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

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Oliver RJ, Clarkson JE, Conway D, Glenny AM, Macluskey M, Pavitt S, Sloan P, The CSROC Expert Panel, Worthington HV

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

Primary objective

To determine which surgical treatment modalities for oral/oropharyngeal cancer lead to the best outcome in terms of disease-free survival, mortality (or overall survival), recurrent disease and quality of life compared with other surgical, radiotherapy or chemotherapy combinations.

Secondary objective

To determine the implication of treatment modalities in terms of morbidity, costs, hospital days of treatment, quality-adjusted-life-years (QALYs), complications and harms.

BACKGROUND

Oral cancer is a significant disease globally with an estimated 268,000 new cases worldwide in 2000 (Parkin 2001). 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). In some parts of the world there is evidence that the incidence is increasing (Hindle 1996; Parkin 1999; Robinson 2003). There is overwhelming support that tobacco and alcohol consumption are responsible for the aetiology of intraoral cancer and that fresh fruit and vegetable consumption offers a degree of protection (La Vecchia 1997; Macfarlane 1995). Cancer of the lip is largely caused by chronic exposure to ultraviolet light from sun exposure and therefore of different aetiology to the majority of intraoral cancers.

In many countries surgery remains the first line of treatment for oral cancer (Day 2003). In some anatomical sites such as the tongue, surgery is preferred over radiotherapy due to the mobility of this structure and proximity to the adjacent radiosensitive structures of the teeth and jaw bones. Although patients do often receive post-operative radiotherapy to improve locoregional control rates.

Surgery can be combined with radiotherapy and chemotherapy. It is a widespread practice to give adjuvant radiotherapy or chemotherapy following surgery, as surgery in tissue previously irradiated is troublesome. Neoadjuvant treatment may also be given before surgery; chemotherapy is more commonly administered in this way.

The local control of the primary tumour is one of the criteria of successful surgical 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). Margins apparently histologically free of tumour may demonstrate molecular changes at the margins which may account for recurrence of these tumours (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 his-

tory of oral cancer and is an important prognostic factor (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 is usually 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 post-operative morbidity. When such a neck dissection is combined en-bloc with mandibular resection either for access or disease within the mandible, this is known as the 'commando' procedure. Because of the morbidity associated with such procedures, modifications of the radical neck dissection to preserve some or all of the associated structures are now undertaken as selective neck dissections - which for oral cancer commonly involve the lymph node groups at risk of metastasis (Levels I to IV) (Carew 2003) with control rates equal to radical neck dissections. 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).

When small tumours (T1, less than 2 centimetres or T2, 2 to 4 centimetres) present with apparently clinically negative neck, there is controversy over the management of the cervical lymph nodes. 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 1999; 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).

OBJECTIVES

Primary objective

To determine which surgical treatment modalities for oral/oropharyngeal cancer lead to the best outcome in terms of disease-free survival, mortality (or overall survival), recurrent disease and quality of life compared with other surgical, radiotherapy or chemotherapy combinations.

Secondary objective

To determine the implication of treatment modalities in terms of morbidity, costs, hospital days of treatment, quality-adjusted-life-years (QALYs), complications and harms.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

It is anticipated that there will be no studies comparing any of the treatment modalities with placebo (although if there are such studies they will be included), therefore randomised controlled trials comparing different treatment modalities will be included in the review.

Types of participants

Patients with oral cancer as defined by the International Classification of Diseases for Oncology (ICD-O) as C01-C02, C03, C04, C05-C06 (oral cavity). Cancer of the oropharynx will be included (ICD-O: C10) but hypopharynx (ICD-O: C13) and larynx (ICD-O: C32) will be excluded. Studies of head and neck cancer where there are cases of oral cancer will be included (so long as data are available separately for those participants who have cancer of the oral cavity or oropharynx). Cancers of the lip (ICD-O: C00) and nasopharynx (ICD-O: C11) will be excluded (WHO 1992). 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. Trials that incorporate carcinoma in situ will be included, however trials that deal exclusively with carcinoma in situ will be excluded. 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 intervention

Surgical treatment of the primary tumour must be one of the primary interventions. Surgical treatment may include traditional scalpel based surgery, laser cutting or ablation, or harmonic scalpel. Surgical treatment may be compared to other surgical interventions, radiotherapy, chemotherapy, immunotherapy, cryotherapy, radiofrequency ablation, photodynamic therapy, electroporation or complementary therapies; any combinations will be considered providing they are compared to surgery in at least one arm of the study.

Surgical treatment of the neck lymph nodes (cervical lymph nodes) may precede, occur simultaneously with or subsequent to the surgical treatment of the primary tumour. When there is no treatment of the primary tumour but only surgical treatment of the cervical lymph nodes these studies will not be considered.

The treatments received and compared must be 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 will be:

- Disease-free survival or time to recurrence
- Total mortality (disease related mortality will also be studied if possible)
- Quality of life (using any appropriate scales, for example those produced by the University of Washington (Deleyiannis 1997; Hassan 1993) and the European Organization for Research and Treatment of Cancer (EORTC) (Bjordal 1992; Hammerlid 1997).

Secondary outcome measures will be:

- Morbidity including: function (ability to talk, eat including need for tube feeding, swallow, need for permanent tracheostomy), psychosocial, and disfigurement
- Harms associated with treatment (for example nerve damage, nutritional problems)
- Complications of treatment (such as wound infection, flap necrosis, late treatment effects, nerve damage, fistula, bleeding, treatment related death)
- Salvage treatment
- Direct and indirect costs to patients and health services
- Length of hospital stay/hospital days of treatment
- Hospital readmission
- Patient satisfaction.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

A search strategy will be developed and adapted for use in the following databases:

- The Cochrane Oral Health Group Trials Register
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, current issue)
- MEDLINE (1966 to present)
- OLDMEDLINE (1950 to 1965)
- EMBASE (1980 to present)
- AMED (1985 to present)
- National Cancer Trials Database.

Because studies involving oral cancer are often included with those of the head and neck, a broad search will be undertaken to include all possible studies. Articles of any language will be considered and only excluded if it is not possible to translate them to English language. The reference lists of relevant articles will be searched and authors contacted in order to identify unpublished or ongoing trials.

For the search strategy developed for MEDLINE *see* 'Additional Table 01' and that adapted for EMBASE *see* 'Additional Table 02' and CENTRAL 'Additional Table 03'.

METHODS OF THE REVIEW

The titles and abstracts (when available) of all reports identified through the electronic searches will be 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 will be obtained. The full reports obtained from all the electronic and other methods of searching will be assessed independently by two review authors to establish whether the studies meet the inclusion criteria or not. Disagreements will be resolved by discussion. Where resolution is not possible, a third review author will be consulted. All studies meeting the inclusion criteria will then undergo a validity assessment and data extraction. Studies rejected at this or subsequent stages will be recorded in the 'Characteristics of excluded studies' table, and reasons for exclusion recorded. The key inclusion and exclusion criteria are listed in 'Additional Table 04'.

Quality assessment

The quality assessment of the included trials will be undertaken independently and in duplicate by two or more review authors as part of the data extraction process.

Three main quality criteria will be examined:

(1) Allocation concealment, recorded as:
(i) Adequate
(ii) Unclear
(iii) Inadequate

(2) Treatment blind to outcomes assessors, recorded as:
(i) Yes
(ii) No
(iii) Unclear
(iv) Blinding not possible

(3) Clear explanation for withdrawals and drop outs in each treatment group, assessed as:
(i) Clear explanation of numbers of, and reasons for, withdrawals and drop outs
(ii) Description of numbers of or reasons for withdrawals and drop outs or both unclear
(iii) Partial explanation but clarity is not achieved.

After taking into account the additional information provided by the authors of the trials, studies will be grouped into the following categories.
(I) Low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria are met (all i's).
(II) Moderate risk of bias (plausible bias that raises some doubt about the results) if one or more criteria are partly met (when authors respond that they had made some attempts to conceal the allocation of patients, to blind the assessors or to give an explanation for withdrawals, but these attempts are not judged to be ideal, these criteria will be categorized as 'partly').
(III) High risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria are not met as described in the *Cochrane Handbook for Systematic Reviews of Interventions* 4.2.5, section 6.7.

Further quality assessment will be carried out to assess the randomisation procedure, sample size calculations, the definition of exclusion/inclusion criteria, adequate definitions of success criteria and comparability of control and treatment groups at entry. The quality assessment criteria will be pilot tested using several articles.

Data extraction
Data will be extracted by two review authors independently using a specially designed data extraction form. The data extraction form will be piloted on several papers and modified as required before use. Any disagreement will be discussed and a third review author consulted where necessary. All authors will be contacted for clarification or missing information. Data will be excluded until further clarification is available or if agreement cannot be reached.

For each trial the following data will be recorded:
Year of publication, country of origin and source of study funding
Details of the participants including demographic characteristics and criteria for inclusion
Details of the type of intervention
Details of the outcomes reported, including method of assessment, and time intervals.

Data synthesis
For dichotomous outcomes, the estimates of effect of an intervention will be expressed as risk ratios together with 95% confidence intervals. For continuous outcomes, mean differences and standard deviations will be used to summarize the data for each group. The survival data will be analysed in two ways depending on what data are presented in study reports, or obtained from authors. The proportion surviving at 1, 2, 5, 10 years will be analysed as dichotomous outcomes. Where presented the hazard ratios will also be used for comparison in meta-analysis. If hazard ratios are not quoted in studies, then they will be calculated from available summary statistics (observed events, expected events, variance, confidence intervals, P values or survival curves) according to the methods proposed by Parmar et al (Parmar 1998), or we will request these from authors.

Where possible, similar stage lesions will be analysed. Due to the different natural history and treatment regimen for cancers of the oral cavity and oropharynx they will be analysed separately. Clinical heterogeneity will be assessed by examining the types of participants, interventions and outcomes in each study. Meta-analyses will be conducted only if there are studies of similar comparisons reporting the same outcome measures. Risks ratios will be combined for dichotomous data, mean differences for continuous data and hazard ratios for survival data, using random-effects models. The significance of any discrepancies in the estimates of the treatment effects from the different trials will be assessed by means of Cochran's test for heterogeneity and the I^2 statistic, and any heterogeneity investigated.

It is planned to undertake a sensitivity analysis to examine the effects of randomisation, allocation concealment, blind outcome assessment (if appropriate) and quality of follow up/completeness of data set.

Further investigation
Once the Cochrane review has been completed and published using summary statistics from the study reports we may undertake an individual patient data analysis (IPD) if the results of the standard Cochrane review warrant this level of investigation. The following methods are adapted from a published Cochrane protocol (Pignon 2000). For eligible studies, therefore, the investigators will be contacted to provide the following data for each patient:

- age
- sex
- social class or socio-economic status
- site of primary tumour (International Classification of Diseases (ICD) code)
- stage of tumour (TNM Classification of Malignant Tumours (TNM), clinical (cTNM) and pathological (pTNM) where possible)
- allocated treatment
- date of randomisation
- date of last follow up
- survival status
- cause of death
- date of first event (local or regional recurrence, distant metastasis, second primary tumour)
- if excluded from trial analysis and reason for exclusion
- geographical region or country.

The methods for IPD outlined in section 11.0 of the *Cochrane Handbook for Systematic Reviews of Interventions* 4.2.5 will be used (Higgins 2005).

POTENTIAL CONFLICT OF INTEREST

None known.

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Internal sources of support

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- Cochrane Oral Health Group UK
- The University of Dundee UK
- The University of Glasgow UK

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Haddadin KJ, Soutar DS, Webster MH, Robertson AG, Oliver RJ, MacDonald DG. Natural history and patterns of recurrence of tongue tumours. *British Journal of Plastic Surgery* 2000;**53**(4):279–85.

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Xi 2003
Xi S, Grandis JR. Gene therapy for the treatment of oral squamous cell carcinoma. *Journal of Dental Research* 2003;**82**(1):11–6.

ADDITIONAL TABLES

Table 01. MEDLINE, OLDMEDLINE, AMED search strategy

Form: (oral cancer) and (interventions) and (RCT filter, part 1 only)

Database: Ovid MEDLINE(R) In-Process, Other Non-Indexed Citations, Ovid MEDLINE(R), OLDMEDLINE(R), AMED(R).
Search strategy:

---

1 ((cancer$ or tumor$ or tumour$ or neoplas$ or malignan$ or carcinoma$ or metasta$) adj5 (oral$ or intra-oral$ or gingiva$ or oropharyn$ or mouth$ or tongue$ or cheek or cheeks or gum or gums or palatal or palate or intraoral or (head adj2 neck))).mp.
2 "head and neck neoplasms"/ or mouth neoplasms/ or gingival neoplasms/ or palatal neoplasms/ or tongue neoplasms/
3 1 or 2
4 palliative.mp.
5 chemoradiotherap$.mp.
6 surg$.mp.
7 radiotherap$.mp.
8 chemotherap$.mp.
9 (neck adj1 dissection$).mp.

Table 01. MEDLINE, OLDMEDLINE, AMED search strategy (*Continued*)

10 brachytherap$.mp.
11 (adjuvant or neo-adjuvant).mp.
12 photodynamic.mp.
13 teletherap$.mp.
14 plesiotherap$.mp.
15 excision$.mp.
16 excise$.mp.
17 (hyperfractionate$ or hyper-fractionate$).mp.
18 dahanca.mp.
19 arcon.mp.
20 radiat$.mp.
21 irradiat$.mp.
22 resect$.mp.
23 lymphadenectom$.mp.
24 curett$.mp.
25 neoadjuvant.mp.
26 glossectom$.mp.
27 antineoplas$.mp.
28 ((alternative or combined or gene or genetic or nutrition$) adj2 (therapy or therapies)).mp.
29 (onyx-015 or amifostine$ or misonidazole$ or erythropoietin$).mp.
30 fluorouracil$.mp.
31 5-fluorouracil$.mp.
32 cisplatin$.mp.
33 paclitaxel$.mp.
34 vinblastine$.mp.
35 bleomycin$.mp.
36 5fu.mp.
37 adriamycin$.mp.
38 doxorubicin$.mp.
39 methotrexa$.mp.
40 docetaxel$.mp.
41 carboplatin$.mp.
42 hydroxyurea.mp.
43 ((vitamin or nutrition$) adj2 supplement$).mp.
44 (herb or herbs).mp.
45 herbal.mp.
46 (locoregional$ adj5 (recurren$ or control$ or treat$ or lymph$)).mp.
47 aromatherap$.mp.
48 homeopath$.mp.
49 surg$.mp.
50 surg$.mp.
51 osteopath$.mp.
52 naturopath$.mp.
53 (wholistic or holistic).mp.
54 reflexolog$.mp.
55 massage$.mp.
56 (essential adj1 oil$).mp.
57 exp Radiotherapy/
58 exp Antineoplastic Agents/
59 exp surgical procedures, operative/ or lymph node excision/

Table 01. MEDLINE, OLDMEDLINE, AMED search strategy (*Continued*)

60 exp Antimetabolites/
61 exp nursing care/ or palliative care/ or perioperative care/ or terminal care/
62 exp combined modality therapy/ or exp complementary therapies/ or exp nutrition therapy/ or exp rehabilitation/ or exp remission induction/ or exp salvage therapy/
63 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
64 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
65 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62
66 63 or 64 or 65
67 randomized controlled trial.pt.
68 controlled clinical trial.pt.
69 Randomized Controlled Trials/
70 Random Allocation/
71 Double-Blind Method/
72 Single-Blind Method/
73 or/67-72
74 Animal/ not Human/
75 73 not 74
76 3 and 66 and 75

Table 02. EMBASE search strategy

Form: (oral cancer) and (interventions) and (RCT filter)

Database: EMBASE (from 1980 to present)
Search strategy:
---
1 "head and neck tumor"/ or "head and neck cancer"/ or mouth cancer/ or mouth carcinoma/ or oropharynx cancer/ or oropharynx carcinoma/ or tongue cancer/ or tongue carcinoma/ or tonsil cancer/ or tonsil carcinoma/ or mouth tumor/ or oropharynx tumor/ or tongue tumor/ or tonsil tumor/
2 ((cancer$ or tumor$ or tumour$ or neoplas$ or malignan$ or carcinoma$ or metasta$) adj5 ((oral$ not "Oral Drug Administration") or (intra-oral$ or gingiva$ or oropharyn$ or mouth$ or tongue$ or cheek or cheeks or gum or gums or palatal or palate or intraoral or (head adj2 neck)))).mp.
3 1 or 2
4 palliative.mp.
5 chemoradiotherap$.mp.
6 surg$.mp.
7 radiotherap$.mp.
8 chemotherap$.mp.
9 (neck adj1 dissection$).mp.
10 brachytherap$.mp.
11 (adjuvant or neo-adjuvant).mp.
12 photodynamic.mp.
13 teletherap$.mp.
14 plesiotherap$.mp.
15 (excision$ or excise$).mp.
16 (amifostine$ or misonidazole$ or erythropoietin$).mp.
17 (hyperfractionate$ or hyper-fractionate$).mp.
18 dahanca.mp.
19 arcon.mp.
20 radiat$.mp.

Table 02. EMBASE search strategy (*Continued*)

21 irradiat$.mp.
22 resect$.mp.
23 lymphadenectom$.mp.
24 curett$.mp.
25 neoadjuvant.mp.
26 glossectom$.mp.
27 antineoplas$.mp.
28 ((alternative or combined or gene or genetic or nutrition$) adj2 (therapy or therapies)).mp.
29 onyx-015.mp.
30 fluorouracil$.mp.
31 5-fluorouracil$.mp.
32 cisplatin$.mp.
33 paclitaxel$.mp.
34 vinblastine$.mp.
35 bleomycin$.mp.
36 5fu.mp.
37 adriamycin$.mp.
38 doxorubicin$.mp.
39 methotrexa$.mp.
40 docetaxel$.mp.
41 carboplatin$.mp.
42 hydroxyurea.mp.
43 ((vitamin or nutrition$) adj2 supplement$).mp.
44 (herb or herbs).mp.
45 herbal.mp.
46 (locoregional$ adj5 (recurren$ or control$ or treat$ or lymph$)).mp.
47 aromatherap$.mp.
48 homeopath$.mp.
49 osteopath$.mp.
50 naturopath$.mp.
51 (wholistic or holistic).mp.
52 reflexolog$.mp.
53 massage$.mp.
54 (essential adj1 oil$).mp.
55 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
56 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
57 exp therapy/
58 surgery/ or exp cancer surgery/ or "head and neck surgery"/ or oral surgery/ or glossectomy/ or mandible osteotomy/ or mandible reconstruction/ or mandible resection/ or maxilla osteotomy/ or maxilla resection/ or palatoplasty/ or uvulopalatopharyngoplasty/ or surgical technique/ or anastomosis/ or electrosurgery/ or endoscopic surgery/ or excision/ or implantation/ or incision/ or laser surgery/ or ligation/ or microsurgery/ or myotomy/ or radiosurgery/ or surgical drainage/ or suture/
59 terminal care/
60 alternative medicine/
61 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60
62 random$.ti,ab.
63 factorial$.ti,ab.
64 placebo$.ti,ab.
65 (doubl$ adj blind$).ti,ab.
66 (singl$ adj blind$).ti,ab.
67 assign$.ti,ab.

Table 02. EMBASE search strategy (*Continued*)

68 allocat$.ti,ab.
69 volunteer$.ti,ab.
70 double-blind procedure.sh.
71 randomized controlled trial.sh.
72 single blind procedure.sh.
73 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72
74 animal/ or nonhuman/ or animal experiment/
75 human/
76 75 and 74
77 74 not 76
78 73 not 77
79 3 and 61 and 78

Table 03. CENTRAL search strategy

Form: (interventions) and (oral cancer)

(palliative or chemoradiotherap* or surg* or radiotherap* or chemotherap* or brachytherap*)
(neck next dissection*)
(adjuvant or neo-adjuvant or neoadjuvant)
(photodynamic or teletherap* or plesiotherap* or excision* or excise* or hyperfractionate* or hyper-fractionate*)
(dahanca or arcon or radiat* or irradiat*)
(resect* or lymphadenectom* or curett* or glossectom* or antineoplas*)
(retroviral or retro-viral)
(alternative or combined or gene or genetic or nutrition*)
(therapy or therapies)
(#8 and #9)
onyx-015 or amifostine* or misonidazole* or erythropoietin*
(fluorouracil* or 5-fluorouracil*)
(cisplatin* or paclitaxel* or vinblastine* or bleomycin* or 5fu or adriamycin* or doxorubicin* or methotrexa* or docetaxel* or carboplatin* or hydroxyurea)
(vitamin next supplement*)
(nutrition next supplement*)
(herb or herbs or herbal)
(locoregional* near recurren*)
(locoregional* near treatment)
(locoregional* near treatments)
(locoregional* near lymph*)
(aromatherap* or homeopath* or osteopath* or naturopath* or wholistic or holistic or reflexolog* or massage*)
(essential next oil*)
RADIOTHERAPY
ANTINEOPLASTIC AGENTS
SURGICAL PROCEDURES OPERATIVE
LYMPH
LYMPH NODE EXCISION
ANTIMETABOLITES
NURSING CARE
PALLIATIVE CARE
PERIOPERATIVE CARE
TERMINAL CARE

Table 03. CENTRAL search strategy (*Continued*)

COMBINED MODALITY THERAPY
COMPLEMENTARY THERAPIES
NUTRITION THERAPY
REHABILITATION
REMISSION INDUCTION
SALVAGE THERAPY
(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #10)
(#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20)
(#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30)
(#31 or #32 or #33 or #34 or #35 or #36 or #37 or #38)
(#39 or #40 or #41 or #42)
#43
(head near neck near cancer*)
(head near neck near tumor*)
(head near neck near tumour*)
(head near neck near neoplas*)
(head near neck near malignan*)
(head near neck near carcinoma*)
(head near neck near metasta*)
(#45 or #46 or #47 or #48 or #49 or #50 or #51)
(oral* near cancer*)
(oral* near tumor*)
(oral* near tumour*)
(oral* near neoplasm*)
(oral* near neoplas*)
(oral* near malignan*)
(oral* near carcinoma*)
(oral* near metasta*)
(intra-oral* near cancer*)
(intra-oral* near tumor*)
(intra-oral* near tumour*)
(intra-oral* near neoplas*)
(intra-oral* near malignan*)
(intra-oral* near carcinoma*)
(intra-oral* near metasta*)
(gingiva* near metasta*)
(gingiva* near carcinoma*)
(gingiva* near malignan*)
(gingiva* near neoplas*)
(gingiva* near tumour*)
(gingiva* near tumor*)
(gingiva* near cancer*)
(oropharyn* near cancer*)
(oropharyn* near tumour*)
(oropharyn* near tumor*)
(oropharyn* near neoplas*)
(oropharyn* near malignan*)
(oropharyn* near carcinoma*)
(oropharyn* near metasta*)
(mouth* near metasta*)

Table 03. CENTRAL search strategy (*Continued*)

(mouth* near carcinoma*)
(mouth* near malignan*)
(mouth* near neoplas*)
(mouth* near tumour*)
(mouth* near tumor*)
(mouth* near cancer*)
(tongue* near cancer*)
(tongue* near tumour*)
(tongue* near tumor*)
(tongue* near neoplas*)
(tongue* near malignan*)
(tongue* near carcinoma*)
(tongue* near metasta*)
(cheek* near metasta*)
(cheek* near carcinoma*)
(cheek* near malignan*)
(cheek* near neoplas*)
(cheek* near tumor*)
(cheek* near tumour*)
(cheek* near cancer*)
(gum near cancer*)
(gum near tumor*)
(gum near tumour*)
(gum near neoplas*)
(gum near malignan*)
(gum near carcinoma*)
(gum near metasta*)
(gums near metasta*)
(gums near carcinoma*)
(gums near malignan*)
(gums near neoplas*)
(gums near tumor*)
(gums near tumour*)
(gums near cancer*)
(palat* near cancer*)
(palat* near tumor*)
(palat* near tumour*)
(palat* near neoplas*)
(palat* near malignan*)
(palat* near carcinoma*)
(palat* near metasta*)
(intraoral* near metasta*)
(intraoral* near carcinoma*)
(intraoral* near malignan*)
(intraoral* near neoplas*)
(intraoral* near tumor*)
(intraoral* near tumour*)
(intraoral* near cancer*)
HEAD AND NECK NEOPLASMS
MOUTH NEOPLASMS

Table 03. CENTRAL search strategy (*Continued*)

GINGIVAL NEOPLASMS
PALATAL NEOPLASMS
TONGUE NEOPLASMS
(#52 or #53 or #54 or #55 or #56 or #57 or #58 or #59)
(#60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69)
(#70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79)
(#80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89)
(#90 or #91 or #92 or #93 or #94 or #95 or #96 or #97 or #98 or #99)
(#100 or #101 or #102 or #103 or #104 or #105 or #106 or #107 or #108 or #109)
(#110 or #111 or #112 or #113 or #114 or #115 or #116 or #117 or #118 or #119)
(#120 or #121 or #122 or #123 or #124 or #125 or #126 or #127 or #128 or #129)
(#130 or #131 or #132 or #133 or #134 or #135 or #136 or #137 or #138 or #139)
(#140 or #141 or #142 or #143 or #144)
(#145 and #43)

Table 04. Summary of inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Primary oral cancer	Lip
Squamous cell carcinoma (SCC)	Salivary gland malignancies
Histological variants of SCC	Nasopharyngeal cancer
Randomised controlled trials	Hypopharynx, nasopharynx and larynx
Primary and secondary outcomes included	Sarcomas and lymphomas
Surgical treatment of the primary tumour	Odontogenic tumours
Surgical management of the cervical lymph nodes when combined with surgical management of the primary tumour	

COVER SHEET

Title	Interventions for the treatment of oral cancer: surgical treatment
Authors	Oliver RJ, Clarkson JE, Conway D, Glenny AM, Macluskey M, Pavitt S, Sloan P, The CSROC Expert Panel, Worthington HV
Contribution of author(s)	Richard Oliver (RO), Jan Clarkson (JC), Helen Worthington (HW), Anne-Marie Glenny (AMG) and Emma Tavender (ET) conceived, designed and sought funding for the review. RO and Susan Pavitt (SP) co-ordinated the review, collected data and developed the search strategy. RO, Michaelina Macluskey (MM), JC, Phil Sloan (PS), David Conway (DC), HW, AMG and SP plan to screen the titles and abstracts. SP will organise retrieval of papers. RO, MM, JC, PS, DC, HW, AMG and SP will screen retrieved papers against the inclusion criteria, appraise the quality of the papers, and extract data; additionally, some members of the Cochrane Systematic Reviews on Oral Cancer (CSROC) Expert Panel will assist in the data extraction process. RO and MM will obtain and screen data on unpublished studies and additional data on published studies.

	RO, SP and HW will enter data into RevMan, be responsible for data management for the review, and analyse the data. RO, JC, HW and MM will interpret the data. HW and AMG will provide a methodological perspective. RO, JC, MM, PS and members of the CSROC Expert Panel will provide a clinical perspective. JC and PS will provide a policy perspective. RO and MM will write the review. The CSROC Expert Panel will provide comment /assist in the final review development. The CSROC Expert Panel comprises: Baujat B, Humphris G, Hutchison I, O'Brien C, Pignon J-P, Robertson G, Rogers S, Shah J, Slevin N, Soutar D, Tavender E, Vermorken JB, Wardell S, Warnakulasuriya S, Webster K.
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