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Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment

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Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment (Review)

Bessell A, Glenny AM, Furness S, Clarkson JE, Oliver R, Conway DI, Macluskey M, Pavitt S, Sloan P, Worthington HV

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[Intervention Review]

Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment

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ABSTRACT

Background

Surgery is an important part of the management of oral cavity cancer with regard to both the removal of the primary tumour and removal of lymph nodes in the neck. Surgery is less frequently used in oropharyngeal cancer. Surgery alone may be treatment for early stage disease or surgery may be used in combination with radiotherapy, chemotherapy and immunotherapy/biotherapy. There is variation in the recommended timing and extent of surgery in the overall treatment regimens of people with these cancers.

Objectives

To determine which surgical treatment modalities for oral cavity and oropharyngeal cancers result in increased overall survival, disease free survival, progression free survival and reduced recurrence.

Search methods

The following electronic databases were searched: the Cochrane Oral Health Group Trials Register (to 17 February 2011), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011, Issue 1), MEDLINE via OVID (1950 to 17 February 2011) and EMBASE via OVID (1980 to 17 February 2011). There were no restrictions regarding language or date of publication.

Selection criteria

Randomised controlled trials where more than 50% of participants had primary tumours of the oral cavity or oropharynx, and which compared two or more surgical treatment modalities or surgery versus other treatment modalities.

Data collection and analysis

Data extraction and assessment of risk of bias was undertaken independently by two or more review authors. Study authors were contacted for additional information as required. Adverse events data were collected from published trials.

Main results

Seven trials (n = 669; 667 with cancers of the oral cavity) satisfied the inclusion criteria, but none were assessed as low risk of bias. Trials were grouped into three main comparisons. Four trials compared elective neck dissection (ND) with therapeutic neck dissection in patients with oral cavity cancer and clinically negative neck nodes, but differences in type of surgery and duration of follow-up made meta-analysis inappropriate. Three of these trials reported overall and disease free survival. One trial showed a benefit for elective supraomohyoid neck dissection compared to therapeutic ND in overall and disease free survival. Two trials found no difference between elective radical ND and therapeutic ND for the outcomes of overall survival and disease free survival. All four trials found reduced locoregional recurrence following elective ND.

A further two trials compared elective radical ND with elective selective ND and found no difference in overall survival, disease free survival or recurrence. The final trial compared surgery plus radiotherapy to radiotherapy alone but data were unreliable because the trial stopped early and there were multiple protocol violations.

None of the trials reported quality of life as an outcome. Two trials, evaluating different comparisons reported adverse effects of treatment.

Authors' conclusions

Seven included trials evaluated neck dissection surgery in patients with oral cavity cancers. The review found weak evidence that elective neck dissection of clinically negative neck nodes at the time of removal of the primary tumour results in reduced locoregional recurrence, but there is insufficient evidence to conclude that elective neck dissection increases overall survival or disease free survival compared to therapeutic neck dissection. There is very weak evidence from one trial that elective supraomohyoid neck dissection may be associated with increased overall and disease free survival. There is no evidence that radical neck dissection increases overall survival compared to conservative neck dissection surgery. Reporting of adverse events in all trials was poor and it was not possible to compare the quality of life of patients undergoing different surgeries.

PLAIN LANGUAGE SUMMARY

Surgical interventions for the treatment of oral cavity (mouth) and oropharyngeal (throat) cancers

The studies in this review focused on patients with cancers in the oral cavity. These studies have not shown that surgery to remove the lymph nodes in the neck, which appear to be cancer-free, at the same time as the cancer is removed is associated with longer survival, but there is evidence that early neck surgery reduces recurrence of the cancer. Neither is there evidence that removal of all the lymph nodes in the neck results in longer survival compared to selective surgical removal of affected lymph nodes. Although removal of lymph nodes from the neck is associated with significant adverse effects related to appearance and functions such as eating, drinking and speaking, the studies in this review did not measure quality of life.

BACKGROUND

Oral cancers are a significant disease group globally with more than 404,000 new cases worldwide in 2002 (Parkin 2005; Warnakulasuriya 2009). Oral cancers are the sixth most common cancer worldwide, accounting for an estimated 4% of all cancers. The incidence and mortality from oral cancers varies geographically; the highest age standardised rates of oral cancers are reported in parts of Europe (France, Hungary), Botswana and south central Asia (Sri Lanka, Pakistan, Banglasdesh and India) (Parkin 2005). There is overwhelming evidence that tobacco use, alcohol consumption and betel quid chewing are the main risk factors in the aetiology of intraoral cancer (La Vecchia 1997; Macfarlane 1995). There is also strong evidence that low socio-economic status is associated with a higher incidence and poorer survival of oral cancers (Faggiano 1997). There is a higher incidence of oral cancers in men (Freedman 2007) that is generally attributed to a greater exposure to the known risk factors and vast majority of cases occur in men over 50 (Warnakulasuriya 2009) and among low socio-economic groups (Conway 2008). However, the ratio of males to females diagnosed with oral cancers has declined from approxi-

mately 5:1 in the 1960s to less than 2:1 in 2002 (Parkin 2005). Another recent trend is the increasing incidence of oral cavity and oropharyngeal cancers in younger adults in the European Union and the United States (Warnakulasuriya 2009).

The epidemiological data concerning 'oral cancer' obscures the fact that 'oral cancer' includes both oral cavity and oropharyngeal cancers which have clinically different aetiology, are generally diagnosed at different stages and managed in different ways. In the past, clinical trials have recruited patients with head and neck cancers as if this was a single disease entity (Adelstein 2009). However patients with oral cavity cancers generally present with early stage disease and the primary treatment is surgery or radiotherapy or both. Oropharyngeal cancers are likely to be advanced at the time of diagnosis and primary treatment for these patients is more likely to be radiation therapy or chemoradiation. It is now recognised that oral infection with human papilloma virus (HPV) is strongly associated with the development of oropharyngeal cancer where HPV infection is found in 40% to 60% of patients, especially younger male patients (Adelstein 2009; D'Souza 2007), and HPV is associated with the increased incidence of oropharyngeal cancer (Adelstein 2009; Hammarstedt 2006). The link between oncogenic HPV and oropharyngeal cancer is strong and has been documented in numerous studies, fulfilling the epidemiological criteria for disease causality, especially in the development of oropharyngeal cancer in non-smokers (Sturgis 2007). The proportion of patients with oropharyngeal cancer who are HPV positive has increased dramatically over recent years (Attner 2010; Ryerson 2008) but it is interesting to note that this group of patients have significantly improved rates of both overall survival and disease free survival (Adelstein 2009; Fakhry 2006; Fakhry 2008; Licitra 2006).

The most common cancer of the oral cavity is the squamous cell carcinoma that arises from the lining of the oral cavity; over 95% of all oral cavity cancers are squamous cell carcinomas. Despite significant technical advances in the treatment of oral cancer, it still has a significant mortality with 128,000 deaths recorded, representing nearly half of the incident cases (48%) (Parkin 2001). Survival following a diagnosis of oral cavity or oropharyngeal cancer remains poor with 5-year survival around 50% overall, with only limited improvement in the past 3 decades (Warnakulasuriya 2009).

Description of the intervention

Surgery can be combined with any combination of radiotherapy, chemotherapy and immunotherapy/biotherapy; the sequence of these combination therapies is also considered important. Radiotherapy is typically now administered postoperatively. Chemotherapy can be given: i) before surgery (induction/neoadjuvant - when treatment is administered before the primary therapy, e.g. it is used to shrink a tumour prior to surgery or radiation); ii) after surgery (adjuvant - cancer treatment that is administered after the primary therapy, e.g. when the primary therapy to treat a cancerous tumour is surgery, chemotherapy would be considered an adjuvant therapy) and before radiotherapy; iii) at the same time as radiotherapy (concomitant/concurrent - it may also be referred to as chemo/radiotherapy); or iv) alternating with radiotherapy.

The locoregional control of the primary tumour is the main criterion of successful treatment. Tumours are excised with a margin of clinically normal tissue (this can be typically a margin of between 1 and 2 centimetres in the UK). Despite this apparent complete clinical surgical excision, the tumour may still be demonstrated at the margins histopathologically; this has prognostic implications (Batsakis 1999; Sutton 2003). Margins apparently histologically free of tumour may demonstrate molecular changes and the presence of such tumour clonogen populations at the margins may be predictive for disease progression (Partridge 2000).
Spread of the tumour to the regional lymph nodes within the neck (cervical nodes) is an early and consistent event in the natural history of oral and oropharyngeal cancers (Haddadin 2000). The extent of cervical involvement is reflected in the staging of the tumour and has prognostic implications (Shah 1990). Therefore, surgical dissection of the cervical lymph nodes at risk of metastasis may be undertaken as part of the management of the primary tumour. The classic radical neck dissections removed all of the cervical lymph nodes from levels I to V combined with the sternocleidomastoid muscle, internal jugular vein, submandibular gland and the spinal accessory nerve with resultant significant postoperative morbidity. This is now only reserved for advanced neck disease. Modifications of the neck dissection to preserve some or all of the associated structures have reduced morbidity and may now be undertaken as selective neck dissections (Carew 2003; Robbins 2002). There has been an increasing trend in using the selective neck dissection as a therapeutic procedure in the clinically N0 neck (nodal status - no palpable nodes). In addition to the extent of neck disease at presentation, spread of the tumour out with the capsule of the lymph nodes (extracapsular spread) has also been shown to be a poor prognostic indicator (Woolgar 2003). Historically clinicians treating oral cancer have not focused on distant metastatic disease. This has been because locoregional control had been the main cause of death and there were also less effective chemotherapeutic agents to deal with distant metastases. With improvements in locoregional control distant metastases are an increasing issue in the management of oral cancer.
When small tumours (T1, less than 2 centimetres or T2, 2 to 4 centimetres) present with apparently clinically negative neck nodes, there is controversy over the management of the cervical lymph nodes (Woolgar 2003). Studies have demonstrated an improved outcome when a neck dissection has been undertaken at the same time as the resection of the primary tumour rather than waiting

for neck disease to present subsequently (Haddadin 2000; Hughes 1993) although others adopt a 'wait and see' policy. In cancer of the tongue the thickness of the tumour reflects the risk of nodal metastasis (Pentenero 2005).

Why it is important to do this review

The management of advanced oral cavity and oropharyngeal cancers is problematic and has traditionally relied on surgery and radiotherapy, both of which are associated with substantial adverse effects. Although there have been new treatments developed there has been limited improvement in survival over the past 3 decades (Warnakulasuriya 2009). Oropharyngeal cancers have relatively 'silent' symptoms which may not be present during the early stages of the disease, which is a possible explanation for the fact that stage of disease at diagnosis has not altered in the past 40 years despite public education (McGurk 2005). Tumour recurrence and the development of multiple primary tumours are the major causes of treatment failure (Day 1992; Partridge 2000; Woolgar 2003). Surgical treatment may be disfiguring and result in a substantially reduced quality of life as patients are socially isolated, due to difficulties with altered appearance, speech, eating and drinking. Developments in the way in which surgery is delivered aim to improve its efficacy and reduce the impact on patients' quality of life. This review is undertaken as part of a series of reviews looking at the different treatment modalities of oral cancer (Furness 2011; Glenny 2010). These reviews have been categorised into four intervention groups: surgery, chemotherapy, radiotherapy and immunotherapy. For this surgical review we will aim to answer the broad questions 'Does surgery, in addition to chemotherapy and/or radiotherapy, improve the outcomes for patients with oral cavity and oropharyngeal cancers?' and 'Which type of surgery improves the outcomes for patients with oral cavity and oropharyngeal cancers?'.

For this surgical review we will include all randomised controlled trials where more than 50% of participants included have primary tumours in the oral cavity or oropharynx. Only trials where patients in each treatment arm receive different surgical interventions (either different techniques or timing), or radiotherapy and/or chemotherapy plus or minus surgery, or surgery versus no surgery will be included.

OBJECTIVES

Primary objective

To determine which surgical treatment modalities for oral and oropharyngeal cancers result in increased overall survival, disease free survival, locoregional control and reduced recurrence.

Secondary objective

To determine the implication of treatment modalities in terms of morbidity, quality of life, costs, hospital days of treatment, complications and harms.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) comparing different surgical treatment modalities or trials of other treatment interventions with and without surgery including radiotherapy and chemotherapy were included in the review. It is anticipated that there will be no studies comparing surgery with placebo (although if there are such studies they will be included).

Types of participants

Patients with oral cancer as defined by the International Classification of Diseases for Oncology (ICD-O) codes as C01-C02, C03, C04, C05-C06 (oral cavity) and cancer of the oropharynx (ICD-O: C09, C10) will be included but hypopharynx (ICD-O: C13), nasopharynx (ICD-O: C11) and larynx (ICD-O: C32) will be excluded. Cancers of the lip (ICD-O: C00) will also be excluded (WHO 1990).

Studies of head and neck cancer with cases of oral cancer will be included (so long as at least 50% of participants have oral cavity or oropharyngeal cancer, or data for these cancers alone is available separately).

Cancers will be primary squamous cell carcinomas arising from the oral mucosa. Histological variants of squamous cell carcinomas will be included (adenosquamous, verrucous, basaloid, papillary etc) although they are known to have differing natural history to the majority of conventional squamous cell carcinomas they have a common aetiology, their incidence is low and they are generally managed in the same way. Carcinoma in situ will be included. Epithelial malignancies of the salivary glands, odontogenic tumours, all sarcomas and lymphomas will be excluded as these have a different aetiology and are managed differently.

Types of interventions

Surgical treatment of the primary tumour is typically one of the primary treatment interventions. Surgical treatment could include traditional scalpel based surgery, laser cutting or ablation, or harmonic scalpel. Surgical treatment could have been compared to

other surgical interventions, or to different treatment modalities such as radiotherapy, chemotherapy, immunotherapy/biotherapy with or without surgery; any combinations were considered providing they were compared to surgery in at least one arm of the study. Salvage surgery and palliative surgery were not considered in this review.

Surgical treatment of the neck lymph nodes (cervical lymph nodes) could have preceded, occurred simultaneously with or subsequent to the surgical treatment of the primary tumour. When there was no treatment of the primary tumour but only surgical treatment of the cervical lymph nodes these studies were not considered. Studies concerned with cervical lymph node management in the surgical treatment of the primary tumour were included. The treatments received and compared must have been the primary treatment for the tumour and patients should not have received any prior intervention other than diagnostic biopsy.

Types of outcome measures

Primary outcome measures

- Overall survival / total mortality (disease related mortality will also be studied if possible)
- Disease-free survival
- Local regional control
- Recurrence

Secondary outcome measures

- Harms associated with treatment
- Quality of life
- Direct and indirect costs to patients and health services
- Patient satisfaction

Search methods for identification of studies

This review is part of a series of Cochrane reviews on the treatment modalities for treating oral cavity and oropharyngeal cancer. The reviews have been broadly divided into four themes concerning: surgery, chemotherapy, radiotherapy or immunotherapy/targeted therapies. A search strategy was developed that would encompass three of the four broad themes simultaneously (surgery, chemotherapy, radiotherapy) and further adapted for use in the following databases (date of the most recent searches as indicated):

- MEDLINE via OVID (1950 to 17 February 2011) (Appendix 1);
- The Cochrane Oral Health Group's Trials Register (to 17 February 2011) (Appendix 2);
- The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, 2011, Issue 1) (Appendix 3);
- EMBASE via OVID (1980 to 17 February 2011) (Appendix 4).

As studies involving oral cancer are often included with those of the head and neck, a broad search was undertaken to include all possible studies. The searches attempted to identify all relevant trials irrespective of language. Papers not in English were data extracted/translated by members of The Cochrane Collaboration. Trials were excluded if it was not possible to translate them into the English language. The reference lists of relevant articles were searched and authors were contacted in order to identify unpublished or ongoing trials.

Sensitive search strategies were developed for each database using a combination of free text and MeSH terms; these were based on the search strategy developed for MEDLINE (Appendix 1) but revised appropriately for each database. The search strategy combined the subject search with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity maximising version (2009 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011) (Higgins 2011). The search of EMBASE was linked to the Cochrane Oral Health Group filter for identifying RCTs in this database (Appendix 4). Only handsearching carried out by The Cochrane Collaboration is included in the search (*see* master list www.cochrane.org).The reference lists of related reviews and all articles obtained were checked for further trials. Authors of trial reports and specialists in the field known to the review authors were written to concerning further published and unpublished trials.

Data collection and analysis

Selection of studies

The titles and abstracts (when available) of all reports identified through the electronic searches were scanned independently by two review authors. For studies appearing to meet the inclusion criteria, or for which there are insufficient data in the title and abstract to make a clear decision, the full report was obtained. The full reports obtained from all the electronic and other methods of searching were assessed independently by two review authors to establish whether the studies meet the inclusion criteria or not. Disagreements were resolved by discussion. Where resolution was not possible, a third review author was consulted. All studies meeting the inclusion criteria underwent a risk of bias assessment and data extraction using a specially designed data extraction form. Studies rejected at this or subsequent stages were recorded in the 'Characteristics of excluded studies' table, and reasons for exclusion recorded.

Data extraction and management

Data were extracted by two review authors independently using specially designed data extraction forms. The data extraction forms were piloted on several papers and modified as required before use. Any disagreements were discussed and a third review author consulted where necessary. However, group discussion was often required following data extraction due to the complexity of the data presented. When necessary, authors were contacted for clarification or missing information.

For each trial the following data were recorded.

- Year of publication, country of origin and source of study funding.
- Details of the participants including demographic characteristics and criteria for inclusion and exclusion, proportion with oral cavity and oropharyngeal cancer.
- Details of the type of intervention, timing and duration.
- Details of the outcomes reported, including method of assessment, and time intervals.

Head and neck cancer trials with only combined data (i.e. no outcome data available by primary tumour site) where greater than 50% of participants presented with oral/oropharyngeal cancer were planned to be included in this review. However, where separate 'pure' oral/oropharyngeal cancer data were available for a trial, these 'pure' data were extracted and analysed and the combined head and neck data ignored.

Assessment of risk of bias in included studies

For the studies included in this review, assessment of risk of bias was conducted independently by at least two review authors using the Cochrane risk of bias assessment tool (Higgins 2011). We assessed six domains for each included study: sequence generation, allocation concealment, blinding (of patient, carer, outcome assessor), completeness of outcome data, risk of selective outcome reporting and risk of other potential sources of bias. An overall risk of bias assessment was also made.

For this systematic review we assessed risk of bias according to the following.

- Sequence generation: use of a random number table, use of a computerised system, central randomisation by statistical co-ordinating centre, randomisation by an independent service using minimisation technique, permuted block allocation or Zelan technique. If the paper merely stated randomised or randomly allocated with no further information this was assessed as being unclear.
- Allocation concealment: centralised allocation including access by telephone call or fax, or pharmacy-controlled randomisation, sequentially numbered, sealed, opaque envelopes.
- Blinding: unless the trial was specifically described as double blind, or there was a statement about blinding in the methods section of the paper it was assumed that blinding of patients, clinical staff and outcome assessors did not occur due to lack of feasibility.
- Outcome data: outcome data were considered complete if all patients randomised were included in the analysis of the outcome(s). However, in trials of treatment for cancer this is rarely the case. Trials where less than 10% of those randomised were excluded from the analysis, and where reasons for exclusions were described for each group, and where both numbers and reasons were similar in each group, were assessed as being at low risk of bias due to incomplete outcome assessment. Where post-randomisation exclusions were greater than 10%, or reasons were not given for exclusions from each group, or where rates and reasons were different for each group, the risk of bias due to (in)complete outcome data was assessed as unclear.
- Selective outcome reporting: a trial was assessed as being at low risk of bias due to selective outcome reporting if the outcomes of interest described in the methods section, were systematically reported in the results section. Where reported outcomes did not include those outcomes specified or expected in trials of treatments for oral cancer, or where additional analyses were reported this domain was assessed as unclear.
- Other bias: imbalance in potentially important prognostic factors between the treatment groups at baseline, or the use of a co-intervention in only one group (for example nasogastric feeding) are examples of potential sources of bias noted.

Measures of treatment effect

The primary outcome is total mortality expressed as a hazard ratio (it is acknowledged that it is preferable to talk in terms of overall survival, however, statistically the estimate of effect is the hazard ratio of death). These data were entered into the meta-analysis using the inverse variance method. If hazard ratios were not quoted in studies, we calculated the log hazard ratio and the standard error (SE) from the available summary statistics or Kaplan-Meier curves, according to the methods proposed by Parmar et al (Parmar 1998), or these data were requested from authors.

For dichotomous outcomes, the estimates of effect of an intervention were expressed as risk ratios together with 95% confidence intervals. Dichotomous data were only used for primary outcomes where hazard ratios were unavailable or could not be calculated.

Assessment of heterogeneity

Meta-analyses were conducted only if there were studies of similar comparisons reporting the same outcome measures. The significance of any discrepancies in the estimates of the treatment effects from the different trials was assessed by means of Cochran's test for heterogeneity and the I^2 statistic, and any heterogeneity investigated.

Data synthesis

Meta-analyses were conducted only if there were studies of similar comparisons reporting the same outcome measures. Risk ratios were combined for dichotomous data, and hazard ratios for survival data, using a fixed-effect model, unless there were more than four trials to be combined, when a random-effects model was used.

Subgroup analysis and investigation of heterogeneity

Due to the different natural history and treatment regimens for oral cavity and oropharyngeal cancers we planned to analyse these cancer types separately if possible.

Sensitivity analysis

A sensitivity analysis (to examine the effects of randomisation, allocation concealment, blinded outcome assessment (if appropriate) and quality of follow-up/completeness of data set) was planned but there were insufficient data.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

Over 2940 research papers were identified through the electronic searching. Screening of the titles and abstracts resulted in the identification of 32 potentially relevant trials for inclusion in the review. Full text copies of these articles were retrieved, and assessed further. Further assessment of the papers resulted in seven trials being included in this update of the review. Two of these trials were newly identified (BHNCSG 1998; Yuen 2009).

Included studies

Of the seven trials included in the review, five were multicentred, with the number of centres ranging from two to 12. One trial was undertaken in India (Fakih 1989), two in Brazil (BHNCSG 1998; Kligerman 1994), one in centres across Europe (Austria, Germany and Switzerland) (Bier 1994), one in France (Vandenbrouck 1980), one in China (Yuen 2009) and one in the UK (Robertson 1998). Twenty-four trials, previously included in this review, have now been excluded, because they better fit in the other oral cancer treatment reviews (*see* Characteristics of excluded studies for details).

Characteristics of the Trial Participants

Participants were recruited over periods ranging from 2 years to 7 years, with the earliest recruitment commencing in 1966 (Vandenbrouck 1980). A total of 669 patients were randomly allocated to treatments and 570 were included in the outcome evaluations. Only two of the trial participants had oropharyngeal tumours and all the remainder had oral cavity tumours.

Tumour extent (TNM) was reported in all of the included trials, three of which included patients with T1 to T2 tumours (Fakih 1989; Kligerman 1994; Yuen 2009), two with T2 to T4 tumours (BHNCSG 1998; Robertson 1998) and one with T1 to T3 tumours (Vandenbrouck 1980). In five of the trials participants had clinically negative neck nodes (BHNCSG 1998; Fakih 1989; Kligerman 1994; Vandenbrouck 1980; Yuen 2009) and one trial included participants with neck nodes clinically staged as N0-2 (Robertson 1998). The trial by Bier 1994 did not record the tumour stage or node status of the participants at trial entry (Table 1).

Of the seven included trials, six included recruited participants with oral cavity cancer only (BHNCSG 1998; Bier 1994; Fakih 1989; Kligerman 1994; Vandenbrouck 1980; Yuen 2009) and a further one included those with oral cavity or oropharyngeal cancer (Robertson 1998).

Characteristics of the Interventions

None of the included trials compared different surgical approaches to the excision of the primary tumour.

The six trials of participants with oral cavity cancers all compared different surgical techniques for management of the lymph nodes in the neck (BHNCSG 1998; Bier 1994; Fakih 1989; Kligerman 1994; Vandenbrouck 1980; Yuen 2009). Four trials compared the timing of neck dissection; either elective neck dissection at the same time as excision of the primary tumour or therapeutic neck dissection (delayed until nodes became clinically positive) (Fakih 1989; Kligerman 1994; Vandenbrouck 1980; Yuen 2009). Kligerman 1994 used a supraomohyoid approach for the elective neck dissection in a group of patients with clinically negative neck nodes and in Yuen 2009 elective selective neck dissection at the time of glossectomy was compared with glossectomy alone plus therapeutic neck dissection if nodes became clinically positive. In the trial by Fakih 1989, elective radical neck dissection was used at the same time as resection of the primary tumour in a group with clinically negative neck nodes. In Vandenbrouck 1980, elective radical neck dissection within 2 months of resection of the primary tumour, was compared with therapeutic neck dissection.

Two trials compared different types of neck dissection surgery. In the trial by Bier 1994 both groups had a radical resection of the primary tumour. One group had radical neck dissection at the same time as resection and the other had selective neck dissection surgery. The Brazilian Study group (BHNCSG 1998) compared a modified radical neck dissection at the time of primary resection of

the tumour, with a supraomohyoid neck dissection in conjunction with resection of the primary tumour.
The trial by Robertson 1998 compared surgery followed by radiotherapy with radiotherapy alone in a group of patients with either oral cavity or oropharyngeal cancer.

Characteristics of outcome measures

The duration of follow-up in the included trials ranged from approximately 15 months (Bier 1994) to 122 months (Yuen 2009). All trials except one (Yuen 2009) reported either total mortality or overall survival but not all provided data in a form suitable for inclusion in meta-analysis. Disease free survival was reported in four trials (Fakih 1989; Kligerman 1994; Vandenbrouck 1980; Yuen 2009) and recurrence was reported in five trials (BHNCSG 1998; Fakih 1989; Kligerman 1994; Robertson 1998; Yuen 2009).
Harms/adverse events were mentioned in two trials (BHNCSG 1998; Robertson 1998). BHNCSG 1998 reported the total number of adverse events in each group but not the number of patients affected and Robertson 1998 reported the percentages of participants in each group who experienced adverse effects.
The following outcomes were not reported in any of the included studies:

- hospital days of treatment
- quality-adjusted-life-years (QALYs)
- costs.

Excluded studies

Twenty-four trials, previously included in this review, have now been excluded because they better fit in the other oral cancer treatment reviews. Four previously included trials (Ang 2001; Lawrence 1974; Sanguinetti 2005; Terz 1981), are now included in the radiotherapy review (Glenny 2010); 17 previously included trials (Bernier 2004; Cooper 2004; Lam 2001; Laramore 1992; Licitra 2003; Luboinski 1985; Maipang 1995; Mohr 1994; Paccagnella 1994; Rao 1991; Rentschler 1987; Richard 1991; Schuller 1988; Szabo 1999; Szpirglas 1978; Volling 1999; Weissler 1992) are now included in the chemotherapy review (Furness 2011), and 3 previously included trials are being considered for inclusion in the immunotherapy review which is currently being prepared. One trial was excluded from this review because less than 50% of the participants had oral cavity of oropharyngeal cancer and their data could not be extracted separately (Hintz 1979a).

Risk of bias in included studies

Allocation

Two of the included trials reported adequate sequence generation methods (Fakih 1989; Robertson 1998) and in the remaining five trials the methods of sequence generation were unclear. Adequate allocation concealment was reported in two trials also (Robertson 1998; Vandenbrouck 1980), but only one trial was assessed as being at low risk of bias in both of these domains (Robertson 1998).

Blinding

Blinding of participants and clinicians is not feasible in surgical trials, but blinding of outcome assessment is both possible and desirable. A decision was made to assess those trials which do not explicitly report blinding of outcome assessors, as being at unclear risk of bias for this domain. None of the included studies reported that outcome assessors were blinded to allocated treatment group. It was felt that for objective outcomes (such as total mortality) the lack of blinding was unlikely to result in bias. However, for more subjective outcomes, such as disease free survival, lack of blinding was considered to represent a potential risk of bias.

Incomplete outcome data

Five of the included trials were assessed as being at low risk of bias with regard to incomplete outcome data (BHNCSG 1998; Kligerman 1994; Robertson 1998; Vandenbrouck 1980; Yuen 2009) because all the randomised participants were adequately accounted for in the outcome evaluation. The remaining trials (Bier 1994; Fakih 1989) were assessed as at high risk with regard to this domain. Both Bier 1994 and Fakih 1989 present an interim analysis of a subgroup of participants and the final analysis has not been published as far as we are aware. In both of these trials it is unclear how many participants were randomly allocated to each intervention group, and how many in each group were subsequently excluded from the analysis and/or analysed in a different group from that to which they were originally allocated. It is likely that those excluded from the analysis (because they refused surgery or had extracapsular rupture during surgery) had a different outcome from those included in the analysis.

Selective reporting

Six of the included trials were assessed as being free of selective reporting bias, reporting on expected, clinically important outcomes. Yuen 2009 did not report total mortality or overall survival, so was assessed at high risk of bias for this domain.

Other potential sources of bias

Three trials, (BHNCSG 1998; Vandenbrouck 1980; Yuen 2009) were assessed at low risk of other bias because the intervention groups appeared to be similar at baseline and no other sources of bias were identified.
Three trials (Bier 1994; Fakih 1989; Kligerman 1994) provided no information regarding the baseline characteristics of participants

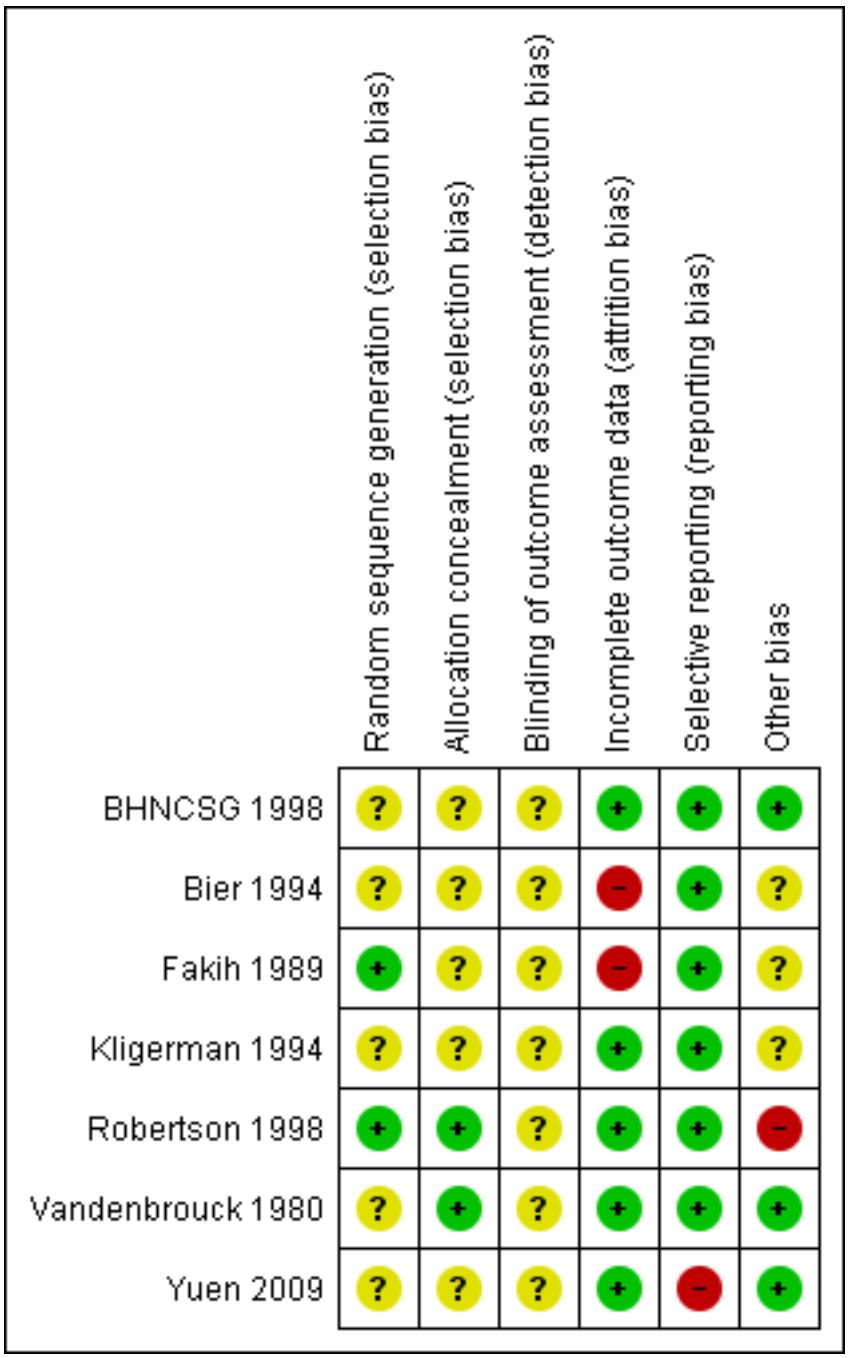
in each group, and so these trials were assessed as being at unclear risk of other bias.

Robertson 1998 was assessed at high risk of other bias because although planned recruitment was 350 patients, this trial was stopped after only 35 patients were recruited because clinicians felt it was unethical to continue. While appropriate procedures were followed and an interim analysis was conducted and reported, it is not clear from this report whether a priori stopping rules were in place. Additionally more than half of the patients in this trial did not receive radiotherapy as planned due to problems with the equipment breaking down. It is likely that this would have had a greater effect on the outcomes the of radiotherapy-only arm of the trial.

Overall risk of bias

A summary of the Risk of Bias assessment is presented in Figure 1. Overall we assessed four studies to be at high risk of bias (Bier 1994; Fakih 1989; Robertson 1998; Yuen 2009) and three trials to be at unclear risk of bias (BHNCSG 1998; Kligerman 1994; Vandenbrouck 1980) for all of the outcomes evaluated.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Effects of interventions

Comparison 1: Elective neck dissection versus therapeutic delayed neck dissection

Four trials (Fakih 1989; Kligerman 1994; Vandenbrouck 1980; Yuen 2009) in this comparison compared the timing of the neck dissection; either at the same time as resection of the primary tumour or as a separate procedure subsequent to resection of the primary, with dissection of the neck nodes being undertaken only after there was clinical evidence of disease in the neck nodes. All participants had oral cavity cancers, specifically tongue or floor of mouth tumours and clinically negative neck nodes on study entry. There were differences between the trials in the surgical procedures and in the duration of follow-up so meta-analysis was not undertaken.

Fakih 1989 and Vandenbrouck 1980 performed classical radical neck dissection procedures and data are reported after 1 year and 3 years of follow-up in these two trials respectively. Yuen 2009 performed selective neck dissection of level I to III nodes. Kligerman 1994 used a supraomohyoid (SOH) elective neck dissection procedure, and reported data after 3.5 years of follow-up. Fakih 1989 and Yuen 2009 were assessed as being at high risk of bias and Kligerman 1994 and Vandenbrouck 1980 were at unclear overall risk of bias.

Two of the three trials, which reported overall survival and disease free survival found no difference between elective radical neck dissection and therapeutic neck dissection (Fakih 1989; Vandenbrouck 1980) for either of these outcomes (Analysis 1.1; Analysis 1.2; Analysis 1.4). However in the trial by Kligerman 1994, where elective surgery was the less extensive SOH, there was a difference in both overall survival and disease free survival after 3.5 years of follow-up, favouring elective SOH neck dissection compared to therapeutic neck dissection (Analysis 1.1; Analysis 1.3). Yuen 2009 did not report either total mortality or disease free survival.

There is some evidence that elective neck resection appears to reduce locoregional recurrence rates from all of the four studies but the data was not suitable for meta-analysis due to the differences between studies in the type of surgery and the duration of follow-up (Analysis 1.5).

Two of these trials (Vandenbrouck 1980; Yuen 2009) reported recurrence rates at different sites, but numbers were too small to determine whether there may have been a difference between the groups in rate of recurrence of either a second primary tumour or distant metastases (data not shown).

None of these four trials reported on quality of life, or any measure of patient satisfaction in the two groups.

Comparison 2: Radical neck dissection versus selective neck dissection

The two trials (BHNCSG 1998; Bier 1994) in this comparison compared neck dissection surgery of differing extent. There were differences between the two studies with regard to patient characteristics at baseline and surgical procedures so meta-analysis was not undertaken.

BHNCSG 1998 compared a modified classical neck dissection procedure with accessory nerve preservation, to a supraomohyoid neck dissection (SOH) to achieve a compartmental excision of levels I to III neck nodes in 148 patients with T2 to T4 primary lesions in the oral cavity and clinically negative necks. Frozen sections were carried out on the nodes during surgery and 3 patients in the SOH group who were found to have histologically positive nodes then underwent the modified classical neck dissection instead. This trial was at unclear risk of bias.

In Bier 1994 104 patients with either clinically negative or positive but movable, neck nodes were randomised to either radical neck dissection or a selective neck dissection where the platysma, the sternocleidomastoid muscle, the internal jugular vein and the accessory nerve were left in place. Primary tumours were in the oral cavity and the study was assessed at high risk of bias.

There is no evidence from these two trials of a difference in overall survival, disease free survival or disease recurrence between the radical or more selective neck dissection surgery (Analysis 2.1; Analysis 2.2; Analysis 2.3).

The following adverse effects were reported in the BHNCSG 1998 trial: flap necrosis, wound infection, fistula, vascular rupture, hematoma, seroma, chyle fistula. There were no complications in 45 patients (59%) in the modified radical neck dissection group and none in 54 patients (75%) in the supraomohyoid neck dissection group. There were two postoperative deaths in the modified radical neck dissection group and one in the supraomohyoid neck dissection group.

Comparison 3: Radiotherapy plus surgery versus radiotherapy alone

One trial compared surgery plus postoperative radiotherapy with radiotherapy alone (Robertson 1998). Those in the surgery group had wide local excision of the primary tumour together with either a radical neck dissection or a more selective neck dissection at the discretion of the surgeon. It was planned to accrue 175 patients to each arm of the trial but after 35 patients had been recruited the trial was stopped due to the high death rate in the radiotherapy alone arm. Data in Analysis 3.1 are from an interim analysis of 35 participants after 23 months and show a hazard ratio for total mortality of 0.24 (95% confidence interval (CI) 0.10 to 0.59), favouring the surgery group. This estimate should be interpreted

with extreme caution for a number of reasons. The authors state that "the difference in survival is likely to be inflated" due to the small number of participants in the analysis, the fact that only 41% of patients in the radiotherapy only arm received their radiotherapy as planned due to problems with machine breakdown/servicing, and that there were a number of other protocol violations in the trial. In the surgery plus radiotherapy arm of this trial 50% of the patients received their radiotherapy as planned, but 12% of participants in this group received neither surgery to the mandible nor neck dissection.

The following severe acute side effects were reported in both groups (Robertson 1998): subcutaneous fibrosis, telangiectasia (1 to 4 cm^2), and moderate to severe oedema, xerostomia, trismus and dysphagia. Subcutaneous fibrosis was reported as more prevalent in the surgery plus radiotherapy group (P = 0.042), but the prevalence of other side effects appeared to be similar in each group.

DISCUSSION

Summary of main results

This systematic review was undertaken to answer the question 'Does treatment with surgery improve the outcomes for patients with oral cavity and oropharyngeal cancers?'. There were seven randomised controlled trials (RCTs) included in this review with a combined total of 669 patients randomised. All but two of these patients had oral cavity cancers. None of the trials were at low risk of bias.

None of the included trials compared different surgical approaches to the removal of the primary tumour. Four of the included trials evaluated the timing of neck dissection surgery in the course of treatment and two included trials evaluated the extent of neck dissection.

- Four trials compared elective neck dissection surgery undertaken at the same time as excision of the primary tumour with the option of excision of the primary alone, followed by subsequent neck dissection surgery if and when neck nodes showed clinical signs of cancer (therapeutic neck dissection). All patients had oral cavity cancers, specifically tongue or floor of mouth tumours, and clinically negative neck nodes. One trial showed a difference in overall survival and disease free survival after three and a half years of follow-up, favouring elective SOH neck dissection compared to therapeutic neck dissection. In two trials where the elective procedure was a radical neck dissection there was no difference between the elective and therapeutic groups with regard to either overall or disease free survival. The fourth trial in this group did not report overall or disease free survival. There is some evidence from that locoregional disease recurrence is reduced following elective neck resection, but data were unsuitable for meta-analysis.

- A further two trials, compared elective radical (comprehensive) neck dissection with a selective neck dissection in patients with oral cavity cancers. One trial included only patients with clinically negative neck nodes and the other included those with movable positive neck nodes as well. There is no evidence from these two trials of a difference in overall survival between the two types of surgery, and in the single trial that reported disease free survival and disease recurrence there was no difference between the two types of surgery.

- The third comparison was between surgery plus postoperative radiotherapy and radiotherapy alone but the only trial in this comparison was stopped early due to an unacceptably high death rate in the radiotherapy alone group. There was a difference in overall survival favouring the surgery plus radiotherapy group. These results should be interpreted with caution because the nature of the interim analysis on 35 patients (10% of planned recruitment) may inflate the difference between the groups. Also there were a number of protocol violations (more than half of the participants did not receive their radiotherapy as planned due to machine breakdown/servicing) which may partially explain the poor outcome in the radiotherapy alone group.

While there is weak evidence from these included trials that early or extensive dissection of the lymph nodes in the clinically negative neck reduces locoregional recurrence, there is no strong evidence of a difference in overall survival, or disease free survival. There is no information from these trials on quality of life of the patients who have undergone the different neck dissection procedures.

Overall completeness and applicability of evidence

This review originally sought to evaluate the benefits of all surgical treatment modalities used alone or in conjunction with other treatment regimens such as radiotherapy, chemotherapy and radiotherapy. However, this led to multiple treatment comparisons of studies that did not necessarily differ purely on the surgical treatment method. This review is one of a series of reviews in oral cancer looking at surgery, radiotherapy, chemotherapy and immunotherapy. Therefore for this update, the protocol for this review was modified to only include studies where different surgical treatment modalities were directly compared against one another, or surgery was compared to a different treatment regimen such as radiotherapy, chemotherapy or immunotherapy. All other studies were removed from the updated review, and where appropriate were incorporated into the other oral cancer reviews (Furness 2011; Glenny 2010).

The inclusion criteria for this review specified that trials of surgery where participants had either oral cavity or oropharyngeal cancer would be included. However for this update of the review only seven trials were identified and 667 of the total of 669 participants

in these trials had oral cavity cancers, most commonly in either the tongue or floor of mouth. The trials, each including between 35 and 167 participants, recruited patients over four decades between 1966 and 2004. There have been significant developments in both the surgical and adjuvant treatments for oral cavity cancer patients over the past decade and these are incompletely evaluated in this systematic review due to the lack of randomised controlled trials in this condition. It is encouraging to note that there are currently three large trials ongoing (NCT00193765; NCT01334320; NCT00571883 (SEND)) which will provide further information concerning the benefits and harms of different surgical options for neck dissection in oral cavity cancer patients.

Only two of the included studies reported harms or adverse events to treatment (BHNCSG 1998; Robertson 1998) but neither presented outcomes per person. Aggressive surgery to remove the cancer and reduce the risk of recurrence has been associated with very significant adverse effects on both appearance and functions such as breathing, speech and swallowing. Less aggressive surgery, such as selective lymph node dissection is associated with a greater risk of recurrence, but preservation of function and appearance. Incorporation of quality of life outcomes into randomised trials is essential if the true benefits and harms of different types of surgery are to be evaluated. It is noteworthy that while some of the trials included in this review reported that some patients, randomly allocated to surgery, refused surgical treatment and were withdrawn from the trials, there is no report of the quality of life of these patients compared to those included in the trials.

We did not identify any trials of surgery in patients with oropharyngeal cancer, probably because the current therapeutic approach to oropharyngeal cancer is either radiotherapy or chemoradiotherapy. Over the past decade the percentage of patients with oropharyngeal cancer who test positive for human papilloma virus (HPV) has increased steadily. It is now recognised that HPV status of patients with oropharyngeal cancer is an important factor in their prognosis (Adelstein 2009; Brizel 2011).

Quality of the evidence

The overall quality of the evidence included in this systematic review is poor. All of the included trials were at either high or unclear risk of bias. Patients were recruited over 4 decades. For objective outcomes such as total mortality, trials assessed as adequate with regard to the domains of sequence generation, allocation concealment, complete outcome data and absence of selective reporting, were planned to be assessed as being at low risk of bias. None of the included studies met all these criteria. None of the trials included in this systematic review used, or reported using, blinding of either the participants or the outcome assessors. It is recognised that blinding is difficult to maintain in trials of surgery and it may not be either possible or indeed ethical, to blind trial participants. It is likely that many outcome assessments are performed by the clinicians treating the patients.

There has been substantial development in the surgical and non-surgical treatments for both oral and oropharyngeal cancers over recent years. Further objective assessments of current surgical treatments for these cancers are needed in order to inform both patients and clinicians about the benefits and risks of different treatments.

Potential biases in the review process

The search strategy employed was comprehensive with no language restrictions, and inclusion criteria for the review were clearly specified in line with the other reviews in this series (Furness 2011; Glenny 2010) so the risk of biased selection of studies was minimal.

Agreements and disagreements with other studies or reviews

Two reviews of treatment of neck dissection in the surgical treatment of oral cavity cancer have been published based on the same included studies (Fasunla 2011; Kowalski 2007). Kowalski 2007 looked at dichotomous outcomes (percentages in each group) in three RCTs. No meta-analysis was undertaken and only the summary outcome estimates were noted, without regard to the variance of these. Their conclusions are based on "vote-counting".

Fasunla 2011 reviewed four RCTs and reported the dichotomous outcome of disease-specific death after approximately 3 years of follow-up. This review found that the risk ratio (RR) of disease specific death favoured elective neck dissection (RR 0.57; 95% confidence interval (CI) 0.36 to 0.89).

We have chosen to use the outcome of overall survival/total mortality because we believe this is the more important outcome for patients, and we have used hazard ratios where possible, as they have the advantage of incorporating all available information, including data from patients who fail to complete the trial, in the outcome. We look forward to the addition of data from the three ongoing trials identified to the next update of this review.

AUTHORS' CONCLUSIONS

Implications for practice

The trials included in this review do not address different surgical approaches to removal of the primary tumour. From the four trials of patients with oral cavity cancers there is no strong evidence that elective dissection of clinically negative neck nodes compared to therapeutic neck dissection results in better or worse overall survival or disease free survival. From two trials there is no evidence that radical neck dissection results in better or worse overall survival or disease free survival compared to selective neck dissection. However elective neck dissection does reduce locoregional

recurrence. More information about the effects of these surgeries on patients' quality of life is required in order to fully assess the benefits and harms of these surgical procedures.

Implications for research

We would make the following recommendations for future research involving the surgical treatment of oral or oropharyngeal tumours.

(1) Trialists are encouraged to follow the CONSORT guidelines when reporting on their trials. Ideally trials should report hazard ratios with 95% confidence intervals for survival data, or present data that allows for the calculation of this estimate of effect.

(2) Health-related quality of life is an important outcome measure that should be integral to all trials of oral cavity and oropharyngeal cancers.

(3) There should be a standardised and consistent reporting of adverse events and morbidity associated with treatment, with results reported per patient.

(4) Future trials of oral cavity and oropharyngeal cancers should report data based on the location of the primary tumour.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

BHNCSG 1998

Methods	Location of trial: Brazil Number of centres: Multicentre (8) Funding: Not stated Trial ID: Not stated
Participants	Inclusion criteria: Resectable T2 to T4 lesions, clinically negative neck (N0), no prior treatment, histologic diagnosis of squamous cell carcinoma of the oral tongue, floor of the mouth, inferior gingiva, or retromolar trigone, no need for myocutaneous or free flaps for reconstruction, and a Karnofsky's score of 60 or greater Exclusion criteria: Significant cardiac or pulmonary diseases, distant metastases and/or multiple primary cancers Recruitment period: May 1990 to December 1993 Number randomised: 148 (all OC - 42% tongue, 33% FOM, 8% inferior gingiva, 17% retromolar trigone) Number analysed: 148
Interventions	**Modified radical classical neck dissection (MRND) versus supraomohyoid neck dissection (SOH)** Gr 1 (n = 76): MRND - surgery conducted centripetally toward the submandibular triangle Gr 2 (n = 72): SOH - dissection performed to achieve a compartmental excision of levels I, II and III lymph nodes. Where a positive node was confirmed during the procedure the operation was converted to a MRND For both groups, postoperative radiotherapy was indicated in cases with positive margins and/or positive lymph nodes in the specimen. Radiotherapy was over 5 consecutive weeks to deliver a total dose of 50 Gy All patients had primary tumour resection.
Outcomes	Primary: Overall survival Secondary: Recurrence, length of hospital stay, adverse events Duration of follow-up: 5 years
Notes	HR data taken from Kaplan-Meier graph (no numbers at risk).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were stratified by institution and laterality (unilateral or bilateral) and subsequently randomised". Method of sequence generation not described

BHNCSG 1998 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blind outcome assessment not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop outs.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	Groups appeared similar at baseline. No evidence of other potential sources of bias

Bier 1994

Methods	Location of trial: Germany, Austria and Switzerland Number of centres: Multicentre Funding: Not stated Trial ID: Not stated (part of The German-Austrian-Swiss Association for Head and Neck Tumours (DOSAK))
Participants	Inclusion criteria: Untreated SCC of the oral cavity without metastases, primary tumour on one side postcanine or postmolar, i.e. second or third part of the tongue, respectively, nonpalpable or clinically negative, or clinically positive, movable lymph nodes in the neck Exclusion criteria: Fixed lymph nodes in the neck. Recruitment period: Uncertain Number randomised: 167 (all OC - 37% tongue, 21% FOM, 16% RMT, 14% mandible, 8% maxilla, 3% cheek, 1% other) Number analysed: 104
Interventions	**Radical neck dissection versus selective neck dissection** Gr 1 (n = 48): Radical neck dissection (ipsilateral) on the draining lymph nodes. Radical dissection designated as removal of: i) platysma, sternocleidomastoid muscle, omohyoid muscle, stylohyoid muscle, the distal part of the biventer cervicis and the fascia colli; ii) the accessory nerve, the descending branch of the hypoglossus nerve, the branches of the cervical plexus; iii) the cervical vein, the superficial jugular vein and the internal jugular vein; iv) fat tissue, the submandibular gland and the lower part of the parotid gland Gr 2 (n = 56): Selective neck dissection (ipsilateral) on the draining lymph nodes. Selective dissection designated as retention of the platysma, sternocleidomastoid muscle, internal jugular vein and the accessory nerve All patients underwent radical resection of the primary tumour
Outcomes	Primary: Overall survival Secondary: Recurrence, metastases Duration of follow-up: 4 years

Bier 1994 (*Continued*)

Notes	Preliminary report. Neck dissection was followed by radiotherapy and/or chemotherapy in patients not undergoing radical resection of the primary tumour and in patients with capsular rupture in at least one lymph node. These patients were not included in the analysis HR data taken from Kaplan-Meier graph (no numbers at risk).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized according to the treatment-dependant prognostic index (TPI) of the DOSAK". Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blind outcome assessment not mentioned.
Incomplete outcome data (attrition bias) All outcomes	High risk	Interim analysis of 104/167 patients randomised published in 1994. No subsequent publication identified. Patients who did not have radical surgery at the primary site and those who had extracapsular rupture of at least one lymph node are not included in the evaluation
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Unclear risk	No information about comparability of groups at baseline.

Fakih 1989

Methods	Location of trial: India Number of centres: 1 Funding: Not stated Trial ID: Not stated
Participants	Inclusion criteria: T1 to T2, N0 M0, histologically proven SCC of the anterior two thirds of the oral tongue Exclusion criteria: Not stated. Recruitment period: July 1985 to September 1988 Number randomised: 100 (all OC -100% tongue) Number analysed: 70

Fakih 1989 (*Continued*)

Interventions	**Elective radical neck dissection versus therapeutic radical neck dissection** Gr 1 (n = 30): Radical neck dissection (ipsilateral). Gr 2 (n = 40): Only those developing neck node metastasis underwent radical neck dissection All patients underwent resection of the primary tumour (standard anterior two-thirds hemiglossectomy)
Outcomes	Primary: Disease free survival Secondary: Overall survival, disease related mortality, recurrent disease Duration of follow-up: 1 year
Notes	No data available for calculation of HR.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomised from previously generated random numbers".
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blind outcome assessment not mentioned.
Incomplete outcome data (attrition bias) All outcomes	High risk	Interim analysis, no final analysis reported. 73 participants entered into protocol, 12 refused treatment and 2 were declared unfit for surgery. Of the remaining 59 who completed initial treatment, 35 who completed a median of 22 months follow-up are included in the analysis (approximately 48%)
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting.
Other bias	Unclear risk	No information about comparability of groups at baseline.

Kligerman 1994

Methods	Location of trial: Brazil Number of centres: 1 Funding: Government (personal communication) Trial ID: Not stated
Participants	Inclusion criteria: Resectable early stage (T1 to T2, N0) SCC of tongue and floor of mouth Exclusion criteria: Not stated. Recruitment period: 1987 to 1992 Number randomised: 67 (all OC - 61% tongue, 39% FOM) Number analysed: 67
Interventions	**Elective neck dissection versus therapeutic neck dissection** Gr 1 (n = 34): Elective supraomohyoid neck dissection. Dissection of levels 1 to 3 plus resection of submandibular gland, preserving the sternocleidomastoid muscle, spinal accessory nerve and internal jugular vein. Gr 2 (n = 33): Therapeutic neck dissection. All patients underwent resection of the primary tumour.
Outcomes	Primary: Total mortality Secondary: Disease free survival, locoregional failures, recurrent disease, disease related mortality Duration of follow-up: 3.5 years
Notes	Paper reports that overall survival assessed by Kaplan-Meier actuarial method, but not presented HR data taken from Kaplan-Meier graph (no numbers at risk) for DFS Locoregional failure data unclear.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"All 67 patients were stratified by stage ... and those in each stage were randomised". Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no'.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blind outcome assessment not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop outs.

Kligerman 1994 (*Continued*)

Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting.
Other bias	Unclear risk	No information about comparability of groups at baseline.

Robertson 1998

Methods	Location of trial: UK Number of centres: Multicentre (4) Funding: Not stated Trial ID: Not stated
Participants	Inclusion criteria: Resectable, stage T2 to T4, N0 to N2, M0 H&N tumours Exclusion criteria: Stage I (T1N0M0), history of previous malignancy, apart from basal cell carcinoma of the skin, or intraepithelial carcinoma of the cervix Recruitment period: December 1991 to December 1993 Number randomised: 35 (intended 350 but trial stopped early due to concern of the number of deaths in the radiotherapy alone arm) (33/35 OC - 40% tongue, 43% FOM, 11% RMT, 6% tonsil) Number analysed: 35
Interventions	**Surgery plus radiotherapy versus radiotherapy alone** Gr 1 (n = 17): Radical resection and neck dissection plus postoperative radiotherapy. Radical surgery involved wide local excision of the primary tumour with a 1 cm margin. A radical or functional neck dissection was carried out at the same time at the discretion of the surgeon. Reconstruction of the oral cavity was carried out immediately. Postoperative radiotherapy comprised 60 Gy in 30 fractions over 6 weeks, commencing within 6 to 8 weeks of surgery. Gr 2 (n = 18): Radiotherapy alone 66 Gy in 33 fractions over 6.5 weeks, receiving 2 Gy per day
Outcomes	Primary: Locoregional control Secondary: Overall survival, disease free interval, recurrent disease, adverse events Duration of follow-up: 3 years
Notes	HR data taken from Kaplan-Meier graph (no numbers at risk). Data presented in Kaplan-Meier estimates for disease free survival, but not used as graph starts at 50% for XTR alone arm. Authors provided additional information relating to allocation concealment and the characteristics of tumours

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Robertson 1998 (*Continued*)

Random sequence generation (selection bias)	Low risk	"Random permuted blocks of four were used for randomization" following stratification according to institution and site of primary disease
Allocation concealment (selection bias)	Low risk	Randomisation via a telephone call to the West of Scotland Clinical Trials Office
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blind outcome assessment not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop outs.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting of outcomes.
Other bias	High risk	Anticipated enrolment of 350 patients, but trial stopped after 35 patients recruited because clinicians felt it was unethical to continue. Appropriate procedures and analysis were conducted. More than half of those recruited had either delays or interruptions to the planned radiotherapy schedule. It is likely that this would have had a greater effect on the outcomes of the radiotherapy alone arm of this trial

Vandenbrouck 1980

Methods	Location of trial: France Number of centres: One Funding: Not stated Trial ID: Not stated
Participants	Inclusion criteria: T1 to T3, N0, SCC oral cavity, tongue or lower floor of mouth. Patients were any age or sex with no previous transcutaneous radiotherapy or interatrial chemo infusion. Neck free of disease or with moveable submaxillary node/s no larger than 1 cm Exclusion criteria: Not stated. Recruitment period: 1966 to 1973 Numbers randomised: 80 (all OC - 56% tongue, 44% FOM) Numbers analysed: 75
Interventions	**Elective radical neck dissection versus therapeutic radical neck dissection** Gr 1 (n = 39): Elective neck dissection within 2 months of treatment of primary lesion. In cases of lateral tumour an ipsilateral radical neck dissection with removal of sternocleidomastoid muscle, internal jugular vein without sparing the spinal accessory nerve

Vandenbrouck 1980 (*Continued*)

	was performed. When tumour crossed or close to midline submental, submaxillary and jugulodigastric contralateral dissection performed. Nodal involvement resulted in post-operative radiotherapy. Gr 2 (n = 36): Delayed therapeutic dissection. These patients were followed for at least 3 years and underwent neck dissection if a cervical node became enlarged All patients received interstitial radiotherapy to the primary tumour site prior to randomisation
Outcomes	Primary: Overall survival Secondary: Disease free survival, disease related mortality, other mortality, recurrent disease Duration of follow-up period: 5 years
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomisation was under the control of a statistician who observed the strictest protocol". However, method of sequence generation was not described
Allocation concealment (selection bias)	Low risk	"Randomisation was under the control of a statistician who observed the strictest protocol". Assumed that this was adequate
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blind outcome assessment not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop outs.
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting.
Other bias	Low risk	No evidence of other potential sources of bias.

Yuen 2009

Methods	Location of trial: Hong Kong, China Number of centres: 3 Funding: Not stated Trial ID: Not stated
Participants	Inclusion criteria: AJCC, St I to II, SCC oral tongue. No nodal metastases, no prior surgery, chemotherapy of radiotherapy Exclusion criteria: Oral cancer of other sub sites, or cancer of base of tongue Recruitment period: 1996 to 2004 Numbers randomised: 72 (all OC - 100% tongue) Numbers analysed: 71
Interventions	**Elective selective neck dissection versus therapeutic radical neck dissection** Gr 1 (n = 36): Elective ipsilateral selective neck dissection of level I, II, or III neck nodes. Gr 2 (n = 36): Delayed therapeutic dissection. These patients were followed, and received ultrasound examinations every 3 months for the first 3 years. If nodal recurrence was detected these patients underwent either radical or modified radical neck dissection followed by radiotherapy All patients in the trial had transoral glossectomy with 1.5 resection margins
Outcomes	Nodal recurrence, disease recurrence, death due to tumour, 5 year tumour specific survival
Notes	Duration of follow-up: 34 to 122 months

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation stratified by tumour stage. Method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Used sealed envelopes to contain the allocation. Insufficient information to determine whether allocation was concealed from investigators
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 patient allocated to observation group was subsequently found to have T3 tumour and was withdrawn. All other randomised participants included in the outcome evaluations
Selective reporting (reporting bias)	High risk	Reported nodal and local recurrence, disease free survival and disease specific death.

Yuen 2009 (*Continued*)

		No reporting of mortality in each group
Other bias	Low risk	Groups appeared similar at baseline.

Gr = group; H&N = head and neck; OC/OP = oral cancer/oropharyngeal cancer; PORT = postoperative radiotherapy; RT = radiotherapy; SCC = squamous cell carcinoma; SE = standard error;

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ang 2001	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: radiotherapy'
Bernier 2004	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy'
Bier 1981	RCT to be included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: immunotherapy'
Cooper 2004	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy'
De Stefani 2002	RCT to be included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: immunotherapy'
Hintz 1979	H&N cancer study with < 50% oral cancer/oropharyngeal cancer
Hintz 1979a	H&N cancer study with < 50% oral cancer/oropharyngeal cancer
Kramer 1987	Insufficient detail in published report to establish what the surgical procedures involved and whether these were the same in all groups. Insufficient information to enable either risk of bias assessment to be undertaken
Lam 2001	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy'
Laramore 1992	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy'
Lawrence 1974	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: radiotherapy'
Licitra 2003	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy'

(*Continued*)

Luboinski 1985	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy'
Maipang 1995	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy'
Mohr 1994	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy'
Neifield 1985	RCT to be included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: immunotherapy'
Paccagnella 1994	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy'
Rao 1991	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy'
Rentschler 1987	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy'
Richard 1991	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy'
Sanguinetti 2005	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: radiotherapy'
Schuller 1988	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy'
Szabo 1999	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy'
Szpirglas 1978	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy'
Terz 1981	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: radiotherapy'
Volling 1999	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy'
Weissler 1992	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy'

H&N = head and neck; IPD = individual patient data; OC = oral cancer; OP = oropharyngeal cancer; RCT = randomised controlled trial; SCC = squamous cell carcinoma.

Characteristics of ongoing studies *[ordered by study ID]*

NCT00193765

Trial name or title	Elective versus therapeutic neck dissection in the treatment of early node negative squamous carcinoma of the oral cavity (NCT00193765)
Methods	RCT.
Participants	histologically proven T1 to T2, N0 M0, SCC of buccal mucosa, lower alveolus, oral tongue or floor of mouth
Interventions	Elective neck dissection versus therapeutic neck dissection.
Outcomes	Survival (5 years), role of ultrasound in diagnosis and follow-up, accuracy of surgeon assessment of tumour thickness, identification of histological prognostic factors
Starting date	January 2004. Planned enrolment 710.
Contact information	Dr Anil D'cruz, Tata Memorial Hospital, Mumbai, India (adcruz@vsnl.com)
Notes	Currently recruiting March 2010.

NCT00571883 (SEND)

Trial name or title	Neck surgery in treating patients with early-stage oral cancer (SEND trial) (NCT00571883)
Methods	RCT.
Participants	Patients with oral squamous cell carcinoma 1 to 3 cm at primary site, no clinical or preoperative imaging evidence of neck involvement (N0)
Interventions	Selective elective neck dissection plus resection of primary tumour versus resection of primary alone
Outcomes	Overall survival, disease free survival, local and regional recurrence, completeness of primary resection, quality of life, psychological well being, costs
Starting date	January 2007.
Contact information	Study chair: Iain Hutchison, Facial Surgery Research Foundation, UK (send@savingfaces.info)
Notes	Currently recruiting July 2009.

NCT01334320

Trial name or title	Survival benefit of elective neck dissection in T1, 2 N0 M0 oral squamous cell carcinoma (NCT01334320)
Methods	RCT.
Participants	Histologically proven T1 or T2 N0 M0 (clinical) squamous cell carcinoma of oral tongue, buccal mucosa, gingiva, floor of mouth or hard palate
Interventions	Elective superior omohyoid neck dissection versus watch and wait (resection of primary tumour and therapeutic dissection of neck when clinical evidence of disease)
Outcomes	Overall and disease free survival at 5 years, recurrence, quality of life
Starting date	April 2011. Planned enrolment 448.
Contact information	Dr Guiqing Lao, Hospital of Stomatology, Sun Yat-sen University, Guangdong, China (drliaoguiqing@hotmail.com)
Notes	

DATA AND ANALYSES

Comparison 1. Elective neck dissection versus therapeutic (delayed) neck dissection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total mortality	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Elective radical neck dissection versus therapeutic neck dissection (1 year)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Elective SOH neck dissection vs therapeutic neck dissection (3.5 years)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Total mortality	1		Hazard Ratio (Fixed, 95% CI)	Totals not selected
2.1 Elective radical neck dissection versus therapeutic radical neck	1		Hazard Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Disease-free survival	1		Hazard Ratio (Fixed, 95% CI)	Totals not selected
3.1 Elective SOH neck dissection vs therapeutic neck dissection (3.5 years)	1		Hazard Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Disease-free survival	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Elective radical neck dissection versus therapeutic neck dissection (1 year)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Elective radical neck dissection versus therapeutic radical neck dissection (3 years)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Locoregional recurrence	4		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Elective radical neck dissection versus therapeutic neck dissection (1 year)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Elective SOH neck dissection versus therapeutic neck dissection (3.5 years)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Elective selective neck dissection vs therapeutic neck dissection	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.4 Elective radical neck dissection versus therapeutic radical neck dissection (3 years)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Radical neck dissection versus selective neck dissection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total mortality	2		Hazard Ratio (Fixed, 95% CI)	Totals not selected
1.1 Modified radical classical neck dissection (MRND) vs supraomohyoid neck dissection (SOH)	1		Hazard Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Radical neck dissection versus selective neck dissection	1		Hazard Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Disease-free survival	1		Hazard Ratio (Fixed, 95% CI)	Totals not selected
2.1 Radical neck dissection versus selective neck dissection	1		Hazard Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Disease Recurrence	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Resection plus elective supraomohyoid dissection versus resection alone (5 years)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 3. Surgery plus radiotherapy versus radiotherapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total mortality	1		Hazard Ratio (Fixed, 95% CI)	Totals not selected

ADDITIONAL TABLES

Table 1. Stage of cancer

Study		
BHNCSG 1998	T2 to T4	Negative neck
Bier 1994	ns	Negative or positive neck
Fakih 1989	T1 or T2	Negative neck
Kligerman 1994	T1 or T2	Negative neck
Robertson 1998	T2 to T4	Negative or positive neck
Vandenbrouck 1980	T1 to T3	Negative neck

WHAT'S NEW

Last assessed as up-to-date: 16 February 2011.

Date	Event	Description
4 July 2011	New citation required and conclusions have changed	Two new trials added. New comparisons, and conclusions. Twenty-four previously included trials now moved to other oral cancer reviews on chemotherapy and radiotherapy
4 July 2011	New search has been performed	Searches updated to 17 February 2011.

HISTORY

Protocol first published: Issue 4, 2006

Review first published: Issue 4, 2007

Date	Event	Description
28 April 2009	Amended	Minor changes to the data.
20 June 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

- Richard Oliver (RO), Jan Clarkson (JC), Helen Worthington (HW) and Anne-Marie Glenny (AMG) conceived, designed and sought funding for the review.

- Alyson Bessell (AB) co-ordinated and managed the review update.

- The trials search strategy was refined with input from Anne Littlewood (AL), AMG & Susan Furness (SF).

- SF, AMG and AB screened the titles and abstracts.

- SF organised retrieval of papers.

- AB, AMG and SF screened retrieved papers against the inclusion criteria.

- AB, SF, HW and AMG appraised the quality of the papers, and extracted data.

- Sue Pavitt (SP) obtained additional data on published studies; these were then analysed by HW, SP and AMG in the original review.

- HW, AMG and SP provided a methodological perspective.

- David Conway (DC), RO, Michaelina Maclusky (MM), and Philip Sloan (PS) provided a clinical perspective.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- School of Dentistry, The University of Manchester, UK.
- Cochrane Oral Health Group, UK.
- The University of Dundee, UK.
- The University of Glasgow, UK.

External sources

- National Institute of Health, National Institute of Dental & Craniofacial Research, USA.
- Central Manchester & Manchester Children's University Hospitals NHS Trust, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of interventions: The intervention under evaluation must be surgery. Trials where all participants receive the same surgical regimen and are randomised to other treatments were excluded.

Search methods: The search strategy has been updated.

Quality assessment has been replaced by the new risk of bias tool (Higgins 2011).

Data synthesis has been updated. The primary outcome is total mortality expressed as a hazard ratio. For dichotomous outcomes, the estimates of effect of an intervention were expressed as risk ratios together with 95% confidence intervals. Dichotomous data were only used for primary outcomes where hazard ratios were unavailable or could not be calculated.

INDEX TERMS

Medical Subject Headings (MeSH)

*Lymph Node Excision [methods; mortality]; Disease-Free Survival; Mouth Neoplasms [mortality; *surgery]; Oropharyngeal Neoplasms [mortality; *surgery]; Randomized Controlled Trials as Topic; Surgical Procedures, Elective [methods; mortality]

MeSH check words

Humans