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

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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. This is an update of a review originally published in 2007 and first updated in 2011.

Objectives

To determine which surgical treatment modalities for oral and oropharyngeal cancers result in increased overall survival, disease-free survival and locoregional control and reduced recurrence. To determine the implication of treatment modalities in terms of morbidity, quality of life, costs, hospital days of treatment, complications and harms.

Search methods

Cochrane Oral Health's Information Specialist searched the following databases: Cochrane Oral Health's Trials Register (to 20 December 2017), the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 11), MEDLINE Ovid (1946 to 20 December 2017) and Embase Ovid (1980 to 20 December 2017). We searched the US National Institutes of Health Trials Registry (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform for ongoing trials. There were no restrictions on the 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, or where separate data could be extracted for these participants, and that compared two or more surgical treatment modalities, or surgery versus other treatment modalities.

Data collection and analysis

Two or more review authors independently extracted data and assessed risk of bias. We contacted study authors for additional information as required. We collected adverse events data from included studies.

Main results

We identified five new trials in this update, bringing the total number of included trials to 12 (2300 participants; 2148 with cancers of the oral cavity). We assessed four trials at high risk of bias, and eight at unclear. None of the included trials compared different surgical approaches for the excision of the primary tumour. We grouped the trials into seven main comparisons.

Future research may change the findings as there is only very low-certainty evidence available for all results.

Five trials compared elective neck dissection (ND) with therapeutic (delayed) ND in participants with oral cavity cancer and clinically negative neck nodes, but differences in type of surgery and duration of follow-up made meta-analysis inappropriate in most cases. Four of these trials reported overall and disease-free survival. The meta-analyses of two trials found no evidence of either intervention leading to greater overall survival (hazard ratio (HR) 0.84, 95% confidence interval (CI) 0.41 to 1.72; 571 participants), or disease-free survival (HR 0.73, 95% CI 0.25 to 2.11; 571 participants), but one trial found a benefit for elective supraomohyoid ND compared to therapeutic ND in overall survival (RR 0.40, 95% CI 0.19 to 0.84; 67 participants) and disease-free survival (HR 0.32, 95% CI 0.12 to 0.84; 67 participants). Four individual trials assessed locoregional recurrence, but could not be meta-analysed; one trial favoured elective ND over therapeutic delayed ND, while the others were inconclusive.

Two trials compared elective radical ND with elective selective ND, but we were unable to pool the data for two outcomes. Neither study found evidence of a difference in overall survival or disease-free survival. A single trial found no evidence of a difference in recurrence.

One trial compared surgery plus radiotherapy with radiotherapy alone, but data were unreliable because the trial stopped early and there were multiple protocol violations.

One trial comparing positron-emission tomography-computed tomography (PET-CT) following chemoradiotherapy (with ND only if no or incomplete response) versus planned ND (either before or after chemoradiotherapy), showed no evidence of a difference in mortality (HR 0.92, 95% CI 0.65 to 1.31; 564 participants). The trial did not provide usable data for the other outcomes.

Three single trials compared: surgery plus adjunctive radiotherapy versus chemoradiotherapy; supraomohyoid ND versus modified radical ND; and super selective ND versus selective ND. There were no useable data from these trials.

The reporting of adverse events was poor. Four trials measured adverse events. Only one of the trials reported quality of life as an outcome.

Authors' conclusions

Twelve randomised controlled trials evaluated ND surgery in people with oral cavity cancers; however, the evidence available for all comparisons and outcomes is very low certainty, therefore we cannot rely on the findings. The evidence is insufficient to draw conclusions about elective ND of clinically negative neck nodes at the time of removal of the primary tumour compared to therapeutic (delayed) ND. Two trials combined in meta-analysis suggested there is no difference between these interventions, while one trial (which evaluated elective supraomohyoid ND) found that it may be associated with increased overall and disease-free survival. One trial found elective ND reduced locoregional recurrence, while three were inconclusive. There is no evidence that radical ND increases overall or disease-free survival compared to more conservative ND surgery, or that there is a difference in mortality between PET-CT surveillance following chemoradiotherapy versus planned ND (before or after chemoradiotherapy). Reporting of adverse events in all trials was poor and it was not possible to compare the quality of life of people undergoing different surgical treatments.

PLAIN LANGUAGE SUMMARY

Surgical treatments for oral cavity (mouth) and oropharyngeal (throat) cancers

Review question

We evaluated clinical trials of surgical treatments for oral and oropharyngeal cancers to find out which were most likely to result in people with these cancers living longer (overall survival). living longer without symptoms (disease-free survival), and not experiencing a recurrence of the cancer at the same site or spread to other sites. We also wanted to find out how different treatments affect disease symptoms, quality of life, time in hospital, complications, side effects and cost.

Background

Oral cancer is among the most common cancers worldwide, with more than 400,000 new cases diagnosed in 2012. The treatment of these cancers can involve surgery, chemotherapy, radiotherapy, or a combination of two or all three therapies. This topic area was identified as a priority by an expert working group for oral and maxillofacial surgery in 2014. Authors working with Cochrane Oral Health conducted this review, which is an update of a review originally published in 2007 and first updated in 2011. The evidence is current to 20 December 2017.

Study characteristics

We included 12 trials (five new for this update) that investigated the success of surgical treatment for oral cancers. The studies involved 2300 participants, 2148 of whom had mouth cancers. The trials included seven comparisons of different treatment options. None of them compared different surgical approaches for cutting out the primary tumour.

Key results

The findings of the studies are mixed and it is not possible to draw firm conclusions about the optimal surgical approach for mouth and throat cancers.

Surgical removal of the lymph nodes in the neck that appear to be cancer-free, at the same time as the cancer is removed did not seem to be associated with longer survival in two studies whose results were combined. Another study, however, suggested there may be a benefit of early neck surgery in terms of overall survival and 'disease-free survival' (length of time after primary treatment without signs and symptoms of disease). One study found cancer recurrence at or around the same site was less likely with the early surgery, while three other studies did not favour either treatment.

There was no evidence that removal of all the lymph nodes in the neck resulted in longer survival compared to selective surgical removal of affected lymph nodes.

One study evaluated use of a special scan (positron-emission tomography-computed tomography (PET-CT)), after a combination of chemotherapy and radiotherapy, to guide decisions about neck dissection, and found no difference in mortality (death) compared with undertaking a planned neck dissection before or after chemoradiotherapy.

There were a number of other surgical approaches compared in the studies, but we were unable to use the results in this review.

Although removal of lymph nodes from the neck is known to be associated with significant negative effects related to appearance and functions such as eating, drinking and speaking, the studies reported poorly on these side effects and did not measure quality of life accurately enough or in large enough numbers to be included in any of our analyses.

Certainty of the evidence

The certainty of the evidence was very low as there were few studies for each comparison and they were at risk of bias because of the way they were designed. Some comparisons and outcomes had no useable results.

Summary of findings for the main comparison. Elective neck dissection versus therapeutic (delayed) neck dissection

Elective neck dissection versus therapeutic (delayed) neck dissection

Patient: adults with oral or oropharyngeal cancer

Setting: inpatient

Intervention: elective neck dissection

Comparison: therapeutic (delayed) neck dissection

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Therapeutic neck dissection	Elective neck dissection				
Total mortality (follow-up: 3 years)	500[a] per 1000	441 per 1000 (247 to 696)	**HR 0.84** (0.41 to 1.72)	571 (2)	⊕⊖⊖⊖ **Very low**[b,c,d]	These data were from the HR for overall survival. Other binary data from 2 trials could not be pooled. 1 trial indicated no clear evidence of either intervention leading to lower mortality; however, 1 small trial indicated elective neck dissection led to lower mortality (RR 0.40, 95% CI 0.19 to 0.84) (very low-certainty evidence).
New disease, progression or mortality (follow-up: 3 years)	500[e] per 1000	397.1 per 1000 (159 to 768)	**HR 0.73** (0.25 to 2.11)	571 (2)	⊕⊖⊖⊖ **Very low**[b,c]	These data were from the HR for disease-free survival. Binary data from 2 trials did not favour either intervention. 1 trial provided some very low-certainty evidence for elective SOH leading to lower mortality (HR 0.32, 95% CI 0.12 to 0.84).
	250[e] per 1000	190 per 1000 (69 to 455)				
Locoregional recurrence	—	—	—	278 (4)	⊕⊖⊖⊖ **Very low**[c,f]	Binary data; unable to pool data (different timings). Three studies were inconclusive and one favoured elective procedure.
Recurrence	—	—	—	0	—	No data presented

		(0)
Adverse events	1 study showed that 6.6% of elective-surgery participants reported adverse events, while 3.6% of participants in therapeutic-surgery group reported adverse events. These adverse events included: neck haematoma, chyle leak, oral bleeding, postoperative infection and anaphylaxis. None of the other trials reported on adverse events.	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio; **SOH:** supraomohyoid neck dissection.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Based on data presented by Warnakulasuriya 2009.
[b]Downgraded once as two trials at unclear risk of bias.
[c]Downgraded twice for imprecision.
[d]Downgraded once for heterogeneity.
[e]Purely illustrative, unable to find any epidemiological estimates.
[f]Downgraded once for study design; four heterogeneous trials, two at high risk of bias and two at unclear risk of bias.

Summary of findings 2. Elective radical neck dissection versus elective selective neck dissection

Radical neck dissection versus selective neck dissection

Patient: adults with oral or oropharyngeal cancer

Setting: inpatient

Intervention: elective radical neck dissection

Comparison: elective selective neck dissection

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Selective neck dissection	Radical neck dissection				

Total mortality	—	—	—	252 (2)	⊕⊖⊖⊖ **Very low**[a,b]	HR from 2 trials, but unable to pool data as different surgical procedures. Neither trial indicated that mortality was different for the 2 interventions.
New disease, progression or mortality (follow-up: 5 years)	500[c] per 1000	326 per 1000 (182 to 537)	**HR 0.57** (0.29 to 1.11)	104 (1)	⊕⊖⊖⊖ **Very low**[b,d]	These data were from the HR for disease-free survival. 1 study, indicating no difference between the interventions.
	250[c] per 1000	151 per 1000 (80 to 273)				
Locoregional recurrence	—	—	—	—	—	Not reported
Recurrence (5 years)	180[e] per 1000	213 per 1000 (118 to 370)	**RR 1.21** (0.63 to 2.33)	143 (1)	⊕⊖⊖⊖ **Very low**[b,f,g]	1 study, indicating no difference between the interventions.
Adverse events	1 trial reported the following adverse effects: flap necrosis, wound infection, fistula, vascular rupture, haematoma, seroma and chyle fistula. There were 0 complications in 45 participants (59%) in the modified radical neck dissection group and 0 in 54 participants (75%) in the supraomohyoid neck dissection group. There were 2 postoperative deaths in the modified radical neck dissection group and 1 in the supraomohyoid neck dissection group. The other studies did not report adverse events					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded twice, two heterogeneous studies at unclear and high risk of bias.
[b]Downgraded once for imprecision.
[c]Purely illustrative, unable to find any epidemiological estimates.
[d]Downgraded twice as single study at high risk of bias.
[e]Estimated from BHNCSG 1998.
[f]SDowngraded once as single study at unclear risk of bias.
[g] Downgraded twice for imprecision

Summary of findings 3. Surgery plus radiotherapy versus radiotherapy alone

Surgery plus radiotherapy versus radiotherapy alone

Patient: adults with oral or oropharyngeal cancer

Setting: inpatient

Intervention: surgery + radiotherapy

Comparison: radiotherapy alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Radiotherapy alone	Surgery + radiotherapy				
Total mortality (follow-up: 3 years)	500 per 1000	153 per 1000 (67 to 336)	**HR 0.24** (0.10 to 0.59)	35 (1)	⊕⊖⊖⊖ **Very low**[a]	These data were from the HR for overall survival. 1 study, result favouring the surgery group; however, data were unreliable because trial stopped early and there were multiple protocol violations.
Disease-free survival	—	—	—	—	—	Not reported
Locoregional recurrence	—	—	—	—	—	Not reported
Recurrence	—	—	—	—	—	Not reported
Adverse events	Both groups reported the following severe acute adverse effects: subcutaneous fibrosis, telangiectasia (1–4 cm^2), and moderate-to-severe oedema, xerostomia, trismus and dysphagia. Subcutaneous fibrosis was reported as more prevalent in the surgery + radiotherapy group (P = 0.042), but the prevalence of other adverse effects appeared to be similar in each group.					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR**: hazard ratio.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.

Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded three levels as high risk of bias, interim analysis of 35 participants after 23 months.

Summary of findings 4. PET-CT following chemoradiotherapy versus planned neck dissection either before or after chemoradiotherapy

PET-CT following chemoradiotherapy versus planned neck dissection either before or after chemoradiotherapy

Patient: adults with oral or oropharyngeal cancer

Setting: inpatient

Intervention: PET-CT following chemoradiotherapy

Comparison: planned neck dissection either before or after chemoradiotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Planned neck dissection	PET-CT				
Total mortality (follow-up: 2 years)	500 per 1000	471 per 1000 (363 to 597)	**HR 0.92** (0.65 to 1.31)	564 (1)	⊕⊖⊖⊖ **Very low**[a,b]	These data were from the HR for overall survival. 1 study, no evidence of a difference in mortality
Disease-free survival	—	—	—	—	—	Outcome not reported in a usable way.
Locoregional recurrence	—	—	—	—	—	Outcome not reported in a usable way.
Recurrence	—	—	—	—	—	Outcome not reported in a usable way.
Adverse events	22 surgical complications in PET-CT group compared with 83 in planned surgery group.					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard ratio; **PET-CT:** positron-emission tomography–computed tomography.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[a]Downgraded once as one study at unclear risk of bias.
[b]Downgraded twice for imprecision.

Summary of findings 5. Surgery plus adjuvant radiotherapy versus chemotherapy

Surgery plus adjuvant radiotherapy versus chemotherapy

Patient: adults with oral or oropharyngeal cancer

Setting: inpatient

Intervention: surgery + adjuvant radiotherapy

Comparison: chemotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Chemotherapy	Surgery + adjuvant radiotherapy				
Total mortality (follow-up: 2 years)	—	—	—	—	—	1 study report stated, "For the oral cavity, survival was significantly better in patients who underwent surgery and RT compared with the CRT [chemoradiotherapy] group." However, there were no useable data.
Disease-free survival	—	—	—	—	—	Reported as statistically significant in favour of the surgery group (P = 0.038), but there were no useable data.

Locoregional recurrence	—	—	—	—	—	Reported as not statistically significant between groups (P = 0.355), but there were no useable data.
Recurrence (5 years)	—	—	—	—	—	Reported as not statistically significant between the groups, but there were no useable data.
Adverse events	—	—	—	—	—	Not reported

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

Summary of findings 6. Supraomohyoid neck dissection versus modified radical neck dissection

Supraomohyoid neck dissection versus modified radical neck dissection

Patient: adults with oral or oropharyngeal cancer

Setting: inpatient

Intervention: supraomohyoid neck dissection

Comparison: modified radical neck dissection

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Modified radical neck dissection	Supraomohyoid neck dissection				
Total mortality	—	—	—	—	—	1 study, unable to use the data.

(follow-up: 2 years)						
Disease-free survival	—	—	—	—	—	Outcome not reported in a usable way.
Locoregional recurrence	—	—	—	—	—	Outcome not reported in a usable way.
Recurrence (5 years)	—	—	—	—	—	Outcome not reported in a usable way.
Adverse events	Significant difference in complication rates with lower rates for supraomohyoid procedure. UW-QOL scores for all disease-free survivors were assessed at 1 year after treatment. Scores from 9 disease-specific domains appeared to show that supraomohyoid neck dissection was superior to modified radical neck dissection in the domains of pain relief (78.8% vs 75.2%, P = 0.013) and shoulder function (81.1% vs 68.1%, P < 0.001), but not in any of the other domains.					

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

CI: confidence interval; **UW-QOL:** University of Washington Quality of Life Questionnaire.

Summary of findings 7. Super-selective neck dissection versus selective neck dissection

Super-selective neck dissection versus selective neck dissection

Patient: adults with oral or oropharyngeal cancer

Setting: inpatient

Intervention: super-selective neck dissection

Comparison: selective neck dissection

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				

	Selective neck dissection	Super-selective neck dissection				
Total mortality (follow-up: 2 years)	—	—	—	—	—	Outcome not reported
Disease-free survival	—	—	—	—	—	Outcome not reported
Locoregional recurrence	—	—	—	—	—	Data not presented in a useable way. Report concluded that super-selective procedure showed a lower rate of recurrence.
Recurrence (5 years)	—	—	—	—	—	Outcome not reported in a usable way.
Adverse events	Shoulder morbidity data indicated improvement for super-selective group, as well as better quality of life.					

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

BACKGROUND

Description of the condition

Head and neck cancers (HNC) comprise laryngeal, pharyngeal and oral cancers. Collectively, they are the sixth most common cancer in the world, accounting for approximately 5% of all malignant tumours (Torre 2015). HNC generally have common risk factors and aetiology (Winn 2015); however, since the late 2000s, oropharyngeal (throat) cancers have increasingly been associated with human papillomavirus (HPV), unlike other oral cancers (D'Souza 2007). The tumours do not always recognise the boundaries between the oral cavity and oropharynx, with tumours frequently overlapping these sites (Tapia 2011).

HNCs are increasingly treated by multidisciplinary HNC teams in centralised units (Hughes 2012; Lo Nigro 2017). Clinical trials have generally recruited people with HNCs as if this was a single disease entity (Adelstein 2009). This influences the evidence base available to draw from in a systematic review.

Oral cancer (defined here to include both oral cavity and oropharynx cancers) is among the most common cancers worldwide, with approximately 442,760 incident cases and 241,418 deaths reported in 2012 (Ferlay 2013; Stewart 2014). There are geographical variations in the incidence of oral cancers, with increase among men and women in some European countries, stabilisation in certain Asian countries, and decrease in Canada and USA (Chaturvedi 2013; Simard 2014). In the UK, incidence trends are continuing to rise, driven mainly by oropharyngeal cancer rates (Louie 2015; Purkayastha 2016). Survival following a diagnosis of oral cavity or oropharyngeal cancer remains poor with five-year survival around 50% overall, with only limited improvement since the late 1980s (Warnakulasuriya 2009).

There is overwhelming evidence that tobacco use, alcohol consumption and betel quid chewing are the main risk factors in the aetiology of oral cancer (Gupta 2014; La Vecchia 1997; Macfarlane 1995; Winn 2015). There is also strong evidence that low socioeconomic status (educational attainment and income) is associated with substantial increased risk not explained by tobacco and alcohol (Conway 2015). There is a higher incidence of oral cancers among men (Freedman 2007), and the vast majority of cases occur in men over 50 years of age (Warnakulasuriya 2009), and among low socioeconomic groups (Conway 2008). However, the ratio of males to females diagnosed with oral cancers has changed from approximately 5:1 in the 1960s to less than 2:1 after 2000 (Parkin 2005; Purkayastha 2016).

Two distinct types of oropharyngeal cancer exist as classified according to HPV status. HPV-negative oropharyngeal cancer is epidemiologically similar to the traditional type of cancer of the upper aerodigestive tract, in which long-term exposure to tobacco and alcohol products leads to development of malignancy. HPV-positive oropharyngeal cancer starts with exposure to high-risk HPV, most often HPV 16, and can develop independently of tobacco or alcohol exposure (Gillison 2000). People with HPV-positive oropharyngeal cancer are more likely to be male and of a relatively younger age than their HPV-negative counterparts (Chaturvedi 2008; Chaturvedi 2015; Gillison 2007). Moreover, they have a better overall performance and are less likely to be smokers or heavy alcohol consumers (Gillison 2000). In the US, it is suggested that more the 70% of oropharyngeal cancers are HPV positive (Chaturvedi 2011).

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). Since the early 1990s, the proportion of people with oropharyngeal cancer who are HPV positive has increased dramatically (Attner 2010; Ryerson 2008), but it is interesting to note that this group of people have significantly improved rates of both overall survival and disease-free survival (Adelstein 2009; Fakhry 2006; Fakhry 2008; Licitra 2006), and more recent trials are beginning to treat HPV-positive oropharyngeal cancers differently (Blanchard 2011; Holsinger 2015; Parsons 2002). There is evidence to suggest that the rate of oral cavity cancer has reached a plateau, whereas the proportion of people developing oropharyngeal cancer is increasing and is projected to continue to increase (Purkayastha 2016).

Description of the intervention

Surgery can be combined with one or more other treatments, that is, radiotherapy, chemotherapy and immunotherapy/biotherapy; the sequence of these combination therapies is considered important. Radiotherapy is typically now administered postoperatively. Chemotherapy can be given: 1. before surgery (induction/neoadjuvant – when treatment is administered before the primary therapy, e.g. to shrink a tumour prior to surgery or radiation); 2. after surgery (adjuvant – 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; 3. at the same time as radiotherapy (concomitant/concurrent – it may also be referred to as chemoradiotherapy); or 4. alternating with radiotherapy. In recent years, a form of radiotherapy called intensity-modulated radiotherapy (IMRT) has been used to treat oral cancers, which uses use higher radiation doses than traditional therapies with a better chance of locoregional control while sparing more of the surrounding healthy oral tissue from harmful doses and effects of radiation (Brennan 2017; Studer 2007).

The locoregional control of the primary tumour is the main criterion of successful treatment. Tumours are excised with a margin of clinically normal tissue (typically between 1 cm and 2 cm 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 (RND) 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 particularly in relation to loss of the accessory nerve. In one study of 100 cases following RND, almost half of the participants experienced shoulder pain, shoulder droop and a reduction in the range of motion (Ewing 1952). One more recent study comparing RND with accessory nerve-sparing surgery found all of the cases with RND had severe shoulder dysfunction compared with only 7% of the cases who had nerve-sparing surgery (Umeda 2010). RND 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 of using selective neck dissection as a therapeutic procedure in the clinically N0 neck (indicating no palpable nodes on clinical examination). In addition to the extent of neck disease at presentation, spread of the tumour outside the capsule of the lymph nodes (extracapsular spread) is also an indicator of a poor prognosis (Woolgar 2003). Distant metastasis is uncommon in HNC with one study reporting 13.8% in 1022 cases (Duprez 2017). Locoregional disease recurrence remains the dominant mode of treatment failure for people with advanced tumours (Brizel 1998). Historically, clinicians treating oral cancer did not focus on distant metastatic disease because locoregional control had been the main cause of death and there were fewer 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 early stage tumours (T1, less than 2 cm, or T2, 2 cm to 4 cm) present with apparently clinically negative neck nodes, there is controversy over the management of the cervical lymph nodes (Woolgar 2003). To date, imaging of the head and neck region is not sensitive enough to identify nodal micrometastases as the rate of occult metastases has been reported as 23% to 43% (Ebrahimi 2012). 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 ' policy. One current clinical guideline recommends that T1 and T2 oral cancer with a clinically negative neck should receive prophylactic neck treatment (Paleri 2016). However, this implies overtreatment and treatment-associated morbidity in the majority of people (Dias 2001). There is evidence of improved overall and disease-free survival in people with early-stage oral squamous-cell cancer (SCC) who had an elective neck dissection in comparison with therapeutic neck dissection (D'Cruz 2015).

The use of sentinel node biopsy (SNB) is now being advocated for small tumours with a clinically negative neck. One UK guideline recommends that biopsy should be offered to people with oral cancer (T1-T2N0), as it is in the Netherlands and Denmark (Holden 2018; NICE 2018). One European study reported a sensitivity of 86% and negative predictive value of 95% with SNB and concluded that this is a reliable and safe oncological technique for staging the clinically N0 neck in people with T1 and T2 oral cancer (Schilling 2015). Yang 2017 also indicated that a high sensitivity and negative predictive value have been reported with SNB in a larger study including meta-analysis of cT1/T2N0 people with tongue SCC. The widespread introduction of SNB for oral SCC will result in individual treatment that enables people at high risk to be suitably treated early in the disease process, and people at low risk to be spared unnecessary surgery (Schilling 2017).

Why it is important to do this review

Cochrane Oral Health undertook an extensive prioritisation exercise in 2014 to identify a core portfolio of titles that were the most clinically important ones to maintain on the Cochrane Library (Worthington 2015). The Oral and Maxillofacial Surgery Expert Panel identified this review as a priority (Cochrane Oral Health Priority Reviews).

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 since the late 1970s (Warnakulasuriya 2009). Oropharyngeal cancers have relatively 'silent' symptoms, which may not be present during the early stages of the disease. This is a possible explanation for the fact that the disease stage at diagnosis has not altered since the 1960s 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 people with oral and oropharyngeal cancers 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 people's quality of life.

This review was undertaken as part of a series of reviews looking at the different treatment modalities for oral cancer (Furness 2011; Glenny 2010): surgery, chemotherapy, radiotherapy and immunotherapy. In this update of our surgical review, we aimed to answer two broad questions.

- Does surgery, in addition to chemotherapy, radiotherapy or chemoradiotherapy, improve outcomes for people with oral cavity and oropharyngeal cancers?
- Which type of surgery improves outcomes for people with oral cavity and oropharyngeal cancers?

In this surgical review, we included all randomised controlled trials (RCTs) where more than 50% of participants had primary tumours in the oral cavity or oropharynx or where separate data could be extracted for these types of cancer. We included only trials where participants in each treatment arm received different surgical interventions (either different techniques or timing); or radiotherapy, chemotherapy or chemoradiotherapy with or without surgery; or surgery versus no surgery.

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, complications, harms and adverse events)

and Utilization of the Health care services (costs, hospital days of treatment).

METHODS

Criteria for considering studies for this review

Types of studies

RCTs comparing different surgical treatment modalities or trials of other treatment interventions with and without surgery including radiotherapy and chemotherapy. We anticipated that there would be no studies comparing surgery with placebo (although if there were such studies they would have been included).

Types of participants

People 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). We excluded hypopharynx (ICD-O: C13), nasopharynx (ICD-O: C11), larynx (ICD-O: C32) and cancers of the lip (ICD-O: C00) (WHO 1990).

We included studies of HNC with cases of oral cancer (as long as at least 50% of participants had oral cavity or oropharyngeal cancer, or data for these cancers alone are available separately).

Cancers were primary SCCs arising from the oral mucosa. We included histological variants of SCCs (e.g. adenosquamous, verrucous, basaloid, papillary). Although they are known to have differing natural history to most conventional SCCs, they have a common aetiology, incidence is low and they are generally managed in the same way. We included carcinoma in situ.

We excluded epithelial malignancies of the salivary glands, odontogenic tumours, all sarcomas and lymphomas 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 have included traditional scalpel-based surgery, laser cutting or ablation, or harmonic scalpel. We included trials that compared surgical treatment with another surgical intervention; 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. We did not consider salvage or palliative surgery.

We included studies that carried out surgical treatment of the neck lymph nodes (cervical lymph nodes) before, after or at the same time as surgical treatment of the primary tumour. We did not consider studies when there was surgical treatment of the cervical lymph nodes but no treatment of the primary tumour. We included studies concerned with cervical lymph node management in the surgical treatment of the primary tumour.

The treatments received and compared must have been the primary treatment for the tumour and participants should not have received any prior intervention other than diagnostic biopsy.

Types of outcome measures

As we did not expect many data, we planned to report outcomes at all time points reported, other than for 'time to event' data as the hazard ratios (HR) would be used to summarise this.

Primary outcomes

- Overall survival (or total mortality) (disease-related mortality will also be studied, if possible).
- Disease-free survival (or new disease, progression and mortality).
- Locoregional recurrence.
- Recurrence.

Secondary outcomes

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

Search methods for identification of studies

For previous versions of this review, searches were conducted as part of a series of Cochrane Reviews on the treatment modalities for treating oral cavity and oropharyngeal cancer. The reviews were divided into four themes: surgery, chemotherapy, radiotherapy and immunotherapy/targeted therapies. A search strategy was developed that would encompass three of the four broad themes simultaneously (surgery, chemotherapy, radiotherapy, see Bessell 2011 for details of the search strategy). From 2011 onwards, we conducted a more specific search for the surgery theme.

Electronic searches

Cochrane Oral Health's Information Specialist conducted systematic searches in the following databases for RCTs and controlled clinical trials. There were no language, publication year or publication status restrictions.

- Cochrane Oral Health's Trials Register (searched 20 December 2017; Appendix 1);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 11) in the Cochrane Library (searched 20 December 2017; Appendix 2);
- MEDLINE Ovid (1946 to 20 December 2017; Appendix 3);
- Embase Ovid (1980 to 20 December 2017; Appendix 4).

Subject strategies were modelled on the search strategy designed for MEDLINE Ovid. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying RCTs and controlled clinical trials as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Chapter 6 (Lefebvre 2011).

Searching other resources

We searched the following trial registries for ongoing studies:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov; searched 20 December 2017; Appendix 5);

- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 20 December 2017; Appendix 6).

When necessary, we contacted authors of key papers and abstracts to request further information about their trials.

We searched the reference lists of included studies and relevant systematic reviews for further studies.

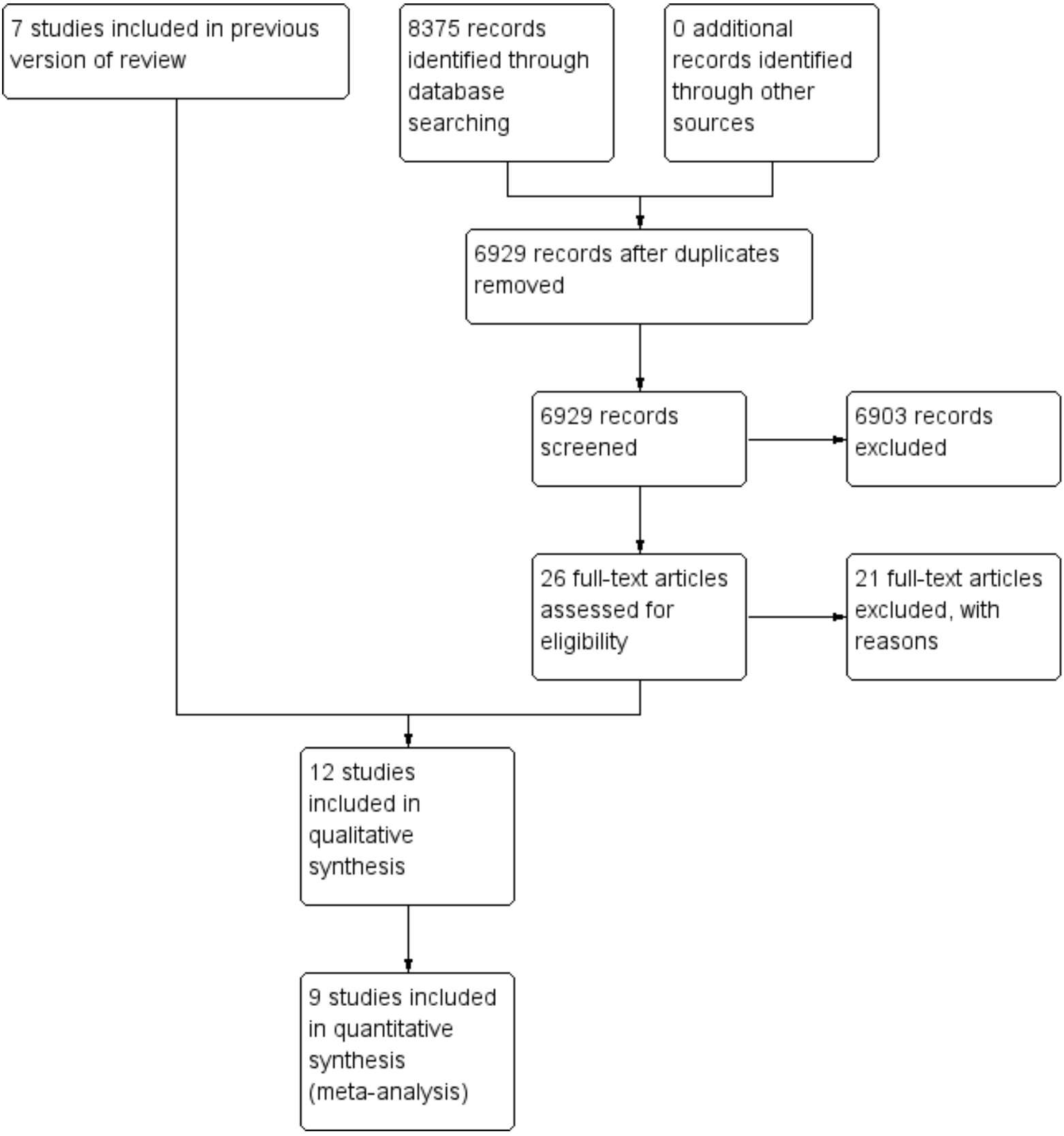
We did not perform a separate search for adverse effects of interventions used; we considered adverse effects described in included studies only.

Data collection and analysis

Selection of studies

At least two review authors (from HW, VB, AMG, DC, MM) independently scanned the titles and abstracts (when available) of all reports identified through the electronic searches. The search was designed to be sensitive and include controlled clinical trials; these were filtered out early in the selection process if they were not randomised. As studies involving oral cancer are often included with those of the head and neck, we undertook a broad search to include all possible studies (Figure 1). For studies appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision, we obtained the full report. We excluded data from conference abstracts alone from the review. Two review authors independently assessed full reports obtained from the searches to establish whether the studies met the inclusion criteria or not. We resolved disagreements by discussion or by consulting a third review author if necessary. We recorded studies rejected at this or subsequent stages in the Characteristics of excluded studies table, and recorded our reasons for exclusion.

Figure 1. Study flow diagram.



Data extraction and management

At least two review authors independently extracted data from included studies. The data extraction forms were piloted on several papers and modified as required before use. We discussed any disagreements and a third review author was consulted where necessary. However, group discussion was often required following data extraction due to the complexity of the data presented. When necessary, we contacted study authors for clarification or missing information.

For each trial, we recorded the following data.

- 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.

We planned to include HNC 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; however, where separate 'pure' oral/oropharyngeal cancer data were available for a trial, we extracted and analysed these 'pure' data and analysed and ignored the combined head and neck data.

Assessment of risk of bias in included studies

At least two review authors independently conducted assessment of risk of bias in included studies using the Cochrane 'Risk of bias' tool (Higgins 2011). We assessed six domains for each included study: sequence generation, allocation concealment, blinding (of participant, carer, outcome assessor), completeness of outcome data, selective outcome reporting and other potential sources of bias. We made an overall risk of bias assessment for each study.

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

- Sequence generation: low risk if use of a random number table, 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, we assessed this as being unclear.
- Allocation concealment: low risk if centralised allocation including access by telephone call or fax, or pharmacy-controlled randomisation, sequentially numbered, sealed, opaque envelopes.
- Blinding: as mortality is the primary outcome that is most frequently and reliably reported, we decided to assess all trials as being at low risk of bias for this domain.
- Outcome data: outcome data were considered complete if all participants 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 at low risk of bias due to incomplete outcome assessment. Where postrandomisation 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, we assessed the risk of bias due to (in)complete outcome data as unclear.
- Selective outcome reporting: we assessed a trial at low risk of bias due to selective outcome reporting if the outcomes of interest that were 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, we assessed this domain as unclear.
- Other bias: we noted examples of potential sources of bias such as imbalance in potentially important prognostic factors between the treatment groups at baseline, or the use of a cointervention in only one group (e.g. nasogastric feeding). If information was not available about the intervention groups at baseline, we assessed studies as being at unclear risk of bias.

Measures of treatment effect

The primary outcome most frequently and reliably reported was total mortality, expressed as an HR. An HR provides an estimate of the ratio of the hazard rates, for a particular event, between the experimental group and a control group over the duration of the entire study. For overall survival, the event of interest is death (total mortality). It is acknowledged that it is preferable to talk in terms of overall survival; however, statistically, the estimate of effect is the HR of death.

We entered these data into the meta-analysis using the inverse variance method. If studies did not quote HRs, we calculated the log HR and the standard error from the available summary statistics or Kaplan-Meier curves, according to the methods proposed by Parmar and colleagues (Parmar 1998), or requested these data from authors.

For dichotomous outcomes, we expressed the estimates of effect of an intervention as risk ratios (RR) together with 95% confidence intervals (CI). Dichotomous data were only used for primary outcomes where HRs were unavailable or could not be calculated. We planned to combine data of similar follow-up periods.

Assessment of heterogeneity

We conducted meta-analyses only if there were studies of similar comparisons reporting the same outcome measures. We assessed the significance of any discrepancies in the estimates of the treatment effects from the different trials using Cochrane's test for heterogeneity and the I^2 statistic, and we investigated any heterogeneity.

Data synthesis

We conducted meta-analyses only if there were studies of similar comparisons reporting the same outcome measures. We combined RR for dichotomous data, and HRs for survival data, using random-effect models.

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

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

RESULTS

Description of studies

Results of the search

We identified 6929 research papers through the electronic searching for this update, after the removal of duplicates (Figure 1). Screening of the titles and abstracts resulted in the identification of 26 potentially relevant trials for inclusion in the review. We retrieved full-text copies of these articles. Further assessment of the papers resulted in five trials being included in this update of the review. Four of these trials were newly identified (Guo 2014; Iyer 2015; Mehanna 2017; Rastogi 2018), and one trial had previously been identified (D'Cruz 2015).

Included studies

Of the 12 trials included in the review, five were multicentred, with the number of centres ranging from two to 37. Three trials were undertaken in India (D'Cruz 2015; Fakih 1989; Rastogi 2018), two in Brazil (BHNCSG 1998; Kligerman 1994), two in China (Guo 2014; Yuen 2009), two in the UK (Mehanna 2017; Robertson 1998), one in centres across Europe (Austria, Germany and Switzerland) (Bier 1994), one in France (Vandenbrouck 1980), and one in Singapore (Iyer 2015). 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). Three trials required personal communication with the authors of the papers for retrieval of extra information (Kligerman 1994; Mehanna 2017; Robertson 1998).

Participants

Participants were recruited over periods ranging from two years to 11 years, with the earliest recruitment commencing in 1966 (Vandenbrouck 1980). A total of 2300 participants were randomly allocated to treatments and 2090 were included in the outcome evaluations. Most of the participants (2148) had oral cavity tumours and the remainder had oropharyngeal tumours.

All included trials reported tumour extent (TNM), four of which included participants with T1 to T2 tumours (D'Cruz 2015; Fakih 1989; Kligerman 1994; Yuen 2009), two with T2 to T4 tumours (BHNCSG 1998; Robertson 1998), two with T1 to T3 tumours (Rastogi 2018; Vandenbrouck 1980), and three with T1 to T4 tumours (Guo 2014; Iyer 2015; Mehanna 2017). In seven of the trials, participants had clinically negative neck nodes (BHNCSG 1998; D'Cruz 2015; Fakih 1989; Kligerman 1994; Rastogi 2018; Vandenbrouck 1980; Yuen 2009), three trials included participants with neck nodes clinically staged as N0-2 (Guo 2014; Iyer 2015; Robertson 1998), and one trial included participants with clinically staged N2-3 nodes (Mehanna 2017). The trial by Bier 1994 did not record the tumour stage or node status of the participants at trial entry (Table 1).

Of the 12 included trials, eight included recruited participants with oral cavity cancer only (BHNCSG 1998; Bier 1994; D'Cruz 2015; Fakih 1989; Kligerman 1994; Rastogi 2018; Vandenbrouck 1980; Yuen 2009); two included participants with oral cavity or oropharyngeal cancer (Guo 2014; Robertson 1998); one included participants with cancer of the oral cavity, oropharynx, hypopharynx, larynx and maxillary sinus (Iyer 2015); and one included participants with cancer of the oral cavity, tonsil, base of tongue, supraglottis and glottis or subglottis (Mehanna 2017).

Interventions

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

Nine trials of participants with oral cavity cancers compared either different surgical techniques for management of the lymph nodes in the neck or different timing for removal of the lymph nodes in the neck (BHNCSG 1998; Bier 1994; D'Cruz 2015; Fakih 1989; Guo 2014; Kligerman 1994; Rastogi 2018; Vandenbrouck 1980; Yuen 2009). Five 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) (D'Cruz 2015; Fakih 1989; Kligerman 1994; Vandenbrouck 1980; Yuen 2009). Kligerman 1994 used a supraomohyoid (SOH) approach for the elective neck dissection in a group of participants with clinically negative neck nodes compared with a therapeutic neck dissection if the nodes became clinically positive. Yuen 2009 compared an elective selective neck dissection at the time of glossectomy with glossectomy alone plus therapeutic neck dissection if nodes became clinically positive. Fakih 1989 used elective RND at the same time as resection of the primary tumour in a group with clinically negative neck nodes. Vandenbrouck 1980 compared elective RND within two months of resection of the primary tumour with therapeutic neck dissection. D'Cruz 2015 compared a selective neck dissection with a modified therapeutic neck dissection.

Four trials compared different types of neck dissection surgery at the time of removal of the primary tumour (BHNCSG 1998; Bier 1994; Guo 2014; Rastogi 2018). In the trial by Bier 1994, both groups had a radical resection of the primary tumour. One group had RND at the same time as resection and the other had selective neck dissection surgery. The Brazilian Study group compared a modified RND with a SOH neck dissection in conjunction with resection of the primary tumour (BHNCSG 1998). Rastogi 2018 compared superselective neck dissection with SOH neck dissection in conjunction with resection of the primary tumour. Guo 2014 compared SOH neck dissection with modified RND 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 participants with either oral cavity or oropharyngeal cancer. Iyer 2015 compared surgery and adjuvant radiotherapy with concurrent chemoradiotherapy. Mehanna 2017 compared positron-emission tomography-computed tomography (PET-CT) guided watch and wait policy (with neck dissection undertaken only if no/incomplete response to chemoradiotherapy identified) with planned neck dissection before or after radical chemoradiotherapy for locally advanced head and neck SCC.

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 reported either total mortality or overall survival (Yuen 2009), but not all provided data in a form suitable for inclusion in meta-analysis. Six trials reported disease-free survival (Bier 1994; D'Cruz 2015; Fakih 1989; Kligerman 1994; Vandenbrouck 1980; Yuen 2009), and seven trials reported recurrence (BHNCSG 1998; D'Cruz 2015; Fakih 1989; Kligerman 1994; Rastogi 2018; Robertson 1998; Yuen 2009).

Five trials mentioned harms/adverse events (BHNCSG 1998; D'Cruz 2015; Guo 2014; Mehanna 2017; Robertson 1998). BHNCSG 1998 reported the total number of adverse events in each group but not the number of participants affected. Two trials reported the percentages of participants in each group who experienced adverse effects (D'Cruz 2015; Robertson 1998). One trial reported quality-adjusted-life-years (QALYs), costs and harms/adverse events (Mehanna 2017). One trial reported hospital days of treatment (Guo 2014).

Excluded studies

We excluded 24 trials that were previously included in this review because they better fit in the other oral cancer treatment reviews. Four previously included trials (Ang 2001; Lawrence 1974; Sanguineti 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 2001; 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 three 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 or oropharyngeal cancer and their data could not be extracted separately (Hintz 1979a).

Risk of bias in included studies

Allocation

Four of the included trials reported adequate sequence generation methods (D'Cruz 2015; Fakih 1989; Mehanna 2017; Robertson 1998); in the remaining eight trials, the methods of sequence generation were unclear. Two trials reported adequate allocation concealment (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. However, as mortality is the primary outcome that is most frequently and reliably reported, a decision was made to assess all trials as being at low risk of bias for this domain.

Incomplete outcome data

We assessed nine of the included trials at low risk of bias with regard to incomplete outcome data because all the randomised participants were adequately accounted for in the outcome evaluation (BHNCSG 1998; Guo 2014; Iyer 2015; Kligerman 1994; Mehanna 2017; Rastogi 2018; Robertson 1998; Vandenbrouck 1980; Yuen 2009). Of the remaining trials, we assessed two at high risk with regard to this domain (Bier 1994; Fakih 1989), and one at unclear (D'Cruz 2015). Both Bier 1994 and Fakih 1989 presented 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 was unclear how many participants were randomly allocated to each intervention group, and how many in each group were subsequently excluded from the analysis or analysed in a different group from that to which they were originally allocated (or both). 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

We assessed 11 of the included trials as free of selective reporting bias as they reported on expected, clinically important outcomes. Yuen 2009 did not report total mortality or overall survival, so was at high risk of bias for this domain.

Other potential sources of bias

We assessed eight trials at low risk of other bias because the intervention groups appeared to be similar at baseline and there were no other sources of bias (BHNCSG 1998; D'Cruz 2015; Guo 2014; Iyer 2015; Mehanna 2017; Rastogi 2018; Vandenbrouck 1980; Yuen 2009).

Three trials provided no information regarding the baseline characteristics of participants in each group, and so these trials were at unclear risk of other bias (Bier 1994; Fakih 1989; Kligerman 1994).

We assessed Robertson 1998 at high risk of other bias because, although planned recruitment was 350 participants, this trial was stopped after only 35 participants 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 participants in this trial did not receive radiotherapy as planned due to problems with faulty equipment. 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 2. Overall, we assessed four studies at high risk of bias (Bier 1994; Fakih 1989; Robertson 1998; Yuen 2009), and eight trials at unclear risk of bias (BHNCSG 1998; D'Cruz 2015; Guo 2014; Iyer 2015; Kligerman 1994; Mehanna 2017; Rastogi 2018; Vandenbrouck 1980), for all of the outcomes evaluated.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

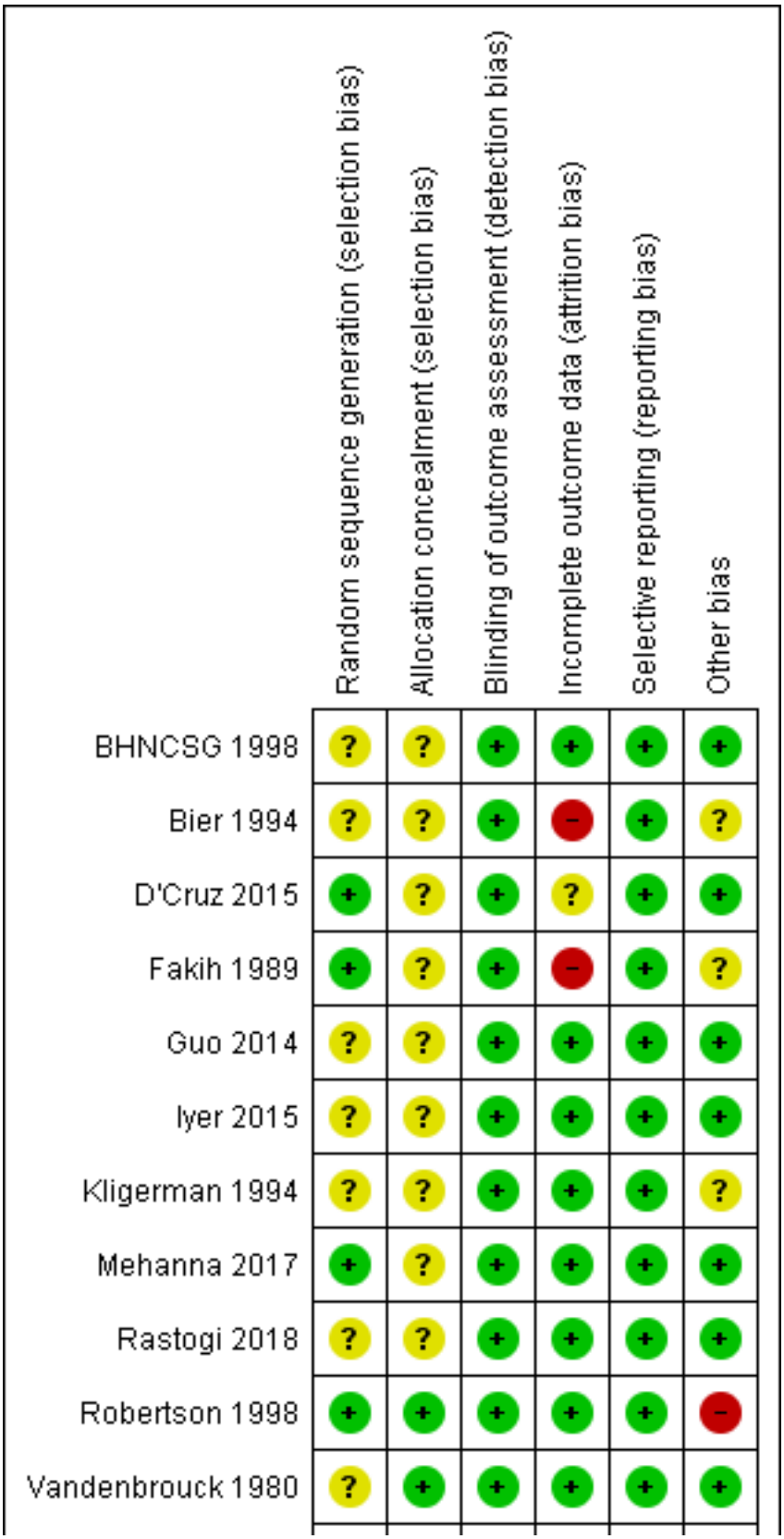


Figure 2. (Continued)

Effects of interventions

See: **Summary of findings for the main comparison** Elective neck dissection versus therapeutic (delayed) neck dissection; **Summary of findings 2** Elective radical neck dissection versus elective selective neck dissection; **Summary of findings 3** Surgery plus radiotherapy versus radiotherapy alone; **Summary of findings 4** PET-CT following chemoradiotherapy versus planned neck dissection either before or after chemoradiotherapy; **Summary of findings 5** Surgery plus adjuvant radiotherapy versus chemotherapy; **Summary of findings 6** Supraomohyoid neck dissection versus modified radical neck dissection; **Summary of findings 7** Super-selective neck dissection versus selective neck dissection

Comparison 1: elective neck dissection versus therapeutic (delayed) neck dissection

See Summary of findings for the main comparison.

Five trials 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 (D'Cruz 2015; Fakih 1989; Kligerman 1994; Vandenbrouck 1980; Yuen 2009). All participants had oral cavity cancers, specifically tongue or floor of mouth tumours and clinically negative neck nodes on study entry.

Fakih 1989 and Vandenbrouck 1980 performed classical RND procedures and pooled data after one year (Fakih 1989) and three years (Vandenbrouck 1980) of follow-up. D'Cruz 2015 and Yuen 2009 performed selective neck dissection of level I to III nodes with D'Cruz 2015 reporting data at three years. Kligerman 1994 used a SOH elective neck dissection procedure, and reported data after 3.5 years of follow-up. Fakih 1989 and Yuen 2009 was at overall high risk of bias and Kligerman 1994, Vandenbrouck 1980, and D'Cruz 2015 were at unclear overall risk of bias.

Overall survival (or total mortality)

Two trials presented overall survival data as HRs (D'Cruz 2015; Vandenbrouck 1980) and two trials as RRs (Fakih 1989 at one year; Vandenbrouck 1980 at three years). The meta-analysis for the HRs showed no evidence of a difference between the interventions (Analysis 1.1; very low-certainty evidence)). We were unable to pool the binary data due to different follow-up periods. Fakih 1989 found no evidence of a difference between elective RND and therapeutic neck dissection at one-year follow-up (very low-certainty evidence); however, Kligerman 1994, where elective surgery was the less extensive SOH, found a difference in overall survival after 3.5 years of follow-up, favouring elective SOH neck dissection compared to therapeutic neck dissection (Analysis 1.2; very low-certainty evidence).

Disease-free survival (or new disease, progression and mortality)

Three trials reported the data for disease-free survival as HRs (D'Cruz 2015; Kligerman 1994; Vandenbrouck 1980), and two trials as RRs (Fakih 1989 at one year; Vandenbrouck 1980 at three years). The pooled HR showed no evidence of a difference between elective neck dissection and therapeutic neck dissection (HR 0.73, 95% CI 0.25 to 2.11; Analysis 1.3; very low-certainty evidence). One study provided very low-certainty evidence of a benefit from elective SOH neck dissection when compared to therapeutic neck dissection (HR 0.32, 95% CI 0.12 to 0.84; Analysis 1.3) (Kligerman 1994). The binary data showed no evidence of a difference between the interventions (Analysis 1.4; very low-certainty evidence).

Locoregional recurrence

Four trials reported binary data on locoregional recurrence (D'Cruz 2015; Fakih 1989; Kligerman 1994; Vandenbrouck 1980), but the data were 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; very low-certainty evidence). The results were mixed, with three trials suggesting neither intervention was superior, while the study evaluating elective SOH neck dissection concluding this approach may reduce locoregional recurrence more than therapeutic delayed ND.

Recurrence

Two trials 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) (Vandenbrouck 1980; Yuen 2009).

Secondary outcomes

In D'Cruz 2015, 6.6% of the elective-surgery participants showed adverse events, while 3.6% of participants in the therapeutic-surgery group reported adverse events. These included neck haematoma, chyle leak, oral bleeding, postoperative infection and anaphylaxis. None of the other trials reported on adverse events.

None of the trials reported on quality of life, costs or any measure of participant satisfaction.

Comparison 2: elective radical neck dissection versus elective selective neck dissection

See Summary of findings 2.

Two trials compared neck dissection surgery of differing extent (BHNCSG 1998; Bier 1994). There were differences between the two studies with regard to participant 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 SOH neck dissection to achieve a compartmental excision of levels I to III neck nodes in 148 participants with T2 to T4 primary lesions in the oral cavity and clinically negative nodes. Frozen sections were carried out on the nodes during surgery and three participants in the SOH group who had histologically positive nodes then underwent the modified classical neck dissection instead. This trial was at overall unclear risk of bias.

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

Overall survival (or total mortality)

There was no evidence of a difference in overall survival (Analysis 2.1; very low-certainty evidence).

Disease-free survival (or new disease, progression and mortality)

Only Bier 1994 reported disease-free survival and there was no evidence of a difference (Analysis 2.2; very low-certainty evidence).

Locoregional recurrence

Neither trial reported locoregional recurrence.

Recurrence

Only BHNCSG 1998 reported recurrence as binary data at five years, and there was no evidence of a difference in disease recurrence (Analysis 2.3; very low-certainty evidence).

Secondary outcomes

BHNCSG 1998 reported the following adverse effects: flap necrosis, wound infection, fistula, vascular rupture, haematoma, seroma and chyle fistula. There were no complications in 45/76 participants in the modified RND group and none in 54/72 participants in the SOH neck dissection group. There were two postoperative deaths in the modified RND group and one in the SOH neck dissection group.

Neither trial reported other secondary outcomes.

Comparison 3: surgery plus radiotherapy versus radiotherapy alone

See Summary of findings 3.

One trial compared surgery plus postoperative radiotherapy with radiotherapy alone (Robertson 1998). Participants in the surgery group had wide local excision of the primary tumour together with either a RND or a more selective neck dissection at the discretion of the surgeon. It was planned to accrue 175 participants, with oral cavity or oropharyngeal cancer (neck nodes clinically staged as N0 to 2) to each arm of the trial but after 35 participants had been recruited the trial was stopped due to the high death rate in the radiotherapy alone arm.

Overall survival (or total mortality)

Data in Analysis 3.1 are from an interim analysis of 35 participants after 23 months and showed an HR for total mortality of 0.24 (95% CI 0.10 to 0.59), favouring the surgery group. This estimate should be interpreted with extreme caution for several reasons. The authors stated 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 participants in the radiotherapy only arm received their radiotherapy as planned due to problems with faulty machines, and that there were several other protocol violations in the trial. In the surgery plus radiotherapy arm, 50% of the participants received radiotherapy as planned, but 12% of participants received neither surgery to the mandible nor neck dissection.

Disease-free survival (or new disease, progression and mortality)

The trial did not report this outcome.

Locoregional recurrence

The trial did not report locoregional recurrence.

Recurrence

The trial did not report recurrence.

Secondary outcomes

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

The trial did not report other secondary outcomes.

Comparison 4: PET-CT following chemoradiotherapy versus planned neck dissection either before or after chemoradiotherapy

See Summary of findings 4.

One trial at overall unclear risk of bias compared PET-CT-guided surveillance (with neck dissection only if no response or incomplete response to chemoradiotherapy) to planned neck dissection (either before or after chemoradiotherapy) in participants with stage N2 or N3 disease (Mehanna 2017). The study recruited 564 participants.

Overall survival (or total mortality)

There was no evidence of a difference in total mortality between PET-CT 'watch-and-wait' and planned neck dissections (HR 0.92, 95% CI 0.65 to 1.31; Analysis 4.1; very low-certainty evidence).

Disease-free survival (or new disease, progression and mortality)

There were limited data that we were unable to use. Mehanna 2017 reported that "Disease-specific mortality and mortality from other causes did not differ significantly between the two groups (P = 0.80 and 0.41, respectively, according to Gray's test for differences)."

Locoregional recurrence

There were limited data that we were unable to use. Mehanna 2017 reported that "The 2-year rate of locoregional control was 91.9% (95% CI, 88.5 to 95.3) in the surveillance group and 91.4% (95% CI, 87.8 to 95.0%) in the planned-surgery group. In the latter group, the 2-year rate of locoregional control was 90.4% (95% CI, 86.0 to 94.7) among patients who underwent neck dissection after chemoradiotherapy and 94.8% (95% CI, 89.0 to 100) among patients who underwent neck dissection before chemoradiotherapy."

Recurrence

There were limited data that we were unable to use. Mehanna 2017 reported that "Documented recurrence in the nodes only (without concurrent disease in the primary site) occurred in 1 patient in the planned-surgery group and in 3 patients in the surveillance group. Distant metastases were identified in 23 patients in the planned-surgery group and in 21 patients in the surveillance group."

Secondary outcomes

There were 22 surgical complications after neck dissection in the surveillance group compared with 83 in the planned-surgery group.

Mehanna 2017 assessed quality of life using EORTC QLQ-C30 questionnaire. There was a small difference in global health status scores in favour of the surveillance group at six months after randomisation relative to planned-surgery group (mean change 4.94; P = 0.09). This difference narrowed at 12 months (mean change 3.03; P = 0.09) and was no longer apparent at 24 months (mean change –0.81; P = 0.85).

There was an economic evaluation undertaken consisting of two components: a within-trial analysis and a decision analytic model. The primary analysis was conducted from a National Health Service (NHS) secondary care perspective (i.e. including NHS hospital costs). PET-CT guided surveillance was more cost effective than planned neck dissection. Compared with planned neck dissection, PET-CT surveillance produced an incremental net health benefit of 0.16 quality-of-life years (QALYs) (95% CI 0.03 to 0.28) over the trial period, and 0.21 QALYs (95% CI to 0.41 to 0.85) over the modelled lifetime horizon.

The trial reported none of the other secondary outcomes.

Comparison 5: surgery plus adjuvant radiotherapy versus chemotherapy

See Summary of findings 5.

One trial at overall unclear risk of bias compared neck dissection surgery plus adjuvant radiotherapy versus chemotherapy in 119 participants with histologically confirmed respectable stage III/IV head and neck SCC (excluding nasopharynx and salivary gland SCC) (Iyer 2015). The median follow-up for surviving participants was 13 years.

Overall survival (or total mortality)

The study report stated, "For the oral cavity, survival was significantly better in patients who underwent surgery and RT compared with the CRT group." However, there were no useable data.

Disease-free survival (or new disease, progression and mortality)

The study reported that disease-free survival was statistically significant in favour of the surgery group (P = 0.038), but there were no useable data.

Locoregional recurrence

The study reported that locoregional recurrence-free survival was not statistically significant between the groups (P = 0.355), but there were no useable data.

Recurrence

The study reported that distant recurrent-free survival was not statistically significant between the groups, but there were no useable data.

The study report stated, "The 5-year DSS rates were 68% for the S [surgery] arm versus 12% for the C [chemotherapy] arm (P5.038) (Fig. 3a). Similarly, rates of distant metastasis were higher among patients on the C arm, with 5-year DRFS [distant recurrent-free survival] rates of 50% compared with 92% for patients on the S arm (P5.05) (Fig. 3b). However, no statistically significant difference was observed in locoregional disease recurrence rates between the treatment arms (P5.355) (Fig. 3c), although there may have been a trend favoring the S arm."

Secondary outcomes

The trial reported no secondary outcomes.

Comparison 6: supraomohyoid neck dissection versus modified radical neck dissection

See Summary of findings 6.

One trial at overall unclear risk of bias compared SOH neck dissection versus modified RND (Guo 2014). Participants, with oral cavity or oropharyngeal cancer, had T1 to T4 tumours with neck nodes clinically staged as N0 to 2.

Overall survival (or total mortality)

The study reported overall survival/total mortality during the follow-up period (with different follow-up times), so could not be used for analysis. The study report stated, "During the follow-up period 113 (35.1%) of the 322 patients died (SOND [supraomohyoid neck dissection]: 53 cases, MRND [modified radical neck dissection]: 60 cases).

Disease-free survival (or new disease, progression and mortality)

The study reported data for disease-specific survival but we were unable to use them in an analysis. The study report stated, "There was no significant difference between the SOND [supraomohyoid neck dissection] group and the MRND [modified radical neck dissection] group in the 3-year disease-specific survival (DSS) rate (79.0% vs. 76.9%, P = 0.659)."

The Kaplan Meier survival curve for neck recurrence-free survival had insufficient information to calculate the HR. The study report stated, "By the Kaplan-Meier test, the patients in the SOND [supraomohyoid neck dissection] group had a better 3-year NCR [neck control rate] than those in the MRND [modified radical neck

dissection] group, but the difference was not significant (92.6% vs. 87.5%, P = 0.108)."

Locoregional recurrence

The trial did not report locoregional recurrence.

Recurrence

The trial did not report recurrence.

Secondary outcomes

There was some limited information on adverse events in the text. The study report stated, "There was a significant difference in the complication rates between both groups (SOND [supraomohyoid neck dissection] group vs. MRND [modified radical neck dissection] group: 13.0% vs. 21.9%, P = 0.040). The most frequent complication was wound infection." The report summarised other significant complications. The study assessed University of Washington Quality of Life Questionnaire (UW-QOL) scores for all disease-free survivors at one year after treatment (Deleyiannis 1997), scores from nine disease-specific domains appeared to show that SOH neck dissection was superior to modified RND in the domains of pain relief (78.8% versus 75.2%; P = 0.013) and shoulder function (81.1% versus 68.1%; P < 0.001), but not in any of the other domains.

Comparison 7: selective neck dissection versus super-selective neck dissection

See Summary of findings 7.

One trial at overall unclear risk of bias compared selective neck dissection versus super-selective neck dissection in participants with oral cavity cancer (T1 to T3 tumours; clinically negative neck nodes) (Rastogi 2018).

Overall survival (or total mortality)

The study did not report this outcome.

Disease-free survival (or new disease, progression and mortality)

The study did not report this outcome.

Locoregional recurrence

The study investigated locoregional recurrence for 2.5 years. Survival analysis (rate of recurrence) was measured using the Kaplan-Meier model (survival analysis regression model), however HRs could not be calculated from the data provided. The study report stated, "the P value by Kaplan-Meier survival analysis was less than .05. Therefore, the SSND (super selective) group showed a lower rate of recurrence compared with the SND (selective group (P < .5)."

Recurrence

The study did not report recurrence.

Secondary outcomes

The study analysed data for shoulder morbidity subjectively and objectively. The results for both measures showed less shoulder morbidity and improved quality of life for superselective neck dissection compared with selective neck dissection. Only P values were presented so we were unable to use the data provided.

The study authors performed subjective analysis measuring shoulder morbidity using the Neck Dissection Quality of Life (ND-QOL) questionnaire. Data showed that the mean score for the super-selective neck dissection group (30.4) was significantly higher (P = 0.01) than for the selective neck dissection group (19.4).

The study authors stated that quality of life for the super-selective neck dissection group was significantly better than the selective neck dissection group based on the outcome of the ND-QOL questionnaire. There were no other data presented to confirm this position other than the scores on the ND-QOL questionnaire.

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?' We included 12 RCTs with a combined total of 2300 randomised participants. Approximately 2148 of these participants had oral cavity cancers. None of the trials were at overall low risk of bias.

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

- Comparison 1: elective neck dissection versus therapeutic (delayed) neck dissection: included five trials that 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 participants had oral cavity cancers, specifically tongue or floor of mouth tumours, and clinically negative neck nodes. All the evidence was graded as very low certainty. 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 RND, 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 was inconclusive evidence concerning the effect of elective neck dissection on locoregional disease recurrence; findings were mixed and the data were unsuitable for meta-analysis.
- Comparison 2: elective RND versus elective selective neck dissection: included two trials that compared elective radical (comprehensive) neck dissection with a selective neck dissection in participants with oral cavity cancers. One trial included only participants with clinically negative neck nodes and the other included those with movable positive neck nodes as well. There was 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. All the evidence was very low certainty.
- Comparison 3: surgery plus radiotherapy versus radiotherapy alone: involved one trial that compared surgery plus postoperative radiotherapy and radiotherapy alone, but this

trial was stopped early due to an unacceptably high death rate in the radiotherapy alone group. There was very low-certainty evidence of 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 participants (10% of planned recruitment) may have inflated the difference between the groups. Also, there were several protocol violations (more than half of the participants did not receive their radiotherapy as planned due to faulty machines), which may partially explain the poor outcome in the radiotherapy alone group.

  - While there was very low-certainty evidence from these included trials that early or extensive dissection of the lymph nodes in the clinically negative neck reduced locoregional recurrence, there was no strong evidence of a difference in overall survival or disease-free survival. There was no information from these trials on quality of life of the people who had undergone the different neck dissection procedures.

- Comparison 4: PET-CT following chemoradiotherapy versus planned neck dissection either before or after chemoradiotherapy: involved one trial comparing PET-CT (with neck dissection only if no/incomplete response to chemoradiotherapy identified) versus planned neck dissection (either before or after chemoradiotherapy), there was very low-certainty evidence of no difference in mortality. The trial did not provide usable data for the other outcomes.
- Comparison 5: surgery plus adjuvant radiotherapy versus chemotherapy: involved one trial comparing surgery plus adjunctive radiotherapy versus chemoradiotherapy. There were no useable data from this trial.
- Comparison 6: SOH neck dissection versus modified RND involved one trial comparing SOH neck dissection versus modified RND. There were no useable data from this trial.
- Comparison 7: selective neck dissection versus super-selective neck dissection involved one trial that compared super selective neck dissection versus selective neck dissection. There were no useable data from this trial.

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, or 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, we modified the protocol for this review to include only studies that directly compared different surgical treatment modalities against one another, or compared surgery to a different treatment regimen such as radiotherapy, chemotherapy or immunotherapy. We removed all other studies from the updated review, and, where appropriate, incorporated them 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, the search identified only 12 trials and 2148 of the total of 2300 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 564 participants, recruited participants over five decades between 1966 and 2017. There have been significant developments in both the surgical and adjuvant treatments for people with oral cavity cancer since the late 2000s and these are incompletely evaluated in this systematic review due to the lack of RCTs in this condition. It is encouraging to note that there are currently three large trials ongoing that will provide further information concerning the benefits and harms of different surgical options for neck dissection in people with oral cavity cancer (NCT00571883 (SEND); NCT01334320; Nichols 2013 (formerly NCT01590355)).

Only two of the included studies reported harms or adverse events to treatment, but neither presented outcomes per person (BHNCSG 1998; Robertson 1998). 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 participants randomly allocated to surgery refused surgical treatment and were withdrawn from the trials, there was no report of the quality of life of these people compared to those included in the trials.

We identified no trials of surgery in people with oropharyngeal cancer, probably because the current therapeutic approach to oropharyngeal cancer is either radiotherapy or chemoradiotherapy. Since the late 2000s, the percentage of people with oropharyngeal cancer who test positive for HPV has increased steadily. It is now recognised that HPV status of people with oropharyngeal cancer is an important factor in their prognosis (Adelstein 2009; Brizel 2011). In updates of this review, we will undertake a subgroup analysis for the surgical management of HPV-related oral cavity cancer and the surgical management of non-HPV related oral cavity cancer, provided there are a sufficient number of trials reporting this.

Quality of the evidence

The overall certainty of the evidence included in this systematic review was very low. All of the included trials were at either high or unclear risk of bias. Participants were recruited over five decades (1966 to 2017). For objective outcomes such as total mortality, we had planned that trials we assessed as adequate with regard to the domains of sequence generation, allocation concealment, complete outcome data and absence of selective reporting would be assessed as being at low risk of bias overall. 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 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 participants.

There has been substantial developments in the surgical and non-surgical treatments for both oral and oropharyngeal cancers over recent years. Further objective assessments of current surgical

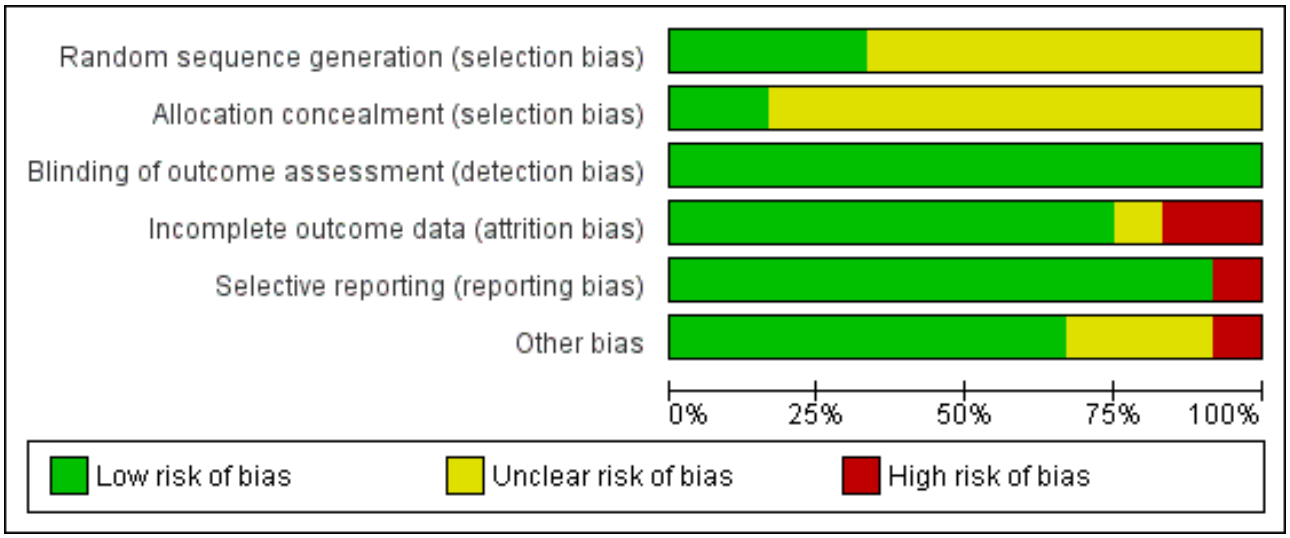
treatments for these cancers are needed to inform both patients and clinicians about the benefits and risks of different treatments.

Potential biases in the review process

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

Figure 3 provides an indication of the review authors' judgements about each risk of bias item presented as percentages across all included studies. The decision to look at blinding for overall survival (low risk of bias assessment), which is then used for all nine outcomes, is a source of bias in the review process.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Agreements and disagreements with other studies or reviews

We found two reviews of treatment of neck dissection in the surgical treatment of oral cavity cancer 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 were based on "vote-counting."

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

We chose to use the outcome of overall survival/total mortality because we believe this is the more important outcome for patients, and we have used HRs where possible, as they have the advantage of incorporating all available information, including data from participants who failed 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

This review includes 12 randomised controlled trials that evaluated neck dissection surgery in participants with oral cavity cancers. We found insufficient evidence to draw conclusions about elective neck dissection of clinically negative neck nodes at the time of removal of the primary tumour compared to therapeutic neck dissection. Two studies using radical neck dissection as the elective procedure did not find a difference between interventions, while one trial found that elective supraomohyoid neck dissection may be associated with increased overall and disease-free survival when compared to a therapeutic neck dissection. Three studies had inconclusive results for locoregional recurrence, and one found this was reduced with elective neck dissection. There is no evidence that elective radical neck dissection increases overall survival compared to more conservative neck dissection surgery. There is no evidence of a difference in mortality between PET-CT surveillance following chemoradiotherapy versus planned ND (before or after chemoradiotherapy). Reporting of adverse events in all trials was poor and it was not possible to compare the quality of life of participants undergoing different surgeries. Available evidence for all comparisons and outcomes is very low certainty and results should be interpreted in light of this.

Implications for research

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

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

- There should be a standardised and consistent reporting of adverse events and morbidity associated with treatment, with results reported per participant.
- 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

BHNCSG 1998 *(Continued)*

Participants	Inclusion criteria: resectable T2 to T4 lesions; clinically negative neck (N0); no prior treatment; histological diagnosis of SCC of the oral tongue, FOM, inferior gingiva or RMT; no need for myocutaneous or free flaps for reconstruction; Karnofsky score ≥ 60. Exclusion criteria: significant cardiac or pulmonary diseases, distant metastases or multiple primary cancers (or both). Recruitment period: May 1990 to December 1993 Number randomised: 148 (all OC: 42% tongue, 33% FOM, 8% inferior gingiva, 17% RMT) Number analysed: 148
Interventions	**MRND vs SOH** Group 1 (n = 76): MRND: surgery conducted centripetally toward the submandibular triangle. Group 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 an MRND. For both groups, PORT was indicated in cases with positive margins or positive lymph nodes (or both) in the specimen. RT was over 5 consecutive weeks to deliver a total dose of 50 Gy. All participants had primary tumour resection.
Outcomes	Primary: overall survival, recurrence Secondary: 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	Quote: "Patients were stratified by institution and laterality (unilateral or bilateral) and subsequently 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	Low risk	Mortality was primary outcome and considered an objective outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
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 1 side post-canine or postmolar, i.e. second (postcanine) or third (postmolar) part of the tongue, non-palpable 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 ND vs selective ND** Group 1 (n = 48): radical ND (ipsilateral) on the draining lymph nodes. Radical dissection designated as removal of: 1. platysma, sternocleidomastoid muscle, omohyoid muscle, stylohyoid muscle, distal part of the biventer cervicis and fascia colli; 2. the accessory nerve, descending branch of the hypoglossus nerve and branches of the cervical plexus; 3. the cervical vein, superficial jugular vein and internal jugular vein; 4. fat tissue, submandibular gland and lower part of the parotid gland. Group 2 (n = 56): selective ND (ipsilateral) on the draining lymph nodes. Selective dissection designated as retention of the platysma, sternocleidomastoid muscle, internal jugular vein and the accessory nerve. All participants underwent radical resection of the primary tumour.
Outcomes	Primary: overall survival, recurrence Secondary: metastases Duration of follow-up: 4 years
Notes	Preliminary report ND was followed by RT or chemotherapy (or both) in participants not undergoing radical resection of the primary tumour and in participants with capsular rupture in ≥ 1 lymph node. These participants 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	Quote: "Randomized according to the treatment-dependant prognostic index (TPI) of the DOSAK." Method of sequence generation not described.

Bier 1994 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine 'yes' or 'no.'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Mortality was primary outcome and considered an objective outcome.
Incomplete outcome data (attrition bias) All outcomes	High risk	Interim analysis of 104/167 participants randomised published in 1994. No subsequent publication identified. Participants who did not have radical surgery at the primary site and participants who had extracapsular rupture of ≥ 1 lymph node were 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.

D'Cruz 2015

Methods	Location of trial: India Number of centres: 1 Funding: Tata Memorial Centre Trial ID: NCT00193765
Participants	Inclusion criteria: aged 18–75 years with histopathologically confirmed, invasive SCC of the oral cavity (tongue, FOM or buccal mucosa) that met the staging criteria of the Union for International Cancer Control tumour stage T1 (measuring ≤ 2 cm) or T2 (measuring > 2 cm but < 4 cm) that was lateralised to 1 side of the midline. In addition, all participants had received no previous treatment, were amenable to undergoing oral excision, and had no history of head and neck cancer. Exclusion criteria: previous surgery in the head and neck region, upper alveolar or palatal lesions, large heterogeneous leukoplakias or diffuse oral submucous fibrosis. Recruitment period: 2004–2014 Number randomised: 596 Number analysed: 496
Interventions	**Elective vs therapeutic ND in node-negative OC** Group 1 (n = 298): underwent elective surgery (ipsilateral selective ND with clearance of the submandibular (level I), upper jugular (level II), and midjugular (level III) nodes). Participants with metastatic nodal disease that was discovered during surgery (operative findings or frozen section), had a modified ND performed with nodal clearance extended to include the lower jugular (level IV) and posterior triangle (level V) nodes. Group 2 (n = 298): underwent therapeutic surgery (the same surgical procedure for the primary tumour and were then monitored, with modified ND (levels I–V) only at the time of nodal relapse. All participants underwent oral excision of the primary tumour with adequate margins (i.e. ≥ 5 mm). All participants underwent secondary randomisation for follow-up (to receive either physical examination or physical examination + ultrasonography of the neck).
Outcomes	Primary: overall survival, DFS, nodal relapse, regional recurrence

D'Cruz 2015 *(Continued)*

	Secondary: none noted Duration of follow-up: median 39 months
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used a computer random number generator (i.e. prepared computerised block design).
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk.'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Survival was primary outcome and considered an objective outcome.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	45 participants excluded from elective surgery group (1 withdrew consent, 1 had previous chemotherapy, 43 did not complete 9-month follow-up). 55 participants excluded from therapeutic surgery group (2 had lesion crossing midline, 53 did not complete 9-month follow-up
Selective reporting (reporting bias)	Low risk	Study protocol available and all of the study's prespecified (primary and secondary) outcomes that were of interest in the review were reported as per the protocol.
Other bias	Low risk	No other apparent bias

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 confirmed 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
Interventions	**Elective radical ND vs therapeutic radical ND** Group 1 (n = 30): radical ND (ipsilateral) Group 2 (n = 40): only participants developing neck node metastasis underwent radical ND

Fakih 1989 *(Continued)*

	All participants underwent resection of the primary tumour (standard anterior two-thirds hemiglossectomy).
Outcomes	Primary: overall survival, DFS, disease-related mortality, recurrent disease Secondary: none noted. 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	Quote: "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	Low risk	Survival was primary outcome and considered an objective outcome.
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 were 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.

Guo 2014

Methods	Location of trial: China Number of centres: 1 Funding: not stated Trial ID: not stated
Participants	Inclusion criteria: tumour located in the tongue, gingiva, buccal area, FOM, oropharynx or hard palate; no evidence of distant metastasis; no previous treatment Exclusion criteria: not stated Recruitment period: June 1999 to May 2010 Number randomised: 332 Number analysed: 322
Interventions	**SOH ND vs modified radical ND for clinically node-negative oral SCC**

Guo 2014 *(Continued)*

	Group 1 (n = 166): allocated to SOH ND arm (received surgery alone (n = 109), received surgery + PORT (n = 57)) Group 2 (n = 166): allocated to MRND arm (received surgery alone (n = 114), received surgery + PORT (n = 52))
Outcomes	Primary: DSS, NCR Secondary: quality of life (QoL) assessments Duration of follow-up: median 76 months (1 year for QoL)
Notes	NCR defined as proportion of participants who did not develop postoperative nodal metastases within 3 years.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement of 'low risk' or 'high risk.'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk.'
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Mortality was primary outcome and considered an objective outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	10 (3%) participants lost to follow-up soon after randomisation were unable to be included in the analysis (4 in SOH ND treatment arm, 6 in MRND treatment arm).
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting.
Other bias	Low risk	No other apparent bias.

Iyer 2015

Methods	Location of trial: Singapore Number of centres: not stated Funding: not stated Trial ID: not stated
Participants	Inclusion criteria: people newly diagnosed with histologically confirmed, resectable, non-metastatic stage III/IV HNSCC who had a good Eastern Cooperative Oncology Group performance status (0 or 1) and adequate bone marrow, hepatic and renal function. Exclusion criteria: nasopharynx and salivary glands Recruitment period: August 1996 to February 2002 Number randomised: 119

Iyer 2015 *(Continued)*

	Number analysed: 118
Interventions	**Surgery and adjuvant RT vs concurrent CRT** Group 1 (n = 60): radical surgery + adjuvant RT Group 2 (n = 59): combination chemotherapy with cisplatin and 5-fluorouracil and concurrent RT Randomisation was stratified according to primary tumour site (oral cavity/oropharynx, larynx/hypopharynx, others) and lymph node status (lymph-node positive vs lymph-node negative).
Outcomes	To determine whether concurrent chemotherapy was superior to the prevailing conventional treatment at that time, namely surgery and adjuvant RT, with survival as the endpoint. Primary: overall survival, DSS, locoregional recurrence-free survival, distant recurrence-free survival Secondary: none noted Duration of follow-up for all participants: 10 years
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Survival was primary outcome and considered an objective outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant missing from analysis as histopathological assessment confirmed adenocarcinoma, therefore excluded.
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting.
Other bias	Low risk	No other apparent bias.

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 FOM Exclusion criteria: not stated

Kligerman 1994 *(Continued)*

	Recruitment period: 1987–1992 Number randomised: 67 (all OC: 61% tongue, 39% FOM) Number analysed: 67
Interventions	**Elective ND vs therapeutic ND** Group 1 (n = 34): elective SOH ND. Dissection of levels 1–3 + resection of submandibular gland, preserving the sternocleidomastoid muscle, spinal accessory nerve and internal jugular vein Group 2 (n = 33): therapeutic ND All participants underwent resection of the primary tumour.
Outcomes	Primary: overall survival, DFS, locoregional recurrence, disease-related mortality Secondary: none noted Duration of follow-up: 3.5 years
Notes	Paper reported 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	Quote: "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	Low risk	Mortality was primary outcome and considered an objective outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	No evidence of selective outcome reporting
Other bias	Unclear risk	No information about comparability of groups at baseline

Mehanna 2017

Methods	Location of trial: UK Number of centres: 38

Mehanna 2017 *(Continued)*

	Funding: Health Technology programme of National Institute for Health Research Technology Assessment Programme and Cancer Research UK Trial ID: ISRCTN13735240
Participants	Inclusion criteria (must have met all): • histological diagnosis of oropharyngeal, laryngeal, oral, hypopharyngeal or occult HNSCC; • clinical and CT/MRI imaging evidence of nodal metastases staged N2 (a, b or c) or N3; • indication to receive curative radical concurrent CRT for primary; • fitness for ND surgery; • ND was technically feasible to perform and remove nodal disease (e.g. no carotid encasement, no direct extension between tumour and nodal disease); • aged ≥ 18 years; • able to give informed consent; • receiving 1 of the CRT regimens approved by the study. Exclusion criteria (any criteria met ruled patients ineligible): • undergoing resection for primary tumour (diagnostic tonsillectomy was not considered an exclusion criteria); • distant metastases to chest, liver, bones or other sites; • previous treatment for HNSCC; • pregnant; • another cancer diagnosis in the past 5 years (except basal cell carcinoma or carcinoma of the cervix in situ). Recruitment period: 2 October 2007 to 23 August 2012 Number randomised: 564 (84.4% OP cancer) Number analysed: 564 (personal communication)
Interventions	**PET-CT surveillance (following CRT) vs planned ND (either before or after CRT) in advanced head and neck cancer** Assessed the non-inferiority of PET-CT-guided surveillance (performed 12 weeks after the end of CRT, with ND performed only if PET-CT showed an incomplete or equivocal response) to planned ND (either before or after CRT) in people with stage N2 or N3 disease. Group 1 (n = 282): PET-CT 12 weeks after completion of CRT (surveillance group) Group 2 (n = 282): planned ND (either before or after CRT)
Outcomes	Primary: overall survival Secondary: quality of life, surgical complications Follow-up period: 36 months (median)
Notes	Before randomisation, each participating centre had to specify on a per-participant basis whether planned ND would be performed within 4 weeks before or within 4–8 weeks after completion of CRT. In addition, before randomisation, clinicians selected CRT regimens from a list of the approved study regimens. Intention-to-treat analysis was carried out for all 564 participants. Kaplan-Meier analysis was used to estimate survival rate due to the loss of some participants.
Risk of bias	

Mehanna 2017 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Minimisation algorithm used; table 1 listed variables for comparison.
Allocation concealment (selection bias)	Unclear risk	Unclear how allocation concealment occurred.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Survival was primary outcome and considered an objective outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants assessed as part of the intention-to-treat analysis.
Selective reporting (reporting bias)	Low risk	Study protocol was published and outcomes were published according to protocol.
Other bias	Low risk	No other potential sources of bias identified.

Rastogi 2018

Methods	Location of trial: India Number of centres: 1 Funding: not stated Trial ID: not stated
Participants	Inclusion criteria: aged > 18 years, established diagnosis of SCC as defined by the AJCC classification, T1–T3 lesions of the oral cavity with N0 neck. Exclusion criteria: requiring radical ND or modified radical ND; history of surgery or RT of the head and neck region; history of shoulder pain, dysfunction or weakness including myopathy, neuropathy or arthropathy; any type of implanted electrical device prior to surgery; previous or current neurological illness; did not provide written informed consent; unwilling to attend follow-up appointments. Recruitment period: August 2014 to March 2017 Number randomised: 20 Number analysed: 20
Interventions	**Selective ND vs super-selective ND for people with oral carcinoma and N0 neck in terms of shoulder morbidity and recurrence rate** Group 1 (n = 10): selective ND of levels I, IIa, IIb and III Group 2 (n = 10): super selective ND of levels I, IIa and III
Outcomes	Primary: rate of recurrence over 2.5 years Secondary: Arm Abduction Test, quality of life assessed by subjective questionnaire (Neck Dissection Quality of Life Questionnaire) Duration of follow-up period for all participants: 2.5 years

Rastogi 2018 *(Continued)*

Notes	Small sample size

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear how the randomisation occurred using the "slot method."
Allocation concealment (selection bias)	Unclear risk	Unclear if the investigators utilised appropriate allocation concealment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Mortality was primary outcome and considered an objective outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the trial with analysis undertaken for all.
Selective reporting (reporting bias)	Low risk	Outcomes clearly stated in methods section and appropriately measured in results section.
Other bias	Low risk	No other sources of bias noted.

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–T4, N0–N2, M0 head and neck tumours Exclusion criteria: stage I (T1N0M0); history of 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 RT alone arm) (33/35 OC: 40% tongue, 43% FOM, 11% RMT, 6% tonsil) Number analysed: 35
Interventions	**Surgery + RT vs RT alone** Group 1 (n = 17): radical resection and ND + PORT. Radical surgery involved wide local excision of the primary tumour with 1 cm margin. A radical or functional ND was carried out at the same time at the discretion of the surgeon. Reconstruction of the oral cavity was carried out immediately. PORT comprised 60 Gy in 30 fractions over 6 weeks, commencing within 6–8 weeks of surgery. Group 2 (n = 18): RT alone; 66 Gy in 33 fractions over 6.5 weeks, receiving 2 Gy per day
Outcomes	Primary: overall survival, disease-free interval, recurrent disease, locoregional control

Robertson 1998 *(Continued)*

	Secondary: 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 DFS, but not used as graph started at 50% for RT alone arm. Authors provided additional information relating to allocation concealment and the characteristics of tumours.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "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	Low risk	Mortality was primary outcome and considered an objective outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting of outcomes.
Other bias	High risk	Anticipated enrolment of 350 participants, but trial stopped after 35 participants recruited because clinicians felt it was unethical to continue. Appropriate procedures and analysis were conducted. More than half of participants recruited had either delays or interruptions to the planned RT schedule. It is likely that this would have had a greater effect on the outcomes of the RT alone arm of this trial.

Vandenbrouck 1980

Methods	Location of trial: France Number of centres: 1 Funding: not stated Trial ID: not stated
Participants	Inclusion criteria: T1–T3, N0, SCC oral cavity, tongue or lower FOM; any age or sex with no previous transcutaneous RT 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: 1966–1973 Numbers randomised: 80 (all OC; 56% tongue, 44% FOM)

Vandenbrouck 1980 *(Continued)*

	Numbers analysed: 75
Interventions	**Elective radical ND vs therapeutic radical ND** Group 1 (n = 39): elective ND within 2 months of treatment of primary lesion. In cases of lateral tumour, an ipsilateral radical ND with removal of sternocleidomastoid muscle, internal jugular vein without sparing the spinal accessory nerve was performed. When tumour crossed or close to midline submental, submaxillary and jugulodigastric contralateral dissection performed. Nodal involvement resulted in PORT. Group 2 (n = 36): therapeutic (delayed) dissection. These participants were followed for ≥ 3 years and underwent ND if a cervical node became enlarged. All participants received interstitial RT to the primary tumour site prior to randomisation.
Outcomes	Primary: overall survival, DFS, disease-related mortality, recurrent disease Secondary: none noted Duration of follow-up period: 5 years
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "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	Quote: "Randomisation was under the control of a statistician who observed the strictest protocol." Assumed this was adequate.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Survival was primary outcome and considered an objective outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
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

Yuen 2009 *(Continued)*

	Trial ID: not stated
Participants	Inclusion criteria: AJCC, Stage I to II, SCC oral tongue; no nodal metastases; no prior surgery, chemotherapy or RT Exclusion criteria: OC of other subsites, or cancer of base of tongue Recruitment period: 1996–2004 Numbers randomised: 72 (all OC: 100% tongue) Numbers analysed: 71
Interventions	**Elective selective ND vs therapeutic radical ND** Group 1 (n = 36): elective ipsilateral selective ND of level I, II or III neck nodes. Group 2 (n = 36): therapeutic (delayed) dissection. These participants were followed, and received ultrasound examinations every 3 months for the first 3 years. If nodal recurrence was detected, these participants underwent either radical or modified radical ND followed by RT. All participants in the trial had transoral glossectomy with 1.5 resection margins.
Outcomes	Primary: nodal recurrence, disease recurrence, death due to tumour, 5-year tumour-specific survival Duration of follow-up: 34–122 months
Notes	

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	Low risk	Mortality was primary outcome and considered an objective outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant 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, DFS and disease-specific death. No reporting of mortality in each group.
Other bias	Low risk	Groups appeared similar at baseline.

AJCC: American Joint Committee on Cancer; CRT: chemoradiotherapy; CT: computer tomography; DFS: disease-free survival; DSS: disease-specific survival; FOM: floor of mouth; HNSCC: head and neck squamous-cell carcinoma; HR: hazard ratio; MRI: magnetic resonance imaging; MRND: modified radical classical neck dissection; n: number of participants; NCR: neck control rate; ND: neck dissection; OC: oral cancer; OP: oropharyngeal cancer; PET-CT: positron-emission tomography–computed tomography; PORT: postoperative radiotherapy; RMT: retromolar trigone; RT: radiotherapy; SCC: squamous-cell carcinoma; SE: standard error; SOH: supraomohyoid neck dissection.

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

Study	Reason for exclusion
Abbade 2015	Study was about basal cell carcinoma, which is not related to oral cavity cancer.
Ajmani 2017	Not an RCT
Ang 2001	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: radiotherapy' (Glenny 2010).
Batra 2016	Short-term outcomes only (wound closure).
Bernier 2004	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy' (Furness 2011).
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' (Furness 2011).
De Stefani 2002	RCT to be included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: immunotherapy.'
Dean 2013	Short-term outcomes only (e.g. operative time, reduces blood loss during surgery, time drains are kept in place, amount of drainage).
Fan 2017	Short-term outcomes only (e.g. postoperative immune response and surgical stress).
Fritz 2016	Short-term outcomes only (e.g. blood loss and operating time).
Funahara 2017	Short-term outcomes only (e.g. surgical wound infections).
George 2014	Not an RCT
Gundale 2017	Abstract, insufficient information
Hintz 1979a	Head and neck cancer study with < 50% oral cancer/oropharyngeal cancer.
Hintz 1979b	Head and neck cancer study with < 50% oral cancer/oropharyngeal cancer.
Howard 2016	Systematic review
Jinyun 2015	Not an RCT
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' (Furness 2011).
Laramore 1992	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy' (Furness 2011).

Study	Reason for exclusion
Lawrence 1974	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: radiotherapy' (Glenny 2010).
Licitra 2001	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy' (Furness 2011).
Lin 2016	Short-term study only looking at immediate postsurgical outcomes.
Luboinski 1985	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy' (Furness 2011).
Maipang 1995	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy' (Furness 2011).
McCaul 2012	Abstract, insufficient information
McCaul 2017	Abstract, insufficient information
Minkovich 2011	Short-term outcomes only (e.g. malpositions of peripherally inserted central venous catheters).
Mohr 1994	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy' (Furness 2011).
Neifeld 1985	RCT to be included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: immunotherapy.'
Oswal 2017	Short-term outcomes only (e.g. wound closure).
Paccagnella 1994	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy' (Furness 2011).
Poh 2011	6 months post-treatment; short-term follow-up only.
Rao 1991	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy' (Furness 2011).
Rentschler 1987	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy' (Furness 2011).
Richard 1991	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy' (Furness 2011).
Sanguineti 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' (Furness 2011).
Szabo 1999	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy' (Furness 2011).
Szpirglas 1978	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy' (Furness 2011).
Terz 1981	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: radiotherapy.'

Study	Reason for exclusion
Tingting 2016	Not different surgical term
Uppal 2012	Unable to access the original article.
Verma 2017	Short-term study only looking at immediate postsurgical outcomes.
Volling 1999	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy' (Furness 2011).
Walen 2011	Short-term study on postoperative pain.
Weissler 1992	RCT now included in review 'Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy' (Furness 2011).
Zhang 2010	Abstract, insufficient information
Zhong 2013	Surgery was not the comparison, mainly chemotherapy.
Zhong 2015	Surgery was not the comparison, mainly chemotherapy

RCT: randomised controlled trial.

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

NCT00571883 (SEND)

Trial name or title	Neck surgery in treating patients with early-stage oral cancer (SEND trial)
Methods	RCT
Participants	People with oral squamous-cell carcinoma 1–3 cm at primary site, no clinical or preoperative imaging evidence of neck involvement (N0)
Interventions	Selective elective neck dissection + resection of primary tumour vs resection of primary alone
Outcomes	Overall survival, disease-free survival, local and regional recurrence, completeness of primary resection, QoL, psychological wellbeing, 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
Methods	RCT
Participants	Histologically confirmed T1 or T2 N0 M0 (clinical) squamous-cell carcinoma of oral tongue, buccal mucosa, gingiva, floor of mouth or hard palate

NCT01334320 *(Continued)*

Interventions	Elective superior omohyoid neck dissection vs 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, QoL
Starting date	April 2011
Contact information	Dr Guiqing Lao, Hospital of Stomatology, Sun Yat-sen University, Guangdong, China (drliaoguiqing@hotmail.com)
Notes	Planned enrolment 448 participants

Nichols 2013 (formerly NCT01590355)

Trial name or title	Early-stage squamous cell carcinoma of the Oropharynx: Radiotherapy vs. Trans-Oral Robotic Surgery (ORATOR) – study protocol for a randomized phase II trial
Methods	RCT. Phase II
Participants	People with oropharyngeal squamous-cell carcinoma who would be unlikely to require chemotherapy postresection, people with N0 disease will receive radiotherapy alone, whereas people with N1-2 disease will receive concurrent chemoradiotherapy.
Interventions	Participants will undergo transoral robotic surgery along with selective neck dissections, which may be staged.
Outcomes	Primary endpoint QoL score using M.D. Anderson Dysphagia Inventory, with secondary endpoints including survival, toxicity, other QoL outcomes and swallowing function.
Starting date	2013
Contact information	david.palma@lhsc.on.ca Department of Otolaryngology-Head and Neck Surgery, London Health Sciences Centre and Western University, London, ON, Canada
Notes	Sample of 68 participants is required.

QoL: quality of life; RCT: randomised controlled trial.

DATA AND ANALYSES

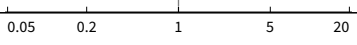
Comparison 1. Elective neck dissection (ND) versus therapeutic (delayed) neck dissection

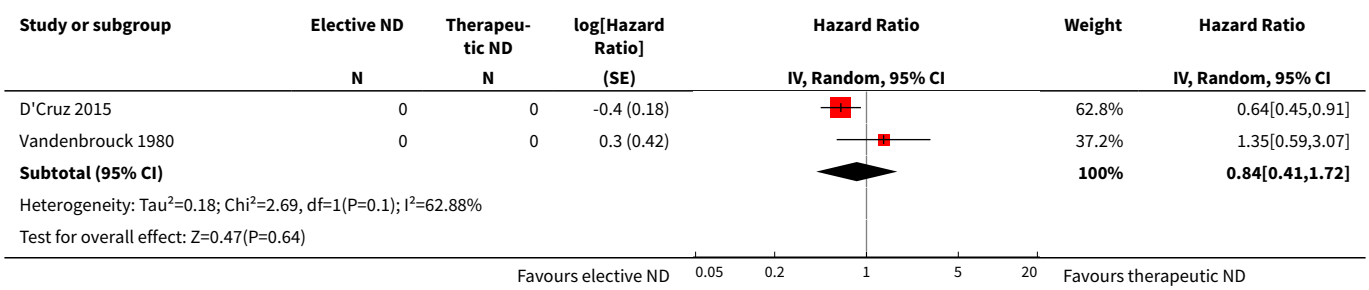
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total mortality (HR for overall survival)	2		Hazard Ratio (Random, 95% CI)	Subtotals only
1.1 Elective radical neck dissection vs therapeutic radical neck	2		Hazard Ratio (Random, 95% CI)	0.84 [0.41, 1.72]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Total mortality	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Elective radical neck dissection vs therapeutic neck dissection (1 year)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Elective supraomohyoid neck dissection (SOH) neck dissection vs therapeutic neck dissection (3.5 years)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 New disease, progression or mortality (HR for disease-free survival)	3		Hazard Ratio (Random, 95% CI)	Subtotals only
3.1 Elective radical neck dissection vs therapeutic radical neck	2		Hazard Ratio (Random, 95% CI)	0.73 [0.25, 2.11]
3.2 Elective SOH neck dissection vs therapeutic neck dissection (3.5 years)	1		Hazard Ratio (Random, 95% CI)	0.32 [0.12, 0.84]
4 New disease, progression or mortality	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Elective radical neck dissection vs 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 vs 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 vs 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 vs 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 vs therapeutic radical neck dissection (3 years)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

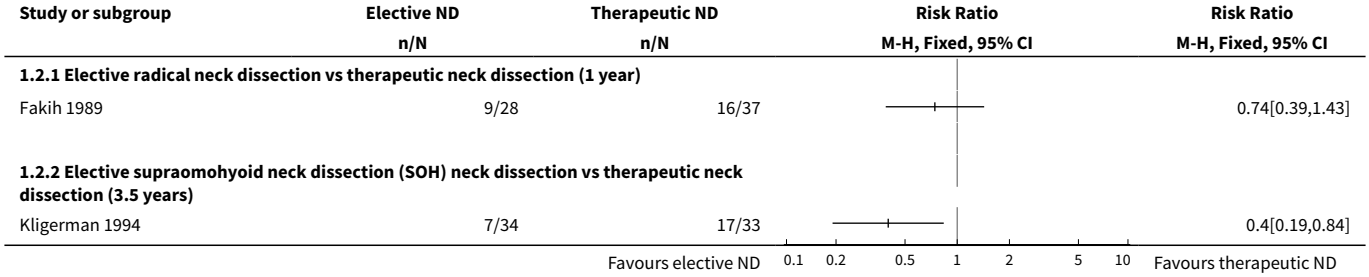
Analysis 1.1. Comparison 1 Elective neck dissection (ND) versus therapeutic (delayed) neck dissection, Outcome 1 Total mortality (HR for overall survival).

Study or subgroup	Elective ND	Therapeutic ND	log[Hazard Ratio]	Hazard Ratio	Weight	Hazard Ratio
	N	N	(SE)	IV, Random, 95% CI		IV, Random, 95% CI
1.1.1 Elective radical neck dissection vs therapeutic radical neck						

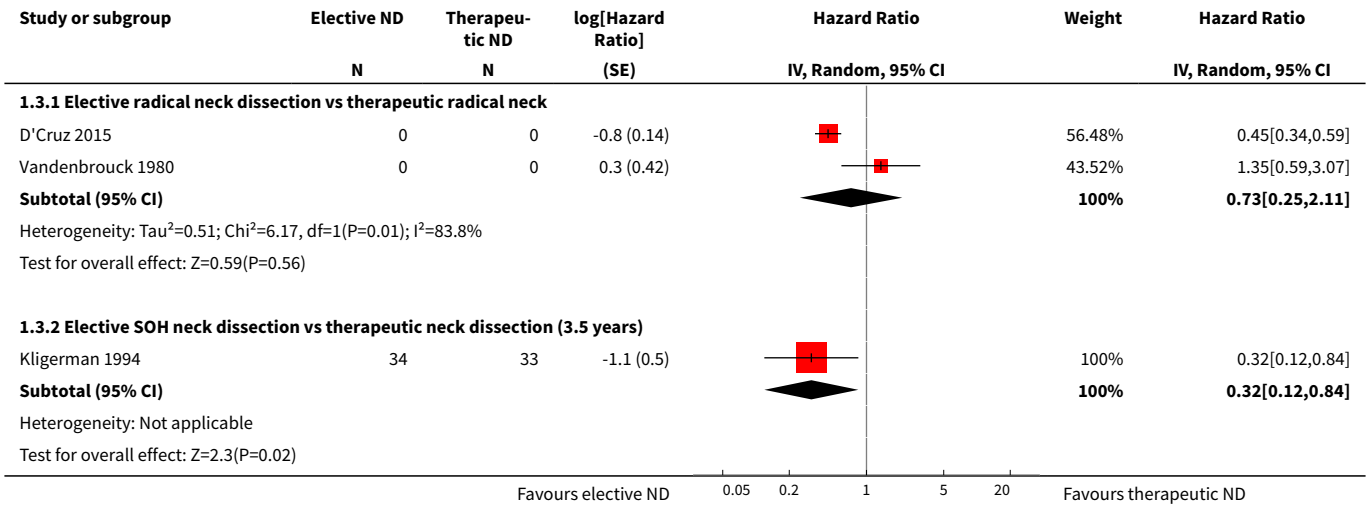




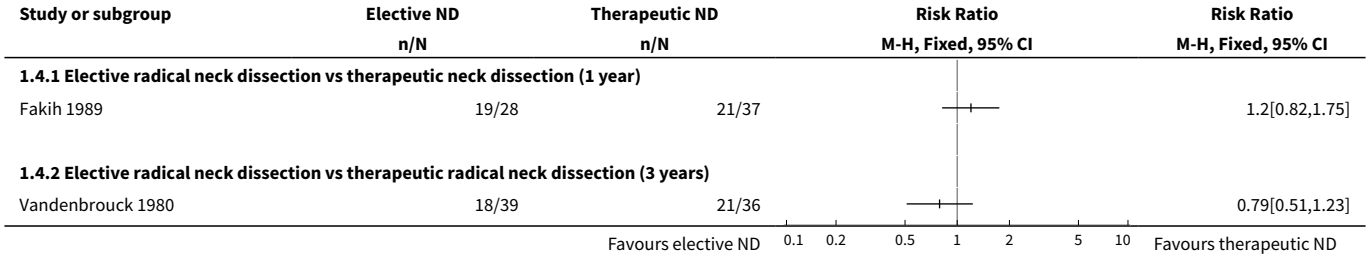
Analysis 1.2. Comparison 1 Elective neck dissection (ND) versus therapeutic (delayed) neck dissection, Outcome 2 Total mortality.



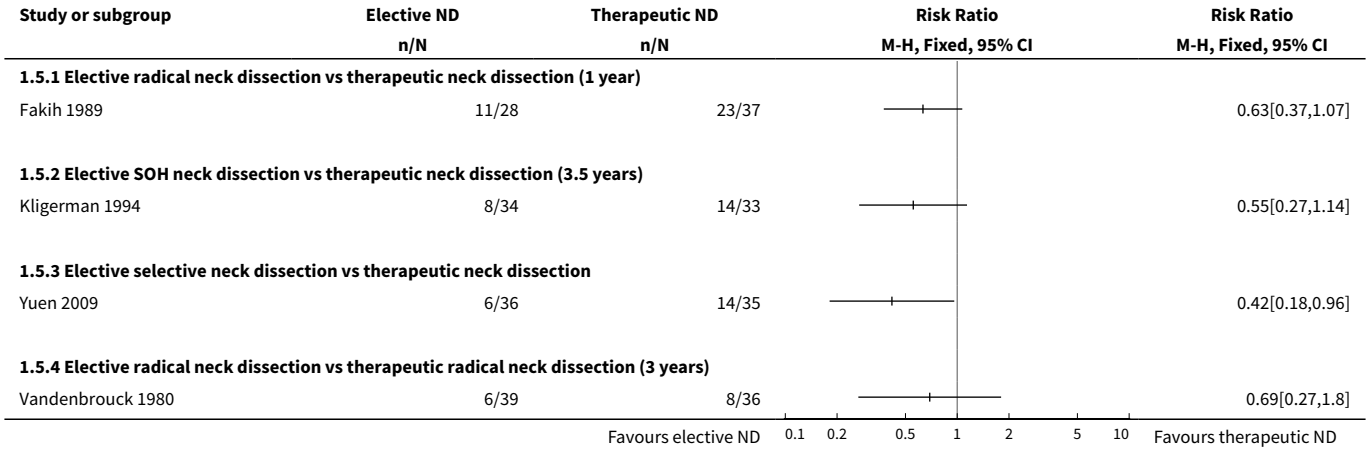
Analysis 1.3. Comparison 1 Elective neck dissection (ND) versus therapeutic (delayed) neck dissection, Outcome 3 New disease, progression or mortality (HR for disease-free survival).



Analysis 1.4. Comparison 1 Elective neck dissection (ND) versus therapeutic (delayed) neck dissection, Outcome 4 New disease, progression or mortality.



Analysis 1.5. Comparison 1 Elective neck dissection (ND) versus therapeutic (delayed) neck dissection, Outcome 5 Locoregional recurrence.



Comparison 2. Radical neck dissection (ND) versus selective neck dissection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total mortality (HR for overall survival)	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 vs selective neck dissection	1		Hazard Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]
2 New disease, progression or mortality (HR for disease-free survival)	1		Hazard Ratio (Fixed, 95% CI)	Totals not selected
2.1 Radical neck dissection vs selective neck dissection	1		Hazard Ratio (Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Recurrence	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Resection + elective supraomohyoid dissection vs resection alone (5 years)	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Radical neck dissection (ND) versus selective neck dissection, Outcome 1 Total mortality (HR for overall survival).

Study or subgroup	Radical ND N	Selective ND N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
2.1.1 Modified radical classical neck dissection (MRND) vs supraomohyoid neck dissection (SOH)					
BHNCSG 1998	72	76	0.1 (0.25)		1.14[0.7,1.86]
2.1.2 Radical neck dissection vs selective neck dissection					
Bier 1994	48	56	-0.1 (0.38)		0.87[0.41,1.83]

Favours radical ND — Favours selective ND

Analysis 2.2. Comparison 2 Radical neck dissection (ND) versus selective neck dissection, Outcome 2 New disease, progression or mortality (HR for disease-free survival).

Study or subgroup	Radical ND N	Selective ND N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
2.2.1 Radical neck dissection vs selective neck dissection					
Bier 1994	48	56	-0.6 (0.34)		0.57[0.29,1.11]

Favours radical ND — Favours selective ND

Analysis 2.3. Comparison 2 Radical neck dissection (ND) versus selective neck dissection, Outcome 3 Recurrence.

Study or subgroup	Radical ND n/N	Selective ND n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.3.1 Resection + elective supraomohyoid dissection vs resection alone (5 years)				
BHNCSG 1998	16/72	13/71		1.21[0.63,2.33]

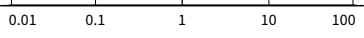
Favours radical ND — Favours selective ND

Comparison 3. Surgery plus radiotherapy (RT) versus radiotherapy alone

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

Analysis 3.1. Comparison 3 Surgery plus radiotherapy (RT) versus radiotherapy alone, Outcome 1 Total mortality (HR for overall survival).

Study or subgroup	Surgery + RT N	RT alone N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Fixed, 95% CI	Hazard Ratio IV, Fixed, 95% CI
Robertson 1998	0	0	-1.4 (0.456)		0.24[0.1,0.59]



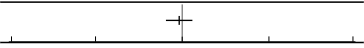
Favours surgery + RT | Favours RT alone

Comparison 4. Positron-emission tomography-computed tomography (PET-CT) versus planned neck dissection

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

Analysis 4.1. Comparison 4 Positron-emission tomography-computed tomography (PET-CT) versus planned neck dissection, Outcome 1 Total mortality (HR for overall survival).

Study or subgroup	PET-CT N	Planned neck dissection N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
Mehanna 2017	0	0	-0.1 (0.18)		0.92[0.65,1.31]



Favours PET-CT | Favours planned ND

ADDITIONAL TABLES

Table 1. Stage of cancer

Study	TNM stage	Nodal status
BHNCSG 1998	T2 to T4	Negative neck
Bier 1994	NS	Negative or positive neck
D'Cruz 2015	T1 or T2	Negative neck
Fakih 1989	T1 or T2	Negative neck

Table 1. Stage of cancer *(Continued)*

Guo 2014	T1–T4	Negative or positive neck
Iyer 2015	T3 or T4	Negative or positive neck
Kligerman 1994	T1 or T2	Negative neck
Mehanna 2017	T1–T4	N2 or N3
Rastogi 2018	T1–T3	Negative neck
Robertson 1998	T2–T4	N0 to N2
Vandenbrouck 1980	T1–T3	Negative neck
Yuen 2009	T1 or T2	Negative neck

NS: not stated.

APPENDICES

Appendix 1. Cochrane Oral Health's Trials Register search strategy

1 MESH DESCRIPTOR Head and Neck Neoplasms AND INREGISTER
2 MESH DESCRIPTOR Mouth Neoplasms AND INREGISTER
3 MESH DESCRIPTOR Gingival Neoplasms AND INREGISTER
4 MESH DESCRIPTOR Palatal Neoplasms AND INREGISTER
5 MESH DESCRIPTOR Tongue Neoplasms AND INREGISTER
6 ((cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*) AND (oral* or intra-oral* or intraoral* or "intra oral*" or gingiva* or oropharyn* or mouth* or tongue* or cheek* or gum* or palatal* or palate* or "head and neck")) AND INREGISTER
7 #1 or #2 or #3 or #4 or #5 or #6
8 MESH DESCRIPTOR Surgical Procedures, Operative EXPLODE ALL AND INREGISTER
9 (surgery or surgical or operat*):ti,ab AND INREGISTER
10 (dissect* NEAR2 neck*):ti,ab AND INREGISTER
11 (excision or excise or resect*):ti,ab AND INREGISTER
12 MESH DESCRIPTOR Lymph Node Excision EXPLODE ALL AND INREGISTER
13 MESH DESCRIPTOR Oral Surgical Procedures AND INREGISTER
14 (lymphadenectom* or glossectom* or maxillectom* or micrographic or mandibulectom* or hemi-mandibulectom* or hemimandibulectom*):ti,ab AND INREGISTER
15 #8 or #9 or #10 or #11 or #12 or #13 or #14
16 #7 and #15

Appendix 2. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

1. MESH DESCRIPTOR Head and Neck Neoplasms AND CENTRAL:TARGET
2. MESH DESCRIPTOR Mouth Neoplasms AND CENTRAL:TARGET
3. MESH DESCRIPTOR Gingival Neoplasms AND CENTRAL:TARGET
4. MESH DESCRIPTOR Palatal Neoplasms AND CENTRAL:TARGET
5. MESH DESCRIPTOR Tongue Neoplasms AND CENTRAL:TARGET
6. ((cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*) AND (oral* or intra-oral* or intraoral* or "intra oral*" or gingiva* or oropharyn* or mouth* or tongue* or cheek* or gum* or palatal* or palate* or "head and neck")) AND CENTRAL:TARGET
7. #1 or #2 or #3 or #4 or #5 or #6
8. MESH DESCRIPTOR Surgical Procedures, Operative EXPLODE ALL AND CENTRAL:TARGET
9. (surgery or surgical or operat*):ti,ab AND CENTRAL:TARGET
10. (dissect* NEAR2 neck*):ti,ab AND CENTRAL:TARGET
11. (excision or excise or resect*):ti,ab AND CENTRAL:TARGET

12. MESH DESCRIPTOR Lymph Node Excision EXPLODE ALL AND CENTRAL:TARGET
13. MESH DESCRIPTOR Oral Surgical Procedures AND CENTRAL:TARGET
14. (lymphadenectom* or glossectom* or maxillectom* or micrographic or mandibulectom* or hemi-mandibulectom* or hemimandibulectom*):ti,ab AND CENTRAL:TARGET
15. #8 or #9 or #10 or #11 or #12 or #13 or #14
16. #7 and #15

Appendix 3. MEDLINE Ovid search strategy

1 "Head and neck neoplasms"/
2 "Mouth neoplasms"/
3 "Gingival neoplasms"/
4 "Palatal neoplasms"/
5 "Tongue neoplasms"/
6 ((cancer$ or tumour$ or tumor$ or neoplas$ or malignan$ or carcinoma$ or metatasta$) adj5 (oral$ or intra-oral$ or intraoral$ or "intra oral$" or gingiva$ or oropharyn$ or mouth$ or tongue$ or cheek$ or gum$ or palatal$ or palate$ or "head and neck")).mp.
7 or/1-6
8 exp Surgical procedures, operative/
9 (surgery or surgical or operat$).mp.
10 (dissect$ adj2 neck$).mp.
11 (excision or excise or resect$).mp.
12 exp Lymph node excision/
13 Oral surgical procedures/
14 (lymphadenectom$ or glossectom$ or maxillectom$ or micrographic or mandibulectom$ or hemi-mandibulectom$ or hemimandibulectom$).ti,ab.
15 or/8-14
16 7 and 15

This subject search was linked to the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 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) (Lefebvre 2011).

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

Appendix 4. Embase Ovid search strategy

1. "Head and neck tumor"/
2. "Mouth tumor"/
3. "Gingiva tumor"/
4. "Jaw tumor"/
5. "Tongue tumor"/
6. ((cancer$ or tumour$ or tumor$ or neoplas$ or malignan$ or carcinoma$ or metatasta$) adj5 (oral$ or intra-oral$ or intraoral$ or "intra oral$" or gingiva$ or oropharyn$ or mouth$ or tongue$ or cheek$ or gum$ or palatal$ or palate$ or "head and neck")).ti,ab.
7. or/1-6
8. exp Oral surgery/
9. (surgery or surgical or operat$).ti,ab.
10. (dissect$ adj2 neck$).ti,ab.
11. (excision or excise or resect$).ti,ab.
12. "Lymph node dissection"/
13. (lymphadenectom$ or glossectom$ or maxillectom$ or micrographic or mandibulectom$ or hemi-mandibulectom$ or hemimandibulectom$).ti,ab.
14. or/8-13

15. 7 and 14

The above subject search was linked to adapted version of the Cochrane Embase Project filter for identifying RCTs in Embase Ovid (see www.cochranelibrary.com/help/central-creation-details.html for information):

1. Randomized controlled trial/
2. Controlled clinical study/
3. Random$.ti,ab.
4. randomization/
5. intermethod comparison/
6. placebo.ti,ab.
7. (compare or compared or comparison).ti.
8. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.
9. (open adj label).ti,ab.
10. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
11. double blind procedure/
12. parallel group$1.ti,ab.
13. (crossover or cross over).ti,ab.
14. ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant $1)).ti,ab.
15. (assigned or allocated).ti,ab.
16. (controlled adj7 (study or design or trial)).ti,ab.
17. (volunteer or volunteers).ti,ab.
18. trial.ti.
19. or/1-18
20. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
21. 19 not 20

Appendix 5. US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov) search strategy

Advanced search: “oral cancer” AND surgery

Limited to interventional studies

Appendix 6. World Health Organization International Clinical Trials Registry Platform search strategy

Advanced search: oral cancer

WHAT'S NEW

Date	Event	Description
4 December 2018	New citation required and conclusions have changed	Conclusions for comparisons already included remain the same, and have low- to very low-certainty evidence, but new comparisons have been added.
20 December 2017	New search has been performed	Search updated and five new studies included. New comparisons added. New lead author and byline.

HISTORY

Protocol first published: Issue 4, 2006
Review first published: Issue 4, 2007

Date	Event	Description
4 July 2011	New search has been performed	Searches updated to 17 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.
28 April 2009	Amended	Minor changes to the data.
20 June 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

- VB and HW co-ordinated and managed the review update.
- The trials search strategy was refined with input from VB. (It was designed by Cochrane Oral Health Information Specialist Anne Littlewood.)
- HW, VB, AMG, DC and MM screened the titles and abstracts.
- HW organised retrieval of papers.
- HW and VB screened retrieved papers against the inclusion criteria.
- VB, HW and AMG extracted data, appraised the risk of bias in the included studies, and assessed the certainty of the body of evidence for each main comparison and outcome.
- HW and AMG provided a methodological perspective.
- DC, MM and JC provided a clinical perspective.

DECLARATIONS OF INTEREST

VB: none known.
HW: none known. I am a Co-ordinating Editor of Cochrane Oral Health.
AMG: none known. I am Deputy Co-ordinating Editor of Cochrane Oral Health.
JC: none known. I am a Co-ordinating Editor of Cochrane Oral Health.
DC: none known.
MM: none known.

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- Cochrane Oral Health Global Alliance, Other.

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This section includes changes that have been made since the previous iterations of the review as well as from protocol.

Types of interventions: the intervention under evaluation must have been surgery. We excluded trials where all participants received the same surgical regimen and were randomised to other treatments.

Outcomes: local regional control was renamed as locoregional recurrence.

Search methods: the search strategy was updated.

It was considered more appropriate to use random-effect models for any pooling of studies.

The original quality assessment approach was replaced by use of the Cochrane 'Risk of bias' tool (Higgins 2011).

We updated the data synthesis section. The primary outcome that was most reliably and frequently reported was total mortality expressed as a hazard ratio. For dichotomous outcomes, we expressed the estimates of effect of an intervention as RRs with 95% confidence intervals. Dichotomous data were only used for primary outcomes where hazard ratios were unavailable or could not be calculated.

We performed no subgroup analyses for this update.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans