Evaluation of screening for oral cancer against NSC Criteria

THE CONDITION

1. The condition should be an important health problem

Oral cancer is typically defined as cancers of the lip (ICD10: C00), tongue (C01-02), gum (C03), floor of mouth (C04), palate (C05), other unspecified parts of the mouth (C06), oropharynx (C09-10), other pharyngeal sites (C12-13) and other and ill-defined sites within lip, oral cavity and pharynx (C14), but excludes cancers of the salivary glands and the nasopharynx (1).

Oral Cancers contribute about 2% of all malignant neoplasms in the UK (1). It is one of the most disfiguring and debilitating of all the malignancies, the incidence and mortality have been rising in recent years, but the overall survival has shown only slight improvements over many decades. Overall survival for intra-oral lesions remains at only about 50%, but is significantly worse for low socioeconomic groups (1). Most patients present with lesions that are already advanced – in stages III or IV.

2. The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

Oral squamous cell carcinoma (OSCC) is the sixth most common cancer worldwide with 650,000 new cases and 350,000 deaths each year (2,3). In 2006, there were 5,325 new cases and 1851 deaths in 2007 from oral cancer in the UK (1). In England and Wales the number of new cases has increased from 1900 in 1975 to 4,515 in 2006, an increase of almost 250%. In the last 10 years there has been an increase of 42% in the UK (1). The incidence and mortality rates for oral cancer are higher in Scotland than in England and Wales (4). Fig 1 illustrates new registrations (1990-1999) for the UK and Scotland separately. Within England and Wales there is a north-south gradient for oral cancer with the higher rates in the north. Approximately twice as many cases of oral cancer are reported in males than in females. The majority of cases (85%) of oral cancer are in people aged over 50 years, but recent rising trends were higher in younger age groups with an average annual increase of 3.5% (4).

The prognosis is poor, with less than 54% overall 5 year survival and it is associated with disfiguring surgical treatment unless detected and treated early. If detected early the prognosis and outcome is excellent with 90% five-year survival for stage 1 lesions.

There is good evidence that tobacco in all forms (both smoked and smokeless, including snuff) and betel quid (a mixture of ingredients including areca nut, slaked lime, with or without added tobacco, which is wrapped in a betel leaf and chewed), are carcinogenic in the upper aerodigestive tract, which includes the mouth (5). There is also convincing evidence that alcoholic drinks are also carcinogenic and
act synergistically with tobacco (6). In the UK there is evidence that the increasing incidence of oral cancer, especially affecting younger people, is associated with increased intake of alcohol rather than tobacco use (7).

There is evidence for an increasing incidence of oral cancer among younger people who may not smoke and drink or who may have had only a short exposure to conventional risk factors (8). It should be noted that a conventional screening programme targeting older or high-risk individuals may miss this younger cohort.

The natural history of oral cancer is only partly understood (9). It is clear that OSCC is preceded by changes in the oral mucosa, but the extent or nature of these changes is uncertain. However it is thought that the majority of cancers are preceded by a detectable preclinical phase manifested as potentially malignant disorders (PMD) (8,9). These most often present as white lesions of unknown cause (leukoplakia), but may also be red patches or erythroplakia. The overall prevalence of PMD has been calculated to be 2.6% (11) and in a UK population 2.5% of individuals over the age of forty were found to have white or red lesions (12).

Overall however only about 5% of these lesions will progress to malignancy and although some clinical features are associated with higher risk (eg. non-homogeneous, speckled or red lesions) there are still no reliable ways to predict which individuals or lesions will develop OSCC (9). In a cohort of oral precancers diagnosed in a London Hospital and followed up for 10 years 2.7% of cases transformed to cancer (12,562 person-years follow up time)(13).

Despite this, most OSCC will be preceded by a potentially malignant lesion or will have an early pre-symptomatic stage when detection and treatment may result in a significantly improved prognosis. Most early OSCC present with features similar to PMD, as white, red or speckled lesions, or as non-healing ulcers.

3. All cost-effective primary prevention interventions should have been implemented as far as practicable.

Primary prevention strategies include smoking cessation measures, attempts to reduce the use of betel chewing, areca nut and other smokeless tobacco products, measures to promote reduced alcohol consumption and good dietary practice. There is greater involvement of dental professionals in these programmes (14,15) although there are few if any cost-effectiveness studies. A tobacco cessation pathway as a learning resource for dentists and for use in dental practices has been published (16).

A major factor in the poor outcome for oral cancer is late presentation due in part to lack of awareness. A number of national initiatives are aimed at increasing public and professional awareness. These include, Mouth Cancer Action Month, the West of Scotland Mouth Cancer Awareness Project (WoSCAP) and the work of charities such as The Ben Walton Trust and the Mouth Cancer Foundation. An evaluation of WoSCAP showed that 41% of dentists reported non-registered patients seeking advice regarding a ‘worrying’ lesion (17) during the awareness campaign.
4. Carriers of a mutation

Oral cancers have not been reported in hereditary cancer syndromes except in dyskeratosis congenita, a rare genetic disorder that may present with oral white lesions in young people that have a risk of transformation to cancer. So far, inherited polymorphisms that may contribute to any genetic predisposition, specifically to oral cancer have not been demonstrated.

THE TEST

5. There should be a simple, safe, precise and validated screening test

The simplest, most widely accepted and most evaluated test is a systematic visual examination of the oral soft tissues. Studies in the UK have shown that dentists can detect relevant lesions (white or red patches and non-healing ulcers) with a sensitivity and specificity of 0.74 and 0.99 respectively (18). A systematic review of worldwide studies showed overall values of sensitivity 0.85, specificity 0.97, PPV 0.70 and NPV 0.98 (19). These data compare well to values for other national screening programmes. Most of these studies have evaluated an oral examination for PMDs – essentially for the presence of leukoplakia, or lesions suspicious for early cancer. As such, all suffer from the fact that the malignant transformation rate of these lesions is low, resulting in an inherent low specificity for the detection of lesions that will truly progress.

Despite this, the only randomized controlled trial in the world (the Kerala study - funded by IARC) which has evaluated visual examination for screening for oral cancer has shown improved survival and a significant stage shift to diagnosis of early stage disease (20). Mortality however was only significantly reduced in high risk groups (males who used tobacco and alcohol). This study was in a high prevalence population and its generalisability to a Western population is uncertain. The key finding however was that, when applied to high risk groups, an oral examination may detect appropriate lesions and save lives. The authors estimated that oral cancer screening has the potential of preventing at least 37,000 oral cancer deaths worldwide.

In the UK, a simulation modeling study has shown that opportunistic screening of high-risk groups in a primary care setting may save lives and be cost-effective (21).

A number of adjunctive techniques for oral cancer detection have described. These may be used as aids to lesion detection, but some have been advocated as potential screening tests. These include vital staining (toluidine blue), oral cytology using brush biopsy (OralCDx) and a number of light based techniques (eg. ViziLite, VELsscope). The use of these techniques has recently been reviewed (22,23,24). All may be useful for detecting or delineating lesions and as diagnostic adjuncts for clinically suspicious lesions. However none have been evaluated as screening tests in primary care settings on patients who are otherwise normal. For the light-based methods in particular there is insufficient data to support or refute their potential value as screening aids.

Current research efforts are directed at using brush biopsy cytology samples
coupled with biomarkers (eg. ploidy analysis, cell surface adhesion molecules, proliferation markers) to identify those screen-detected lesions that are most likely to be dysplastic. If used at point-of-care, such tests could increased the specificity of the programme and reduce unnecessary referrals.

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

For a visual examination of the oral tissues the ‘test cut-off value’ is insufficiently accurate. More robust criteria need to be developed to ensure that screen detected lesions are more likely to be potentially malignant than the current positive test of a white patch, red patch or ulcer. Studies have shown that primary care dentists use a range of cues when making a diagnostic decision, but tend to only refer lesions that have the attributes of established or advanced disease (25).

7. The tests should be acceptable to the population.

A visual oral examination is simple, non-invasive and a routine part of a visit to the dentist. There is no evidence that such a screening methodology would not be acceptable.

The adjunctive methods mentioned, if found to be appropriate, are all simple to carry out. The oral cavity is easily accessible and none of the tests is invasive.

8. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test and on the choices available to those individuals.

There are clear guidelines from NICE for the referral of lesions (26) and for the management of lesion in secondary care (27). However these have not been developed in the context of a screening programme and further work is needed to determine the capacity of secondary care services to absorb the potential increased workload.

9. Mutational analysis is not envisaged in oral cancer screening (see 4 above).

THE TREATMENT

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.
Early detection and treatment of lesions while they are small (Stage I) may result in a 30-50% improvement in survival (1). A meta-analysis has shown that diagnostic delay contributes to a 30% worsening of advanced stage at presentation of oral cancer (RR 1.32 (95%CI: 1.07-1.62) (28). Surgical management of small lesions may also obviate the need for radiotherapy and will result in significantly less morbidity especially with respect to facial appearance, eating and speaking.

11. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.

The evidence base for the management of established lesions of oral cancer is quite strong and is encompassed in the Improving Outcomes Guidance (27). This is informed on a continuous basis by ongoing research.

The evidence base for management of lesions thought to be potentially malignant has recently been questioned by Holmstrup (29,30). He has shown that even if lesions are surgically removed, the risk of malignant change is not removed and may be increased. This is predicated on the evidence that the lesion is merely a small manifestation of a damaged mucosa affected by field change or field cancerisation. Holmstrup challenges the dogma that dysplastic PMD should always be removed and calls for RCTs of the management of these lesions.

One RCT has shown efficacy of oral lycopene (8mg/day) in the management of oral leukoplakia (31) and another on vitamin A & betacarotene showed a small benefit to prevent malignant transformation though data were not significant (32).

12. Clinical management of the condition and patient outcomes should be optimized by all health care providers prior to participation in a screening programme.

There is plenty of scope for review and optimization of management of oral lesions, especially in the context of screening.

THE SCREENING PROGRAMME

13. There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity.

The Kerala study (see 5; Fig 2) has provided evidence from an RCT that screening can reduce mortality among high-risk groups (20). There has been no similar study in a UK, Western or low prevalence population.
14. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.

There is no reason to believe, if an oral screening programme were to be introduced, that it would not be acceptable. By comparison to current programmes an oral screen would be easier to perform and would be less intrusive or invasive. Feasibility of conducting such studies in Asia (Sri Lanka and Japan) have been reported (33,34)

15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).

The benefits, or effectiveness, and cost-effectiveness have been investigated in an RCT and by simulation modeling (20,21). There is no evidence of any potential physical harm from proposed screening tests. There are no data on potential psychological harm, although the consequences of false negative and false positive results will be similar as for other screening programmes.

16. The opportunity cost of the screening programme (including testing, diagnosis and treatment) should be economically balanced in relation to expenditure on medical care as a whole

In the Kerala study (20) they were also able to demonstrate cost-effectiveness (35). This study used a population approach in a high-incidence country. In a UK population simulation modeling suggests that opportunistic screening in primary care may be cost-effective (21).

17. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.

This has not be established for oral cancer screening

18. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme

This has not been determined for oral cancer screening. In the UK dentists in primary care offer screening but their reliability has not recently been tested. The effects on secondary care resources are not known.
19. All other options for managing the condition should have been considered (eg improving treatment, providing other services).

Case-finding or early diagnosis through improved oral examination has been advocated and is promoted by charities and dental organizations, including the British Dental Association (36). Recent initiatives have also increased public and professional awareness. There are no data available to show the effectiveness of these programmes although studies have suggested that further work is needed to improve the criteria for early detection and for referral to secondary care (25). Although improved case finding must be a worthwhile enterprise, it is primarily conducted through dental practices and therefore a significant number of the at-risk population may not be reached. Including other allied oral health care professionals (dental hygienists - with appropriate training) for oral cancer screening was raised in a parliamentary debate in the House of Lords (Hansard, 22 June, 2009). For routine clinical management of dental problems including those in high risk populations please see the relevant professional guidance.

20. No available evidence

21. Reducing screening interval

Most reported oral cancer screening programmes have been limited to a single examination except one study which reported benefits of annual screening (37).

22 Not applicable (see 4)

Summary and recommendations

A number of strategies have been suggested for the implementation of a screening programme for oral cancer. The most cost-effective option would appear to be opportunistic programmes conducted among high-risk individuals attending primary care. However, there is still considerable uncertainty regarding the natural history of the disease. In particular we are still unable to accurately predict which potentially malignant lesions will progress to cancer. Thus the criteria of a ‘white patch, red patch or non-healing ulcer’ are insufficiently specific to be used as a basis for referral to secondary care. Clear guidelines need to be developed for dentists to enable them to recognize the clinical features of those lesions that are most likely to progress. This may be helped by the development of point-of-care tests to identify which screen-detected lesions are most likely to progress would alleviate this problem by allowing more accurate diagnosis and improving the specificity of lesions referred from primary care.

There is no clear evidence-base for the management of potentially malignant lesions and recent studies have cast doubt on the current practice of surgical
removal of all lesions deemed to be ‘high risk’ (moderate or severe dysplasia) as compared to ‘watch and wait’.

Given these substantial obstacles, it seems that screening cannot at the present time be advocated.

Against this background, there is a deep feeling within the profession that there should be some sort of screening programme for oral cancer and a number of organizations and charities have independently promoted ‘case-finding’ or have advocated the use of ‘screening tests’. Programmes to increase awareness and improve case finding are to be encouraged, but further research is needed to provide a sound evidence base for the detection and management of at risk patients and lesions in primary care.

Further research may include:

- Further studies on referral pathways from primary to secondary care. In particular the development and evaluation of clear guidelines for the recognition and referral of lesions most likely to be potentially malignant.
- Prospective studies to determine the feasibility, effectiveness and cost-effectiveness of high-risk opportunistic screening in general dental and medical practice.
- Studies of the effectiveness and cost-effectiveness of using ancillary staff (dental care professionals, nurses) to screen for oral lesions.
- Further studies to evaluate adjunctive methods for the detection of oral lesions. This should include prospective studies of sensitivity and specificity against histology as a gold standard. Such studies should be carried out in a primary care environment.
- Further studies of point-of-care tests to determine which lesions are most likely to progress (using available or new biomarkers). Prospective studies are needed against histology as the gold standard.
- Prospective studies in the form of an RCT to compare the effectiveness and cost effectiveness of active treatment for potentially malignant lesions compared with surveillance.
- Economic evaluations of potential screening programmes to determine the cost effectiveness of use of additional tests.

References


Figure 1

**Fig 1 a - Registrations of Oral Cancer in the UK 1990-99**

**Fig. 1b. Trends in incidence of oral cancer in Scotland**
Numbers of registrations, by year and sex: 1980-1999
Fig 2. Effect of screening in Kerala, India – after 9 years (Sankaranarayanan et al., 2005) (20)

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*Mortality rate ratio (Male tobacco/alcohol users) 0.57 (0.35-0.93)