (N=25)	23	0.75 (0.36–1.58)	0.45	0.50 (0.22–1.10)	0.09	3	1.83 (0.16–20.40)	0.62	1.41 (0.13–14.81)	0.77
RT + partial ADT (N=11)	10	1 (Ref)	–	1 (Ref)	–	1	1 (Ref)	–	1 (Ref)	

Authors' Conclusions	Increasing AA use by 2 months does not appear to impact survival in men with localized unfavourable-risk PC and no or minimal comorbidity but may shorten survival in men with moderate to severe comorbidity raising concern regarding in whom and for how long the AA should be prescribed.

Abbreviations: AA: anti-androgen; ADT, androgen deprivation therapy; AST: aspartate aminotransferase, ALT: alanine aminotransferase, CAPRA: Cancer of the Prostate Risk Assessment; CI: confidence interval; HR: hazard ratio; IQR: interquartile range; LFT: liver function test; NA: not applicable; NR: not reported; RT: radiotherapy.

Table 41k. RTOG 94-08, Voog 2016

Study Reference	**RTOG 94-08,** Voog 2016
Study Design	Study name RTOG 94-08 Design Randomised controlled trial Objective To evaluate the relationship between short-course androgen deprivation therapy and cardiovascular mortality in patients with clinically localised prostate cancer enrolled in a phase 3 trial. Dates 1994 to 2001 Country United States Setting NR
Population Characteristics	Patient recruitment and eligibility NR **Inclusion** Patients had histologically confirmed prostate adenocarcinoma, stage T1b-2b and a PSA level ≤20 ng/ml. **Exclusion** NR **Other** Pre-treatment assessment included digital rectal examination and bone scan. Regional lymph nodes were assessed by surgical sampling, lymphangiography, or pelvic computed tomography. Karnofsky performance score was ≥70. All participating sites were required to have institutional review board approval, and all patients provided written informed consent. Sample size N invited = NR N eligible = NR N enrolled = 1,979 N excluded (with reason) = 0 N lost to follow-up = 0 N completed = 1,979 N excluded from analysis = 0 N included in analysis = 1,979 (RT + ADT: 987; RT alone: 992) Demographics

Parameter	RT and ADT (n=987)	RT alone (n=992)
Age at recruitment/randomisation, years		

Study Reference	**RTOG 94-08,** Voog 2016		
	Mean (SD)	69.6 (6.2)	70.0 (6.1)
	Median	70	71
	Ethnicity, n (%)		
	Non-White	242 (24.5)	236 (23.8)
	White	745 (75.5)	756 (76.2)
	BMI	NR	NR
	PSA level		
	Mean (SD)	8.8 (4.4)	8.9 (4.3)
	Median	7.9	8.1
	<4, n (%)	109 (11.0)	100 (10.1)
	≥4, n (%)	878 (89.0)	892 (89.9)
	Prostate volume	NR	NR
	Number of positive biopsy samples	NR	NR
	T stage, n (%)		
	T1	488 (49.4)	476 (48.0)
	T2	499 (50.6)	516 (52.0)
	M stage	NR	NR
	N stage	NR	NR
	Gleason score, n (%)		
	2–6	623 (63.1)	592 (59.7)
	7	252 (25.5)	286 (28.8)
	8–10	93 (9.4)	87 (8.8)
	Missing	19 (1.9)	27 (2.7)
	Prostate risk group (scale not defined), n (%)	N=968	N=965
	Low	351 (36.3)	334 (34.6)
	Intermediate	524 (54.1)	544 (56.4)
	High	93 (9.6)	87 (9.0)

Methods

Randomisation

Following stratification based on PSA level (<4 vs 4–20 ng/ml), tumour grade (well differentiated, moderately differentiated, poorly differentiated), and surgical versus clinical documentation of clinically negative nodal status, patients were randomized to RT plus short-term ADT or RT alone. All patients began treatment within 21 days after randomisation.

Arm 1

Androgen deprivation therapy + radiotherapy

Patients assigned to short-term ADT received flutamide at a dose of 250 mg orally three times a day and either monthly subcutaneous goserelin at a dose of 3.6 mg or intramuscular leuprolide at a dose of 7.5 mg for 4 months. Radiotherapy commenced after 2 months of androgen deprivation. Flutamide was discontinued if the level of alanine aminotransferase increased to more than twice the upper limit of the normal range.

Radiotherapy

Study Reference	**RTOG 94-08,** Voog 2016

Administered in daily 1.8-Gy fractions prescribed to the isocentre of the treatment volume, consisted of 46.8 Gy delivered to the pelvis (prostate and regional lymph nodes), followed by 19.8 Gy to the prostate, for a total dose of 66.6 Gy. Treatment of the regional lymph nodes was omitted in patients with negative lymph-node dissections or with a PSA level of less than 10 ng per mL and a Gleason score of less than 6. The study cochairs reviewed the simulation and portal films for each treatment field.

Arm 2
Radiotherapy: As above

Duration of follow-up
Median 9.1 years for patients alive at the last data collection (range 0.1–14.1 years)

Outcomes
Primary, secondary and any other relevant outcomes (e.g. mortality, metastasis-free survival, quality of life, functioning, bowel, urinary and sexual dysfunction, psychological effects, endocrinological effects, surgical complications, rates of disease recurrence, treatment-related complications etc) reported in the study, in addition to the methods used to investigate these outcomes.

Primary endpoint

- Cardiovascular mortality: death from coronary artery disease, cardiac arrest, cardiovascular arrythmia, myocardial infarction, congestive heart failure, or sudden cardiac death
- Cause of death was investigator defined and reported on follow-up case report forms by each institution. All corresponding end-point times were measured from data of randomisation until death or last follow-up

Secondary endpoints

- Overall survival (OS): death due to any cause was an OS event.
- Disease-specific survival (DSS): death due to prostate cancer

Harms and Benefits of Interventions

Outcome	Number of events		HR (%, 95% CI)		p-value
	RT + ADT (N=987)	RT (N=992)	RT + ADT	RT	
Cardiovascular mortality					
Number of deaths overall, n	92	99	NR	NR	NR
Number of deaths at 10 years (estimate, % [95% CI])	83 (9.8 [7.7–11.8])	95 (10.7 [8.7–12.8])	Reference	1.07 (0.81–1.42)	0.62
All-cause mortality	NR	NR	Reference	1.17 (0.81–1.42)	0.03
Death	NR	NR	Reference	1.87 (CI NR)	0.001
Overall survival[a]	NR	NR	Reference	1.07 (0.82–1.39)	0.62
Disease-specific survival[a]	NR	NR	Reference	0.64 (0.21–1.95)	0.43
Cardiovascular mortality[a]	NR	NR	Reference	1.13 (0.71–1.79)	0.62

[a] Interaction analysis, Fine-Gray method; death due to other cause is considered as a competing risk

Authors' Conclusions	It was demonstrated that short-course GnRH agonist therapy is not associated with cardiovascular mortality in clinically localised prostate cancer in all patients enrolled in RTOG 94-08. These findings are inclusive of all prostate cancer risk groups and provide important insight

Study Reference	**RTOG 94-08,** Voog 2016
	into low- and intermediate-risk patients with less competing causes of mortality. The lack of cardiac mortality associated with ADT use extends to patients at low risk for cancer-specific mortality and to patients at high risk for cardiac mortality due to the presence of baseline cardiovascular risk factors including CVD and DM. In addition, it was demonstrated that OS and DSS are associated with short-course GnRH agonist therapy and RT, principally in intermediate-risk patients. While treatment decisions must always weigh potential risks and benefits, the data support the continued use of ADT in settings with proven survival benefit.

Abbreviations: ADT: androgen deprivation therapy; CI: confidence interval; CVD: cardiovascular mortality; DM: diabetes mellitus; DSS: disease-specific mortality; HR: hazard ratio; NR: not reported.

Appendix 4 – Guidance on quality assessments

A Measurement Tool to Assess systematic Reviews (AMSTAR) 2

Table 42. Guidance on the use of AMSTAR 2

Question	Literature-Recommended Criteria	Guideline Criteria for Prostate Cancer Rapid Review
Did the research questions and inclusion criteria for the review include the components of PICO? (Yes/No)	To score Yes, appraisers should be confident that the 4 elements of PICO are described somewhere in the report	
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? (Yes/Partial Yes/No)	The research questions and study methods should have been planned ahead of conducting the review (this should be reported at minimum to score a Partial Yes) To score Yes, authors should demonstrate that they worked with a written protocol with independent verification (e.g. in the form of registration, an open publication journal or a date submission to a research office or research ethics board). Appraisers should compare the published review report with the registered protocol (if available); if there are deviations from the protocol, the appraisers should determine whether these are reported and justified by the review authors. Obvious unexplained discrepancies should result in downgrading the rating	
Did the review authors explain their selection of the study designs for inclusion in the review? (Yes/No)	The justification for selection of study designs may have to be inferred from careful reading of the complete study report The general rule is that authors first asked whether a review restricted to RCTs would have given an incomplete summary. If the answer to this is yes, the inclusion of non-randomised studies is justified Restriction to only non-randomised studies is justified when RCTs will not provide the necessary outcome data, or if a review of RCTs has already been completed and the aim is to complement this Inclusion of both RCTs and non-randomised studies may be justified to get a complete picture; in this situation it is recommended that the two study types are assessed and combined independently	AMSTAR 2 is specifically a tool for SLRs that include randomised or non-randomised studies of healthcare interventions. For the prostate cancer rapid review, the appraiser should consider screening as the intervention for the Q1–3 stream
Did the review authors use a comprehensive literature search strategy? (Yes/Partial Yes/No)	To score Yes, appraisers should be satisfied that all relevant aspects of the search have been addressed by review authors	
Did the review authors perform study selection in duplicate? (Yes/No)	If one reviewer carried out selection of all studies with a second reviewer checking agreement on a sample of studies, a Kappa score indicating 'strong' agreement (≥0.80) should have been achieved	

Question	Literature-Recommended Criteria	Guideline Criteria for Prostate Cancer Rapid Review
Did the review authors perform data extraction in duplicate? (Yes/No)	If one reviewer carried out extraction of all studies with a second reviewer checking agreement on a sample of studies, a Kappa score indicating 'strong' agreement (≥0.80) should have been achieved	
Did the review authors provide a list of excluded studies and justify the exclusions? (Yes/Partial Yes/No)	Exclusion should not be based on RoB, which is dealt with separately and later in the review process	
Did the review authors describe the included studies in adequate detail? (Yes/Partial Yes/No)	The detail should be sufficient for an appraiser, or user, to make judgements about the extent to which the studies were appropriately chosen (in relation to the PICO structure)	
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? (Yes/Partial Yes/No)	When the review is confined to RCTs, it is recommended that the Cochrane Handbook is consulted to determine whether review authors made an adequate assessment of RoB in individual RCTs Review authors should have used a systematic approach to RoB assessment, preferably with a properly-developed rating instrument (if they have used a non-standard instrument the appraiser should be satisfied that it was capable of detecting serious methodological flaws) In assessing how RoB has been assessed by review authors it is recommended that appraisers should seek methods and content expert advice (if that is not included in the team), along with guidance on what adjustment techniques for confounding would be appropriate The domains of bias selected from the ROBINS-I instrument as being the most relevant to SLRs that include non-randomised studies of interventions include: confounding, sample selection bias, bias in measurement of exposures and outcomes, selective reporting of outcomes and analyses	
Did the review authors report on the sources of funding for the studies included in the review? (Yes/No)	No additional guidance	

Question	Literature-Recommended Criteria	Guideline Criteria for Prostate Cancer Rapid Review
If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? (Yes/No/No meta-analysis conducted)	Review authors should have stated explicitly in the review protocol the basis of their decision to perform a meta-analysis e.g. desire to obtain a single pooled effect and the extent to which studies are able to be combined Authors should have explained decisions to use fixed or random effects models (for RCTs) and the methods they intended to use to investigate heterogeneity Pooled estimates should be reported separately for different study types (i.e. not combining RCTs and non-randomised studies of interventions) For non-randomised studies of interventions, authors should pool the confounder-adjusted estimates of effect rather than raw data (there should be a clear justification if they do the latter). N.B. different studies are likely to report treatment effects that have been adjusted for different sets of covariates – another source of potential heterogeneity	
If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? (Yes/No/No meta-analysis conducted)	This is particularly important where the review includes RCTs of variable quality. The impact of this should be assessed by regression analysis or by estimating pooled effect sizes with only studies at low RoB For non-randomised studies of interventions, they should estimate pooled effect sizes of low/moderate RoB studies If meta-analyses were not performed, the authors should still comment on the likely impact of RoB on individual study results (see next item)	
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? (Yes/No)	This discussion should not be limited to the impact of RoB on pooled estimates, but should also consider whether it may account for differences between the results of individual studies The authors should make an explicit consideration of RoB if they make any recommendations that are likely to impact clinical care or policy	
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? (Yes/No)	Both the PICO elements and domains of bias (listed in item 9) should be considered as potential sources of heterogeneity in the results Review authors should explore these and discuss the impact of heterogeneity on the results, conclusions and any recommendations	

Question	Literature-Recommended Criteria	Guideline Criteria for Prostate Cancer Rapid Review
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? (Yes/No/No meta-analysis conducted)	This can be a difficult issue to resolve. The key issues are whether review authors have tried to identify publication bias through additional literature searches, shown an awareness of the likely impact of publication bias in their interpretation and discussion or results, and performed a sensitivity analysis to determine how many missing 'null' studies (i.e. those not published because of an insignificant result) would be needed to invalidate the results of the SLR Typically, statistical tests/graphic displays are used and if they are positive it indicates the presence of publication bias, however negative tests do not guarantee its absence as the tests are insensitive Context and setting should also be considered (e.g. a series of industry-sponsored studies may be more likely to be affected by publication bias than similar studies independent of industry)	
Did the review authors report any potential sources of conflict of interest, including any funding they received for the review? (Yes/No)	No additional guidance	

Cochrane Risk of Bias Tool 2

Table 43. Guidance on the use of the Cochrane Risk of Bias Tool 2

Question	Response Options	Literature-Recommended Criteria	Guideline Criteria for Prostate Cancer Rapid Review
RANDOMISATION PROCESS			
1.1 Was the allocation sequence random?	Y (yes), PY (possibly yes), PN (possibly no), N (no), NI (no information)	Y if random component was used in sequence generation process (e.g. computer-generated random numbers, random number table, coin tossing). Use of minimization technique can also be considered random N if no random element used PY if judged likely to be random e.g. experienced clinical trials unit with absence of specific information about generation of randomised sequence in paper with tight word limit PN if e.g. other trials by same investigator/team have used non-random approaches	
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y, PY, PN, N, NI	Y if the process of allocation is controlled by an external unit or organisation, independent of the enrolment personnel (e.g. telephone or internet-based) If envelopes or drug containers used, adequate detail should be given e.g. to the level that envelopes are opaque, sequentially numbered, sealed with a tamper-proof seal and irreversibly assigned to the participant. If this detail is not provided, should assign PY or PN N if reason to suspect that investigator or participant was aware of the allocation	
1.3 Did the baseline differences between intervention groups suggest a problem with the randomization process?	Y, PY, PN, N, NI	N if no apparent imbalances or if imbalances are likely due to chance Y if there are imbalances that indicate problems with the randomisation e.g. large difference in intervention group size, imbalance in ≥1 key prognostic baseline characteristics, or conversely, if baseline characteristics are excessively similar NI if there is no useful baseline information available	
Risk of bias judgement	Low, High, Some concerns	Risk of bias determined using algorithm in Cochrane Risk of Bias Tool 2 crib sheet[210]	
EFFECT OF ASSIGNMENT TO INTERVENTION			

Question	Response Options	Literature-Recommended Criteria	Guideline Criteria for Prostate Cancer Rapid Review
2.1 Were participants aware of their assigned intervention during the trial?	Y, PY, PN, N, NI	N if trial was blinded, however, if participants experience side effects or toxicities that could be attributed to one of the interventions, the answer should be Y or PY	**Screening Questions (Q1 and 2)** N if participants were not aware if they were being screened **Intervention Question (Q4)** N if treatments in different arms were concealed or made to look the same
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y, PY, PN, N, NI	N if trial was blinded, however, if participants experience side effects or toxicities that could be attributed to one of the interventions, the answer should be Y or PY If randomisation allocation was not concealed, it is likely that carers/people delivering intervention were aware of the assignment	
2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	NA, Y, PY, PN, N, NI	The term 'trial context' refers to the effects of recruitment/engagement activities on trial participants e.g. seeking informed consent (so a patient knows their allocation) may lead patients in a placebo group to seek other intervention Y or PY only if there is evidence that the trial context led to failure to implement the protocol or starting of interventions not allowed by the protocol N or PN if there were changes from the protocol, but these could occur outside of the trial context e.g. non-adherence to an intervention	
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA, Y, PY, PN, N, NI	Deviations will only impact the intervention effect estimate if they affect the outcome	
2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA, Y, PY, PN, N, NI	Deviations are more likely to impact the intervention effect estimate if they are not balanced between groups	
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y, PY, PN, N, NI	ITT and mITT (excluding participants with missing outcome data) analyses should be considered appropriate Per protocol and as treated analyses should be considered inappropriate Analyses excluding eligible patients post-randomisation are inappropriate, but excluding ineligible patients post-randomisation (e.g. if eligibility was not yet confirmed) are appropriate	
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA, Y, PY, PN, N, NI	There is no precise rule. It is possible that even if <5% of participants were analysed in the wrong group or excluded, this could have a substantial impact on the results	

Question	Response Options	Literature-Recommended Criteria	Guideline Criteria for Prostate Cancer Rapid Review
Risk-of-bias judgement	Low, High, Some concerns	Risk of bias determined using algorithm in Cochrane Risk of Bias Tool crib sheet[210]	
MISSING OUTCOME DATA			
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y, PY, PN, N, NI	'Nearly all' = the number of participants with missing outcome data is sufficiently small that their outcomes would have made no important difference to the estimated effect of the intervention For continuous outcomes, availability of data for 95% of the participants will often be sufficient. For dichotomous outcomes, the proportion required is directly linked to the risk of the event – if the observed number of events is much greater than the number of missing data, the bias will be small Only report NI if no information is given about missing outcome data – this will usually lead to a judgement that there is a high risk of bias Imputed data should be regarded as missing data for this question	
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA, Y, PY, PN, N	Y or PY if there are analysis methods that correct for bias or sensitivity analyses showing that results are little changed under a range of assumptions about the relationship between missing outcomes and its true value Imputation (e.g. 'last-observation-carried-forward') should not be assumed to correct for bias due to missing outcome data	
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA, Y, PY, PN, N, NI	N/PN if missing outcome data occurred for reasons unrelated to the outcome, the risk of bias due to this will be low Y/PY if it was related to the participant's health status (i.e. discontinuation of study due to adverse effects) In time-to-event analyses, participants censored from the analysis should be considered as having missing data	
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA, Y, PY, PN, N, NI	Possible reasons for answering Y are: differences between intervention groups in terms of amount of missing outcome data; reported reasons for missing outcome data suggest that it depends on the true value or differ between intervention groups; in time-to-event analyses, if follow-up is censored when participants stop or change their intervention e.g. due to toxicity or a need for second-line chemotherapy	
Risk-of-bias judgement	Low, High, Some concerns	Risk of bias determined using algorithm in Cochrane Risk of Bias Tool crib sheet[210]	
MEASUREMENT OF OUTCOME			

Question	Response Options	Literature-Recommended Criteria	Guideline Criteria for Prostate Cancer Rapid Review
4.1 Was the method of measuring the outcome inappropriate?	Y, PY, PN, N, NI	In most cases, for pre-specified outcomes, the answer will be N or PN Y or PY if the method of data collection is inappropriate e.g. it is unlikely to be sensitive to intervention effects (e.g. ranges of outcome values are not detectable using the method) or the measurement instrument has been shown to have poor validity	
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Y, PY, PN, N, NI	N or PN if data collection involves the same measurement methods and thresholds (including number of times measures are taken) across intervention arms	
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	NA, Y, PY, PN, N, NI	N if outcome assessors were blinded to the intervention status. For patient-reported outcomes, the patient should be blinded	
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA, Y, PY, PN, N, NI	Outcomes that are likely influenced by knowledge of the intervention are ones which involve some level of judgement (e.g. level of pain), rather than e.g. all-cause mortality	
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA, Y, PY, PN, N, NI	If there are strong levels of belief in either harmful or beneficial effects of the intervention, it is more likely that the outcome was influenced by knowledge	
Risk-of-bias judgement	Low, High, Some concerns	Risk of bias determined using algorithm in Cochrane Risk of Bias Tool crib sheet[210]	
SELECTION OF THE REPORTED RESULT			
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y, PY, PN, N, NI	If available, planned outcome measurements/analyses can be compared with those presented in published reports. Finalisation of analysis plans must be before unblinded data become available to investigators Changes to analysis plans made before unblinded outcome data were available (or unrelated to the results) do not raise concerns for bias	

Question	Response Options	Literature-Recommended Criteria	Guideline Criteria for Prostate Cancer Rapid Review
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Y, PY, PN, N, NI	It may be possible to report certain outcomes in more than one way (e.g. for pain, different scales, taken at different timepoints). If this is done but results are only reported for one particular method, there is a high risk of bias in the fully reported result Y or PY if there is clear evidence that a domain was measured in multiple eligible ways but data for only a subset of measures is reported (without justification) and the selection was likely influenced by the result of that subset (e.g. more significant) N or PN if there is only one way an outcome can be measured or if results for all eligible measures are reported	
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	Y, PY, PN, N, NI	It may be possible to analyse outcomes in more than one way (e.g. adjusted and unadjusted models, absolute value and change from baseline). As above, if multiple estimates are generated but only one subset reported, there is a high risk of bias Y or PY if there is clear evidence that outcomes were analysed in multiple eligible ways but data for only a subset of analyses is reported (without justification) and the selection of this reporting was likely influenced by its result N or PN if there is only one way the outcome could be analysed or if results for all analyses conducted are reported	
Risk-of-bias judgement	Low, High, Some concerns	Risk of bias determined using algorithm in Cochrane Risk of Bias Tool crib sheet[210]	
OVERALL RISK OF BIAS	Low, some concerns, high	**Low** if the study is judged to be at low RoB for <u>all domains</u> **Some concerns** if the study is judged to raise some concerns in <u>at least one</u> domain, but is <u>not</u> at high RoB for <u>any</u> domain **High** if the study is judged to be at high RoB in <u>at least one</u> domain **or** the study is judged to have some concerns for <u>multiple domains</u> in a way that substantially lowers confidence in the result	

Yes (Y), Possibly Yes (PY), Possibly No (PN), No (N), No information (NI), Not applicable (NA)

Quality Assessment of Diagnostic Accuracy Studies (QUADAS) 2

Table 44. Guidance on the use of QUADAS 2

Question	Literature-Recommended Criteria	Guideline Criteria for Prostate Cancer Rapid Review
PARTICIPANT SELECTION		
Was a consecutive or random sample of participants enrolled? (Yes/No/Unclear)	A study should ideally enrol all consecutive, or a random sample of, eligible patients – otherwise there is potential for bias. Studies that make inappropriate exclusions, e.g. excluding "difficult to diagnose" patients, may result in overoptimistic estimates of diagnostic accuracy	**Yes** if all participants (or a random sample of patients) within the study period were included **No** if patients were selected in a different way, e.g. by referral or convenience sample **Unclear** if all screened participants are enrolled but it is not specified if the screening test is routinely administered at the study site
Was a case-control design avoided? (Yes/No/Unclear)	Studies enrolling patients with known disease and a control group without the condition may exaggerate diagnostic accuracy	**Yes** if the study was a prospective or retrospective cohort study, or an RCT **No** if cases (prostate cancer) were matched to controls
Did the study avoid inappropriate exclusions? (Yes/No/Unclear)	Exclusion of patients with "red flags" for the target condition, who may be easier to diagnose, may lead to underestimation of diagnostic accuracy	**Yes** if all participants were included, or if exclusions were appropriate and unlikely to lead to bias **No** if any group within the screening population was systematically excluded
Could the selection of participants have introduced bias? (Low/High/Unclear)	If all signalling questions for a domain are answered "yes" then risk of bias can be judged "low". If any signalling question is answered "no" this flags the potential for bias	Answered based on the previous questions in this domain with **Low**, **High** or **Unclear** risk
Is there concern that the included participants do not match the review question? (Low/High/Unclear)	There may be concerns regarding applicability if patients included in the study differ, compared to those targeted by the review question, in terms of severity of the target condition, demographic features, presence of differential diagnosis or co-morbidity, setting of the study and previous testing protocols	**Low** if patients overall are low-risk, asymptomatic men representative of the screening population (i.e. similar to the male population in the UK) **High** if patients overall are not representative of the screening population, such as men with at least one moderate risk factor as specified in UK guidelines or demographically dissimilar to the UK population
INDEX TESTS		
Were the index test results interpreted without knowledge of the reference standard? (Yes/No/Unclear)	This item is similar to "blinding" in intervention studies. Interpretation of index test results may be influenced by knowledge of the reference standard	**Yes** if screening results were interpreted before the diagnosis was confirmed **No** if screening results were only examined after the diagnosis was confirmed

Question	Literature-Recommended Criteria	Guideline Criteria for Prostate Cancer Rapid Review
If a threshold was used, was it pre-specified? (Yes/No/Unclear)	Selecting the test threshold to optimise sensitivity and/or specificity may lead to overoptimistic estimates of test performance, which is likely to be poorer in an independent sample of patients in whom the same threshold is used	**Yes** if the criteria used to diagnose prostate cancer were explicitly stated, well-defined, and specified before the study **No** if criteria were not stated, were insufficiently well-defined, or were specified retrospectively
Could the conduct or interpretation of the index test have introduced bias? (Low/High/Unclear)	If all signalling questions for a domain are answered "yes" then risk of bias can be judged "low". If any signalling question is answered "no" this flags the potential for bias	Answered based on the previous questions in this domain with **Low**, **High** or **Unclear** risk. Consider whether the staff conducting the index test could have had foreknowledge of who was at risk by presence of major factors.
Is there concern that the index test, its conduct, or interpretation differ from the review question? (Low/High/Unclear)	Variations in test technology, execution, or interpretation may affect estimates of its diagnostic accuracy. If index tests methods vary from those specified in the review question there may be concerns regarding applicability	**Low** if the screening test is similar to tests or screening tests administered as part of UK clinical practice **High** if any aspect of the index test, including its conduct or interpretation, is substantially different from clinical practice in a UK setting (as outlined in the NG131 NICE guidance)
REFERENCE STANDARD		
Is the reference standard likely to correctly classify the test condition? (Yes/No/Unclear)	Estimates of test accuracy are based on the assumption that the reference standard is 100% sensitive and specific. Disagreements between the reference standard and index test are assumed to result from incorrect classification by the index test	**Yes** if prostate cancer was confirmed via biopsy (template prostate mapping [TPM] or transrectal ultrasound [TRUS]) or was a national cancer registry-reported case **No** if diagnosis was performed inconsistently, or if the methods used are likely to be unreliable
Were the reference standard results interpreted without knowledge of the results of the index test? (Yes/No/Unclear)	Potential for bias is related to the potential influence of prior knowledge on the interpretation of the reference standard	**Yes** if the final diagnosis of prostate cancer was made by an investigator blinded to the index test results **No** if the screening results were known by the investigator making the final diagnosis **Unclear** if it is not clear whether the investigator was aware of the test result when making the final diagnosis
Could the reference standard, its conduct, or its interpretation have introduced bias? (Low/High/Unclear)	If all signalling questions for a domain are answered "yes" then risk of bias can be judged "low". If any signalling question is answered "no" this flags the potential for bias	Answered based on the previous questions in this domain with **Low**, **High** or **Unclear** risk

Question	Literature-Recommended Criteria	Guideline Criteria for Prostate Cancer Rapid Review
Is there concern that the target condition as defined by the reference standard does not match the review question? (Low/High/Unclear)	The reference standard may be free of bias but the target condition that it defines may differ from the target condition specified in the review question. For example, when defining urinary tract infection, the reference standard is generally based on specimen culture but the threshold above which a result is considered positive may vary	**Low** if the prostate cancer is diagnosed based on first-line multiparametric MRI (mp-MRI) followed by mp-MRI-influenced biopsy for people with Likert score ≥3 or systematic prostate biopsy for people with Likert score of 1 or 2 (if they should opt to have a biopsy after a discussion of the risks and benefits) Mapping transperineal template biopsy should not be offered as part of an initial assessment, unless part of a clinical trial. **High** if the reference standard diagnosed prostate cancer in any other way
PARTICIPANT FLOW		
Was there an appropriate interval between the index test(s) and the reference standard? (Yes/No/Unclear)	Ideally results of the index test and reference standard are collected on the same patients at the same time. If there is a delay or if treatment is started between index test and reference standard, misclassification may occur due to recovery or deterioration of the condition. The length of interval leading to a high risk of bias will vary between conditions. A delay of a few days may not be a problem for chronic conditions, while for acute infectious diseases a short delay may be important	**Yes** if men did not receive preventative treatment for prostate cancer between the time of the screening test and a diagnosis **No** if men initiated treatment to prevent or lower the risk of prostate cancer after being identified as being at-risk following a screening test
Did all participants receive a reference standard? (Yes/No Unclear) Did participants receive the same reference standard? (Yes/No/Unclear)	Verification bias occurs when not all of the study group receive confirmation of the diagnosis by the same reference standard. If the results of the index test influence the decision on whether to perform the reference standard or which reference standard is used, estimated diagnostic accuracy may be biased	**Yes** if all screened patients had confirmation of their diagnosis, and all were diagnosed in the same manner (using the same reference standard by similarly trained staff) **No** if patients received different reference standards **Unclear** if there was a high variability in staff diagnosing and recording prostate cancer or the staff may not have received the same training
Were all participants included in the analysis? (Yes/No/Unclear)	All patients who were recruited into the study should be included in the analysis. There is a potential for bias if the number of patients enrolled differs from the number of patients included in the 2x2 table of results, for example because patients lost to follow-up differ systematically from those who remain	**Yes** if all screened men were included in the final analysis **No** if any screened men were not included in the final analysis
Could the participant flow have introduced bias? (Low/High/Unclear)	If all signalling questions for a domain are answered “yes” then risk of bias can be judged “low”. If any signalling question is answered “no” this flags the potential for bias	**Low** if men who underwent the index test were all equally likely to develop and be diagnosed with prostate cancer in the same manner **High** if some men could have been prevented from developing prostate cancer (e.g. by initiating treatment) or if men received different reference standards or a significant proportion were removed from the analysis

Prediction model Risk Of Bias ASsessment Tool (PROBAST)

Table 45. Guidance on the use of PROBAST

Question		Literature-Recommended Criteria		Guideline Criteria for Prostate Cancer Rapid Review
TYPE OF PREDICTION STUDY				
Classify the evaluation based on its aim (i.e. what is the type of prediction study)? (Development only/Development and validation/Validation only)		**Development only** if there is prediction model development without external validation. These studies may include internal validation methods e.g. bootstrapping and cross-validation techniques **Development and validation** if there is prediction model development combined with external validation in other participants in the same article **Validation only** if external validation of an existing (previously developed) model in other participants		
PARTICIPANTS				
Risk of Bias	1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data? (Y/PY/PN/N/NI)	Higher potential for RoB when participant data are from existing sources (e.g. existing cohort studies or routine care registries) because their data are often collected for a different purpose than a model Study design with a lowest RoB for a prognostic model is a **prospective longitudinal cohort design** where methods tend to be defined and consistently applied for participant inclusion/exclusion criteria, predictor assessment and outcome determination across a predefined follow-up (where data are systematically and validly recorded) **Randomised intervention trials** can also be used, however the randomised treatments may need to be included as separate predictors to account for any treatment effects. In addition, the inclusion criteria in RCTs are usually more restricted, resulting in narrower "predictor distributions". Models developed/validated using data with narrower predictor distributions tend to show lower discriminative ability than those with more broadly distributed predictors For **case-cohort** or **nested case-control** studies, low RoB can be considered so long as authors appropriately adjust for the original cohort/registry outcome frequency in the analysis (also applies to question 4.6 later). If not, they are at high RoB	**Y/PY** if cohort design (including RCT or proper registry data) or a nested case-control/-cohort with adjustment for baseline risk/hazard in the analysis **N/PN** if a non-nested case-control (or any other study design)	We are considering prognostic models (predicting whether PCa will occur in the future) rather than diagnostic models

Question		Literature-Recommended Criteria		Guideline Criteria for Prostate Cancer Rapid Review
		because they are from an 'existing source' (i.e. sampled from another cohort or registry). There is further guidance for diagnostic models		
	1.2 Were all inclusions and exclusions of participants appropriate? (Y/PY/PN/N/NI)	This question relates to inclusion/exclusion at the at the enrolment stage (e.g. not loss-to-follow-up). The key issue is whether any inclusion or exclusion criteria or recruitment strategy could have made the included study participants unrepresentative of the target population **Example**: inappropriate inclusion results from including participants already known to have the outcome at the time of the predictor measurement; this will most likely result in a model with overestimated predictive performance	**Y/PY** if inclusion/exclusion appropriate i.e. participants reflect unselected participants of interest **N/PN** if included participants would already have been identified as having the outcome or if specific subgroups excluded that may have altered the performance of the predictive model for the intended target population	Inappropriate inclusion should hopefully not apply as we excluded those at risk of PCa
	What is the risk of bias introduced by selection of participants (Low/High/Unclear)	**Low** if answer to all signalling questions is **Y** or **PY**. If ≥1 of the answers is **N** or **PN**, the judgement could still be low but specific reasons should be provided as to why it can be considered so **High** if the answer to any signalling questions is **N** or **PN**, unless otherwise defined as low above **Unclear** if relevant information is missing for some of the signalling questions and none were judged at high RoB		
Applicability	What is the concern that the included participants and setting do not match the review question? (Low/High/Unclear)	Included participants, the selection criteria used and the setting used in the primary prediction model study should be relevant to the review question **Low** if included participants and clinical setting match the review question **High** if included participants and clinical setting differ from the review question **Unclear** if relevant information is not reported		
PREDICTORS				
Risk of Bias	2.1 Were predictors defined and assessed in a similar way for all participants? (Y/PY/PN/N/NI)	Potential for this bias is higher for predictors that involve subjective judgement e.g. imaging test results (risk of looking at predictive ability of observer rather than predictor)	**Y/PY** if definitions of predictors and their assessment were similar for all participants **N/PN** if different definitions were used for the same predictor or if predictors requiring subjective interpretation were assessed by differently experience	

Question		Literature-Recommended Criteria		Guideline Criteria for Prostate Cancer Rapid Review
			assessors	
	2.2 Were predictor assessments made without knowledge of outcome data? (Y/PY/PN/N/NI)	I.e. blinding or masking. This is also especially important for predictors that involve subjective interpretation or judgement Blinding of assessors to outcome naturally occurs in prognostic studies with a prospective cohort design where the predictors are assessed before the outcome has happened. Bias is more likely in studies that retrospectively record predictors (recall bias) or if predictors and outcomes are assessed at a similar time (cross-sectional studies) If no information on blinding is given, this domain can still be rated as low RoB in overall assessment if predictors were measured/reported a long time before the outcome If predictors are collected by reinterpreting stored data (i.e. samples), assessors may be aware of the outcome	**Y/PY** if outcome information was stated as not used during predictor assessment or was clearly not (yet) to those assessing predictors **N/PN** if it is clear that outcome information was used when assessing predictors	
	2.3 Are all predictors available at the time the model is intended to be used? (Y/PY/PN/N/NI)	I.e. would they be available when the model is intended to be used on a patient at the time of prediction Studies that aim to externally validate existing prediction models are at high RoB when predictor data are missing at the time of validation and the authors validate the model anyway by omitting the missing predictors. This is a common flaw in validation studies (i.e. validating a different model than the original). In these cases, this signalling question should be answered **N**.	**Y/PY** if all included predictors would be available at the time the model is intended to be used for prediction **N/PN** if predictors would not be available at the time the model is intended to be used for prediction	
	What is the risk of bias introduced by predictors or their assessment? (Low/High/Unclear)	**Low** if answer to all signalling questions is **Y** or **PY**. If ≥1 of the answers is **N** or **PN**, the judgement could still be low but specific reasons should be provided as to why it can be considered so e.g. use of objective predictors not requiring subjective interpretation **High** if the answer to any signalling questions is **N** or **PN**, unless otherwise defined as low above **Unclear** if relevant information is missing for some of the signalling questions and none were judged at high RoB		
Applicability	What is the concern that the definition, assessment or timing of predictors in the model do not	**Low** if the definition, assessment, and timing of predictors match the review question **High** if the definition, assessment, or timing of predictors were different from the review question **Unclear** if relevant information about the predictors is not reported		Consider if the predictors used in the model would be typically assessed in a man being screened for prostate cancer

Question		Literature-Recommended Criteria		Guideline Criteria for Prostate Cancer Rapid Review
	match the review question? (Low/High/Unclear)			
		OUTCOME		
Risk of Bias	3.1 Was the outcome determined appropriately? (Y/PY/PN/N/NI)	This is about the level of measurement error within the method of determining the outcome (see concerns for applicability about whether the definition of the outcome is appropriate) If prediction model study uses data from routine care registries or existing studies originally designed/conducted to answer a different research question, their outcome determination methods should be appraised Potential for bias is higher in outcomes that involve subjective judgement, such as imaging, surgical or pathology results	**Y/PY** if a method of outcome determination has been used which is considered optimal or acceptable by guidelines or previous publications on the topic **N/PN** if a clearly suboptimal method that causes unacceptable error in determining outcome status has been used	
	3.2 Was a pre-specified or standard outcome definition used? (Y/PY/PN/N/NI)	RoB is low when a prespecified/standard outcome definition is used and substantiated by a definition from clinical guidelines/previously published study/study protocol RoB is higher if, e.g., an atypical threshold on a continuous scale has been used to defined the outcome – this may be evident if authors test multiple thresholds to obtain the most favourable outcome definition Composite outcomes can also introduce RoB e.g. if model performance is adjusted by excluding typical components and excluding atypical components Many outcomes have consensus-based definitions. Determining whether standard or non-standard definitions have been used may require specialist clinical knowledge	**Y/PY** if the method of outcome determination is objective or if a standard definition is used or if prespecified categories are used to group outcomes **N/PN** if the outcome definition was not standard and not prespecified	
	3.3 Were predictors excluded from the outcome definition? (Y/PY/PN/N/NI)	In some cases, it is not possible to avoid including predictors in outcome determination. E.g., if the outcome is decided by a consensus panel using as much information as is available. If a model predictor forms part of the definition or assessment of the outcome, the association between predictor and outcome will likely by overestimated (incorporation bias)	**Y/PY** if none of the predictors were included in the outcome definition **N/PN** if ≥1 of the predictors forms part of the outcome definition	
	3.4 Was the outcome defined	E.g., same thresholds and categories; same method of combining individual components if a composite outcome;	**Y/PY** if outcomes were defined and determined in a similar way for all	

Question		Literature-Recommended Criteria		Guideline Criteria for Prostate Cancer Rapid Review
	and determined in a similar way for all participants? (Y/PY/PN/N/NI)	same method for establishing the outcome in consensus- or panel-based decisions (e.g. majority vote) Look out for variation between research sites in multicentre studies RoB is higher in models that are based on data collected for a different purpose (e.g. registry, existing study) as inherently different outcome definitions are likely to be applied If outcome is dependent on accuracy of measurement or subjective interpretation, along with if outcomes are measured on several occasions at different frequency for different participants (more frequent visits = more likely to detect), RoB is higher	participants **N/PN** if outcomes were clearly defined/determined in a different way for some participants	
	3.5 Was the outcome determined without knowledge of predictor information? (Y/PY/PN/N/NI)	Similar to 3.3 In consensus or panel decisions on outcome, it may be that as much information as possible is available, which could include the predictor If the aim of a model is to assess the incremental value of a certain predictor or compare the performance of competing models (i.e. validating >1 model on the same data set), the importance of blinded outcome determination is higher	**Y/PY** if predictor information was not known when determining the outcome status **N/PN** if it is clear that predictor information was used when determining the outcome status	
	3.6 Was the time interval between predictor assessment and outcome determination appropriate? (Y/PY/PN/N/NI)	Bias can present in two ways: 1. Outcome determined too early, when relevant outcome cannot be detected or the number of outcomes is unrepresentative 2. Type of outcome may differ depending on time interval, e.g. metastases detected early may be liver metastases, whereas at one year they may mainly be bone metastases Time interval is also relevant to applicability of the review and whether you are trying to determine short- or long-term prognosis	**Y/PY** if the time interval between predictor assessment and outcome determination was appropriate to enable the correct type and representative number of relevant outcomes to be recorded or if no information on time interval is needed to enable this **N/PN** if the time interval is too long or too short to enable the correct type and representative number of relevant outcomes to be recorded	E.g. for metastases, if the time point is too early, metastases may not have grown large enough for detection
	What is the risk of bias introduced by the outcome or its determination? (Low/High/Unclear)	**Low** if answer to all signalling questions is **Y** or **PY**. If ≥1 of the answers is **N** or **PN**, the judgement could still be low but specific reasons should be provided as to why it can be considered so e.g. if outcome was determined with knowledge of predictor information but the outcome assessment did not require much interpretation by the assessor e.g. death from any cause		

Question		Literature-Recommended Criteria		Guideline Criteria for Prostate Cancer Rapid Review
		High if the answer to any signalling questions is **N** or **PN**, unless otherwise defined as low above **Unclear** if relevant information is missing for some of the signalling questions <u>and</u> none were judged at high RoB		
Applicability	What is the concern that the outcome, its definition, timing or determination do not match the review question? (Low/High/Unclear)	**Low** if outcome definition, timing, and method of determination defines the outcome as intended by the review question. **High** if choice of outcome definition, timing, and method of outcome determination defines another outcome as intended by the review question. **Unclear** if relevant information about the outcome, timing, and method of determination is not reported.		
ANALYSIS				
Risk of Bias	4.1 Were there a reasonable number of participants with the outcome? (Y/PY/PN/N/NI)	<u>Model development studies</u> Performance of any prediction model is overestimate (to some extent) when development and assessment of performance both use the same data set – overestimation is larger with smaller sample size and when fewer participants have the outcome, and when model predictors are selected from a large number of candidate predictors (i.e. those considered during the model development process) **EPV** (events per variable) = number of participants with the outcome relative to the number of candidate predictor parameters *For EPV between 10–20, the item should be rated as **PY** or **PN,** depending on the outcome frequency, model performance and distribution of predictors in the model The lower the EPV, the higher the likelihood that the model has been 'overfitted' or 'underfitted' (included spurious predictors or failed to include important predictors). Consider if the predictors used in the model would be typically assessed in a man being screened for prostate cancer <u>Model validation studies</u> Because the aim in a validation study is accurate and precise estimation of model performance, they are recommended to	<u>Model development studies</u> **Y/PY** if EPV ≥20* **N/PN** if EPV <10* <u>Model validation studies</u> **Y/PY** if number of participants with the outcome is ≥100 **N/PN** if number of participants with the outcome is <100	

Question	Literature-Recommended Criteria	Guideline Criteria for Prostate Cancer Rapid Review
	include at least 100 participants	
4.2 Were continuous and categorical predictors handled appropriately? (Y/PY/PN/N/NI)	Both Dichotomisation of **continuous** variables (predictors) requires choosing (often) an arbitrary cut-off point, which leads to loss of information and reduced predictive ability of the model (e.g. two people may have very different values but both be above the cut-off so would be classified as the same) This is particularly a problem if the cut-off is chosen to maximise the predictive effect of the model Model development studies Low RoB when predictors are kept continuous. The association between predictor and outcome risk should still be examined as linear or nonlinear RoB can still be low if a model categorises continuous predictors into 4 or more groups, rather than dichotomises, especially if these are based on widely accepted cut-offs. However, it should be clear that cut-offs were chosen before the data analysis Model validation studies Predictors should have the same format in the model validation study as they did in the development	Both **Y/PY** if continuous predictors are not converted into ≥2 categories (dichotomised) when included in the model or if continuous predictors are examined for nonlinearity or if categorical predictor groups are defined using a prespecified method **N/PN** if categorical predictor groups do not use a prespecified method Model development studies **Y/PY** *No extra criteria* **N/PN** if continuous predictors are converted into ≥2 categories when included in the model Model validation studies **Y/PY** if continuous predictors use the same definitions/transformations and categorical predictors are categorised using the same cut points as in the development study **N/PN** if they use different definitions
4.3 Were all enrolled participants included in the analysis? (Y/PY/PN/N/NI)	For lowest RoB, all enrolled patients should be included. If low %s are excluded from the analysis, RoB may still be low, but 'low' % is hard to define because it depends on which participants were excluded and whether this was a selected subsample or not Model studies based on existing sources (existing study or care database/registry) are particularly susceptible to this type of bias. In such cases, participant selection for the analysis should be based on clear criteria	**Y/PY** if all participants enrolled in the study are included in the analysis **N/PN** if some or a subgroup of participants are inappropriately excluded from the analysis
4.4 Were participants with	When a study report does not mention missing data, participants with any missing data have likely been omitted	**Y/PY** if there are no missing values of predictors or outcomes and the study

Question		Literature-Recommended Criteria		Guideline Criteria for Prostate Cancer Rapid Review
	missing data handled appropriately? (Y/PY/PN/N/NI)	from the analyses ("available-case" or "complete-case" analysis) because statistical packages automatically exclude persons with any missing value on any of the data analysed unless prompted otherwise The most appropriate method for handling missing data is multiple imputation because it leads to the least biased results, whilst missing indicator method (using a separate category to capture missing data) leads to biased results If authors provide further details (e.g. comparison of with- and without missing values), a more informed judgement on the RoB can be made (i.e. if there is not much difference, RoB may still be low) If a model validation study is using data where a specific predictor is missing (e.g. because it was not measured), simply omitting the predictor leads to high RoB and this question should be rated as **N**	explicitly reports that participants are not excluded on the basis of missing data or if missing values are handled using multiple imputation **N/PN** if participants with missing data are omitted from the analysis or if the method of handling missing data is clearly flawed (e.g. missing indicator method or inappropriate use of last value carried forward) or if the study had no explicit mention of methods to handle missing data	
	4.5 Was selection of predictors based on univariable analysis avoided? (Y/PY/PN/N/NI)	In a univariable analysis, individual predictors are tested for their association with the outcome and those with a statistically significant univariable association are often selected for inclusion in the development of the model. This can lead to incorrect predictor selection because they are chosen on the basis of their significance as a single predictor rather than in combination with other predictors This can lead to bias if some predictors are omitted that should not be – some predictors are only important after adjustment for others. Predictors may also be selected by accidental association with the outcome using this approach A better approach is to use non-statistical methods, e.g., existing knowledge of established predictors Some statistical methods that are not based on prior statistical tests between predictor and outcome can be used to reduce the number of modelled predictors (e.g. principal component analysis)	**Y/PY** if the predictors are not selected on the basis of univariable analysis prior to multivariable modelling **N/PN** if the predictors are selected on the basis of univariable analysis prior to multivariable modelling	
	4.6 Were complexities in the data (e.g. censoring,	For case-cohort/case-controls, the analysis method must account for the sampling fractions (from the original cohort) For prognostic models to predict long-term outcomes where censoring occurs, a time-to-event analysis (e.g. Cox	**Y/PY** if complexities in the data are accounted for appropriately or if they have been identified appropriately as unimportant	

Question		Literature-Recommended Criteria		Guideline Criteria for Prostate Cancer Rapid Review
	competing risks, sampling of controls) accounted for appropriately? (Y/PY/PN/N/NI)	regression) should be used to include censored participants up to the end of their follow-up. Excluding censored patients with incomplete follow-up is inappropriate. Competing risks should also be appropriately accounted for If a person can have >1 event, multilevel or random effects modelling methods are needed to avoid underestimation	**N/PN** if data complexities that could affect model performance are ignored	
	4.7 Were relevant model performance measures evaluated appropriately? (Y/PY/PN/N/NI)	Model calibration and discrimination should be assessed appropriately Calibration: agreement between predictions from model and observed outcomes, preferably reported graphically (calibration plot). Calibration is frequently assessed by calculating the Hosmer-Lemeshow goodness-of-fit test; however this has limited suitability to evaluate poor calibration Discrimination: ability of model to distinguish between individuals who do or do not develop the outcome. The most widely reported measure of discrimination is the concordance index (c-index), which is equivalent to the area under the receiver-operating characteristic (ROC) curve for logistic regression models Calibration and discrimination measures should account for the type of outcome being predicted. For survival models, researchers should account for time-to-event and censoring using e.g. Harrell's c-index or the D statistic Classification measures such as sensitivity, specificity or predictive value may also be used. These require the introduction of one or more threshold in the range of model-predicted probabilities which allows reporting of the model's performance at probability thresholds which may be clinically relevant. However, use of thresholds leads to loss of information and choice of thresholds may be data-driven rather than prespecified, which can lead to bias (i.e. thresholds chosen to maximise performance). The choice of threshold should be prespecified for low RoB	**Y/PY** if both calibration and discrimination are evaluated appropriately (including relevant measures tailored for models predicting survival outcomes) **N/PN** if both calibration and discrimination are not evaluated or if only goodness-of-fit tests (e.g. Hosmer-Lemeshow test) are used to evaluate calibration or if for models predicting survival outcomes performance measures accounting for censoring are not used or if classification measures (sensitivity, specificity, predictive values) were presented using predicted probability thresholds derived from the data set at hand	Models predicting survival outcomes likely to be relevant for prostate
	4.8 Were model overfitting and optimism in model performance accounted for?	**This applies to model development studies only** Studies developing models should always include some form of internal validation (i.e. using data of the original sample) e.g. bootstrapping and cross-validation	**Y/PY** if internal validation techniques, such as bootstrapping and cross-validation including all model development procedures, have been used to account for any optimism in model fitting, and	

Question		Literature-Recommended Criteria		Guideline Criteria for Prostate Cancer Rapid Review
	(Y/PY/PN/N/NI)	If optimism is present, an important next step is to adjust or shrink the model predictive performance estimates and predictor effects, however this is not typically done and will lead to bias The need to adjust for overfitting and optimism is greater for studies with a small sample size and low EPV and those using stepwise predictor selection strategies	subsequent adjustment of the model performance (e.g. shrinkage) estimates have been applied **N/PN** if no internal validation has been performed or if internal validation consists only of a single random split-sample of participant data or if the bootstrapping or cross-validation did not include all model development procedures (including any variable selection)	
	4.9 Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis? (Y/PY/PN/N/NI)	**This applies to model development studies only** Predictors and coefficients for the developed model, including intercept or baseline components, should be fully reported to allow others to correctly apply the model to other individuals The final presented model and the results from the multivariable analysis should match, otherwise bias may arise.	**Y/PY** if predictors and regression coefficients in the final model correspond to reported results from multivariable analysis **N/PN** if predictors and regression coefficients in the final model do not correspond to reported results from the multivariable analysis	
	What is the risk of bias introduced by the analysis? (Low/High/Unclear)	**Low** if answer to all signalling questions is **Y** or **PY**. If ≥1 of the answers is **N** or **PN**, the judgement could still be low but specific reasons should be provided as to why it can be considered so **High** if the answer to any signalling questions is **N** or **PN**, unless otherwise defined as low above **Unclear** if relevant information is missing for some of the signalling questions and none were judged at high RoB		
OVERALL ASSESSMENT				
Overall risk of bias judgement (Low risk of bias/High risk of bias/Unclear risk of bias)		**Low risk of bias** if all domains were rated at low risk of bias. For models developed **without** any external validation, only consider at low RoB if all domains rated as low and the model's development was based on a very large data set and included some form of *internal* validation – otherwise, consider high risk of bias **High risk of bias** if at least one domain is judged to be at high risk of bias **Unclear risk of bias** if unclear risk of bias was noted in at least one domain and it was low risk for all others		
Overall applicability judgement (Low concerns for applicability/High concerns for applicability/Unclear concerns for		**Low concerns for applicability** if it is judged as such for all domains **High concerns for applicability** if it is judged as such for at least one domain **Unclear concerns for applicability** if it is judged as unclear for at least one domain and there are no		

Question	Literature-Recommended Criteria	Guideline Criteria for Prostate Cancer Rapid Review
applicability)	domains judged as high concerns for applicability	

Appendix 5 – Appraisal for quality and risk of bias

Questions 1 and 2

Table 46. Cochrane Risk of Bias Tool 2 for RCTs

	Total ERSPC (Hugosson 2019/Auvinen 2016)		Martin 2018 (CAP)		Pinsky 2017 (PLCO)	
RANDOMISATION PROCESS	Answer	Notes	Answer	Notes	Answer	Notes
1.1 Was the allocation sequence random?	Y	Computer-randomised (all locations – randomisation before consent in some; randomisation after consent in others)	Y	Randomisation stratified within geographical groups and block sizes of 10 to 12 neighbouring practices using a computerised random number generator	PY	Details not provided but reported as randomised with balanced characteristics between groups
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	No information on this	N	Because randomisation preceded practices being invited to take part in the study and because the invitation was tailored to the group (intervention or control) to which the practice had been randomised, it was not possible to conceal randomisation while practices decided whether to participate	NI	No information provided on allocation concealment
1.3 Did the baseline differences between intervention groups suggest a problem with the randomization process?	NI	Baseline characteristics are not reported	N	"There were no important differences comparing measured characteristics of practices that did vs did not agree to participate. There were no important differences in measured baseline characteristics between intervention group vs control group practices or men"	N	Balanced between groups
Risk of bias judgement (low, high, some concerns)	Some concerns	Algorithm on Cochrane Risk of Bias Tool 2 crib sheet[210]	Low	Algorithm on Cochrane Risk of Bias Tool 2 crib sheet[210]	Low	Algorithm on Cochrane Risk of Bias Tool 2 crib sheet[210]
EFFECT OF ASSIGNMENT TO INTERVENTION						
2.1 Were participants aware of their assigned intervention during	Y	By nature of the intervention, invitations for screening were only sent to those in the intervention	Y	Not possible to conceal	Y	Not possible to conceal

the trial?		arm, so those in the control arm would know they were not attending screening				
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	As above, necessary by nature of the intervention	Y	Not possible to conceal	Y	Not possible to conceal
2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	Y	Men in control arm attending opportunistic screening ('contamination')	PY	Adherence to intervention was relatively low (36%-40%), but this intervention could not have been blinded and could have happened outside trial context; however, there was an estimated rate of 10-15% contamination in the control group	NI	Deviations from protocol not reported
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	Y	Several studies have demonstrated the effect of it by correcting for 'contamination in the screening arm'	PY	Men undergoing opportunistic testing could dilute or mask the effect of the intervention	Y	Contamination in the PLCO trial explains the only modest increase in PCa intervention in the screening vs control arm over the length of the trial
2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	N	NI, but seems more likely that men in control arm would attend opportunistic screening rather than men in the screening arm not	NA	-	NI	Unclear
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y	Analyses conducted were largely 'intention to screen'	Y	ITT analysis	Y	ITT analysis
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA	-	NA	-	NA	-
Risk of bias judgement (low, high, some concerns)	High risk of bias	Algorithm on Cochrane Risk of Bias Tool 2 crib sheet[210]	Low	Algorithm on Cochrane Risk of Bias Tool 2 crib sheet[210]	Some concerns	Algorithm on Cochrane Risk of Bias Tool 2 crib sheet[210]
MISSING OUTCOME DATA						
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Low	Apart from 148 men who died during randomisation process, all men who were randomised were included in the analysis	Y	All randomised patients included in analyses, "few missing data" so multiple imputation analyses not conducted	Y	All randomised patients included in analyses
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not	NA	-	NA	-	NA	-

biased by missing outcome data?						
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	-	NA	-	NA	-
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	-	NA	-	NA	-
Risk of bias judgement (low, high, some concerns)	Low	Algorithm on Cochrane Risk of Bias Tool 2 crib sheet[210]	Low	Algorithm on Cochrane Risk of Bias Tool 2 crib sheet[210]	Low	Algorithm on Cochrane Risk of Bias Tool 2 crib sheet[210]
MEASUREMENT OF OUTCOME						
4.1 Was the method of measuring the outcome inappropriate?	N	For PCa mortality, medical records were evaluated by a cause of death committee PCa incidence and vital status were monitored regularly in all randomised men and reported biannually to the central database. A scientific committee established quality criteria and other committees monitored the conduct, progress of trial, PSA harmonisation and assignment of Gleason grades.	N	Outcomes defined and data obtained from NHS Digital Organisation, Office for National Statistics for death and cancer registrations, and PHE and routine data for supplementary info. Independent cause of death evaluation committee that was blinded to trial group assignment, unclear for other outcomes	PN	Generally appropriate; deaths ascertained through NDI and medical records, methods slightly differed between original analysis and extended follow-up
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	Standard approach taken for all participants	N	Outcome measurement consistent across study arms	N	While method changes halfway through the study, there is no reason to believe this differed by study arm
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	N	The cause of death committee were masked to the intervention received	PN	Independent cause of death evaluation committee that was blinded to trial group assignment; unclear for other outcomes but knowledge would not affect assessment of outcome (objective)	PN	N for original analysis (up to 13 years) – mortality assessed by blinded process. Unclear about extended
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	-	NA	-	PN	Death: no Incidence: no Complications: possibly but unlikely
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome	NA	-	NA	-	NA	-

was influenced by knowledge of intervention received?						
Risk of bias judgement (low, high, some concerns)	Low risk of bias	Algorithm on crib sheet	Low	Algorithm on crib sheet	Low	Algorithm on crib sheet
SELECTION OF THE REPORTED RESULT						
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PY	States that the present analysis is protocol-based and not driven by statistical significance, however it is unclear if this applies to all analyses and the protocol is not available	Y	SAP provided	NI	Unclear; cannot find SAP
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	Most outcomes only measured in one way; for the study reporting on HRQoL (Booth 2014), 3 scales were used but results were reported for all three.	N	No; death can only occur once	N	The same definition of outcomes were used throughout, although data collection methods for mortality changed once, with data reported once for each time period. Data for other timepoints are reported in previous publications
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	N	For outcomes where results were analysed in multiple ways, these are always reported (usually in separate publications)	N	No evidence of multiple primary analyses, data presented for exploratory analyses and pre-specified analysis plan	N	No evidence of outcomes being analysed in multiple ways
Risk of bias judgement (low, high, some concerns)	Low risk of bias	Algorithm on Cochrane Risk of Bias Tool 2 crib sheet[210]	Low	Algorithm on Cochrane Risk of Bias Tool 2 crib sheet[210]	Some concerns	Algorithm on Cochrane Risk of Bias Tool 2 crib sheet[210]
OVERALL RISK OF BIAS (low, high, some concerns)	**Low**	**Algorithm on Cochrane Risk of Bias Tool 2 crib sheet[210]**	**Low**	**Algorithm on Cochrane Risk of Bias Tool 2 crib sheet[210]**	**Some concerns**	**Algorithm on Cochrane Risk of Bias Tool 2 crib sheet[210]**

Question 3

Table 47. QUADAS 2 for screening test accuracy studies

	Nam 2016		Grenabo Bergdahl 2016 (Göteborg)		Rubio-Briones 2014		Halpern 2017 (PLCO)		Ankerst 2016 (SABOR)	
PARTICIPANT SELECTION	Answer	Notes	Answer	Notes	Answer	Notes	Answer	Notes	Answer	Notes
Was a consecutive or random sample of participants enrolled? (Yes/No/Unclear)	Yes	Consecutive (first 50 men)	Yes	Randomised	Yes	Randomised	Y	Randomised	Unclear	Unclear ho
Was a case-control design avoided? (Yes/No/Unclear)	Yes	No cases (history of any cancer was an exclusion criterion)	Yes	RCT	Yes	RCT	Y	RCT	Y	Not a case-control
Did the study avoid inappropriate exclusions? (Yes/No/Unclear)	Yes	No inappropriate exclusions	Unclear	Exclusion criteria not reported	Yes	No inappropriate exclusions	Y	No inappropriate exclusions	Unclear	Inclusion/exclusion criteria not provided
Could the selection of participants have introduced bias? (Low/High/Unclear)	Unclear	Based on signalling question answers	Unclear	Based on signalling question answers	Unclear	Based on signalling question answers	Low	Based on signalling question answers	Unclear	Minimal information to assess
Is there concern that the included participants do not match the review question? (Low/High/Unclear)	High	Opportunistic rather than population screening. Volunteers responding to news advertisement rather than primary care, are not necessarily representative of the general population	High	Inclusion and exclusion criteria not reported	High	Opportunistic rather than population screening. Volunteers are not necessarily representative of the general population	Low	Unselected from primary care setting	Unclear	Includes men without a prior diagnosis of prostate cancer, but unclear if asymptomatic or unselected in some other way

INDEX TESTS	Answer	Notes	Answer	Notes	Answer	Notes	Answer	Notes	Answer	Notes
Were the index test results interpreted without knowledge of the reference standard? (Yes/No/Unclear)	Yes	Men had MRI before biopsy, to determine type of biopsy	Yes	Men had PSA testing and MRI before biopsy, to determine need for (and type of) biopsy	Yes	Men had PSA, DRE and PCA3 testing before biopsy, to determine need for biopsy	Yes	DRE were considered positive or suspicious as determined by the examiner before reference standard (and only screen-positive received biopsy). Examiners were blinded to PSA results	Yes	Men had PSA testing before biopsy, to determine need for biopsy
If a threshold was used, was it pre-specified? (Yes/No/Unclear)	Yes	Positive MRI (MRI score ≥4)	Yes	PSA ≥3 ng/mL and/or PSA ≥1.8 ng/mL with positive MRI (MRI score ≥3)	Yes	PSA ≥3 ng/mL and/or abnormal DRE results with PCA3 levels ≥35	Yes	Not biochemical, but characteristics for a positive result was reported; for PSA > 4 ng/ was considered abnormal	Yes	<25% for PSA-free, >4 ng/ml for PSA test
Could the conduct or interpretation of the index test have introduced bias? (Low/High/Unclear)	Low	Based on signalling question answers	Low	Based on signalling question answers	Low	Based on signalling question answers	Low	Based on signalling question answers	Low	Based on signalling question answers
Is there concern that the index test, its conduct, or interpretation differ from the review question? (Low/High/Unclear)	Low	Relevant, widely-used tests	Low	Relevant, widely-used tests	Low	Relevant, widely-used tests	Low	Relevant tests	Low	Relevant tests
REFERENCE STANDARD	Answer	Notes	Answer	Notes	Answer	Notes	Answer	Notes	Answer	Notes

Is the reference standard likely to correctly classify the test condition? (Yes/No/Unclear)	Yes	TRUS-guided systematic biopsy, or MRI-targeted biopsy in patients with prostate lesions on MRI	Yes	TRUS-guided systematic biopsy, followed by MRI-targeted biopsy in patients with cancer-suspicious findings on MRI	Unclear	No details on biopsy procedure provided	Unclear	Method of biopsy unclear, likely as screen-positive men were further investigated by primary care physicians	Unclear	No details on biopsy procedure provided
Were the reference standard results interpreted without knowledge of the results of the index test? (Yes/No/Unclear)	No	Type of biopsy performed was dependent on MRI results. No mention whether TRUS-guided systematic biopsy was performed blinded to MRI results	Partially	TRUS-guided systematic biopsy was performed blinded to MRI results, but MRI-targeted biopsy was performed with knowledge of the MRI results	Unclear	No details on biopsy procedure provided	Yes	Likely yes, examiners were blinded to PSA results, and mortality was assessed by blinded verification process	Unclear	No details on biopsy procedure provided
Could the reference standard, its conduct, or its interpretation have introduced bias? (Low/High/Unclear)	High	Based on signalling question answers	Low	Based on signalling question answers	Unclear	Based on signalling question answers	Unclear	No details on biopsy procedure provided but likely okay as blinded to test results and biopsy conducted under direction of primary care physician	Unclear	No details on biopsy procedure provided
Is there concern that the target condition as	Low	Relevant, widely-used tests	Low	Relevant, widely-used tests	Unclear	No details on confirmed diagnosis	Unclear	No details on confirmed diagnosis	Unclear	No details on confirmed diagnosis

defined by the reference standard does not match the review question? (Low/High/Unclear)						procedure provided		procedure provided		procedure provided
PARTICIPANT FLOW	Answer	Notes	Answer	Notes	Answer	Notes	Answer	Notes	Answer	Notes
Was there an appropriate interval between the index test(s) and the reference standard? (Yes/No/Unclear)	Yes	MRI performed before biopsy	Yes	PSA test and MRI performed before biopsy	Yes	PSA, DRE and PCA3 test performed before biopsy	Yes	DRE and PSA measured before biopsy, no preventative treatment apparent	Yes	DRE and PSA measured before biopsy, no preventative treatment
Did all participants receive a reference standard? (Yes/No Unclear)	No	Three patients opted not to receive biopsy after MRI (unclear if this was based on their MRI results)	No	Biopsy only performed in men with PSA ≥3 ng/mL and/or PSA ≥1.8 ng/mL with positive MRI	No	Biopsy only performed on men with PSA ≥3 ng/mL and/or abnormal DRE with PCA3 levels ≥35, and half of men with PSA ≥3 ng/mL and/or abnormal DRE with PCA3 <35	No	Only men with suspicious test results received biopsy, and reference standard not clearly described	No	Only men with suspicious test results received biopsy
Did participants receive the same reference standard? (Yes/No/Unclear)	No	Some received systematic and others received targeted biopsy	No	Analysis compares TRUS-guided systematic biopsy with MRI-targeted biopsy	Unclear	No details on biopsy procedure provided	Unclear	No details on biopsy procedure provided e.g. type of biopsy or staff	Unclear	No details on biopsy procedure provided e.g. type of biopsy or staff
Were all participants included in the analysis? (Yes/No/Unclear)	Partially	3 screened men were not included in the final analysis	Yes	384 men were screened with PSA test. Of these, only	No	2,366 men were screened with PSA test and DRE. Of these, only	Yes	All men following exclusions (with reasons) were reported, and	No	Substantial number of participants missing from analyses (table 2) compared to

				127 were screened with MRI. Of these, only 90 had the reference standard (biopsy)		321 were screened with PCA3. Of these, only 211 had the reference standard (biopsy)		% of missing data was clearly indicated		baseline characteristics (table 1)
Could the participant flow have introduced bias? (Low/High/Unclear)	High	Based on signalling question answers	High	Based on signalling question answers	High	Based on signalling question answers	Unclear	Based on signalling question answers	High	Based on signalling question answers

Table 48. PROBAST for prognostic model studies

		Grönberg 2015 (STHLM3)	
TYPE of PREDICTION STUDY		Answer	Notes
Classify the evaluation based on its aim (i.e. what is the type of prediction study)? (Development only/Development and validation/Validation only)		Development and validation	Includes a development and validation cohort
PARTICIPANTS		Answer	Notes
Risk of Bias	1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data? (Y/PY/PN/N/NI)	Y	Data source was the STHLM3 study was prospective, population-based cohort study
	1.2 Were all inclusions and exclusions of participants appropriate? (Y/PY/PN/N/NI)	Y	Population study, age 50-69 included, men with previous prostate cancer diagnosis excluded
	What is the risk of bias introduced by selection of participants (Low/High/Unclear)	Low	
Applicability	What is the concern that the included participants and setting do not match the review question? (Low/High/Unclear)	Low	Men not recruited from primary care but still recruited by postal address (so were not selected from a high-risk or symptomatic population)
PREDICTORS		Answer	Notes
Risk of Bias	2.1 Were predictors defined and assessed in a similar way for all participants? (Y/PY/PN/N/NI)	Y	Consistent methods
	2.2 Were predictor assessments made without knowledge of outcome data? (Y/PY/PN/N/NI)	Y	Tests conducted before biopsy (reference standard), as test results determined whether biopsy would be performed or which biopsy method

	2.3 Are all predictors available at the time the model is intended to be used? (Y/PY/PN/N/NI)	PY	All pre-biopsy tests
	What is the risk of bias introduced by predictors or their assessment? (Low/High/Unclear)	Low	
Applicability	What is the concern that the definition, assessment or timing of predictors in the model do not match the review question? (Low/High/Unclear)	Low	
OUTCOME		Answer	Notes
Risk of Bias	3.1 Was the outcome determined appropriately? (Y/PY/PN/N/NI)	Yes	According to a standardised biopsy protocol, 10 core biopsies were taken if the prostate volume was less than 35 cm and 12 core biopsies were taken if the volume was greater or equal to 35 cm. A single pathologist assessed all biopsies to reduce interobserver variance.
	3.2 Was a pre-specified or standard outcome definition used? (Y/PY/PN/N/NI)	Y	High-risk prostate cancer (Gleason score ≥7)
	3.3 Were predictors excluded from the outcome definition? (Y/PY/PN/N/NI)	Y	None of the predictors are included in the outcome definition
	3.4 Was the outcome defined and determined in a similar way for all participants? (Y/PY/PN/N/NI)	Y	Consistent methods; biopsy method depended on size but this is common practice
	3.5 Was the outcome determined without knowledge of predictor information? (Y/PY/PN/N/NI)	Y	Participating urologists and the pathologist were blinded to biomarker results and PSA concentration.
	3.6 Was the time interval between predictor assessment and outcome determination appropriate? (Y/PY/PN/N/NI)	PY	Time interval not reported, however, time elapsing is unlikely to affect whether prostate cancer is present or not, but if a long time between index tests and biopsy, cancer may have progressed
	What is the risk of bias introduced by the outcome or its determination? (Low/High/Unclear)	Low	
Applicability	What is the concern that the outcome, its definition, timing or determination do not match the review question? (Low/High/Unclear)	Low	
ANALYSIS		Answer	Notes
Risk of Bias	4.1 Were there a reasonable number of participants with the outcome? (Y/PY/PN/N/NI)	Y	11,130 in training cohort 47,688 in validation cohort, >5000 received biopsy
	4.2 Were continuous and categorical predictors handled appropriately? (Y/PY/PN/N/NI)	PY	All continuous predictors were included as linear effects and the others (family history, previous biopsy, *HOXB13*, and DRE) as indicator variables in a logistic regression model.
	4.3 Were all enrolled participants included in the analysis? (Y/PY/PN/N/NI)	PN	ITS analysis not used; number excluded was reported but reasons provided: PSA and STHLM3 test technical difficulties,

			or because PSA>10 mg/mL, or "because of α-reductase inhibitors"
	4.4 Were participants with missing data handled appropriately? (Y/PY/PN/N/NI)	NI	No information on handling of missing data
	Model development studies only 4.5 Was selection of predictors based on univariable analysis avoided? (Y/PY/PN/N/NI)	PY/NI	Plasma protein biomarkers used in STHLM3 were selected from a scientific literature search and two subsequent validation studies. For the genetic markers, 254 SNPs shown to be associated with prostate cancer in previous studies were tested. These SNPs were combined in a genetic score using odds ratios estimated from cohorts in these previous studies. The SNPs were subsequently ranked according to their p value and included SNPs in the genetic score in the order of the ranked list. SNPs that could not be genotyped reliably were excluded from the score, leaving 232 SNPs in the STHLM3 model. No other information on predictor selection reported.
	4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of controls) accounted for appropriately? (Y/PY/PN/N/NI)	NI	No information provided
	4.7 Were relevant model performance measures evaluated appropriately? (Y/PY/PN/N/NI)	NI	No information on development and calibration provided
	Model development studies only 4.8 Were model overfitting and optimism in model performance accounted for? (Y/PY/PN/N/NI)	PY	5-fold cross-validation used
	Model development studies only 4.9 Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis? (Y/PY/PN/N/NI)	NI	No information e.g. intercepts provided
	What is the risk of bias introduced by the analysis? (Low/High/Unclear)	Unclear	Limited information
OVERALL ASSESSMENT		Answer	Notes
Overall risk of bias judgement (Low risk of bias/High risk of bias/Unclear risk of bias)		Low risk of bias	
Overall applicability judgement (Low concerns for applicability/High concerns for applicability/Unclear concerns for applicability)		Low concerns	

Question 4

Table 49. AMSTAR 2 for SLRs

	NG131 C – Radical RT		NG131 G – AS, RT and prostatectomy		Ng 2019		Yin 2019		Chin 2017	
	Answer	Notes	Answer	Notes	Answer	Notes	Answer	Notes	Answer	Notes
Did the research questions and inclusion criteria for the review include the components of PICO? (Yes/No)	Yes		Yes		Yes		Yes		No	Cannot see any information on outcomes in the Methods. Population and intervention defined, comparator and outcomes not.
Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? (Yes/Partial Yes/No)	Yes	Protocol and any deviations specifically discussed	Yes	Protocol and any deviations specifically discussed	Yes	Protocol described and registered with PROSPERO	Yes	Protocol described and registered with PROSPERO	Partial Yes	States that protocol was 'prespecified' but no evidence that it was registered with an independent body
Did the review authors explain their selection of the study designs for inclusion in the review? (Yes/No)	No	No explanation for selected study design provided, however, the restriction is appropriate	No	No explanation for selected study design provided, however, the restriction is appropriate	No	Does not seem to be an explanation for only including SLRs	No	Does not seem to be an explanation for only including SLRs	No	Does not seem to be an explanation for only including SLRs
Did the review authors use a comprehensive literature search strategy? (Yes/Partial Yes/No)	Yes		Yes		Yes		No	No justification of language restriction	No	No justification of language restriction
Did the review authors perform study selection in duplicate? (Yes/No)	Yes	Explicitly stated	Yes	Explicitly stated	Yes	Explicitly stated	Yes	Explicitly stated	Unclear	"Literature search results were reviewed and deemed appropriate for full text review by one

										ASCO staff reviewer in consultation with the Panel Co-Chairs"
Did the review authors perform data extraction in duplicate? (Yes/No)	Unclear	Not explicitly stated but likely given that study selection was performed in duplicate	Unclear	Not explicitly stated by likely given that study selection was performed in duplicate	Unclear	Not explicitly stated but likely given that study selection was performed in duplicate	Unclear	Not explicitly stated but likely given that study selection was performed in duplicate	Yes	"Data were extracted by one staff reviewer and subsequently checked for accuracy… by another ASCO staff member"
Did the review authors provide a list of excluded studies and justify the exclusions? (Yes/Partial Yes/No)	Yes	Reasons for exclusion given	Yes	Reasons for exclusion given	Yes	Reasons for exclusion given	No	No list of studies excluded at full text review stage	No	No list of studies excluded at full text review stage
Did the review authors describe the included studies in adequate detail? (Yes/Partial Yes/No)	Yes	Full details in evidence tables	Partial Yes	Only missing doses of treatments	Partial Yes	Describes all elements of PICO, but not in detail	Yes	Describes all elements of PICO, including clinical stage of patients and treatment doses	Yes	Describes all elements of PICO, including clinical stage of patients and treatment doses
Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? (Yes/Partial Yes/No)	Yes	Cochrane risk of bias tool	Yes	Cochrane risk of bias tool	Yes	Cochrane risk of bias tool	No	Methods state that Cochrane risk of bias tool was used, but results are not reported	Yes	Cochrane risk of bias tool or similar (tool not explicitly named)
Did the review authors report on the sources of funding for the studies included in the review? (Yes/No)	Yes	Included in evidence table	Yes	Included in evidence table	Yes	In the supplementary information	No		No	Methods state that funding was considered, but not reported in the results
If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results? (Yes/No/No meta-analysis conducted)	Yes	Detailed in methods section	Yes	Detailed in methods section	Yes	Detailed in methods section	Yes	Detailed in methods section	No meta-analysis conducted	

If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? (Yes/No/No meta-analysis conducted)	Yes		Yes		Yes	Included only low risk of bias RCTs	No	Risk of bias not considered	No meta-analysis conducted	
Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review? (Yes/No)	Yes	Accounted for in evidence statements	Yes	Accounted for in evidence statements	Yes	Included only low risk of bias RCTs	No	Risk of bias not considered	Yes	Included only low risk of bias RCTs (Morton study had intermediate risk of bias but did not meet inclusion criteria and was not featured in the included studies tables)
Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? (Yes/No)	Yes		Yes		Yes	Heterogeneity reported in Results and explored in the Discussion	No	Heterogeneity reported in Results but not explored in the Discussion	No	Heterogeneity not discussed in any detail (there is no Discussion section)
If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? (Yes/No/No meta-analysis conducted)	No	Mentioned publication bias in the protocol but no graphical or statistical test to account for it, however a sensitivity analysis excluding any studies at high risk of bias was conducted	No	Mentioned publication bias in the protocol but no graphical or statistical test to account for it, however a sensitivity analysis excluding any studies at high risk of bias was conducted	Yes	Performed a measure of publication bias (GRADE assessment) and reported the outcome: no risk of publication bias.	No	Publication bias was not assessed	No meta-analysis conducted	
Did the review authors report any potential sources of conflict of interest, including any funding they received for the review? (Yes/No)	Yes	Declarations of conflicts of interest were reported according to NICE's 2014 and	Yes	Declarations of conflicts of interest were reported according to NICE's 2014 and	Yes	The authors declared that there was no conflict of interest	Yes	The authors reported no conflicts of interest	Yes	Conflicts of interest considered in detail

		2018 CoI policies		2018 CoI policies						

Table 50. Cochrane Risk of Bias Tool 2 for RCTs

	McPartlin 2016 (PMH 9907)		Bolla 2016 (EORTC Trial 22991)		Lennernäs 2015		Voog 2016		Hackman 2019		Sanford 2017	
RANDOMISATION PROCESS	Answer	Notes	Answer	Notes	Answer	Notes	Answer	Notes	Answer	Notes	Answer	Notes
1.1 Was the allocation sequence random?	PY	Details on allocation sequence not explicitly reported, but judged likely	Y	Minimisation technique used	Y	Randomisation performed centrally by telephone	Y	Permuted-block randomisation	PY	Randomised but specific method not reported	PY	Reported as a prospective randomised trial but no information on method reported
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI		NI	No information on allocation concealment	Y	Telephone-based randomisation	NI	No details given	NI	No details given	NI	No details given
1.3 Did the baseline differences between intervention groups suggest a problem with the randomization process?	N	No apparent imbalances	PN	P values not given, but described as "well balanced between the two groups" in the results section	N	"There were no statistically significant differences between the two randomization groups"	N	Appear roughly balanced between groups	N	Appear roughly balanced between groups	N	Appear roughly balanced between groups
Risk of bias judgement (low, high, some concerns)	Low	According to algorithm on crib sheet	Low	According to algorithm on crib sheet	Low	According to algorithm on crib sheet	Low risk	Algorithm	Low risk	Algorithm	Low risk	Algorithm
EFFECT OF ASSIGNMENT TO INTERVENTION												

2.1 Were participants aware of their assigned intervention during the trial?	NI	Likely that they were aware	Y	There was no blinding in the study	Y	Impossible to conceal difference between prostatectomy and radiotherapy	PY	No details on blinding given, so knowledge of intervention likely	Y	Open-label	PY	No details on blinding given, so knowledge of intervention likely
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PY		Y	There was no blinding in the study	Y	Impossible to conceal difference between prostatectomy and radiotherapy	PY	No details on blinding given, so knowledge of intervention likely	Y	Open-label	PY	No details on blinding given, so knowledge of intervention likely
2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	Y	"Because of patient choice, 6 patients who were randomised to receive bicalutamide received RT alone"	NI	There were deviations from the trial protocol in each arm but no reasons for these are given	NI	"One of the patients randomized to RT underwent EBRT only and got 70 Gy, and thus no brachytherapy" . No reason for this is given	PN	All patients initiated intervention to which randomised	Y	Patients decline randomised treatment or chose the other treatment	NI	No information provided
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	PN	Small number of protocol violations	NI	Unclear	PN	Only one protocol violation	NA	-	PN	Small percentage (4% RT and 1.6% observation)	NA	-
2.5 If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA		Y	N=20 in one arm, n=19 in the other	NA		NA	-	NA	-	NA	-
2.6 Was an appropriate analysis used to estimate the effect of assignment to	Y	ITT	Y	ITT	Y	"All patients were evaluated according to the intention-to-treat	PY	Appears to be mITT – patients with missing outcome data were	Y	ITT	Y	ITT

intervention?						principle."		excluded				
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA		NA		NA		NA	-	NA	-	NA	-
Risk of bias judgement (low, high, some concerns)	Some concerns	According to algorithm on crib sheet	Some concerns	According to algorithm on crib sheet	Some concerns	According to algorithm on crib sheet	Low risk	Algorithm	Some concerns	Algorithm	Some concerns	Algorithm
MISSING OUTCOME DATA												
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Y	95.6% participants with outcome data = "nearly all" and large number of events compared to missing	Y	94.99% with outcome data = "nearly all" and a large number of events compared to missing	N	"A total of 59 patients (66%) completed the questionnaires on all three assessment occasions."	NI	Patients with missing data were excluded, but numbers are not reported	Y	All patients included in analyses	Y	All patients included in analyses in Sanford. As Royce 2017 is a subgroup analysis, not all randomised patients were included but those who met the subgroup criteria were all included in the analyses
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing	NA		NA		N	No analysis methods that correct for bias or sensitivity analyses were	N	No analyses were done to correct for potential bias	NA	-	NA	-

outcome data?						used						
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA		NA		NI	No information given on why patients did not complete questionnaires	NI	No information on missing data reported	NA	-	NA	-
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA		NA		NI	No information given on why patients did not complete questionnaires	NI	No information on missing data reported	NA	-	NA	-
Risk of bias judgement (low, high, some concerns)	Low risk	According to algorithm on crib sheet	Low risk	According to algorithm on crib sheet	High risk	According to algorithm on crib sheet	High risk	Algorithm	Low risk	Algorithm	Low risk	Algorithm
MEASUREMENT OF OUTCOME												
4.1 Was the method of measuring the outcome inappropriate?	N	Widely-used methods for measuring outcomes	N	Widely-used methods	N	Widely-used methods	N	Investigator defined and reported on follow-up case report forms by each institution, cardiovascular death defined, death due to PCa not defined however	PN	All outcomes defined apart from mortality, PCa survival	N	Patients' oncologists determined cause of death, PC-related death defined
4.2 Could measurement or ascertainment of the outcome have differed between intervention	N	Measurements and time periods same in both arms	N		N	Measurements and time periods same in both arms	PN	Measurement of mortality will not differ	N	Methods did not differ	N	Measurement of mortality will not differ, analysis methods equal

groups?												
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	PY	Unlikely blinded	Y	No blinding in the study	Y	Participant-reported outcomes used, and participants were not blinded to intervention	PY	No blinding reported	Y	Open-label	PY	No details on blinding given
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN	Biochemical failure defined by specific criteria and questionnaires used for QoL. Only one that could be is biopsy analysis, so have put PN	PN	Likely only clinical relapse	Y	Participant-reported outcomes included level of pain	N	Outcome was mortality	PY	Possible that reporting of adverse events may have been influenced by knowledge of intervention received, questionnaires with subjective components	PN	Cause of death was unlikely to be influenced by knowledge of intervention
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA		NA		PN	No evidence that patients had strong beliefs about the harms and benefits of the treatments	NA	-	PY	Possible that assessment of adverse events may have been influenced by knowledge of intervention received	NA	-
Risk of bias judgement (low, high, some concerns)	Low risk	According to algorithm on crib sheet	Low risk	According to algorithm on crib sheet	Some concerns	According to algorithm on crib sheet	Low risk	Algorithm	High risk		Some concerns	Algorithm
SELECTION OF THE REPORTED RESULT												
5.1 Were the data that produced this result analysed in	NI	Analysis plan not reported, no protocol	Y	Pre-specified analysis plan reported in protocol	NI	Analysis plan not reported, no protocol	NI	SAP not reported, no information	NI	SAP not reported	N	No protocol or SAP available

accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?		identified		(downloaded)		identified						
5.2. Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	Outcomes only measured in one way each	N	Outcomes only measured in one way each	N	Outcomes only measured in one way each	N	Objective outcome of mortality	PN	Objective outcomes at the same timepoint	N	Objective outcomes were assessed at the same timepoints
5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	PN	No evidence of outcomes being analysed in multiple ways	PN	No evidence of outcomes being analysed in multiple ways	PN	No evidence of outcomes being analysed in multiple ways	PN	Death reported for 'overall' and estimated for '10 years'	N	There does not appear to be multiple analyses for each outcome	PN	Results for all analyses appear to be reported
Risk of bias judgement (low, high, some concerns)	Some concerns	According to algorithm on crib sheet	Low risk	According to algorithm on crib sheet	Some concerns	According to algorithm on crib sheet	Some concerns	Algorithm	Some concerns	Algorithm	Some concerns	Algorithm
OVERALL RISK OF BIAS (low, high , some concerns)	**Some concerns**	The study is judged to raise concerns in at least one domain, but is not at high RoB in any domain	**Some concerns**	The study is judged to raise concerns in at least one domain, but is not at high RoB in any domain	**High risk**	The study is judged to be at high RoB in at least one domain	Some concerns	Algorithm	Some concerns	Algorithm	Some concerns	

Appendix 6 – UK NSC reporting checklist for evidence summaries

All items on the UK NSC Reporting Checklist for Evidence Summaries have been addressed in this report. A summary of the checklist, along with the page or pages where each item can be found in this report, is presented in Table 51.

Table 51. UK NSC reporting checklist for evidence summaries

	Section	Item	Page no.
1.	TITLE AND SUMMARIES		
1.1	Title sheet	Identify the review as a UK NSC evidence summary.	Title page: 1
1.2	Plain English summary	Plain English description of the executive summary.	5
1.3	Executive summary	Structured overview of the whole report. To include: the purpose/aim of the review; background; previous recommendations; findings and gaps in the evidence; recommendations on the screening that can or cannot be made on the basis of the review.	6
2.	INTRODUCTION AND APPROACH		
2.1	Background and objectives	Background – Current policy context and rationale for the current review – for example, reference to details of previous reviews, basis for current recommendation, recommendations made, gaps identified, drivers for new reviews	13
		Objectives – What are the questions the current evidence summary intends to answer? – statement of the key questions for the current evidence summary, criteria they address, and number of studies included per question, description of the overall results of the literature search.	24

	Section	Item	Page no.
		Method – briefly outline the rapid review methods used.	27
2.2	Eligibility for inclusion in the review	State all criteria for inclusion and exclusion of studies to the review clearly (PICO, dates, language, study type, publication type, publication status etc.) To be decided *a priori*.	28–30
2.3	Appraisal for quality/risk of bias tool	Details of tool/checklist used to assess quality, e.g. QUADAS 2, CASP, SIGN, AMSTAR.	32
3.	SEARCH STRATEGY AND STUDY SELECTION (FOR EACH KEY QUESTION)		
3.1	Databases/ sources searched	Give details of all databases searched (including platform/interface and coverage dates) and date of final search.	32
3.2	Search strategy and results	Present the full search strategy for at least one database (usually a version of Medline), including limits and search filters if used. Provide details of the total number of (results from each database searched), number of duplicates removed, and the final number of unique records to consider for inclusion.	120–130
3.3	Study selection	State the process for selecting studies – inclusion and exclusion criteria, number of studies screened by title/abstract and full text, number of reviewers, any cross checking carried out.	27, 132, 133
4.	STUDY LEVEL REPORTING OF RESULTS (FOR EACH KEY QUESTION)		
4.1	Study level reporting, results and risk of bias assessment	For each study, produce a table that includes the full citation and a summary of the data relevant to the question (for example, study size, PICO, follow-up period, outcomes reported, statistical analyses etc.). Provide a simple summary of key measures, effect estimates and confidence intervals for each study where available. For each study, present the results of any assessment of quality/risk of bias.	Study level reporting: 174–307 Summaries of key measures: 43, 47, 53, 56, 74, 94, 97, 101, 104, 107 Quality assessment: 39, 66, 69,87, 90, 91, 331–350
5.	QUESTION LEVEL SYNTHESIS		

	Section	Item	Page no.
5.1	Description of the evidence	For each question, give numbers of studies screened, assessed for eligibility, and included in the review, with summary reasons for exclusion.	Q1 and Q2: 35 Q3: 61 Q4: 83
5.2	Combining and presenting the findings	Provide a balanced discussion of the body of evidence which avoids over reliance on one study or set of studies. Consideration of four components should inform the reviewer's judgement on whether the criterion is 'met', 'not met' or 'uncertain': quantity; quality; applicability and consistency.	Q1 and Q2: 39 Q3: 66 Q4: 86
5.3	Summary of findings	Provide a description of the evidence reviewed and included for each question, with reference to their eligibility for inclusion. Summarise the main findings including the quality/risk of bias issues for each question. Have the criteria addressed been 'met', 'not met' or 'uncertain'?	Q1: 50 Q2: 58 Q3: 80 Q4: 113
6.	REVIEW SUMMARY		
6.1	Conclusions and implications for policy	Do findings indicate whether screening should be recommended? Is further work warranted? Are there gaps in the evidence highlighted by the review?	115
6.2	Limitations	Discuss limitations of the available evidence and of the review methodology if relevant.	118

References

1. Prostate Cancer UK. About prostate cancer. Volume 2019: Prostate Cancer UK, 2019.
2. Cancer Research UK. Prostate cancer: statistics. Volume 2019: Cancer Research UK, 2019.
3. National Prostate Cancer Audit. NPCA Annual Report 2018. , 2019.
4. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. New England Journal of Medicine 2016;375:1415-1424.
5. Partin AW, Hanks GE, Klein EA, et al. Prostate-specific antigen as a marker of disease activity in prostate cancer. Oncology (Williston Park) 2002;16:1024-38, 1042; discussion 1042, 1047-8, 1051.
6. Louie KS. Screening for prostate cancer review update: review against programme appraisal cirteria for the UK National Screening Committee (UK NSC), 2015.
7. Ilic D, Neuberger MM, Djulbegovic M, et al. Screening for prostate cancer. Cochrane Database of Systematic Reviews 2013:Cd004720.
8. US Preventive Services Task Force. Screening for Prostate Cancer: US Preventive Services Task Force Recommendation Statement. JAMA 2018;319:1901-1913.
9. Mahal BA, Yang DD, Wang NQ, et al. Clinical and Genomic Characterization of Low-Prostate-specific Antigen, High-grade Prostate Cancer. European urology 2018;74:146-154.
10. Hugosson J, Roobol MJ, Mansson M, et al. A 16-yr Follow-up of the European Randomized study of Screening for Prostate Cancer(Figure presented.). European Urology 2019;76:43-51.
11. Bokhorst LP, Bangma CH, van Leenders GJ, et al. Prostate-specific antigen-based prostate cancer screening: reduction of prostate cancer mortality after correction for nonattendance and contamination in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. European urology 2014;65:329-336.
12. Martin RM, Donovan JL, Turner EL, et al. Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality: The CAP Randomized Clinical Trial. JAMA 2018;319:883-895.
13. Pinsky PF, Miller E, Prorok P, et al. Extended follow-up for prostate cancer incidence and mortality among participants in the Prostate, Lung, Colorectal and Ovarian randomized cancer screening trial. BJU International 2019;123:854-860.
14. Kilpelainen TP, Pogodin-Hannolainen D, Kemppainen K, et al. Estimate of Opportunistic Prostate Specific Antigen Testing in the Finnish Randomized Study of Screening for Prostate Cancer. Journal of Urology 2017;198:50-57.
15. Pinsky PF, Black A, Parnes HL, et al. Prostate cancer specific survival in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. Cancer Epidemiol 2012;36:e401-6.
16. Shoag JE, Mittal S, Hu JC. Reevaluating PSA Testing Rates in the PLCO Trial. New England Journal of Medicine 2016;374:1795-1796.
17. Miller EA, Pinsky PF, Black A, et al. Secondary prostate cancer screening outcomes by race in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial. Prostate 2018;78:830-838.
18. Prorok PC, Wright P, Riley TR, et al. Overall and Multiphasic Findings of the Prostate, Lung, Colorectal and Ovarian (PLCO) Randomized Cancer Screening Trial. Rev Recent Clin Trials 2018;13:257-273.

19. Pashayan N, Pharoah PD, Schleutker J, et al. Reducing overdiagnosis by polygenic risk-stratified screening: findings from the Finnish section of the ERSPC. Br J Cancer 2015;113:1086-93.
20. Pinsky PF, Parnes HL, Andriole G. Mortality and complications after prostate biopsy in the Prostate, Lung, Colorectal and Ovarian Cancer Screening (PLCO) trial. BJU international 2014;113:254-259.
21. Chiu PK, Alberts AR, Venderbos LDF, et al. Additional benefit of using a risk-based selection for prostate biopsy: an analysis of biopsy complications in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. BJU International 2017;120:394-400.
22. Booth N, Rissanen P, Tammela TL, et al. Health-related quality of life in the Finnish trial of screening for prostate cancer. Eur Urol 2014;65:39-47.
23. Chiu PK, Alberts AR, Venderbos LDF, et al. Additional benefit of using a risk-based selection for prostate biopsy: an analysis of biopsy complications in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. BJU Int 2017;120:394-400.
24. Grenabo Bergdahl A, Wilderang U, Aus G, et al. Role of Magnetic Resonance Imaging in Prostate Cancer Screening: A Pilot Study Within the Goteborg Randomised Screening Trial. Eur Urol 2016;70:566-573.
25. Rubio-Briones J, Casanova J, Dumont R, et al. Optimizing prostate cancer screening; prospective randomized controlled study of the role of PSA and PCA3 testing in a sequential manner in an opportunistic screening program. Actas Urol Esp 2014;38:217-23.
26. Nam RK, Wallis CJ, Stojcic-Bendavid J, et al. A Pilot Study to Evaluate the Role of Magnetic Resonance Imaging for Prostate Cancer Screening in the General Population. J Urol 2016;196:361-6.
27. Strom P, Nordstrom T, Aly M, et al. The Stockholm-3 Model for Prostate Cancer Detection: Algorithm Update, Biomarker Contribution, and Reflex Test Potential. Eur Urol 2018;74:204-210.
28. Martin RM, Donovan JL, Turner EL, et al. Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality: the CAP Randomized Clinical Trial. JAMA 2018;319:883-895.
29. Cancer Research UK. Prostate cancer: number staging system. Volume 2019: Cancer Research UK, 2019.
30. Prostate Cancer UK. Prostate cancer symptoms. Volume 2019: Prostate Cancer UK, 2019.
31. Cancer Research UK. Prostate cancer: symptoms. Volume 2019. Cancer Research UK, 2019.
32. Lloyd T, Hounsome L, Mehay A, et al. Lifetime risk of being diagnosed with, or dying from, prostate cancer by major ethnic group in England 2008-2010. BMC Medicine 2015;13:171.
33. Office for National Statistics (ONS). Cancer registration statistics, England: 2017. England: ONS, 2017.
34. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians 2018;68:394-424.
35. Mazhar D, Waxman J. Prostate cancer. Postgraduate Medical Journal 2002;78:590.
36. McNeal JE, Redwine EA, Freiha FS, et al. Zonal distribution of prostatic adenocarcinoma. Correlation with histologic pattern and direction of spread. American Journal of Surgical Pathology 1988;12:897-906.

37. Rosenberg MT, Froehner M, Albala D, et al. Biology and natural history of prostate cancer and the role of chemoprevention. International Journal of Clinical Practice 2010;64:1746-53.
38. Goluboff E, Burzon D, Zinner N, et al. Men with high-grade prostatic intraepithelial neoplasia (PIN) remain at high risk for prostate cancer even with a subsequent negative biopsy: Results of a prospective study. Journal of Clinical Oncology 2005;23:1024-1024.
39. Harris WP, Mostaghel EA, Nelson PS, et al. Androgen deprivation therapy: progress in understanding mechanisms of resistance and optimizing androgen depletion. Nature Clinical Practice. Urology 2009;6:76-85.
40. Huggins C, Hodges CV. Studies on Prostatic Cancer. I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate. Cancer Research 1941;1:293-297.
41. Fenton JJ, Weyrich MS, Durbin S, et al. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. Prostate-Specific Antigen-Based Screening for Prostate Cancer: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Rockville (MD): Agency for Healthcare Research and Quality (US), 2018.
42. National Institute for Health and Care Excellence (QS91). Prostate cancer Quality standard [QS91] - Introduction, 2015.
43. Breast Cancer Linkage Consortium. Cancer risks in BRCA2 mutation carriers. Journal of the National Cancer Institute 1999;91:1310-6.
44. Page EC, Bancroft EK, Brook MN, et al. Interim Results from the IMPACT Study: Evidence for Prostate-specific Antigen Screening in BRCA2 Mutation Carriers. European Urology 2019.
45. Al Olama AA, Kote-Jarai Z, Berndt SI, et al. A meta-analysis of 87,040 individuals identifies 23 new susceptibility loci for prostate cancer. Nature genetics 2014;46:1103-1109.
46. Schumacher FR, Al Olama AA, Berndt SI, et al. Association analyses of more than 140,000 men identify 63 new prostate cancer susceptibility loci. Nat Genet 2018;50:928-936.
47. Benafif S, Eeles R. Genetic predisposition to prostate cancer. British Medical Bulletin 2016;120:75-89.
48. Bruner DW, Moore D, Parlanti A, et al. Relative risk of prostate cancer for men with affected relatives: systematic review and meta-analysis. International Journal of Cancer 2003;107:797-803.
49. Johns LE, Houlston RS. A systematic review and meta-analysis of familial prostate cancer risk. BJU International 2003;91:789-94.
50. Kicinski M, Vangronsveld J, Nawrot TS. An epidemiological reappraisal of the familial aggregation of prostate cancer: a meta-analysis. PLoS One 2011;6:e27130.
51. Hu MB, Liu SH, Jiang HW, et al. Obesity affects the biopsy-mediated detection of prostate cancer, particularly high-grade prostate cancer: a dose-response meta-analysis of 29,464 patients. PLoS One 2014;9:e106677.
52. Kyrgiou M, Kalliala I, Markozannes G, et al. Adiposity and cancer at major anatomical sites: umbrella review of the literature. BMJ 2017;356:j477.
53. Lewis-Mikhael AM, Bueno-Cavanillas A, Ofir Giron T, et al. Occupational exposure to pesticides and prostate cancer: a systematic review and meta-analysis. Occupational and Environmental Medicine 2016;73:134-44.
54. Johansson J-E, Andrén O, Andersson S-O, et al. Natural History of Early, Localized Prostate Cancer. JAMA 2004;291:2713-2719.

55. Gleason DF, Mellinger GT, Arduino LJ, et al. Prediction of Prognosis for Prostatic Adenocarcinoma by Combined Histological Grading and Clinical Staging. The Journal of Urology 1974;111:58-64.
56. Hernandez DJ, Nielsen ME, Han M, et al. Contemporary evaluation of the D'amico risk classification of prostate cancer. Urology 2007;70:931-5.
57. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical Outcome After Radical Prostatectomy, External Beam Radiation Therapy, or Interstitial Radiation Therapy for Clinically Localized Prostate Cancer. JAMA 1998;280:969-974.
58. Shaw GL, Thomas BC, Dawson SN, et al. Identification of pathologically insignificant prostate cancer is not accurate in unscreened men. British Journal of Cancer 2014;110:2405-11.
59. Tikkinen KAO, Dahm P, Lytvyn L, et al. Prostate cancer screening with prostate-specific antigen (PSA) test: a clinical practice guideline. BMJ 2018;362:k3581.
60. Prostate Cancer UK. Prostate cancer tests: PSA test. Volume 2019: Prostate Cancer UK, 2019.
61. Chow K, Mangiola S, Vazirani J, et al. Obesity suppresses tumor attributable PSA, affecting risk categorization. Endocrine-Related Cancer 2018;25:561-568.
62. Thompson IM, Pauler DK, Goodman PJ, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level < or =4.0 ng per milliliter. New England Journal of Medicine 2004;350:2239-46.
63. Wolf AM, Wender RC, Etzioni RB, et al. American Cancer Society guideline for the early detection of prostate cancer: update 2010. CA: A Cancer Journal for Clinicians 2010;60:70-98.
64. Thompson IM, Ankerst DP, Chi C, et al. Assessing Prostate Cancer Risk: Results from the Prostate Cancer Prevention Trial. JNCI: Journal of the National Cancer Institute 2006;98:529-534.
65. Dickerman BA, Ahearn TU, Giovannucci E, et al. Weight change, obesity and risk of prostate cancer progression among men with clinically localized prostate cancer. International Journal of Cancer 2017;141:933-944.
66. Palsdottir T, Nordstrom T, Karlsson A, et al. The impact of different prostate-specific antigen (PSA) testing intervals on Gleason score at diagnosis and the risk of experiencing false-positive biopsy recommendations: a population-based cohort study. BMJ Open 2019;9:e027958.
67. Arsov C, Becker N, Hadaschik BA, et al. Prospective Randomized Evaluation of Risk-adapted Prostate-specific Antigen Screening in Young Men: The PROBASE Trial. European Urology 2013;64:873-875.
68. Andriole GL, Crawford ED, Grubb RL, 3rd, et al. Mortality results from a randomized prostate-cancer screening trial. New England Journal of Medicine 2009;360:1310-9.
69. Hugosson J, Roobol MJ, Mansson M, et al. A 16-yr Follow-up of the European Randomized study of Screening for Prostate Cancer. European Urololgy 2019;76:43-51.
70. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet 2014;384:2027-35.
71. UK National Screening Committee (UK NSC). The UK NSC recommendation on Prostate cancer screening/PSA testing in men over the age of 50: UK NSC, 2016.
72. Hummel S, Chilcott J. Option appraisal: screening for prostate cancer. Model update. Report to the UK National Screening Committee. Volume Version 1.0: University of Sheffield School of Health and Related Research, 2013.
73. Public Health England. Prostate cancer risk management programme: overview. Volume 2019, 2016.

74. Bell N, Gorber SC, Shane A, et al. Recommendations on screening for prostate cancer with the prostate-specific antigen test. Canadian Medical Association Journal 2014;186:1225.
75. Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. European Urology 2017;71:618-629.
76. Parker C, Gillessen S, Heidenreich A, et al. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Annals of Oncology 2015;26:v69-v77.
77. American Academy of Family Physicians (AAFP). Clinical Preventive Service Recommendation, Prostate Cancer, 2019.
78. American Cancer Society (ACS). American Cancer Society Recommendations for Prostate Cancer Early Detection: ACS, 2016.
79. Wilt TJ, Harris RP, Qaseem A, et al. Screening for Cancer: Advice for High-Value Care From the American College of Physicians. Annals of Internal Medicine 2015;162:718-725.
80. Carter HB, Albertsen PC, Barry MJ, et al. Early detection of prostate cancer: AUA Guideline. The Journal of Urology 2013;190:419-26.
81. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer Early Detection: NCCN, 2018.
82. Carlsson SV, Roobol MJ. Improving the evaluation and diagnosis of clinically significant prostate cancer in 2017. Current Opinion in Urology 2017;27:198-204.
83. Osses DF, Roobol MJ, Schoots IG. Prediction Medicine: Biomarkers, Risk Calculators and Magnetic Resonance Imaging as Risk Stratification Tools in Prostate Cancer Diagnosis. International Journal of Molecular Sciences 2019;20:1637.
84. Public Health England. Prostate cancer risk management programme (PCRMP): benefits and risks of PSA testing, 2016.
85. National Institute for Health and Care Excellence (NG131). Prostate cancer: diagnosis and management. NICE guideline [NG131], 2019.
86. Ahmed HU, El-Shater Bosaily A, Brown LC, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet 2017;389:815-822.
87. Kasivisvanathan V, Rannikko AS, Borghi M, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. New England Journal of Medicine 2018;378:1767-1777.
88. Steiger P, Thoeny HC. Prostate MRI based on PI-RADS version 2: how we review and report. Cancer Imaging 2016;16:9-9.
89. Guazzoni G, Nava L, Lazzeri M, et al. Prostate-specific antigen (PSA) isoform p2PSA significantly improves the prediction of prostate cancer at initial extended prostate biopsies in patients with total PSA between 2.0 and 10 ng/ml: results of a prospective study in a clinical setting. European Urology 2011;60:214-22.
90. Lazzeri M, Haese A, de la Taille A, et al. Serum isoform [-2]proPSA derivatives significantly improve prediction of prostate cancer at initial biopsy in a total PSA range of 2-10 ng/ml: a multicentric European study. European Urology 2013;63:986-94.
91. de la Calle C, Patil D, Wei JT, et al. Multicenter Evaluation of the Prostate Health Index to Detect Aggressive Prostate Cancer in Biopsy Naive Men. The Journal of Urology 2015;194:65-72.
92. Nicholson A, Mahon J, Boland A, et al. The clinical effectiveness and cost-effectiveness of the PROGENSA(R) prostate cancer antigen 3 assay and the Prostate Health Index in the diagnosis of prostate cancer: a systematic review and economic evaluation. Health Technol Assess 2015;19:i-xxxi, 1-191.

93. Steyerberg EW, Roobol MJ, Kattan MW, et al. Prediction of Indolent Prostate Cancer: Validation and Updating of a Prognostic Nomogram. Journal of Urology 2007;177:107-112.
94. Louie KS, Seigneurin A, Cathcart P, et al. Do prostate cancer risk models improve the predictive accuracy of PSA screening? A meta-analysis. Annals of Oncology 2015;26:848-64.
95. Pereira-Azevedo N, Verbeek JFM, Nieboer D, et al. Head-to-head comparison of prostate cancer risk calculators predicting biopsy outcome. Translational Andrology and Urology 2018;7:18-26.
96. Van Neste L, Hendriks RJ, Dijkstra S, et al. Detection of High-grade Prostate Cancer Using a Urinary Molecular Biomarker-Based Risk Score. European Urololgy 2016;70:740-748.
97. Gronberg H, Adolfsson J, Aly M, et al. Prostate cancer screening in men aged 50-69 years (STHLM3): a prospective population-based diagnostic study. Lancet Oncology 2015;16:1667-76.
98. He BM, Chen R, Sun TQ, et al. Prostate cancer risk prediction models in Eastern Asian populations: current status, racial difference, and future directions. Asian Journal of Andrology 2019.
99. Catalona WJ, Partin AW, Sanda MG, et al. A multicenter study of [-2]pro-prostate specific antigen combined with prostate specific antigen and free prostate specific antigen for prostate cancer detection in the 2.0 to 10.0 ng/ml prostate specific antigen range. The Journal of Urology 2011;185:1650-5.
100. Tomlins SA, Day JR, Lonigro RJ, et al. Urine TMPRSS2:ERG Plus PCA3 for Individualized Prostate Cancer Risk Assessment. European Urology 2016;70:45-53.
101. Punnen S, Pavan N, Parekh DJ. Finding the Wolf in Sheep's Clothing: The 4Kscore Is a Novel Blood Test That Can Accurately Identify the Risk of Aggressive Prostate Cancer. Reviews in Urology 2015;17:3-13.
102. Little J, Wilson B, Carter R, et al. Multigene panels in prostate cancer risk assessment: a systematic review. Genetics in Medicine 2016;18:535-44.
103. Partin AW, Van Neste L, Klein EA, et al. Clinical validation of an epigenetic assay to predict negative histopathological results in repeat prostate biopsies. Journal of Urology 2014;192:1081-7.
104. Endzelins E, Melne V, Kalnina Z, et al. Diagnostic, prognostic and predictive value of cell-free miRNAs in prostate cancer: a systematic review. Molecular Cancer 2016;15:41.
105. Creed J, Klotz L, Harbottle A, et al. A single mitochondrial DNA deletion accurately detects significant prostate cancer in men in the PSA 'grey zone'. World Journal of Urololgy 2018;36:341-348.
106. Prostate Cancer UK. Prostate cancer treatments. Volume 2019: Prostate Cancer UK, 2019.
107. Lepor H, Gold S, Wysock J. Focal Ablation of Prostate Cancer. Reviews in Urology 2018;20:145-157.
108. Friberg AS, Dalton SO, Larsen SB, et al. Risk of Depression After Radical Prostatectomy-A Nationwide Registry-based Study. Eur Urol Oncol 2019.
109. Watts S, Leydon G, Birch B, et al. Depression and anxiety in prostate cancer: a systematic review and meta-analysis of prevalence rates. BMJ Open 2014;4:e003901.
110. Yin Z, You J, Wang Y, et al. Moderate hypofractionated radiotherapy vs conventional fractionated radiotherapy in localized prostate cancer: A systemic review and meta-analysis from phase III randomized trials. OncoTargets and Therapy 2019;12:1259-1268.
111. Lennernäs B, Majumder K, Damber JE, et al. Radical prostatectomy versus high-dose irradiation in localized/locally advanced prostate cancer: a Swedish multicenter

randomized trial with patient-reported outcomes. Acta oncologica (stockholm, sweden) 2015;54:875-881.
112. Hackman G, Taari K, Tammela TL, et al. Randomised Trial of Adjuvant Radiotherapy Following Radical Prostatectomy Versus Radical Prostatectomy Alone in Prostate Cancer Patients with Positive Margins or Extracapsular Extension. European urology. 2019;17.
113. NICE Guideline Updates Team. Prostate cancer: diagnosis and management [C] Evidence review for radical radiotherapy. UK: National Institute for Health and Care Excellence, 2019.
114. Higgins J, Sterne J, Savović J, et al. A revised tool for assessing risk of bias in randomized trials. Chandler J, McKenzie J, Boutron I, Welch V (editors). Cochrane Methods. Cochrane Database of Systematic Reviews 2016.
115. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of Internal Medicine 2011;155:529-36.
116. Wolff RF, Moons KG, Riley RD, et al. PROBAST: a tool to assess the risk of bias and applicability of prediction model studies. Annals of internal medicine 2019;170:51-58.
117. Andriole GL, Crawford ED, Grubb RL, 3rd, et al. Prostate cancer screening in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: mortality results after 13 years of follow-up. J Natl Cancer Inst 2012;104:125-32.
118. Labrie F, Candas B, Cusan L, et al. Screening decreases prostate cancer mortality: 11-year follow-up of the 1988 Quebec prospective randomized controlled trial. Prostate 2004;59:311-8.
119. Schroder FH, Hugosson J, Roobol MJ, et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 2012;366:981-90.
120. Sandblom G, Varenhorst E, Rosell J, et al. Randomised prostate cancer screening trial: 20 year follow-up. Bmj 2011;342:d1539.
121. Kjellman A, Akre O, Norming U, et al. 15-year followup of a population based prostate cancer screening study. J Urol 2009;181:1615-21; discussion 1621.
122. Loeb S, Bjurlin MA, Nicholson J, et al. Overdiagnosis and overtreatment of prostate cancer. Eur Urol 2014;65:1046-55.
123. Pashayan N, Duffy SW, Pharoah P, et al. Mean sojourn time, overdiagnosis, and reduction in advanced stage prostate cancer due to screening with PSA: implications of sojourn time on screening. Br J Cancer 2009;100:1198-204.
124. Heijnsdijk EA, Wever EM, Auvinen A, et al. Quality-of-life effects of prostate-specific antigen screening. N Engl J Med 2012;367:595-605.
125. Auvinen A, Moss SM, Tammela TL, et al. Absolute Effect of Prostate Cancer Screening: Balance of Benefits and Harms by Center within the European Randomized Study of Prostate Cancer Screening. Clin Cancer Res 2016;22:243-9.
126. Buzzoni C, Auvinen A, Roobol MJ, et al. Metastatic prostate cancer incidence and prostate-specific antigen testing: New insights from the European Randomized Study of Screening for Prostate Cancer. European Urology 2015;68:885-890.
127. Carlsson SV, Mansson M, Moss S, et al. Could Differences in Treatment Between Trial Arms Explain the Reduction in Prostate Cancer Mortality in the European Randomized Study of Screening for Prostate Cancer? European Urology 2019;75:1015-1022.
128. Hakama M, Moss SM, Stenman UH, et al. Design-corrected variation by centre in mortality reduction in the ERSPC randomised prostate cancer screening trial. Journal of medical screening 2017;24:98-103.

129. Walter SD, De Koning HJ, Hugosson J, et al. Impact of cause of death adjudication on the results of the European prostate cancer screening trial. British journal of cancer 2017;116:141-148.
130. Arnsrud Godtman R, Holmberg E, Lilja H, et al. Opportunistic testing versus organized prostate-specific antigen screening: outcome after 18 years in the Goteborg randomized population-based prostate cancer screening trial. Eur Urol 2015;68:354-60.
131. Hugosson J, Godtman RA, Carlsson SV, et al. Eighteen-year follow-up of the Göteborg Randomized Population-based Prostate Cancer Screening Trial: effect of sociodemographic variables on participation, prostate cancer incidence and mortality. Scandinavian Journal of Urology 2018;52:27-37.
132. Bokhorst LP, Venderbos LD, Schröder FH, et al. Do Treatment Differences between Arms Affect the Main Outcome of ERSPC Rotterdam? Journal of urology 2015;194:336-342.
133. Neupane S, Steyerberg E, Raitanen J, et al. Prognostic factors of prostate cancer mortality in a Finnish randomized screening trial. International Journal of Urology 2018;25:270-276.
134. Kilpelainen TP, Tammela TLJ, Malila N, et al. The Finnish prostate cancer screening trial: Analyses on the screening failures. International Journal of Cancer 2015;136:2437-2443.
135. Kilpelainen TP, Makinen T, Karhunen PJ, et al. Estimating bias in causes of death ascertainment in the Finnish Randomized Study of Screening for Prostate Cancer. Cancer Epidemiol 2016;45:1-5.
136. Lindberg A, Talala K, Kujala P, et al. Bias-corrected estimates of effects of PSA screening decisions on the risk of prostate cancer diagnosis and death: Analysis of the Finnish randomized study of screening for prostate cancer. International Journal of Cancer 2019;145:632-638.
137. Pakarainen T, Raitanen J, Talala K, et al. Number of Screening Rounds and Postscreening Prostate Cancer Incidence: Results from the Finnish Section of the European Randomized Study of Screening for Prostate Cancer Study. European Urology 2016;70:499-505.
138. Pakarainen T, Nevalainen J, Talala K, et al. The number of screening cycles needed to reduce prostate cancer mortality in the Finnish section of the European Randomized Study of Prostate Cancer (ERSPC). Clinical Cancer Research 2019;25:839-843.
139. Luján M, Páez Á, Angulo JC, et al. Update of the results of the Spanish branch of the European Randomized Study on Screening for Prostate Cancer (ERSPC). Actas urologicas espanolas 2015;39:405-413.
140. Lujan M, Paez A, Angulo JC, et al. Prostate cancer incidence and mortality in the Spanish section of the European Randomized Study of Screening for Prostate Cancer (ERSPC). Prostate Cancer Prostatic Dis 2014;17:187-91.
141. Pinsky PF, Miller EA, Zhu CS, et al. Overall mortality in men and women in the randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Journal of medical screening 2019:969141319839097.
142. Pinsky PF, Black A, Daugherty SE, et al. Metastatic prostate cancer at diagnosis and through progression in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. Cancer 2019;125:2965-2974.
143. Pinsky PF, Prorok PC, Yu K, et al. Extended mortality results for prostate cancer screening in the PLCO trial with median follow-up of 15 years. Cancer 2017;123:592-599.
144. Lewicki P, Shoag J, Golombos DM, et al. Prognostic Significance of a Negative Prostate Biopsy: An Analysis of Subjects Enrolled in a Prostate Cancer Screening Trial. J Urol 2017;197:1014-1019.

145. Shoag J, Mittal S, Halpern JA, et al. Lethal Prostate Cancer in the PLCO Cancer Screening Trial. Eur Urol 2016;70:2-5.
146. Kelly SP, Graubard BI, Andreotti G, et al. Prediagnostic Body Mass Index Trajectories in Relation to Prostate Cancer Incidence and Mortality in the PLCO Cancer Screening Trial. J Natl Cancer Inst 2017;109.
147. Tsodikov A, Gulati R, Heijnsdijk EAM, et al. Reconciling the Effects of Screening on Prostate Cancer Mortality in the ERSPC and PLCO Trials. Annals of Internal Medicine 2017;167:449-455.
148. Public Health England. Prostate cancer risk management programme: overview. 2015 (updated 2016). Available at: https://www.gov.uk/guidance/prostate-cancer-risk-management-programme-overview. Last accessed 15.05.20.
149. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
150. Gulati R, Tsodikov A, Wever EM, et al. The impact of PLCO control arm contamination on perceived PSA screening efficacy. Cancer Causes Control 2012;23:827-35.
151. Statistical Analysis Plan for CAP. Available at: https://clinicaltrials.gov/ProvidedDocs/04/NCT01783704/SAP_001.pdf. Last accessed: 15.05.20.
152. European Randomized Study of Screening for Prostate Cancer (ERSPC). Study Book. 1998 (4th Version). Available at: https://www.erspc.org/wp-content/uploads/Study-protocol-ERSPC.pdf. Last accessed: 15.05.20.
153. Kilpeläinen TP, Mäkinen T, Karhunen PJ, et al. Estimating bias in causes of death ascertainment in the Finnish Randomized Study of Screening for Prostate Cancer. Cancer epidemiology 2016;45:1-5.
154. Otto SJ, van der Cruijsen IW, Liem MK, et al. Effective PSA contamination in the Rotterdam section of the European Randomized Study of Screening for Prostate Cancer. International Journal of Cancer 2003;105:394-399.
155. Kale MS, Korenstein D. Overdiagnosis in primary care: framing the problem and finding solutions. BMJ 2018;362:k2820.
156. Walter SD, Day NE. Estimation of the duration of a pre-clinical disease state using screening data. Am J Epidemiol 1983;118:865-86.
157. Halpern JA, Shoag JE, Mittal S, et al. Prognostic Significance of Digital Rectal Examination and Prostate Specific Antigen in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Arm. J Urol 2017;197:363-368.
158. Ankerst DP, Gelfond J, Goros M, et al. Serial Percent Free Prostate Specific Antigen in Combination with Prostate Specific Antigen for Population Based Early Detection of Prostate Cancer. J Urol 2016;196:355-60.
159. Ankerst DP, Hoefler J, Bock S, et al. Prostate Cancer Prevention Trial risk calculator 2.0 for the prediction of low- vs high-grade prostate cancer. Urology 2014;83:1362-7.
160. Ankerst DP, Goros M, Tomlins SA, et al. Incorporation of Urinary Prostate Cancer Antigen 3 and TMPRSS2:ERG into Prostate Cancer Prevention Trial Risk Calculator. Eur Urol Focus 2019;5:54-61.
161. Ankerst DP, Boeck A, Freedland SJ, et al. Evaluating the Prostate Cancer Prevention Trial High Grade Prostate Cancer Risk Calculator in 10 international biopsy cohorts: results from the Prostate Biopsy Collaborative Group. World J Urol 2014;32:185-91.
162. Ankerst DP, Straubinger J, Selig K, et al. A Contemporary Prostate Biopsy Risk Calculator Based on Multiple Heterogeneous Cohorts. Eur Urol 2018;74:197-203.
163. Kim EH, Andriole GL, Crawford ED, et al. Detection of High Grade Prostate Cancer among PLCO Participants Using a Prespecified 4-Kallikrein Marker Panel. J Urol 2017;197:1041-1047.

164. Shoaibi A, Rao GA, Cai B, et al. Prostate Specific Antigen-Growth Curve Model to Predict High-Risk Prostate Cancer. Prostate 2017;77:173-184.
165. Roobol MJ, Verbeek JFM, van der Kwast T, et al. Improving the Rotterdam European Randomized Study of Screening for Prostate Cancer Risk Calculator for Initial Prostate Biopsy by Incorporating the 2014 International Society of Urological Pathology Gleason Grading and Cribriform growth. Eur Urol 2017;72:45-51.
166. Vedder MM, de Bekker-Grob EW, Lilja HG, et al. The added value of percentage of free to total prostate-specific antigen, PCA3, and a kallikrein panel to the ERSPC risk calculator for prostate cancer in prescreened men. Eur Urol 2014;66:1109-15.
167. Verbeek JFM, Bangma CH, Kweldam CF, et al. Reducing unnecessary biopsies while detecting clinically significant prostate cancer including cribriform growth with the ERSPC Rotterdam risk calculator and 4Kscore. Urol Oncol 2019;37:138-144.
168. Verbeek JFM, Nieboer D, Parker C, et al. A Tool for Shared Decision Making on Referral for Prostate Biopsy in the Primary Care Setting: Integrating Risks of Cancer with Life Expectancy. J Pers Med 2019;9.
169. van der Leest M, Israel B, Cornel EB, et al. High Diagnostic Performance of Short Magnetic Resonance Imaging Protocols for Prostate Cancer Detection in Biopsy-naive Men: The Next Step in Magnetic Resonance Imaging Accessibility. Eur Urol 2019;76:574-581.
170. Brown LC, Ahmed HU, Faria R, et al. Multiparametric MRI to improve detection of prostate cancer compared with transrectal ultrasound-guided prostate biopsy alone: the PROMIS study. Health technology assessment (Winchester, England) 2018;22:1.
171. Xiong T, Turner RM, Wei Y, et al. Comparative efficacy and safety of treatments for localised prostate cancer: an application of network meta-analysis. BMJ open 2014;4:e004285.
172. Prostate Cancer UK. Active surveillance. 2019. Available at: https://prostatecanceruk.org/prostate-information/treatments/active-surveillance, Last accessed: 04/06/2020.
173. Cancer Research UK. Prostate cancer: Active surveillance and watchful waiting. Available at: https://www.cancerresearchuk.org/about-cancer/prostate-cancer/treatment/monitoring-prostate-cancer. Last accessed: 04/06/2020.
174. Holmberg L, Bill-Axelson A, Helgesen F, et al. A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. New England journal of medicine 2002;347:781-789.
175. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med 2012;367:203-13.
176. Voog JC, Paulus R, Shipley WU, et al. Cardiovascular Mortality Following Short-term Androgen Deprivation in Clinically Localized Prostate Cancer: An Analysis of RTOG 94-08. European Urology 2016;69:204-210.
177. NICE Guideline Updates Team. Prostate cancer: diagnosis and management - intervention comparisons [G] Evidence review for active surveillance, radical prostatectomy or radical radiotherapy in people with localised prostate cancer. UK: National Institute for Health and Care Excellence, 2019.
178. ISRCTN Registry. The ProtecT trial - Evaluating the effectiveness of treatment for clinically localised prostate cancer. Volume 2019. http://www.isrctn.com/ISRCTN20141297, 2019.
179. Fleming ID CJ, Henson DE, et al., editors. AJCC Cancer Staging Manual: Lippinscott-Raven, 1997.
180. Committee on TNM Classification. TNM classification of malignant tumors. Geneva: International Union Against Cancer, 1978.

181. Committee on TNM Classification. TNM classification of malignant tumors. Berlin: Springer, 1987.
182. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. N Engl J Med 2014;370:932-42.
183. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical Prostatectomy or Watchful Waiting in Prostate Cancer - 29-Year Follow-up. N Engl J Med 2018;379:2319-2329.
184. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. Bmj 2017;358:j4008.
185. Ng KT, Kwok PE, Teoh WY. Conservative management and radical treatment in localised prostate cancer: A systematic review with meta-analysis and trial sequential analysis. Journal of Clinical Urology 2019;12:228-238.
186. Chin J, Rumble RB, Kollmeier M, et al. Brachytherapy for Patients With Prostate Cancer: American Society of Clinical Oncology/Cancer Care Ontario Joint Guideline Update. J Clin Oncol 2017;35:1737-1743.
187. National Institute for Health and Care Excellence. Prostate cancer: diagnosis and management – intervention comparisons [G] Evidence review for active surveillance, radical prostatectomy or radical radiotherapy in people with localised prostate cancer. NICE guideline NG131: National Institute for Health and Care Excellence,, 2019.
188. Bolla M, Maingon P, Carrie C, et al. Short androgen suppression and radiation dose escalation for intermediate-and high-risk localized prostate cancer: Results of EORTC trial 22991. Journal of Clinical Oncology 2016;34:1748-1756.
189. McPartlin AJ, Glicksman R, Pintilie M, et al. PMH 9907: Long-term outcomes of a randomized phase 3 study of short-term bicalutamide hormone therapy and dose-escalated external-beam radiation therapy for localized prostate cancer. Cancer 2016;122:2595-2603.
190. Sanford NN, Chen MH, Loffredo M, et al. Duration of the anti-Androgen in men undergoing 6 months of an LHRH agonist and radiation therapy for unfavorable-risk prostate cancer and the risk of death. Prostate Cancer and Prostatic Diseases 2017;20:79-84.
191. Royce TJ, Chen MH, Wu J, et al. Surrogate End Points for All-Cause Mortality in Men With Localized Unfavorable-Risk Prostate Cancer Treated With Radiation Therapy vs Radiation Therapy Plus Androgen Deprivation Therapy: a Secondary Analysis of a Randomized Clinical Trial. JAMA oncology 2017;3:652-658.
192. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in prostate cancer - 29-year follow-up. New England Journal of Medicine 2018;379:2319-2329.
193. Lane A, Metcalfe C, Young GJ, et al. Patient-reported outcomes in the ProtecT randomized trial of clinically localized prostate cancer treatments: study design, and baseline urinary, bowel and sexual function and quality of life. BJU Int 2016;118:869-879.
194. Royce TJ, Chen MH, Wu J, et al. A comparison of surrogate endpoints for all cause mortality in men with localized unfavorable-risk prostate cancer. Journal of clinical oncology 2017;35.
195. Michalski JM, Moughan J, Purdy J, et al. Effect of Standard vs Dose-Escalated Radiation Therapy for Patients With Intermediate-Risk Prostate Cancer: The NRG Oncology RTOG 0126 Randomized Clinical Trial. JAMA Oncol 2018;4:e180039.
196. Morton G, Chung HT, McGuffin M, et al. Prostate high dose-rate brachytherapy as monotherapy for low and intermediate risk prostate cancer: Early toxicity and quality-of life results from a randomized phase II clinical trial of one fraction of 19Gy or two fractions of 13.5Gy. Radiother Oncol 2017;122:87-92.

197. Bratt O, Holmberg E, Andren O, et al. The Value of an Extensive Transrectal Repeat Biopsy with Anterior Sampling in Men on Active Surveillance for Low-risk Prostate Cancer: A Comparison from the Randomised Study of Active Monitoring in Sweden (SAMS). Eur Urol 2019;76:461-466.
198. Asimakopoulos AD, Topazio L, De Angelis M, et al. Retzius-sparing versus standard robot-assisted radical prostatectomy: a prospective randomized comparison on immediate continence rates. Surg Endosc 2019;33:2187-2196.
199. Yaxley JW, Coughlin GD, Chambers SK, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. The Lancet 2016;388:1057-1066.
200. Gaudet M, Vigneault É, Foster W, et al. Randomized non-inferiority trial of Bicalutamide and Dutasteride versus LHRH agonists for prostate volume reduction prior to I-125 permanent implant brachytherapy for prostate cancer. Radiotherapy and Oncology 2016;118:141-147.
201. Zapatero A, Guerrero A, Maldonado X, et al. High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): a randomised, controlled, phase 3 trial. Lancet Oncol 2015;16:320-7.
202. Registry I. The GÖTEBORG prostate cancer screening 2 trial (SRCTN94604465). Volume 2020. http://www.isrctn.com/ISRCTN94604465?q=&filters=conditionCategory:Cancer&sort=&offset=1&totalResults=1949&page=1&pageSize=10&searchType=basic-search, 2020.
203. Williams N, Hughes LJ, Turner EL, et al. Prostate-specific antigen testing rates remain low in UK general practice: a cross-sectional study in six English cities. BJU Int 2011;108:1402-8.
204. Nieboer D, Vergouwe Y, Roobol MJ, et al. Nonlinear modeling was applied thoughtfully for risk prediction: the Prostate Biopsy Collaborative Group. J Clin Epidemiol 2015;68:426-34.
205. Yin Z, You J, Wang Y, et al. Moderate hypofractionated radiotherapy vs conventional fractionated radiotherapy in localized prostate cancer: a systemic review and meta-analysis from Phase III randomized trials. Onco Targets Ther 2019;12:1259-1268.
206. Lane JA, Donovan JL, Davis M, et al. Active monitoring, radical prostatectomy, or radiotherapy for localised prostate cancer: study design and diagnostic and baseline results of the ProtecT randomised phase 3 trial. Lancet Oncol 2014;15:1109-18.
207. Lennernäs B, Majumder K, Damber JE, et al. Radical prostatectomy versus high-dose irradiation in localized/locally advanced prostate cancer: a Swedish multicenter randomized trial with patient-reported outcomes. Acta oncologica 2014;54:875-881.
208. Hoffman KE, Skinner H, Pugh TJ, et al. Patient-reported Urinary, Bowel, and Sexual Function After Hypofractionated Intensity-modulated Radiation Therapy for Prostate Cancer: Results From a Randomized Trial. Am J Clin Oncol 2018;41:558-567.
209. Johansson E, Steineck G, Holmberg L, et al. Quality of Life after Radical Prostatectomy or Watchful Waiting With or Without Androgen Deprivation Therapy: The SPCG-4 Randomized Trial. Eur Urol Oncol 2018;1:134-142.
210. Higgins JPT, Savović J, Page MJ, et al. Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) SHORT VERSION (CRIBSHEET). Version of 22 August 2019. Available at: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool/current-version-of-rob-2. Last accessed: 20/02/20.