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Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy (Review)

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[Intervention Review]

Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy

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ABSTRACT

Background

Oral cavity and oropharyngeal cancers are the most common cancers arising in the head and neck. Treatment of oral cavity cancer is generally surgery followed by radiotherapy, whereas oropharyngeal cancers, which are more likely to be advanced at the time of diagnosis, are managed with radiotherapy or chemoradiation. Surgery for oral cancers can be disfiguring and both surgery and radiotherapy have significant functional side effects. The development of new chemotherapy agents, new combinations of agents and changes in the relative timing of surgery, radiotherapy, and chemotherapy treatments may potentially bring about increases in both survival and quality of life for this group of patients. This review updates one last published in 2011.

Objectives

To determine whether chemotherapy, in addition to radiotherapy and/or surgery for oral cavity and oropharyngeal squamous cell carcinoma results in improved overall survival, improved disease-free survival and/or improved locoregional control, when incorporated as either induction therapy given prior to locoregional treatment (i.e. radiotherapy or surgery), concurrent with radiotherapy or in the adjuvant (i.e. after locoregional treatment with radiotherapy or surgery) setting.

Search methods

An information specialist searched 4 bibliographic databases up to 15 September 2021 and used additional search methods to identify published, unpublished and ongoing studies.

Selection criteria

We included randomised controlled trials (RCTs) where more than 50% of participants had primary tumours in the oral cavity or oropharynx, and that evaluated the addition of chemotherapy to other treatments such as radiotherapy and/or surgery, or compared two or more chemotherapy regimens or modes of administration.

Data collection and analysis

For this update, we assessed the new included trials for their risk of bias and at least two authors extracted data from them. Our primary outcome was overall survival (time to death from any cause). Secondary outcomes were disease-free survival (time to disease recurrence or death from any cause) and locoregional control (response to primary treatment).

We contacted trial authors for additional information or clarification when necessary.

Main results

We included 100 studies with 18,813 participants. None of the included trials were at low risk of bias.

For induction chemotherapy, we reported the results for contemporary regimens that will be of interest to clinicians and people being treated for oral cavity and oropharyngeal cancers. Overall, there is insufficient evidence to clearly demonstrate a survival benefit from induction chemotherapy with platinum plus 5-fluorouracil prior to radiotherapy (hazard ratio (HR) for death 0.85, 95% confidence interval (CI) 0.70 to 1.04, P = 0.11; 7427 participants, 5 studies; moderate-certainty evidence), prior to surgery (HR for death 1.06, 95% CI 0.71 to 1.60, P = 0.77; 198 participants, 1 study; low-certainty evidence) or prior to concurrent chemoradiation (CRT) with cisplatin (HR for death 0.71, 95% CI 0.37 to 1.35, P = 0.30; 389 participants, 2 studies; low-certainty evidence). There is insufficient evidence to support the use of an induction chemotherapy regimen with cisplatin plus 5-fluorouracil plus docetaxel prior to CRT with cisplatin (HR for death 1.08, 95% CI 0.80 to 1.44, P = 0.63; 760 participants, 3 studies; low-certainty evidence).

There is insufficient evidence to support the use of adjuvant chemotherapy over observation only following surgery (HR for death 0.95, 95% CI 0.73 to 1.22, P = 0.67; 353 participants, 5 studies; moderate-certainty evidence). Among studies that compared post-surgical adjuvant CRT, as compared to post-surgical RT, adjuvant CRT showed a survival benefit (HR 0.84, 95% CI 0.72 to 0.98, P = 0.03; 1097 participants, 4 studies; moderate-certainty evidence).

Primary treatment with CRT, as compared to radiotherapy alone, was associated with a reduction in the risk of death (HR for death 0.74, 95% CI 0.67 to 0.83, P < 0.00001; 2852 participants, 24 studies; moderate-certainty evidence).

Authors' conclusions

The results of this review demonstrate that chemotherapy in the curative-intent treatment of oral cavity and oropharyngeal cancers only seems to be of benefit when used in specific circumstances together with locoregional treatment. The evidence does not show a clear survival benefit from the use of induction chemotherapy prior to radiotherapy, surgery or CRT. Adjuvant CRT reduces the risk of death by 16%, as compared to radiotherapy alone. Concurrent chemoradiation as compared to radiation alone is associated with a greater than 20% improvement in overall survival; however, additional research is required to inform how the specific chemotherapy regimen may influence this benefit.

PLAIN LANGUAGE SUMMARY

Chemotherapy for mouth and throat cancer

What is the problem?

Oral cavity (mouth) and oropharynx (throat) cancers that are detected early are treated primarily with surgery or radiotherapy. These treatments are effective in curing the cancer and improving survival. However, with surgery and radiotherapy alone there remains a chance that the cancer will recur, which can shorten survival for patients. The addition of chemotherapy to surgery or radiotherapy may help improve survival.

Why is this topic important?

Chemotherapy treatments are drugs that work by killing rapidly dividing cells such as cancer cells. There are other rapidly dividing cells in our body, such as those on our skin or in our gut. Chemotherapy can affect these healthy cells as well, which is why these treatments can have unpleasant side effects.

In the treatment of cancer, chemotherapy can be given before surgery or radiotherapy, during radiotherapy or after treatment with surgery or radiotherapy. There are also different types of chemotherapy that can be given either as pills or through the veins (intravenously). These differences in the ways of giving chemotherapy and types of chemotherapy are likely to have different effects on survival. At this time, we do not know which way is best.

This review updates one previously published in 2011.

What did we want to find out?

We wanted to know if chemotherapy given with either surgery or radiotherapy improved survival. We also wanted to know if chemotherapy given with surgery or radiotherapy improved the likelihood of shrinking the cancer and if these treatments reduced the risk of the cancer coming back (recurrence).

What did we do?

We searched several electronic databases for studies that evaluated the addition of chemotherapy before, during or after either radiotherapy or surgery in adult (age ≥ 18 years) patients with cancers of the oral cavity or oropharynx.

We categorised studies into four groups and combined results within each category. We assessed the reliability of the evidence we found.

What studies did we find?

We found 100 studies that assessed the use of chemotherapy with surgery or radiotherapy. In total, over 18,000 patients from all over the world were included. Thirty-six studies evaluated the use of chemotherapy before surgery or radiotherapy; 11 studies evaluated the use of chemotherapy after surgery or radiotherapy; 30 studies evaluated the use of chemotherapy together with radiotherapy; and 23 studies assessed different chemotherapy drugs given before, during or after surgery or radiotherapy.

What were the main results?

We found no clear evidence that chemotherapy given before surgery or radiotherapy improved survival. Similarly, chemotherapy given after surgery did not seem to lead to an improvement in survival.

We found treatment with radiotherapy and chemotherapy together after surgery, as compared to radiotherapy alone following surgery, may increase the likelihood of survival. Also, in patients who are not eligible for surgery, it may improve survival if chemotherapy is added to radiotherapy, as compared to radiotherapy treatment alone. There was not enough evidence to judge which chemotherapy drug is best to use.

How reliable are the results?

There were differences among the included studies in the type and number of participants they included, as well as the type of chemotherapy drug administered. These differences may impact the results. As such, we cannot be certain about these results and future research could change our conclusions.

What does this mean?

These results support the addition of chemotherapy together with radiotherapy in patients who have undergone surgery for cancers of the oral cavity or oropharynx. In patients who are not eligible for surgery, our results support the use of chemotherapy with radiotherapy as compared to radiotherapy alone.

We conclude that there is insufficient evidence to support the use of chemotherapy outside of these situations. We believe this highlights the need for further study into the use of chemotherapy together with surgery or radiotherapy.

How up-to-date is this review?

This review has been updated to September 2021.

Summary of findings 1. Induction chemotherapy plus locoregional treatment compared to locoregional treatment alone for the treatment of oral cavity and oropharyngeal cancer: chemotherapy

Induction chemotherapy plus locoregional treatment compared to locoregional treatment alone for the treatment of oral cavity and oropharyngeal cancer: chemotherapy

Population: people receiving treatment for oral cavity and oropharyngeal cancer
Setting: curative intent treatment
Intervention: induction chemotherapy plus locoregional treatment
Comparison: locoregional treatment alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk of death with locoregional treatment alone	Risk of death with induction chemotherapy plus locoregional treatment				
Overall survival - platinum + 5-FU + RT vs. RT	Low		HR 0.85 (0.70 to 1.04)	7427 (5 RCTs)	⊕⊕⊕⊖ MODERATE [1]	
	200 per 1000	173 per 1000 (145 to 207)				
	Moderate					
	500 per 1000	445 per 1000 (384 to 514)				
	High					
	700 per 1000	641 per 1000 (569 to 714)				
Overall survival - platinum + 5-FU + surgery vs. surgery	Low		HR 1.06 (0.71 to 1.60)	198 (1 RCT)	⊕⊕⊖⊖ LOW [2]	
	200 per 1000	211 per 1000 (147 to 300)				
	Moderate					
	500 per 1000	520 per 1000 (389 to 670)				

	High				
	700 per 1000	721 per 1000 (575 to 854)			
Overall survival - cisplatin + 5-FU + docetaxel + CRT (cisplatin) vs. CRT (cisplatin)	Low		HR 1.08 (0.80 to 1.44)	760 (3 RCTs)	⊕⊕⊖⊖ LOW [3,4]
	200 per 1000	214 per 1000 (163 to 275)			
	Moderate				
	500 per 1000	527 per 1000 (426 to 631)			
	High				
	700 per 1000	728 per 1000 (618 to 823)			
Overall survival - cisplatin + 5-FU + CRT (cisplatin) vs. CRT (cisplatin)	Low		HR 0.71 (0.37 to 1.35)	389 (2 RCTs)	⊕⊕⊖⊖ LOW [3,4]
	200 per 1000	147 per 1000 (79 to 275)			
	Moderate				
	500 per 1000	389 per 1000 (226 to 631)			
	High				
	700 per 1000	575 per 1000 (359 to 823)			

*__The risk in the intervention group__ (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); assumed risk based on 5-year survival data (McGurk 2005).
CI: confidence interval; **RR:** risk ratio; **OR:** odds ratio; **Platinum:** either cisplatin or carboplatin

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Downgraded once due to heterogeneity in patient characteristics in the included trials
[2] Downgraded twice due to imprecision in effect
[3] Downgraded once due to imprecision in effect
[4] Downgraded once due to inconsistency in results

Summary of findings 2. Surgery + adjuvant treatment A compared to surgery + adjuvant treatment B for the treatment of oral cavity and oropharyngeal cancer: chemotherapy

Surgery + adjuvant treatment A compared to surgery + adjuvant treatment B for the treatment of oral cavity and oropharyngeal cancer: chemotherapy

Population: people receiving treatment for oral cavity and oropharyngeal cancer
Setting: curative intent treatment
Intervention: surgery + adjuvant treatment A
Comparison: surgery +/- adjuvant treatment B

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk of death with surgery + adjuvant treatment B	Risk of death with surgery + adjuvant treatment A				
Overall survival - adjuvant chemotherapy vs. observation alone	Low		HR 0.95 (0.73 to 1.22)	353 (5 RCTs)	⊕⊕⊕⊖ MODERATE [1]	
	200 per 1000	191 per 1000 (150 to 238)				
	Moderate					
	500 per 1000	482 per 1000 (397 to 571)				
	High					
	700 per 1,000	681 per 1,000 (585 to 770)				
Overall survival - adjuvant CRT vs. adjuvant RT	Low		HR 0.84 (0.72 to 0.98)	1097 (4 RCTs)	⊕⊕⊕⊖ MODERATE [2]	
	200 per 1000	171 per 1000 (148 to 196)				

Moderate	
500 per 1000	441 per 1000 (393 to 493)
High	
700 per 1000	636 per 1000 (580 to 693)

*__The risk in the intervention group__ (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); assumed risk based on 5-year survival data (McGurk 2005).
CI: confidence interval; **RR:** risk ratio; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Downgraded once due to imprecision in effect estimate
[2] Downgraded once due to heterogeneity of uncertain significance in patient characteristics in one of the included trials

Summary of findings 3. Concomitant chemoradiotherapy compared to radiotherapy alone (non-resectable) for the treatment of oral cavity and oropharyngeal cancer: chemotherapy

Concomitant chemoradiotherapy compared to radiotherapy alone (non-resectable) for the treatment of oral cavity and oropharyngeal cancer: chemotherapy

Population: people receiving treatment for oral cavity and oropharyngeal cancer
Setting: curative intent treatment
Intervention: concomitant chemoradiotherapy
Comparison: radiotherapy alone (non-resectable)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk of death with radiotherapy alone (non-resectable)	Risk of death with concomitant chemoradiotherapy				
Overall survival - CRT vs. RT	Low		HR 0.74 (0.67 to 0.83)	2852 (24 RCTs)	⊕⊕⊕⊖ MODERATE [1]	
	200 per 1000	156 per 1000				

	(143 to 169)
Moderate	
500 per 1000	410 per 1000 (380 to 437)
High	
700 per 1000	599 per 1000 (564 to 632)

*__The risk in the intervention group__ (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); assumed risk based on 5-year survival data (McGurk 2005).
CI: confidence interval; **RR:** risk ratio; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Downgraded once due to considerable heterogeneity among included trials (radiation therapy scheduled varied across included studies)

BACKGROUND

Description of the condition

Oral cancers are a significant disease group globally, with more than 200,000 new cases worldwide in 2012 (Shield 2017). Oral cancers are the 16th most common cancer worldwide, accounting for an estimated 2% of all cancers (Global Burden of Disease Cancer Collaboration 2018). The incidence and mortality from oral cancers varies geographically; the highest age standardised rates of oral cancers are reported in south central Asia (Sri Lanka, Pakistan, Banglasdesh and India) (Parkin 2005; Shield 2017). There is overwhelming evidence that tobacco use, alcohol consumption and betel quid chewing are the main risk factors in the aetiology of intraoral cancer (Anantharaman 2011; La Vecchia 1997; Macfarlane 1995). There is also strong evidence that low socioeconomic status is associated with a higher incidence and poorer survival of oral cancers (Conway 2008; Conway 2014). There is higher incidence of oral cancers in men (Freedman 2007) that is generally attributed to a greater exposure to the known risk factors. The vast majority of cases occur in men over 50 years (Warnakulasuriya 2009) and among low socioeconomic groups (Conway 2008; Conway 2014). However, the ratio of males to females diagnosed with oral cancers has declined from approximately 5:1 in the 1960s to less than 2:1 in 2002 (Parkin 2005). Another identified trend is the increasing incidence of oral cavity and oropharyngeal cancers in younger adults in the European Union and the United States (Warnakulasuriya 2009).

The epidemiological data concerning 'oral cancer' obscures the fact that 'oral cancer' includes both oral cavity and oropharyngeal cancers, which have clinically different aetiology, are generally diagnosed at different stages, and are managed in different ways. People with oral cavity cancers generally present with early stage disease and the primary treatment is surgery or radiotherapy. In contrast, oropharyngeal cancers are likely to be advanced at the time of diagnosis and primary treatment is more likely to be radiation therapy or chemoradiation. It is now recognised that oral infection with human papilloma virus (HPV) is strongly associated with the development of oropharyngeal cancer, as HPV infection is found in 40% to 60% of patients diagnosed with cancers of the oropharynx (D'Souza 2007; Hammarstedt 2006). The link between oncogenic HPV and oropharyngeal cancer is strong and has been documented in numerous studies, fulfilling the epidemiological criteria for disease causality, especially in the development of oropharyngeal cancer in non-smokers (Sturgis 2007). The proportion of patients with oropharyngeal cancer who are HPV positive has increased dramatically over the past decade (Attner 2010; Ryerson 2008). However, this group of patients has significantly improved rates of both overall survival, with two-year survival rates of approximately 95%, as compared to oropharyngeal cancers which are HPV negative, with two-year survival rates of approximately 62% (Fakhry 2006; Fakhry 2008; Licitra 2006).

The most common cancer of the oral cavity is squamous cell carcinoma that arises from the mucosal surface of the oral cavity. Over 95% of all oral cavity cancers are squamous cell carcinomas. Advances in treatments have led to an improvement in survival outcomes over the past three decades (Cheraghlou 2018) but, despite significant technical advances, oral cancer still has a significant mortality rate, with over 140,000 deaths recorded, representing nearly half of the incident cases (48%) (Gupta 2016; Parkin 2001).

Description of the intervention

The primary treatment modality for oral cavity cancer and oropharyngeal cancers is either surgery or radiation. Surgery can have substantial functional side effects, with impairments in the ability to eat, drink and talk (Kolokythas 2010). As a consequence, there has been considerable research into non-surgical treatment modalities such as radiotherapy with or without concurrent chemotherapy.

Chemotherapy is the administration of anticancer or 'cytotoxic' drugs. These drugs work by attacking rapidly-dividing cancer cells, disrupting the growth of cancer cells and destroying them. The drugs used in chemotherapy affect the life cycle of the cancer cells. Different types of chemotherapeutic agents interrupt the life cycle of cancer cells at different stages; thus combining different agents into a chemotherapy regimen may be more effective in inducing cell death than single-agent chemotherapy. Similarly, combined modality treatment with the administration of concurrent chemotherapy alongside radiation therapy may act synergistically to promote tumour cell death through complementary activity on the cellular replication machinery (Mierzwa 2010). However, as well as increased benefits, combination chemotherapy may also be associated with increased toxicity, effects that may be exacerbated by the simultaneous use of radiotherapy.

How the intervention might work

Chemotherapy agents can be classified into groups according to their mode of action (Additional Table 1). Most chemotherapy drugs used in the treatment of oral cavity and oropharyngeal cancer are administered intravenously; however, other modes of systemic delivery, such as intra-arterial chemotherapy, have also been evaluated (Homma 2016). The timing of chemotherapy can also vary. It may be given as 'induction' therapy, with the intent to shrink a tumour prior to surgery or radiotherapy, concurrently with radiotherapy, as a 'radiosensitiser' to improve the efficacy of radiation therapy, or may be provided in the 'adjuvant' setting following surgery or radiotherapy (Pignon 2009). As a radiosensitiser, chemotherapy inhibits the repair of the DNA damage induced by radiation (Lawrence 2003). Surgery is used to remove the cancer through resection.

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 (Worthington 2015), and this review was identified as a priority title by the oral and maxillofacial surgery expert panel (Cochrane OHG priority review portfolio). Its selection as being especially important was confirmed at an updated priority setting process in 2020.

The management of advanced oral cavity and oropharyngeal cancers has traditionally relied on surgery and radiotherapy, both of which are associated with substantial adverse effects. Oropharyngeal cancers have relatively 'silent' symptoms that may not be present during the early stages of the disease, which may explain why the stage of disease at diagnosis has not altered in the past 40 years despite public education (McGurk 2005). Despite comprehensive treatment regimens, some patients never achieve disease-free status, others experience tumour recurrence and for some the late or long-term effects of treatment cause significant morbidity (Day 1992; Partridge 2000). Although the

primary treatment for oral cavity cancer and oropharyngeal tumours remains surgery and/or radiation therapy, there has been ongoing interest in the use of chemotherapy to reduce tumour volume, improve the efficacy of primary radiation treatment and help manage micrometastatic disease (i.e. non-visible cancer cells) following primary locoregional treatment. As such, the development of new chemotherapy agents, new combinations of agents, and changes in the relative timing of treatments should be studied to see if they can improve survival and quality of life.

This update of the Cochrane Review on chemotherapy for oral cancers attempts to answer the broad question 'Does treatment with chemotherapy, in addition to radiotherapy and/or surgery, improve the outcomes for patients with oral cavity and oropharyngeal cancers?'. It is part of a series of Cochrane reviews looking at the treatment modalities for oral cavity and oropharyngeal cancers categorised into four intervention groups: chemotherapy, surgery (Bulsara 2018), radiotherapy (Glenny 2010) as well as targeted therapy and immunotherapy (Chan 2015).

OBJECTIVES

Primary objective

To determine whether chemotherapy, in addition to radiotherapy and/or surgery for oral cavity and oropharyngeal cancer, results in improved overall survival when incorporated as induction therapy given prior to locoregional treatment (i.e. surgery and/or radiotherapy), concurrent with radiotherapy or in the adjuvant (i.e. after locoregional treatment) setting.

Secondary objective

To determine whether chemotherapy, in addition to radiotherapy and/or surgery for oral cavity and oropharyngeal cancer, results in improved disease-free survival and/or locoregional control when incorporated as induction therapy prior to locoregional treatment, concurrent with radiotherapy, or in the adjuvant setting.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) comparing chemotherapy treatment, with locoregional treatment (radiotherapy or surgery) +/- concurrent chemotherapy, or an alternative chemotherapy regimen, or chemotherapy given at different times relative to locoregional treatment (either induction, concurrent or adjuvant chemotherapy), with a minimum follow-up of six months.

Types of participants

We included trials involving participants with oral cancer as defined by the International Classification of Diseases for Oncology (ICD-O) codes as C01-C06 (oral cavity including mouth, tongue, gum, or palate), tonsil (ICD-O: C09) or oropharynx, (ICD-O: C10). We excluded trials where patients have cancer of the hypopharynx (ICD-O: C13), nasopharynx (ICD-O: C11), larynx (ICD-O: C32) or lip (ICD-O: C00) (WHO 1992). Clinical trials frequently recruit patients with any type of squamous cell carcinoma of the head and neck - i.e. primary tumours in oral cavity, oropharynx, hypopharynx or larynx. Where trials reported the results separately for the different primary tumour sites, we used data from the oral cavity and oropharynx. However, excluding trials of treatments for head and neck cancer, where data from all primary tumour sites are combined, loses a great deal of information; we therefore decided to include trials that involved patients with head and neck cancer, including cases of oral cavity and oropharyngeal cancer, provided data were available separately for those who had cancer of the oral cavity or oropharynx, or where those with oral cavity/oropharyngeal cancers made up more than 50% of trial participants.

Cancers were primary squamous cell carcinomas arising from the oral mucosa. Histological variants of squamous cell carcinomas were included (adenosquamous, verrucous, basaloid, papillary, etc). Although these histological variants are known to have different natural history to the majority of conventional squamous cell carcinomas, they have a common aetiology, their incidence is low, and they are generally managed in the same way. Oral carcinoma in situ (OCIS) is considered to be an early or incipient form of cancer that may, if left untreated long enough, transform into invasive squamous cell cancer. OCIS is usually treated with surgery alone. Accordingly, studies evaluating treatment for OCIS were excluded from this review. 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

Chemotherapy was defined as cytotoxic or antineoplastic drug(s) given by any mode of administration (oral, intravenous, intra-arterial, intramuscular or intratumoural) to patients with squamous cell cancer of the oral cavity or oropharynx, with the intent of killing or damaging cancer cells or preventing the development or spread of the cancer.

The following interventions were included in which participants were randomised to one of the following:

1. induction chemotherapy plus locoregional treatment versus locoregional treatment alone;
2. surgery followed by adjuvant treatment A versus surgery followed with or without adjuvant treatment B;
3. concurrent chemoradiotherapy versus radiotherapy alone;
4. chemotherapy A in combination with locoregional treatment versus chemotherapy B in combination with locoregional treatment

To be eligible, treatments received and compared must have been the primary treatment for the tumour and patients should not have received any prior intervention other than diagnostic biopsy, or surgery. Therefore, trials where participants presented with recurrent or metastatic disease were excluded.

Trials where all participants received the same chemotherapy regimen or were randomised to other treatments such as complementary or alternative medicines, a radiosensitiser (for example amifostine) and/or chemosensitiser treatments (for example, leucovorin or vitamins), in settings where these 'other treatments' were the intervention being compared (i.e. they were the only difference in intervention between the experimental and control groups) were excluded.

Trials of targeted therapies, or monoclonal antibodies, were excluded as these are evaluated in a separate review that evaluates immunotherapies and targeted therapies (Chan 2015).

Types of outcome measures

Primary outcomes

- Overall survival, defined as the time to death from any cause (or total mortality)

Secondary outcomes

- Disease-free survival, defined as the time to disease recurrence or death from any cause
- Locoregional control, defined as response to primary treatment

Search methods for identification of studies

Electronic searches

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

- Cochrane Oral Health's Trials Register (searched 15 September 2021) (Appendix 1);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 8) in the Cochrane Library (searched 15 September 2021 (Appendix 2);
- MEDLINE Ovid (1946 to 15 September 2021) (Appendix 3);
- Embase Ovid (1980 to 15 September 2021) (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 strategies designed by Cochrane for identifying randomised controlled trials and controlled clinical trials, as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, Version 6.1 (Lefebvre 2020).

Searching other resources

Cochrane Oral Health's information specialist searched the following trial registries for ongoing trials:

- US National Institutes of Health Trials Registry (ClinicalTrials.gov) (searched 15 September 2021) (Appendix 4);
- WHO International Clinical Trials Registry Platform (searched 15 September 2021) (Appendix 5).

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

We checked that none of the included studies in this review were retracted due to error or fraud.

This updated review is part of a series of Cochrane reviews on the treatment modalities for treating oral cavity and oropharyngeal cancer. The reviews have been broadly divided into four themes: surgery, chemotherapy, radiotherapy and immunotherapy/targeted therapies. The original search strategy was used for three cancer treatment reviews and so it encompassed all treatment modalities and combinations of treatment (see Appendix 6 for the original search strategies). For this update, a new search was run from December 2010, tailored to only address radiotherapy and chemotherapy treatments as interventions.

Data collection and analysis

Selection of studies

We used Cochrane's Screen4Me workflow to help assess the search results. Screen4Me comprises three components: known assessments – a service that matches records in the search results to records that have already been screened in Cochrane Crowd and been labelled as an RCT or as Not an RCT; the RCT classifier – a machine learning model that distinguishes RCTs from non-RCTs; and, if appropriate, Cochrane Crowd – Cochrane's citizen science platform where the Crowd help to identify and describe health evidence. For more information about Screen4Me and the evaluations that have been done, please go to the Screen4Me webpage on the Cochrane Information Specialists' Portal. The searches were run in December 2018, and updated in October 2019, September 2020 and September 2021. The search in December 2018 used all components of the Screen4Me workflow, but the updated searches used only the RCT Classifier and known assessments components.

The remaining titles and abstracts were scanned independently by two review authors for eligibility for the oral cancer reviews. 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. 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, the full report was obtained. The full reports obtained from all the electronic and other methods of searching were assessed independently by two review authors to establish whether the studies met the inclusion criteria or not. We excluded studies published only as abstracts. Disagreements were resolved by discussion. Where resolution was not possible, a third review author was consulted.

Data extraction and management

All studies meeting the inclusion criteria underwent a risk of bias assessment and data extraction using a specially designed comprehensive data extraction form. Studies rejected at this or subsequent stages were recorded in the Characteristics of excluded studies tables, and reasons for exclusion recorded.

As the majority of trials were for head and neck cancers, the proportion of oral/oropharyngeal cancer patients was recorded (Additional Table 2). In all trials where only combined head and neck data were presented, the authors were contacted to see if separate data for the oral cavity/oropharyngeal cancer patients could be made available. Head and neck cancer trials with only combined data (i.e. no outcome data available by primary tumour site) and where more than 50% of participants presented with oral/oropharyngeal cancer were included in this review. However, where separate 'pure' oral/oropharyngeal cancer data were available for a trial, these 'pure' data were extracted and analysed and the combined head and neck data ignored. Where possible, oral and oropharyngeal cancer data were also analysed separately.

Data were extracted by at least two review authors independently using a specially designed data extraction form. The data extraction form was piloted on several papers and modified before use.

Any disagreement was discussed and a third review author consulted where necessary. However, group discussion was often required following data extraction due to the complexity of the data presented. When necessary, authors were contacted for clarification or missing information.

For each trial, 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.

Assessment of risk of bias in included studies

For the studies included in this review, assessment of risk of bias was conducted by at least one review author using the Cochrane Risk of Bias assessment tool (Higgins 2009). We assessed eight domains for each included study: sequence generation, allocation concealment, blinding (of participant, carer, outcome assessor), completeness of outcome data, risk of selective outcome reporting, and risk of other potential sources of bias. An overall risk of bias assessment was also made. We judged a study as at overall low risk of bias if it was classified as low risk of bias across all domains (including other risk of bias), overall unclear risk of bias if the study was classified as unclear risk in at least one domain, and overall high risk of bias if the study was classified as high risk in at least one domain.

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

- Sequence generation: use of a random number table, use of a computerised system, central randomisation by statistical co-ordinating centre, randomisation by an independent service using minimisation technique, permuted block allocation or Zelan technique (i.e. randomisation prior to informed consent). If the paper merely stated 'randomised' or 'randomly allocated' with no further information, we assessed this as being unclear.
- Allocation concealment: centralised allocation including access by telephone call or fax, or pharmacy-controlled randomisation, sequentially numbered, sealed, opaque envelopes.
- Blinding: in most of the included studies, blinding of participants and clinical carers to treatment allocation was not done. Unless the trial was specifically described as double-blind, or there was a statement about blinding in the methods section of the paper, we assumed that blinding of participants, clinical staff and outcome assessors did not occur. Where a reasonable attempt to achieve blinding of outcome assessors was described, we judged the study to be at low risk of detection bias.
- 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 as being at low risk of bias due to incomplete outcome assessment. Where post-randomisation exclusions were greater than 10%, or reasons were not given for exclusions from each group, we assessed the risk of bias as unclear due to incomplete outcome data.
- Selective outcome reporting: we assessed a trial as being at low risk of bias due to selective outcome reporting if the outcomes of interest described in the methods and/or protocol, 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 high risk. Studies were assessed as being at unclear risk where there was insufficient information to assess full per-protocol outcome reporting.
- Other bias: this included the use of a co-intervention in only one group (for example nasogastric feeding) as an example of potential sources of other bias.

Measures of treatment effect

The primary outcome was overall survival, as measured by a hazard ratio for death. When hazard ratios were not quoted in studies, we calculated the log hazard ratio and standard error (SE) from available summary statistics (observed events, expected events, variance, confidence intervals, P values or Kaplan-Meier survival curves), according to the methods proposed by Parmar 1998, or we requested these data from trial authors. We have presented overall survival as log hazard ratios, either calculated from Kaplan-Meier graphs, or from data presented in the Pignon meta-analysis of chemotherapy in head and neck cancer (MACH-NC) (Pignon 2000 or Pignon 2009), where possible.

For dichotomous outcomes, we expressed the estimates of intervention effects as risk ratios (RRs) together with 95% confidence intervals (CIs). We analysed overall survival at a specific time point and disease-free survival in two ways depending on the data presented in study reports or obtained from trial authors.

Unit of analysis issues

The unit of analysis was the individual patient. We did not include trials that used cluster-randomisation, allowed for cross-over or used repeated measurements.

Dealing with missing data

We contacted trial authors to retrieve missing data when unavailable from the primary literature or when further clarification on trial conduct or data was required.

Assessment of heterogeneity

We assessed the significance of any discrepancies in the estimates of the treatment effects from the different trials by means of Cochran's test for heterogeneity as well as the I^2 statistic, and investigated any heterogeneity. We considered heterogeneity to be significant if the P value was less than 0.10 for the Chi^2 test.

Assessment of reporting biases

We conducted a comprehensive search of multiple databases without any language restriction. In addition, we performed a search of unpublished and ongoing trials to address publication bias.

Data synthesis

The included studies were grouped into four main comparisons:

1. induction chemotherapy plus locoregional treatment versus locoregional treatment alone;
2. surgery followed by adjuvant treatment A versus surgery followed by adjuvant treatment B;
3. concurrent chemoradiotherapy versus radiotherapy alone;
4. chemotherapy A in combination with locoregional treatment versus chemotherapy B in combination with locoregional treatment.

Some trials were deemed to meet the review's inclusion criteria but insufficient data were presented to enable these trials to be included in the 'Data and analyses' section. Providing these trials had used an appropriate statistical approach, they were included in the review and their salient findings summarised in the text of the 'Results' section of the review.

We conducted meta-analyses only if there were studies of similar comparisons reporting the same outcome measures. We combined risk ratios for dichotomous data, and hazard ratios for survival data where possible, using random-effects models. We used the inverse variance method to enter the data into the meta-analyses.

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 separately if possible. Investigation of clinical heterogeneity (to examine the types of participants, interventions and outcomes in each study) was planned but there were insufficient data.

We conducted subgroup analyses based upon the type of locoregional treatment that was evaluated (i.e. surgery, radiation therapy, concurrent chemoradiation).

Sensitivity analysis

We planned to perform sensitivity analyses by excluding studies with unclear or high risk of bias in settings where there was a sufficient number of studies included for meta-analysis. This was not possible as there were no low-risk studies.

Summary of findings and assessment of the certainty of the evidence

We developed a Summary of findings table for the primary outcome of overall survival for the three primary treatment comparisons of induction chemotherapy plus locoregional treatment versus locoregional treatment alone, surgery followed by adjuvant treatment A versus surgery followed by observation or adjuvant treatment B, and concurrent chemoradiotherapy versus radiotherapy alone. We did not create a summary of findings table for chemotherapy A in combination with locoregional treatment versus chemotherapy B in combination with locoregional treatment because of the heterogeneity in treatment comparisons. For the summary of findings table specific to the comparison of induction chemotherapy plus locoregional treatment versus locoregional treatment alone, we reported the results for contemporary chemotherapy regimens used as induction chemotherapy that may be of interest to treating clinicians and people being treated for oral cavity and oropharyngeal cancers. The summary of findings tables were developed using GRADE methods and GRADEPro software (GRADE 2013; GRADEPro2020). We assessed the certainty of the body of evidence by evaluating the overall risk of bias, directness of evidence, consistency of results, precision of the estimates, and risk of publication bias.

RESULTS

Description of studies

Results of the search

The search for this update identified a total of 16,256 search results from December 2010 to September 2021, which was reduced to 13,156 after duplicate records were removed. In assessing the studies, we used Cochrane's Screen4Me workflow to help identify potential reports of randomised trials. We then assessed the remaining 5044 records left in after Screen4Me. These were put into a bibliographic database and the titles and abstracts were screened against the inclusion criteria for this review. Full-text copies of papers that appeared to meet our inclusion criteria were obtained and from these, we identified 11 studies to be included in the update, four potential studies that await classification as they are abstracts only and three ongoing studies. In combination with the 89 trials included in the original review, we have a total of 100 included studies in this review (Figure 1).

Figure 1.

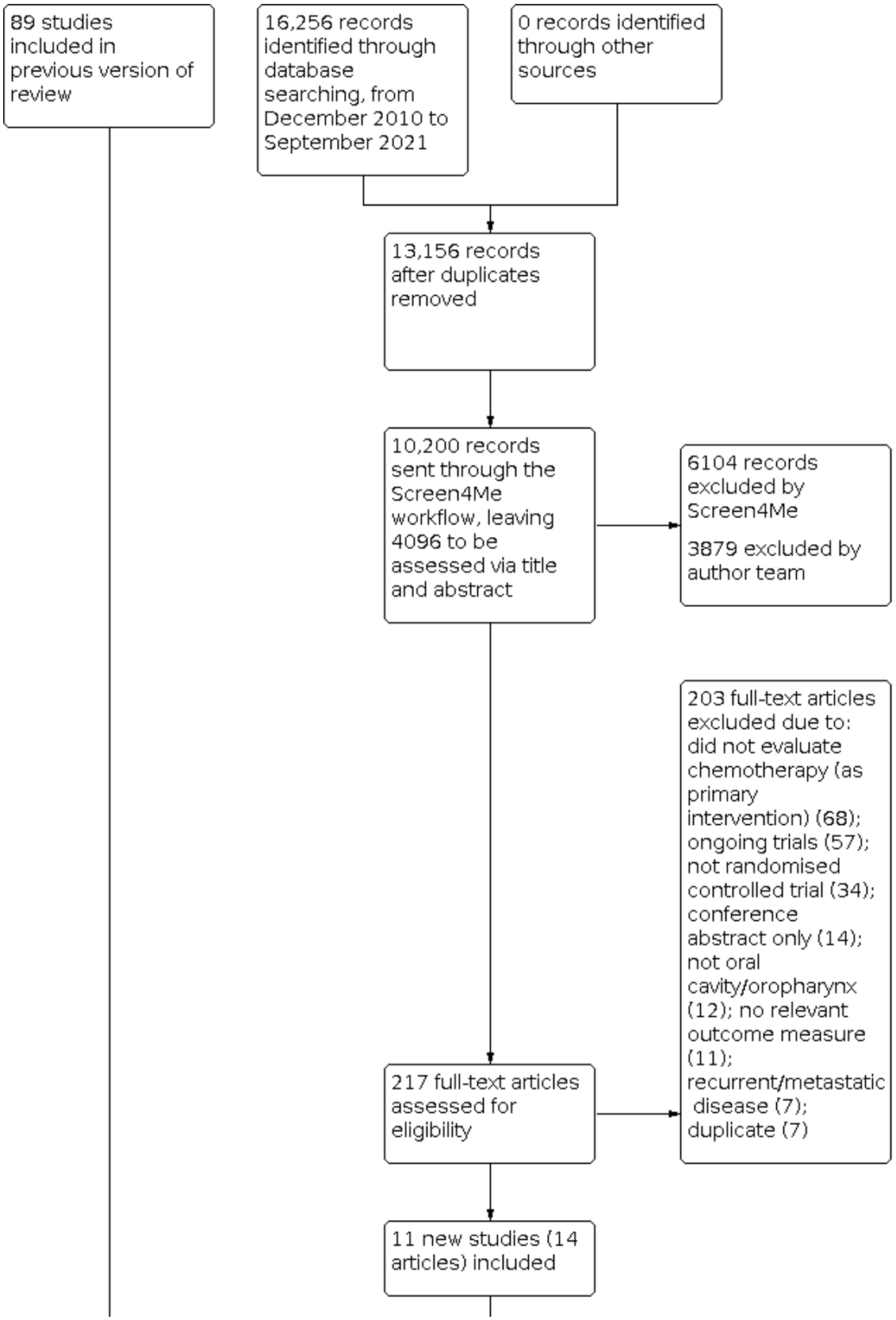
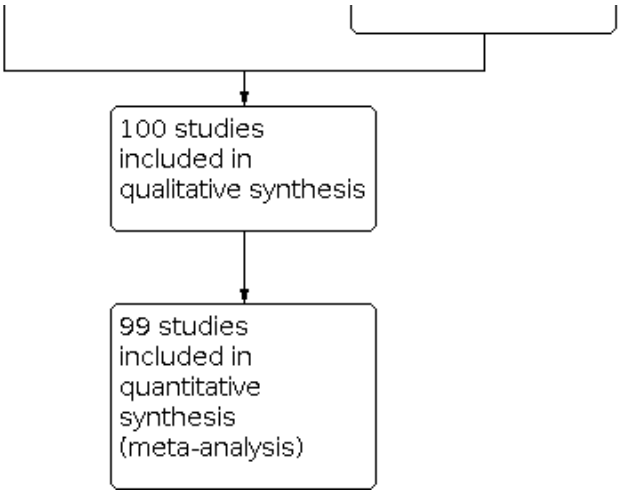


Figure 1. (Continued)



Location

Trials were undertaken all over the world, with 19 based in the USA, 15 in France, 13 in Italy, 6 in Germany, 11 in India, 5 in Spain, 2 each in Canada, UK, South America and Scandinavia, 1 trial in Russia, 1 trial in Australasia, 1 trial in Switzerland, 1 trial in Hungary, 3 conducted worldwide, 13 multicentre trials in Europe and 3 multicentre trials in Asia.

Participants

A total of 18,813 participants (2046 additional from the update) were randomly allocated to treatments and individual trials varied in size between 23 and 966 participants. Participants were recruited over periods ranging between one and 10 years, with the first study starting recruitment in 1965 (Richard 1974) and the most recent completing recruitment in 2017 (Noronha 2018).

Twenty-eight of the included studies from our 2011 review were included in a published meta-analysis produced by the MACH-NC Collaborative Group (Pignon 2000) and a further 13 included studies were included in a subsequent meta-analysis published by the same group (Pignon 2009). With the permission of these authors, we have used the published data for overall survival from these meta-analyses, because they are from individual patient data from the included trials (details of the data source for overall survival data are recorded in Additional Table 2, and in the Characteristics of included studies tables). For the remainder of the included trials, we have extracted data from the published papers, and sought clarification from the authors where necessary.

Only 23 of the included trials restricted inclusion to patients with oral cavity and oropharyngeal cancer. In the remainder, at least 50% of included participants had either oral cavity or oropharyngeal cancer (for details see Additional Table 2).

Interventions

The included studies had originally been divided into four comparison groups:

Comparison 1: induction chemotherapy plus locoregional treatment (LRT) versus LRT alone;
Comparison 2: surgery ± radiotherapy + chemotherapy versus surgery ± radiotherapy alone;
Comparison 3: concurrent chemoradiotherapy versus radiotherapy alone (non-resectable);
Comparison 4: chemotherapy A (± LRT) versus chemotherapy B (± LRT).

For this update, we restructured the comparison groups to better depict clinical treatment scenarios of interest. The comparisons have been classified as:

Comparison 1: induction chemotherapy plus locoregional treatment (LRT) versus LRT alone;
Comparison 2: surgery plus adjuvant treatment A versus surgery +/- adjuvant treatment B;
Comparison 3: concurrent chemoradiotherapy versus radiotherapy alone;
Comparison 4: chemotherapy A (+ LRT) versus chemotherapy B (+ LRT).

As part of the restructuring, slight modifications to study classification within each comparison group were made. These modifications are outlined within each comparison group below.

Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone

There were 36 RCTs included in this comparison (Adelstein 1993; Brunin 1989; Buffoli 1992; Cohen 2014; Depondt 1993; Domenge 2000; Fazekas 1980; Ghi 2017; Gupta 2009; Haddad 2013; Hitt 2014; Holoye 1985; Jaulerry 1992; Knowlton 1975; Kumar 1996; Lewin 1997; Licitra 2003; Luboinski 1985; Maipang 1995; Mazeron 1992; Merlano 1991 Mohr 1994; Nervi 1978; Paccagnella 1994; Paccagnella 2010; Pinnaro 1994; Petrovich 1981; Richard 1974; Richard 1991; Salvajoli 1992; Schuller 1988; Szabo 1999; Szpirglas 1988; Takasci-Nagy 2015; Tejedor 1992; Volling 1999). This included 14 re-classified trials from the primary review (12 included in the current comparison (Adelstein 1993; Buffoli 1992; Cohen 2014; Ghi 2017; Gupta 2009; Haddad 2013; Hitt 2014; Kumar 1996; Merlano 1991;Paccagnella 2010; Pinnaro 1994; Takasci-Nagy 2015)) and two trials that were removed from the current comparison (Giglio 1997; Olmi 2003) as these evaluated alternating chemotherapy with radiotherapy or concurrent chemoradiation, as compared

to radiotherapy, respectively). Each trial compared the addition of induction chemotherapy to locoregional treatment (either radiotherapy or surgery or both) with locoregional treatment alone.

Sixteen trials evaluated induction chemotherapy prior to locoregional treatment with radiotherapy (Brunin 1989; Depondt 1993; Domenge 2000; Fazekas 1980; Holoye 1985; Jaulerry 1992; Knowlton 1975; Lewin 1997; Mazeron 1992; Nervi 1978; Paccagnella 1994; Petrovich 1981; Richard 1974; Salvajoli 1992; Szpirglas 1988; Tejedor 1992). The most common induction chemotherapy regimen given prior to radiotherapy that was evaluated was platinum (either cisplatin or carboplatin) combined with 5-fluorouracil (Depondt 1993; Domenge 2000; Lewin 1997; Paccagnella 1994; Tejedor 1992), with one trial evaluating the platinum and 5-fluorouracil combination together with vindesine (Jaulerry 1992). Four trials evaluated induction methotrexate given either intravenously (Fazekas 1980; Knowlton 1975) or intra-arterially (Nervi 1978; Richard 1974). The remaining trials evaluated alternative induction chemotherapy regimens of multi-combination chemotherapies (Brunin 1989; Holoye 1985; Mazeron 1992; Petrovich 1981; Salvajoli 1992; Szpirglas 1988).

Seven trials evaluated induction chemotherapy prior to locoregional treatment with surgery (Licitra 2003; Luboinski 1985; Maipang 1995; Paccagnella 1994; Richard 1991; Schuller 1988; Volling 1999). Similar to the prior comparison, the most common induction chemotherapy regimen given prior to surgery that has been evaluated was platinum (either cisplatin or carboplatin) combined with 5-fluorouracil (Licitra 2003; Paccagnella 1994; Volling 1999). Intra-arterial chemotherapy prior to surgery was also evaluated in two trials (Luboinski 1985; Richard 1991). The remaining two trials evaluated alternative multi-chemotherapy induction regimens (Maipang 1995; Schuller 1988).

Induction chemotherapy prior to concurrent chemoradiation, as compared to chemoradiation alone, was evaluated in seven trials (Cohen 2014; Ghi 2017; Gupta 2009; Haddad 2013; Hitt 2014; Paccagnella 2010; Takasci-Nagy 2015), of which five were identified in the update (Cohen 2014; Ghi 2017; Haddad 2013; Hitt 2014; Takasci-Nagy 2015). This included three trials that evaluated combination cisplatin plus 5-fluorouracil plus docetaxel prior to concurrent chemoradiation with cisplatin (Ghi 2017; Hitt 2014; Takasci-Nagy 2015) and two trials that evaluated induction cisplatin plus 5-fluorouracil plus docetaxel prior to concurrent chemoradiation with carboplatin (Haddad 2013) and concurrent chemoradiation with cisplatin plus 5-fluorouracil (Paccagnella 2010). Two trials evaluated induction cisplatin plus 5-fluorouracil prior to concurrent chemoradiation with cisplatin (Gupta 2009; Hitt 2014). Induction chemotherapy with docetaxel plus 5-fluorouracil plus hydroxyurea prior to concurrent chemoradiation with the same chemotherapy regimen was evaluated in one trial (Cohen 2014).

The remaining trials in this comparison group examined outcomes associated with:

- Induction chemotherapy followed by radiotherapy, as compared to concurrent chemoradiation (Adelstein 1993; Pinnaro 1994)
- Induction chemotherapy followed by concurrent chemoradiation, as compared to radiotherapy (Kumar 1996)
- Induction chemotherapy followed by surgery, as compared to induction radiotherapy followed by surgery (Szabo 1999)
- Induction concurrent chemoradiation followed by surgery, as compared to surgery (Mohr 1994)
- Induction chemotherapy followed by radiotherapy as compared to alternating chemotherapy and radiotherapy (Buffoli 1992; Merlano 1991).

Comparison 2: Surgery + adjuvant treatment A versus surgery +/- adjuvant treatment B

There were 11 trials in this comparison (Argiris 2008; Bernier 2004; Bitter 1979; Cooper 2004; HNCProg 1987; Lam 2001; Laramore 1992; Rao 1994; Rentschler 1987; Szpirglas 1979; UKHAN 2010). All of the participants included in the trials in this comparison had surgical resection with curative intent. Following surgery, participants were randomised to either of:

- Chemotherapy versus observation (HNCProg 1987; Lam 2001; Rao 1994; Rentschler 1987; Szpirglas 1979)
- Chemotherapy versus radiotherapy (Bitter 1979)
- Chemotherapy followed by radiotherapy versus radiotherapy (Laramore 1992)
- Concurrent chemoradiation versus radiotherapy (Argiris 2008; Bernier 2004; Cooper 2004; Laramore 1992; UKHAN 2010)

Of studies that compared adjuvant chemotherapy versus observation only following surgery, two studies evaluated chemotherapy with methotrexate (Rao 1994; Rentschler 1987) and one study evaluated a combination chemotherapy regimen of methorexate, bleomycin and citrovorum (Szpirglas 1979). In two of these studies, induction chemotherapy was also included as part of the treatment regimen for the experimental arm (Lam 2001), as well as in both the experimental and control arm (HNCProg 1987).

In the study that evaluated adjuvant chemotherapy versus adjuvant radiotherapy, the chemotherapy was a combination regimen of methotrexate, bleomycin and vincristine (Bitter 1979).

Four studies evaluated adjuvant concurrent chemoradiation compared to adjuvant radiation alone (Argiris 2008; Bernier 2004; Cooper 2004; UKHAN 2010). Concurrent chemotherapy included methotrexate (UKHAN 2010), carboplatin (Argiris 2008) and cisplatin (Bernier 2004; Cooper 2004).

Comparison 3: Concurrent chemoradiotherapy versus radiotherapy

This category included 30 trials (Adelstein 2003; Bensadoun 2006; Brizel 1998; Browman 1994; Budach 2005; Chauhan 2008; Corvo 2001; Denis 2004; Dobrowsky 2000; Eschwege 1988; Giglio 1997; Grau 2003; Gupta 2001; Haddad 1996; Huguenin 2004; Jeremic 1997; Jeremic 2000; Krishnamurthi 1990; Merlano 1992; Morita 1980; Olmi 2003; Parvinen 1985; Ruo 2010; Salvajoli 1992; Shanta 1980; Smid 1995; Staar 2001; UKHAN 2010; Weissler 1992; Wendt 1998).

In this comparison, the trials were broadly categorised into those trials which included standard fractionation radiotherapy as the local therapy backbone and those that included altered fractionation radiotherapy as the local therapy backbone. For those trials that included standard fractionation, the trials were divided into:

- Concurrent chemoradiation with platinum (either cisplatin or carboplatin) chemotherapy, as compared to radiotherapy
- Concurrent chemoradiation with platinum plus 5-fluorouracil, as compared to radiotherapy
- Concurrent chemoradiation with non-platinum chemotherapy, as compared to radiotherapy

For those trials that included altered fractionation, the trials were divided into:

- Concurrent chemoradiation with platinum (either cisplatin or carboplatin) chemotherapy, as compared to radiotherapy
- Concurrent chemoradiation with platinum plus 5-fluorouracil, as compared to radiotherapy
- Concurrent chemoradiation with non-platinum chemotherapy, as compared to radiotherapy

This comparison also included those trials that evaluated alternating chemotherapy and radiotherapy, as compared to radiotherapy alone, as evaluated with standard fractionation radiotherapy (Merlano 1992) or altered fractionation radiotherapy (Corvo 2001; Giglio 1997).

In the trials included in this comparison, the oral cavity or oropharyngeal cancer had to be considered unresectable at the time of initial diagnosis. The two most common comparisons were concurrent chemoradiation with platinum (either cisplatin or carboplatin) and 5-fluorouracil together with standard fractionation radiotherapy, as compared to standard fractionation radiotherapy alone (Denis 2004; Haddad 1996; Weissler 1992; Wendt 1998) or concurrent chemoradiation with platinum (either cisplatin or carboplatin) and 5-fluorouracil with altered fractionation radiotherapy, as compared to altered fractionation radiotherapy alone (Bensadoun 2006; Brizel 1998; Staar 2001). One trial evaluated concurrent chemotherapy with cisplatin and bleomycin (Salvajoli 1992).

Three trials evaluated concurrent chemoradiation with platinum (either cisplatin or carboplatin), as compared to radiation alone, with different types and schedules of concurrent platinum administration including 3-weekly cisplatin (Adelstein 2003), daily cisplatin (Jeremic 1997) and daily carboplatin (Ruo 2010). In the two trials that included altered fractionation radiotherapy as the primarily local therapy, concurrent platinum administration evaluated included daily cisplatin (6 mg/m^2) (Jeremic 2000) and daily cisplatin (20 mg/m^2) administered for five consecutive days on week one and five of radiotherapy (Huguenin 2004).

Thirteen trials evaluated alternative non-platinum-containing concurrent chemotherapy regimens with standard fractionation radiotherapy (Browman 1994; Chauhan 2008; Eschwege 1988; Grau 2003; Gupta 2001; Krishnamurthi 1990; Morita 1980; Parvinen 1985; Shanta 1980; Smid 1995; UKHAN 2010) or with altered fractionation radiotherapy (Budach 2005; Dobrowsky 2000). Of these trials of non-platinum concurrent chemotherapy, bleomycin was the most common chemotherapy evaluated either as monotherapy (Eschwege 1988; Morita 1980; Parvinen 1985; Shanta 1980) or in combination with mitomycin C (Smid 1995). Other chemotherapy regimens evaluated included methotrexate (Gupta 2001; UKHAN 2010), mitomycin C (Grau 2003), gemcitabine (Chauhan 2008), peplomycin (Krishnamurthi 1990) and 5-fluorouracil (Browman 1994), with standard fractionation radiotherapy. Additional chemotherapy regimens evaluated with altered fractionation radiotherapy included mitomycin C (Dobrowsky 2000) and mitomycin C with 5-fluorouracil (Budach 2005).

Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)

This comparison included a total of 23 trials (Browman 1986; Chauvergne 1988; De Andres 1995; Garden 2004; Gasparini 1993; Gladkov 2007; Gonzalez-Larriba 1997; Le 2006; Mathur 2018; Marechal 1987; Molinari 1982; Noronha 2018; Olasz 2000; Posner 2007; Prevost 2005; Rasch 2010; Rawat 2016; Rischin 2005; Rischin 2010; Sahoo 2017; Segura 2002; Vermorken 2007; Vokes 1990). Chemotherapy regimens in these trials differed in terms of agents used and timing relative to locoregional treatment. We grouped these comparisons into five subsections:

- Induction chemotherapy A prior to radiotherapy versus induction chemotherapy B prior to radiotherapy
- Induction chemotherapy A prior to surgery versus induction chemotherapy B prior to surgery
- Induction chemotherapy A prior to concurrent chemoradiation versus induction chemotherapy B prior to concurrent chemoradiation
- Concurrent chemoradiation with chemotherapy A versus concurrent chemoradiation with chemotherapy B
- Induction chemotherapy A prior to locoregional treatment (either surgery or radiotherapy) versus induction chemotherapy B prior to locoregional treatment

Eight studies compared two induction chemotherapy regimens prior to definitive radiotherapy (Browman 1986; Chauvergne 1988; De Andres 1995; Gonzalez-Larriba 1997; Marechal 1987; Prevost 2005; Segura 2002; Vermorken 2007). The induction chemotherapy regimens compared included:

- Cisplatin plus 5-fluorouracil plus docetaxel versus cisplatin plus 5-fluorouracil (Vermorken 2007)
- Cisplatin plus 5-fluorouracil versus cisplatin plus vinorelbine (Segura 2002)
- Cisplatin plus 5-fluorouracil versus carboplatin plus 5-fluorouracil (De Andres 1995)
- Cisplatin plus 5-fluorouracil versus cisplatin and UFT (oral formulation of tegafur and uracil) (Gonzalez-Larriba 1997)
- Cisplatin plus etoposide versus cisplatin (Marechal 1987)
- Cisplatin plus etoposide versus cisplatin plus 5-fluorouracil (Prevost 2005)
- Cisplatin versus cisplatin plus methotrexate plus bleomycin plus vincristine (Chauvergne 1988)
- Methotrexate plus 5-fluorouracil given simultaneously versus methotrexate and 5-fluorouracil given sequentially (Browman 1986)

One study evaluated induction chemotherapy regimens prior to definitive surgery. Olasz 2000 randomised patients to induction chemotherapy with either bleomycin, vincristine, cisplatin and methotrexate or bleomycin, vincristine and methotrexate.

Two studies evaluated induction chemotherapy regimens prior to definitive local therapy with concurrent chemoradiation. In this trial, participants were randomly allocated to either two

cycles of cisplatin plus 5-fluorouracil, followed by concurrent chemoradiation with cisplatin plus 5-fluorouracil or two cycles of cisplatin, 5-fluorouracil and tirapazamine followed by concurrent chemoradiation with cisplatin plus 5-fluorouracil (Le 2006). Posner 2007 compared three cycles of induction chemotherapy with platinum plus 5-fluorouracil plus docetaxel followed by concurrent chemoradiotherapy (weekly carboplatin), with cisplatin plus 5-fluorouracil also followed by the same concurrent chemoradiotherapy with weekly carboplatin.

A total of nine studies compared concurrent chemotherapy regimens (Garden 2004; Gasparini 1993; Gladkov 2007; Noronha 2018; Rasch 2010; Rawat 2016; Rischin 2005; Rischin 2010; Sahoo 2017). This included comparisons of:

- Concurrent daily cisplatin versus 3-weekly cisplatin (Gladkov 2007)
- Concurrent weekly cisplatin versus 3-weekly cisplatin (Gladkov 2007; Noronha 2018; Rawat 2016; Sahoo 2017)
- Concurrent 3-weekly cisplatin versus carboplatin (Gasparini 1993)
- Concurrent cisplatin plus tirapazamine versus concurrent cisplatin (Rischin 2010)
- Concurrent cisplatin plus tirapazamine versus concurrent cisplatin plus 5-fluorouracil (Rischin 2005)
- Concurrent cisplatin plus 5-fluorouracil versus concurrent hydroxyurea plus 5-fluorouracil (Garden 2004)
- Concurrent cisplatin plus 5-fluororuacil versus concurrent cisplatin plus paclitaxel (Garden 2004)
- Concurrent intra-arterial cisplatin versus intravenous cisplatin (Rasch 2010)

One trial evaluated two different concurrent chemotherapy regimens with different radiation therapy schedules, comparing concurrent chemotherapy with cisplatin plus paclitaxel with a lower total dose of radiation therapy, as compared to concurrent chemotherapy with cisplatin plus 5-fluorouracil at standard doses of radiation therapy (Fietkau 2020).

One trial evaluated induction chemotherapy with intra-arterial methotrexate compared to intra-arterial bleomycin prior to locoregional treatment with either surgery or radiotherapy (Molinari 1982). Two trials identified in the update evaluated induction chemotherapy prior to definitive local treatment; however the definitive local treatment was not specified. This included Mathur 2018 which evaluated induction chemotherapy with cisplatin plus paclitaxel where patients were randomly allocated to receive the paclitaxel component every three weeks or on a weekly regimen, prior to definitive locoregional treatment. In addition, Tousif 2020 evaluated induction chemotherapy with docetaxel, cisplatin and 5-fluorouracil at different doses and schedules prior to definitive locoregional treatment.

Excluded studies

We excluded 250 studies from this review. The reasons for exclusion are found in the Characteristics of excluded studies table. These are summarised as follows:

- Abstract only (Abele 1984; Abele 1985; Andreadis 1999; Bier 1986; Bradley 1982; Brigham 1998; Carugati 1988; Cruz 1997; Dalley 1995; De la Torre 1991; Domenge 1987; Gabriele 1994; Gabriele 1996; Haas 1985; Hasegawa 1996; Kamioner 1994; Ksiezniak-Baran 2020; Le 1998; Lopes 1991; Moro 1994; Phillips 1980; Platzer 1990; Sharma 2019; Shetty 1985; Woods 1984)
- Study was not randomised controlled trial (Ahmad Khalil 2016; Amichetti 1989; Ansfield 1970; Armstrong 2006; Auersperg 1977; Autorino 2017; Baliga 2017; Bari 2018; Berger 1995; Chang 2017; Coninx 1986; Deka 1983; Ebeling 1994; Feng 2018; Fujii 1996; Fujii 1999; Gollin 1972; Handa 1980; Inhestern 2017; Iyer 2015; Kaneda 1987; Katori 2007; Mackiewicz 2017; Manocha 2006; Marta 2015; Melotek 2016; Melotek JM 2016; Olasz 2004; Pant 1973; Pothamsetty 2017; Rades 2016; Sanguineti 1999; Skillington 2017; Tao 2017; Von Heyden 1982; Von Heyden 1984; Von Heyden 1985)
- Less than 50% of participants had oral cavity or oropharyngeal cancer (Adelstein 1997; Adelstein 2000; Anonymous 1976; Asif 2003; Bachaud 1996; Bakowski 1978; Boidi 1991; Buntzel 1998; Buntzel 1998a; Campbell 1987; Cappelaere 1981; Cummings 2007; DeConti 1981; Domenge 1988; Dutta 2013; Eschwege 1997; Ezzat 2005; Fety 1994; Fety 1998; Fonseca 2005; Fountzalis 2004; Fu 1987; Furukawa 1994; Gedouin 1986; Gedouin 1996; Gehanno 1992; Ghali 2011; Groselj 2017; Haas 1986; Haffty 1993; Haffty 1997; Haffty 1997a; Haselow 1990; Henk 1984; Hitt 2005; Homma 2004; Hussey 1975; Jones 1992; Jortay 1990; Kapstad 1978; Kapstad 1979; Kitani 2017; Laccourreye 1983; Lavertu 1998; Lim 2017; Lim 2020; Lippman 1988; Magno 1994; Martin 1994; Mashkour 2020; Mechl 1987; Mitra 2006; Morton 1985; Morton 1987; Nair 2017; Papac 1978; Porceddu 2017; Racadot 2008; Rastogi 2019; Rodrigo 2004; Sanchiz 1990; Sarkar 2008; Schuller 1989; Sealy 1978; SECOG 1986; Siodlak 1989; Smid 2003; Snow 1981; Soo 2005; Stell 1983; Stell 1990; Stolwijk 1985; Sun Y 2020; Suwinski 2005; Taylor 1997; Toohill 1987; Tsukuda 1994; Tsukuda 2005; Tsukuda 2010; Vega 1981; Vermund 1985; Weissberg 1989; Woods 1977; Yi 2017; Yoshino 1991; Yoshino 1994)
- Included patients with recurrent and/or metastatic disease (Browman 1983; Browman 1988; Browman 1990; Cappelaere 1990; Clavel 1987; Coates 1984; Coninx 1988; Drelichman 1983; Forastiere 2001; Gasparini 1992; Gibson 2005; Grose 1985; Haffty 2005; Joshi 2017; Kityota 2017; Klima 1988; Kotani 1994; Lee 1989; Liverpool HNOG 1990; Machiels 2016; O'Connor 1979; Panis 1984; Pearlman 1985; Price 1978; Schildhauer 2005; Scwiecicki 2016; Shaw 1978; Stefani 1971; Stefani 1980; Taylor 1979; Taylor 1984; Taylor 1994; Veronesi 1985; Woods 1981)
- Publication continued insufficient information to assess eligibility (Bezwoda 1979; Caponigro 2002; Dobrowsky 1996; Jain 1979; Peng 2007; Taylor 1985)
- No reported relevant outcome measure (Beryhy 2017; Corvo 1997; Driessen 2016; Ghadjar 2014; Li 2018; Mehanna 2017; Nichols 2013; Nissenbaum 1984; Patil 2017; Proto 1993; Viswanath 2009; Wang 2017)
- Did not evaluate chemotherapy (Addeo 2018; Alam 2016; Antanadou 2002; Argiris 2016; Babu 2010; Barney 2017; Bell 2017; Bhattasali 2016; Bolla 1994; Bonner 2006; Buentzel 2006; Burtness 2017; Caroline 2016; Cheng 2017; Cohen 2016; Eriksen 2013; Fayette 2016; Ferris 2018; Fonseca 1997; Gaffor 2016; Gillison 2017; Grandis 2008; Gupta 2017; Korde 2016; Li 2014; Machiels 2017; Machtay 2004; Mak 2017; Mantovani 1998; Melotek J 2016; Merlano 2020; Nevens 2017; Overgaard 2007; Park 2017; Poddar 2017; Rosen 2003; Rosenthal 2016; Roy 2016; Siu 2017; Specenier 2017; Sun 2017; Sun 2020; Szturz 2016; Taylor 1978; Tian 2018; Venkatachalam 1998; Wolf 2017)

Risk of bias in included studies

We assessed each included study for risk of bias with the Cochrane risk of bias assessment tool using the eight domains described in the methods section. Of the studies identified in the update, the majority were assessed as having unclear risk of bias (9 of 11) for the outcome of overall survival. See Figure 2; Figure 3.

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

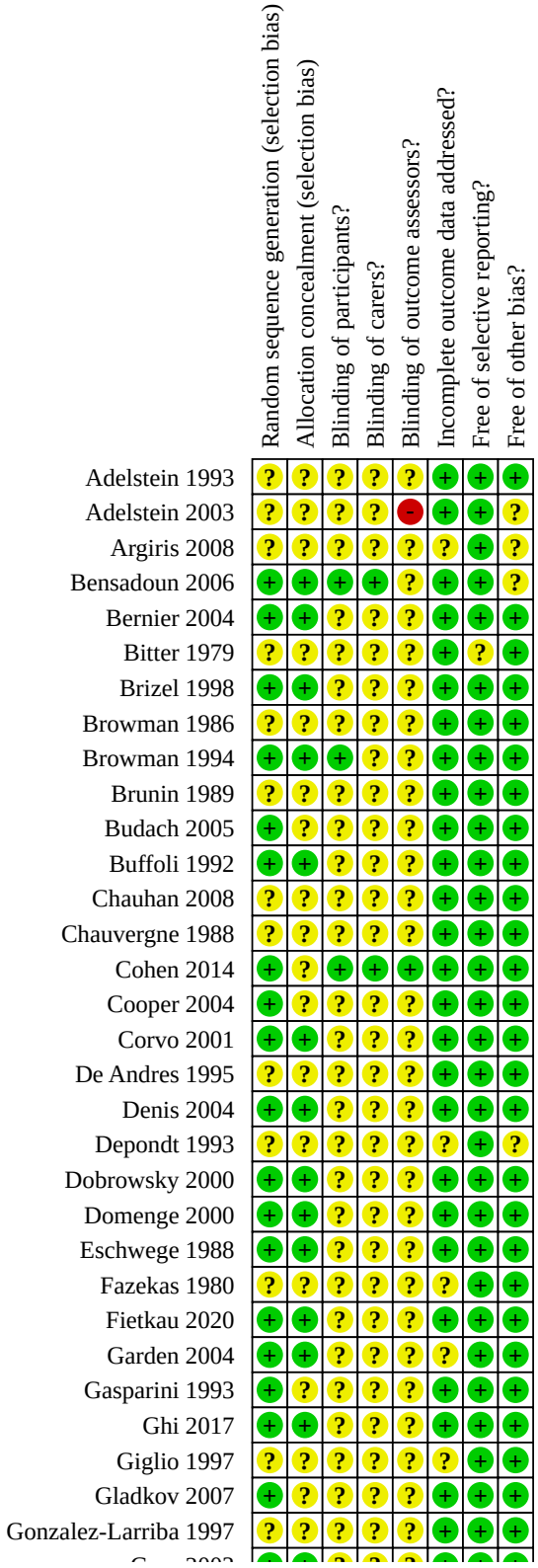


Figure 2. (Continued)

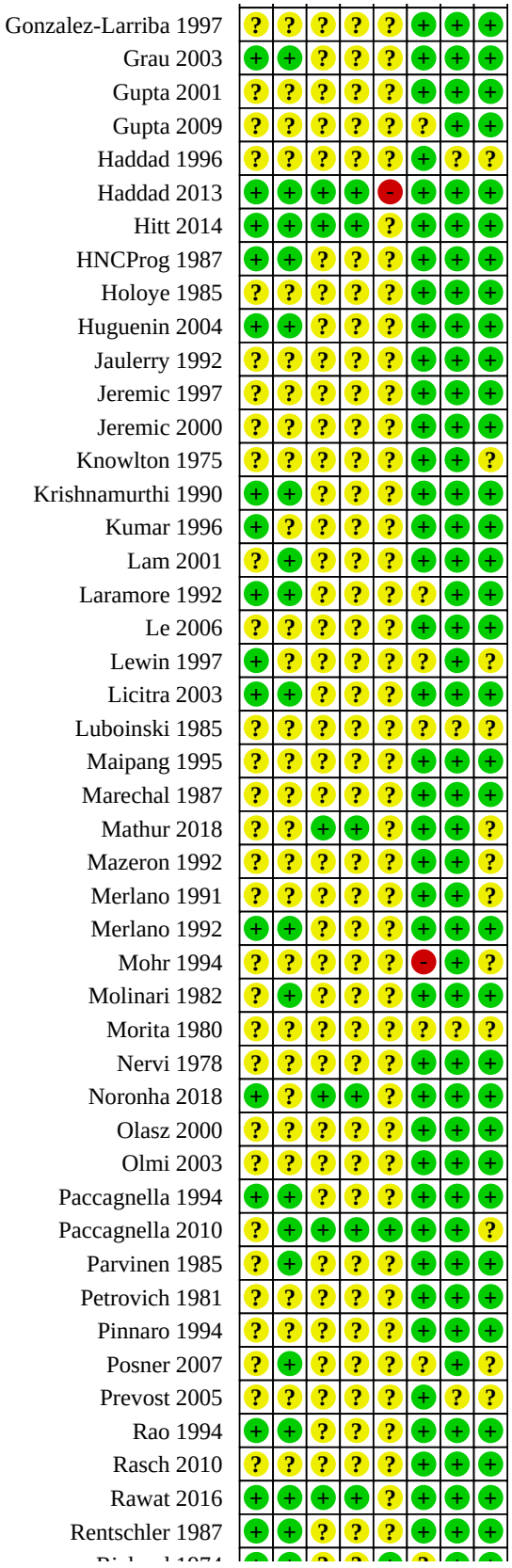


Figure 2. (Continued)

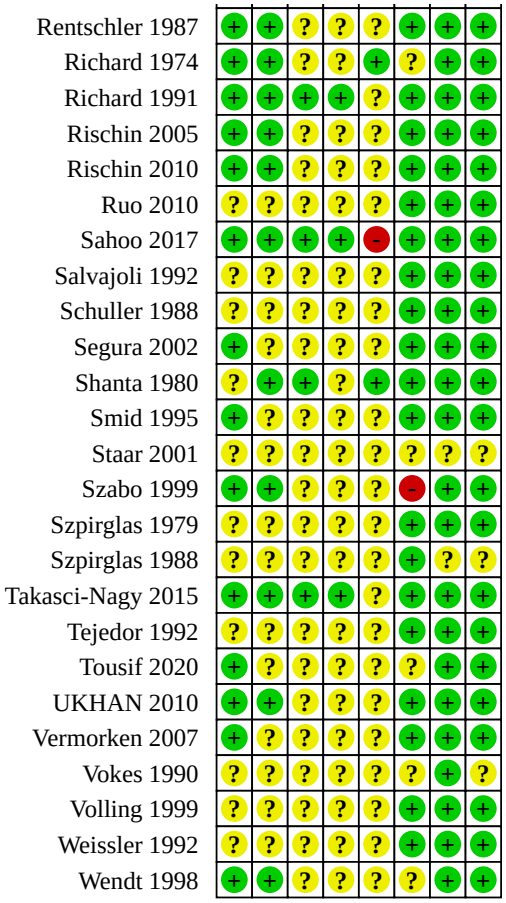
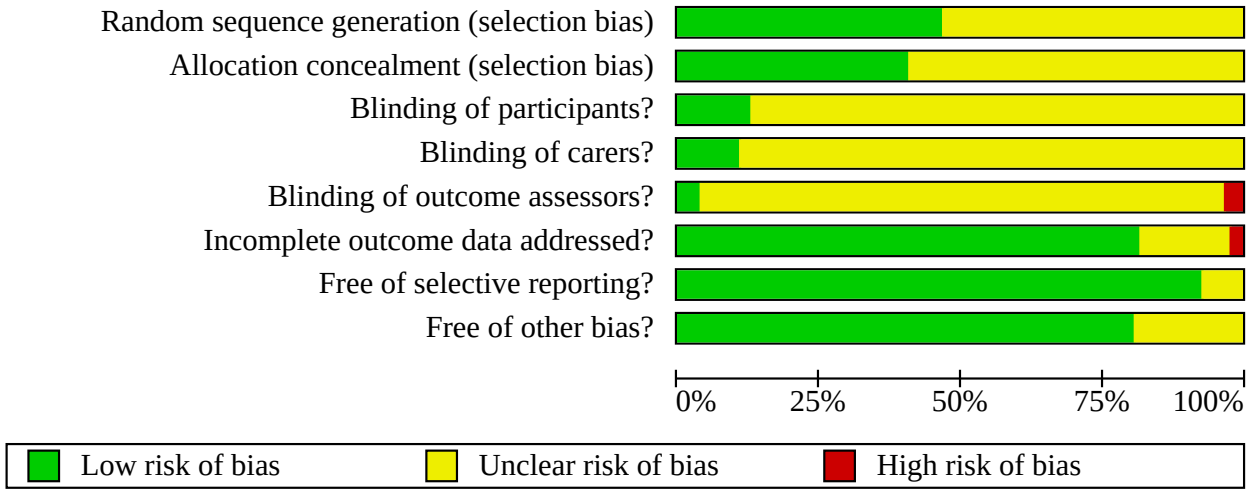


Figure 3.



Allocation

All of the included studies were described as being randomised with the method of sequence generation described as either adequate or unclear.

Random sequence generation was found to be at low risk of bias for 47 of the included studies (Bensadoun 2006; Bernier 2004; Brizel 1998; Browman 1994; Budach 2005; Buffoli 1992; Cohen 2014; Cooper 2004; Corvo 2001; Denis 2004; Dobrowsky 2000; Domenge 2000; Eschwege 1988; Fietkau 2020; Garden 2004; Gasparini 1993; Ghi 2017; Gladkov 2007; Grau 2003; Haddad 2013; Hitt 2014; HNCProg 1987; Huguenin 2004; Krishnamurthi 1990; Kumar 1996; Laramore 1992; Lewin 1997; Licitra 2003; Merlano 1992; Noronha 2018; Paccagnella 1994; Rao 1994; Rawat 2016; Rentschler 1987; Richard 1974; Richard 1991; Rischin 2005; Rischin 2010; Sahoo 2017; Segura 2002; Smid 1995; Szabo 1999; Takasci-Nagy 2015; Tousif 2020; UKHAN 2010; Vermorken 2007; Wendt 1998).

Allocation concealment from the investigators/assessors was found to be at low risk of bias for 41 of the included studies (Bensadoun 2006; Bernier 2004; Brizel 1998; Browman 1994; Buffoli 1992; Corvo 2001; Denis 2004; Dobrowsky 2000; Domenge 2000; Eschwege 1988; Fietkau 2020; Garden 2004; Ghi 2017; Grau 2003; Haddad 2013; Hitt 2014; HNCProg 1987; Huguenin 2004; Krishnamurthi 1990; Lam 2001; Laramore 1992;Licitra 2003; Merlano 1992;Molinari 1982; Paccagnella 1994; Paccagnella 2010; Parvinen 1985; Posner 2007;Rao 1994; Rawat 2016; Rentschler 1987; Richard 1974; Richard 1991; Rischin 2005; Rischin 2010; Sahoo 2017; Shanta 1980; Szabo 1999; Takasci-Nagy 2015; UKHAN 2010; Wendt 1998).

Blinding

In most studies of chemotherapy, blinding of patients and clinicians would be difficult and possibly unethical. We have taken a pragmatic approach and assumed that, where outcomes were objective (e.g. overall survival), the lack of blinding of participants or carers in the included studies was unlikely to result in bias. However, it is acknowledged that for outcomes that may be seen as more subjective, such as disease-free survival or locoregional recurrence, the absence of blinding of trial personnel, especially of those assessing these outcomes, may represent a potential risk of bias. Only 13 of the included studies used blinding of either participants or outcome assessors (Figure 2) (Bensadoun 2006; Browman 1994; Cohen 2014; Haddad 2013; Hitt 2014; Mathur 2018; Noronha 2018; Paccagnella 2010; Rawat 2016; Richard 1974; Sahoo 2017; Shanta 1980; Takasci-Nagy 2015).

Incomplete outcome data

In 16 trials, some outcome data were missing and it was unclear whether missing data from those who withdrew or were excluded represented a possible risk of bias. In two studies (Mohr 1994; Szabo 1999), outcome data were missing on more than 25% of those randomised and reasons and distribution of those not included were not described. In our assessment, this represents a significant risk of bias in these two studies. In the remaining studies, all outcome data were complete.

Selective reporting

Assessment of possible selective reporting was based on the publications related to the trial and through contact with authors when data were not available in the primary literature. Seven trials were assessed as being unclear with regard to selective reporting of outcomes, because insufficient information was available to the review authors from the published paper and contact with the authors.

Other potential sources of bias

Various other potential sources of bias were identified in 19 trials (Adelstein 2003; Argiris 2008; Bensadoun 2006; Depondt 1993; Haddad 1996; Knowlton 1975; Lewin 1997; Luboinski 1985; Mathur 2018; Mazeron 1992; Merlano 1991; Mohr 1994; Morita 1980; Paccagnella 2010; Posner 2007; Prevost 2005; Staar 2001; Szpirglas 1988; Vokes 1990) (see risk of bias tables in the Characteristics of included studies on each study for details).

Effects of interventions

See: **Summary of findings 1** Induction chemotherapy plus locoregional treatment compared to locoregional treatment alone for the treatment of oral cavity and oropharyngeal cancer: chemotherapy; **Summary of findings 2** Surgery + adjuvant treatment A compared to surgery + adjuvant treatment B for the treatment of oral cavity and oropharyngeal cancer: chemotherapy; **Summary of findings 3** Concomitant chemoradiotherapy compared to radiotherapy alone (non-resectable) for the treatment of oral cavity and oropharyngeal cancer: chemotherapy

Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone

Overall survival

The 36 trials in this group that compared induction chemotherapy plus locoregional treatment with locoregional treatment alone can be found in Analysis 1.1, of which 32 evaluated overall survival.

The most common induction chemotherapy evaluated was combination platinum (either cisplatin or carboplatin) and 5-fluorouracil, as evaluated prior to radiotherapy or surgery (Analysis 1.1). Among the individual studies that assessed these treatment approaches, none demonstrated a difference in overall survival with the use of induction platinum plus 5-fluorouracil prior to radiotherapy, as compared to radiotherapy alone (Depondt 1993; Domenge 2000; Lewin 1997; Paccagnella 1994; Tejedor 1992). The pooled estimate across the five trials showed a possible reduction in the risk of death, but there is also some possibility of a small increase in risk between induction therapy followed by radiotherapy and radiotherapy alone (hazard ratio (HR) 0.85, 95% confidence interval (CI) 0.70 to 1.04, P = 0.11; 7427 participants; moderate-certainty evidence; Summary of findings 1) (Analysis 1.1; Comparison 1.1.4).

Only one trial that evaluated induction cisplatin plus 5-fluorouracil prior to surgery reported on overall survival (Licitra 2003) and similarly, did not demonstrate a difference in the risk of death with the use of this induction regimen prior to surgery, as compared to surgery alone (HR 1.06, 95% CI 0.71 to 1.60, P = 0.77; 198 participants; low-certainty evidence; Summary of findings 1) (Analysis 1.1; Comparison 1.1.12).

Induction chemotherapy prior to concurrent chemoradiation has also been evaluated across seven trials (Cohen 2014; Ghi 2017; Gupta 2009; Haddad 2013; Hitt 2014; Paccagnella 2010; Takasci-Nagy 2015). Across this comparison, the most common induction chemotherapy evaluated was cisplatin plus 5-fluorouracil plus

docetaxel prior to concurrent chemoradiation with cisplatin (Ghi 2017; Hitt 2014; Takasci-Nagy 2015) (Analysis 1.1, Comparison 1.1.20). The individual trials showed no difference in overall survival with the use of induction chemotherapy. The overall pooled estimate for risk of death across these three trials similarly showed no evidence of difference (HR 1.08, 95% CI 0.80 to 1.44, P = 0.63; 760 participants; low-certainty evidence; Summary of findings 1). Similarly, a pooled estimate for the risk of death across two trials (Gupta 2009; Hitt 2014) does not support the use of induction cisplatin plus 5-fluorouracil followed by concurrent chemoradiation with cisplatin, as compared to concurrent chemoradiation with cisplatin alone (HR 0.71, 95% CI 0.37 to 1.35, P = 0.30; 398 participants; low-certainty evidence; Summary of findings 1) (Analysis 1.1, Comparison 1.1.21).

A summary of the results for the use of platinum plus 5-fluorouracil with or without docetaxel as induction chemotherapy prior to locoregional treatment is found in Table 3.

We did not pool the data overall because of the heterogeneity in the evaluated induction regimens (with respect to the number of chemotherapy agents included and mode of administration), as well as the heterogeneity in the type of locoregional treatment (radiotherapy +/- chemotherapy or surgery).

Disease-free survival

Disease-free survival outcomes were reported across three trials that evaluated induction chemotherapy with platinum (either cisplatin or carboplatin) plus 5-fluorouracil prior to radiotherapy, as compared to radiotherapy alone, and provided evidence of a benefit for disease-free survival in favour of induction chemotherapy with platinum plus 5-fluorouracil (HR 0.78, 95% CI 0.63 to 0.97, P = 0.03; 332 participants; Analysis 1.2, Comparison 1.2.1).

Similarly, for induction chemotherapy with carboplatin plus 5-fluorouracil prior to surgery, compared to surgery alone (Analysis 1.2, Comparison 1.2.6), a benefit was found in favour of induction chemotherapy (HR 0.55, 95% CI 0.32 to 0.93, P = 0.03; one trial (Volling 1999)).

However, across trials evaluating induction chemotherapy with cisplatin plus 5-fluorouracil plus docetaxel prior to concurrent chemoradiation with cisplatin, compared to concurrent chemoradiation with cisplatin alone, no difference in disease-free survival was noted (HR 0.95, 95% CI 0.68 to 1.33, P = 0.77; Analysis 1.2, Comparison 1.2.10).

Similarly, in the one trial that evaluated induction chemotherapy with cisplatin plus 5-fluorouracil prior to concurrent chemoradiation with cisplatin, no difference in disease-free survival was demonstrated (HR 0.90, 95% CI 0.69 to 1.17, P = 0.44) (Hitt 2014) (Analysis 1.2; Comparison 1.2.12).

As with the primary outcome of overall survival, we did not pool the data on disease-free survival across all studies because of the heterogeneity in the induction chemotherapy and locoregional treatment.

Locoregional control

Eight trials reported outcomes for locoregional control with the use of induction chemotherapy. Among the more common chemotherapy regimens, no trials that evaluated induction chemotherapy with platinum plus 5-fluorouracil prior to radiotherapy reported on this outcome. Only one trial (Licitra 2003) evaluated cisplatin plus 5-fluorouracil chemotherapy prior to surgery, as compared to surgery alone, demonstrating no benefit for locoregional control (risk ratio (RR) 0.92, 95% CI 0.92 to 1.42; Analysis 1.5).

Only one trial reported outcomes for locoregional control with induction cisplatin plus 5-fluorouracil prior to concurrent chemoradiation with cisplatin (Hitt 2014). The point estimate showed a possible improvement in locoregional control, but the confidence interval also included the possibility of a small deterioration with this induction treatment, as compared to concurrent chemoradiation alone (RR 0.78, 95% CI 0.60 to 1.02, P = 0.07; Analysis 1.4, Comparison 1.4.5).

In contrast, the use of induction cisplatin plus 5-fluorouracil plus docetaxel prior to concurrent chemoradiation with cisplatin led to an improvement in locoregional control (Ghi 2017; Hitt 2014; Takasci-Nagy 2015) (RR 0.80, 95% CI 0.64 to 0.99, P = 0.05; Analysis 1.4, Comparison 1.4.4).

Comparison 2: Surgery + adjuvant treatment A versus surgery +/- adjuvant treatment B

Overall survival

No benefit in overall survival was seen from any of the evaluated adjuvant chemotherapies versus observation alone post-surgery (Analysis 2.1).

All four studies that evaluated adjuvant concurrent chemoradiation compared to adjuvant radiation reported data on overall survival (Argiris 2008; Bernier 2004; Cooper 2004; UKHAN 2010). A benefit with the use of adjuvant chemoradiation, as compared to adjuvant radiation alone, was seen in the pooled estimate across these four studies (HR 0.84, 95% CI 0.72 to 0.98, P = 0.03; 1097 participants; moderate-certainty evidence; Summary of findings 2) (Analysis 2.2). However, when assessed independently by type of chemotherapy in the concurrent chemoradiation regimen, only treatment with concurrent cisplatin led to an improvement in overall survival (HR 0.79, 95% CI 0.65 to 0.98, P = 0.03; Analysis 2.1, Comparison 2.1.7).

Another trial randomised participants to either adjuvant cisplatin plus 5-fluorouracil followed by radiotherapy or adjuvant radiotherapy alone (Laramore 1992). There was no difference between the groups compared with regard to overall survival (Analysis 2.3).

A summary of the key results for comparison 2 are found in Table 4.

Disease-free survival

Disease-free survival was reported by nine trials in this comparison.

Across the two trials that evaluated adjuvant chemotherapy with methotrexate as compared to observation, a benefit in disease-free survival was suggested by the point estimate, but the wide confidence interval meant the result was also compatible with no difference between the groups (HR 0.59, 95% CI 0.34 to 1.03, P = 0.06) (Rentschler 1987; Rao 1994) (Analysis 2.4, Comparison 2.4.1).

One trial evaluated adjuvant chemotherapy with combination methotrexate, bleomycin and vincristine, as compared to adjuvant radiotherapy, demonstrating no difference in disease-free survival (HR 0.90, 95% CI 0.19 to 4.21, P = 0.89) (Bitter 1979) (Analysis 2.4; Comparison 2.4.2).

Four trials reported disease-free survival for concurrent adjuvant chemoradiotherapy, as compared to adjuvant radiotherapy alone (Argiris 2008; Bernier 2004; Cooper 2004; UKHAN 2010). The pooled estimate for these trials revealed evidence of a difference in disease-free survival (HR 0.84, 95% CI 0.72 to 0.97, P = 0.02) (Analysis 2.4; Comparison 2.4.3, 2.4.4, 2.4.5). When examined by type of concurrent chemotherapy, the benefit in disease-free survival was only seen in those trials that used concurrent cisplatin (HR 0.77, 95% CI 0.64 to 0.92, P = 0.004) (Bernier 2004; Cooper 2004).

One trial evaluated disease-free survival with the use adjuvant cisplatin plus 5-fluorouracil, followed by radiation therapy, revealing no difference as compared to adjuvant radiation therapy alone (HR 0.90, 95% CI 0.72 to 1.14, P = 0.40) (Laramore 1992) (Analysis 2.4; Comparison 2.4.6).

Another trial evaluated adjuvant chemotherapy with cisplatin, as compared to no adjuvant treatment, among patients who received induction chemotherapy with cisplatin plus bleomycin prior to surgery, revealing no difference in disease-free survival (HR 1.55, 95% CI 0.93 to 2.58, P = 0.09) (HNCProg 1987) (Analysis 2.4; Comparison 2.4.7).

Comparison 3: Concurrent chemoradiotherapy versus radiotherapy

Overall survival

Twenty four trials reported on overall survival with concurrent chemoradiation versus radiation therapy alone (Adelstein 1993; Bensadoun 2006; Brizel 1998; Browman 1994; Budach 2005; Denis 2004; Dobrowsky 2000; Eschwege 1988; Grau 2003; Gupta 2001; Haddad 1996; Huguenin 2004; Jeremic 1997; Jeremic 2000; Morita 1980; Parvinen 1985; Ruo 2010; Salvajoli 1992; Shanta 1980; Smid 1995; Staar 2001; UKHAN 2010; Weissler 1992; Wendt 1998). There was a notable benefit with the addition of concurrent chemotherapy (HR 0.74, 95% CI 0.67 to 0.83, P < 0.00001; 2852 participants; moderate-certainty evidence; Summary of findings 3) (Analysis 3.1). Upon examination by type of concurrent chemotherapy, the benefit of concurrent chemotherapy was the highest with concurrent platinum (Adelstein 1993; Jeremic 1997; Ruo 2010) (HR 0.66, 95% CI 0.55 to 0.79, P < 0.00001) (Analysis 3.1, Comparison 3.1.1) and concurrent platinum-5-fluorouracil (Bensadoun 2006; Brizel 1998; Denis 2004; Haddad 1996; Staar 2001; Weissler 1992; Wendt 1998) (HR 0.65, 95% CI 0.55 to 0.77, P < 0.00001) (Analysis 3.1, Comparison 3.1.2). No evidence of a benefit in overall survival was seen with the use of concurrent 5-fluorouracil (Analysis 3.1, Comparison 3.1.3), methotrexate (Analysis 3.1, Comparison 3.1.4), mitomycin C (Analysis 3.1, Comparison 3.1.5), bleomycin (Analysis 3.1, Comparison 3.1.6), combination bleomycin and mitomycin C (Analysis 3.1, Comparison 3.1.7) or bleomycin and cisplatin (Analysis 3.1, Comparison 3.1.9).

Four trials examined alternating chemotherapy and radiotherapy, as compared to radiotherapy alone (Corvo 2001; Giglio 1997; Merlano 1992; UKHAN 2010). The pooled analysis found no evidence of a difference in the risk of death (RR 0.85, 95% CI 0.71 to 1.01, P = 0.07) (Analysis 3.2). UKHAN 2010 evaluated concurrent chemoradiation with a concurrent methotrexate-containing chemotherapy regimen as compared to radiotherapy in which both experimental and control arms received adjuvant chemotherapy (with the same methotrexate-containing regimen). From this trial, no difference in overall survival was demonstrated (RR 0.96, 95% CI 0.74 to 1.24, P = 0.76) (Analysis 3.2, Comparison 3.2.3).

A summary of the key results for comparison 3 are found in Table 5.

Disease-free survival

Thirteen trials that evaluated concurrent chemoradiation, as compared to radiotherapy alone reported on disease-free survival. Across these trials, the pooled estimate for disease-free survival was HR 0.74 (95% CI 0.67 to 0.80, P < 0.00001) (Analysis 3.3; Comparison 3.3.1 to 3.3.8). When examined by concurrent chemotherapy regimen, a benefit in disease-free survival was demonstrated with the use of concurrent platinum (either cisplatin or carboplatin) plus 5-fluorouracil (HR 0.71, 95% CI 0.60 to 0.83, P < 0.0001) (Analysis 3.3, Comparison 3.3.3), concurrent methotrexate (HR 0.65, 95% CI 0.43 to 0.98, P = 0.04) (Analysis 3.3, Comparison 3.3.4), concurrent bleomycin plus mitomycin C (HR 0.45, 95% CI 0.22 to 0.93, P = 0.03) Analysis 3.3, Comparison 3.3.6) and concurrent 5-fluorouracil plus mitomycin C (HR 0.60, 95% CI 0.44 to 0.83, P = 0.002) Analysis 3.3, Comparison 3.3.8). Results from UKHAN 2010, which evaluated both methotrexate or a methotrexate combination with 5-fluorouracil-bleomycin-vincristine, also demonstrated a benefit in terms of disease-free survival with a HR 0.72 (95% CI 0.57 to 0.91, P = 0.006); however, as the results were not reported as per methotrexate monotherapy or methotrexate-containing combination treatment, it remains unclear whether combination treatment is required to derive this benefit.

Locoregional control

Eleven trials of concurrent chemoradiotherapy presented data for this outcome (Budach 2005; Chauhan 2008; Dobrowsky 2000; Gupta 2001; Haddad 1996; Huguenin 2004; Krishnamurthi 1990; Parvinen 1985; Ruo 2010; Staar 2001; Wendt 1998).

Eight trials evaluated locoregional control with the use of concurrent chemotherapy with standard fractionation radiotherapy (Budach 2005; Gupta 2001; Haddad 1996; Huguenin 2004; Merlano 1992; Ruo 2010; Staar 2001; Wendt 1998). We pooled the three studies that evaluated platinum plus 5-fluorouracil and found a benefit from concurrent chemotherapy (RR 0.75, 95% CI 0.61 to 0.93, P < 0.009) (Analysis 3.4).

Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)

Overall survival

Eight of eleven studies that evaluated two induction chemotherapy regimens prior to definitive radiotherapy reported data on overall survival. However, given the heterogeneity in the evaluated regimens, pooled estimates were not possible. The only statistically significant difference in the risk of death was seen in the Vermorken 2007 study demonstrating a reduction in risk of death favouring the cisplatin plus 5-fluorouracil plus docetaxel regimen used as induction (HR 0.73, 95% CI 0.57 to 0.93, P = 0.01) (Analysis 4.1, Comparison 4.1.1).

Of the two studies that evaluated induction chemotherapy regimens prior to definitive concurrent chemoradiation, only one trial demonstrated a survival benefit in favour of the cisplatin plus 5-fluorouracil plus docetaxel regimen, as compared to cisplatin plus 5-fluorouracil, prior to definitive concurrent chemoradiation with carboplatin (HR 0.70, 95% CI 0.54 to 0.91, P = 0.007) (Analysis 4.1, Comparison 4.1.17).

Across the trials that evaluated different chemotherapies with definitive concurrent chemoradiation, no difference in overall survival was noted. (Analysis 4.1; Comparisons 4.1.8 to 4.1.15). This included the one study comparing concurrent cisplatin administered every three weeks (100 mg/m^2) versus weekly (30 mg/m^2) in the Noronha 2018 trial. Importantly, this trial was powered as a non-inferiority trial, conducted to evaluate whether weekly cisplatin was non-inferior to a 3-weekly regimen. This trial did not meet its primary endpoint. Similarly, different administration schedules of concurrent cisplatin chemotherapy concurrent with radiotherapy were evaluated in the Gladkov 2007 trial, which examined daily cisplatin (6 mg/m^2), weekly cisplatin (40 mg/m^2) and 3-weekly cisplatin (100 mg/m^2). Overall survival was not evaluated in this study.

Given the heterogeneity in chemotherapy comparisons for included trials that reported on overall survival, no pooled estimates were conducted.

Disease-free survival

Only two of the 11 studies that evaluated two induction chemotherapy regimens prior to definitive radiotherapy reported data on disease-free survival (Gonzalez-Larriba 1997; Vermorken 2007). Induction chemotherapy with cisplatin plus 5-fluorouracil plus docetaxel, as compared to cisplatin plus 5-fluorouracil was the only regimen that revealed a statistically significant benefit in disease-free survival (HR 0.72, 95% CI 0.57 to 0.91, P = 0.006) (Analysis 4.2; Comparison 4.2.2).

Of the two studies that evaluated induction chemotherapy regimens prior to definitive concurrent chemoradiation, only Posner 2007 reported outcomes on disease-free survival demonstrating a benefit with the use of induction cisplatin plus 5-fluorouracil plus docetaxel, as compared to cisplatin plus 5-fluorouracil prior to concurrent chemoradiation with carboplatin (HR 0.71, 95% CI 0.56 to 0.90, P = 0.005) (Analysis 4.2; Comparison 4.2.8)

One trial evaluated induction chemotherapy with cisplatin plus 5-fluorouracil plus docetaxel given in two different schedules, as either weekly treatment (for nine weeks) versus every three weeks (for three cycles) prior to locoregional treatment (Tousif 2020). In this study, the locoregional treatment received was not characterised. No difference in disease-free survival was found (Analysis 4.2; Comparison 4.2.9).

There was no evidence for a disease-free survival benefit among the concurrent chemotherapy regimens evaluated (Analysis 4.2; Comparison 4.2.3 to 4.2.7).

Locoregional control

Locoregional control was reported in 12 studies (Gladkov 2007; Mathur 2018; Molinari 1982; Noronha 2018; Olasz 2000; Prevost 2005; Rasch 2010; Rawat 2016; Rischin 2005; Rischin 2010; Sahoo 2017; Tousif 2020).

In the assessment of induction chemotherapy regimens, treatment with combination bleomycin-methotrexate-cisplatin-vinorelbine revealed a benefit for locoregional control, as compared to combination bleomycin plus methotrexate plus vinorelbine (RR 0.50, 95% CI 0.26 to 0.96, P = 0.04) (Olasz 2000) (Analysis 4.5; Comparison 4.5.1).

Prevost 2005 randomly allocated participants to induction chemotherapy with either cisplatin plus 5-fluorouracil or cisplatin plus etoposide, to be followed by radiotherapy. The results of this trial demonstrated an improvement in locoregional control with cisplatin plus etoposide (RR 1.48, 95% CI 1.04 to 2.11, P = 0.03) (Analysis 4.5; Comparison 4.5.2).

In the trial conducted by Molinari 1982, which compared intra-arterial methotrexate to intra-arterial bleomycin prior to locoregional treatment, a difference favouring bleomycin was observed (RR 0.35, 95% CI 0.19 to 0.66, P = 0.001) (Analysis 4.5; Comparison 4.5.3).

No difference in locoregional control was demonstrated with weekly, as compared to three-weekly administration of induction cisplatin plus docetaxel plus 5-fluorouracil prior to locoregional treatment (Tousif 2020) (RR 1.03, 95% CI 0.79 to 1.36, P = 0.81) (Analysis 4.5; Comparison 4.5.8).

The major updates within this comparison was in the comparison of concurrent chemotherapy used for chemoradiation, specifically the comparison of weekly cisplatin as compared to three-weekly cisplatin (Gladkov 2007; Noronha 2018; Rawat 2016; Sahoo 2017). Despite the addition of three additional trials evaluating this comparison, no cisplatin administration schedule demonstrated benefit for locoregional control (RR 1.10, 95% CI 0.63 to 1.89, P = 0.74) (Analysis 4.5; Comparison 4.5.6). However, it is important to note that the dose of cisplatin for the weekly administration across three of the included trials was less than 40 mg/m^2 (Noronha 2018; Rawat 2016; Sahoo 2017).

Studies not included in the meta-analysis

Vokes 1990 described a small trial of 29 participants, who were randomly allocated to either four cycles of cisplatin, fluorouracil and methotrexate or four cycles of cisplatin, fluorouracil, methotrexate and bleomycin alternating with cisplatin and 5-fluorouracil. After induction chemotherapy, locoregional therapy was planned but 32% of Arm A and 15% of Arm B did not receive locoregional therapy as per-protocol. The aim of the study was to demonstrate a greater than 50% complete response rate to induction chemotherapy but, as this was not evident after 29 people were randomised, the study was stopped early. The changes to the planned treatment protocol in the small number of participants included makes it difficult to draw valid conclusions from this trial.

DISCUSSION

Summary of main results

This systematic review was undertaken to answer the question 'Does treatment with chemotherapy, in addition to radiotherapy and/or surgery, improve the outcomes for patients with oral cavity

and oropharyngeal cancers?'. A wide range of chemotherapeutic agents, regimens and timing of chemotherapy treatments relative to radiotherapy and surgery were evaluated in the 100 RCTs included in this systematic review. As such, due to the heterogeneity in the chemotherapy regimens evaluated and clinical indications, we were limited in the meta-analyses we could undertake.

We divided the trials into four major comparisons according to how chemotherapy was integrated into a locoregional treatment approach. Our primary outcome was overall survival as measured by hazard ratios for mortality.

Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone

The first comparison concerned the addition of induction chemotherapy to definitive locoregional treatment with either surgery or radiotherapy (with or without concurrent chemotherapy) for oral cavity and oropharyngeal cancer. A wide range of chemotherapeutic agents were used in the trials included in this comparison. These included cisplatin, carboplatin, adriamycin, bleomycin, cyclophosphamide, epirubicin, methotrexate, mitomycin C, vinblastine, vincristine, vindesine, 5-fluorouracil, either as single agents, or more commonly as combinations of two or more agents.

The most common contemporary chemotherapy regimens evaluated as induction chemotherapy were either combination platinum (either cisplatin or carboplatin) and 5-fluorouracil or combination cisplatin, 5-fluorouracil and docetaxel. The pooled estimate from five studies evaluating induction chemotherapy with a regimen including either cisplatin or carboplatin plus 5-fluorouracil revealed some evidence of a possible benefit with the use of induction chemotherapy prior to definitive radiotherapy, however there was also the possibility of a small increase in risk. However, in one trial that evaluated this same induction regimen prior to surgery, as well as across two trials that evaluated this induction treatment prior to definitive concurrent chemoradiation, no evidence of a difference in overall survival was identified, as compared to definitive treatment alone. In addition, the use of induction chemotherapy with either platinum plus 5-fluorouracil with or without docetaxel prior to concurrent chemoradiation did not change mortality outcomes.

Overall, the conclusions from these updated results still suggest that there is a lack of strong supportive evidence for the use of induction chemotherapy prior to definitive locoregional treatment, apart from a possible benefit for chemotherapy with platinum plus 5-fluorouracil prior to radiotherapy. As the certainty of this evidence is low to moderate, further investigation to establish the role of induction chemotherapy prior to locoregional treatment is warranted.

Comparison 2: Surgery + adjuvant treatment A versus surgery +/- adjuvant treatment B

There were 11 trials in this comparison, involving a range of chemotherapeutic agents, with most regimens including either methotrexate or a platinum (either cisplatin or carboplatin). The studies were those in the previous version of this review; we found no new studies for this comparison.

The results of this comparison revealed no benefit of adjuvant chemotherapy with respect to overall survival, as compared to observation (we judged the certainty of this evidence as moderate); however, compared to radiotherapy alone, adjuvant concurrent chemoradiation was shown to improve survival by up to 16%. In particular, the use of adjuvant chemoradiation with concurrent cisplatin was associated with an improvement in survival, as compared to radiotherapy alone.

Comparison 3: Concurrent chemoradiotherapy versus radiotherapy

Of the 30 trials included in this comparison, 27 included data on overall survival, of which 24 evaluated overall survival associated with concurrent chemoradiation (versus standard fractionation radiotherapy alone) and four evaluated alternating chemotherapy with radiation therapy (versus radiation therapy alone).

A benefit was observed for a reduction in the risk of death with the use of concurrent chemotherapy. This improvement in survival was most commonly seen with the use of platinum (either cisplatin or carboplatin) and 5-fluorouracil combinations or platinum monotherapy. There was heterogeneity in the evaluated radiation therapy schedules and we judged the certainty of the evidence to be moderate.

The studies in this comparison were included in the original version of review; we did not identify any new studies for this update.

Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)

Twenty-three trials compared different chemotherapeutic agents, regimens, and timing relative to locoregional treatment. This included trials that evaluated different induction chemotherapy regimens prior to definitive radiotherapy, concurrent chemoradiation or surgery, as well as trials that evaluated different concurrent chemotherapy regimens with chemoradiation. The analyses indicated that many of the regimens compared showed no differences in the outcomes evaluated.

Consistent with the original review, the only regimen that led to a benefit in overall survival was the use of induction cisplatin plus 5-fluorouracil plus docetaxel chemotherapy, prior to radiotherapy, as compared to induction cisplatin-5-fluorouracil, as evaluated by Vermorken 2007. This regimen was also found to improve survival outcomes prior to concurrent chemoradiation, with cisplatin, as compared to induction cisplatin-5-fluorouracil (Posner 2007). The updated search did not find any additional trials that had evaluated this regimen.

The primary update to this comparison was in the evaluation of concurrent chemotherapy with radiation, specifically comparing weekly cisplatin versus three-weekly cisplatin. Three additional trials evaluating these two concurrent chemotherapy regimens were added to the current review (Noronha 2018; Rawat 2016; Sahoo 2017). Despite this addition, no clear superior choice was identified between these two administration schedules of cisplatin, for locoregional control (moderate-certainty of evidence). Only one of the updated trials evaluated overall survival outcomes; however, this trial was designed as a non-inferiority trial, and did not meet its primary end point of demonstrating non-inferiority of weekly to three-weekly cisplatin. Heterogeneity was evident in the chemotherapy dose for weekly cisplatin used in each of these trials

(two trials at 30 mg/m^2 [Noronha 2018 and Sahoo 2017], one trial at 35 mg/m^2 [Rawat 2016], one trial at 40 mg/m^2 [Gladkov 2007]), which also limits the ability to derive conclusions from the pooled estimates.

Overall completeness and applicability of evidence

We originally sought to evaluate the benefits of chemotherapy in addition to locoregional therapies, against the potential increase in the adverse effects of treatment-associated toxicity. However, we found very little quantitative data in the reports of the RCTs concerning harms associated with treatment, with the majority of reported data in a form unsuitable for analysis and considerable heterogeneity in reporting procedures across trials. Therefore, this review was conducted according to the latest modified protocol to focus on the effect of chemotherapy on survival (both overall survival and disease-free survival) and locoregional control. However we acknowledge that the addition of chemotherapy to radiotherapy and/or surgery may be associated with additional toxicity. From the data available in the trials, it is not possible to quantify the expected increase in toxicity associated with a given agent or regimen. Overall toxicity is related to the chemotherapeutic agent(s) and the dose and duration of therapy, but may also be related to factors including the age, bodyweight and overall health status of the individual patient(s). Close monitoring of patients undergoing chemotherapy for oral cavity and oropharyngeal cancers will detect adverse effects at an early stage, and enable clinicians to modify or interrupt chemotherapy to avoid and/or manage severe toxicity.

The applicability of this evidence is limited to patients who have characteristics similar to the clinical trial populations. It is thus unclear how outcomes with the different chemotherapies may change dependent on patient-specific factors such as age, comorbidity or patient functional status; the latter two characteristics were frequently not reported in the included studies. These are important considerations for the treating clinician who must make treatment recommendations that balance the potential benefits that may be derived from specific chemotherapies alongside their potential toxicities.

Additionally, there was heterogeneity in the included studies with respect to radiation therapy schedules used, in those trials that evaluated concurrent chemoradiation and/or included a comparison of radiation therapy. This heterogeneity creates uncertainty in the added benefit of chemotherapy along with, or against, radiation therapy in all its different forms.

Finally, the included trials in this review span over almost 50 years and some of the evaluated chemotherapy regimens are no longer clinically relevant. Although these trials have been included in the systematic review for completeness, we have focused on those chemotherapy regimens that are consistent with contemporary clinical practice.

Quality of the evidence

None of the included studies was found to be at low risk of bias with the majority assessed as being at unclear risk of bias. Blinding of participants, carers and outcome assessors was uncommon. We recognise that blinding is difficult to maintain in trials of chemotherapy and it may not be either possible, or indeed ethical, to blind trial participants or their clinicians to the treatment being administered, as different agents and regimens require differences in monitoring patients for both benefits and harms. However, blinded outcome assessment should be encouraged to limit bias in the assessment of qualitative outcomes, such as radiographic assessment of disease-free survival or response rate.

For assessment of overall survival, the certainty of evidence was moderate- to low-certainty among the different comparisons, with downgrading of evidence most commonly due to inconsistencies in trial design (e.g. imbalances among intervention and controls, heterogeneity in radiation therapy schedules). Overall, this limits the conclusions that can be drawn from these results.

Potential biases in the review process

We included 100 studies in this review. It is possible there are studies that were not included in this review, particularly those which are phase I or phase II in design. These trials are often excluded from systematic reviews as they are not comparative in design, do not report on the primary outcome and/or have immature data.

Agreements and disagreements with other studies or reviews

Overall, the results of the current systematic review and meta-analysis are consistent with prior literature. For instance, Browman 2001 conducted a systematic review and meta-analysis of RCTs that evaluated concurrent chemotherapy with radiotherapy, as compared to radiotherapy alone, for primary definitive treatment of head and neck squamous cell carcinoma. A total of 20 studies were identified in their systematic review, of which the majority are included in the current analysis. Those trials that were not identical were generally excluded from the current review due to the proportion of patients with oral cavity/oropharyngeal tumours. Through this review, they identified a survival benefit with the use of concurrent chemoradiation, which was most common when platinum-based chemotherapy regimens were chosen. This finding is identical to our findings in this review.

The updated MACH-NC meta-analysis of chemotherapy in head and neck cancer, Pignon 2009, also found no statistically significant difference in overall survival associated with the use of induction chemotherapy prior to locoregional treatment. Similar to the current results, the MACH-NC meta-analysis found a statistically significant benefit in favour of concurrent chemoradiotherapy.

Winquist 2017 conducted a systematic review and meta-analysis of RCTs to evaluate similar objectives to the current analysis, including defining the optimal concurrent chemotherapy to be used with radiation therapy in the definitive and postoperative setting, as well as defining which induction chemotherapy regimens provided the highest efficacy. Like the other published reviews, it was inclusive of all patients with head and neck squamous cell carcinoma. Consistent with the current review, a benefit for postoperative adjuvant cisplatin-based chemoradiation was identified.

In a systematic review and meta-analysis of studies not restricted to RCTs, Szturz 2017 evaluated the efficacy and toxicity differences between concurrent weekly versus three-weekly cisplatin. In the curative-intent treatment of squamous cell carcinomas of the oral cavity and oropharynx, the results of this analysis did not show any differences in survival outcomes between these two cisplatin

administration schedules. Although our analysis could not pool estimates for overall survival, given the limited trials reporting this outcome, data on treatment efficacy with our pooled estimate of locoregional control similarly demonstrated no difference in outcomes between weekly and three-weekly cisplatin.

AUTHORS' CONCLUSIONS

Implications for practice

This updated review of the literature indicated that induction chemotherapy with platinum plus 5-fluorouracil prior to locoregional treatment with either radiotherapy, surgery or CRT is not associated with a survival benefit. Following surgery, adjuvant concurrent chemoradiation may be associated with a significant improvement in survival, as compared to adjuvant radiation alone. However, adjuvant chemotherapy alone, as compared to observation, is unlikely to offer clinical benefit. In patients with unresectable tumours, primary definitive therapy with concurrent chemoradiation is very likely to be associated with an improvement in survival, particularly with the use of concurrent platinum-based chemotherapy regimens. However, the choice for the optimal schedule for cisplatin monotherapy remains unclear with no clearly superior choice among daily cisplatin, weekly cisplatin and three-weekly cisplatin administration schedules.

Implications for research

Despite the efforts of many investigators, there remains insufficient evidence to guide clinicians on the optimal dosing schedule for concurrent cisplatin administration in the definitive treatment of oral cavity and oropharyngeal cancers. Further research evaluating these schedules is ongoing.

Further, although a survival benefit was demonstrated for the use of postoperative adjuvant chemoradiation, as compared to radiation alone, it is important to note that current data highlights the preferential survival benefit in patients with specific high-risk features. This is an important consideration to limit the potential short- and long-term toxicities associated with primarily platinum-based chemotherapy to our patients in the absence of clinical benefit. Trials evaluating de-intensification of treatment in the postoperative setting are underway.

Finally, given the success of novel therapies such as targeted therapy and immunotherapy in the recurrent and metastatic setting, there is growing interest in the use of these agents in the curative intent treatment of oral cavity and oropharyngeal cancers, with active clinical trials (as per clinicaltrials.gov) evaluating these novel therapies as induction therapy, concurrent treatment and as adjuvant therapy.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Adelstein 1993

Study characteristics	
Methods	Randomised controlled trial conducted in: Cleveland USA
	Number of centres: 1

Adelstein 1993 *(Continued)*

	Recruitment period: November 1985 to June 1988 Funding source: PS Grant #P30 CA 43703 from National Cancer Institute DHHS Trial identification number: CMGH
Participants	Inclusion: adults with histologically proven, measurable squamous cell carcinoma of the head & neck (excluding nasopharynx) with no prior treatment except for "minimal surgery" Exclusion: T1N0 or M1 disease, serum creatinine > 20 mg/dL, bilirubin > 2.5 mg/dL or abnormal pre-treatment haemogram 48 patients randomised
Interventions	**Comparison 1: Induction chemotherapy followed by locoregional treatment (LRT) versus LRT alone** Gr A (n = 24): SEQ induction chemotherapy 3 cycles 5-FU 1000 mg/m^2/day as continuous infusion on days 1-5 + cisplatin 100 mg/m^2 IV on day 1 Gr B (n = 24): SIM 30 Gy external beam radiotherapy in 15 daily fractions over 3 weeks together with 1000 mg/m^2 FU on days 1-4 of radiotherapy and cisplatin 75 mg/m^2 IV on day 1 of RT. Weeks 5-7 a second cycle of chemotherapy given but no further radiotherapy At a minimum of 8 weeks after SIM and 9 weeks after SEQ, patients were evaluated for surgery. Where resection with clear margins was deemed possible, based on extent of disease after induction treatment, surgery was undertaken
Outcomes	Overall survival, local response, toxicity, relapse-free survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on sequence generation given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All those randomised accounted for in analysis
Free of selective reporting?	Low risk	Planned outcomes described and reported
Free of other bias?	Low risk	No other bias identified

Adelstein 2003

Study characteristics	
Methods	Randomised controlled trial conducted in: USA Number of centres: 2 Recruitment period: March 1992 to December 1999 Funding source: Public Health Service Grants CA23318, CA66636, CA21115, CA04919, CA73590, CA58416, VA14028, CA04920 & CA16116 Trial identification number: Int 126a & Int 0126b
Participants	Inclusion: adults with histologically confirmed squamous cell or undifferentiated carcinoma of head & neck, excluding a primary tumour originating in nasopharynx, paranasal sinus, or parotid gland. Stage 3 or 4, (AJCC1988) M0, unresectable (criteria specified) ECOG performance status 0, 1 with adequate haematological, renal, hepatic function and normal serum calcium Exclusion: prior treatment for cancer, any previous cancer from which patient had been disease-free for less than 5 years, pregnant or lactating women 295 randomised, 271 evaluable
Interventions	**Comparison 3: Concomitant chemoradiotherapy versus radiotherapy alone** Gr A (n = 97): radiotherapy - total dose of 70 Gy given in single daily 2 Gy fractions plus concomitant cisplatin (100 mg/m^2) intravenously on days 1, 22 & 43 of RT Gr B (n = 96): 3 cycles of 4 days continuous infusion of 5-FU (1000 mg/m^2/day) + cisplatin bolus 75 mg/m^2 on day 1 repeated every 4 weeks, together with concomitant RT 36 Gy during first cycle chemotherapy and remainder during 3rd chemotherapy cycle 30-40 Gy Gr C (n = 102): radiotherapy - total dose of 70 Gy given in single daily 2 Gy fractions
Outcomes	Total mortality, disease-specific survival (unable to use these data)
Notes	Data for total mortality taken from Pignon 2009

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients stratified by primary tumour site, tumour extent (T1-3 vs T4) & nodal status (N0 vs N1 vs N2-3), and then randomly assigned to treatment - no details on sequence generation given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	High risk	Not mentioned
Incomplete outcome data addressed?	Low risk	Numbers and reasons for exclusion and withdrawal clearly stated and similar in each group (2 in each group did not receive the allocated treatment and

Adelstein 2003 *(Continued)*

		7, 10 and 7 patients from groups A, B & C respectively were either ineligible or had no data)
Free of selective reporting?	Low risk	Planned outcomes described and reported
Free of other bias?	Unclear risk	In toxicity results (table 4, p. 95) data from ineligible patients were included. Unclear whether ineligible patients were included in other outcome data

Argiris 2008

Study characteristics	
Methods	Randomised controlled trial conducted in: USA Number of centres: Multicentre Recruitment period: April 1994 to April 2002 Funding: Not stated
Participants	Inclusion: patients with previously untreated pathologically confirmed squamous cell carcinoma of head & neck, M0, who have had surgical resection. Patients were deemed high risk due to either: 3 or more positive lymph nodes, extracapsular spread in 1 lymph node, perineural invasion at primary site, intravascular invasion, surgical margins less that 5 mm. Aged over 18 years, PS 0-2, adequate haematological & biochemistry parameters Exclusion: history of previous malignancy in past 5 years, previous chemotherapy or radiotherapy 76 randomised, 72 evaluated
Interventions	**Comparison 2: Surgery + adjuvant treatment A versus surgery + adjuvant treatment B** Gr A (n = 36): radiotherapy 1.8 Gy/day, 5 x per week to total dose of 59.4 Gy over 6.5 weeks + carboplatin 100 mg/m^2 over 60 mins IV, weekly, prior to RT for 6 weeks Gr B (n = 36): radiotherapy 1.8 Gy/day, 5 x per week to total dose of 59.4 Gy over 6.5 weeks
Outcomes	Primary outcome disease-free survival, also total mortality, toxicity, patterns of relapse
Notes	Planned to have sample size of 100 patients per arm to give adequate power. However, due to slow accrual (76 patients over 8 years), authors calculated that power of study to detect a 15% difference between groups in 2 year DFS was 48%.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned, no stratification factors". No information on sequence generation provided
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment provided
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned

Argiris 2008 *(Continued)*

Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Unclear risk	4/76 subsequently found to be ineligible and 2 refused treatment. Not stated which groups these were from
Free of selective reporting?	Low risk	Planned outcomes of DFS, OS, patterns of relapse and toxicity reported
Free of other bias?	Unclear risk	There was some imbalance between groups at baseline - Gr A had 80% of larynx cancer patients and Gr B had 70% of oral cavity cancer patients. Details of high risk features of Gr A largely unknown (table 1)

Bensadoun 2006

Study characteristics	
Methods	Randomised controlled trial conducted in: France Number of centres: 8 Recruitment period: November 1997 to March 2002 Funding source: N/A
Participants	Inclusion: patients with unresectable Stage 4 (T4 or large pan pharyngeal T3) previously untreated squamous cell carcinoma of the oropharynx or hypopharynx, histologically confirmed (N0- N3, M0 with Karnofsky Performance Status > 60% and adequate haematological, renal and liver function) 171 patients recruited (123 oropharynx, 40 hypopharynx, 54 T3 and 109 T4), 163 evaluable Age: Gr A 72:10 Gr B 72:9 M/F: 144:19 OC + OP = 123/163 = 75%
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A (n = 81): radiotherapy with chemotherapy. 3 cycles (starting on days 1, 22, 43) of cisplatin (100 mg/m^2 on day 1) followed by 5-day infusion of 5-FU (750 mg/m^2/d reduced to 430 mg/m^2/d for the second and third courses) given concurrently with radiotherapy Gr B (n = 82): radiotherapy 2 daily fractions of 1.2 Gy 5 days a week for 7 weeks. 2 parallel opposed fields were used, max spinal cord dose = 40.8 Gy. At 57.6 Gy, the fields were reduced to include the primary only. The total dose was 80.4 Gy to the oropharynx and 75.6 Gy to the hypopharynx.
Outcomes	Total mortality, disease-free survival and specific survival all presented as Kaplan-Meier with log rank tests for 5 years
Notes	Sample size calculation given: "For an expected gain of roughly 20% overall survival at 2 years in the tested arm with an α risk of 0.05 and a β risk of 0.20 (i.e. 80% study power) the inclusion of a minimum of 68 patients in each arm was essential. It was decided (given the possibility that some patients would be lost to the trial) to include 80 patients per arm, (160 in all) over 54 months (4.5 years)".
Risk of bias	
Bias	**Authors' judgement** **Support for judgement**

Bensadoun 2006 *(Continued)*

Random sequence generation (selection bias)	Low risk	Carried out centrally by independent service using a minimisation technique with stratification according to location of primary tumour
Allocation concealment (selection bias)	Low risk	No other information given but likely to have been concealed
Blinding of participants?	Low risk	Open-label
Blinding of carers?	Low risk	Open-label
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	8 patients excluded from analysis (4 died before trial commenced, 2 patients erroneously included, 2 patients refused treatment and lost to follow-up)
Free of selective reporting?	Low risk	Primary and secondary outcomes clearly stated and results presented
Free of other bias?	Unclear risk	Nutritional support was provided to those who required it - 54/81 (67%) of Gr A and 38/82 (46%) of Gr B. Possible indication of differences in disease severity between groups

Bernier 2004

Study characteristics	
Methods	Randomised controlled trial conducted pan-Europe Multicentre (27 centres) Recruitment period: July 1987-July 1990. It was planned to recruit 338 patients but the trial stopped after the 178th event (death or progression of disease). An interim analysis was conducted and published and a final analysis followed after an additional 26 months of follow-up. Funding source: Industrial (Roberts Laboratories, USA) and Government/charity (Ligue Nationale Francaise Contre le Cancer, France) Trial Number: EORTC 22931
Participants	Inclusion: patients with stage III or IV SCC of the H & N (87 with oral cavity and 101 with oropharynx equivalent to 56% oral cavity/oropharynx cancer patients) (Included patients with stage pT3-pT4 any nodal stage (N) except pT3 N0 of the larynx, with negative resection margins, or a tumour stage of 1 or 2 and no distant metastasis (M0). Patients with stage T1 or T2 N0 or N1 who had unfavourable pathological findings (extranodal spread, positive resection margins, perineural involvement or vascular tumour embolism) were also eligible, as were those with OC or OP tumours with involved lymph nodes at level IV-V. Tumour stage T1-T4, N0-N4, M0) Results presented on intention-to-treat, protocol deviations presented for each arm Patient were recruited from specialist radio-oncology clinics 334 randomised. Aged 18-70 years
Interventions	**Comparison 2: Surgery + adjuvant treatment A versus surgery + adjuvant treatment B** Gr A (n = 167): surgery with curative intent followed by concomitant CT (cisplatin 100 mg/m^2 on days 1, 22 and 43 of the radiotherapy regimen) plus RT PORT (66 Gy over a period of 6.5 weeks)

Bernier 2004 *(Continued)*

	Gr B (n = 167): surgery with curative intent followed by RT PORT (66 Gy over a period of 6.5 weeks)
Outcomes	Total mortality (presented as hazard ratios for death). Follow-up period: 8 years Death or recurrent disease (presented as hazard ratios for disease progression (authors definition of disease progression included death)). Follow-up period: 8 years Complications of treatment - toxicity/adverse events
Notes	Data for total mortality taken from Pignon 2009 Progression-free survival: hazard ratios for death or recurrent disease given in text and used to calculate log [hazard ratio] SE Power: "trial was designed to detect and increase in progression-free survival of 15% (40-55%) with a 2-sided 5% significance level and a statistical power of 80%".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed centrally by EORTC DATA co-ordinating centre. Randomisation was by Pocock minimisation technique stratified by centre, site and T stage (T1-T3 vs T4)
Allocation concealment (selection bias)	Low risk	Allocation was revealed by telephone call or internet connection to randomisation centre.
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Insufficient information provided
Incomplete outcome data addressed?	Low risk	All randomised participants accounted for and included in analysis
Free of selective reporting?	Low risk	Primary and secondary outcomes clearly stated and results reported
Free of other bias?	Low risk	No other bias identified

Bitter 1979

Study characteristics

Methods	Randomised controlled trial conducted in: assumed to be Germany & Austria Number of centres: 13 Recruitment period: not explicitly stated - "2 years ago" Funding source: not stated
Participants	Inclusion: adults with operable T3, Nx M0 tumours of buccal cavity. 100% OC
Interventions	**Comparison 2: Surgery + adjuvant treatment A versus surgery + adjuvant treatment B**

Bitter 1979 *(Continued)*

	Gr A (n = 16): received postoperative chemotherapy methotrexate, bleomycin and vincristine (dosages and regimen not stated) Gr B (n = 17): received postoperative radiotherapy cobalt-60 (regimen and dosage not stated) Mean age Gr A: 51 years, Gr B: 55 years
Outcomes	Locoregional recurrence, total mortality, disease-free survival
Notes	It was planned to enrol 100 patients into the trial but after 33 patients enrolled a clear difference in outcome was evident and recruitment was stopped. Information from translation by A Bluemle

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on sequence generation given. Numbers of patients from each hospital were different in Groups A & B - potentially this could mean that the groups varied with respect to extent of disease at baseline.
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All 33 patients randomised to treatment were included in the analysis of outcomes at 2 years.
Free of selective reporting?	Unclear risk	No primary or secondary outcomes specified
Free of other bias?	Low risk	Numbers of patients from each hospital were different in Groups A & B - potentially this could mean that the groups varied with respect to extent of disease at baseline.

Brizel 1998

Study characteristics

Methods	Randomised controlled trial conducted in USA Multicentre trial (2 institutions) Recruitment period: June 1990 to December 1995 Funding source: Government - National Cancer Institute
Participants	Inclusion: patients with advanced head & neck cancer recruited (previously untreated stage 3 or stage 4, N0-N3, M0 SCC for patients with cancer of the tongue, T2N0 were also eligible), 116 were evaluable. Most patients had unresectable disease. 122 randomised

Brizel 1998 *(Continued)*

	*Our analysis based on IPD data provided by authors (100% OC/OP from IPD data authors provided) Adults aged 18-75 years eligible
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A (n = 26*): concomitant CT (5 days of cisplatin by daily bolus of 12 mg/m^2/day to a total of 60 mg/m^2 and 5-FU by continuous infusion 600 mg/m^2/day). CT was administered during weeks 1 and 6 of hyperfractionated radiotherapy with 2 further cycles planned on completion of radiotherapy. RT consisted of 1.25 Gy twice daily with a 6-hour interfraction interval, to a total of 70 Gy, over 7-week period Gr B (n = 32*): hyperfractionated RT alone, 1.25 Gy twice daily with a 6-hour interfraction interval, to a total of 75 Gy over a 6-week period
Outcomes	Total mortality* IPD Disease-free survival *IPD Toxicity data/adverse events
Notes	*Authors provided IPD data on patients with cancer of the tongue, tonsil and oral cavity (58 patients in total) Total mortality: log [hazard ratio] SE calculated from IPD data for total mortality Death or recurrent disease-free survival: log [hazard ratio] SE calculated IPD data for disease-free survival

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Strategy designed by biostatistics unit. PI telephoned the protocol officer to receive the patients treatment allocation. A permuted block design was used with equal opportunity of assignment to Gr A or Gr B and randomisation stratified by resectability of the cancer and haemoglobin concentration (< 12 or > 12 g per dL)
Allocation concealment (selection bias)	Low risk	Third party allocation by biostatistics unit
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Insufficient information given
Incomplete outcome data addressed?	Low risk	All randomised participants accounted for and included in analysis
Free of selective reporting?	Low risk	Primary and secondary outcomes clearly stated and results presented
Free of other bias?	Low risk	No additional threats to validity

Browman 1986

Study characteristics

Methods	Randomised controlled trial conducted in: Canada Number of centres: multicentre

Browman 1986 *(Continued)*

	Recruitment period: October 1980-September 1982 Funding source: not stated
Participants	Inclusion: histologically confirmed and measurable squamous cell carcinoma of head & neck, stage III or stage IV disease with a known primary site or recurrent disease, aged less than 75 years, ECOG performance status 0-2, normal hepatic, renal and bone function Exclusion: third space fluid accumulation, evidence of distant metastatic disease beyond head and neck region Total of 82 patients randomised, 47 cases previously untreated, 30/47 untreated cases of oral cavity cancer Review has used data from 30/47 cases of previously untreated oral cavity cancer.
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** Gr A (n = 23 prev untreated): sequential MTX, 200 mg/m^2, IV bolus at time 0, then 5-FU 600 mg/m^2, IV bolus 1 hour after MTX, then calcium leucovorin 10 mg/m^2 orally every 6 hours x 6 doses, starting 24 hours after MTX Gr B (n = 24 prev untreated): simultaneous 5-FU, 600 mg/m^2, IV bolus at time 0, MTX, 200 mg/m, IV bolus within 15 minutes of 5-FU, calcium leucovorin, 10 mg/m^2 orally every 6 hours x 6 doses, starting 24 hours after MTX
Outcomes	Response rate Survival presented as Kaplan-Meier survival curves for up to 48 months
Notes	Only oral cavity new cases with no previous treatment were included in this review. Data for this subgroup were available. 35 participants in this trial had recurrent disease and 32 of these had prior treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information given
Allocation concealment (selection bias)	Unclear risk	Insufficient information given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All randomised participants accounted for and included in analysis
Free of selective reporting?	Low risk	Primary outcomes clearly stated and results reported
Free of other bias?	Low risk	No additional threats to validity

Browman 1994

Study characteristics	
Methods	Randomised controlled trial conducted in Canada Multicentre trial (4 institutions) Recruitment period: April 1987-August 1991 Funding source: Government National Cancer Insitute of Canada, Medical Research Council of Canada Trial identification number: Ontario
Participants	267 patients were recruited and 175 randomised with histologically confirmed SSC of the head & neck Stage III or IV (21 (12%) with cancer of the oral cavity and 74 (42%) with oropharyngeal cancer; combined 54% OC/OP cancer patients). Withdrawals and dropouts accounted for
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A (n = 88): concomitant fluorouracil I-FU 1.2 g/day delivered in dextrose/saline solution over a 72-hour infusion period beginning 6 hours after the first weekly RT dose, in the first and third weeks of RT. RT consisted of 66 Gy by conventional fractionation scheme of 2 Gy per day, 5 times a week for 6.5 weeks Gr B (n = 87): placebo + RT alone. Placebo was saline in the diluting solution used for the CT administration. RT consisted of 66 Gy by conventional fractionation scheme of 2 Gy per day, 5 times a week for 6.5 weeks. In both groups, the first 50 Gy was delivered to the treatment volume with appropriate prophylactic margins. The cord dose was 40 Gy. The final 16 Gy was delivered as a sequential boost to the initial macroscopic disease, including electron field when required. Doses delivered to subclinical disease areas was 50 Gy.
Outcomes	Disease-free survival (presented as Kaplan-Meier estimates). Follow-up period: 4 years Total mortality* IPD Toxicity/adverse events
Notes	Log [hazard ratio] SE calculated from data provided from Pignon 2000

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Carried out centrally according to a computer-generated series of numbers using stratified (by treatment centre, primary disease site and tumour stage) block randomisation with variable block size
Allocation concealment (selection bias)	Low risk	Treatment centres contacted a central randomisation office to obtain allocation.
Blinding of participants?	Low risk	Patients randomised to receive either radiotherapy + 1-FU or radiotherapy + placebo
Blinding of carers?	Unclear risk	Insufficient information provided
Blinding of outcome assessors?	Unclear risk	Insufficient information provided

Browman 1994 *(Continued)*

Incomplete outcome data addressed?	Low risk	All randomised participants accounted for and included in analysis
Free of selective reporting?	Low risk	Primary and secondary outcomes clearly stated and results presented
Free of other bias?	Low risk	No additional threats to validity

Brunin 1989

Study characteristics	
Methods	Randomised controlled trial conducted in France Single centre Recruitment period: March 1983-June 1986 Funding source: unclear Trial identification number: HNCGIC02
Participants	Inclusion: adults with advanced stage III or IV SCC of the H & N (37 (37%) with oral cavity - tongue, floor of mouth, retro-molar fossa and gingiva and 37 (37%) with oropharynx equivalent to 74% combined OC/OP cancer patients) T2-T4, N0-N3 Patients were recruited from specialist cancer hospital. Median age of Gr A: 54.8 years and Gr B: 54.4 years. 100 randomised; analysed Gr A: 44/48 and Gr B: 46/52 events/patients
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** Gr A (n = 48): induction chemotherapy with cisplatin 20 mg/m^2/day in 2-hour continuous infusions on days 1-4; bleomycin 12.5 mg/m^2/day given as a continuous infusion on days 1-4; vindesine 2.5 mg/m^2/day given by IV on day 1; mitomycin C 10 mg/day given given by IV on day 2 and methylprednisolone 60 mg/m^2/day on days 1-4. The patients started a second cycle on day 21 and radiotherapy 2 or 3 weeks after completion of the second cycle of chemotherapy. Gr B (n = 52): radiotherapy of the primary tumour and cervical lymph node areas up to a dose of 50-55 Gy Patients were re-evaluated by radiotherapist and head & neck surgeon by clinical examination, computed tomography, and if necessary, fibroscopic examination under general anaesthetic. If the regression was judged satisfactory (i.e. > 50%) radiotherapy was completed to a total tumour dose of 65-75 Gy in 1.8 to 2.2 Gy per fraction. If there was a poor response, surgery was performed.
Outcomes	Total mortality* IPD
Notes	*Data supplied from Pignon 2000. Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000; based on individual patient data

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information given

Brunin 1989 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All randomised participants accounted for and included in analysis
Free of selective reporting?	Low risk	Primary and secondary outcomes clearly stated and results presented
Free of other bias?	Low risk	No additional threats to validity identified

Budach 2005

Study characteristics	
Methods	Randomised controlled trial conducted in: Germany Number of centres: 10 Recruitment period: March 1995 to June 1999 Funding source: Grant from Deutsche Krebshilfe eV Trial identification number: ARO 95-06
Participants	Inclusion: patients with previously untreated, unresectable, stage 3 or 4 (UICC) squamous cell carcinoma of the head and neck (oropharynx, hypopharynx, & oral cavity) M_0, aged 18-70 years, Karnofsky Performance Status > 70% Exclusion: previous or synchronic cancer, surgery, previous CT or RT, severe vascular risk factors, insulin dependant diabetes mellitus, symptomatic liver cirrhosis, HIV, pregnancy, serum creatinine > 1.5 mg/dL or clearance < 80 mL Age: 54.5 (33-71); Gr A = 55 (35-71), Gr B = 54 (33-71) M/F: 322:62; Gr A = 165:29, Gr B= 157:33
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A (n = 190): (C-HART) concomitant CT & RT. FU administered as a continuous infusion for 120 hours at 600 mg/m^2/d on days 1-5, and on days 5 & 36 MMC was administered as a single bolus injection of 10 mg/m^2. RT (HART = hyperfractionated accelerated radiotherapy) consisted of matched opposing lateral fields and an anterior neck field matched below. Central lead shielding was used to protect the larynx, spinal cord and lung apices. Radiotherapy was performed with 6 MV photons with up to 36-40 Gy when the posterior neck was blocked to shield the spinal cord max of 45 Gy to cord, total dose 70.6 Gy. Gr B (n = 194): (HART = hyperfractionated accelerated radiotherapy) consisted of matched opposing lateral fields and an anterior neck field matched below. Central lead shielding was used to protect the larynx, spinal cord and lung apices. Radiotherapy was performed with 6 MV photons with up to 36-40

Budach 2005 *(Continued)*

	Gy when the posterior neck was blocked to shield the spinal cord max of 45 Gy to cord RT alone & total dose of 77.6 Gy.
Outcomes	Locoregional control, total mortality, progression-free survival, freedom from metastasis rates shown as Kaplan-Meier curves with log rank test and cox regression analysis Data were given at 2, 3 and 5 years follow-up. Hazard ratios were given. Data for total mortality taken from Pignon 2009
Notes	NOTE: RADIOTHERAPY DIFFERED between groups - C-HART has lower total dose compared to HART. Sample size calculation given "Estimating a 15% difference between HART and C-HART with respect to LRC, a first kind error of 5%, a power of 85% and accrual of 4 years, a follow-up of 2 years, and a loss to follow-up of 10% for a time base of survival of 3 years, a total sample size of 350 patients was calculated to test a 2 sided alternative hypothesis of differences between HART and C-HART using the log rank test".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation carried out in blocks of 4 patients to obtain fully balanced treatment groups". Randomisation scheme allowed for stratification by stage, site and centre.
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	Post-randomisation exclusions and withdrawals clearly described in each group. 7 patients were withdrawn form the C-HART and four from HART another 32 C-HART and 15 HART were excluded due to incorrect radiotherapy or chemotherapy, noncompliance or death (total 20% in C-HART & 10% in HART); intention-to-treat, available for therapy and per-protocol populations analysed
Free of selective reporting?	Low risk	Outcomes clearly described and reported
Free of other bias?	Low risk	No other bias identified

Buffoli 1992

Study characteristics

Methods	Randomised controlled trial conducted in: Brescia, Italy Number of centres: 1

Buffoli 1992 *(Continued)*

	Recruitment period: January 1981 to November 1983 Funding source: not stated
Participants	Inclusion: previously untreated patients with histologically and clinically confirmed diagnosis of upper aerodigestive tract cancer, T3 or T4, any N. Aged < 75 years, primary tumour in either oral cavity, oropharynx, larynx or hypopharynx, measurable disease, Karnofsky performance status ≥ 60%, adequate haematological function, no evidence of liver, lung, heart or kidney disease 49 randomised, 49 evaluated 36/49 = 73% had oral cavity or oropharyngeal primary tumours
Interventions	**Comparison 1: Induction chemotherapy followed by locoregional treatment (LRT) versus LRT alone** Gr A (n = 29): induction CT. Day 1 2 g/m^2 hydroxyurea orally + 15 mg/m^2 IV bleomycin, Day 2 50 mg/m^2 IV methotrexate + 6 hours later 45 mg/m^2 IV folinic acid. Day 1 & 2 repeated on Day 3 & 4, and these 4 days of CT repeated every week for 4 weeks. On week 5, RT started, 2 Gy/day, 5 days/week to total dose of 60 GY over 6 weeks Gr B (n = 29): alternating RT/CT/RT. 2 weeks of RT 2 Gy/day 5 x/week (20 Gy) as first phase, then CT - Day 1 2 g/m^2 hydroxyurea orally + 15 mg/m^2 IV bleomycin, Day 2 50 mg/m^2 IV methotrexate + 6 hours later 45 mg/m^2 IV folinic acid. Day 1 & 2 repeated on Day 3 & 4, and these 4 days of CT repeated every week for 4 weeks. Then final 40 Gy of RT over 4 weeks to total dose of 60 Gy Radiotherapy was given using a single Co_{60} 6 MV machine, with an single protocol for all the patients, using 2 opposing and parallel fields to include the primary tumour and lymph nodes to a total dose of 42 Gy. The treatment was then modified to exclude the spinal area, & spinal nodes were irradiated with electron fields until the prescribed total dose was reached.
Outcomes	Tumour response at end of CT, 2 months after end of treatment, OS & DFS at 5 years
Notes	From translation by Dr Nicoletta Bobola. No sample size calculation was performed. Objectives were to investigate the feasibility and curability of combined RT/CT. Pignon 2000 data not used as discrepancy between this paper and Buffoli 1992 with regard to direction of effect and denominators in each group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence generation was by means of random numbers generated by computer. Allocations were placed in sealed envelopes.
Allocation concealment (selection bias)	Low risk	Sealed envelopes were distributed by Insitute secretary as each patient was included in the study.
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All randomised patients included in evaluation of survival, tumour response and toxicities
Free of selective reporting?	Low risk	Planned outcomes of OS, DFS at 5 years and tumour response reported

Buffoli 1992 *(Continued)*

Free of other bias?	Low risk	No additional threats to validity identified

Chauhan 2008

Study characteristics	
Methods	Randomised controlled trial conducted in: India Number of centres: 1 Recruitment period: November 2000 to March 2003 Funding source: not stated
Participants	Adults with locally advanced (T3,T4, any N, M0) previously untreated squamous cell carcinoma of the head & neck. Patients had unresectable disease or had refused surgery, KPS ≤ 70%, adequate liver function, bone marrow reserve and renal function 80 randomised 40 in each group, 84% oral or oropharyngeal cancer
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A (n = 40): radiation therapy 2 Gy per fraction, one fraction per day, 5 times per week to a total dose of 64 Gy + gemcitabine, 100 mg/m^2 IV over 30 minutes, once a week 1-2 hours before radiation therapy Gr B (n = 40): radiation therapy 2 Gy per fraction, one fraction per day, 5 times per week to a total dose of 64 Gy. In both groups, treatment was individualised according to the site & extent of disease, and the spinal cord was excluded from radiation after dose of 44 Gy.
Outcomes	Toxicity (haematological, skin reaction, mucositis, nausea, vomiting, weight loss) and locoregional control
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Prospectively randomised"; no details of sequence generation methods given
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All randomised patients included in toxicity and locoregional control outcomes

Chauhan 2008 *(Continued)*

Free of selective reporting?	Low risk	Planned outcomes of toxicity and locoregional control reported
Free of other bias?	Low risk	Groups appeared well balanced at baseline.

Chauvergne 1988

Study characteristics	
Methods	Randomised controlled trial conducted in: France Number of centres: not stated Recruitment period: August 1981 to November 1985 Funding source: not stated
Participants	Inclusion: adults with advanced squamous cell carcinoma of head & neck initially assessed as inoperable. Mean age: Gr A 54 (SD 7.8); Gr B 53.1 (SD 7.3) 143/241 = 59% oral cavity/oropharyngeal cancer
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** Gr A (n = 119) induction CT cisplatin 80 mg/m^2 every 3 weeks for 3 cycles Gr B (n = 122) induction CT cisplatin 80 mg/m^2 (day 4) + vincristine 1 mg/m^2 (day 1) + methotrexate 10 mg/m^2/d (days 1-3) and bleomycin 10 mg/m^2/d (days 1-3), repeated every 3 weeks for 3 cycles
Outcomes	Total mortality, relapse-free survival, toxicity
Notes	From translation by A-M Glennie

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned", no details of sequence generation given
Allocation concealment (selection bias)	Unclear risk	Insufficient information given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	2 post-randomisation exclusions in each group - unlikely to bias results
Free of selective reporting?	Low risk	Total mortality, relapse-free survival and toxicity planned and reported

Chauvergne 1988 *(Continued)*

Free of other bias?	Low risk	No significant differences between the groups at baseline

Cohen 2014

Study characteristics	
Methods	Randomised controlled trial conducted in: United States of America Number of centres: 20 Recruitment period: December 2004 to May 2009 Funding source: Sanofi Aventis, Robert and Valda Svendsen Foundation Trial identification number: NCT00117572
Participants	Inclusion: adults (age ≥ 18 years) with diagnosis of N2 or N3 squamous cell carcinoma of the head and neck (according to AJCC 6th edition). Included patients were of Karnofsky Performance Status ≥ 70 with normal haematological and hepatic function. Exclusion: evidence of metastatic disease, symptomatic peripheral neuropathy or prior therapy A total of 285 patients were randomised. 272 patients were evaluable.
Interventions	**Comparison 1: Induction chemotherapy followed by locoregional treatment (LRT) versus LRT alone** Gr A (n = 138): Induction chemotherapy with two cycles of docetaxel-cisplatin-5-fluorouracil followed by concurrent chemoradiotherapy with docetaxel-5-fluorouracil-hydroxyurea and twice-daily radiation (total radiation dose guidelines included 74-75 Gy to gross tumour, 54 Gy to high-risk microscopic disease and 39 Gy to low-risk microscopic disease). Gr B (n = 135): Concurrent chemoradiotherapy with docetaxel-5-fluorouracil-hydroxyurea and twice-daily radiation (total radiation dose guidelines included 74-75 Gy to gross tumour, 54 Gy to high-risk microscopic disease and 39 Gy to low-risk microscopic disease).
Outcomes	Overall survival, distant failure-free survival, recurrence-free survival, response rate.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants?	Low risk	Participants not blinded
Blinding of carers?	Low risk	Carers not blinded

Cohen 2014 *(Continued)*

Blinding of outcome assessors?	Low risk	Outcome assessors were blinded (independent review)
Incomplete outcome data addressed?	Low risk	Almost all randomised patients had outcome data available.
Free of selective reporting?	Low risk	All outcomes reported
Free of other bias?	Low risk	No other bias identified

Cooper 2004

Study characteristics	
Methods	Randomised controlled trial conducted in USA Multicentre (12 centres) mixture of general and specialist centres. Part of the Radiation Therapy Oncology Group (RTOG). Supported by the Eastern and South West Oncology groups (ECOG & SWOG). Intergroup phase 3 trial: RTOG 9501, ECOG R9051 and SWOG 9501 Recruitment period: September 1995-April 2000 Funding source: Government - National Cancer Institute, grants (CA 21661 & CA 32115)
Participants	Inclusion: adults with squamous cell carcinoma of oral cavity, oropharynx, larynx or hypopharynx who had undergone complete resection, had high-risk characteristics, (any 2 of histological evidence of invasion of at least 2 lymph nodes, extracapsular extension of nodal disease, microscopically involved mucosal margins of resection) 459 randomised, 416 evaluable patients (consisting of 27% OC, 43% OP - combined 70% OC/OP)
Interventions	**Comparison 2: Surgery + adjuvant treatment A versus surgery + adjuvant treatment B** Both groups underwent total surgical resection of all visible and palpable disease. Gr A (n = 228): surgery plus postoperative concomitant CRT (cisplatin 100 mg/m^2 intravenously on days 1, 22, 43) plus RT - 60 Gy in 30 fractions over a period of weeks with or without a boost of 6 Gy in 3 additional fractions over a period of 3 days to high-risk sites Gr B (n = 231): surgery plus radiotherapy alone - 60 Gy in 30 fractions over a period of weeks with or without a boost of 6 Gy in 3 additional fractions over a period of 3 days to high-risk sites Radiotherapy was initiated as soon after surgery as adequate healing had occurred, typically 4-6 weeks post-surgery but no later than 8 weeks (56 calendar days).
Outcomes	Total mortality (presented as hazard ratio for death. Additionally, authors provide overall survival presented as Kaplan-Meier estimates). Follow-up period: 5 years Death or recurrent disease (presented as hazard ratio for disease or death). Follow-up period: 5 years Recurrent disease (presented as hazard ratio for local or regional reoccurrence). Follow-up period: 5 years (median 45.9 months) Complications of treatment - toxicity/adverse events
Notes	Data for total mortality taken from Pignon 2009

Cooper 2004 *(Continued)*

	Sample size calculation given: randomisation of 398 eligible patients was required to have the statistical power to detect an absolute improvement of 15% in 2-year rate of local or regional recurrence, with 0.80 statistical power and significance level of 0.05.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation stratified by age (< 70 vs 70+) and presence or absence of tumour in margins, and was performed at headquarters using the permuted block allocation (Zelan) where treatment assignments were balanced by institution and then according to patient factors.
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	Reasons for post-randomisation exclusions clearly described and similar in both groups
Free of selective reporting?	Low risk	Prespecified outcomes described and reported
Free of other bias?	Low risk	No other bias identified

Corvo 2001

Study characteristics

Methods	Randomised controlled trial conducted in Italy Multicentre centre (6 institutions) Recruitment period: 1992-1998 Funding source: government Trial identification number: INRC-HN-9
Participants	136 patients randomised and evaluable with advanced stage II (unfavourable tongue cancer)-IV SCC of the head and neck (consisting of 26 (19%) OC, 52 (38%) OP - combined 57% OC/OP) Withdrawals and dropouts accounted for Patients were adults aged < 75 years
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A (n = 70): alternating CT and RT. Treatment consisted of 4 cycles of IV cisplatin (20 mg/m^2 of body surface area/day for 5 consecutive days) and 5-FU (200 mg/m^2 of body surface area/day for 5 consecutive days, weeks 1, 4 and 7) alternated with 3 2-week courses of RT (20 Gy/course, 2 Gy/day, 5 days/week)

Corvo 2001 *(Continued)*

	Gr B (n = 66): high-dose, partly accelerated RT (PA-RT). Treatment consisted of partly accelerated RT with a final second course using concomitant boost technique. Total planned dose of PA-RT was 75 Gy in 40 fractions over 6 weeks.
Outcomes	Disease-free survival (presented as Kaplan-Meier estimates). Follow-up period: 4 years Total mortality (overall survival presented as Kaplan-Meier estimates). Follow-up period: 4 years
Notes	Data for total mortality taken from Pignon 2009 NOTE: RADIOTHERAPY DIFFERED BETWEEN THE TWO GROUPS.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was performed by making a telephone call to a central office that had responsibility over randomisation and data management". Randomisation was stratified by institution.
Allocation concealment (selection bias)	Low risk	Maintained by central office, accessed by telephone
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	Analysis by intention-to-treat. Exclusions, withdrawals and discontinuation clearly described for each group
Free of selective reporting?	Low risk	All outcomes reported
Free of other bias?	Low risk	All outcomes reported

De Andres 1995

Study characteristics

Methods	Randomised controlled trial conducted: Spain Number of centres: 1 Recruitment period: May 1986 to December 1988 Funding source: not stated
Participants	Inclusion: adults aged < 70 years with histologically proven squamous cell carcinoma of head & neck stage 4, M0, without prior treatment. Patients must have assessable disease, Karnofsky performance status > 70%, serum creatinine < 130 µmol/L or creatinine clearance > 50 mL/min, ALT/AST < 100 IU/L, WBC > 3500/µL, & platelets > 100, 000/µL 96 patients randomised, 1 withdrew consent prior to start of treatment
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)**

De Andres 1995 *(Continued)*

	Gr A (n = 49): cisplatin 100 mg/m^2 on day 1 + FU 500 mg/m^2 by continuous infusion over 120 hours, repeated every 21 days. All patients were given metoclopromide and diphenhydramine as antiemetics. Gr B (n = 47): carboplatin 400 mg/m^2 by continuous infusion over 24 hours + FU 5000 mg/m^2 by continuous infusion over 120 hours repeated every 21 days. Patients were given metoclopromide as antiemetics. Patients from both groups were then offered radiotherapy 1.8 to 2 Gy/day, 5 times/week to a total dose of 65-70 Gy
Outcomes	Tumour response, toxicity
Notes	Trial stopped early due to significant differences detected in favour of control arm. 5-year follow-up is available on the patients randomised before the trial was stopped.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on sequence generation given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	1 patient randomised withdrew consent prior to start of treatment but the other 95 patients included in evaluation. 2 patients lost to follow-up after treatment completion
Free of selective reporting?	Low risk	Planned outcomes of response and toxicity were reported.
Free of other bias?	Low risk	No other bias identified

Denis 2004

Study characteristics

Methods	RCT conducted pan-France Multicentre centre (8 institutions) Recruitment period: July 1994 to September 1997. Funding source: government - French Ministry of Health Trial identification number: GORTEC study ('Groupe d'Oncolgie Radiothérape Tête et Cou - GORTEC) 9401

Denis 2004 *(Continued)*

Participants	226 adults aged less than 75 years recruited and 222 were evaluable all with histologically confirmed SCC of the oropharynx (base of the tongue, tonsillar fossa or posterior wall and soft palate; T1-T4 stage III-IV, N1-N3, M0)
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A: concomitant CT (carboplatin and 5-FU) plus RT (n = 109) Gr B: RT alone (n = 113) CT was concomitant (administered weeks 1, 4 and 7) and consisted of 3 cycles of a 4-day regimen containing carboplatin (daily bolus dose of 70 mg/m^2/day) and 5-FU (600 mg/m^2/day by continuous infusion over 24 hours). CT was administered during the RT treatment period. Patients also received antiemetics (metoclopramide and dexamethasone). The CT cycle was initiated on days 1, 22 and 43; RT consisted of conventional fractionation 70 Gy in 35 2 Gy fractions, 1 fraction per day. If there were no palpable lymph nodes, 44 Gy was delivered in the lower part of the neck and in the spinal lymph nodes, and 56 Gy was delivered in the cervical areas adjacent to involved lymph node areas. The dose to the spinal cord was kept below 44 Gy.
Outcomes	Disease-free survival (presented as Kaplan-Meier estimates). Follow-up period: 4 years Total mortality (overall survival presented as Kaplan-Meier estimates). Follow-up period: 4 years Complications of treatment - early (acute) and late toxicity
Notes	Data for total mortality taken from Pignon 2009

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomly assigned to a treatment group by a central office. Randomisation balanced by institution and clinical stage"
Allocation concealment (selection bias)	Low risk	Performed centrally
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	Withdrawals clearly described in each group
Free of selective reporting?	Low risk	Reporting complete for all outcomes and withdrawals, if applicable
Free of other bias?	Low risk	No other bias identified

Depondt 1993

Study characteristics

Methods	Randomised controlled trial conducted in France

Depondt 1993 *(Continued)*

	Multicentre (9 centres), mixture of cervicofacial surgery or radiotherapy departments Recruitment period: January 1988-July 1991 Funding source: unknown Trial identification number: CFHNS
Participants	Inclusion: adults < 70 years, T2-T4 epidermoid carcinoma of head & neck, life expectancy greater than 12 weeks and Karnofsky performance status > 70% Exclusion: tumours localised to glottis or sinuses, multiple tumour sites, distant metastases, previous treatment for upper aerodigestive tract tumours, unresectable, contraindications to chemotherapy. 324 randomised; 300 analysed. 79/300 patients with OC and 106/300 with OP (26% OC, 35% OP - combined 61% OC/OP)
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** Gr A (n = 150): induction CT (3 cycles of carboplatin (400 mg/m^2/day) day 1 and 5-FU (1 g/m^2) days 1-5, repeated every 3 weeks) plus locoregional treatment (all receivde RT; some received surgery) Gr B (n = 150): radiotherapy (all received RT; some received surgery) Radiotherapy consisted of cobalt-60 at 75 Gy when used alone on tumours and palpable nodes; this dose was reduced to 45-50 Gy on node area in N0 patients. Baslingual and T2 tonsillar tumours were exposed to cobalt-60 45-50 Gy, followed by brachytherapy 30-35 Gy. Surgical excision sites were irradiated at 45-75 Gy depending on the degree of resection. The level of radiation applied to cervical nodes depended on histologic status: N0 patients 45 Gy, N+ patients 55-60 Gy and N+R+ patients 70-75 Gy. LRT for T2 cancer consisted of brachytherapy combined with lymph node dissection. LRT for T3 and T4 tongue cancer consisted of radiation and surgery. For floor of the mouth cancer - surgical removal of primary tumour followed by cobalt-60 treatment, depending on the nodal status and resection results. For oropharyngeal tumours on the base of the tongue, posterior pharyngeal wall and T2 tumours of the tonsillar fossa - cobalt-60 alone. T3-T4 tonsillar fossa surgery and radiotherapy
Outcomes	Total mortality* IPD
Notes	*Data supplied from Pignon 2000. Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000; based on individual patient data Preliminary report for oral cancer patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned

Depondt 1993 *(Continued)*

Incomplete outcome data addressed?	Unclear risk	24/324 (7%) patients randomised were subsequently excluded (17 dropped out, 1 was randomised twice and 6 were found to be ineligible) but not stated which groups they were from
Free of selective reporting?	Low risk	Planned outcomes described and reported
Free of other bias?	Unclear risk	Patients were initially randomised to locoregional control (radiotherapy and/or surgery) alone or locoregional control plus chemotherapy. However, there was considerable variation between patients as to the nature of LRT received (brachytherapy, radiotherapy, surgery) and those who had tumour regression had cobalt-60 treatment regardless of LRT strategy to which they were originally assigned.

Dobrowsky 2000

Study characteristics	
Methods	Randomised controlled trial conducted in: Vienna, Austria Number of centres: 1 Recruitment period: October 1990 to December 1997 Funding source: Medizinischwissenschaftlicher Fonds des Burgermeisters der Bundeshauptstadt Wien Trial idenitfication: Vienna
Participants	Inclusion: adults with T1-4, N0-3 histologically confirmed squamous cell carcinoma of head & neck Exclusion: distant metastases 239 randomised, 239 evaluated. OC 29%, OP 44%, OC+OP = 73%
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Conventional RT versus HFx Acc RT versus HFx Acc RT + concomitant CT Gr A (n = 81): conventional fraction radiotherapy - total of 70 Gy delivered over 7 weeks, 2 Gy/dose, 5 doses per week Gr B (n = 78): (V-CHART) continuous hyperfractionated accelerated radiotherapy given over 17 consecutive treatment days. Day 1: 2.5 Gy, Day 2-17: 1.65 Gy/fraction, 2 fractions per day, with 6-hour minimum inter fraction, interval to total dose of 55.3 Gy Gr C (n = 80): (V-CHART + MMC) continuous hyperfractionated accelerated radiotherapy given over 17 consecutive treatment days. Day 1: 2.5 Gy, Day 2-17: 1.65 Gy/fraction, 2 fractions per day, with 6-hour minimum inter fraction, interval to total dose of 55.3 Gy + bolus injection 20 mg/m^2 mitomycin C on day 5 prior to RT dose
Outcomes	(Primary), tumour response, toxicity
Notes	Study power: " a difference in survival of 15% (from 25-40%) after 3 years between 2 of the treatment groups was detected with a probability of 85% at a significance level of 0.05 (unilateral test)". Recruitment was stopped early after an interim analysis in 1998 showed significant benefit for accelerated RT + MMC. OS Data from Pignon 2009 was included in the analysis (3.1.15), ln (HR) = -0.15, SE = 0.18.

Dobrowsky 2000 *(Continued)*

	However, OS estimate calculated from Fig 1, p. 122 of paper gave ln (HR) = -0.35, SE = 0.19 (non-significant difference)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was stratified by stage (T & N) site, age, performance status and gender. Randomisation was performed by Documentation Office of first Surgical University Clinic, Vienna. Details on method of sequence generation not described
Allocation concealment (selection bias)	Low risk	Patients were allocated to treatment groups by means of a phone call from investigator to randomisation centre.
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All 239 randomised patients were included in the outcome assessment.
Free of selective reporting?	Low risk	Primary outcome was overall survival and tumour response and toxicity also reported.
Free of other bias?	Low risk	4 patients were randomised twice but second randomisation was discarded.

Domenge 2000

Study characteristics

Methods	Randomised controlled trial conducted in France Recruitment period: 1986-1992 Funding source: government and industry Trial identification number: GETTEC neo1 (LRT = RT) (French Groupe d'Etude des Tumeurs de la Tête et du Cou) and GETTEC neo2 (LRT = RT + surgery)
Participants	318 adults aged 18-70 years with biopsy-confirmed SCC of all sites of the oropharynx except for the posterior wall and the anterior surface of the epiglottis, classified as T2-T4, N0-N2b, M0. The trial was interrupted after 6 years of accrual as the accrual rate was so low. Exclusions: contraindications to chemotherapy, previous treatment for malignancy, multiple tumours
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** Gr A (n = 157): induction CT (cisplatin (100 mg/m^2) given in 1 hour IV infusion on day 1 followed by a 24-hour IV infusion of 5-FU (1000 mg/m^2/day) for 5 days. This treatment was repeated on day 22 unless tumour progression exceeded 25% and repeated again on day 43 only if tumour regression had been observed) plus LRT (LRT = RT + surgery, n = 71, LRT = RT alone, n = 86) Gr B (n = 161): LRT (LRT = surgery + RT, n = 73, or RT alone, n = 88)

Domenge 2000 *(Continued)*

	LRT consisted of surgery + RT or RT alone. RT alone commenced 2-3 weeks after the end of the CT. Post-operative RT, within 10 weeks of surgery, consisted of daily 2 Gy fractions, 5 fractions per week over 7 weeks to a total of 70 Gy. In all cases, the posterior spinal area was treated with 42 Gy. In patients with free margins, 50 Gy to the bilateral superior and inferior cervical areas, with a boost of 15 Gy in cases of extracapsular spread. In patients with positive surgical margins, 65 Gy were delivered in 6.5 weeks to the tumour site and bi-lateral superior cervical areas, and 50 Gy to the inferior cervical areas with a boost of 15 Gy in the case of extracapsular spread.
Outcomes	Disease-free survival (presented as Kaplan-Meier estimates). Follow-up period: 8 years *Total mortality (overall survival presented as Kaplan-Meier estimates). Follow-up period: 8 years
Notes	Disease-free survival: hazard ratios for death or recurrent disease given in text and used to calculate log [hazard ratio] SE *Pignon data for GETTEC neo1 and GETTEC neo2 were identical to the trial report, just split according to LRT strata. Used combined overall data from published trial in review. Sample size calculation given - planned to include 760 participants in the study, 400 in the surgery group and 360 in the RT group to give 90% power to detect a 10% difference in survival (α = 5%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomised by telephone .... randomisation was stratified by centre and local treatment (surgery +/- radiotherapy or radiotherapy alone)".
Allocation concealment (selection bias)	Low risk	Randomisation performed centrally, allocated by telephone
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	Withdrawals and dropouts accounted for
Free of selective reporting?	Low risk	All outcomes and withdrawals/dropouts reported
Free of other bias?	Low risk	No other bias identified

Eschwege 1988

Study characteristics

Methods	Randomised controlled trial conducted pan-Europe (France, Belgium, Italy, Germany) Multicentre centre (15 institutions, data from only 13 used in final analysis) Recruitment period: April 1973-December 1974

Eschwege 1988 *(Continued)*

	Funding source: unknown Trial identification number: EORTC73-0
Participants	Inclusion: adults with histologically confirmed SCC of the oropharynx (base of the tongue, tonsillar fossa or posterior wall and soft palate who had tumours > 2 cm or infiltrating regardless of nodal status T2-T4, N1-N3, M0) Exclusions: previous treatment, second primary tumour, poor general status, bone marrow depression, kidney failure, chronic pulmonary disease, diabetes mellitus 224 patients randomised and 199 evaluable
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A (n = 107): concomitant CT (15 mg BLM administered IM or IV twice a week from the start of RT for 5 weeks. Each injection of BLM was given 2 hours prior to the session of RT to a total dose of 150 mg) plus RT. Gr B (n = 92): RT alone RT comprised irradiation of the primary tumour and lymph nodes to a dose of 70 Gy for 7-8.5 weeks, while clinically uninvolved nodes received 50-55 Gy for 5-6 weeks.
Outcomes	Total mortality* IPD Complications of treatment - toxicity/adverse events
Notes	*Data supplied from Pignon 2000

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Tables of random numbers were used to prepare randomisation envelopes for each centre. The randomisation was stratified according to institution and was balanced after every 4. Generation of randomisation sequence and concealment performed by statistical unit"
Allocation concealment (selection bias)	Low risk	Generation of randomisation sequence and concealment performed by statistical unit
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	"25 patients were excluded for different reasons; these patients were well balanced within the two treatment groups".
Free of selective reporting?	Low risk	Primary and secondary outcomes clearly stated and results presented
Free of other bias?	Low risk	2/15 centres were excluded from the analysis because they each only randomised one patient. This was unlikely to have influenced the results of the trial.

Fazekas 1980

Study characteristics	
Methods	Randomised controlled trial conducted pan-USA Multicentre centre (16 RTOG institutions) Recruitment period: 1968-1972 Funding source: unclear Trial identification number: RTOG 6801
Participants	Inclusion: adults with histologically confirmed squamous cell carcinoma or lymphoepithelioma, either T1-2 with N2-3 cervical nodes or T3-4 N0-3 neck disease. Patients with history of previous malignancy but not H & N location were accepted into trial providing they had not received previous chemotherapy and must have been disease-free for > 5 years. Exclusion: previous chemotherapy for malignancy or previous surgery or radiotherapy to head & neck area, distant metastases, 2 simultaneous tumours, general medical reasons such as < 60% standard weight, WBC < 3500, platelets < 100,000 or severely abnormal renal or hepatic function 712 randomised, 638 evaluable (146 (23%) with oral cavity and 354 (56%) with oropharynx, combined OC/OP = 79%)
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** Gr A (n = 340): chemotherapy (methotrexate) 25 mg every third day for 5 injections followed by RT Gr B (n = 340): RT alone - RT was to begin immediately if possible and no later than 2 weeks of completion of CT. For both groups, RT comprised irradiation to primary tumour and cervical nodal drainage area. Doses from 5500 to 8000 rad in 5-10 weeks Surgical intervention (either resection of the primary site or radical neck dissection) was permitted after the completion of RT.
Outcomes	Total mortality* IPD
Notes	*Data supplied from Pignon 2000. Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000; based on individual patient data

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation stratified by primary site, stage and institution. Generation of randomisation sequence unclear
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Unclear risk	712 participants randomised, 44 later found to be ineligible and further 33 lost to follow-up (11%). Not clear how many were from each group, but paper stat-

Fazekas 1980 *(Continued)*

		ed that "more patients who received combined treatment failed to complete irradiation (9%) than the irradiation group alone (4%)" suggesting some imbalance between groups.
Free of selective reporting?	Low risk	Planned outcomes described and reported
Free of other bias?	Low risk	No other bias identified

Fietkau 2020

Study characteristics		
Methods	Randomised controlled trial Multicentre center Recruitment period: 2010-2015 Funding source: supported by the German Cancer Aid Trial identification number: NCT01126216	
Participants	Inclusion: adults (age > 18 years) with stage III-IVB squamous cell carcinoma of the head and neck assessed as ECOG performance status < 2 Exclusion: inadequate haematological, biochemical or renal function, uncontrolled severe somatic or psychological disease, acute infection, reduced hearing or neuropathy, concurrent malignancies, prior radiation therapy or distant metastases/recurrent disease 221 randomised, 216 evaluable	
Interventions	**Comparison 4: Chemotherapy A (+ LRT) versus chemotherapy B (+ LRT)** Gr A (n = 111): concurrent paclitaxel (20 mg/m^2 on day 2, 5, 8, 11, 25, 30, 33, 36) plus cisplatin (20 mg/m^2 on day 1-4, 29-32) with RT to a total dose of 63.6 Gy Gr B (n = 105): concurrent 5-fluorouracil (600 mg/m^2 day 1-5, 29-33) plus cisplatin (20 mg/m^2 day 1-5, 29-33) with RT to a total dose of 70.6 Gy	
Outcomes	Disease-free survival, overall survival	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Reported random sequence generation
Allocation concealment (selection bias)	Low risk	Reported allocation concealment
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned

Fietkau 2020 *(Continued)*

Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	Majority of patients included for outcome assessment
Free of selective reporting?	Low risk	All planned outcomes reported
Free of other bias?	Low risk	No other bias identified

Garden 2004

Study characteristics	
Methods	Randomised controlled trial conducted in: USA Number of centres: multicentre Recruitment period: July 1997 to June 1999 Funding source: National cancer Institute Grants (CA 21661, CCOP U10, CA 37422, STATU 10, CA 32115) Trial name: RTOG 97-03
Participants	Inclusion: patients aged > 18 years, with Karnofsky performance status >/= 70%, with histologically confirmed squamous cell carcinoma of the head and neck, previously untreated. Adequate bone marrow, hepatic, renal and coagulation function was required for participation in trial. Exclusion: prior or synchronous malignancy, clinically significant heart disease 231 randomised
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** Gr A (n = 78): radiotherapy 70 Gy in 35 fractions over 7 weeks plus with cisplatin 10 mg/m^2 daily + 5-FU 400 mg daily, for final 10 days of RT Gr B (n = 76): radiotherapy 70 Gy in 35 fractions (every other week for 13 weeks) with 1 g HU every 12 hours (to total of 11 doses/cycle) + FU 800 mg/m^2/day by continuous infusion concurrent with RT. Treatment given every second week for 13 weeks Gr C (n = 77): (RT + cisplatin + paclitaxel) - radiotherapy 70 Gy in 35 fractions (over 7 weeks) + paclitaxel 30 µg/m^2 every Monday + cisplatin 20 mg/m^2 every Tuesday before RT
Outcomes	Tolerance, toxicity, locoregional control, disease-free survival, overall survival
Notes	HR for total mortality calculated from Kaplan-Meier curves

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was stratified by Karnofsky Performance Status(90-100 vs 70-80). Randomisation method of Zelen was used to obtain balance (only those patients randomised to the experimental groups 1 and 3 were required to give consent). Patients were consented and randomised to groups 1 and 3.

Garden 2004 *(Continued)*

Allocation concealment (selection bias)	Low risk	Patients were enrolled and randomised by a telephone call to the RTOG centre.
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Unclear risk	10 post-randomisation exclusions - not stated which groups these patients were from. 231/241 were included in the acute toxicity and disease recurrence results.
Free of selective reporting?	Low risk	Many outcomes described and reported
Free of other bias?	Low risk	No other bias identified

Gasparini 1993

Study characteristics	
Methods	Randomised controlled trial conducted in: Italy Number of centres: 1 Recruitment period: May 1989 to September 1992 Funding source: not stated
Participants	Inclusion: adults aged 18-75, with histologically proven squamous cell carcinoma of the head and neck, previously untreated and unresectable, stage 3-4 disease (UICC-TNM) M_0, Karnofsky performance status ≥ 70, normal renal function, adequate bone marrow function & life expectancy > 6 months Exclusion: second neoplasms, active infection, history of nephropathy 63 screened, 53 randomised
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** Gr A (n = 27): CDDP - cisplatin 80 mg/m^2 IV infusion on days 1, 21 & 42 starting 2 hours after the start of RT given as daily fractions 5 days/week, to a total of 64 Gy Gr B (n = 26): CRP - carboplatin 375 mg/m^2 as short IV infusion on days 1, 21 & 42, 2 hours after start of RT for 60 mins. RT given as daily fractions 5 days/week, to a total of 64 Gy Both groups received ondansetron.
Outcomes	Disease-free survival, total mortality
Notes	
Risk of bias	

Bias	Authors' judgement	Support for judgement

Gasparini 1993 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomisation stratified by clinical stage, performance status and primary site and treatment was balanced in blocks of 4, using a list of random numbers
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All patients assigned to treatment groups were included in analyses of DFS & OS.
Free of selective reporting?	Low risk	Primary and secondary outcomes described and reported
Free of other bias?	Low risk	No other bias identified

Ghi 2017

Study characteristics	
Methods	Randomised controlled trial conducted in: Italy Number of centres: 48 Recruitment period: January 2003 to January 2006 Funding source: Sanofi Aventis, AVAPO Trial identification number: NCT01086826
Participants	Inclusion: adults (age ≥ 18 years) with diagnosis of histologically/cytologically-confirmed, previously untreated stage III/IV locally advanced squamous cell carcinoma of the head and neck (oral cavity, oropharynx, hypopharynx). Included patients were of Eastern Cooperative Oncology Group Performance Status 0-1 with normal haematological, renal and hepatic function and a life-expectancy of > 6 months. Patients must have been deemed unsuitable for radical surgery for technical reasons or low surgical curability. Exclusion: peripheral neuropathy or altered hearing ≥ grade 2, weight loss > 20% in the preceding 3 months or deemed unresectable due to "medical conditions" 272 patients were evaluable.
Interventions	**Comparison 1: Induction chemotherapy followed by locoregional treatment (LRT) versus LRT alone** Gr A (n = 206): Induction chemotherapy with three cycles of docetaxel (75 mg/m^2), cisplatin (80 mg/m^2) and 5-fluorouracil (800 mg/m^2 on day 1-4) followed by concurrent chemoradiotherapy with either: a) two cycles of cisplatin (20 mg/m^2) and 5-fluorouracil (800 mg/m^2 on day 1-4) in week 1 and 6 of radiation therapy or; b) weekly cetuximab (begin with loading dose 400 mg/m^2 followed by 250 mg/m^2 weekly during radiation therapy). Radiation therapy was 70 Gy delivered 2 Gy per day, 5 days a week. Gr B (n = 208): Concurrent chemoradiotherapy with either: a) two cycles of cisplatin (20 mg/m^2) and 5-fluorouracil (800 mg/m^2 on day 1-4) in week 1 and 6 of radiation therapy or; b) weekly cetuximab (be-

Ghi 2017 *(Continued)*

	gin with loading dose 400 mg/m^2 followed by 250 mg/m^2 weekly during radiation therapy). Radiation therapy was 70 Gy delivered 2 Gy per day, 5 days a week.
Outcomes	Overall survival, response rate, locoregional control rate, progression-free survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random sequence generation
Allocation concealment (selection bias)	Low risk	Reported allocation concealment
Blinding of participants?	Unclear risk	No blinding of participants
Blinding of carers?	Unclear risk	No blinding of carers
Blinding of outcome assessors?	Unclear risk	Unclear if outcome assessors blinded
Incomplete outcome data addressed?	Low risk	Outcome data available for nearly all participants
Free of selective reporting?	Low risk	All outcomes reported
Free of other bias?	Low risk	No other bias identified

Giglio 1997

Study characteristics

Methods	Randomised controlled trial conducted in: Argentina Number of centres: 1 Recruitment period: February 1992 to December 1994 Funding source: not stated Trial identification number: IAR-92
Participants	Inclusion: adults with inoperable squamous cell carcinoma of head & neck 68 patients randomised
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A (n = 37): cisplatin 20 mg/m^2 + 5-FU 300 mg/m^2 + folinic acid 20 mg/m^2 on days 1-4 in weeks 1, 4, 7 & 10 alternating with radiotherapy 2 Gy/day in weeks 2-3 & 1.5 Gy/day in 2 fractions separated by 6-hour intervals on weeks 5 & 6, and 8 & 9 to total dose of 80 Gy

Giglio 1997 *(Continued)*

	Gr B (n = 17): hyperfractionated radiotherapy alone - 2 fractions of 1.2 Gy/day separated by 6-hour intervals for 6.5 weeks to total dose of 79.2 Gy
Outcomes	Tumour response (end of treatment) toxicity, time to progression
Notes	Data for taken from Pignon 2009 (based on Giglio 1999) Translation from original Spanish by L Fernandez-Mauleffinch

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised". No information on sequence generation given. Planned 2:1 ratio Gr A: Gr B
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Unclear risk	15 did not complete treatment (11 from Gr A & 4 from Gr B - reasons given) and unclear how many were included in outcome assessment
Free of selective reporting?	Low risk	Planned outcomes - response, toxicity, survival, time to progression reported
Free of other bias?	Low risk	Groups appeared similar at baseline.

Gladkov 2007

Study characteristics

Methods	Randomised controlled trial conducted in: Russia Number of centres: 1 (Chelybinsk Regional Oncology Centre) Recruitment period: 2005-7 Funding source: not stated
Participants	Inclusion: stage II, III & IV oral cavity and oropharyngeal cancer, without prior treatment 64 randomised, median age 54
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** Gr A (n = 22): radiotherapy + cisplatin (6 mg/m^2 IV once per day) Gr B (n = 26): radiotherapy + cisplatin (40 mg/m^2 IV once per week) + NaCl (up to 2500 mL intravenously)

Gladkov 2007 *(Continued)*

	Gr C (n = 12): radiotherapy + cisplatin (100 mg/m^2 IV once per 3 weeks) + NaCl (up to 2500 mL intravenously) Pre-medication with antiemetics, glucocorticoids, metoclopramide. Duration of CT was not specified. RT consisted of 2 Gy daily fractions 5 days per week to a total dose 68-70 Gy.
Outcomes	Tumour response, adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed using the computer generator of random numbers".
Allocation concealment (selection bias)	Unclear risk	Insufficient Information provided
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All randomised patients accounted for and included in analysis
Free of selective reporting?	Low risk	Primary and secondary outcomes clearly stated and results presented
Free of other bias?	Low risk	No additional threats to validity

Gonzalez-Larriba 1997

Study characteristics

Methods	Randomised controlled trial conducted in: Spain Number of centres: 1 Recruitment period: 1988 to 1992 Funding source: not stated
Participants	Adults with locally advanced squamous cell or undifferentiated cancer of the head & neck, histologically confirmed, with locoregional spread, stage 3-4, M_0, Karnofsky performance status ≥ 70%, no previous treatment, evaluable/measurable tumour lesions, adequate renal & liver function, no previous neoplasia
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** Gr A (n = 34): cisplatin 100 mg/m^2 day 1 + continuous 5-FU 1000 mg/m^2 on days 2-6. 4 x 21-day cycles

Gonzalez-Larriba 1997 *(Continued)*

	Gr B (n = 33): cisplatin 100 mg/m^2 on day 1+ fluorouracil 300 mg/m^2/day in 3 doses on days 2-20. 4 x 21-day cycles Patients in both groups who had a response to induction chemotherapy were then given radiotherapy.
Outcomes	Total mortality, progression-free survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly assigned" - no further details given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All randomised patients included in the analyses
Free of selective reporting?	Low risk	Primary and secondary outcomes described and reported
Free of other bias?	Low risk	No other bias reported

Grau 2003

Study characteristics

Methods	Randomised controlled trial conducted pan-world (Bulgaria, India, Malaysia, Pakistan, Sri Lanka and Turkey) Multicentre (7 institutions) Recruitment period: February 1996-December 1999 Funding source: government and industry - IAEA Co-ordinated Research Project E3.30.13 Trial identification number: IAEA-MMC
Participants	Inclusion: patients with locally advanced (UICC TNM St 3 & 4) squamous cell carcinoma of the pharynx, larynx & oral cavity, aged over 18 years, WHO performance status < 2, with normal haematological, liver and kidney function Exclusion: prior or planned surgical excision 558 patients were recruited with advanced head & neck cancer. Insufficient accrual and reporting led to the exclusion of 3 centres. The final evaluable study population consisted of 478 patients from 7 cen-

Grau 2003 *(Continued)*

	tres. Patients had stage III (n = 223) or stage IV (n = 255) SCC oral cavity n = 230 (48%), oropharynx n = 140 (29%), combined OC/OP = 77%
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A (n = 251): concomitant CT (mitomycin C as an IV infusion over at least 15 min in a dose of 15 mg/m^2. To reduce the risk of extravasation of MMC, it was recommended not to inject in cubital veins or below the wrist. MMC was administered at the end of the first week of RT. On the day of drug treatment, RT was given first and the interval between RT and MMC was at least 2 hours) + RT (conventional) Gr B (n = 227): RT (conventional) alone No patients received surgery. All were advanced tumours, but treatment was with curative intent. RT for both groups consisted of external RT given by Co-60 or linear accelerator. The treatment was given by photons or electrons at a dose of 0.5-5 Gy per minute. The fields covering the clinical target volume (CTV) included the primary tumour in T- and N-position, allowing a margin of approximately 2 cm (at least 1 cm, depending on size of tumour and technique used). In cases of involved palpable lymph nodes, the neighbouring (more caudal) lymph node group was included in the CTV, i.e. at least 3 cm distally from the lower part of the palpable lymph node. The fields covering the gross tumour volume (GTV) included only macroscopic tumour tissue, i.e. the tumour and possible lymph node metastases with at least a 1 cm margin. All fields were treated each time. RT was administered in 5 fractions/week, to a centrally absorbed dose of 2 Gy per fraction. The CTV dose was at least 46 Gy. The spinal cord region did not receive more than 50 Gy total. The GTV received a minimum dose of 66 Gy in 33 fractions.
Outcomes	Limited data available; not in a useable form to include in 'Analyses'; OS data taken from Pignon 2009 Complications of treatment - toxicity/adverse events
Notes	Sample size calculation given - "planned to accrue 1000 patients based on the following assumptions. If the true frequency of persistent locoregional tumour control was changed by 15% (from 45 to 60%), the probability calculated by a double sided test, was greater than 99% for a significant difference (P < 0.05). If the true frequency of tumour control was changed by 10% (from 45 to 55%) the probability of observing a significant difference (P < 0.05) was greater than 85%". Study randomised 558 patients and analysed data from 478.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was stratified by tumour localisation (oropharynx, hypopharynx, larynx, buccal mucosa, other oral cavity), tumour stage (T1-2 vs T3-4) nodal stage (N0 vs N1-3), institution. Generation of randomisation sequence and concealment were performed centrally using a random permuted block size of 4 with a 1:1 ratio between arms.
Allocation concealment (selection bias)	Low risk	The randomisation results were returned to the investigator within a working day by fax.
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	3/10 centres not included in analysis (1 centre randomised only 1 patient who died pre-treatment), 2 centres provided insufficient data (n = 13 & 66 patients respectively). This exclusion is unlikely to have influenced the results of the study.

Grau 2003 *(Continued)*

Free of selective reporting?	Low risk	Planned outcomes described and reported
Free of other bias?	Low risk	No other bias identified

Gupta 2001

Study characteristics	
Methods	Randomised controlled trial conducted in Manchester, UK Single centre (Christie Hospital, Manchester) Recruitment period: 1978-1984 Funding source: government and industry Trial identification number: MANCHESTER
Participants	Inclusion: patients recruited with advanced, histologically confirmed, squamous cell carcinoma of head & neck (T3 - T4, including oral cavity and oropharynx cancer patients n = 173) (consisting of 22% OC, 33% OP - combined 55% OC/OP) Exclusion: aged > 75 years, poor general condition, previous treatment Total 313 patients randomised
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A (n = 156): 100 mg/m^2 of methotrexate by IV the first dose 24 hours prior to RT, then on day 14 of the 3-week course of RT Gr B (n = 157): RT alone RT for both groups comprised Megavoltage RT using a 4 MeV linear accelerator in 15-16 fractions over 3 weeks. The radiation dose prescribed was that considered at the Institute to be the level of tolerance of the volume irradiated and was not reduced because of the addition of CT. 271 (87%) patients received dose equal or in excess of 50 Gy in 15-16 fractions over 3 weeks.
Outcomes	Total mortality* IPD Disease-free survival (presented as Kaplan-Meier estimates) for OC and OP. Follow-up period: 5 years Total mortality (overall survival presented as Kaplan-Meier estimates) OC and OP. Follow-up period: 5 years
Notes	*Data supplied from Pignon 2000. Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000; based on individual patient data: log [hazard ratio] SE calculated from data presented in Kaplan-Meier estimates for primary disease-free survival Death or recurrent disease-free survival: log [hazard ratio] SE calculated from data presented in Kaplan-Meier estimates for cancer-specific-free survival

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomly allocated" - stratified for both site of disease and stage of disease

Gupta 2001 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	No withdrawals/dropouts - all patients randomised accounted for and included in the analyses
Free of selective reporting?	Low risk	Primary and secondary outcomes described and reported
Free of other bias?	Low risk	No other bias identified

Gupta 2009

Study characteristics	
Methods	Randomised controlled trial conducted in: India Number of centres:1 Recruitment period: March 2005 to July 2007 Funding source: not stated
Participants	Inclusion: biopsy proven, previously untreated St III or IV squamous cell carcinoma of oropharynx with measurable disease, ECOG performance status 0-1, neutrophils > 1500/mm^3, platelets > 100,000/mm^3, total bilirubin < 1.25 x upper limit of normal, creatinine clearance > 50 mL/min Exclusion: ECOG performance status > 2, treatment protocol changed during study, previous chemotherapy or radiotherapy, any abnormal organ function 105 randomised
Interventions	**Comparison 1: Induction chemotherapy followed by locoregional treatment (LRT) versus LRT alone** Gr A (n = 48): induction PF: 2-3 cycles of 3 weekly cisplatin 75 mg/m^2 on day 1, + 5-FU 800 mg/m^2 IV over 9 hours on days 1-3, followed by concomitant chemoradiotherapy 1.8-2.2 Gy/fraction, 5 fractions/week to total dose 65-70 Gy + weekly cisplatin 35 mg/m^2 IV Gr B (n = 57): concomitant chemoradiotherapy 1.8-2.2 Gy/fraction, 5 fractions/week to total dose 65-70 Gy + weekly cisplatin 35 mg/m^2 IV
Outcomes	Tumour response, acute toxicity, disease-free survival
Notes	
Risk of bias	
Bias	**Authors' judgement** / **Support for judgement**

Gupta 2009 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Stratified by age, stage, ECOG performance status then 'randomised'. No details of sequence generation method described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Unclear risk	18/48 = 38% excluded from Gr A (8 protocol violations during induction CT, 2 took complementary medications, 3 had RT elsewhere, 3 went straight to surgery) 11/57 = 19% excluded from control arm (2 died, 1 had TB, 4 protocol violations, 3 took herbal medications)
Free of selective reporting?	Low risk	Appeared that planned outcomes were reported
Free of other bias?	Low risk	No other bias identified

Haddad 1996

Study characteristics	
Methods	Randomised controlled trial conducted in: Creteil, France Number of centres: 2 Recruitment period: April 1987 to October 1992
Participants	Inclusion: adults with inoperable squamous cell carcinoma of oral cavity, oropharynx, larynx or hypopharynx Exclusion: previous treatment, tumour T1N0, presence of metastases, Karnofsky performance status < 70%, contraindications to chemotherapy 67 randomised, 56 analysed (28 in each group)
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** All patients received induction chemotherapy at baseline, comprising 3 cycles of 2-hour continuous infusion cisplatin + 5 day infusion 5-FU on days 1, 22 and 43 Gr A (n = 34): starting day 64, RT 1.8 Gy daily, 5 x/week to total dose of 70 Gy + 2-hour infusion cisplatin 50 mg/m^2 + 5 mg/kg 5-FU IM 3 x/week, repeated on days 79, 93 & 107 after the start of induction CT Gr B (n = 33): RT alone - 1.8 Gy daily, 9 Gy/week for 8 weeks to total dose of 70 Gy
Outcomes	Total mortality, locoregional control
Notes	Original paper in French - risk of bias information based on information translated by J-H Vergnes

Haddad 1996 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation stratified by stage (1 & 2 vs 3 & 4), lymph node involvement (N_0 vs N_{1-2} vs N_3), and primary tumour site (OC vs OP vs L vs HyphP)
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	Post-randomisation clearly described and numbers similar in both groups. In Gr A, 3/34 died during induction CT, 2/34 refused further treatment & 1/34 protocol violation). In Gr B, 2/33 died during induction CT, 2/33 refused further treatment & 1 protocol violation
Free of selective reporting?	Unclear risk	Little information available
Free of other bias?	Unclear risk	Little information available

Haddad 2013

Study characteristics	
Methods	Randomised controlled trial conducted in: United States of America Number of centres: 16 Recruitment period: August 2004 to December 2008 Funding source: Sanofi Aventis Trial identification number: NCT00095875
Participants	Inclusion: adults (age $\geq$ 18 years) with diagnosis of previously untreated non-metastatic, histologically proven stage III/IV squamous cell carcinoma of the head and neck (oral cavity, oropharynx, hypopharynx or larynx) that was deemed unresectable. Included patients were of World Health Organization Performance Status of 0-1 with normal haematological, renal and hepatic function. Exclusion: prior chemotherapy, radiation therapy or surgery, cancer diagnosis in the past 5 years, severe weight loss (> 25% in the preceding 2 months), symptomatic altered hearing, peripheral neuropathy or "serious illness". A total of 145 patients were randomised and 126 patients were evaluable.
Interventions	**Comparison 1: Induction chemotherapy followed by locoregional treatment (LRT) versus LRT alone** Gr A (n = 70): Induction chemotherapy with three cycles of docetaxel (75 mg/m^2), cisplatin (100 mg/m^2) and 5-fluorouracil (1000 mg/m^2 on day 1-4) every three weeks followed by concurrent chemoradiother-

Haddad 2013 *(Continued)*

	apy with carboplatin (AUC 1.5) weekly during radiation therapy (72 Gy delivered 2 Gy per day). If there was poor response to induction chemotherapy, concurrent chemotherapy was with docetaxel (20 mg/m^2) given weekly during radiation therapy. Gr B (n = 75): Concurrent chemoradiotherapy with cisplatin (100 mg/m^2) on day 1, 22 during radiation therapy (72 Gy delivered 2 Gy per day)
Outcomes	Overall survival, progression-free survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Reported allocation concealment
Blinding of participants?	Low risk	Participants not blinded
Blinding of carers?	Low risk	Carers not blinded
Blinding of outcome assessors?	High risk	Outcome assessors aware of treatment
Incomplete outcome data addressed?	Low risk	Outcome data available for nearly all
Free of selective reporting?	Low risk	All outcomes reported
Free of other bias?	Low risk	No other bias identified

Hitt 2014

Study characteristics

Methods	Randomised controlled trial conducted in: Spain Number of centres: Not defined Recruitment period: December 2002 to May 2007 Funding source: Sanofi Aventis Trial identification number: NCT00261703
Participants	Inclusion: adults (age ≥ 18 years) with diagnosis of previously untreated non-metastatic, histologically proven stage III/IV locally advanced squamous cell carcinoma of the head and neck (oral cavity, oropharynx, hypopharynx or larynx) that was deemed unresectable. Included patients had normal haematological, renal and hepatic function. Exclusion: prior chemotherapy, radiation therapy or surgery or grade ≥ 2 neuropathy.

Hitt 2014 *(Continued)*

	A total of 439 patients were randomised and evaluable.
Interventions	**Comparison 1: Induction chemotherapy followed by locoregional treatment (LRT) versus LRT alone** Gr A (n = 155): Induction chemotherapy with three cycles of docetaxel (75 mg/m^2), cisplatin (75 mg/m^2) and 5-fluorouracil (750 mg/m^2 on day 1-4) every three weeks followed by concurrent chemoradiotherapy with cisplatin (100 mg/m^2) on day 1, 22 and 43 during radiation therapy (70 Gy delivered 2 Gy per day) Gr B (n = 156): Induction chemotherapy with three cycles of cisplatin (100 mg/m^2) and 5-fluorouracil (1000 mg/m^2 on day 1-4) every three weeks followed by concurrent chemoradiotherapy with cisplatin (100 mg/m^2) on day 1, 22 and 43 during radiation therapy (70 Gy delivered 2 Gy per day) Gr C (n = 128): Concurrent chemoradiotherapy with cisplatin (100 mg/m^2) on day 1, 22 and 43 during radiation therapy (70 Gy delivered 2 Gy per day).
Outcomes	Locoregional control rates, time to treatment failure, progression-free survival, overall survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported random sequence generation
Allocation concealment (selection bias)	Low risk	Reported allocation concealment
Blinding of participants?	Low risk	No blinding of participants
Blinding of carers?	Low risk	No blinding of carers
Blinding of outcome assessors?	Unclear risk	Unclear if blinding of outcome assessors
Incomplete outcome data addressed?	Low risk	Almost all patients were evaluated for response.
Free of selective reporting?	Low risk	All outcomes reported
Free of other bias?	Low risk	No other bias identified

HNCProg 1987

Study characteristics

Methods	Randomised controlled trial conducted in: USA Number of centres: multicentre Recruitment period: 1978 to 1982 Funding source: contract with National Cancer Institute/National Institutes of Health

HNCProg 1987 *(Continued)*

	Trial identification number: HNCP
Participants	Inclusion: adults with stages 2 (pyriform sinus), 3 & 4 (oral cavity, hypopharynx & larynx) resectable head & neck squamous cell cancers 462 randomised; 443 "assessable"
Interventions	**Comparison 2: Surgery ± radiotherapy + chemotherapy versus surgery ± radiotherapy alone** Gr A (n = 69): standard care - surgery followed by radiotherapy (S) Gr B (n = 62): induction CT - 1 cycle cisplatin 100 mg/m^2 + bleomycin 15 mg/m^2 for 5 days + standard care (surgery followed by radiotherapy) (I) Gr C (n = 61): induction CT + standard care + subsequent CT - 1 cycle cisplatin 100 mg/m^2 + bleomycin 15 mg/m^2 for 5 days + standard care + monthly cisplatin 80 mg/m^2 for 6 months (M)
Outcomes	Disease-free survival
Notes	Data taken from the subgroup of oral cavity patients published separately in Jacobs 1990, not Pignon 2000

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified by institution, primary tumour site and stage and randomised to treatment at a central site
Allocation concealment (selection bias)	Low risk	Randomisation was done by a phone call to a central office.
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	Stated that "patients were analysed in the group to which they were randomised even if they did not complete the entire treatment program, except for one patient". Data used were from Jacobs 1990, a subset analysis.
Free of selective reporting?	Low risk	Planned outcomes clearly defined and analyses presented
Free of other bias?	Low risk	No other bias identified

Holoye 1985

Study characteristics

Methods	Randomised controlled trial conducted in: USA Number of centres: 3 hospitals Recruitment period: July 1979 to September 1982

Holoye 1985 *(Continued)*

	Funding source: not stated Trial identification number: MCW-1
Participants	Inclusion: stage 2 squamous cell carcinoma of pyriform sinus, or stage 3 or 4 SCC of oral cavity, oropharynx, nasopharynx, nasal cavity, paranasal sinus larynx or hypopharynx Exclusion: T3 N0 lesions of glottic larynx and stage 3 tonsil cancer, distant metastases, life expectancy less than 12 months, granulocytes < 2000/mm^3, white blood cells < 3500/mm^3, platelets < 100,000/mm^3, hepatic disease (oedema, ascites, hypoalbuminaemia, raised serum bilirubin), concurrent malignancy, chronic mental illness, addiction to drugs or alcohol 133 patients screened; 83 randomised; 83 evaluated
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** Gr A (n = 43): neoadjuvant CT consisted of 4 drugs given over 5 days; bleomycin 10 units in 1000 mL of 5% dextrose in 0.25% saline IV over 8 hours for 12 doses over 4 days; cytoxan 200 mg/m^2/day IV for 5 consecutive days; methotrexate 30 mg/m^2/day in 50 mL of 5% dextrose in water IV over no more than 5 mins on days 1 and 5; 5-FU 400 mg/m^2/day IV for 5 consecutive days Patients showing tumour regression underwent second round of CT after 3-week interval. Gr B (n = 40): RT (preoperative irradiation followed by radical resection of primary tumour and regional lymph nodes, or primary irradiation with or without lymph node dissection)
Outcomes	Tumour response Survival (Kaplan-Meier) Disease-free survival (Kaplan-Meier)
Notes	*Data supplied from Pignon 2000. Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000; based on individual patient data Study stopped early following advice from statistician

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All randomised patients included in analysis
Free of selective reporting?	Low risk	Planned outcomes described and reported

Holoye 1985 *(Continued)*

Free of other bias?	Low risk	No other bias identified

Huguenin 2004

Study characteristics	
Methods	Randomised controlled trial conducted in: Switzerland & Italy Number of centres: 12 Recruitment period: July 1994 to July 2000 Funding source: not stated. Stated no conflict of interest Trial identification number: SAKK 10-94
Participants	Inclusion: adults aged 20-75, with SCC of H & N, with WHO performance status ≤ 2, with adequate haematological, renal, cardiovascular and neurological function Exclusion: those with tumours of nasopharynx or paranasal sinuses, metastatic disease 24 patients randomised; 223 analysed. Age: Gr A median age 57 years (range 38-74); Gr B median age 53.5 years (range 33-73) M/F: Gr A 101/11; Gr B 89/23
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A (n = 112): concomitant CT (cisplatin 20 mg/m^2 on 5 days, of weeks 1 and 5) plus RT HFx RT, 1.2 Gy twice daily with inter-fraction interval of 6 hours, 5 x/week to a median dose of 74.4 Gy Gr B (n = 112): RT HFx RT (1.2 Gy twice daily with inter-fraction interval of 6 hours, 5 x/week to a median dose of 74.4 Gy)
Outcomes	Total mortality Time to LR failure Time to treatment failure
Notes	OS data taken from Pignon 2009 Adverse events: acute toxicity (no significant difference between groups)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisation was performed using the minimisation method at the Swiss Institute for Applied Cancer Research Co-ordination and was stratified by institution, site of primary tumour and nodal stage".
Allocation concealment (selection bias)	Low risk	Randomisation performed centrally
Blinding of participants?	Unclear risk	Not mentioned

Huguenin 2004 *(Continued)*

Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	4 withdrawals Gr A; protocol violations described in detail for each group; intention-to-treat analysis
Free of selective reporting?	Low risk	All outcomes and withdrawals/protocol violations reported
Free of other bias?	Low risk	No other bias identified

Jaulerry 1992

Study characteristics	
Methods	Randomised controlled trial conducted in France Number of centres: 1 Recruitment period: 1986 to1989 Funding source: unclear
Participants	108 recruited and randomised patients with advanced stage III or IV SCC of the H & N Patient were recruited from specialist cancer hospital Adults were recruited with a median age of Gr A: 54 years and Gr B: 56 years.
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** Gr A (n = 55): cisplatin 40 mg/m^2/day IV by continuous infusion on days 2, 3, 4 of each cycle + 5-FU 600 mg/m^2/day IV by continuous infusion on days 1-5 + vindesine 3 mg/m^2/day IT on days 1 & 5, repeated every 3 weeks for 3 cycles. 3 weeks after end of CT, RT commenced to the primary tumour and cervical lymph node areas to total dose of 55-70 Gy in fractions of 1.8 to 2.2 Gy. Gr B (n = 53): RT only of the primary tumour and cervical lymph node areas to total dose of 55-70 Gy in fractions of 1.8 to 2.2 Gy In both groups, patients were re-evaluated by radiotherapist and head & neck surgeon by clinical examination, computed tomography and, if necessary, fibroscopic examination under general anaesthetic. If the regression was judged satisfactory (i.e. > 50%) radiotherapy was completed to a total tumour dose of 65-75 Gy. If there was a poor response, surgery was performed; otherwise radiotherapy was continued to full dose.
Outcomes	Survival, tumour response, toxicity
Notes	*Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000; based on individual patient data Presented data from 2 trials. Trial 1 previously published as Brunin 1989 (included in review) and risk of bias information for trial 2 below is taken from Brunin 1989 as Jaulerry 1992 stated that trial design was the same in both studies.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Jaulerry 1992 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Insufficient information given
Allocation concealment (selection bias)	Unclear risk	Insufficient information given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All randomised patients included in the outcome data used from Pignon 2000
Free of selective reporting?	Low risk	Tumour response, toxicity and overall survival planned and reported
Free of other bias?	Low risk	No other bias identified

Jeremic 1997

Study characteristics	
Methods	Randomised controlled trial conducted in Yugoslavia Single centre Funding source: unknown Recruitment period: January 1988-December 1990. The trial stopped in 1990 before patient accrual had reached its number due to staff relocation. Trial identification: KRAGUJEVAC
Participants	159 patients recruited with histologically confirmed locally advanced, non-metastatic (M0), unresectable stage III-IV squamous cell carcinoma of the head and neck including oral cavity and oropharynx cancer patients. Karnofsky permance status > 50%, age > 18 years and adequate haematological, renal and hepatic function (parameters specified) with no previous treatment (26 patients with OC 16%, and 59 patients with OP 37%, combined OC/OP = 53%) Patients aged 34-70 years (median 59 years)
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A (n = 53): concomitant CT (low dose daily 6 mg/m^2 of cisplatin CDPP) plus standard fraction radiotherapy (70 Gy) Gr B (n = 53): concomitant CT (low dose daily 25 mg/m^2 of carboplatin CBDCA) plus standard fraction radiotherapy (70 Gy) Gr C (n = 53): control - standard fraction RT alone (70 Gy) Carboplatin (CBDCA) is CDDP analogue with similar properties but with less renal, ear, or neurotoxicity. RT target volume included the primary tumour, the lymph nodes of the neck and supraclavicular fossa. The tumour bearing area received 70 Gy and the uninvolved neck and supraclavicular nodes 45 Gy. Daily fractions of 1.8 Gy
Outcomes	Total mortality* IPD (Gr A and Gr B versus Gr C)

Jeremic 1997 *(Continued)*

	Toxicity/adverse events - acute and late high-grade toxicity
Notes	*Data supplied from Pignon 2000. Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000 Sample size calculation given: 85 patients were thought to be required per arm to detect a difference in the 3-year survival rate of 20% with a significance level of P = 0.05 and a power of 0.8 assuming a baseline survival rate of 25%. However, study closed to accrual in December 1990 before these numbers were reached. The 159 participants were sufficient to show a 25% difference in survival rate between groups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomised" - no further details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All patients randomised were accounted for and included in analysis.
Free of selective reporting?	Low risk	Planned outcomes clearly described and reported
Free of other bias?	Low risk	No other bias identified

Jeremic 2000

Study characteristics

Methods	Randomised controlled trial conducted in: Yugoslavia Number of centres: 1 Recruitment period: January 1991 to March 1993 Funding source: government. Grants-in-Aid for Scientific Research (B)10557087, 11470190, and 11877152 from the Japanese Ministry of Education, Science, and Culture Trial identification number: KRAGUJEVAC2
Participants	Inclusion: adults with histologically confirmed, locally advanced, non-metastatic, (Stage 3 or 4, M0) squamous cell carcinoma of the nasopharynx, oropharynx, oral cavity, or larynx, with Karnofsky performance status >/= 50%, WBC > 4000, platelets > 100,000, creatinine < 1.5 mg/dL, bilirubin < 1.5 mg/dL, a measurable tumour mass and no previous treatment Exclusion: serious concomitant disease, history of previous or concurrent cancer, tumours of nasal cavity, paranasal sinuses, or salivary gland

Jeremic 2000 *(Continued)*

	154 patients recruited, 130 randomised (27/130 patients with OC 21%, and 48/130 patients with OP 37%, combined OC/OP = 58%) (Withdrawals and dropouts accounted for). Patients aged 39-70 years, median 60 years
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A (n = 65): concomitant CRT - low-dose daily 6 mg/m^2 of cisplatin (CDDP) as IV bolus in the interfraction interval on every RT treatment day plus hyperfractionated (HFx) radiation therapy - 2 daily fractions of 1.1 Gy with inter-fraction interval of 4.5-6 hours Gr B (n = 65): hyperfractionated radiotherapy alone 2 daily fractions of 1.1 Gy with inter-fraction interval of 4.5-6 hours RT target volume included the primary tumour, the lymph nodes of the neck and supraclavicular fossa. The primary tumour and upper neck nodes were treated with 2 lateral opposed fields with 50.6 Gy in 46 fractions in 23 treatment days over 4.5 weeks, after which reduced lateral fields were used to boost the dose to the primary tumour and involved nodes to 77 Gy in 70 fractions in 35 treatment days over 7 weeks. The dose to the spinal cord was kept at 50.6 Gy. The uninvolved lower neck and supraclavicular nodes were treated with a single anterior field and with a total dose of 50.6 Gy. In case of acute high-grade (> grade 3) toxicity, patients temporarily interrupted their treatment for up to 2 weeks, but no dose reductions (for either HFx RT or CDDP) were allowed. Even in cases of treatment interruptions (for both HFx RT and CDDP), subsequent treatment was not modified.
Outcomes	Disease-free survival (presented as Kaplan-Meier estimates). Follow-up period: 8 years Total mortality (overall survival presented as Kaplan-Meier estimates). Follow-up period: 8 years Toxicity/adverse events - acute and late toxicity
Notes	OS data available from Pignon 2009 Log [hazard ratio] SE calculated from data presented in Kaplan-Meier estimates Requested info from authors on randomisation - no response Sample size calculation given - "a total of 129 patients in the 2 treatment groups were thought to be required to detect a difference in the 2-year survival rate of 25% with a significance level of P < 0.05 and a power of 0.8, assuming a baseline survival rate of 45%".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised" - no details given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All randomised participants included in the analyses
Free of selective reporting?	Low risk	Planned outcomes described and reported

Jeremic 2000 *(Continued)*

Free of other bias?	Low risk	No other bias identified

Knowlton 1975

Study characteristics	
Methods	Randomised controlled trial conducted in: USA Number of centres: 1 Recruitment period: not stated Funding source: not stated
Participants	96 patients with biopsy proven advanced squamous cell carcinoma of the head & neck Age: median 57 years M/F: Gr A 40/8; Gr B 35/13
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** Phase 1: Gr A (n = 28): neoadjuvant CT (0.2 mg/kg methotrexate IV per day for 5 days) + RT (4 or 6 MeV liner accelerations or a 2 MeV Van de Graaf treatment 5 days/week. Minimum tumour dose 6000-6600 rads in 6-6.5 weeks at rate of 1000 rads/weekly) Gr B (n = 28): RT (4 or 6 MeV liner accelerations or a 2 MeV Van de Graaf treatment 5 days/week Minimum tumour dose 6000-6600 rads in 6-6.5 weeks at rate of 1000 rads/weekly) After 56 patients randomised, it was decided to increase chemotherapy dose. Phase 2: Gr A (n = 20): high-dose neoadjuvant CT (240 mg/m^2 methotrexate IV per day on days 1, 5 & 9, followed by leucovorin 75 mg/m^2 IV over 6-hour period, then every 6 hours as 15 mg/m^2 for 4 doses) + RT (4 or 6 MeV linear accelerations or a 2 MeV Van de Graaf treatment 5 days/week. Minimum tumour dose 6000-6600 rads in 6-6.5 weeks at rate of 1000 rads/week) Gr B (n = 20): RT (4 or 6 MeV liner accelerations or a 2 MeV Van de Graaf treatment 5 days/week. Minimum tumour dose 6000-6600 rads in 6-6.5 weeks at rate of 1000 rads/week)
Outcomes	Overall survival, toxicity
Notes	Adverse events: no difference in groups reported, but Table IV showed difference between groups for phase 2 toxicity.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomised"; no details given
Allocation concealment (selection bias)	Unclear risk	No details given

Knowlton 1975 *(Continued)*

Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All randomised participants included in the analysis
Free of selective reporting?	Low risk	All outcomes reported
Free of other bias?	Unclear risk	Little information provided but chemotherapy doses increased after first 56 participants randomised. In phase 2, there was shorter follow-up and Gr A study participants had higher toxicity.

Krishnamurthi 1990

Study characteristics	
Methods	Randomised controlled trial conducted in: India Number of centres: 1 Recruitment period: January 1984 to August 1987 Funding source: grant from Department of Science & Tecnology, Government of India, under Project number 1/37/82 - STP - III
Participants	Inclusion: T3-T4 histologically confirmed squamous cell carcinoma of buccal mucosa with or without cervical node metastases, except for those with fixed N3 masses outside submandibular region. Those with external fungation, muscle invasion were eligible. Exclusion: distant metastases, total trismus 114 randomised; 101 evaluated
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A (n = 37): pepleomycin (5 mg IV bolus in 10 mL normal saline given 24 hours prior to RT) + RT (minimum tumour dose of 2.5 Gy per fraction 3 times per week to total dose of 55-60 Gy) Gr B (n = 38): placebo + RT (minimum tumour dose of 2.5 Gy per fraction 3 times per week to total dose of 55-60 Gy) + hyperthermia (deep tissue heating to 42° C using a capacitive unit generating radiofrequency radiations of 8 MHz) Gr C (n = 39): pepleomycin (5 mg IV bolus in 10 mL normal saline given 24 hours prior to RT) + RT (minimum tumour dose of 2.5 Gy per fraction 3 times per week to total dose of 55-60 Gy) + hyperthermia
Outcomes	Locoregional response
Notes	
Risk of bias	

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

Krishnamurthi 1990 *(Continued)*

Random sequence generation (selection bias)	Low risk	"Used MRC sealed envelope technique" referring to the method used by Bradford Hill in 1947 trial of streptomycin for tuberculosis. A table of random numbers was used to allocate participants to groups.
Allocation concealment (selection bias)	Low risk	Allocation was concealed in sealed envelopes.
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	Reasons for post-randomisation exclusions given and numbers small and similar in each group (6/37, 4/38 & 3/36 excluded in each group - reasons given)
Free of selective reporting?	Low risk	Planned outcomes described and reported
Free of other bias?	Low risk	No other bias identified

Kumar 1996

Study characteristics	
Methods	Randomised controlled trial conducted in: India Number of centres: 1 Recruitment period: April 1990 to March 1991 Funding source: not stated Trial identification number: Lucknow1
Participants	38 participants with previously untreated inoperable primary malignancy of the oral cavity (n = 9, 24%), oropharynx (n = 16, 42%), laryngopharynx (n = 13) Exclusion: metastatic disease, deranged liver/kidney function, Karnofsky performance status < 60 Mean age (SD): Gr A 52.3 years (10.4); Gr B 53.8 years (12.5) M/F: Gr A 19/2; Gr B 14/3
Interventions	**Comparison 1: Induction chemotherapy followed by locoregional treatment (LRT) versus LRT alone** Gr A (n = 21): induction CT (cyclophosphamide 600 mg/m^2 and methotrexate 60 mg/m^2 IV bolus on days 1 and 14, followed by concomitant 5-FU 600 mg/m^2 IV bolus on days 28, 35, 42, 49 followed by RT-35 fractions over 7 weeks (delivered by shrinking field technique) to total dose of 70 Gy Gr B (n = 17): RT- 35 fractions over 7 weeks (delivered by shrinking field technique) to total dose of 70 Gy
Outcomes	Tumour response, progression of disease, acute morbidity, late morbidity
Notes	OS data taken from Pignon 2009; Group A received both induction and concomitant chemotherapy

Kumar 1996 *(Continued)*

	Adverse events: deaths due to treatment (Gr A n = 7; Gr B n = 0)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomised using a table of random digits"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All randomised patients accounted for in analysis
Free of selective reporting?	Low risk	All outcomes and withdrawals reported
Free of other bias?	Low risk	No other bias identified

Lam 2001

Study characteristics	
Methods	Randomised controlled trial conducted in Hong Kong Single centre Recruitment period: 1993-1995 Funding source: unknown
Participants	Inclusion: adults with Stage 3 or 4 (T2-T4 N0-N3, M0) squamous cell carcinoma of oral cavity, oropharynx, hypopharynx, or larynx with no distant metastases, who were undergoing planned resection 65 patients randomised; 63 evaluated 32% of sample with oral cavity; 21% oropharynx; 53% combined OC/OP
Interventions	**Comparison 2: Surgery + adjuvant treatment A versus surgery + adjuvant treatment B** Gr A (n = 31): prior to surgery treated with levamisole 50 mg 3 times/day for 3 days (repeated every 2 weeks in case surgery postponed). Adjuvant postoperative chemotherapy with levamisole and UFT (futraful & uracil) was commenced in the third week after surgery. Each cycle included levamisole 50 mg 3 times/day from day 1-3 and UFT 200 mg 3 times/day from day 8-14. The cycle was repeated every 2 weeks with no treatment break and lasted for 1 year or until tumour recurrence (n = 31). Gr B (n = 34): control - surgery no chemotherapy (n = 34) All patients received curative surgical treatment.

Lam 2001 *(Continued)*

Outcomes	Overall survival
Notes	Sample size calculation given - "the sample size was estimated to be 65 cases, according to the tumour response rate to UFT in phase II trials of head and neck cancers and the survival benefit of levamisole/fluorouracil in colorectal cancer (α value = 0.05 and β= 0.2)".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was stratified by tumour site, stage & prior radiotherapy. Generation of allocation sequence was unclear.
Allocation concealment (selection bias)	Low risk	Allocation was revealed by drawing sealed envelopes.
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	2 patients (6%) from Gr A excluded from analysis due to postoperative death
Free of selective reporting?	Low risk	Survival outcome planned and reported
Free of other bias?	Low risk	No other bias identified

Laramore 1992

Study characteristics

Methods	Randomised controlled trial conducted in USA Multicentre. Intergroup study IG-0034 - co-operative groups participating: Radiation Therapy Oncology Group (RTOG), South West Oncology Group (SWOG), Cancer and Leukaemia Group B (CALGB), Northern California Oncology Group (NCOG) and South East Group (SEG) Recruitment period: January 1985-January 1990 Funding source: USA government Trial identification: Int 0034
Participants	Inclusion: adults, aged over 18 years, with histologically confirmed, resectable, squamous cell carcinoma of head & neck, with primary tumour sites in oral cavity, oropharynx & larynx. Karnofsky performance status >/= 60%, WBC >/= 4000, platelets >/= 100,000, creatinine clearance > 60 mL/min Exclusion: distant metastases, prior or concurrent malignancy, prior treatment with radiotherapy, chemotherapy or surgery 696 patients were registered, 499 patients were randomised, 448 were evaluable: Gr A 223, Gr B 225. Some 43 evaluable patients were carried over from the original RTOG 83-22 trial. 122 patients with oral cavity cancer (27%) and 113 patients with oropharyngeal cancer (25%); combined OC/OP = 52%

Laramore 1992 *(Continued)*

Interventions	**Comparison 2: Surgery + adjuvant treatment A versus surgery + adjuvant treatment B** All patients in both groups underwent total surgical resection of all visible and palpable disease, then were staged according to primary tumour site, pathological stage, tumour margin status, risk factors (high risk defined as extracapsular nodal extension,surgical margins less than 5 mm or carcinoma in situ at margins) and low-risk absence of these. Patients were randomised within 3 weeks of surgery and postoperative treatment started within 4 weeks of surgery. Gr A (n = 223): postoperative CT (cisplatin 100 mg/m^2) on day 1 with infusion of 5-FU at 1 g/m^2 over 24 hours on days 1-5 with the sequence repeated every 21 days plus radiotherapy - 50-54 Gy to low-risk treatment volumes and 60 Gy to high-risk volumes, delivered at 1.8-2.0 Gy per fraction on a 5 day-a-week basis Gr B (n = 225): control - postoperative radiotherapy 50-54 Gy to low-risk treatment volumes and 60 Gy to high-risk volumes, delivered at 1.8-2.0 Gy per fraction on a 5 day-a-week basis Radiotherapy was initiated 2-3 weeks after completion of the preceding modality.
Outcomes	Disease-free survival. Follow-up period: 4 years Total mortality. Follow-up period: 4 years Total mortality* IPD Recurrence (locoregional recurrence). Follow-up period: 4 years Complications of treatment - toxicity/adverse events
Notes	*Some data supplied from Pignon 2000. Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000; based on IPD: Gr A: 161/251 and control Gr B: 163/248 (events/patients)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were stratified by tumour location, pathological staging and surgical margins. Then randomisation was performed by headquarters office. Generation of allocation sequence was adequate (author personal communication).
Allocation concealment (selection bias)	Low risk	Allocation concealment was adequate (author personal communication).
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Unclear risk	Of the 51 randomised patients excluded from the analyses, reasons were given for 42 but paper did not state how many patients were randomised to each group and how many of each group were then included in analysis.
Free of selective reporting?	Low risk	Tumour response, overall survival, patterns of recurrence described and reported
Free of other bias?	Low risk	No additional threats to validity identified

Le 2006

Study characteristics	
Methods	Randomised controlled trial conducted in USA Single centre Recruitment period: July 1996-June 2001 Funding source: government - Public Health Sevice Grant CA67166 awarded by the National Cancer Institute
Participants	Inclusion: adults aged more than 17 years with resectable stage 4 squamous cell carcinoma of the head & neck with metastases to cervical lymph nodes. ECOG performance status 0-2, no prior radiotherapy or chemotherapy, adequate bone marrow, hepatic & renal function, no concurrent malignancy, no prior malignancy within 5 years Original report on 62 patients where OP + OC = 69% of H & N SCC. However, authors provided IPD data on 43 oropharynx (n = 39) and oral cavity patients (n = 4). Gr A: n = 25/33 OC/OP only; Gr B: n = 18/29 OC/OP only
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** 2 cycles of induction chemotherapy with cisplatin 100 mg/m^2/day on days 1 & 22 + continuous infusion 5-FU (1000 mg/m^2/day) for 120 hours/cycle on days 1 & 22 Gr A (n = 33): induction CT + concomitant CRT A: 2 cycles of induction chemotherapy with tirapazamine* prior to cisplatin 100 mg/m^2/day on days 1 & 22 + continuous infusion 5-FU (1000 mg/m^2/day) for 120 hours/cycle on days 1 & 22. Followed by 2 more cycles of concomitant chemoradiotherapy (tirapazamine* 1-2 hours prior to cisplatin 20 mg/m^2/day on days 43, 45, 47 & 71, 73, 75 + continuous infusion 5-FU (600 mg/m^2/day) for 120 hours/cycle on days 43 to 47 & 71 to 75) together with conventional RT administered within 3 hours of the end of tirapazamine infusion - dose of the parallel opposed fields at the central axis was 2 Gy per fraction per day given 5 days per week up to a total dose of 66-70 Gy to the areas of the macroscopic tumour. The dose to the supraclavical region was 50 Gy prescribed at a depth of 3 cm and delivered in 25 fractions. *The first 4 patients had tirapazamine (TPZ) induction doses of 300 mg/m^2 and 160 mg/m^2 during concomitant chemoradiotherapy (level 1). The next 4 patients received 330 mg/m^2 TPZ induction and 260 mg/m^2 concomitant (level 2). The remaining 25 patients had 300 mg/m^2 TPZ during induction phase and 220 mg/m^2 during concomitant phase (level 3, n = 25) Gr B (n = 29): induction CT (PF regimen) + concomitant CRT B: 2 cycles of induction chemotherapy with cisplatin 100 mg/m^2/day on days 1 & 22 + continuous infusion 5-FU (1000 mg/m^2/day) for 120 hours/cycle on days 1 & 22. Then 2 more cycles concomitant chemoradiotherapy consisting of cisplatin at a dose of 20 mg/m^2 given 3 times per week (Monday, Wednesday and Friday) and continuous infusion 5-FU at a dose of 600 mg/m^2 for 96 hours per cycle in weeks 1 and 5 of RT Patients who did achieve a complete response at 50 Gy underwent surgical resection and those achieving CR at the primary site and in the neck completed RT to a total dose of 66 Gy to the primary site and involved lymph nodes.
Outcomes	Total mortality**IPD (Gr A versus Gr B) over 5 years Toxicity - acute toxicity
Notes	**IPD provided by author and used to calculate log [hazard ratio] SE for site specific cancers i.e. OP & OC and OP alone Phase II RCT - Primary end point was complete lymph node response. Sample size calculation given "Assuming a complete lymph node response rate of 50% in the control arm, we estimated that 60 patients would yield 80% power to detect a 32% improvement rate with TPZ with a 2-sided level of significance = 0.05".

Le 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified by tumour site, nodal status (N0 vs N2-3), mean tumour oxygen tension (</= 12 mm vs > 12 mm). Randomisation used permuted block procedure. There were more patients with T3 and T4 tumours in the non-TPZ arm and this difference was statistically significant (P = 0.03), and more patients with N3 lymph nodes in the TPZ arm although difference not statistically significant (P = 0.35)
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All randomised participants (except one who withdrew prior to any treatment) were included in analyses
Free of selective reporting?	Low risk	Primary outcome of lymph node response and secondary outcome of survival and toxicity planned and reported
Free of other bias?	Low risk	No other bias identified. As noted above, there was baseline imbalance but we considered this as risk of selection bias.

Lewin 1997

Study characteristics	
Methods	Randomised controlled trial conducted in Norway, Denmark and Sweden Multicentre centre (18 Scandinavian centres) Recruitment period: 1986-1991 Funding source: government/charity - Swedish Cancer Society Trial identification number: SHNG-85
Participants	Inclusion: adults with squamous cell carcinoma of oral cavity, oropharynx, hypopharynx, larynx, stages 2-4 (some variation between centres), both resectable & unresectable, Zubrod Performance Status 0-2, life expectancy >/= 3 months Exclusion: those with clinical evidence of distant metastases, or any medical condition that was a contraindication to chemotherapy 461 patients were randomised; 423 met the inclusion criteria; 374 (81%) were evaluable (175/423 (41%) with oral cavity and 144 (34%) with oropharynx; combined OC/OP = 75%) 356 patients had non-resectable cancer and 67 had resectable cancer of the OC.
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone**

Lewin 1997 *(Continued)*

	Gr A (n = 233): neoadjuvant CT - cisplatin 100 mg/m^2 IV on day 1 + 5-FU 1000/m^2/day on days 1-5, repeated every 21 days for 3 cycles followed by radiotherapy 64-70 Gy, 2 Gy per fraction 5 times per week. A few patients regardless of treatment arm received a boost dose of brachytherapy to tumours of the OC. Gr B (n = 228): RT alone - 64-70 Gy, 2 Gy per fraction 5 times per week. A few patients regardless of treatment arm received a boost dose of brachytherapy to tumours of the OC. Tumour response evaluation was performed 1-2 months after RT. Surgery was considered in cases with resectable residual tumour.
Outcomes	Total mortality* IPD
Notes	*Data supplied from Pignon 2000. Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000; based on individual patient data. Sample size calculation:"to detect a survival benefit of 15% with a power of 80%, 320 patients would be required..... a p value of 5% was considered significant".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation process: stratified by primary site, resectability, sex and institution. The random permuted blocks method was used for randomisation.
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Unclear risk	374/461 (81%) of those randomised were evaluable. 38/461 (8%) found to be ineligible after randomisation, and a further 49/461 (11%) not evaluable. Paper stated that "Many patients were lost to clinical follow-up after 2 months".
Free of selective reporting?	Low risk	Tumour response 2 months after RT and survival outcomes planned and reported
Free of other bias?	Unclear risk	"Slight imbalance between treatment arms in the different subsites due to misclassification". OC patients 54% in Gr A & 46% in Gr B. Were there other imbalances between groups? No table of baseline characteristics/group given

Licitra 2003

Study characteristics

Methods	Randomised controlled trial performed in Italy Multicentre trial (4 centres) Recruitment period: June 1989-December 1999 Funding source: external but source unknown

Licitra 2003 *(Continued)*

Participants	Inclusion: adults with biopsy-proven, resectable, stage T2-T4, N0-N2, M0 - previously untreated oral cavity SCC. T2 lesions were included if > 3 cm. Tumours extending into oropharynx were acceptable, provided that the lesion was contained in the oral cavity by more than 50%. 198 randomised; 191 evaluable
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** Gr A (n = 99): surgery plus chemotherapy - cisplatin 100 mg/m^2 and fluorouracil 1000 mg/m^2 (5-FU)given as 120-hour infusion, for 3 cycles every 21 days. Patients with either progressive or stable disease after 2 cycles were addressed for surgical resection. Patients received the third cycle only when a response ≥ 50% tumour regression was observed. Gr B (n = 99): control - surgery alone (n = 99; evaluable patients n = 95) Surgical choice left to judgement of clinician. Macroscopic safe margin of 1.5 cm mandatory After surgical resection, high-risk patients received postoperative radiotherapy, started 4-5 weeks after surgery (13/63).
Outcomes	Disease-free survival. Follow-up period: 5 years Total mortality. Follow-up period: 5 years Disease-related mortality. Follow-up period: 5 years Recurrent disease - primary site, new primary site, distant metastases. Follow-up period: 5 years Length of hospital stay Complications of treatment - toxicity/adverse events (morbidity)
Notes	Log [hazard ratio] SE calculated from data presented in Kaplan-Meier estimates Sample size calculation given: "The required sample size for the trial was 258 patients equally divided in the 2 study arms. This was calculated by using the Freedman's formula, based on the following assumptions: 50% 5-year risk of cancer recurrence in the control group, 5% type 1 error probability level (for a 2-sided test) and 90% power to detect a 20% absolute risk reduction in the treatment arm". Because of difficult patient accrual, the study was closed after enrolling 198 patients. Study power thus diminished to 78%. The authors noted that "the lack of statistical significance was not because of low power".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomly assigned ... after stratification by institution and nodal stage (N0 vs N1-3)"
Allocation concealment (selection bias)	Low risk	Randomisation was performed on the phone by central operations office in accordance with stratified lists from permuted blocks of length 4.
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	Post-randomisation withdrawals and exclusions clearly described for each group. 96% of those randomised were evaluable.

Licitra 2003 *(Continued)*

Free of selective reporting?	Low risk	Planned outcomes clearly described and reported
Free of other bias?	Low risk	No other bias identified

Luboinski 1985

Study characteristics	
Methods	Randomised controlled trial performed in France Single-centre trial. Part of the EORTC Head & Neck Group. GETTEC neo1 Recruitment period: not stated Funding source: not stated
Participants	Inclusion: patients with tumours of the floor of mouth (100% oral cavity) with extension to the mandible or with a borderline or more than 2 cm with the mandible. Tumour stage T2-T4, N0-N3 (n = 126) Exclusion: patients with prior treatment or severe disease requiring major reconstruction
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** Gr A (n = 64): neoadjuvant intra-arterial chemotherapy, 15 mg of bleomycin daily for 12 days by continuous infusion and 1 mg of vincristine on days 1, 5 and 9 in 1-hour infusions + surgery alone or with postoperative radiotherapy (determined by the quality of the margins and extension to cervical nodes) Gr B (n = 62): control - surgery alone or with postoperative radiotherapy (determined by the quality of the margins and extension to cervical nodes) CT was given intra-arterially on 1 or both sides depending on extent of tumour. Surgery was performed 10-21 days after completion of chemotherapy. It consisted of composite resection with or without interruption of the mandible. Margins were as large as possible. Patients classified as N0 were treated by bilateral suprahyoid neck dissection. A radical neck dissection was undertaken if histologically confirmed node metastasis. For patients with homolateral node involvement, a radical neck dissection was performed with ipsilateral modified neck dissection. Radiotherapy was an optional treatment, performed 3-6 weeks postoperatively determined by the quality of the margins and extension to cervical nodes (data not presented by +/- radiotherapy treatment).
Outcomes	Overall survival
Notes	Radiotherapy was an optional treatment for non-responders.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants?	Unclear risk	Not mentioned

Luboinski 1985 *(Continued)*

Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Unclear risk	74% of those randomised actually received IA chemotherapy. Not clear how many participants were included in the outcome assessments
Free of selective reporting?	Unclear risk	Preliminary results only reported. Unclear as to which were planned primary or secondary outcome measures
Free of other bias?	Unclear risk	Considerable variation in the treatment within each group

Maipang 1995

Study characteristics	
Methods	Randomised controlled trial performed in Thailand Single-centre trial - Songklangarind Hospital a referral centre for southern Thailand Recruitment period: October 1988-June 1993 Funding source: Thai government Trial identification: Songkhla
Participants	Inclusion: adults aged less than 75 years with histologically proven squamous cell carcinoma of oral cavity, oropharynx, hypopharynx, or larynx, with ECOG performance status of 0-2, adequate renal, hepatic & bone marrow function (parameters specified), stage 3-4 disease with resectable tumour, free of infection & distant metastases, no other primary cancer within 5 years, available for long-term follow-up Exclusion: tumours of nasopharynx and paranasal sinuses 54 patients randomised 76% OC, 9% OP, combined OC/OP = 85%
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** Gr A (n = 30): neoadjuvant (induction) chemotherapy with cisplatin 20 mg/m^2, a 2-hour continuous intravenous infusion on days 1-5; bleomycin 10 mg/m^2/day was given as a continuous infusion from days 3-7. On days 15 and 22, methotrexate 40 mg/m^2 was administered intravenously. A second induction cycle started on day 29. Chemotherapy was followed by surgery as per pre-CT plan, and then patients had postoperative radiotherapy within 6 weeks - 6000 rads to primary tumour and 4500 rads to nodes Gr B (n = 24): control - standard treatment of surgery followed by postoperative radiotherapy - 6000 rads to primary tumour and 4500 rads to nodes The extent of surgery was determined prior to chemotherapy and consisted of ipsilateral (and/or contralateral) neck dissection and resection of the primary tumour. Reconstruction was performed by local skin flap, myocutaneous flap, or microvascular free flap.
Outcomes	Total mortality* IPD
Notes	*Some data supplied from Pignon 2000
Risk of bias	

Maipang 1995 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly allocated" - no details given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All randomised patients included in analyses
Free of selective reporting?	Low risk	Tumour response and survival outcomes planned and reported
Free of other bias?	Low risk	No other bias identified

Marechal 1987

Study characteristics	
Methods	Randomised controlled trial conducted in: France Number of centres: 1 Recruitment period: not stated Funding source: grants from FNLCC & 'Ligue Departmentate de L'Aube'
Participants	Inclusion: males, with previously untreated unresectable, biopsy proven, stage 3 or 4 squamous cell carcinoma of head & neck, an evaluable/measurable tumour, life expectancy > 2 months, Karnofsky performance status > 40%, WBC > 4000/mm^3,platelets > 100,000/mm^3, serum creatinine < 130 µmol/L 136 randomised; 117 evaluated
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** Gr A (n = 69): day 1 hydration and diuresis protocol followed by cisplatin 100 mg/m^2 IV as bolus, 3 courses at 3-week intervals Gr B (n = 67): etoposide 100 mg/m^2 orally days 1-5 and cisplatin 100 mg/m^2 on day 4, repeated at 3-week intervals 108 of the 136 participants underwent further radiotherapy. Details not provided
Outcomes	Overall survival, tumour response, toxicity, median survival
Notes	Sample size calculation given: "the aim of the trial was to demonstrate a 20% superiority of Group B (cisplatin-etoposide) compared to Group A (cisplatin alone), giving an error of the first kind of α = 0.05 and an error of the second kind of β = 0.2, the target sample size was n = 64 patients for each group".

Marechal 1987 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified by primary tumour site, presence/absence of associated tumour, tumour stage (T1-2 vs T3-4), and nodal stage (N0-1 vs N2-3). No details of sequence generation methods given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	9 excluded from Gr A (2 deaths & 7 severe toxicity) and 10 excluded from Gr B (8 deaths & 2 'other'); unlikely to have resulted in bias
Free of selective reporting?	Low risk	Tumour response, toxicity, and overall survival reported
Free of other bias?	Low risk	No other threats to validity identified

Mathur 2018

Study characteristics	
Methods	Randomised controlled trial conducted in: India Number of centres: 1 Recruitment period: not reported Funding source: not reported Trial identification number: not reported
Participants	Inclusion: Locally advanced squamous cell carcinoma of the head and neck. Exclusion: not reported. A total of 50 patients were randomised and evaluable.
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** Gr A (n = 25): Induction chemotherapy with three-weekly paclitaxel (175 mg/m^2) and carboplatin (AUC 5) followed by radiation therapy Gr B (n = 25): Induction chemotherapy with weekly paclitaxel (80 mg/m^2) and carboplatin (AUC 5) followed by radiation therapy
Outcomes	Response rate
Notes	

Mathur 2018 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants?	Low risk	Participants not blinded
Blinding of carers?	Low risk	Carers not blinded
Blinding of outcome assessors?	Unclear risk	Not reported
Incomplete outcome data addressed?	Low risk	All participants evaluable for response
Free of selective reporting?	Low risk	All outcomes reported
Free of other bias?	Unclear risk	Unclear statistical plan

Mazeron 1992

Study characteristics	
Methods	Randomised controlled trial performed in France Multicentre trial (2 centres) specialist department/centres within general hospital Recruitment period: December 1982-October 1986 Funding source: unknown
Participants	Inclusion: biopsy-proven squamous cell carcinoma of the oropharynx or oral cavity without metastases Exclusion: stage 1 disease, presence of distant metastases, previous or concurrent malignancy, prior treatment, contraindications to chemotherapy, Karnofsky performance status </= 60% 131 randomised; 116 evaluable Oral cavity cancer patients 43/116 (37%); oropharyngeal cancer patients 73/116 (63%); combined OC/OP = 100%
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** Gr A (n = 63): neoadjuvant CT followed by LRT: bleomycin 10 mg/m^2/day as a continuous infusion from day 1-5, methotrexate 120 mg/m^2 as a 2-hour continuous infusion followed 24 hours later by folinic acid, 10 mg orally every 6 hours for 24 hours. 5-FU, 600 mg/m^2, was given as a short intravenous infusion 2 hours after methotrexate on day 2. Cisplatin 120 mg/m^2 was administered as a 2-hour continuous infusion on day 4 with appropriate hydration infusion and antiemetics. The chemotherapy cycle was repeated on days 29 and 57. LRT RT +/- surgery Gr B (n = 68): locoregional treatment alone (i.e. RT +/- surgery)

Mazeron 1992 *(Continued)*

	Treatment modality of locoregional treatment determined prior to randomisation. Standard treatment for resectable patients consisted of en bloc or composite resection of the primary in conjunction with neck dissection. The mandible was resected when necessary and various flap techniques were used for reconstruction. Frozen sections were used to assess margins during surgery. All patients received post-operative radiotherapy consisting of 55 Gy given at 1.8 Gy per fraction; 5 fractions/week for a period of 6 weeks. The area of residual disease was boosted to 70 Gy in case of incomplete resection.
Outcomes	Overall survival
Notes	*Data supplied from Pignon 2000

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Prior to randomisation, stratified by site (OC vs OP), tumour size (T1-2 vs T3-4) and nodal status (N0 vs N1-3). No details given on sequence generation
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	Reasons and numbers for post-randomisation exclusions described and are similar in each group
Free of selective reporting?	Low risk	Planned outcomes described and reported
Free of other bias?	Unclear risk	"Patients with unresectable disease were assigned to external radiotherapy alone" (p. 86) - not sure if these patients were included in the control group.

Merlano 1991

Study characteristics

Methods	Randomised controlled trial conducted in: Italy Number of centres: 7 Recruitment period: August 1983 to December 1986 Funding source: government/charity - Italian Research Council Trial identification number: INRC HN-7
Participants	Inclusion: adults with inoperable, stage 3 & 4 squamous cell carcinoma of head & neck, aged < 76 years, ECOG performance status </= 3, no major impairment of kidney, liver, bone marrow, heart or lung function. No metastases

Merlano 1991 *(Continued)*

	Exclusion: prior treatment for malignancy, distant metastases, squamous cell carcinoma of paranasal sinuses or larynx, life expectancy < 3 months, age > 76 years, major abnormalities of liver, heart, bone marrow, lung or kidney 116 were randomised (29/116, 25% with oral cavity; 55/116, 47% with oropharynx;equivalent to 72% oral cavity/oropharynx cancer patients)
Interventions	**Comparison 1: Induction chemotherapy followed by locoregional treatment (LRT) versus LRT alone** Gr A (n = 55): induction chemotherapy. Day 1 vinblastine 6 mg/m^2 IV, followed by bleomycin 30 IU IM 6 hours later, day 2 methotrexate 200 mg IV, day 3 leucovorin rescue 45 mg orally. Cycle repeated every 14 days for 4 cycles, followed by RT within 3 weeks. 70 Gy to the involved areas and 50 Gy to the uninvolved neck nodes at 2 Gy fractions, 5 fractions/week Gr B (n = 61): alternating combination chemotherapy: Day 1 vinblastine 6 mg/m^2 IV, followed by bleomycin 30 IU IM 6 hours later, day 2 methotrexate 200 mg IV, day 3 leucovorin rescue 45 mg orally.Total of 4 cycles CT. 2 cycles CT then RT started, 20 Gy each course - 2 Gy in 10 fractions over 2 weeks (60 Gy to the affected areas and 50 Gy to uninvolved areas). RT was administered after the second, third and fourth chemotherapy courses. In Gr B, RT was individualised according to site, extent of the disease with differential loading, shrinking field and boosting dose. Tumours of the OC and OP were treated through 2 opposite fields with dose distribution 2:1 to the involved side in unilateral tumours.
Outcomes	Total mortality* IPD Toxicity
Notes	*Data supplied from Pignon 2000. Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000; based on individual patient data: Gr A: 51/55 and control Gr B: 46/61 (events/patients) (note error in Pignon paper; he has groups the wrong way round but results favoured alternating therapy group)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Prospectively randomised" and stratified by T and N status
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	No withdrawals or dropouts - all patients evaluable for survival
Free of selective reporting?	Low risk	Planned outcomes described and reported
Free of other bias?	Unclear risk	Little information available

Merlano 1992

Study characteristics	
Methods	Randomised controlled trial conducted in Italy Multicentre centre (12 Italian centres) Recruitment period: February 1987-December 31st 1990 Funding source: government/charity Trial identification number: INRC HN-8
Participants	Inclusion: adults aged < 76 years, with histologically confirmed squamous cell carcinoma of pharynx, larynx and oral cavity, unresectable, stage 3 or 4, M0, ECOG performance status 0-3, no major impairment of hepatic, renal, bone marrow, pulmonary or cardiac function, life expectancy >/= 6 months, no other neoplasm, resident near study centre. 157 patients recruited and evaluable (46/157, 29% with oral cavity and 53/157, 34% with oropharynx equivalent to 63% oral cavity/oropharynx cancer patients). Accrual was lower than the planned 180 due to participating centres refusing to recruit to Gr B in light of the poorer response observed in the interim analysis.
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A (n = 80): CT (cisplatin, 5-FU) alternating with RT. Treatment consisted of 4 cycles (weeks 1, 4, 7 & 10) of intravenous cisplatin 20 mg/m^2 of body surface/day and 5-FU 200 mg/m^2/day for 5 consecutive days, alternating with RT in 3, 2-week courses (weeks 2 & 3, 5 & 6, and 8 & 9) at 20 Gy/course, 2 Gy fraction/day 5 days/week Gr B (n = 77): RT alone up to 70 Gy, 2 Gy fraction/day 5 days/week, n = 77 At the end of the treatment patients were re-evaluated. Patients with complete response received no further treatment. Patients with partial response underwent surgical evaluation and some, independent of treatment group, received optional surgical treatment. Those with unresectable disease and in Gr A, received a booster dose to residual tumours, up to a total dose of 70 Gy and those in Gr B received no further treatment unless their disease progressed. Patients with no response (stable disease) underwent palliative chemotherapy treatment. Patients with disease progression during treatment were withdrawn from the study and treated with palliative chemotherapy.
Outcomes	Disease-free survival (presented as Kaplan-Meier estimates). Follow-up period: 6 years Total mortality* IPD
Notes	Log [hazard ratio] SE calculated from data presented in Kaplan-Meier estimates *Data supplied from Pignon 2000

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation process: stratified by primary site, resectability, sex and institution. The random permuted blocks methods was used for randomisation. Specific lists of random numbers were available to each participating centre. Treatment assignment was balanced in blocks of 6-8.
Allocation concealment (selection bias)	Low risk	Allocation was obtained by a phone call to central trial centre.
Blinding of participants?	Unclear risk	Not mentioned

Merlano 1992 *(Continued)*

Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	No withdrawals or dropouts. All patients assigned to treatment groups were included in analysis of PFS and survival.
Free of selective reporting?	Low risk	Planned outcomes described and reported
Free of other bias?	Low risk	No other bias identified

Mohr 1994

Study characteristics	
Methods	Randomised controlled trial performed in Germany as part of DOSAK study Multicentre trial (7 centres) Recruitment period: January 1989-June 1992 Funding source: charitable foundation - Deutsche Krebshilfe, Mildred Scheel Stiftung
Participants	Inclusion: adults with advanced biopsy-proven squamous cell carcinoma of oral cavity and oropharynx, with a minimum tumour size of 2 cm, T2-T4, N0-3, M0 Exclusion: lip carcinoma 377 patients recruited; paper stated 316 evaluable; only 268 included in outcomes OC/OP cancers; combined OC/OP = 100%
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** Gr A (n = 141): preoperative RT conventional fractionated irradiation on the primary and regional nodes, (5 x 2 Gy per week) to a total dose of 36 Gy and preoperative CT, low-dose 12.5 mg cisplatin/m^2/d on first 5 days of radiotherapy, followed by radical surgery Gr B (n = 127): radical surgery alone Radical surgery was defined by DOSAK and performed after a delay of 10-14 days.
Outcomes	Overall survival from Kaplan-Meier graph
Notes	Part of DOSAK study

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stratified by primary site of tumour, depth of infiltration, stage of lymph node disease and age of patient; generated 17 subgroups similarly distributed between arms of study. No information on sequence generation given

Mohr 1994 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	High risk	109/377 = 29% of those randomised were not included in the analysis of the 2 treatments being compared: 23/377 due to protocol violations, 25/377 randomised to RT + surgery did not have surgery, and the remainder "incomplete files" but allocated treatment group not stated.
Free of selective reporting?	Low risk	L/R recurrence, mortality, survival planned and reported
Free of other bias?	Unclear risk	Baseline comparability for participant demographics and stage, but no information as to how many of those randomised were included in these figures

Molinari 1982

Study characteristics	
Methods	Randomised controlled trial conducted in:France & Italy Number of centres: not stated Recruitment period: 1973 to 1977 Funding source: not stated
Participants	Inclusion: adults with histologically-proven squamous cell carcinoma of the head and neck, with or without neck nodes, no metastases Exclusion: female, diabetic, > 70 years of age, previous treatment, second primary tumour, contraindications to chemotherapy such as kidney failure, bone marrow depletion, chronic pulmonary disease, neck nodes which prevented the catheterisation of the arteries for chemotherapy 72 patients randomised
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT) Intra-arterial** Gr A (n = 36): intra-arterial MTX 50 mg/day over 8 hours for 10 days + intramuscular leucovorin 6 mg every 6 hours starting 2 hours after MTX Gr B (n = 36): intra-arterial BLM 15 mg/day over 12-20 hours for 13 days Patients in both groups were then offered either radiotherapy or surgery "depending on the routine protocol of each participating centre". The outcome of regression of the tumour was evaluated prior to the start of radiotherapy or surgery.
Outcomes	Tumour regression expressed as percentage of initial tumour size, toxicity
Notes	

Molinari 1982 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on sequence generation provided. Patients were paired according to age, primary tumour site, tumour extension and clinical nodes. Treatment was allocated randomly to the first patient of the pair and the second patient received the alternative treatment.
Allocation concealment (selection bias)	Low risk	Randomisation and pairing performed by central office and accessed by telephone.
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All 72 patients randomised were included in the tumour regression analysis.
Free of selective reporting?	Low risk	Planned outcomes of tumour regression and toxicity reported
Free of other bias?	Low risk	No other bias identified

Morita 1980

Study characteristics	
Methods	Randomised controlled trial conducted in: Japan Number of centres: 1 Recruitment period: not stated Funding source: not stated
Participants	Inclusion: adults with squamous cell carcinoma of the tongue, T2-3, N0, 1 45 patients randomised
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A (n = 23): radiotherapy plus bleomycin 5 mg/day, 5 times/week to a total dose of 60 mg Gr B (n = 22): radiotherapy, 400 rads Patients in both groups were then offered phase 2 treatment with interstitial radium needles.
Outcomes	Overall survival
Notes	Data from Pignon 2000
Risk of bias	

Morita 1980 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details on method of randomisation given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Unclear risk	Unclear how many patients were included in the outcomes assessment
Free of selective reporting?	Unclear risk	Unclear outcome reporting
Free of other bias?	Unclear risk	Authors provided insufficient detail concerning methods used to enable reader to evaluate sources of bias.

Nervi 1978

Study characteristics	
Methods	Randomised controlled trial conducted in: Italy Number of centres: not stated Recruitment period: 1966 to 1971 Funding source: Stefano Siglienti Fund and generous gift of Mrs L. Shenker
Participants	Inclusion: adults with squamous cell carcinoma of head & neck without clinical evidence of disease beyond neck 142 patients, oral cavity (82 cases, 58%) oropharynx (35 cases, 25%) maxillary antrum (25 cases)
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone (intra-arterial)** Gr A (n = 72): neoadjuvant intra-arterial methotrexate 3-5 mg/day for 25 to 35 days to a total dose of 90-120 mg followed by RT - 40-50 Gy over 4-5 weeks followed by a boost dose of 20-25 Gy for maxillary, or 30-35 Gy by interstitial radium therapy for intra-oral tumours Gr B (n = 70): RT - 40-50 Gy over 4-5 weeks followed by a boost dose of 20-25 Gy for maxillary, or 30-35 Gy by interstitial radium therapy for intra-oral tumours
Outcomes	Overall survival
Notes	Data from Arcangeli 1983
Risk of bias	

Nervi 1978 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients were stratified by site of cancer and then randomised.
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All patients included in analyses
Free of selective reporting?	Low risk	Planned outcomes described and reported
Free of other bias?	Low risk	No other bias identified

Noronha 2018

Study characteristics	
Methods	Randomised controlled trial conducted in: India Number of centres: 1 Recruitment period: 2013 to 2017 Funding source: Tata Memorial Center Research Administration Council Trial identification number: CTRI 2012/10/003062
Participants	Inclusion: adults (age ≤70 years) with diagnosis of locally advanced, stage III/IV squamous cell carcinoma of the head and neck (oral cavity, oropharynx, hypopharynx or larynx). Included patients were of Eastern Cooperative Oncology Group Performance Status of 0-2 with normal renal function. Patients must have been planned for curative concurrent chemoradiotherapy in the primary or adjuvant setting (with presence of close [< 5mm] or positive margin, extra-capsular extension, more than 2 involved lymph nodes or T4 primary). Exclusion: distant metastases or moderate/severe sensorineural deafness or receipt of induction chemotherapy A total of 300 patients were randomised and were evaluable.
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** Gr A (n = 150): Concurrent chemoradiotherapy with cisplatin (30 mg/m^2 weekly) during radiation therapy (70 Gy delivered in 35 fractions for primary curative or 60 Gy in 35 fractions for adjuvant) Gr B (n = 150): Concurrent chemoradiotherapy with cisplatin (100 mg/m^2 every 3 weeks) during radiation therapy (70 Gy delivered in 35 fractions for primary curative or 60 Gy in 35 fractions for adjuvant)

Noronha 2018 *(Continued)*

Outcomes	Locoregional control, response rate, progression-free survival or overall survival
Notes	Non-inferiority trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants?	Low risk	Participants not blinded
Blinding of carers?	Low risk	Carers not blinded
Blinding of outcome assessors?	Unclear risk	Not reported
Incomplete outcome data addressed?	Low risk	All patients had outcome data available.
Free of selective reporting?	Low risk	All outcomes reported
Free of other bias?	Low risk	No other bias identified

Olasz 2000

Study characteristics

Methods	Randomised controlled trial conducted in: Hungary Number of centres: 1 Recruitment period: January 1996 to November 1998 Funding source: not stated
Participants	Adults with primary tumour T2-4, with N0-2, M0, with no prior treatment & Karnofsky performance status 70-100
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** Gr A (n = 19): (BVM) days 1 & 2, 4 mg/m^2 bleomycin IM every 12 hours, day 3, 1.5 mg/m^2 vincristine IV, day 4 60 mg/m^2 methotrexate IV & day 5 7 mg/m^2 leucovorin IM. Cycle 2 started on week 2 and dose of vincristine was increased by 25%, methotrexate dose was increased by 100%. Weeks 3 & 4 no chemotherapy, & week 5 cycle 3 at the increased doses Gr B (n = 19): (BVCM) days 1 & 2, 4 mg/m^2 bleomycin IM, day 3 1.5 mg/m^2 vincristine IV, day 4 30 mg/m^2 cisplatin IV (together with anti-emetic ondansetron and usual hydration protocol), day 5 60 mg/m^2 methotrexate IV & day 6 7 mg/m^2 leucovorin IM. Cycle 2 started on week 2 and dose of vincristine was increased by 25%, methotrexate dose was increased by 100% and cisplatin dose was increased by 50%. Weeks 3 & 4 no chemotherapy, & week 5 cycle 3 at the increased doses

Olasz 2000 *(Continued)*

	3 weeks after the end of chemotherapy, all patients had surgery for lymph node resection. Repeat surgery was undertaken after recurrence of cancer.
Outcomes	Local control, overall survival, time to recurrence
Notes	From translation by Daniel Bereczki

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was not stratified; details of sequence generation not given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All randomised patients were included in the the outcome assessments.
Free of selective reporting?	Low risk	Outcomes local control, overall survival, time to recurrence and site of recurrence planned and reported
Free of other bias?	Low risk	Groups appeared similar at baseline.

Olmi 2003

Study characteristics

Methods	Randomised controlled trial conducted in: Italy Number of centres: 18 Recruitment period: January 1993 to June 1998 Funding source: Consiglio Nazionalle della Recherche Trial number: ORO-9301
Participants	Inclusion: histologically-proven squamous cell carcinoma of oropharynx, stage III or IV, M0, no prior surgery radiotherapy or chemotherapy, age < 70 years, Karnofsky performance status ≥ 70% or ECOG performance status 0-2, adequate bone marrow reserve, renal, hepatic, cardiac and pulmonary function (criteria specified), available for follow-up, informed consent Exclusion: T1N1 & T2N1 disease, previous tumours, active infectious disease, psychosis 192 randomised; 182 evaluated
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone**

Olmi 2003 *(Continued)*

	Gr A (n = 64): 66-70 Gy in 33-35 fractions (2 Gy/fraction) 5 days per week over 6.5-7 weeks. 50 Gy to uninvolved neck nodes, tolerance dose for spinal cord 44 Gy + carboplatin 75 mg/m^2 IV over 30 min days 1-4 and 5-FU 1000 mg/m^2/day IV by continuous infusion over 96 hours on days 1-4, 3 courses on weeks 1, 5, & 9 Gr B (n= 65): 64-67.2 - 2 fractions of 1.6 Gy daily, 4-6 hours apart, 5 x/week. After 38.4 Gy over 2 weeks, 2-week split planned, followed by the second phase same as first Gr C (n = 63): 66-70 Gy in 33-35 fractions (2 Gy/fraction) 5 days per week over 6.5-7 weeks. 50 Gy to uninvolved neck nodes, tolerance dose for spinal cord 44 Gy
Outcomes	5-year survival, toxicity, overall survival, locoregional disease control, relapse-free survival, event-free survival
Notes	OS data taken from Pignon 2009

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation performed by Instituto Mario Negri, Milan. Patients were stratified by centre and stage (stage 3 & 4 N0-N1 vs St IV N2-N3). No details on sequence generation given
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	Missing data and exclusions described (2, 4, 4 excluded in Gr A, B, C, respectively), numbers similar in each group
Free of selective reporting?	Low risk	Long-term follow-up in Fallai 2006
Free of other bias?	Low risk	Groups similar at baseline

Paccagnella 1994

Study characteristics

Methods	Randomised controlled trial conducted in Italy Multicentre Recruitment period: March 1986-February 1990 Funding source: unknown Trial number: GSTTC-86

Paccagnella 1994 *(Continued)*

Participants	Inclusion: histologically confirmed squamous cell carcinoma of hypopharynx, oropharynx, oral cavity and paranasal sinuses, Stage 3-4, M0, previously untreated, < 70 years old, Karnofsky performance status >/= 50% and normal cardiac, hepatic and renal function, white blood cell count > 4000/µL, and platelets > 100,000/µL Exclusion: previous or concurrent malignancy 237 patients recruited (66 operable). 37/237 = 16% oral cavity, 135/237 = 57% oropharynx, combined = 73% of sample
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** Gr A (n = 118, operable n = 34): initial chemotherapy (cisplatin IV 100 mg/m^2 on day 1 followed by fluorouracil 1000 mg/m^2 by continuous IV infusion on days 1-5, repeated every 21 days for 4 cycles) followed by locoregional treatment, including surgery. Standard hydration and antiemetic protocols were administered. Operable patients then had surgical resection followed by 45-50 Gy of radiotherapy Gr B (n = 119, operable n = 32): locoregional treatment alone Evaluation for surgery on T & N (removal of the primary tumour and total neck dissection) was performed prior to randomisation. For operable patients, locoregional treatment comprised resection (as determined in initial evaluation) followed by 45-50 Gy adjuvant radiotherapy. For inoperable patients, locoregional treatment comprised radical irradiation using either MeV linear accelerator or Co-60 equipment with a planned dose of 65-70 Gy to the involved areas at a 2 Gy fraction per day, 5 fractions per week. A dose of 45-50 Gy was also planned to the uninvolved neck. Spinal cord shield placed after 44 Gy had been administered
Outcomes	*Total mortality (overall survival presented as Kaplan-Meier estimates) Follow-up period: 5 years Death or recurrent disease (disease-free survival presented as Kaplan-Meier estimates). Follow-up period: 5 years
Notes	*Data supplied from Pignon 2000. Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000; based on individual patient data Sample size calculation given: "to accept the alternative hypothesis of a 2-year survival of 40% for group A and 25% for group B, with α = 0.05 and power (1-β = 0.80) it was planned to enrol 59 patients/year for 4 years".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified by institution, initial tumour stage (III versus IV) and Karnofsky PS (< 70 vs >/= 70) . Generation of randomisation sequence performed by Central Operations Office by phone and assignment was balanced in blocks of 4-6.
Allocation concealment (selection bias)	Low risk	Allocation obtained by telephone call to trial office at Padua general hospital
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All randomised patients included in analysis

Paccagnella 1994 *(Continued)*

Free of selective reporting?	Low risk	Outcomes of overall survival, tumour response and time to relapse planned and reported
Free of other bias?	Low risk	No other threat to validity identified

Paccagnella 2010

Study characteristics	
Methods	Randomised controlled trial conducted in: Italy Number of centres: 18 Recruitment period: January 2003 to January 2006 Funding source: Sanofi Aventis Italy
Participants	Inclusion: stage 3-4 M0 squamous cell carcinoma of head & neck, with ECOG performance status 0-2, unresectable, primary tumours in oral cavity, oropharynx or hypopharynx, adequate haematological, renal and hepatic function, no peripheral neuropathy or altered hearing Exclusion: primary tumour in larynx, weight loss greater than 20% in previous 3 months OC 18/101 = 18%, OP 53/101 = 52%, OC+OP = 70%
Interventions	**Comparison 1: Induction chemotherapy followed by locoregional treatment (LRT) versus LRT alone** Gr A (n = 50): induction chemotherapy with TPF - docetaxel 75 mg/m^2 day 1 then cisplatin 80 mg/m^2 (30-min infusion day 1) + 5-FU 800 mg/m^2/day for 96-hour continuous IV infusion starting after cisplatin, repeated every 3 weeks for 3 cycles. 5-6 weeks later, concomitant chemoradiotherapy standard fractionated RT 2 Gy/day, 5 x/week for 7 weeks to total dose of 70 Gy to primary and 50-60 to neck + cisplatin 20 mg/m^2/day on days 1-4 and 5-FU 800 mg/m^2/day in 96-hour continuous IV infusion on weeks 1 & 6 of RT Gr B (n = 51): concomitant chemoradiotherapy only; standard fractionated RT 2 Gy/day, 5 x/week for 7 weeks to total dose of 70 Gy to primary and 50-60 to neck + cisplatin 20 mg/m^2/day on days 1-4 and 5-FU 800 mg/m^2/day in 96-hour continuous IV infusion on weeks 1 & 6 of RT
Outcomes	Median PFS and OS. Median duration of follow-up 42 months
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Registration and randomisation carried out centrally but no information on sequence generation provided
Allocation concealment (selection bias)	Low risk	Treatment allocation obtained by phone or fax to centre
Blinding of participants?	Low risk	Open study
Blinding of carers?	Low risk	Open study

Paccagnella 2010 *(Continued)*

Blinding of outcome assessors?	Low risk	"Radiologic responses in our study were centrally reviewed by an internal committee in a blinded fashion to minimise possible bias".
Incomplete outcome data addressed?	Low risk	1 patient found to be ineligible in Gr B, and further 8 not evaluable. (Gr A: 1 incorrect treatment, 1 protocol deviation, 2 withdrew consent) (Gr B: 1 dropped out pretreatment, 1 early progression, 1 withdrew consent, 1 had no imaging). ITT undertaken for PFS and OS
Free of selective reporting?	Low risk	Progression-free survival, overall survival, toxicity reported
Free of other bias?	Unclear risk	Groups similar at baseline except that more women with performance status 0 in Gr B. Trial funded by Sanofi-Aventis and 2 of the 10 investigators have declared financial/other interest and one of the investigators is employed by Sanofi-Aventis.

Parvinen 1985

Study characteristics	
Methods	Randomised controlled trial conducted in: Finland Number of centres: 1 Recruitment period: 1975 to 1978 Funding source: not stated Trial identification number: TURKU
Participants	Inclusion: squamous cell carcinoma of the head and neck OC 71%, OP 8%, OC + OP = 79%
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A (n = 23) :RT and CT - radiotherapy consisting of 5 fractions per week, to total dose of 30-32 Gy over 3 weeks to primary tumour and regional lymph nodes on both sides of neck, with bleomycin IM (7-15 mg) given 30-60 min prior to each RT treatment during weeks 1-3 to total dose of 75-150 mg Gr B (n = 23): RT alone - radiotherapy consisting of 5 fractions per week, to total dose of 30-32 Gy over 3 weeks to primary tumour and regional lymph nodes on both sides of neck Final decision about surgery made at completion of RT and, if indicated, surgery occurred 3 weeks after RT
Outcomes	Local recurrence, survival*, toxicity
Notes	*Data supplied from Pignon 2000. Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Envelope method - no details about sequence generation

Parvinen 1985 *(Continued)*

Allocation concealment (selection bias)	Low risk	Envelope method
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All randomised patients included in analyses
Free of selective reporting?	Low risk	Planned outcomes described and reported
Free of other bias?	Low risk	Similar numbers in each group underwent surgery post-RT.

Petrovich 1981

Study characteristics	
Methods	Randomised controlled trial conducted in: USA Number of centres: 2 Recruitment period: July 1975-February 1978 Funding source: Solo Cup Foundation of Urbana Illinois
Participants	23 adults aged 48-70 with biopsy-confirmed squamous cell carcinoma of the upper respiratory and digestive tracts, with no prior treatment Exclusions: prior treatment, distant metastases, initial performance status of < 50%, impaired renal, liver function (parameters specified)
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** Gr A (n = 12): CT followed by RT. Vincristine 0.015 mg/kg IV 12 hours and 1 hour before methotrexate 50-100 mg/kg IV in 6-hour continuous infusion, followed by citrovorum factor given 15 mg IM every 6 hours for 12 doses. Course of chemo repeated once after 3 weeks. 2-3 weeks after end of chemo, radiotherapy was given as for Gr B. Gr B (n = 11): RT alone cobalt and clinac-18 linear accelerator (10 mV) given through 3 portals with an average tumour dose of 70 Gy over 7 weeks
Outcomes	Complete response, partial response (> 50% reduction in tumour size), progressive disease, total mortality
Notes	Small study - likely to lack power

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Prospectively randomised"; no further information given

Petrovich 1981 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	Reasons for protocol violations described, and numbers similar in both groups
Free of selective reporting?	Low risk	Planned outcomes reported
Free of other bias?	Low risk	No other bias identified

Pinnaro 1994

Study characteristics	
Methods	Randomised controlled trial conducted in: Rome, Italy Number of centres: 1 Recruitment period: February 1986 to February 1991 Funding source: CNR grant #880059444
Participants	Inclusion: adults aged less than 76 years with histologically documented, measurable, stage 3 or 4 inoperable squamous cell carcinoma of the head & neck without prior treatment. Patients who have WHO performance status 0-2, adequate renal and hepatic function 93 patients randomised
Interventions	**Comparison 4: Induction chemotherapy followed by locoregional treatment (LRT) versus LRT alone** Gr A (n = 44): SEQ 3 cycles of cisplatin 100 mg/m^2 on day 1 + 5-FU 1000 mg/m^2/day by continuous infusion over 120 hours, followed by radiotherapy 10-20 days after last chemotherapy dose, 2 Gy/day to a total dose of 65-70 Gy Gr B (n = 49): SIM 3 cycles 100 mg/m^2 cisplatin on day 1 repeated every 3 weeks, followed by radiotherapy 2 Gy/day, 5 times/week to a total dose of 65-70 Gy
Outcomes	Response, toxicity, progression-free survival, overall survival, time to progression, time to metastases
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Patients were stratified by performance status, primary site, T stage, N stage and then randomised. No details of sequence generation given

Pinnaro 1994 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	4 post-randomisation exclusions (3 Gr A and 1 Gr B), and a further 11 not evaluable due to protocol violation (numbers same in each group)
Free of selective reporting?	Low risk	Planned outcomes described and reported
Free of other bias?	Low risk	No other bias identified

Posner 2007

Study characteristics	
Methods	Randomised controlled trial conducted in: USA, Canada, Argentina & Europe Number of centres: 55 Recruitment period: May 1999 to December 2003 Funding source: Sanofi-Aventis TAX 324 study
Participants	Inclusion: patients over 18 with measurable, non-metastatic histologically-proven Stage III or IV squamous cell carcinoma of oral cavity, oropharynx or larynx with either unresectable tumour or decreased surgical curability due to stage III or IV N2 or N3 or if patient was candidate for organ preservation, WHO performance status < 2 and adequate bone marrow, liver and renal function Exclusion: previous chemotherapy or radiotherapy, previous cancer diagnosis, previous surgery for cancer of head & neck, > 20% weight loss in preceding 3 months, chronic obstructive pulmonary disease requiring hospitalisation within previous 12 months. 539 enrolled, 38 excluded due to a computer error in randomisation, 501 randomised, 334/501 = 67% oral cavity or oropharyngeal
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** Gr A (n = 255): (TPF) docetaxel 75 mg/m^2 in 1-hour infusion + 100 mg cisplatin IV over 0.5-3 hours then FU (1000 mg/m^2/day) as continuous infusion for 5 days, repeated every 3 weeks for 3 cycles. Patients were given dexamethasone & antibiotic prophylaxis days 5-15 of each cycle. Gr B (n = 246): (PF) cisplatin 100 mg/m^2 IV + FU 1000 mg/m^2/day as continuous infusion for 5 days, every 3 weeks for 3 cycles All patients received 3 cycles of induction therapy unless there was disease progression, unacceptable toxicity, withdrawal of consent, reduction of < 25% at the end of cycle 2. Patients in both groups, 3-8 weeks post-cycle 3, started planned CRT, weekly carboplatin + 2 Gy/day 5 x/week radiotherapy to a total dose of 70-74 Gy, followed by surgery 6-13 weeks later.

Posner 2007 *(Continued)*

Outcomes	Overall survival (primary outcome), progression-free survival, relapse rate after induction chemotherapy, toxicity
Notes	Sample size/power calculation given: "The study had a power of 91% to detect a hazard ratio for death of 0.65 on the basis of an assumed median survival of 43 months in the TPF group and 28 months in the PF group, with use of a 2-sided log-rank test at a level of significance of 0.05. A minimum follow-up of 24 months and a total of 227 events were required".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation performed centrally with biased coin minimisation technique. Randomisation was stratified by site of primary tumour, N0-N1 vs N2-N3, institution. There were more T4 patients in the TPF group (49% vs 37%, P = 0.04). Bias due to this would be likely to underestimate the effectiveness of the TPF regimen.
Allocation concealment (selection bias)	Low risk	Not described, but considered likely
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Unclear risk	539 patients enrolled but 38 (8%) excluded due to computer randomisation error; allocated groups not given
Free of selective reporting?	Low risk	Primary and secondary outcomes clearly described and reported
Free of other bias?	Unclear risk	Fewer TPF patients compared to PF did not complete induction chemotherapy due to progressive disease.

Prevost 2005

Study characteristics

Methods	Randomised controlled trial conducted in: France Number of centres: not stated Recruitment period: December 1985 to December 1989 Funding source: not stated
Participants	Inclusion: men aged < 75 years with histologically-confirmed squamous cell carcinoma of head & neck. Tumours were inoperable, with an evaluable/measurable lesion, previously untreated, Karnofsky performance status > 40%, expected survival > 8 weeks, adequate haematological renal & hepatic function. Patients with multiple primary cancers were eligible.
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)**

Prevost 2005 *(Continued)*

	Gr A (n = 98): cisplatin 100 mg/m^2 given as 15-min rapid IV infusion + 5-FU 1000 mg/m^2/day over 120 hours, repeated every 3 weeks for total of 3 cycles Gr B (n = 99): etoposide (VP16) 60 mg/m^2 as 2-hour infusion on days 1-5 + cisplatin 100 mg/m^2 as 15-min rapid infusion on day 4
Outcomes	Tumour response, toxicity, overall survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Patients paired by tumour sites and UICC stage through "sequential closed plans". The first patient in each pair was allocated centrally by the statistician, and the second patient in the pair received the alternate treatment.
Allocation concealment (selection bias)	Unclear risk	No information provided on allocation concealment
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All randomised patients were included in outcomes of tumour response and toxicity.
Free of selective reporting?	Unclear risk	Tumour response and toxicity outcomes planned and reported. Results of analysis of overall survival not reported, only described as not significantly different
Free of other bias?	Unclear risk	Email from Dr Prevost stated that "the results were expressed according to the 'all or none law'..... for the data analysis, only the pairs which show a difference between both treatments were kept".

Rao 1994

Study characteristics

Methods	Randomised controlled trial conducted in: India Number of centres: 1 Recruitment period: January 1st 1987 to August 31st 1989 Funding source: not stated Trial identification number: TMH R-4
Participants	Inclusion: adults with clinical stage III-IV T3-T4 N0-N2b M0, with resectable squamous cell carcinoma of the alveolobuccal complex considered potentially curable by conventional radical surgery. Karnofsky performance status ≥ 80%, no residual disease and clear margins after surgery

Rao 1994 *(Continued)*

	135 patients recruited, 116 evaluable patients, 100% OC
Interventions	**Comparison 2: Surgery + adjuvant treatment A versus surgery + adjuvant treatment B** Gr A (n = 65): adjuvant chemotherapy - methotrexate 50 mg/m^2, 3 IV bolus doses on days 3, 10 and 17 postoperative. If leukopenia or low platelet count or severe mucositis, injection deferred for 1 week (evaluable, n = 54) Gr B (n = 70): control - postoperative observation (evaluable, n = 62) All patients underwent surgery. A wide excision of the lesion with resection of a segment of the mandible along with neck dissection. Node status N0 -> supramohyoid neck dissection with removal of nodes level I-III. Node status N1-N2 -> classical radical neck dissection with removal of nodes levels I-V. If minor, skin closure; if large, flap performed
Outcomes	Disease-free survival. Follow-up period: 1 and 2 years Total mortality. Follow-up period: 1 and 2 years Total mortality* IPD Disease-related mortality. Follow-up period: 2 years Recurrent disease: total. Follow-up period: 1 and 2 years Complications of treatment - toxicity/adverse events
Notes	Very specific oral cancer location i.e. alveolobuccal complex *Some data supplied from Pignon 2000.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed by Department of Statistics using random number tables
Allocation concealment (selection bias)	Low risk	Assignment was conveyed to the surgical unit in sealed envelopes.
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	Exclusions and withdrawals described for each group. Gr A 11/65 and Gr B 9/70
Free of selective reporting?	Low risk	Planned outcomes described for planned 24-month follow-up. Paper reported 12 month follow-up.
Free of other bias?	Low risk	No other threats to validity identified

Rasch 2010

Study characteristics

Methods	Randomised controlled trial conducted in: Netherlands & New Zealand Number of centres: 5

Rasch 2010 *(Continued)*

	Recruitment period: January 2000 to November 2004 Funding source: not stated
Participants	Inclusion: unresectable squamous cell carcinoma of oropharynx, oral cavity, or hypopharynx, stage IV, T3-4, any N, M0 WHO performance status 0-1, adequate renal function, no previous malignancies, cerebrovascular accident or use of anticoagulants OC 18%, OP 63%, OC + OP = 81%
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** Gr A (n = 118): 4 x 150 mg/m^2 cisplatin administered into femoral artery on days 1, 8, 15, 22 followed by systemic rescue with sodium thiosulphate together with 35 x 2 Gy fractions of radiotherapy to total dose of 70 Gy Gr B (n = 119): 3 x 100 mg/m^2 cisplatin on days 1, 22 & 43 together with 35 x 2 Gy fractions of radiotherapy to total dose of 70 Gy Patients randomised to the intra-arterial group underwent arteriography prior to treatment. Those for whom intra-arterial administration was not feasible reverted to the intravenous protocol (n = 10).
Outcomes	Primary locoregional control, secondary outcomes: overall survival, disease-free survival, quality of life and toxicity. Median follow-up 33 months
Notes	It was estimated that to detect a difference of 15% in locoregional control (from 60% to 75%) between treatment arms, it would require 100 events in each arm to give 80% power.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was stratified by centre, T classification, N classification and site of primary tumour. No information about the method of sequence generation was provided.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	2 patients were excluded post-randomisation. Authors stated that ITT analysis was used but outcomes were reported as percentages only. Compliance was described for 224/237 patients.
Free of selective reporting?	Low risk	Primary outcome was locoregional control and secondary outcomes were disease-free survival, overall survival, quality of life and toxicity.
Free of other bias?	Low risk	Groups appeared similar at baseline. Intra-arterial treatment was not feasible in 10 patients randomised to this group and they were then treated by intravenous therapy but analysed in the intra-arterial group (ITT).

Rawat 2016

Study characteristics	
Methods	Randomised controlled trial conducted in: India Number of centres: 1 Recruitment period: June 2013 to March 2014 Funding source: not reported Trial identification number: not reported
Participants	Inclusion: adults (age 18-65 years) with diagnosis of locally advanced, histologically-proven, stage III/IVB squamous cell carcinoma of the head and neck (oral cavity, oropharynx, hypopharynx or larynx). Included patients had normal haematological, renal and hepatic function. Exclusion: distant metastases, previously treated head and neck malignancy or comorbid conditions (except uncontrolled hypertension, diabetes or active cardiac conditions) A total of 60 patients were randomised and were evaluable.
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** Gr A (n = 150): Concurrent chemoradiotherapy with cisplatin (35 mg/m^2 on day 1, 8, 15, 22, 29 and 36) during radiation therapy (70 Gy delivered in 35 fractions) Gr B (n = 150): Concurrent chemoradiotherapy with cisplatin (100 mg/m^2 on day 1, 22 and 43) during radiation therapy (70 Gy delivered in 35 fractions)
Outcomes	Response rate
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported as computer-generated
Allocation concealment (selection bias)	Low risk	Reported allocation concealment
Blinding of participants?	Low risk	Participants not blinded
Blinding of carers?	Low risk	Carers not blinded
Blinding of outcome assessors?	Unclear risk	Not reported
Incomplete outcome data addressed?	Low risk	All participants evaluated for outcome
Free of selective reporting?	Low risk	All outcomes reported
Free of other bias?	Low risk	No other bias identified

Rentschler 1987

Study characteristics	
Methods	Randomised controlled trial conducted in USA Multicentre (2 centres - Loma Linda, California) Recruitment period: January 1979-February 1983 Funding source: not specified
Participants	Inclusion: patients with potentially resectable, histologically-proven, primary squamous cell carcinoma of head & neck, WBC ≥ 4000, platelets ≥ 100,000 serum creatinine < 2, stage III or IV oral cavity, oropharynx, hypopharynx, pyriform sinus, nasopharynx or larynx cancers Exclusions: salivary gland lesions, distant metastases, prior surgery or radiation therapy to head & neck, or prior methotrexate therapy 60 patients recruited, 55 evaluable patients (planned to accrue 100 patients but trial was stopped early due to poor accrual) 33% cases oral cavity, 22% oropharynx, combined = 55% of sample
Interventions	**Comparison 2: Surgery + adjuvant treatment A versus surgery + adjuvant treatment B** Patients were randomised to receive LRT + CT (methotrexate) or LRT alone Gr A (n = 28): chemotherapy - escalating dose methotrexate (weekly x 4) then surgery then postoperative methotrexate (weekly x 4) then radiotherapy then methotrexate (weekly x 8) Gr B (n = 27): control - surgery plus postoperative radiotherapy For patients with primary tumours in oral cavity, oropharynx, hypopharynx, pyriform sinus or larynx, LRT comprised both standard surgery (radical neck dissection) and postoperative radiotherapy. Those with palpable bilateral neck nodes underwent simultaneous bilateral neck dissection with preservation of the internal jugular vein on the least involved side. Radiotherapy started approximately 4 weeks after surgery. Once fraction of 1.8 to 2 Gy/day, 5 x/week continuous course with all fields treated with Co-60 and/or 10-25 mV x-ray and 6-20 mV electron beam. The operative field received 60 Gy when surgical margins > 1 cm or 65 Gy if surgical margins < 1 cm. Extent of radiotherapy was based on the original size and location of the lesion before chemotherapy.
Outcomes	Total mortality (overall survival presented as Kaplan-Meier estimates). Follow-up period: 6 years Death or recurrent disease (disease-free survival presented as Kaplan-Meier estimates). Follow-up period: 5 years
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were stratified by primary site (6 strata) and nutritional status (2 strata). Patients were paired to minimise significant imbalance. Allocation was determined using random number table for one patient of each pair and the other was allocated to the alternative treatment.
Allocation concealment (selection bias)	Low risk	Assignment was conveyed by envelopes (presumed sealed).
Blinding of participants?	Unclear risk	Not mentioned

Rentschler 1987 *(Continued)*

Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	5 patients were excluded because their cancer was deemed unresectable (4 MTX group and 1 from control group). One patient from each group was lost to follow-up (withdrawals and dropouts accounted for).
Free of selective reporting?	Low risk	All outcomes and deviations were reported.
Free of other bias?	Low risk	No other bias identified

Richard 1974

Study characteristics	
Methods	Randomised controlled trial conducted in: Gustave-Roussy Institute, Villejuif, France Number of centres: 1 Recruitment period: June 1965 to October 1967 Funding source: unclear Trial identification number: IGR-65
Participants	125 patients considered but only 39 included with T4 Inclusion criteria: epidermoid carcinomas of tongue, floor of mouth, soft palate, retromolar trigone or buccal mucosa Exclusion criteria: > 70 years old, in poor general health, unfavourable psychosocial condition, intercurrent diseases that would worsen prognosis, those with extensive lymph node involvement that would make it difficult to place intra-arterial catheter, more than one primary tumour site, previous treatment Age: Group A 54.7; Group B 57.2
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** Gr A (n = 21): CT: methotrexate 50 mg/day intra-arterially for 6-12 days to total dose of 300-600 mg, then 14 days no treatment period followed by 30 Gy over 2 weeks, continued up to 60 Gy Gr B (n = 18): RT 30 Gy over 2 weeks, continued up to 60 Gy
Outcomes	Mean tumour regression, overall survival
Notes	*Data supplied from Pignon 2000. Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000; based on individual patient data Trial stopped prematurely because tumour regression with combined treatments showed clear advantage over radiotherapy alone
Risk of bias	
Bias	**Authors' judgement** / **Support for judgement**

Richard 1974 *(Continued)*

Random sequence generation (selection bias)	Low risk	Random allocation of treatments into groups had been prepared by the statistician.
Allocation concealment (selection bias)	Low risk	Numbers in sequence were given to patients as they were included in the study and a sealed envelope marked with the same number contained indication of treatment group.
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Low risk	3 independent outcome assessors evaluated each patient at each assessment visit. Comparison of observers described in table 4 p. 494
Incomplete outcome data addressed?	Unclear risk	Not clear how many patients were included in the outcomes assessments at each point
Free of selective reporting?	Low risk	Primary and secondary outcomes clearly stated and reported
Free of other bias?	Low risk	No other threats to validity identified

Richard 1991

Study characteristics	
Methods	Randomised controlled trial conducted pan-Europe Multicentre (5 centres) with 91% of patients recruited from 3 institutions Recruitment period: February 1978-January 1984 Trial identification: EORTC 78-OCP
Participants	Inclusion: biopsy confirmed squamous cell carcinoma of the floor of mouth, retromolar trigone, glosso tonsillar sulcus or anterior faucial pillar Exclusion: T-1 staged tumour with local extension contraindicating surgery, prior treatment, patients for whom CT or surgery was contraindicated. Metastatic disease, a second primary tumour, or those who could not be followed up 225 randomised, 222 evaluable. 100% OC
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** Gr A (n = 112): surgery plus intra-arterial chemotherapy. Vincristine was delivered at a dose of 1 mg on days 1, 5 and 9 and bleomycin at 15 mg/day for 12 days and starting 6 hours after vincristine on days 1, 5 and 9 Gr B (n = 110): surgery alone
Outcomes	Total mortality* IPD
Notes	*Data supplied from Pignon 2000. Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000; based on individual patient data
Risk of bias	

Richard 1991 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was stratified by tumour site (floor of mouth (FOM) versus posterior oral cavity or oropharynx (POC) and by treatment centre. Randomisation procedure was permuted blocks.
Allocation concealment (selection bias)	Low risk	Assignment was conveyed by sealed envelopes.
Blinding of participants?	Low risk	Not possible
Blinding of carers?	Low risk	Not possible
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	5 post-randomisation exclusions (3 surgery only arm and 2 in CT + surgery arm)
Free of selective reporting?	Low risk	Primary and secondary outcomes clearly stated and reported
Free of other bias?	Low risk	Some differences between the groups at baseline (p. 822) but these were adjusted for in the analysis

Rischin 2005

Study characteristics	
Methods	Randomised controlled trial conducted in: Australia and New Zealand Number of centres: 13 TROG specialist centres Recruitment period: September 1998 to May 2002 Funding source: Sanofi-Synthiabo Trial identification number: TROG 98.02
Participants	Inclusion: patients aged > 18 years, previously untreated squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx, stage III or IV disease, ECOG performance status 0-2, adequate haematological, renal and hepatic function Exclusion: distant metastases, or T1N1, prior radiotherapy, prior cisplatin use, concurrent active cancer in past 5 years (except treated non-melanoma skin cancer or cervical dysplasia), history of unstable cardiac disease, peripheral neuropathy ≥ 2 122 patients randomised, 1 patient excluded Age: G1 - median age 56 (38-74); G2 - median age 55 (43-75) M/F: 103/18
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** Gr A (n = 63): tirapazamine 290 mg/m^2, on second day of weeks 1, 4 & 7, 1-hour rest, then 75 mg/m^2 cisplatin for 1 hour, then radiotherapy. In weeks 2 & 3, 160 mg/m^2 tirapazamine followed by radiation after 30 to 120 min

Rischin 2005 *(Continued)*

	Gr B (n = 58): cisplatin 50 mg/m^2 before radiotherapy on first day of weeks 6 & 7, with 120-hour infusion of 360 mg/m tirapazamine 290 mg/m^2, fluorouracil on days 1-5 of same weeks RT for both groups consisted of 70 Gy in 35 fractions for 7 weeks.
Outcomes	Locoregional control, disease-free survival, overall survival
Notes	Calcuated that 120 patients were required to give 80% power to detect a 22% difference in 2-year failure-free survival rate

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation charts were prepared at trial centre (based on adaptive biased-coin method), in ratio 1:1.
Allocation concealment (selection bias)	Low risk	Allocation was obtained by a telephone call to trial centre following patient recruitment and registration.
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	1 post-randomisation exclusion, no losses to follow-up
Free of selective reporting?	Low risk	All outcomes and withdrawals reported
Free of other bias?	Low risk	Although treatment varied depending on individual requirement, the paper claimed that "each centre adhered to a consistent policy on neck management so that there was no bias in favour of one arm or the other".

Rischin 2010

Study characteristics

Methods	Randomised controlled trial conducted in: 16 countries in Australasia, Europe & America Number of centres: 89 Recruitment period: September 2002 to April 2005 Funding source: Sanofi-Aventis
Participants	Inclusion: previously untreated Stage III & IV squamous cell carcinoma of oral cavity, oropharynx, hypopharynx, or larynx, ECOG performance status 0-2, adequate haematological, liver, renal function, no cardiac disease, peripheral neuropathy, no hearing impairment OC = 109/861 = 13%, OP = 465/861 = 54%, OC + OP = 67%
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)**

Rischin 2010 *(Continued)*

	Gr A (n = 430): on day 1 of weeks 1, 4 & 7, tirapazamine (TPZ) 290 mg/m^2 over 2 hours followed by cisplatin 75 mg/m^2 over 1 hour, followed by radiotherapy, 2 Gy per fraction, 4 fractions per week to total dose of 70 Gy using a shrinking field technique Gr B (n = 431): on day 1 of weeks 1, 4 & 7, cisplatin 100 mg/m^2 over 1 hour, followed by radiotherapy, 2 Gy per fraction, 4 fractions per week to total dose of 70 Gy using a shrinking field technique
Outcomes	2-year overall survival, failure-free survival, time to locoregional failure, and quality of life as measured by Functional Assessment of Cancer Therapy - Head and Neck
Notes	Sample size calculation given: "estimated that 850 patients (425 per arm) would provide 90% power to detect a difference of 60% versus 70% for CIS versus CIS/TPZ in overall survival at 2 years with an overall α = 0.05 with 2-sided testing".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised randomisation stratified by disease stage (III vs IV), primary site (OP/L vs HP/OC) and haemoglobin level. No details of method of sequence generation given
Allocation concealment (selection bias)	Low risk	Centralised assignment
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	5/430 and 3/431 were excluded from primary analysis due to incorrect diagnosis or early withdrawal.
Free of selective reporting?	Low risk	Primary outcome was overall survival after 2 years follow-up; also reported failure-free survival, time to locoregional failure, quality of life and toxicity.
Free of other bias?	Low risk	Groups similar at baseline, and chemotherapy and radiotherapy delivery was similar in both arms.

Ruo 2010

Study characteristics

Methods	Randomised controlled trial conducted in: Italy Number of centres: 6 Recruitment period: November 1992 to December 1995 Funding source: not stated
Participants	Inclusion criteria: biopsy-proven unresectable stage III or IV squamous cell cancer of head and neck, no prior chemotherapy or radiotherapy, aged 18 to less than 70, ECOG performance status 0-2, adequate bone marrow reserve, renal and liver function, adequate nutritional and liquid intake

Ruo 2010 *(Continued)*

	Exclusion: metastatic disease, multiple primary tumours OC = 17%, OP = 49%, OC + OP = 66% M/F: 129/16
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A (n = 82): carboplatin 45 mg/m^2 as IV bolus 45-60 minutes prior to RT on days 1-5 of weeks 1, 3, 5 & 7 with radiotherapy given as 2 Gy per fraction, 1 fraction per day, to total dose of 70 Gy Gr B (n = 82): radiotherapy given as 2 Gy per fraction, 1 fraction per day, to total dose of 70 Gy
Outcomes	Locoregional recurrence-free survival, disease-free survival, overall survival, response rate and toxicity
Notes	Sample size calculation given: "to detect an increase of 15% in local control, in the combined chemotherapy radiotherapy arm (with alpha error of 5% and power of 80%) required 150 participants and an additional 10% were recruited to allow for possible dropouts".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised" - no further information provided. More patients in CRT arm had ECOG performance status of 0 compared to RT group.
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	In CRT group, 2/82 developed distant metastases and were withdrawn and a further 7 died during treatment, and in RT group 5 did not receive treatment and a further 5 died during treatment leaving 73 & 72 patients evaluated in each group respectively.
Free of selective reporting?	Low risk	Primary outcome locoregional recurrence-free survival, and secondary outcomes of disease-free survival, overall survival, response rate and toxicity
Free of other bias?	Low risk	No other bias identified

Sahoo 2017

Study characteristics

Methods	Randomised controlled trial conducted in: India Number of centres: 1 Recruitment period: November 2011 to October 2012 Funding source: not reported

Sahoo 2017 *(Continued)*

	Trial identification number: not reported
Participants	Inclusion: adults (age 18-70 years) with diagnosis of histopathologically-proven T3-4, N0-3, M0 squamous cell carcinoma of the head and neck (oral cavity, oropharynx, hypopharynx or larynx). Included patients were of Karnofsky Performance Status of ≥ 70. Exclusion: prior chemotherapy, radiation therapy or surgery, distant metastases, recurrent disease, synchronous double primaries or pregnancy. A total of 30 patients were randomised and were evaluable.
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** Gr A (n = 15): Concurrent chemoradiotherapy with cisplatin (30 mg/m^2 every week) during radiation therapy (66 Gy delivered in 33 fractions) Gr B (n = 15): Concurrent chemoradiotherapy with cisplatin (100 mg/m^2 on day 1, 22 and 43) during radiation therapy (66 Gy delivered in 33 fractions)
Outcomes	Response rate
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported random sequence generation
Allocation concealment (selection bias)	Low risk	Reported allocation concealment
Blinding of participants?	Low risk	Participants not blinded
Blinding of carers?	Low risk	Carers not blinded
Blinding of outcome assessors?	High risk	Outcome assessors not blinded
Incomplete outcome data addressed?	Low risk	All evaluated patients had outcomes reported.
Free of selective reporting?	Low risk	All outcomes reported
Free of other bias?	Low risk	No other bias identified

Salvajoli 1992

Study characteristics

Methods	Randomised controlled trial conducted in: Brazil Number of centres: 1 Recruitment period: January 1983 to December 1986

Salvajoli 1992 *(Continued)*

	Funding source: unclear Trial identification number: AC Camargo
Participants	90 patients with stage IV SCC of head and neck (oral cavity, oropharynx, hypopharynx), histologically confirmed, randomised to 3 groups Inclusion criteria: unresectable lesions, aged < 65 years, no prior treatment, no pulmonary or cardiovascular disease, Karnofsky performance status > 50%, leucocytes > 4000, platelets > 100,000, creatinine clearance rate > 65 mL/min Exclusion: metastatic disease, multiple primary tumours OC = 47%, OP = 30%, OC + OP = 77% M/F: 84/6
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** **Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A: neoadjuvant chemotherapy followed by radiotherapy - (vinblastine (4 mg/m^2 IV on day 1) + mitomycin (8 mg/m^2 IV on day 1) + cisplatin (30 mg/m^2 IV on days 2 & 4) + bleomycin (10 mg/m^2 IV on days 2 & 4)) repeated after 3 weeks if partial response observed. If disease stable or progressive, then immediate radiotherapy followed (70 Gy in 1.8 Gy fractions over 8 weeks) Gr B: concomitant chemotherapy and radiotherapy - bleomycin 5 mg IV on days 1 & 5 followed by cisplatin (20 mg/m^2 IV on days 2 & 3), repeated every 3 weeks during radiotherapy (70 Gy in 1.8 Gy fractions over 7 weeks) Gr C: radiotherapy alone - 70 Gy in 1.8 Gy fractions over 7 weeks
Outcomes	Tumour response to treatment, overall survival, adverse events
Notes	*Data supplied from Pignon 2000. Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000; based on individual patient data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised" - no further details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All randomised participants accounted for and included in analysis
Free of selective reporting?	Low risk	Primary and secondary outcomes clearly described and reported
Free of other bias?	Low risk	No other bias identified

Schuller 1988

Study characteristics	
Methods	Randomised controlled trial conducted in USA Multicentre (22 institutes) SW USA Oncology group. Phase III trial Recruitment period: August 1980-January 1985 Funding source: government - National Cancer Institute, Bethesda MD USA Trial identification: SWOG 8006
Participants	175 patients were recruited with previously untreated advanced stage, resectable histologically-confirmed SCC of H & N. 149 were evaluable (56 (38%) with oral cavity and 44 (30%) with oropharynx equivalent to 63% oral cavity/oropharynx patients). 100 completed treatment.
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** Gr A (n = 46): neoadjuvant chemotherapy plus surgery plus postoperative radiotherapy (n = 82). Neoadjuvant chemotherapy: cisplatin 50 mg/m^2 IV day 1; methotrexate 40 mg/m^2 IV day 1; bleomycin 15 U/m^2 IV or IM day 1 and 8 and vincristine 2 mg IV day 1 for 3 courses. 21-day rest between courses and surgery Gr B (n = 55): surgery plus postoperative radiotherapy (n = 76) Common treatment: assessment for surgery and extent of surgical resection was determined at time of randomisation and not altered by response to chemotherapy.
Outcomes	Total mortality (presented as overall survival Kaplan-Meier estimates and death hazard ratios (adjusted for stage and race)). Total mortality* IPD Recurrent disease (presented as Kaplan-Meier estimates of time to treatment failure) Complications of treatment - harms/death due to treatment
Notes	*Total mortality: Log [hazard ratio] SE calculated from data provided from Pignon 2000; based on individual patient data

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned..."
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	175 entered into study but 158 eligible. Unclear if all 17 patients excluded at this stage had been randomised or not, but suggested they did not receive treatment. IPD data used in analysis

Schuller 1988 *(Continued)*

Free of selective reporting?	Low risk	Relevant outcome data presented
Free of other bias?	Low risk	No reported threats to validity

Segura 2002

Study characteristics	
Methods	Randomised controlled trial conducted in: Valencia, Spain Number of centres: 1 Recruitment period: October 1996 to July 1999 Funding source: not stated
Participants	Inclusion: patients aged 18-75 years with histologically-confirmed, locally advanced, squamous cell carcinoma of head and neck, stage III or IV, non-resectable, no prior treatment, ECOG PS 0-2 with adequate renal & hepatic function 42 randomised
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** Gr A (n = 21): (PF) IV cisplatin 100 mg/m^2 on day 1+ 5-FU 1000 mg/m^2 IV continuous infusion days 1-5, repeated for 3 cycles Gr B (n = 21): (PV) IV cisplatin 100 mg/m^2 on day 1 + vinorelbine 30 mg/m^2 IV on days 1 & 8 repeated for 3 cycles Those in both groups who showed tumour response then received local therapy.
Outcomes	Tumour response, toxicity, median/overall survival
Notes	Published abstract; emailed first author who supplied a copy of full publication November 2009. Data from translation from original Spanish by L Fernandez-Mauleffinch

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised using a list of random numbers generated by computer
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	39/42 randomised patients included in the outcomes of tumour response and survival. 2 patients in Gr A & 1 in Gr B died during treatment.

Segura 2002 *(Continued)*

Free of selective reporting?	Low risk	Planned outcome measures - tumour response, toxicity and survival were reported.
Free of other bias?	Low risk	No other risks to validity identified

Shanta 1980

Study characteristics	
Methods	Randomised controlled trial conducted in India Single centre Recruitment period: 1971-1973 Funding source: government and industry - Nippon Kayaku Company, Tokyo, Indian Council of Medical Research and the MRC, UK Trial identification number: WIA-OC5a (1971-1972) and WIA-OC5b (1972-1973) (WIA-OC=Cancer Institute (WIA) Oral Cavity (India))
Participants	Inclusion: adults with histologically-proven squamous cell carcinoma of the buccal mucosa (100% OC) T3-T4 and N0-N3, M0. Inclusion criteria - fixed metastatic submandibular lymph nodes were acceptable but fixed cervical lymph nodes elsewhere debarred patients from study. 157 randomised
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A (n = 84): chemotherapy (bleomycin - intra-arterial, intravenous or intramuscular) plus radiotherapy Cobalt-60 teletherapy was delivered by 2 opposing fields in 3 fractions/week (total TD 55-60 Gy over about 7 weeks) CT was administered intra-arterially in 42 patients, intravenously in 22 patients and intramuscularly in 20 patients. Those IA and IV cases received 10-15 mg of bleomycin 2-3 times/week, depending on the oral mucosal reaction, to a total dose of 150-200 mg. The bleomycin was administered on the non-irradiated days. The IM cases received 30 mg bleomycin twice a week for 2 weeks, the RT commencing 2 weeks after the first injection on a 3-fraction per week basis. Another 30 mg bleomycin was administered IM during radiation to a total dose of 150 mg. Gr B (n = 73): control - received physiological saline as placebo (intra-arterial, intravenous or intramuscular) plus radiotherapy Cobalt-60 teletherapy was delivered by 2 opposing fields in 3 fractions/week (total TD 55-60 Gy over about 7 weeks)
Outcomes	Total mortality* IPD
Notes	*Data supplied from Pignon 2000. Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000; based on individual patient data (N.B. numbers in trial report did not correspond to IPD numbers used for Pignon data analysis): W1A-OC5a deals with patients with CT administered intra-arterially Gr 1: 22/25 and control Gr 2: 19/25(events/patients) W1A-OC5b deals with patients with CT administered intravenously or intramuscularly, Gr 1: 27/38 and control Gr 2: 40/41(events/patients)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Shanta 1980 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Generation of randomisation sequence took place in the tumour registry. Some imbalance between groups at baseline - BLM group had higher rate of mandibular invasion and control group more extensive nodal involvement.
Allocation concealment (selection bias)	Low risk	Sealed envelope technique from central tumour registry
Blinding of participants?	Low risk	Not mentioned but it was likely that patients were blinded as placebo infusions were used.
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Low risk	Outcome assessment was conducted by head and neck surgical group who were unaware of type of treatment each patient received
Incomplete outcome data addressed?	Low risk	All outcomes reported
Free of selective reporting?	Low risk	All outcomes reported
Free of other bias?	Low risk	No other bias identified. Imbalance in groups at baseline noted above as risk of selection bias

Smid 1995

Study characteristics	
Methods	Randomised controlled trial conducted in Slovenia Single centre Recruitment period: March 1991 to December 1993 Funding source: government. T3-0005 from the Ministry of Science and Technology, Slovenia Trial identification: LOHNG-91 (LOHNG=Ljubljana Oncology Head and Neck Group (Slovenia))
Participants	Inclusion: adults with previously untreated histologically-confirmed inoperable squamous cell carcinoma of the head and neck region were recruited. 64 were evaluable (10, 16% with oral cavity and 41, 64% with oropharynx equivalent to 80% combined oral cavity/oropharynx patients). 60 patients had stage IV and the remainder stage III cancers; all were free of metastases. Withdrawals and dropouts accounted for
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A (n = 32): concomitant CT intramuscular bleomycin 5 units twice per week, with a planned dose of 70 units and mitomycin C 15 mg/m^2 IV, after delivery of 9-10 Gy of irradiation. The mitomycin C was planned to be repeated on the last day of RT at the dose of 10 mg/m^2 (also received nicotinamide (650 mg/day), chlorpromazine (200 mg with bleomycin) and dicoumarol (300 mg applied on the evening and morning before mitomycin C)). RT= 2 Gy 5 times weekly to a total dose of 66-70 Gy Gr B (n = 32): radiotherapy alone, 2 Gy 5 times weekly to a total dose of 66-70 Gy
Outcomes	Total mortality**IPD
Notes	*Based on Zakotnik 1998 linked to Smid 1995

Smid 1995 *(Continued)*

	**Some data supplied from Pignon 2000.Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000 Power calculation stated. To demonstrate a 10% increase in 2-year survival in the concomitant therapy group, it was calculated that study would need at least 100 patients (α = 0.05 β = 0.80).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation used was permuted blocks and stratified by primary site and whether tumour was inoperable locally, regionally, or both".
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All patients entering study had evaluable data.
Free of selective reporting?	Low risk	All outcomes reported
Free of other bias?	Low risk	No other bias identified

Staar 2001

Study characteristics

Methods	Randomised controlled trial conducted in: Germany Number of centres: 5 Recruitment period: July 1995 to April 1999 Funding source: Deutsche Krebshilfe Trial identification number: Cologne 95
Participants	263 patients recruited from 3 universities/2 community hospitals with stage III or IV unresectable advanced oro- and hypopharyngeal carcinoma. Exclusion criteria: prior malignant neoplasm or previous chemo or radiotherapy Age: median 57 years (range 28-73 years) M/F: 204/36, 240/263 underwent therapy (1 patient died before treatment and 23 did not start treatment).
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone**

Staar 2001 *(Continued)*

	Gr A (n = 116): concomitant CRT: 2 cycles of 5-FU (600 mg/m^2/day)/carboplatin (70 mg/m^2) in weeks 1 and 5 plus 38 days of 1.5-1.8 Gy/day to total radiation dose of 69.9 Gy with concomitant boost in last 2.5 weeks Gr B (n = 124): hyperfractionated accelerated RT. 38 days of 1.5-1.8 Gy/day to total radiation dose of 69.9 Gy with concomitant boost in last 2.5 weeks Participants were additionally also randomised to prophylactic G-CSF (1 centre did not give prophylactic G-CSF, Prophylactic G-CSF administration stopped in March 1999 due to poor outcomes found on interim analysis).
Outcomes	Locoregional control (Kaplan-Meier), total mortality data from Pignon 2009
Notes	Disease-free survival data did not take into account other metastases. Adverse events: mucositis, dermatitis, WBC, anaemia, platelets, feeding problems/tube feeding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment not described
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Unclear risk	Post-randomisation exclusions not described by group. Some randomised to RT actually received CRT and vice versa. 4 patients randomised to CRT received RT alone and one patient randomised to RT received CRT (n = 113 received RCT & n = 127 received RT)
Free of selective reporting?	Unclear risk	Trial found no difference between groups in main outcomes; reported significant outcomes in subgroups (unclear whether these subgroup analyses were pre-planned).
Free of other bias?	Unclear risk	Prophylactic G-CSF was administered by 4/5 centres until March 1999, when it was found to be associated with poorer response. Unsure how this may have influenced results

Szabo 1999

Study characteristics

Methods	Randomised controlled trial conducted in Europe (Hungary, Germany and Austria) Multicentre (4 institutes) Recruitment period: 1986-1991

Szabo 1999 *(Continued)*

	Funding source: unknown
Participants	Inclusion: adults aged less than 70 years with previously untreated, resectable, histologically-confirmed SCC of the tongue (central and posterior third, base of tongue) and/or the floor of the mouth (with or without mandibular destruction). T2-T4 (NXM0). Tumour disease had to be limited to 1 side (right or left) Exclusion: prior treatment (except biopsy), T2-N0 lingual cancer curable by surgery alone, aged > 70 years 131 randomised, and 95 evaluable had at least 5-year follow-up (with 100% oral cavity (tongue) patients). Age range of participants 35-69 years
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** Gr A (n = 47): preoperative chemotherapy (day 1 60 mg epirubicin over 12 hours, day 2 interval, day 3 50 mg cisplatin over 12 hours, day 4 interval, day 5 50 mg cisplatin, day 6 & 7 interval, then repeated days 8-14 Gr B (n = 48): preoperative radiotherapy 46 Gy delivered in 23 fractions over 5 weeks to both primary tumour and cervical lymphatic pathways Both groups then underwent radical surgery of the primary tumour, radical neck dissection and reconstruction dependent on the individual case presenting. The extent of the primary tumour excision was governed by the original tumour size, even if complete remission was achieved in the preoperative treatment. Surgery was performed as early as feasible following completion of pretreatment - within 2 weeks
Outcomes	Total mortality (overall survival presented as Kaplan-Meier estimates). Follow-up period: 5 years Quality of life - using a standardised questionnaire
Notes	Total mortality: log [hazard ratio] SE calculated from data presented in Kaplan-Meier estimates for overall survival Planned to recruit 200 patients over 5 years but only recruited 95 evaluable patients over 10 years

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Generation of randomisation sequence performed by Central Operations Office at University of Vienna, using a computer-assisted procedure
Allocation concealment (selection bias)	Low risk	Allocation by statistics centre - telephone notification
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	High risk	36/131 (27%) patients randomised were not included in evaluation. Reasons and treatment allocation were not given.
Free of selective reporting?	Low risk	Primary outcomes specified and reported

Szabo 1999 *(Continued)*

Free of other bias?	Low risk	No other bias identified

Szpirglas 1979

Study characteristics	
Methods	Randomised controlled trial conducted in: France Number of centres: unknown Recruitment period: March 1992 to December 1999 Funding source: unknown Trial identification: Pité 74
Participants	136 patients were recruited with oral cavity cancer, however in the report only the 95 with SCC of the anterior tongue or the floor of the mouth were considered. Stratified according to stage and initial locoregional treatment Stage A (T1-T2 N0) and stage B (T3 N0 and T1-T2-T3 N+). Large tumours and those associated with fixed nodes were not included in this study. 95 were evaluable by protocol and also had at least 2-year follow-up (with 100% oral tongue/floor of mouth patients). Age range of participants not reported
Interventions	**Comparison 2: Surgery + adjuvant treatment A versus surgery + adjuvant treatment B** Randomised after surgery (+/- radiotherapy) when patient regarded as in remission to 3 groups. Gr A (n = 32): adjuvant chemotherapy (methotrexate 400 mg per month IV) followed by IM injection of 100 mg of citrovorum (leucovorin or folinic acid) factor and bleomycin in 2 15 mg doses intramuscularly per week. The total dose of bleomycin never exceeded 450 mg in 15 weeks of treatment. Methotrexate was administered for 2 years. Gr B (n = 30): adjuvant immunotherapy (subcutaneous or intramuscular injections of 2 mL of C. parvum weekly over 2 years) Gr C (n = 33): surgery (+/- radiotherapy) alone
Outcomes	Total mortality* IPD
Notes	*Some information on trial and data supplied from Pignon 2000.Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000 (based on patients with oral cavity cancer not necessarily specifically those of the anterior tongue or floor of mouth)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized into three groups"
Allocation concealment (selection bias)	Unclear risk	Insufficient detail
Blinding of participants?	Unclear risk	Not mentioned

Szpirglas 1979 *(Continued)*

Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All participants accounted for, and IPD data used within review
Free of selective reporting?	Low risk	All outcomes and withdrawals reported
Free of other bias?	Low risk	No reported threats to validity

Szpirglas 1988

Study characteristics	
Methods	Randomised controlled trial conducted in: Paris, France Number of centres: 1 Recruitment period: 1981-1985 Funding source: CNAMTS Trial identification number: Pitie 81
Participants	Inclusion: unresectable T3/T4 carcinoma or the oral and oropharyngeal cavity most with clinically involved nodes Exclusion: no criteria given 116 patients randomised; 103 evaluable after completing treatment
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** Gr A (n = 58): 3 courses of neoadjuvant GIFA protocol each over 5 days (day 1 adriamycin 60 mg IV over 6 hours, day 2 vincristine 2 mg IV + bleomycin 15 mg IM, days 3 & 4 bleomycin 15 mg IM, day 5 cisplatin 150 mg + diuretics) followed by radiotherapy randomised in 3 arms, classical, bi-fractioned and tri-fractioned Gr B (n = 58): radiotherapy in 3 arms (classical, bi-fractioned and tri-fractioned). 55 evaluable patients (2 patients died before radiotherapy, 1 excluded due to general status) No details on radiotherapy doses given
Outcomes	Complete response, disease-free survival
Notes	*Data supplied from Pignon 2000. Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Radiotherapy "randomised in three arms", patients randomised to CT + RT or RT alone - no further details given

Szpirglas 1988 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	Protocol violations, withdrawals due adverse events clearly described for each group. Gr A 56/58 evaluable patients after chemo, 46 evaluable after chemo + radiotherapy (8 patients did not receive radiotherapy (2 in complete remission after chemo, 1 left country, 2 with little or no response to chemo died before radiotherapy, 3 died during radiotherapy)) Gr B 55/58 evaluable
Free of selective reporting?	Unclear risk	Little information available
Free of other bias?	Unclear risk	Distribution of prognostic factors in each group at baseline not presented

Takasci-Nagy 2015

Study characteristics	
Methods	Randomised controlled trial conducted in: Hungary Number of centres: 1 Recruitment period: January 2007 to June 2009 Funding source: not reported Trial identification number: EUDRACT 2005-001623-11
Participants	Inclusion: adults (age 18-70 years) with diagnosis of histologically confirmed, stage III/IV, non-metastatic, unresectable, squamous cell carcinoma of the head and neck (oral cavity, oropharynx, hypopharynx or larynx). Included patients were of Eastern Cooperative Oncology Group Performance Status of 0-1 with normal haematological, renal and hepatic function and a cardiac ejection fraction > 50%. Exclusion: history of any previous malignant disease or grade 2 or greater peripheral neuropathy A total of 63 patients were randomised and were evaluable.
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** Gr A (n = 30): Induction chemotherapy with three cycles of docetaxel (75 mg/m^2), cisplatin (75 mg/m^2) and 5-fluorouracil (750 mg/m^2 on day 1-4) followed by concurrent chemoradiotherapy with cisplatin (100 mg/m^2) on day 1, 22 and 43 of radiation therapy (70 Gy delivered 2 Gy per day) Gr B (n = 33): Concurrent chemoradiotherapy with cisplatin (100 mg/m^2) on day 1, 22 and 43 of radiation therapy (70 Gy delivered 2 Gy per day)
Outcomes	Local tumourcontrol, response rate, progression-free survival, overall survival

Takasci-Nagy 2015 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported random sequence generation
Allocation concealment (selection bias)	Low risk	Reported allocation concealment
Blinding of participants?	Low risk	Participants not blinded
Blinding of carers?	Low risk	Carers not blinded
Blinding of outcome assessors?	Unclear risk	Not reported
Incomplete outcome data addressed?	Low risk	All outcomes reported for all patients
Free of selective reporting?	Low risk	All outcomes reported for all patients
Free of other bias?	Low risk	No other bias identified

Tejedor 1992

Study characteristics

Methods	Randomised controlled trial conducted in Spain Single centre Randomisation process: unreported Recruitment period: January 1987 to July 1989 Funding source: unknown Trial identification number: Las Palmas
Participants	Inclusion: adults with locally advanced SCC of the head and neck. Stage III-IV, M0 (11 (31%) patients with oral cavity and 13 (36%) with oropharyngeal cancer, combined OC/OP was 67%) 42 randomised; 36 evaluable
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** Gr A: neoadjuvant CT (carboplatin + ftorafur analogue of 5-FU) plus radiotherapy (n = 19) Gr B: RT alone (n = 17) RT consisted of 66-74 Gy (mean 68.8 Gy) by conventional fractionation scheme of 2 Gy per day, 5 times a week. Doses delivered to subclinical disease areas were 50 Gy.

Tejedor 1992 *(Continued)*

	CT consisted of 3 cycles of carb 400 mg/m^2 IV on day 1, ftorafur 1000 mg/m^2 orally once a day for 14 days. Cycles were given every 4 weeks.
Outcomes	Total mortality*IPD
Notes	*Data supplied from Pignon 2000. Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000; based on individual patient data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised but method not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	6/42 participants (14%) were excluded from analysis (4 did not complete treatment and 2 had inadequate follow-up). Not stated which group these were from, and exclusions may have possibly influenced results. However, IPD data used within the review
Free of selective reporting?	Low risk	All outcomes and withdrawals accounted for
Free of other bias?	Low risk	No other threats to validity identified

Tousif 2020

Study characteristics

Methods	Randomised controlled trial conducted in: Bangalore Number of centres: 1 Recruitment period: April 1, 2015 to March 31, 2017 Funding source: not reported Trial identification number: ECR/386/INST/KA/2013
Participants	Inclusion: patients with locally advanced head and neck squamous cell carcinoma Exclusion: not reported A total of 82 patients were randomised and were evaluable.
Interventions	**Comparison 4: Chemotherapy A (+ LRT) versus chemotherapy B (+ LRT)**

Tousif 2020 *(Continued)*

	Gr A (n = 41): Induction chemotherapy with 9 weeks of weekly docetaxel (30 mg/m^2), cisplatin (40 mg/m^2) and 5-fluorouracil (750 mg/m^2 on day 1-4) followed by LRT. Gr B (n = 44): Induction chemotherapy with 3 cycles of docetaxel (75 mg/m^2), cisplatin (75 mg/m^2) and 5-fluorouracil (750 mg/m^2 on day 1-4) followed by LRT given every 3-weeks, followed by LRT
Outcomes	Response rate, disease-free survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Reported random sequence generation
Allocation concealment (selection bias)	Unclear risk	Did not report allocation concealment
Blinding of participants?	Unclear risk	Did not report participant blinding
Blinding of carers?	Unclear risk	Did not report blinding of carers
Blinding of outcome assessors?	Unclear risk	Did not report blinding of outcome assessors
Incomplete outcome data addressed?	Unclear risk	Unclear if all patients evaluated for outcome of disease-free survival
Free of selective reporting?	Low risk	All outcomes reported
Free of other bias?	Low risk	No other bias identified

UKHAN 2010

Study characteristics

Methods	Randomised controlled trial conducted in: United Kingdom (34), Malta (1) & Turkey (1) Number of centres: 36 Recruitment period: 15 January 1990 to 20 June 2000 Funding source: Cancer Research UK with support from University College London and University College London Hospital Comprehensive Biomedical Research Centre
Participants	Inclusion: patients with locally advanced squamous cell carcinoma of the head & neck, judged suitable for radical radiotherapy as either initial treatment or following surgery (generally patients at high risk of recurrence following surgery due to margin status or advanced stage of disease at presentation). Age > 18 years, considered fit enough to receive any of the treatments, histological confirmation of squamous cell carcinoma with T2 to T4 primary lesions (including node negative cases) or node positive, normal full blood count, normal creatinine & urea levels, no evidence of distant metastases and no prior treatment other than surgical excision

UKHAN 2010 *(Continued)*

	966 patients randomised, 966 patients evaluable: 187 oral cavity (19%) & 315 oropharynx (33%); total OC/OP = 52%
Interventions	**Comparison 2: Surgery + adjuvant treatment A versus surgery + adjuvant treatment B** **Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Factorial design: patients who had NOT had surgery (npo) were randomised to 1 of 4 treatment groups, while those who HAD undergone surgery (po) were randomised to either group A or B Gr A (n = 233 (npo) + 135 (po)): radiotherapy alone (RT) Gr B (n = 166 (npo) + 118 (po)): radiotherapy plus simultaneous chemotherapy (RT+ SIM) Gr C (n = 160 (npo)): radiotherapy plus subsequent chemotherapy (RT + SUB) Gr D (n = 154 (npo)): radiotherapy plus simultaneous & subsequent chemotherapy (RT + SIM + SUB) Radiotherapy was given according to local practice at each participating centre, was approved by trial steering committee and was constant for all patients at that centre. 3 regimens in common use: • Manchester regimen - radical course to primary tumour and lymph nodes in 15-16 fractions (5 fr/week) over 3-3.5 weeks to minimum dose of 50-55 Gy for field area of 25-40 cm^2 reduced to 45 Gy for larger fields • SWOG regimen 1.8-2 Gy daily, 5 days/week, to primary tumour and lymph-node drainage area to min total dose of 60 Gy (higher doses permitted) • 55 Gy given in 20 fractions (2.75 Gy/fraction) over 4 weeks to primary tumour & first station lymphatic drainage, & 41.25 Gy to the elective neck. 50 Gy in 20 fractions (2.5 Gy/fraction) given postoperatively Chemotherapy regimens were either methotrexate alone (MTX mono) or vincristine, bleomycin, methotrexate & fluorouracil (VBMF), either started on days 1-14 concurrent with RT (SIM) or 14 & 28 days after completing RT (SUB) Methotrexate given IV in 2 doses of 100 mg/m^2, dose 1, 24 hours before RT and dose 2 on day 14 of RT. Folinic acid rescue was given if serum MTX levels > 0.4 µmol/L 24 hrs post-treatment VBMF comprised vincristine 1.4 mg/m^2 (max 2 mg), bleomycin 30 mg, fluorouracil 500 mg, methotrexate 100 mg - IV by slow bolus injection except for bleomycin which was IM. Hydrocortisone (100 mg IM) was available to minimise bleomycin adverse reactions, and antiemetics were given according to local practice.
Outcomes	Primary endpoints: overall survival, event-free survival (defined as recurrence, new tumour or death, among patients disease-free 6 months post-randomisation) Secondary endpoints: locoregional disease control at 6 months, time to recurrence, death from H & N cancer, toxicity
Notes	Data in Pignon 2009 taken from unpublished study. Because there were more complete data from published study, UKHAN 2009 was used in the analyses. Sample size calculation estimated 100 patients would be required to detect an increase in 5-year survival from 25% in RT alone group to 35% in CT groups combined, with 90% power and 5% two-sided level of significance.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block stratified randomisation, block size of 9 (3:2:2:2 for Gr A, B, C & D giving ratio 2:1 of chemo to RT alone). Stratified on centre & CT regimen

UKHAN 2010 *(Continued)*

Allocation concealment (selection bias)	Low risk	Random number lists generated at co-ordinating centre; each centre obtained randomisation by phone call to co-ordinating centre, which assigned treatment allocation after recording eligibility and stratification factors.
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All randomised patients were included in the analysis (ITT).
Free of selective reporting?	Low risk	Primary and secondary outcomes clearly described, defined and reported
Free of other bias?	Low risk	No other sources of bias identified

Vermorken 2007

Study characteristics	
Methods	Randomised controlled trial conducted in: Europe Number of centres: 15 Recruitment period: April 1999 to March 2002 Funding source: Sanofi-Aventis Trial identification: TAX 323
Participants	Inclusion: adults aged 18-70 years with squamous cell carcinoma of head & neck confirmed by histology or cytology, previously untreated, TNM stage III or IV, M0, WHO performance status ≤ 1 & adequate haematological, renal & hepatic function Exclusion: patients with tumours of nasopharynx and nasal & paranasal sinuses N = 358
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** Gr A (n = 177): (TPF) docetaxel 75 mg/m^2 as 1-hour infusion day 1 + cisplatin 75 mg/m^2 as 1-hour infusion day 1 + 5-FU 750 mg/m^2/day as continuous infusion days 1-5. Repeated every 3 weeks for 4 cycles Gr B (n = 181): (PF) cisplatin 100 mg/m^2 as 1-hour infusion on day 1 + 5-FU 1000 mg/m^2/day as continuous infusion days 1-5. Repeated every 3 weeks for 4 cycles If there was no disease progression; patients from both groups then had radiotherapy starting 4-7 weeks after end of CT (either conventional or hyperfractionated).
Outcomes	Progression-free survival, overall survival, response rate & duration, time to failure, toxicity, HRQOL
Notes	Power calculation given: "a total of 358 patients ... the trial had a power of 90% to detect and improvement of 15% percentage points in the 1 year survival rate (85% in the TPF group and 70% in the TF group)".

Vermorken 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was balanced according to primary tumour site (OC/OP/HP/L) and centre with the use of variance minimisation method.
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	Reasons for small number of post-randomisation exclusions and withdrawals clearly described (Fig 1) and similar in each group. Efficacy analysis was by intention-to-treat.
Free of selective reporting?	Low risk	Primary and secondary endpoints clearly stated and reported
Free of other bias?	Low risk	No other threats to validity detected

Vokes 1990

Study characteristics	
Methods	Randomised controlled trial conducted in: Chicago, USA Number of centres: 1 Recruitment period: January 1986 to March 1987 Funding source: not stated
Participants	Inclusion: adults with stage 3 or 4 locoregionally advanced, biopsy-proven squamous cell carcinoma of head and neck. Creatinine clearance > 50 mL/min & measurable disease, ECOG performance status 0-2 and carbon monoxide diffusion capacity >/= 50% 29 randomised
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** Gr A (n = 16): MPF day 1 methotrexate (120 mg/m^2) + day 2 leucovorin (100 mg/m^2 as 6-hour infusion) followed by 1000 mg/m^2/day infusion 5-FU for 5 days, cycle repeated every 21 days - 4 cycles Gr B (n = 13): PBM/PF Cycles 1 & 3 - Days 1-5 cisplatin (20 mg/m^2) over 2 hours, days 3-7 bleomycin 10 mg/m^2 as continuous infusion, + days 14 & 21 methotrexate (200 mg/m^2) with leucovorin rescue on days 15 & 22 Cycles 2, 4 & 6 - day 1 cisplatin (100 mg/m^2), then 5-day continuous infusion 5-FU (1000 mg/m^2/day) cycle repeated every 21 days Cycle 5 - Days 1-3 cisplatin, days 2-4 bleomycin

Vokes 1990 *(Continued)*

	All patients received standard hydration and antiemetic medications. Gr C (n = 13) - those with ECOG performance status > 2, carbon monoxide diffusion capacity < 50% were not randomised but were treated with MPF protocol.
Outcomes	Overall survival, response to treatment and toxicity
Notes	It was not possible to extract data in a form suitable for meta-analysis from this paper. Study was stopped early.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Pre-randomisation stratification based on T, N stage and performance status. No details given on method of randomisation
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Unclear risk	2/16 excluded from arm A (1 death, 1 refused treatment); protocol violations in 19% and 15% of groups A & B
Free of selective reporting?	Low risk	Planned outcomes described and reported
Free of other bias?	Unclear risk	Small study, 6 strata and 29 patients. Trial stopped early due to lack of efficacy in both arms. Several changes to original protocol noted (p. 209)

Volling 1999

Study characteristics

Methods	Randomised controlled trial conducted in Germany Multicentre (2 centres, 3 departments) (Departments of ENT and Radiotherapy & Oncology at University Hospital Cologne and Hospital ENT, Kassel) Recruitment period: 1988-1995 Funding source: unknown Trial identification: Cologne
Participants	Inclusion: adults with previously untreated histologically proven stage T2-3, N0-2 carcinoma of oral cavity, oropharynx or hypopharynx, with WHO performance status > 2, WBC > 4000/mm^3, platelets >100,000/mm^3 & 24-hour creatinine clearance > 60 mL/min Exclusion: distant metastases, second malignancy, prior chemotherapy or radiotherapy, chronic disease (diabetes or rheumatoid arthritis requiring long-term treatment) any active neurological disorder

Volling 1999 *(Continued)*

	144 randomised; 140 patients evaluable (withdrawals and dropouts accounted for) 100% oral cavity/oropharyngeal cancer
Interventions	**Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone** Gr A (n = 70): neoadjuvant/induction chemotherapy carboplatin 360 mg/m^2 as short infusion over 30 mins on day 1, followed by 120-hour continuous infusion of 5-FU 1000 mg/m^2/day. If no response to first-cycle CT, patients proceeded to surgery. Patients with partial response or better to first cycle, had up to 3 cycles, before proceeding to surgery and radiotherapy. Gr B (n = 74): standard treatment with surgery and radiotherapy Surgery was performed 3-5 weeks after the end of the chemotherapy - radical surgical resection of the primary tumour (resection was orientated to the original tumour margins before chemotherapy) Radiotherapy was started after complete wound healing but at least 6 weeks after surgery. (If wound healing insufficient, radiotherapy was not given.) Radiotherapy to a total dose of 60-66 Gy to the primary tumour site and the involved neck node regions. In patients with pathologically negative nodes, an adjuvant dose of 48 Gy was given to these regions.
Outcomes	Total mortality (overall survival presented as Kaplan-Meier estimates). Tumour response Total mortality* IPD Death or recurrent disease (disease-free survival presented as Kaplan-Meier estimates)
Notes	Pignon 2000 data not used (based on Volling 1994) as Volling 1999 provided more complete data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were selected randomly for the different treatment arms by the secretariat..." Stratified by primary tumour site and neck node status. No details of sequence generation given
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	1 patient in each group died postoperatively so were not available for survival evaluation. 40/48 and 40/47 patients in groups A & B respectively had the planned surgery and radiotherapy. Reasons for dropouts given and similar in each group
Free of selective reporting?	Low risk	Tumour response and overall survival outcomes planned and reported
Free of other bias?	Low risk	No other threats to validity identified

Weissler 1992

Study characteristics	
Methods	Randomised controlled trial conducted in USA Single centre but with 3 departments/divisions recruiting Randomisation: insufficient details of randomisation given Recruitment period: 1988-1995 Funding source: unknown Trial identification: CH-7401
Participants	58 patients recruited, age range 34-78 years; all evaluable Inclusion: patients with advanced stage III-IV, biopsy-proven SCC of the H & N. Other inclusion criteria: age > 18 years, life expectancy > 2 months, ECOG performance status 0-2, adequate nutritional status, non-pregnant, no previous history of malignancy, no prior treatment with chemotherapy or radiation therapy to the head and neck, adequate haematological, renal and liver function Exclusion: pregnant, prior malignancy, prior treatment (16% oral cavity, 39% oropharyngeal, combined OC/OP = 55%)
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A (n = 17): unresectable with multiple dose/day radiation therapy plus CT day 1 cisplatin at 100 mg/m^2 via rapid intravenous infusion, followed by 5-FU at 1000 mg/m^2/day continuous infusion over 96 hours on days 1-4. Chemotherapy was repeated on days 29-32. Vigorous hydration prior to commencement of treatment Gr B (n = 15): unresectable with radiation alone Gr C (n = 13): resectable with multiple dose/day radiation therapy plus CT day 1 cisplatin at 100 mg/m^2 via rapid intravenous infusion, followed by 5-FU at 1000 mg/m^2/day continuous infusion over 96 hours on days 1-4. Chemotherapy was repeated on days 29-32. Vigorous hydration prior to commencement of treatment Gr D (n = 13): resectable plus radiation alone Radiation therapy was delivered using a 6-MV linear accelerator. Initially treated with 1.5 Gy twice/day for 10 days (total 30 Gy) followed by a 2-week break. The field was then reduced to exclude spinal cord and an additional 1.5 Gy fraction was given twice daily for 8-13 days. The minimum dose was 69 Gy for the unresectable group, 54 Gy for the high-risk resected group with negative margins and 60 Gy for the high-risk resected group with positive margins. Radioactive implants were used in 6 patients in the unresectable group.
Outcomes	Overall survival, response to treatment, time to progression and disease-free survival
Notes	Pignon 2000 total mortality: log [hazard ratio] SE available

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stratified into 2 groups: an inoperable group (1 or more of the following: tumour extension into the middle or posterior fossa of the skull, carotid artery, vertebral bone or high surgical risk due to underlying medical condition) and an operable group with less than a 50% chance of 5-year disease-free survival (advanced stage III-IV malignancies, advanced nodal disease N2-N3 and patients with unfavourable pathological findings such as close (less than 5 mm) or positive margins, or extracapsular spread)

Weissler 1992 *(Continued)*

		"Following stratification patients were randomly selected to multiple dose radiotherapy with or without concomitant chemotherapy". No details of method of sequence generation provided. Some imbalance between groups at baseline
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Low risk	All outcomes reported
Free of selective reporting?	Low risk	All outcomes reported
Free of other bias?	Low risk	No other bias identified

Wendt 1998

Study characteristics	
Methods	Randomised controlled trial conducted in: Germany Number of centres: probably 1 Recruitment period: November 1989-October 1993 Funding source: not stated Trial identification number: BAVARIA - 89
Participants	Inclusion: adults with histologically confirmed squamous cell carcinoma of the head & neck, unresectable, Stages 3 & 4 (UICC) aged < 65 years, with no previous treatment except neck dissection, performance status </= 2 (ECOG), no major impairment of of kidney, liver, bone marrow, heart or lung function Exclusions: patients with small tumours and severe medical problems which precluded surgery 298 randomised, 270 analysed. (112 (38%) oropharynx and 60 (20%) oral cavity; 172/298 = 58%)
Interventions	**Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone** Gr A (n = 130): concomitant CRT: hyperhydration with saline 200 mL/hr on day 1, followed by cisplatin 60 mg/m^2 IV as short infusion, then 5-FU 350 mg/m^2 by IV bolus, then leucovorin (LV) 50 mg/m^2 IV bolus on day 2, then 5-FU 350 mg/m^2/24 hours and LV 50 mg/m^2/24 hours as continuous infusion from day 2 to 5 of each cycle. Cycle repeated on days 22 and 44. RT given with CT 15 fractions, each 1.8 Gy given twice daily with 6-hour inter-fraction interval on weeks 1 & 2, 4 & 5 and 7 & 8 with breaks in between Gr B (n = 140): RT alone. RT comprised 39 fractions of 1.8 Gy each, given twice daily with a 6-hour inter-fraction interval, to a total dose of 70.2 Gy over 51 days. 3 cycles of 23.4 Gy each, separated by a rest period of 11 days

Wendt 1998 *(Continued)*

Outcomes	Overall survival, adverse effects, locoregional control
Notes	*Data supplied from Pignon 2000. Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000; based on individual patient data Sample size calculation given "to detect increase in 2-year survival from 45% to 60% by combined modality at significance of 5% and power of 80% a sample of 172 patients per arm is required." Although the study only recruited 270 participants, they found a significant difference in 3-year survival rates suggesting the study had adequate power.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"By telephone randomisation at an independent organisation (Algora, Munich Germany)". Stratified by centre, tumour site and nodal stage. Groups comparable at baseline
Allocation concealment (selection bias)	Low risk	Reported allocation concealment
Blinding of participants?	Unclear risk	Not mentioned
Blinding of carers?	Unclear risk	Not mentioned
Blinding of outcome assessors?	Unclear risk	Not mentioned
Incomplete outcome data addressed?	Unclear risk	Clear reporting of adverse events causing withdrawal. 4 from RT group and 7 from RT/CT group. Also 3 had contraindications to CT and 14 (6%) had incomplete documentation so were excluded from analysis - allocated group unknown
Free of selective reporting?	Low risk	Planned outcomes reported
Free of other bias?	Low risk	No other bias identified

AF = accelerated fractionation
AJCC = American Joint Committee on Cancer
ALT = alanine transaminase
AST = aspartate transaminase
AUC = area under the curve
BCVM = bleomycin, vincristine, cisplatin, methotrexate
BLM = bleomycin
BVM = bleomycin, vincristine, methotrexate
CALGB = Cancer and Leukemia Group B
Carb = carboplatin
CBDCA = carboplatin
CDDP = cisplatin
CF = conventional fractionation
C-HART = concurrent hyperfractionated accelerated radiotherapy
Cis = cisplatin
Co-60 = cobalt-60
CR = complete response
CRP = carboplatin

CT = chemotherapy
CRT = chemoradiotherapy
CTV = clinical target volume
CYC = cyclophosphamide
DFS = disease-free survival
ECOG = Eastern Cooperative Oncology Group
EORTC = European organization for research and treatment of cancer
FOM = floor of mouth
G-CSF = granulocyte colony stimulating factor
GIFA = refers to the protocol – Adriamycin-vincristine-bleomycin-cisplatin
Gr = group
GTV = gross tumour volume
Gy = gray
H & N = head and neck
HF = hyperfractionation
HFx = hyperfractionation
HIV = human immunodeficiency virus
HP = hypopharynx
HR =hazard ratio
HRQOL = health-related quality of life
HU = hydroxyurea
HyphP = hypopharynx
IA = intra-arterially
IL-2 = interleukin-2
IM = intramuscularly
IPD = individual patient data
IT = intrathecal
ITT = intention-to-treat
IU = international units
IV = intravenously
KPS = Karnofsky performance status
LR = likelihood ratio
L/R = locoregional
LRC = locoregional control
LRT = locoregional treatment
LV = leucovorin
M0/1 = metastasis 0 or 1 (for Tumor-Node-Metastasis staging)
MeV = mega electron volt
MMC = mitomycin C
MPF = methotrexate-leukovorin-5FU
MTX = methotrexate
MV = mega-volt
N/A = not applicable
NaCl = sodium chloride
NCOG = Northern California oncology group
npo = nothing by mouth
OC/OP = oral cancer/oropharyngeal cancer
OS = overall survival
PA-RT = partially accelerated radiation therapy
PBM = cisplatin-bleomycin-methotrexate
PF = cisplatin-5fluorouracil
PFS = progression-free survival
PI = principal investigator
po = by mouth
POC = posterior oral cavity
PORT = postoperative radiotherapy

PS = performance status
pT3/4 = pathological T-stage T3 or T4
PV = cisplatin-vinorelbine
RCT = randomised controlled trial
RT = radiotherapy
RTOG = radiation therapy oncology group
SCC = squamous cell carcinoma
SD = standard deviation
SE = standard error
SEG = South East Group
SEQ = sequential
SIM = simultaneous
ST = stage
SUB = subsequent
SWOG = SouthWest Oncology Group
T(1-4) = tumour stage 1-4 (for Tumor-Node-Metastasis staging)
TB = tuberculosis
TD = target dose
TNM = tumour-node-metastasis
TPF = docetaxel-cisplatin-5-fluorouracil
TPZ = tirapazamine
UFT = tegafur/uracil
UICC = union for international cancer control
VBMF = vincristine-bleomycin-methotrexate-5-fluorouracil
V-CHART = continuous hyperfractionated accelerated radiotherapy
vin = vincristine
vs = versus
WBC = white blood-cell
WHO = World Health Organization
1/5-FU = 1/5-fluorouracil

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

Study	Reason for exclusion
Abdel Wahab 2006	Abstract only; insufficient information
Abele 1984	Abstract only; included patients with recurrent disease and a low proportion of oral cavity/oropharyngeal cancer
Abele 1985	Abstract only; included patients with recurrent disease and a low proportion of oral cavity/oropharyngeal cancer
Addeo 2018	Evaluated targeted therapy only
Adelstein 1997	Less than 50% of participants had oral cavity/oropharynx cancers.
Adelstein 2000	Less than 50% of participants had oral cavity/oropharynx cancers.
Ahmad Khalil 2016	Not a randomised controlled trial
Alam 2016	Did not include concurrent chemotherapy (i.e. altered radiation schedule trial)
Amichetti 1989	Non-randomised study
Andreadis 1999	Abstract only, and no subsequent publication found September 09

Study	Reason for exclusion
Anonymous 1976	Less than 50% oral cavity cancer
Ansfield 1970	Non-randomised study
Antanadou 2002	Patients were randomised to receive amifostine or not
Argiris 2016	Evaluated targeted therapy only
Armstrong 2006	Not a randomised controlled trial
Asif 2003	Unclear percentage of oral cavity and oropharyngeal cancer, and it was likely that duration of follow-up for published outcomes was 3 months
Auersperg 1977	Non-randomised study including patients with recurrent disease
Autorino 2017	Not a randomised controlled trial
Babu 2010	Evaluated targeted therapy only
Bachaud 1996	28% oral cavity/oropharynx cancers in this combined head and neck cancer trial (*see* 1991 paper)
Bakowski 1978	Unclear percentage of oral cavity/oropharynx cancer in this combined head and neck cancer trial
Baliga 2017	Not a randomised controlled trial
Bari 2018	Not a randomised controlled trial
Barney 2017	Evaluated targeted therapy only
Bell 2017	Evaluated immunotherapy only
Berger 1995	Non-randomised study
Beryhy 2017	Did not evaluate relevant outcome measures
Bezwoda 1979	Concern as to validity of the data from this study published in 1979. Unable to verify data
Bhattasali 2016	Primary evaluation for targeted therapy
Bier 1986	Abstract only, and no subsequent publication found September 09. No response from email sent to first author
Boidi 1991	50% oral cavity or oropharyngeal cancer and some patients included had metastatic disease
Bolla 1994	Etretinate is not a chemotherapy agent
Bonner 2006	Did not evaluate chemotherapy. This trial was concerned with radiotherapy plus cetuximab, an immunotherapy/biotherapy agent. Therefore, this trial is more suited for analysis in the Cochrane reviews: 1. Interventions for the treatment of oral cancer: radiotherapy treatment and 2. Interventions for the treatment of oral cancer: immunotherapy/biotherapy treatment.
Bouillet 2007	Abstract only; insufficient information

Study	Reason for exclusion
Bradley 1982	Abstract only; less than 50% oral cavity/oropharynx cancer patients included, and no subsequent publication found September 09
Brigham 1998	Abstract only. Patients included those with a variety of primary sites - unsure of proportion with oral cavity or oropharyngeal cancer
Browman 1983	Included patients with recurrent disease
Browman 1988	Included patients with recurrent disease
Browman 1990	Included patients with recurrent disease
Buentzel 2006	Patients randomised to amifostine or none
Buglione 2017	Primary evaluation for targeted therapy
Buntzel 1998	Less than 50% of participants had oral cavity/oropharynx cancers.
Buntzel 1998a	Less than 50% of participants had oral cavity/oropharynx cancers.
Burtness 2017	Primary evaluation of targeted therapy
Campbell 1987	Less than 50% of patients had oral cavity/oropharyngeal cancer. Included patients with recurrent and metastatic disease
Caponigro 2002	Randomisation stopped after accrual of 36 patients to each arm but all 97 treated patients analysed together. Only randomised data was tumour response published in an abstract (Caponigro 2001)
Cappelaere 1981	Less than 50% of patients had oral cavity/oropharyngeal cancer.
Cappelaere 1990	Included patients who had undergone prior treatment for oral cancer
Caroline 2016	Primary evaluation of targeted therapy
Carugati 1988	Abstract only; insufficient information available
Chang 2017	Not a randomised controlled trial
Cheng 2017	Evaluated targeted therapy only
Clavel 1987	Included patients with recurrent disease
Coates 1984	Study included patients with recurrent disease
Cohen 2016	Evaluated targeted therapy and immunotherapy only
Coninx 1986	Quasi-randomised study
Coninx 1988	Study included patients with metastatic disease
Corvo 1997	Pilot clinical trial with no relevant outcomes
Cruz 1997	Abstract only - no subsequent publication found October 09

Study	Reason for exclusion
Cummings 2007	Less than 50% of participants in trial had oral cavity or oropharyngeal cancer.
Dalley 1995	Abstract only; insufficient information available
DeConti 1981	Less than 50% of patients had oral cavity cancer and some had recurrent disease.
Deka 1983	Methodology concerning randomisation unclear - alternation?
De la Torre 1991	1991 abstract - no subsequent publication identified. Unclear what proportion of patients in this study had oral cavity/oropharyngeal cancer
Di Blasio 1994	Abstract only; insufficient information available
Dobrowsky 1996	3 months follow-up only
Domenge 1987	Abstract only. No full publication found and insufficient data in abstract to enable inclusion in review
Domenge 1988	Patients had nasopharyngeal cancer
Drelichman 1983	Included patients with recurrent disease
Driessen 2016	No relevant outcome measures
Dutta 2013	Included < 50% of patients with oral cavity/oropharynx tumors
Ebeling 1994	Non-randomised study
Eriksen 2013	Evaluated targeted therapy only
Eschwege 1997	Head and neck cancer study with < 50% oral cancer/oropharyngeal cancer. Wrote to authors requesting data on oral/oropharyngeal cancer patients separately from head and neck cancers - no response
Ezzat 2005	Less than 50% of patients had oral cavity or oropharyngeal cancer.
Fayette 2016	Evaluated targeted therapy only
Feng 2018	Not a randomised controlled trial
Ferris 2018	Evaluated immunotherapy only in recurrent/metastatic disease
Fety 1994	Less than 50% of participants had oral cavity/oropharynx cancers.
Fety 1998	Less than 50% participants had oral cavity cancer.
Fonseca 1997	Intervention being compared was the addition of folinic acid to chemotherapy.
Fonseca 2005	Less than 50% of participants had oral cavity or oropharyngeal cancer.
Forastiere 2001	Included patients with recurrent disease
Fountzalis 2004	Head and neck cancer study with < 50% oral cancer/oropharyngeal cancer. Wrote to authors requesting data on oral/oropharyngeal cancer patients separately from head and neck cancers - not received

Study	Reason for exclusion
Fu 1987	Less than 50% of participants had oral cavity or oropharyngeal cancer.
Fujii 1996	Not a randomised study
Fujii 1999	Not a randomised study
Furukawa 1994	Less than 50% of participants had oral cavity/oropharynx cancers.
Gabriele 1994	Abstract only. No full publication found and no response from correspondence to first author
Gabriele 1996	Abstract only, less than 50% oral cavity/oropharynx cancer patients included, and no subsequent publication found September 09
Gaffor 2016	Primary evaluation of altered radiation schedules
Gasparini 1992	15% of patients had recurrent disease.
Gedouin 1986	Less than 50% of participants had oral cavity/oropharynx cancers.
Gedouin 1996	Less than 50% of participants had oral cavity/oropharynx cancers.
Gehanno 1992	Less than 50% of participants had oral cavity/oropharynx cancers.
Ghadjar 2014	No relevant outcome measures
Ghali 2011	Included < 50% oral cavity/oropharynx cancers
Ghosh 2006	Abstract only; insufficient information
Gibson 2005	Included patients with recurrent disease
Gillison 2017	Primary evaluation of immunotherapy
Gollin 1972	Quasi-randomised (patients paired and then blinded drawing of cards to allocate first member of pair to treatment, other patient received alternate treatment). Variation in treatment used over the course of the study. Publication too old to be able to contact authors
Grandis 2008	Primary evaluation of targeted therapy
Grose 1985	Included patients with metastatic disease
Groselj 2017	Evaluation of cutaneous SCC
Gupta 2017	Did not evaluate chemotherapy
Haas 1985	Abstract only, and no subsequent publication found September 09
Haas 1986	Less than 50% of participants had oral cavity/oropharynx cancers.
Haffty 1993	Less than 50% of participants had oral cavity/oropharynx cancers.
Haffty 1997	Less than 50% of participants had oral cavity/oropharynx cancers.
Haffty 1997a	Less than 50% of participants had oral cavity/oropharynx cancers.

Study	Reason for exclusion
Haffty 2005	Some patients had recurrent disease and prior chemotherapy.
Handa 1980	Allocation to intervention not truly random
Hasegawa 1996	Abstract only; insufficient information available
Haselow 1990	Preliminary results of a study with less than 50% oral cavity oropharyngeal cancer
Henk 1984	Less than 50% participants had oral cavity/oropharynx cancers.
Hitt 2005	Less than 50% of participants had oral cavity or oropharyngeal cancer.
Homma 2004	Less than 50% participants had oral cavity/oropharynx cancers.
Hussey 1975	Less than 50% participants had oral cavity/oropharynx cancers.
Inhestern 2017	Not a randomised controlled trial
Iyer 2015	Not a randomised controlled trial
Jain 1979	Methods used described very briefly - unclear if patients were randomised to treatment
Jones 1992	Less than 50% participants had oral cavity/oropharynx cancers, including patients with recurrent disease.
Jortay 1990	Less than 50% participants had oral cavity/oropharynx cancers.
Joshi 2017	Primary recurrent/metastatic population
Kamioner 1994	Abstract only more than 10 years old. No subsequent publication found. Insufficient information in abstract to include in review
Kaneda 1987	Non-randomised study which included patients with prior treatment for oral cancer
Kapstad 1978	Less than 50% participants had oral cavity/oropharynx cancers.
Kapstad 1979	Less than 50% participants had oral cavity/oropharynx cancers.
Katori 2007	Not randomised
Kitani 2017	Did not evaluate oral cavity cancers
Kityota 2017	Primary evaluation in recurrent/metastatic population
Klima 1988	Trial included patients with metastatic disease
Korde 2016	Primary evaluation of altered radiation schedule
Kotani 1994	Based on translation by Toru Naito, it appeared that the included patients had a variety of primary treatments before being allocated to subsequent chemotherapy or not.
Ksiezniak-Baran 2020	Abstract only
Laccourreye 1983	Less than 50% participants had oral cavity/oropharynx cancers.

Study	Reason for exclusion
Lavertu 1998	Less than 50% participants had oral cavity/oropharynx cancers.
Le 1998	Abstract only, and no subsequent publication of randomised study found September 09
Lee 1989	Included patients with recurrent disease
Li 2014	Evaluated targeted therapy only
Li 2018	No relevant outcome measure
Lim 2017	No relevant population
Lim 2020	Included less than 50% oropharyngeal or oral cavity cancers.
Lippman 1988	Less than 50% or particpants had oral cavity cancer.
Liverpool HNOG 1990	Included patients with recurrent disease
Lopes 1991	Abstract only, less than 50% oral cavity/oropharynx cancer patients included, and no subsequent publication found September 09
Machiels 2016	Evaluation in recurrent/metastatic population
Machiels 2017	Evaluated immunotherapy only
Machtay 2004	Did not evaluate chemotherapy
Mackiewicz 2017	Not a randomised controlled trial
Magno 1994	Less than 50% participants had oral cavity/oropharynx cancers.
Mak 2017	Trial of adjunct therapy
Manocha 2006	Described as randomised controlled trial but patients in group 1 were selected by good KPS score performance status and ability to afford chemotherapy. Email requesting further information sent 1/10/09 - no reply received
Mantovani 1998	Chemotherapy was same in both groups - patients randomised to immunotherapy or not
Marta 2015	Not a randomised controlled trial
Martin 1994	Head and neck cancer study with < 50% oral cancer/oropharyngeal cancer. Wrote to authors requesting data on oral/oropharyngeal cancer patients separately from head and neck cancers - no response. Pignon has individual patient data for all patients - trial identification CRETEIL 86.
Mashkour 2020	Included less than 50% oropharngeal or oral cavity cancers
Mechl 1987	Less than 50% of participants had oral cavity cancer.
Mehanna 2017	No relevant outcome measure
Melotek 2016	Not a randomised controlled trial
Melotek J 2016	Did not evaluate chemotherapy

Study	Reason for exclusion
Melotek JM 2016	Not a randomised controlled trial (subgroup analysis)
Merlano 2020	Evaluated targeted therapy
Mitra 2006	Less than 50% of included patients had oral cavity/oropharynx cancers.
Moro 1994	Abstract more than 10 years old. Insufficient information in abstract to include this trial. No subsequent publication identified
Morton 1985	Low percentage oral cavity and oropharyngeal cancer and some participants had recurrent disease.
Morton 1987	Low percentage oral cavity and oropharyngeal cancer and some participants had recurrent disease.
Nair 2017	Included < 50% oral cavity/oropharynx tumours
Nevens 2017	Did not evaluate chemotherapy
Nichols 2013	No relevant outcome measure
Nissenbaum 1984	Less than 6 months follow-up
O'Connor 1979	Some patients had prior treatment.
Olasz 2004	Quasi-randomised study - patients allocated to treatment by alternation
Overgaard 2007	Did not evaluate cytotoxic chemotherapy
Panis 1984	35% of participants had received prior treatment for oral cancer.
Pant 1973	Pseudo-randomised (Pignon)
Papac 1978	Unclear what proportion of patients in this study had oral cavity cancer
Park 2017	Did not evaluate chemotherapy
Patil 2017	No relevant outcome measure
Pearlman 1985	Included patients with recurrent disease
Peng 2007	Paper published in Chinese with English abstract. Email sent to Dr Peng requesting more information concerning eligibility of study for inclusion in this review. Reply received 5/11/09, stating that data were lost
Phillips 1980	Abstract only, less than 50% oral cavity/oropharynx cancer patients included, and no subsequent publication found September 09
Platzer 1990	Abstract only, outcomes not relevant, and no subsequent publication found September 09
Poddar 2017	Did not evaluate cytotoxic chemotherapy
Porceddu 2017	Did not include oral cancer
Pothamsetty 2017	Not a randomised controlled trial; no relevant comparison

Study	Reason for exclusion
Price 1978	Linked to Shaw 1978. Many participants had prior treatment.
Proto 1993	Interim report of 8 oral cavity cancer patients randomised to 3 treatment arms. No usable data. No follow-up publication found
Racadot 2008	Less than 50% of participants had oral cavity or oropharyngeal cancer.
Rades 2016	Not a randomised controlled trial
Rastogi 2019	Included less than 50% oropharyngeal or oral cavity cancers
Rodrigo 2004	Less than 50% of participants had oral cavity/oropharynx cancers.
Rosen 2003	Randomised comparison of erythropoietin versus no erythropoietin, therefore did not meet intervention inclusion criteria for this review
Rosenthal 2016	Evaluated targeted therapy
Roy 2016	Primary evaluation of altered radiation schedule
Saber 2005	Abstract only; insufficient information
Sanchiz 1990	Less than 50% participants had oral cavity/oropharynx cancers.
Sanguineti 1999	Data analysis of case series including some patients randomised to treatment and others not randomised
Sarkar 2008	Less than 50% of participants had oral cavity or oropharyngeal cancer.
Schildhauer 2005	Patients had primary metastatic or recurrent disease.
Schuller 1989	Less than 50% of participants had oral cavity/oropharynx cancers.
Scwiecicki 2016	Evaluated a recurrent/metastatic population
Sealy 1978	Unclear concerning proportion of patients with oral cavity/oropharyngeal cancer. Unclear methodology concerning randomisation
SECOG 1986	43% oral cavity cancers only
Sharma 2007	Abstract only; insufficient information
Sharma 2019	Abstract only
Shaw 1978	Linked to Price 1978. Many participants had prior treatment.
Shetty 1985	Abstract only, unable to find subsequent publication. Insufficient information to include in systematic review
Siodlak 1989	Less than 50% participants had oral cavity/oropharynx cancers.
Siu 2017	Evaluated immunotherapy
Skillington 2017	Not a randomised controlled trial

Study	Reason for exclusion
Smid 2003	Less than 50% patients had oral cavity or oropharyngeal cancer.
Snow 1981	Less than 50% of patients had oral cavity/oropharyngeal cancer.
Soo 2005	Less than 50% of patients had oral cavity or oropharyngeal cancer.
Specenier 2017	Evaluated targeted therapy only
Stefani 1971	Included participants with metastatic disease. Linked to Stefani 1980
Stefani 1980	Included participants with metastatic disease. Linked to Stefani 1971
Stell 1983	Less than 50% participants had oral cavity/oropharynx cancers.
Stell 1990	Less than 50% of patients had oral cavity/oropharyngeal cancer.
Stolwijk 1985	Less than 50% participants had oral cavity/oropharynx cancers.
Sun 2017	Evaluated targeted therapy only
Sun 2020	Evaluated targeted therapy
Sun Y 2020	Included less than 50% oropharyngeal or oral cavity cancers
Suwinski 2005	Less than 50% of participants had oral cavity or oropharyngeal cancer.
Szturz 2016	Case study of targeted therapy
Tao 2017	Not a randomised controlled trial
Taylor 1978	Evaluated targeted therapy
Taylor 1979	Included patients who had prior treatment
Taylor 1984	Included patients who had prior treatment
Taylor 1985	Allocated to treatment by alternation, and post-radiotherapy maintenance chemotherapy regimen changed after 29/82 patients treated. Data not available for each regimen separately
Taylor 1994	9% of included patients have recurrent disease and only 51% of patients had oral cavity/oropharynx disease. It is likely that less than 50% of patients included had untreated advanced cancer of oral cavity or oropharynx.
Taylor 1997	Follow-up of patients, only some were randomised to treatment and < 50% had oral cavity cancer.
Tian 2018	Primary evaluation of radiation techniques (i.e. brachytherapy)
Toohill 1987	50% participants had oral cavity/oropharynx cancers, interim report.
Tsukuda 1994	Less than 50% of participants had oral cavity or oropharyngeal cancer.
Tsukuda 2005	Less than 50% of participants had oral cavity or oropharyngeal cancer.
Tsukuda 2010	Included < 50% oral cavity and/or oropharynx tumours

Study	Reason for exclusion
Vega 1981	[Spanish] Some patients in this study had recurrent or metastatic disease and less than 50% had oral cavity/oropharynx primary tumours.
Venkatachalam 1998	Chemotherapy was same in both groups - patients randomised to immunotherapy or not
Vermund 1985	Less than 50% participants had oral cavity/oropharynx cancers.
Veronesi 1985	60% of participants had undergone previous treatment and 19% had metastatic disease. Requested data on participants without prior treatment - no response received
Viswanath 2009	No relevant outcome measure
Von Heyden 1984	Cross-over design
Von Heyden 1985	Cross-over study (n = 79); some patients had prior treatment.
Wang 2017	No relevant outcome measure
Weissberg 1989	Less than 50% oral cavity and oropharynx cancer. Data in Pignon 2000 was for all the included patients. No separate data for oral cavity and oropharyngeal cancer patients available
Wolf 2017	Evaluated targeted therapy (IRX-2)
Woods 1977	Less than 50% oral cavity or oropharyngeal cancer and included patients with recurrent disease
Woods 1981	Included patients with recurrent disease
Woods 1981a	Proportion of patients with oral cavity/oropharyngeal cancer unknown and some patients had prior treatment.
Woods 1984	Abstract only - some patients had prior treatment.
Yi 2017	Less than 50% patients with oral cavity/oropharynx tumours
Yoshino 1991	Less than 50% of participants had oral cavity or oropharyngeal cancer.
Yoshino 1994	Less than 50% of participants had oral cavity or oropharyngeal cancer.

KPS = karnofsky performance status
SCC = squamous cell carcinoma

Characteristics of studies awaiting classification *[ordered by study ID]*

Borel 2020

Methods	RCT
Participants	124 (65 SOC, 59 FHD) between 10 sites Characteristics balanced across the two arms Median age: 60 Male: 85% ECOG 0: 50% Stage IV: 77%, Definitive CRT: 58%

Borel 2020 *(Continued)*

	Oropharynx: 51% (p16+: 43%) Smoking history: 89% of pts (median of 40 pack-years)
Interventions	Standard of care cisplatin versus fractionated high dose cisplatin (25 mg/m^2/d 1-4 q3/w (3 cycles)), with definitive (70 Gy/7 weeks) or postoperative (66 Gy/6.5 weeks) radiotherapy
Outcomes	Cumulative delivered cisplatin dose
Notes	Abstract only Results: "FHD Cis allowed significantly more Cis to be delivered, with significantly lower toxicity, when compared to SOC. LRFFS, PFS and OS were not significantly different between the two arms".

Bourhis 2002

Methods	Randomised controlled trial conducted in: France Number of centres: multi Recruitment period: 1996-2000 GORTEC 96-01
Participants	109 participants
Interventions	Group A: 62-64 Gy in 3 to 3.5 weeks Group B: 62-64 Gy in 5 weeks plus concomitant cisplatin 100 mg/m^2 on days 1, 16, 32, and 5-FU 1000 mg/m^2/day on days 1-5 and 31-35
Outcomes	Locoregional control, distant metastases, disease-free survival and overall survival
Notes	Emailed author 27/10/09 seeking more information on GORTEC 96-01 - no reply. Study was stopped early due to an excess of deaths in the RT-CT arm (group B)

Chaukar 2020

Methods	RCT
Participants	Inclusion criteria: treatment-naive histologically-confirmed cancer of the oral cavity; cancers requiring segmental resection for paramandibular disease without clinicoradiological evidence of bone erosion, clinical T2, T3 and T4, any N, M0 as per TNM (AJCC) 7th edition; at least 18 years old; written informed consent 68 (34 in each grp). Median follow-up of 3.6 years (IQR 0.95 to 7.05 years)
Interventions	Neoadjuvant chemotherapy (NACT) in locally advanced oral cancers versus upfront surgery alone "The patients were randomly assigned (1:1) to receive either upfront surgery followed by adjuvant treatment (standard arm-SA) or receive two cycles of three drugs NACT (docetaxel, cisplatin, 5-flurouracil) at three weekly interval (intervention arm-IA). Depending on the response after two cycles, the patient would either receive an additional third cycle or undergo surgery followed by adjuvant treatment as decided by the tumour board".
Outcomes	Survival Mandible preservation rate at 30% in the experimental arm

Chaukar 2020 *(Continued)*

	Locoregional control Recurrence Treatment-related toxicity
Notes	Conclusion: "NACT seems to be a feasible option for mandibular preservation with acceptable toxicities in a select group of patients without compromising survival. However this needs to be tested in a larger phase III randomized trial".

Fietkau 2017

Methods	Randomised controlled trial Number of centres: multicentre Recruitment period: unknown
Participants	Stage III-IVB non-metastatic head and neck squamous cell cancer
Interventions	Group A: concurrent chemoradiation with slightly reduced dose of RT and cisplatin + paclitaxel Group B: concurrent chemoradiation with cisplatin + 5-fluorouracil
Outcomes	Disease-free survival, overall survival
Notes	Abstract only

He 2017

Methods	Randomised controlled trial
Participants	Locally advanced head and neck squamous cell carcinoma
Interventions	Group A: concurrent chemoradiation with cisplatin + ralitrexed Group B: concurrent chemoradiation with cisplatin + 5-fluorouracil
Outcomes	Disease-free survival Overall survival
Notes	Abstract only

Hitt 2009

Methods	Randomised controlled trial conducted in: Spain Recruitment period: December 2002 to June 2007 Funding source: not stated
Participants	Unresectable measurable locally advanced head and neck cancer, with good performance status

Hitt 2009 *(Continued)*

Interventions	Group A: PF induction - cisplatin 100 mg/m^2/day on day 1 then 5-FU 1000 mg/m^2/day days 1-5 repeated every 3 weeks for 3 cycles followed by chemoradiotherapy - conventional radiotherapy up to 70 Gy plus cisplatin 100 mg/m^2 on days 1, 22 and 43 Group B: TPF induction - docetaxel 75 mg/m^2 on day 1, cisplatin 75 mg/m^2 day 1 and 5-FU 750 mg/m^2 by continuous infusion on days 1-5 repeated every 3 weeks for 3 cycles (G-CSF and ciprofloxacin as well) followed by chemoradiotherapy - conventional radiotherapy up to 70 Gy plus cisplatin 100 mg/m^2 on days 1, 22 and 43 Group C: chemoradiotherapy only - conventional radiotherapy up to 70 Gy plus cisplatin 100 mg/m^2 on days 1, 22 and 43
Outcomes	Time to treatment failure, locoregional control, adverse events
Notes	Unclear percentage of oral cavity + oropharyngeal cancers. No subsequent publication found August 2010

Kiyota 2020

Methods	Multi-institutional randomised phase II/III trial to confirm the non-inferiority of weekly cisplatin + RT versus 3-weekly cisplatin + RT Enrolment: Oct 2012-Dec 2018 Participants were randomised in a 1:1 ratio to arm A or arm B.
Participants	261 people age 20-75 years with postoperative high-risk features (microscopically positive margin and/or extranodal extension) and ECOG PS 0-1
Interventions	Weekly cisplatin + RT versus 3-weekly cisplatin + RT
Outcomes	Primary endpoint phase II: proportion of treatment completion Primary endpoint phase III: overall survival (OS)
Notes	"Result(s): Between Oct 2012 and Dec 2018, 261 pts were enrolled (Arm A 132 pts, Arm B 129 pts). At the planned second interim analysis in phase III with 76/161 events, the Data and Safety Monitoring Committee recommended terminating the trial and publishing the results because the statistical boundary for OS non-inferiority had met the prespecified stop criteria." Conclusion: weekly CDDP + RT is non-inferior to 3-weekly CDDP + RT for postoperative high-risk LASCCHN pts and has a favourable toxicity profile

Suneetha 2016

Methods	Randomised controlled trial conducted in India
Participants	Locally advanced oropharyngeal cancer, stage III-IV
Interventions	Group A: concurrent chemoradiation with weekly cisplatin Group B: concurrent chemoradiation with high-dose cisplatin
Outcomes	Disease-free survival, overall survival

Suneetha 2016 *(Continued)*

Notes	Abstract only

Tepmongkol 1989

Methods	Unclear
Participants	People with advanced squamous sell carcinomas of the oral cavity 141 in intervention group 70 in control group
Interventions	Experimental: neoadjuvant chemotherapy by using methotrexate 50 mg. administered intra-venously, once weekly for 3-5 injections and then followed by radiation therapy 6000–6500 cGy in 6-6.5 weeks Control: radiation therapy alone
Outcomes	Objective primary tumour response, CR, nodal status, survival rate, toxicities
Notes	Unclear whether this is an RCT. Waiting to obtain translation

AJCC: American Joint Committee on Cancer
cGy: centigray
Cis: cisplatin
CR: complete response
CRT: chemoradiotherapy
CT: chemotherapy
d: day
ECOG: Eastern Cooperative Oncology Group
FHD: fractionated high dose
f/up: follow-up
G-CSF: granulocyte colony stimulating factor
grp: group
GY: Gray
IA: intra-arterially
inj: injection
IQR: interquartile range
ITT: intention-to-treat
LRFFS: locoregional failure-free survival
M0: no metastasis (for Tumor-Node-Metastasis staging)
N: node
NACT: neoadjuvant chemotherapy
ORR: objective response rate
OS: overall survival
p16: protein 16
PF: progression free
PFS: progression-free survival
PS: performance status
pts: patients
q3: repeat every 3
RT: radiotherapy
SA: standard arm
SOC: standard of care

T(2/3/4): tumor stage 2, 3 or 4 (for Tumor-Node-Metastasis staging)
TNM: tumour-node-metastasis
TPF: docetaxel-cisplatin-5-fluorouracil
TTP: time to progression
w: week
5-FU: 5-fluorouracil

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

ChiCTR2100041869

Study name	Safety and efficacy of nab-paclitaxel combined with cisplatin and 5-FU versus paclitaxel plus cisplatin and 5-FU for induction chemotherapy in locally advanced head and neck squamous cell carcinoma: a multicenter, open, randomised controlled clinical trial
Methods	
Participants	Inclusion criteria: "1. Aged >= 18 and <= 70 years; 2. Patients diagnosed as head and neck squamous cell carcinoma of the mouth, oropharynx, larynx, and throat by histopathology or cytology; according to AJCC The Tumor Staging Manual (version 8) diagnoses of patients with head and neck squamous cell carcinoma who have no distant metastases in stage III or IV A/B and patients with stage I and stage II P16(+) oropharyngeal cancer with T3 or higher (including T3) or N1 or higher (including N1); 3. Have at least one measurable lesion according to the RECIST 1.1 tumour evaluation criteria; 4. Patients who have not previously received any treatment for disease-related treatment (can undergo a diagnostic primary lesion biopsy or lymph node biopsy); 5. ECOG fitness score 0-1; 6. The expected survival period is more than 3 months; 7. No obvious signs of haematological disease. Before enrolment, ANC >= 1.5 * 10 ^ 9/L, platelet count >=100 * 10 ^ 9/L, Hb >= 90 g/L, WBC >= 3.0 *"
Interventions	Paclitaxel (albumin-bound) + cisplatin + 5-FU versus paclitaxel + cisplatin + 5-FU
Outcomes	Primary: complete response Secondary: objective response rate, progression-free-survival, overall survival, safety
Starting date	
Contact information	
Notes	

CTRI/2021/03/032390

Study name	A study to evaluate the role of chemotherapy (which administered of therapeutic agents before a main treatment) in oral cavity cancer patients
Methods	Open label, parallel-group randomised clinical trial using computer-generated randomisation
Participants	Inclusion criteria: previously untreated biopsy-proven, buccal mucosa/gingivobuccal sulcus/tongue or floor mouth cancers requiring mandibular resection as assessed by two surgeons independently; age than 18 years to 70 years; performance status 0 or 1 (ECOG) or KPS 80 or more; adequate organ function - normal bone marrow function (haemoglobin > 8 gm/dL, total leucocyte count > 3000/cumm, absolute neutrophil count > 1500/cumm, platelet count > 100,000/cumm), normal renal function (normal serum creatinine and calculated creatinine clearance > 60mL/min), normal liver function tests (total bilirubin not more than 2 mg/dL, transaminases < 5 times upper limit of normal, serum albumin > 3 gm/dL); no history of underlying medical disease that might interfere with systemic therapy

CTRI/2021/03/032390 *(Continued)*

Interventions	Neoadjuvant chemotherapy versus standard care 2 cycles of 3 drug neoadjuvant chemotherapy NACT drug regimen: docetaxel at 75 mg/m^2 IV at day -1, cisplatin at 75 mg/m^2 IV at day -1, 5-FU - 750 mg/m^2 IV at day 1-5. All patients will receive GCSF following chemotherapy. Patient will be reassessed after 2 cycles of chemotherapy. Those having [unclear] will be given 3rd cycle of chemotherapy before surgery. Control: standard care: patients receive upfront surgery followed by chemoradiation; patients with other adverse features will receive adjuvant radiotherapy
Outcomes	Primary: disease-free survival Secondary: mandible preservation, overall survival, progression-free survival, quality of life, toxicity profile At 6 years
Starting date	Unclear. Date of registration: 30 March 2021
Contact information	Dr Devendra Chaukar, Tata Memorial Hospital, Mumbai dchaukar@gmail.com
Notes	

NCT00956007

Study name	Radiation therapy with or without cetuximab in treating patients who have undergone surgery for locally advanced head and neck cancer
Methods	Phase III randomised clinical trial
Participants	Locally advanced head and neck squamous cell carcinoma
Interventions	Group A: Primary radiotherapy Group B: Concurrent cetuximab with radiotherapy
Outcomes	Overall survival
Starting date	
Contact information	
Notes	Active, not recruiting

NCT00957086

Study name	Study of post-op adjuvant concurrent chemo-RT with or without nimotuzumab for head & neck cancer
Methods	Phase III randomised clinical trial
Participants	Locally advanced head and neck squamous cell carcinoma
Interventions	Group A: concurrent cisplatin with radiotherapy and nimotuzumab

NCT00957086 *(Continued)*

	Group B: concurrent cisplatin with radiotherapy
Outcomes	Disease-free survival Overall survival Toxicity profile
Starting date	August 2009
Contact information	Professor KC Soo, National Cancer Centre, Singapore
Notes	Active, not recruiting. Completion due June 2021 Sponsors: National Cancer Centre, Singapore; National Medical Research Council (NMRC), Singapore; Innogene Kalbiotech Pte. Ltd

NCT00999700

Study name	Induction chemotherapy followed by cetuximab plus definitive radiotherapy versus radiation plus cisplatin (INTERCEPTOR)
Methods	Phase III randomised clinical trial
Participants	Locally advanced head and neck squamous cell carcinoma
Interventions	Group A: induction cisplatin + 5-fluorouracil + docetaxel followed by concurrent chemoradiation with cetuximab Group B: concurrent chemoradiation with cisplatin
Outcomes	Primary: overall survival Secondary: incidence of acute and late toxicities in the two arms, progression-free survival, locoregional control, response rate (time frame: 5 years)
Starting date	October 2009
Contact information	
Notes	Active, not recruiting

NCT01810913

Study name	Testing docetaxel-cetuximab or the addition of an immunotherapy drug, atezolizumab, to the usual chemotherapy and radiation therapy in high-risk head and neck cancer
Methods	Phase II/III randomised clinical trial
Participants	High-risk stage III/IV head and neck cancer
Interventions	Group A: Concurrent chemoradiation with cisplatin Group B: Concurrent chemoradiation with docetaxel

NCT01810913 *(Continued)*

	Group C: Concurrent chemoradiation with docetaxel + cetuximab Group D: Concurrent chemoradiation with cisplatin + atezolizumab
Outcomes	Disease-free survival Overall survival
Starting date	
Contact information	
Notes	Recruiting

NCT02285530

Study name	GDF15 based TPF induction chemotherapy for OSCC patients
Methods	Phase II randomised clinical trial
Participants	Oral squamous cell carcinoma patients with T3/T4N0M0
Interventions	Group A: TPF induction chemotherapy followed by surgery Group B: Surgery
Outcomes	Overall survival Disease-free survival Local recurrence-free survival Distant metastasis-free survival
Starting date	
Contact information	
Notes	Recruiting

NCT02734537

Study name	Radiation therapy with or without cisplatin in treating patients with stage III-IVA squamous cell carcinoma of the head and neck who have undergone surgery
Methods	Phase II randomised clinical trial
Participants	Stage III-IVA squamous cell carcinoma of the head and neck
Interventions	Group A: Adjuvant concurrent chemoradiation with weekly cisplatin Group B: Adjuvant radiotherapy
Outcomes	Disease-free survival

NCT02734537 *(Continued)*

Starting date	
Contact information	
Notes	Recruiting

NCT03040999

Study name	Study of pembrolizumab (MK-3475) or placebo with chemoradiation in participants with locally advanced head and neck squamous cell carcinoma (MK-3475-412/KEYNOTE-412)
Methods	Phase III randomised clinical trial
Participants	Locally advanced head and neck squamous cell carcinoma
Interventions	Group A: concurrent chemoradiation with cisplatin + pembrolizumab Group B: concurrent chemoradiation with cisplatin + placebo
Outcomes	Primary: event-free survival Secondary: overall survival, adverse events (AEs), treatment discontinuations due to AEs, change From baseline in Global Health Status/Quality of Life (GHS/QoL), change from baseline in swallowing, speech, and pain symptoms, change from baseline in physical functioning,
Starting date	February 2017
Contact information	Merck Sharp & Dohme Corp.
Notes	Active, not recruiting

NCT03117257

Study name	Docetaxel and loplatin induction chemotherapy followed by concurrent chemoradiotherapy for locally advanced SCCHN
Methods	Phase II randomised clinical trial
Participants	Locally advanced head and neck squamous cell carcinoma
Interventions	Group A: Docetaxel plus loplatin induction chemotherapy combined with loplatin chemoradiotherapy Group B: TPF induction chemotherapy combined with cisplatin chemoradiotherapy
Outcomes	Overall survival Progression-free survival
Starting date	
Contact information	

NCT03117257 *(Continued)*

Notes	Recruiting

NCT03258554

Study name	Radiation therapy with durvalumab or cetuximab in treating patients with locoregionally advanced head and neck cancer who cannot take cisplatin
Methods	Phase II/III randomised clinical trial
Participants	Locally advanced head and neck squamous cell carcinoma
Interventions	Group A: Concurrent chemoradiation with cetuximab Group B: Concurrent chemoradiation with durvalumab
Outcomes	Progression-free survival Overall survival
Starting date	
Contact information	
Notes	Recruiting

NCT03452137

Study name	A study of atezolizumab (Anti-Pd-L1 antibody) as adjuvant therapy after definitive local therapy in patients with high-risk locally advanced squamous cell carcinoma of the head and neck
Methods	Phase III randomised clinical trial
Participants	High-risk locally advanced head and neck squamous cell carcinoma
Interventions	Group A: Adjuvant atezolizumab Group B: Adjuvant placebo
Outcomes	Overall survival
Starting date	
Contact information	Recruiting
Notes	

NCT03576417

Study name	A trial evaluating the addition of nivolumab to cisplatin-RT for treatment of cancers of the head and neck (NIVOPOSTOP)

NCT03576417 *(Continued)*

Methods	Phase III randomised clinical trial
Participants	Locally advanced head and neck squamous cell carcinoma
Interventions	Group A: Concurrent chemoradiation with cisplatin Group B: Concurrent chemoradiation with cisplatin + nivolumab
Outcomes	Disease-free survival
Starting date	
Contact information	
Notes	Recruiting

NCT03673735

Study name	Maintenance immune check-point inhibitor following post-operative chemo-radiation in subjects with HPV-negative HNSCC (ADHERE)
Methods	Phase III randomised clinical trial
Participants	HPV-negative squamous cell carcinoma of the head and neck
Interventions	Group A: adjuvant durvalumab Group B: adjuvant placebo
Outcomes	Disease-free survival
Starting date	June 2021
Contact information	
Notes	Recruiting

NCT03678649

Study name	A prospective randomised trial of capecitabine treatment in patients with HNSCC
Methods	Open-label phase II randomised clinical trial
Participants	Adults with locally advanced head and neck squamous cell carcinoma Inclusion criteria: between 18 and 65 years of age, histological type squamous cell carcinoma; head and neck squamous cell carcinoma (HNSCC), tumour staged as III to IVb (according to the 8th AJCC edition); Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1; prior treatment with chemo-radiotherapy (CRT) based platinum drugs; adequate marrow: WBC count ≥ 4000/µL, haemoglobin ≥ 90g/L and platelet count ≥ 100000/µL; normal liver function test: Alanine Amino-transferase (ALT), Aspartate Aminotransferase (AST) ≤ 1.5×upper limit of normal (ULN) concomitant with alkaline phosphatase (ALP) ≤ 2.5×ULN, and bilirubin ≤ 1.5ULN; adequate renal function: crea-tinine clearance ≥60 ml/min; patients must be informed of the investigational nature of this study and give written informed consent.

NCT03678649 *(Continued)*

	Exclusion criteria: nasopharyngeal carcinoma and/or salivary gland carcinoma; any other malignancy (except for primaries, appropriately treated superficial basal cell skin cancer and surgically cured cervical cancer in situ; currently recurrent of metastatic disease; received research drug in 4 weeks; prior treatment with epidermal growth factor receptor (EGFR)-targeted small molecules, EGFR-targeted antibodies, and/or any investigational agents for HNSCC; severe hematological abnormality and intolerance to chemotherapy; evidence of significant medical illness that in the investigator's judgment will substantially increase the risk associated with participation in and completion of the study; pregnant or breastfeeding; people who cannot complete the study
Interventions	Group A: capecitabine given in the adjuvant setting for 6 cycles following definitive radiotherapy Group B: observation
Outcomes	Progression-free survival Overall survival Locoregional failure-free survival Distant failure-free survival
Starting date	September 2018
Contact information	Dr. Xiaozhong Chen, Zhejiang Cancer Hospital, Hangzhou, Zhejiang, China, 310022 cxzfyun@sina.com
Notes	

NCT04780750

Study name	Concurent chemoradiotherapy in head and neck cancers
Methods	Single-blind randomised clinical trial
Participants	60 participants Inclusion criteria: adults, pathologically confirmed squamous cell carcinoma performance status 0-1 adequate renal and hepatic function Exclusion criteria: poor performance status, impaired renal or hepatic function, squamous cell carcinoma of salivary gland, parotid and paranasal carcinomas, patients with ≥ grade 2 pre-existing peripheral neuropathy, history of allergic reactions to the chemotherapeutic agents, uncontrolled intercurrent diseases, HIV positive
Interventions	Group A: concurrent chemoradiotherapy with weekly docitaxel (20 mg\m^2) and cisplatin (80mg\m2 every 3 weeks) Group B: concurrent chemoradiotherapy with cisplatin (100mg\m2 every 3 weeks)
Outcomes	Locoregional recurrence-free survival Overall survival
Starting date	1 April 2021
Contact information	Doaa Abdelaleem Alsayed, dodoalemo@yahoo.com
Notes	

Tao 2020

Study name	Randomized trial of avelumab-cetuximab-radiotherapy versus SOCs in LA SCCHN (REACH)
Methods	Phase III randomised clinical trial
Participants	Locally advanced head and neck squamous cell carcinoma
Interventions	Group A: concurrent chemoradiation with cisplatin Group B: concurrent chemoradiation with cetuximab + avelumab Group C: concurrent chemoradiation with cetuximab
Outcomes	Primary: progression-free survival Secondary: overall survival, safety
Starting date	December 2016
Contact information	Groupe Oncologie Radiotherapie Tete et Cou
Notes	

5-FU: 5-fluorouracil
A/B: refers to either stage 4A or stage 4B
AE: adverse event
AJCC: American Joint Committee on Cancer
ANC: absolute neutrophil count
ECOG: Eastern Cooperative Oncology Group
GCSF: granulocyte colony stimulating factor
GHS: global health scale
Hb: haemoglobin
HNSCC: head and neck squamous cell carcinoma
IV: intravenous
KPS: Karnofsky performance status
M: metastasis
N: node
NACT: neoadjuvant chemotherapy
P16: this is marker of HPV status
PR: partial response
QoL: quality of life
RECIST: Response Evaluation Criteria in Solid Tumors
RT: radiation therapy
RTOG: radiation therapy oncology group
SCCHN: squamous cell carcinoma of the head and neck
T: tumour
TPF: docetaxel-cisplatin-5-fluorouracil
WBC: white blood cell

DATA AND ANALYSES

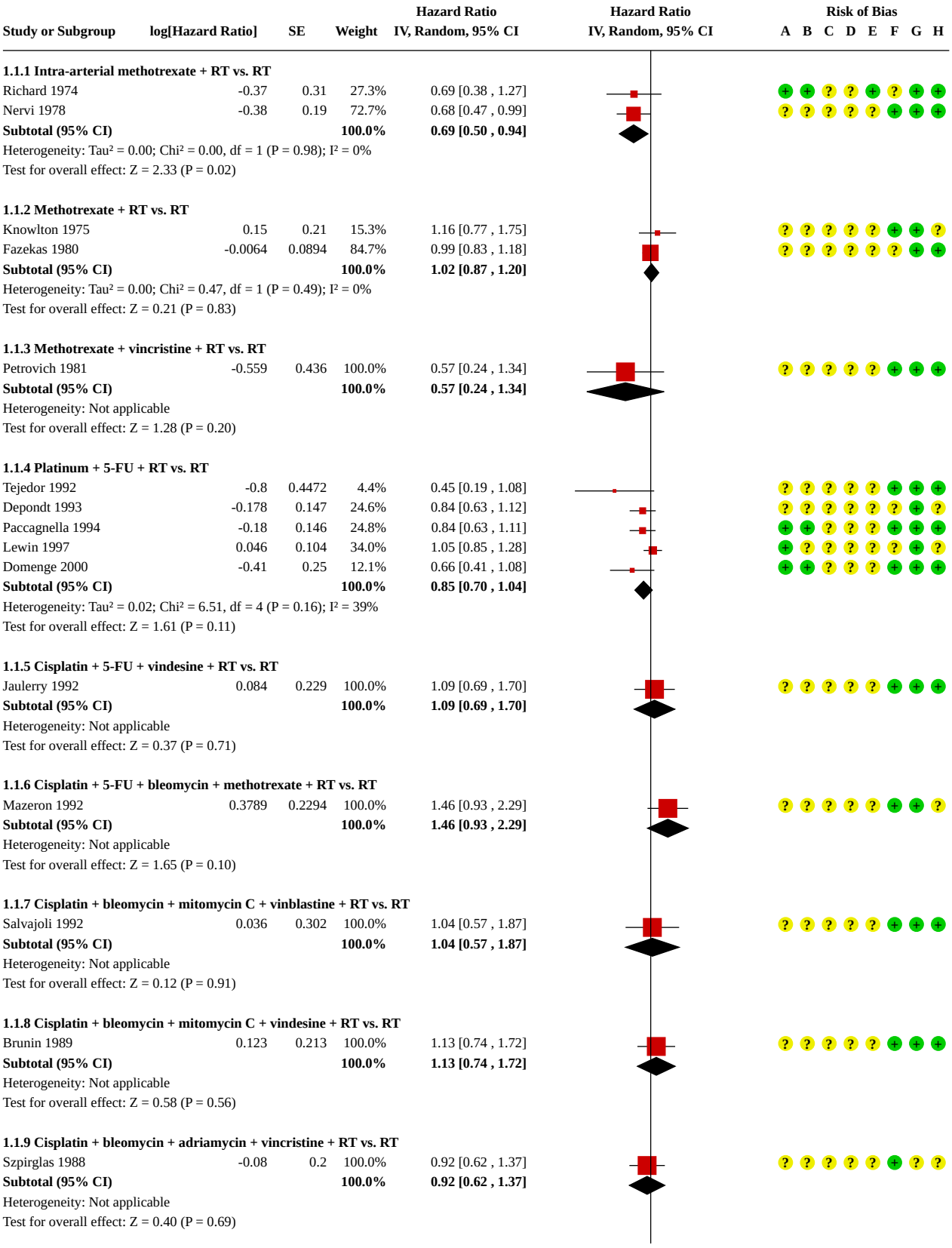
Comparison 1. Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Overall survival	32		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
1.1.1 Intra-arterial methotrexate + RT vs. RT	2		Hazard Ratio (IV, Random, 95% CI)	0.69 [0.50, 0.94]
1.1.2 Methotrexate + RT vs. RT	2		Hazard Ratio (IV, Random, 95% CI)	1.02 [0.87, 1.20]
1.1.3 Methotrexate + vincristine + RT vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	0.57 [0.24, 1.34]
1.1.4 Platinum + 5-FU + RT vs. RT	5		Hazard Ratio (IV, Random, 95% CI)	0.85 [0.70, 1.04]
1.1.5 Cisplatin + 5-FU + vindesine + RT vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	1.09 [0.69, 1.70]
1.1.6 Cisplatin + 5-FU + bleomycin + methotrexate + RT vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	1.46 [0.93, 2.29]
1.1.7 Cisplatin + bleomycin + mitomycin C + vinblastine + RT vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	1.04 [0.57, 1.87]
1.1.8 Cisplatin + bleomycin + mitomycin C + vindesine + RT vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	1.13 [0.74, 1.72]
1.1.9 Cisplatin + bleomycin + adriamycin + vincristine + RT vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	0.92 [0.62, 1.37]
1.1.10 5-FU + bleomycin + methotrexate + cyclophosphamide + RT vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	1.48 [0.91, 2.42]
1.1.11 Intra-arterial bleomycin + vincristine + surgery vs. surgery	2		Hazard Ratio (IV, Random, 95% CI)	0.67 [0.50, 0.91]
1.1.12 Cisplatin + 5-FU + surgery vs. surgery	1		Hazard Ratio (IV, Random, 95% CI)	1.06 [0.71, 1.60]
1.1.13 Cisplatin + bleomycin + methotrexate + vincristine + surgery vs. surgery	1		Hazard Ratio (IV, Random, 95% CI)	1.07 [0.77, 1.49]
1.1.14 Cisplatin + bleomycin + methotrexate + surgery vs. surgery	1		Hazard Ratio (IV, Random, 95% CI)	1.07 [0.56, 2.05]
1.1.15 Cisplatin + epirubicin + surgery vs. RT + surgery	1		Hazard Ratio (IV, Random, 95% CI)	0.88 [0.56, 1.38]
1.1.16 Cisplatin + 5-FU + RT vs. CRT (cisplatin)	1		Hazard Ratio (IV, Random, 95% CI)	0.70 [0.46, 1.05]
1.1.17 Cisplatin + 5-FU + RT vs. CRT (cisplatin + 5-FU)	1		Hazard Ratio (IV, Random, 95% CI)	0.60 [0.27, 1.33]

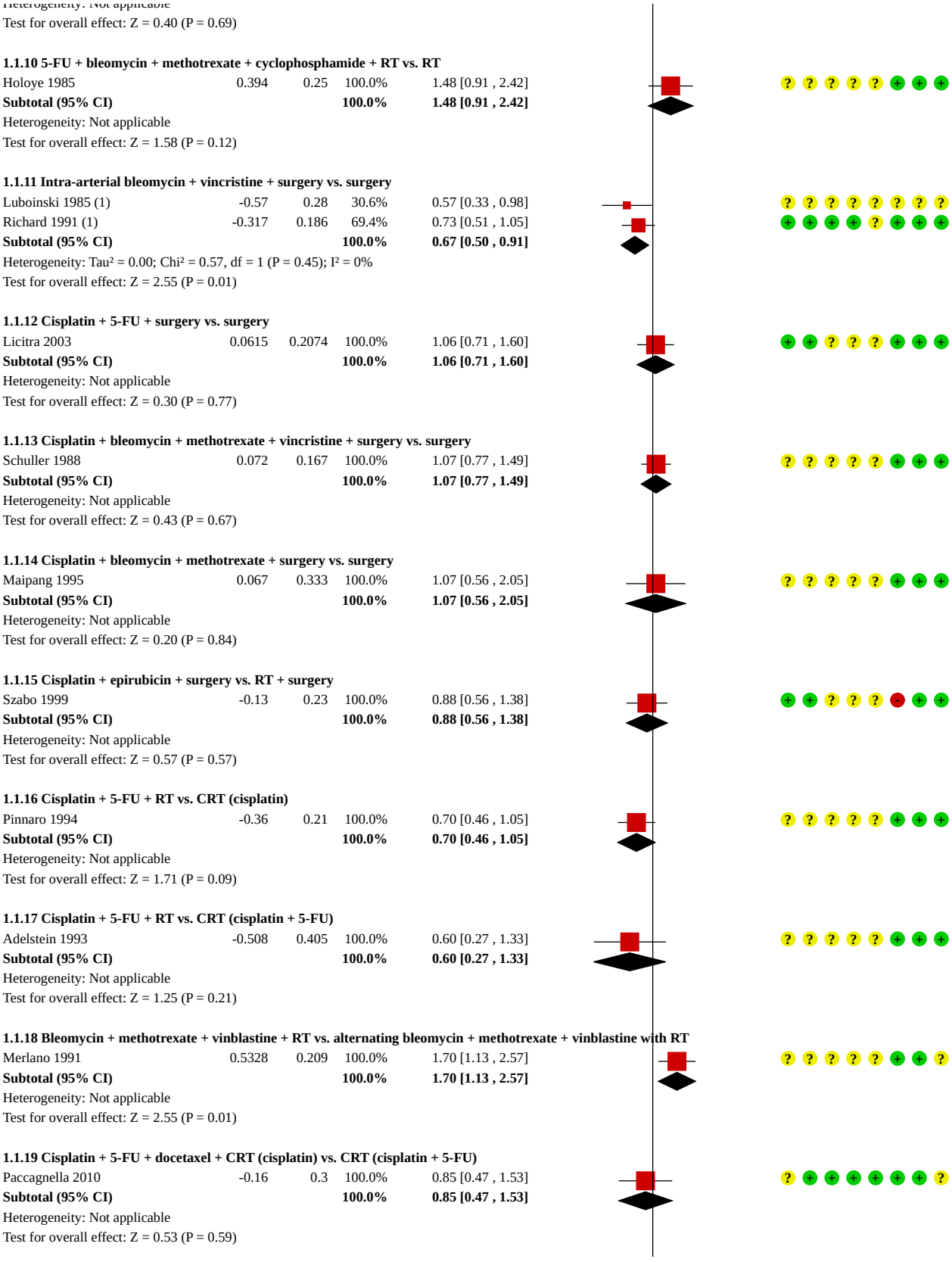
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1.18 Bleomycin + methotrexate + vinblastine + RT vs. alternating bleomycin + methotrexate + vinblastine with RT	1		Hazard Ratio (IV, Random, 95% CI)	1.70 [1.13, 2.57]
1.1.19 Cisplatin + 5-FU + docetaxel + CRT (cisplatin) vs. CRT (cisplatin + 5-FU)	1		Hazard Ratio (IV, Random, 95% CI)	0.85 [0.47, 1.53]
1.1.20 Cisplatin + 5-FU + docetaxel + CRT (cisplatin) vs. CRT (cisplatin)	3		Hazard Ratio (IV, Random, 95% CI)	1.08 [0.80, 1.44]
1.1.21 Cisplatin + 5-FU + CRT (cisplatin) vs. CRT (cisplatin)	2		Hazard Ratio (IV, Random, 95% CI)	0.71 [0.37, 1.35]
1.1.22 Cisplatin + 5-FU + docetaxel + CRT (carboplatin) vs. CRT (cisplatin)	1		Hazard Ratio (IV, Random, 95% CI)	1.09 [0.61, 1.96]
1.1.23 5-FU + docetaxel + hydroxyurea + CRT (5-FU + docetaxel + hydroxyurea) vs. CRT (5-FU + docetaxel + hydroxyurea)	1		Hazard Ratio (IV, Random, 95% CI)	0.91 [0.58, 1.42]
1.2 Disease-free survival	15		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
1.2.1 Platinum + 5-FU + RT vs. RT	3		Hazard Ratio (IV, Random, 95% CI)	0.78 [0.63, 0.97]
1.2.2 Cisplatin + 5-FU + CRT (cisplatin) vs. CRT (cisplatin)	1		Hazard Ratio (IV, Random, 95% CI)	0.52 [0.27, 1.02]
1.2.3 Cisplatin + bleomycin + mitomycin C + vindesine + RT vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	0.93 [0.58, 1.49]
1.2.4 Intra-arterial bleomycin + vincristine + surgery vs. surgery	1		Hazard Ratio (IV, Random, 95% CI)	0.86 [0.56, 1.32]
1.2.5 5-FU + bleomycin + methotrexate + cyclophospohamide + RT vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	0.92 [0.48, 1.76]
1.2.6 Carboplatin + 5-FU + surgery vs. surgery	1		Hazard Ratio (IV, Random, 95% CI)	0.55 [0.32, 0.93]
1.2.7 Cisplatin + 5-FU + RT vs. CRT (cisplatin + 5-FU)	1		Hazard Ratio (IV, Random, 95% CI)	0.46 [0.14, 1.46]
1.2.8 Cisplatin + 5-FU + RT vs. CRT (cisplatin + 5-FU)	1		Hazard Ratio (IV, Random, 95% CI)	1.07 [0.71, 1.62]
1.2.9 Cisplatin + 5-FU + docetaxel + CRT (cisplatin + 5-FU) vs. CRT (cisplatin + 5-FU)	1		Hazard Ratio (IV, Random, 95% CI)	0.77 [0.45, 1.31]
1.2.10 Cisplatin + 5-FU + docetaxel + CRT (cisplatin) vs. CRT (cisplatin)	3		Hazard Ratio (IV, Random, 95% CI)	0.95 [0.68, 1.33]
1.2.11 Cisplatin + 5-FU + docetaxel + CRT (carboplatin) vs. CRT (cisplatin)	1		Hazard Ratio (IV, Random, 95% CI)	1.07 [0.60, 1.92]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.12 Cisplatin + 5-FU + CRT (cisplatin) vs. CRT (cisplatin)	1		Hazard Ratio (IV, Random, 95% CI)	0.90 [0.69, 1.17]
1.3 Disease-free survival	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.3.1 Cisplatin + 5-FU + surgery vs. surgery	1	191	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.83, 1.45]
1.4 Locoregional control	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.4.1 Bleomycin + methotrexate + vinblastine + RT vs. alternating bleomcyin + methotrexate + vinblastine with RT	1	105	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.89, 1.74]
1.4.2 Bleomycin + methotrexate + hydroxyurea + RT vs. alternating bleomycin + methotrexate + hydroxyurea with RT	1	49	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.68, 3.27]
1.4.3 5-FU + docetaxel + hydroxyurea + CRT (5-FU + docetaxel + hydoxyurea) vs. CRT (5-FU + docetaxel + hydroxyurea)	1	249	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.51, 1.28]
1.4.4 Cisplatin + 5-FU + docetaxel + CRT (cisplatin) vs. CRT (cisplatin)	3	760	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.64, 0.99]
1.4.5 Cisplatin + 5-FU + CRT (cisplatin) vs. CRT (cisplatin)	1	284	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.60, 1.02]
1.5 Recurrent disease - locoregional	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.5.1 Cisplatin + 5-FU + surgery vs. surgery	1	191	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.60, 1.42]

Analysis 1.1. Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone, Outcome 1: Overall survival



Analysis 1.1. (Continued)



Analysis 1.1. (Continued)

Heterogeneity: Not applicable
Test for overall effect: Z = 0.53 (P = 0.59)

1.1.20 Cisplatin + 5-FU + docetaxel + CRT (cisplatin) vs. CRT (cisplatin)

Hitt 2014	0.0198	0.1369	36.9%	1.02 [0.78 , 1.33]
Takasci-Nagy 2015	0.3577	0.1576	33.5%	1.43 [1.05 , 1.95]
Ghi 2017	-0.1832	0.1837	29.6%	0.83 [0.58 , 1.19]
Subtotal (95% CI)			**100.0%**	**1.08 [0.80 , 1.44]**

Heterogeneity: Tau² = 0.04; Chi² = 5.35, df = 2 (P = 0.07); I² = 63%
Test for overall effect: Z = 0.49 (P = 0.63)

1.1.21 Cisplatin + 5-FU + CRT (cisplatin) vs. CRT (cisplatin)

Gupta 2009	-0.82	0.44	32.3%	0.44 [0.19 , 1.04]
Hitt 2014	-0.1165	0.1373	67.7%	0.89 [0.68 , 1.16]
Subtotal (95% CI)			**100.0%**	**0.71 [0.37 , 1.35]**

Heterogeneity: Tau² = 0.14; Chi² = 2.33, df = 1 (P = 0.13); I² = 57%
Test for overall effect: Z = 1.05 (P = 0.30)

1.1.22 Cisplatin + 5-FU + docetaxel + CRT (carboplatin) vs. CRT (cisplatin)

Haddad 2013	0.0862	0.299	100.0%	1.09 [0.61 , 1.96]
Subtotal (95% CI)			**100.0%**	**1.09 [0.61 , 1.96]**

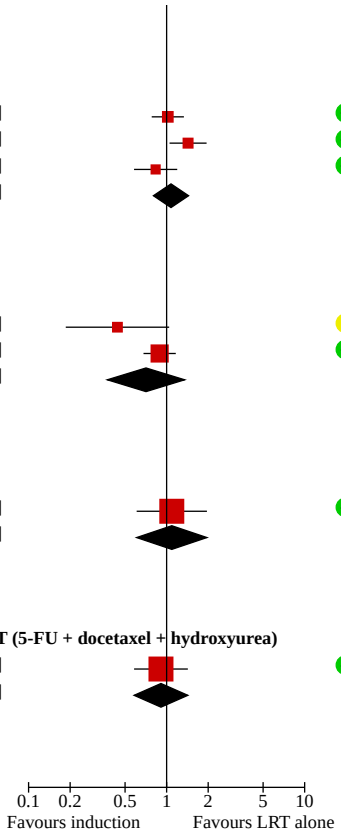
Heterogeneity: Not applicable
Test for overall effect: Z = 0.29 (P = 0.77)

1.1.23 5-FU + docetaxel + hydroxyurea + CRT (5-FU + docetaxel + hydroxyurea) vs. CRT (5-FU + docetaxel + hydroxyurea)

Cohen 2014	-0.0943	0.2287	100.0%	0.91 [0.58 , 1.42]
Subtotal (95% CI)			**100.0%**	**0.91 [0.58 , 1.42]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.68)

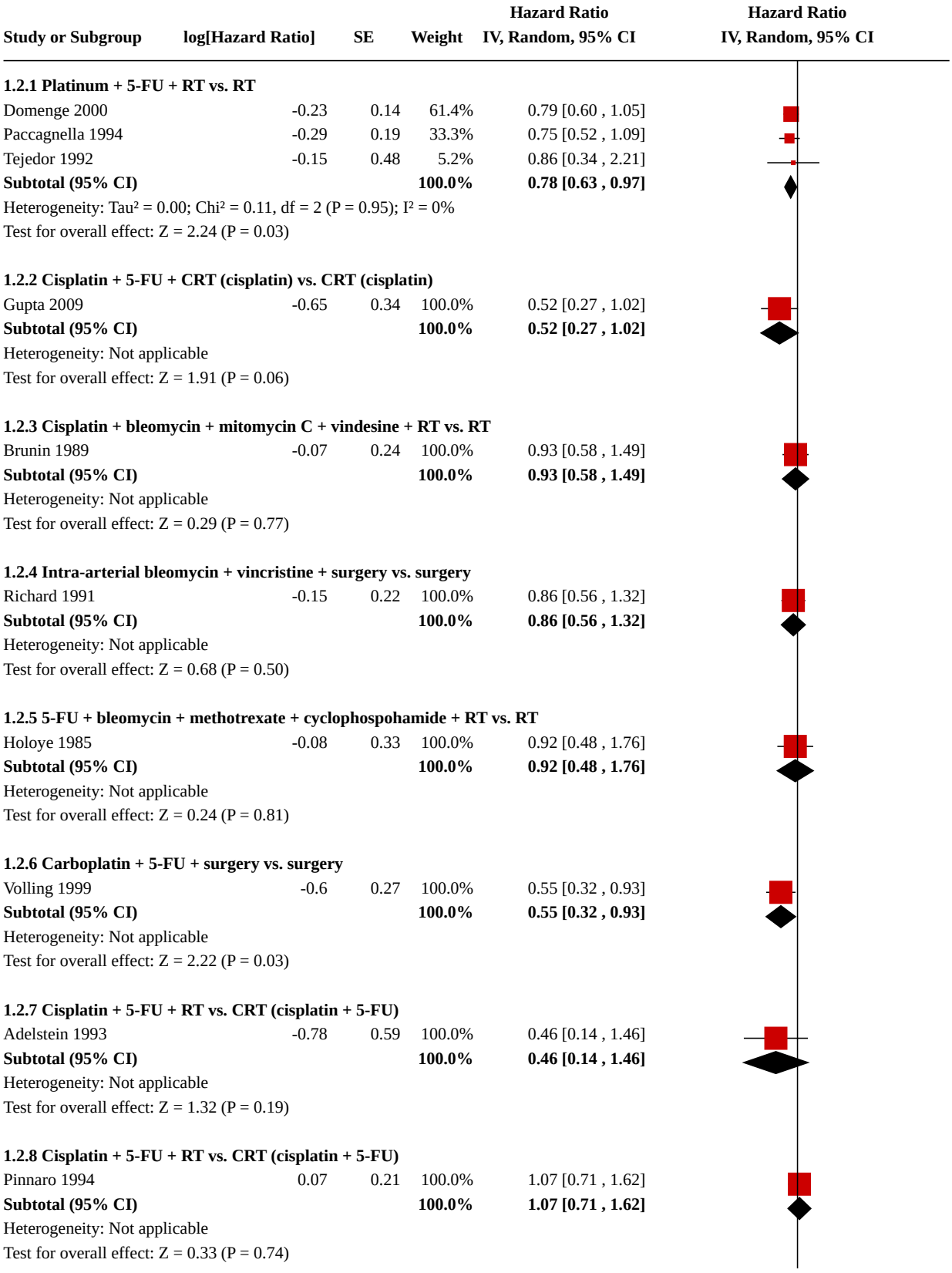
Test for subgroup differences: Chi² = 34.16, df = 22 (P = 0.05), I² = 35.6%



Footnotes
(1) Intra-arterial

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants?
(D) Blinding of carers?
(E) Blinding of outcome assessors?
(F) Incomplete outcome data addressed?
(G) Free of selective reporting?
(H) Free of other bias?

Analysis 1.2. Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone, Outcome 2: Disease-free survival



Analysis 1.2. (Continued)

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)

1.2.9 Cisplatin + 5-FU + docetaxel + CRT (cisplatin + 5-FU) vs. CRT (cisplatin + 5-FU)

Paccagnella 2010	-0.26	0.27	100.0%	0.77 [0.45 , 1.31]
Subtotal (95% CI)			**100.0%**	**0.77 [0.45 , 1.31]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.34)

1.2.10 Cisplatin + 5-FU + docetaxel + CRT (cisplatin) vs. CRT (cisplatin)

Ghi 2017	-0.3285	0.1282	35.0%	0.72 [0.56 , 0.93]
Takasci-Nagy 2015	0.3075	0.1724	30.3%	1.36 [0.97 , 1.91]
Hitt 2014	-0.0834	0.1322	34.6%	0.92 [0.71 , 1.19]
Subtotal (95% CI)			**100.0%**	**0.95 [0.68 , 1.33]**

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 8.78$, df = 2 (P = 0.01); $I^2 = 77\%$
Test for overall effect: Z = 0.29 (P = 0.77)

1.2.11 Cisplatin + 5-FU + docetaxel + CRT (carboplatin) vs. CRT (cisplatin)

Haddad 2013	0.0677	0.2973	100.0%	1.07 [0.60 , 1.92]
Subtotal (95% CI)			**100.0%**	**1.07 [0.60 , 1.92]**

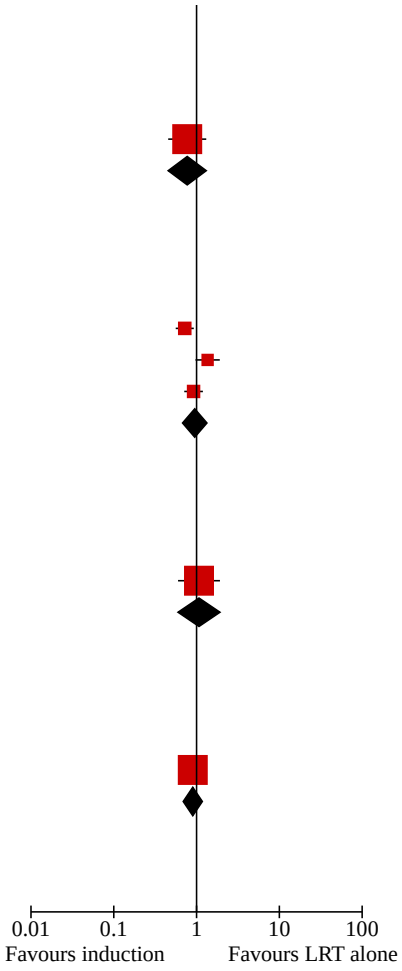
Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)

1.2.12 Cisplatin + 5-FU + CRT (cisplatin) vs. CRT (cisplatin)

Hitt 2014	-0.1054	0.1356	100.0%	0.90 [0.69 , 1.17]
Subtotal (95% CI)			**100.0%**	**0.90 [0.69 , 1.17]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.78 (P = 0.44)

Test for subgroup differences: $Chi^2 = 9.09$, df = 11 (P = 0.61), $I^2 = 0\%$

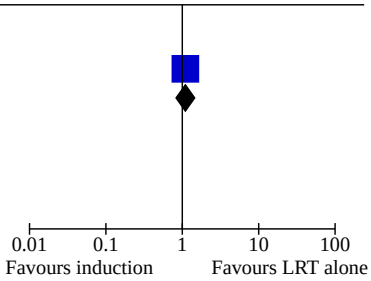


Analysis 1.3. Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone, Outcome 3: Disease-free survival

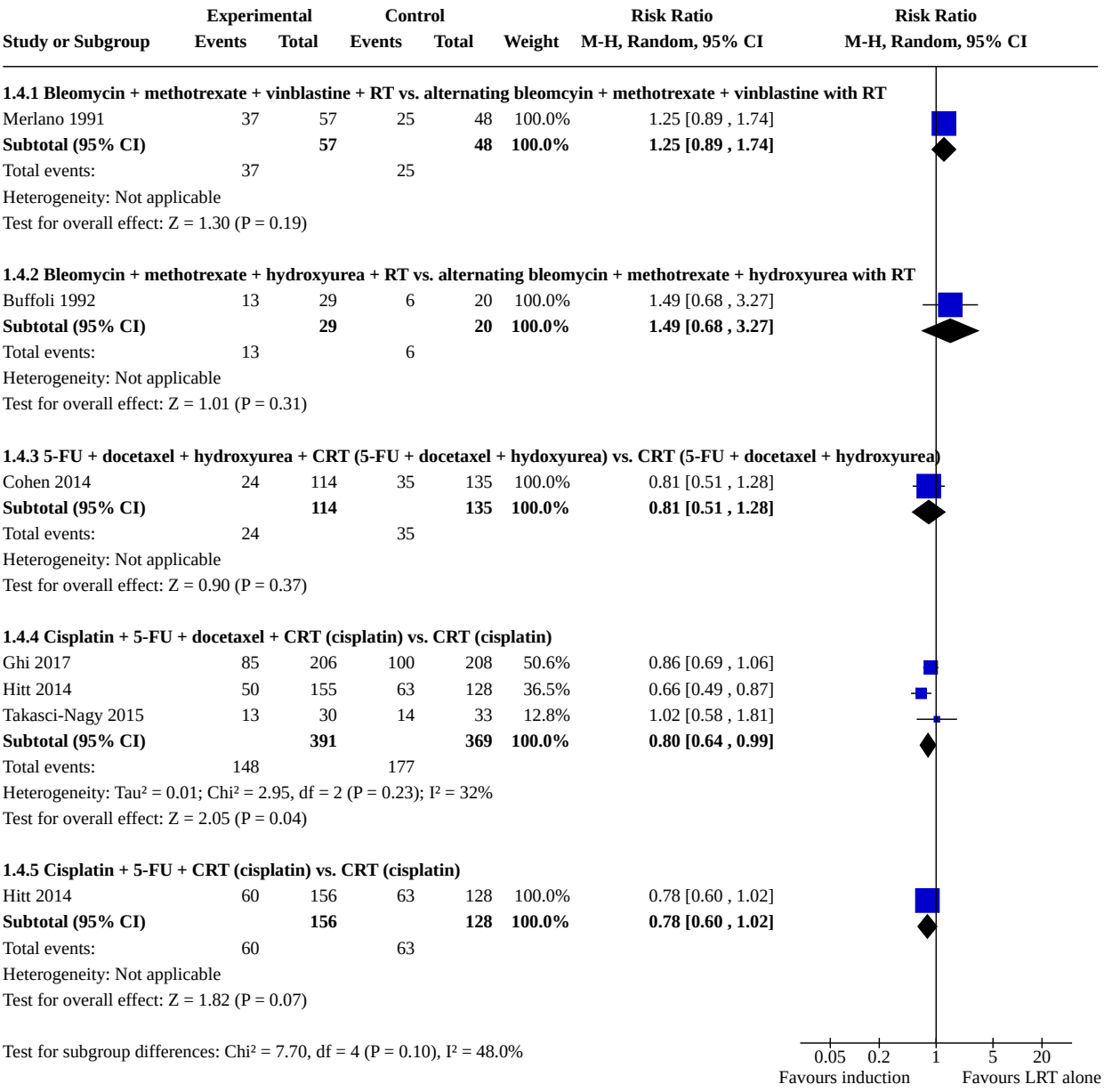
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Cisplatin + 5-FU + surgery vs. surgery						
Licitra 2003	51	96	46	95	100.0%	1.10 [0.83 , 1.45]
Subtotal (95% CI)		**96**		**95**	**100.0%**	**1.10 [0.83 , 1.45]**
Total events:	51		46			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.52)

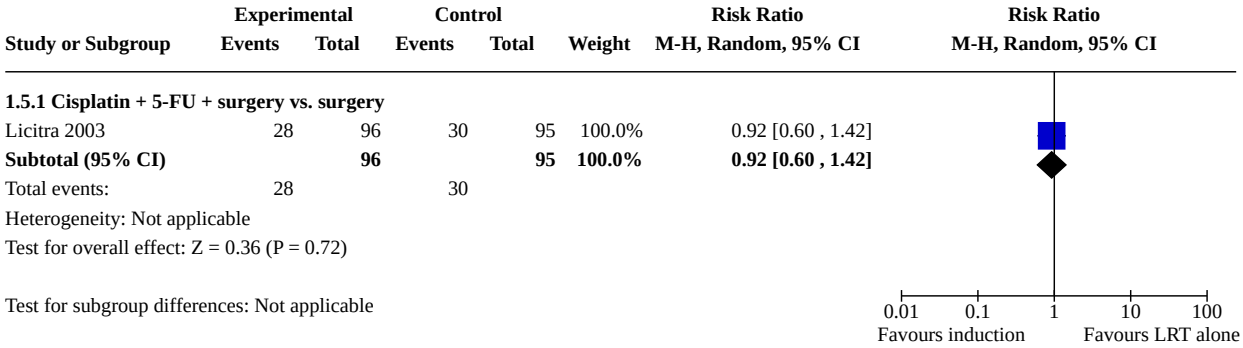
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone, Outcome 4: Locoregional control



Analysis 1.5. Comparison 1: Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone, Outcome 5: Recurrent disease - locoregional

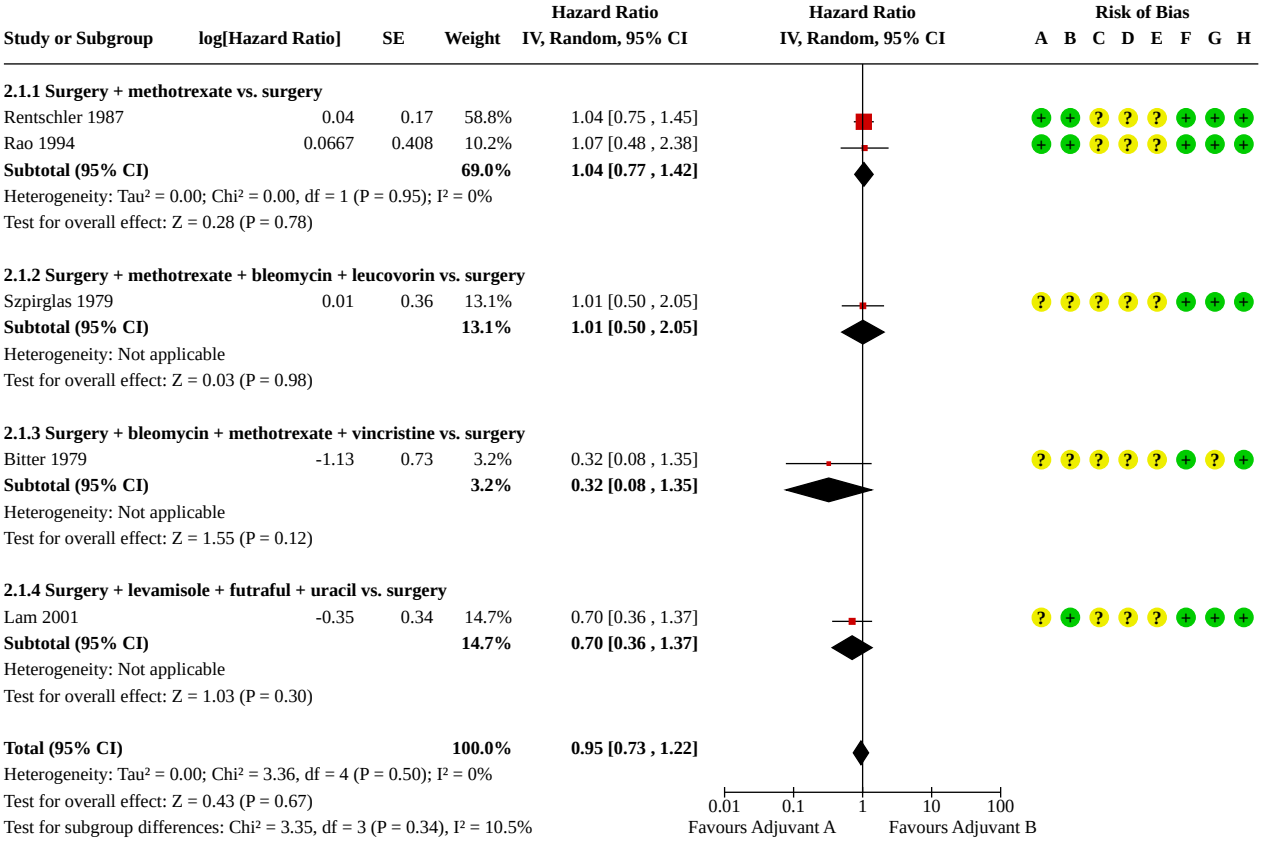


Comparison 2. Surgery + adjuvant treatment A versus surgery + adjuvant treatment B

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Overall survival - adjuvant chemotherapy vs. observation	5		Hazard Ratio (IV, Random, 95% CI)	0.95 [0.73, 1.22]
2.1.1 Surgery + methotrexate vs. surgery	2		Hazard Ratio (IV, Random, 95% CI)	1.04 [0.77, 1.42]
2.1.2 Surgery + methotrexate + bleomycin + leucovorin vs. surgery	1		Hazard Ratio (IV, Random, 95% CI)	1.01 [0.50, 2.05]
2.1.3 Surgery + bleomycin + methotrexate + vincristine vs. surgery	1		Hazard Ratio (IV, Random, 95% CI)	0.32 [0.08, 1.35]
2.1.4 Surgery + levamisole + futraful + uracil vs. surgery	1		Hazard Ratio (IV, Random, 95% CI)	0.70 [0.36, 1.37]
2.2 Overall survival - adjuvant chemoradiotherapy vs radiotherapy	4		Risk Ratio (IV, Random, 95% CI)	0.84 [0.72, 0.98]
2.2.1 Surgery + CRT (carboplatin) vs. surgery + RT	1		Risk Ratio (IV, Random, 95% CI)	0.90 [0.42, 1.92]
2.2.2 Surgery + CRT (methotrexate) vs. surgery + RT	1		Risk Ratio (IV, Random, 95% CI)	0.94 [0.70, 1.26]
2.2.3 Surgery + CRT (cisplatin) vs. surgery + RT	2		Risk Ratio (IV, Random, 95% CI)	0.79 [0.65, 0.98]
2.3 Overall survival - adjuvant chemotherapy + radiotherapy vs. adjuvant radiotherapy	1		Risk Ratio (IV, Random, 95% CI)	0.91 [0.73, 1.13]
2.3.1 Surgery + cisplatin + 5-FU + RT vs. surgery + RT	1		Risk Ratio (IV, Random, 95% CI)	0.91 [0.73, 1.13]
2.4 Disease-free survival	9		Hazard Ratio (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4.1 Surgery + methotrexate vs. surgery	2		Hazard Ratio (IV, Random, 95% CI)	0.59 [0.34, 1.03]
2.4.2 Surgery + CT (methotrexate + bleomycin + vincristine) vs surgery + RT	1		Hazard Ratio (IV, Random, 95% CI)	0.90 [0.19, 4.21]
2.4.3 Surgery + CRT (carboplatin) vs. surgery + RT	1		Hazard Ratio (IV, Random, 95% CI)	0.82 [0.40, 1.66]
2.4.4 Surgery + CRT (methotrexate) vs. surgery + RT	1		Hazard Ratio (IV, Random, 95% CI)	1.03 [0.78, 1.36]
2.4.5 Surgery + CRT (cisplatin) vs. surgery + RT	2		Hazard Ratio (IV, Random, 95% CI)	0.77 [0.64, 0.92]
2.4.6 Surgery + cisplatin + 5-FU + RT vs. surgery + RT	1		Hazard Ratio (IV, Random, 95% CI)	0.90 [0.72, 1.14]
2.4.7 Induction cisplatin + bleomycin + surgery + adjuvant cisplatin vs. induction cisplatin + bleomycin + surgery	1		Hazard Ratio (IV, Random, 95% CI)	1.55 [0.93, 2.58]
2.5 Locoregional recurrence	1		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
2.5.1 Surgery + CRT (cisplatin) vs. surgery + RT	1		Hazard Ratio (IV, Random, 95% CI)	0.61 [0.41, 0.91]
2.6 Recurrent disease (overall)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.6.1 Surgery + CT (methotrexate) vs surgery alone	1	104	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.40, 0.97]

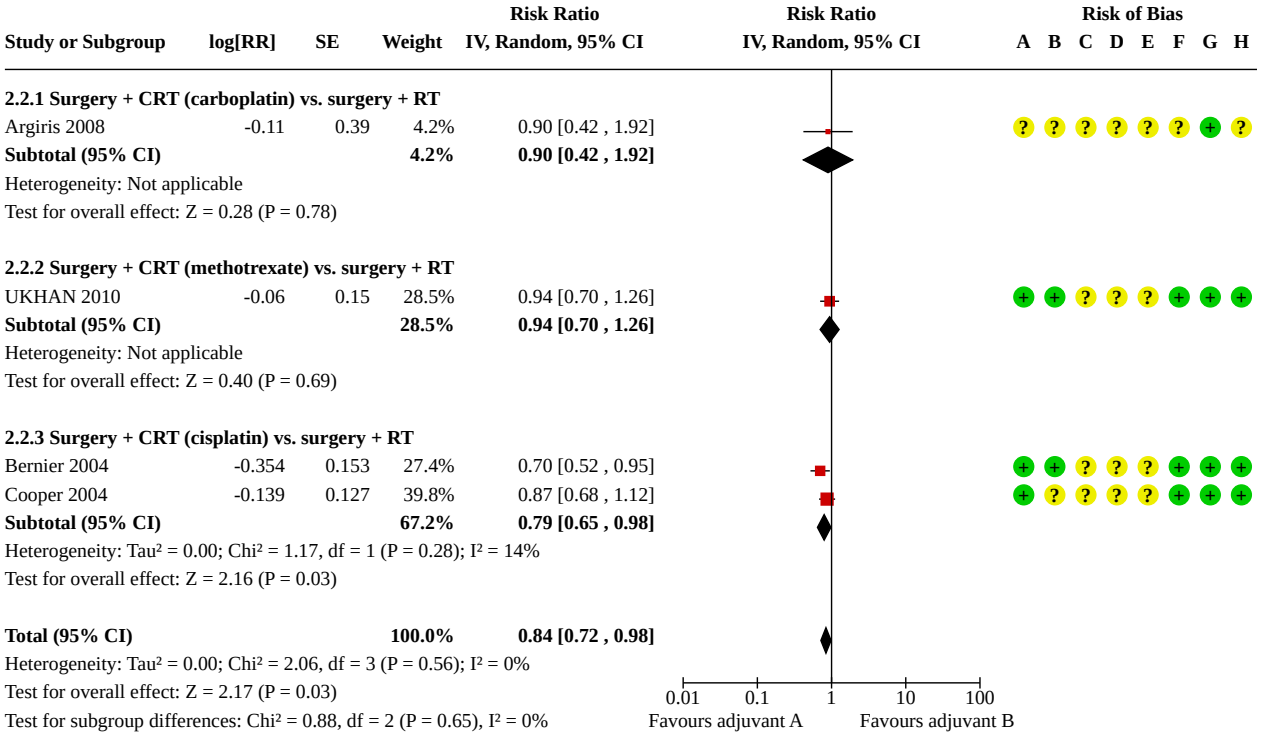
Analysis 2.1. Comparison 2: Surgery + adjuvant treatment A versus surgery + adjuvant treatment B, Outcome 1: Overall survival - adjuvant chemotherapy vs. observation



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants?
(D) Blinding of carers?
(E) Blinding of outcome assessors?
(F) Incomplete outcome data addressed?
(G) Free of selective reporting?
(H) Free of other bias?

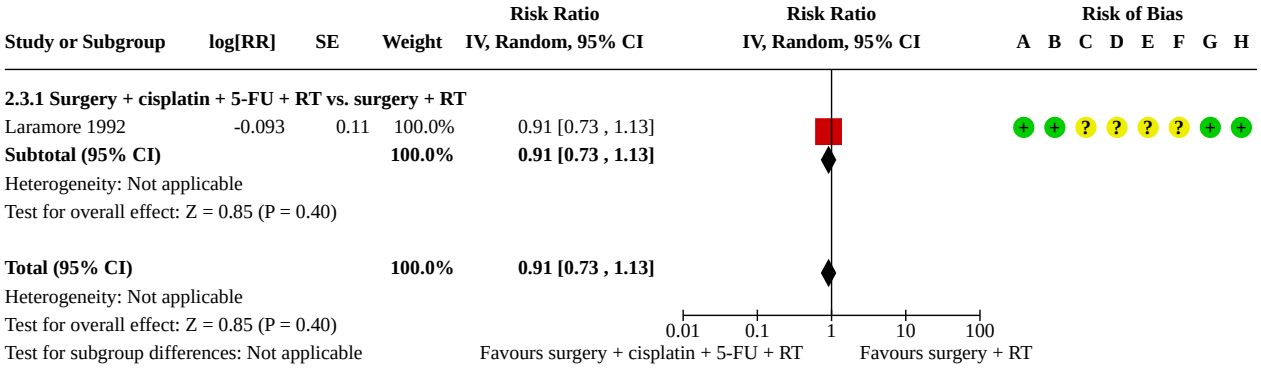
Analysis 2.2. Comparison 2: Surgery + adjuvant treatment A versus surgery + adjuvant treatment B, Outcome 2: Overall survival - adjuvant chemoradiotherapy vs radiotherapy



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants?
(D) Blinding of carers?
(E) Blinding of outcome assessors?
(F) Incomplete outcome data addressed?
(G) Free of selective reporting?
(H) Free of other bias?

Analysis 2.3. Comparison 2: Surgery + adjuvant treatment A versus surgery + adjuvant treatment B, Outcome 3: Overall survival - adjuvant chemotherapy + radiotherapy vs. adjuvant radiotherapy



Risk of bias legend

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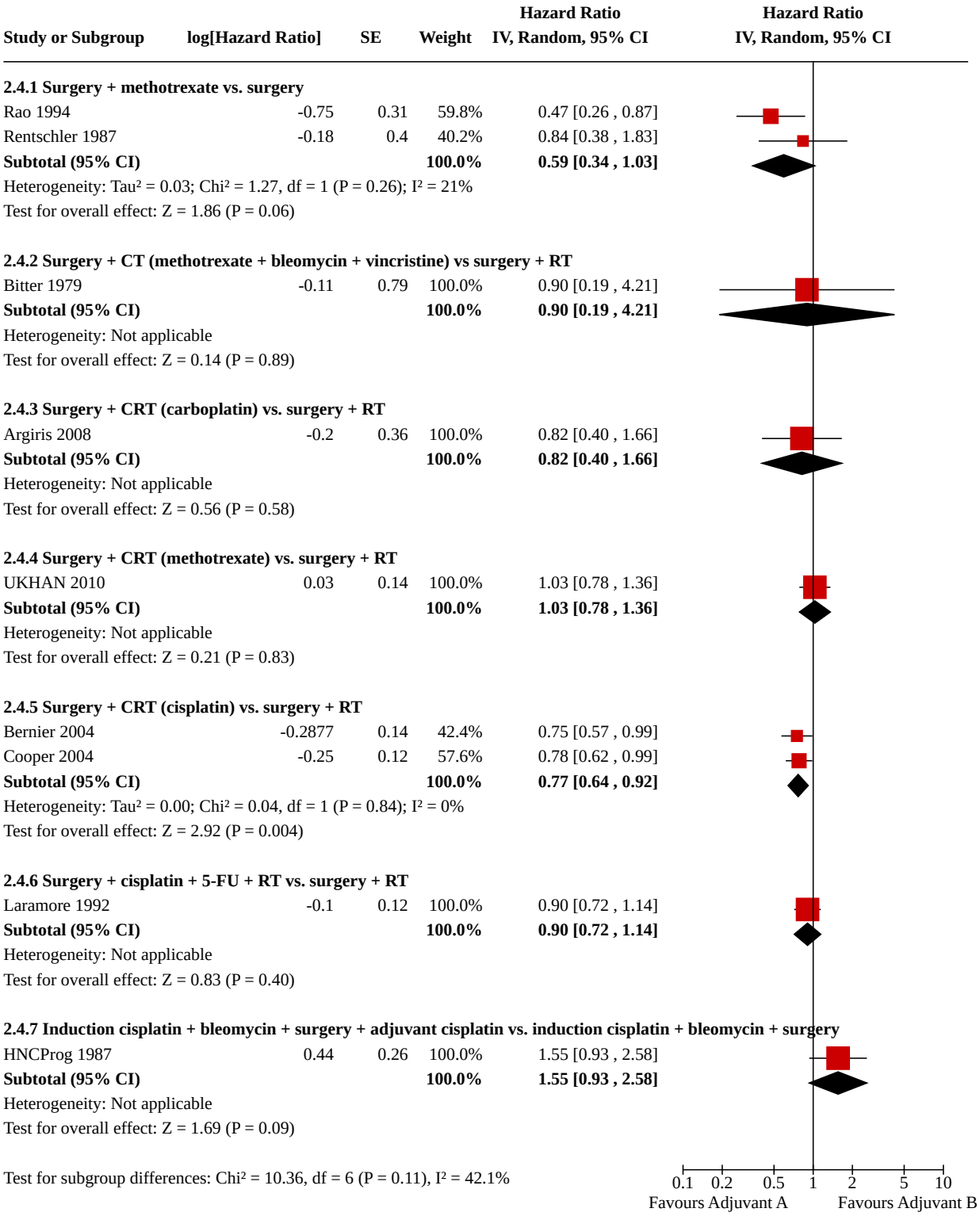
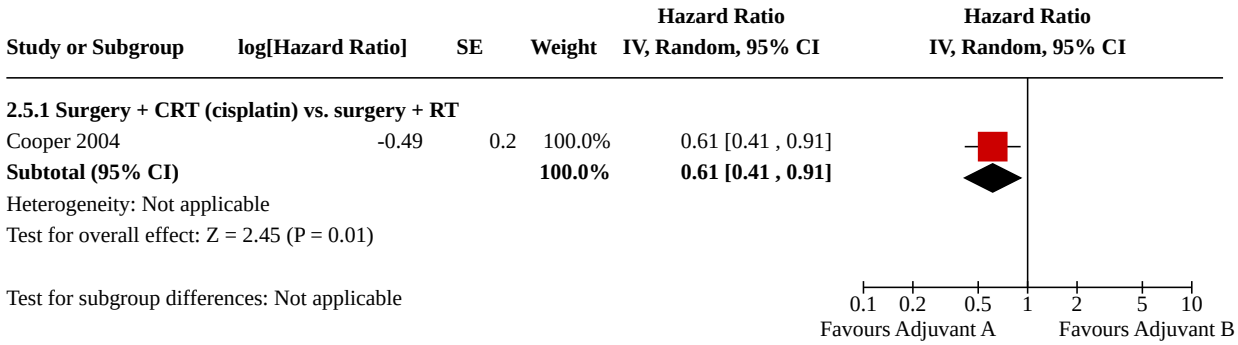
(C) Blinding of participants?
(D) Blinding of carers?
(E) Blinding of outcome assessors?
(F) Incomplete outcome data addressed?
(G) Free of selective reporting?
(H) Free of other bias?

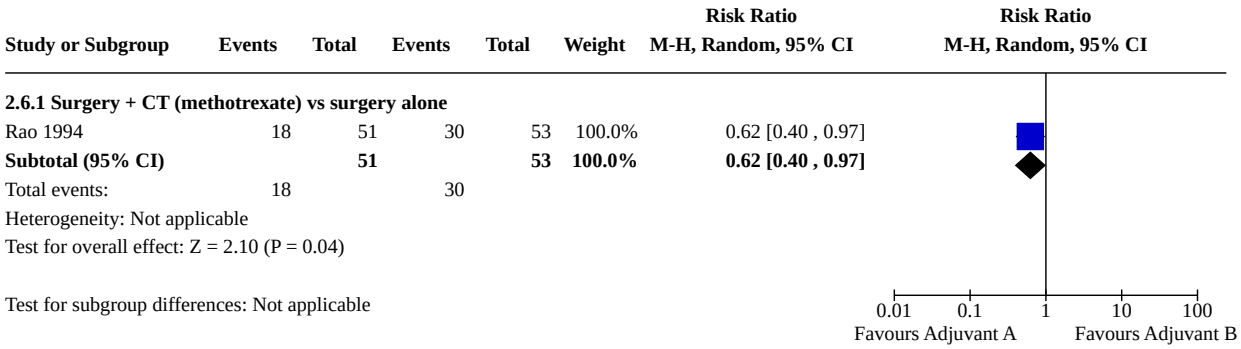
Analysis 2.4. Comparison 2: Surgery + adjuvant treatment A versus surgery + adjuvant treatment B, Outcome 4: Disease-free survival



Analysis 2.5. Comparison 2: Surgery + adjuvant treatment A versus surgery + adjuvant treatment B, Outcome 5: Locoregional recurrence



Analysis 2.6. Comparison 2: Surgery + adjuvant treatment A versus surgery + adjuvant treatment B, Outcome 6: Recurrent disease (overall)



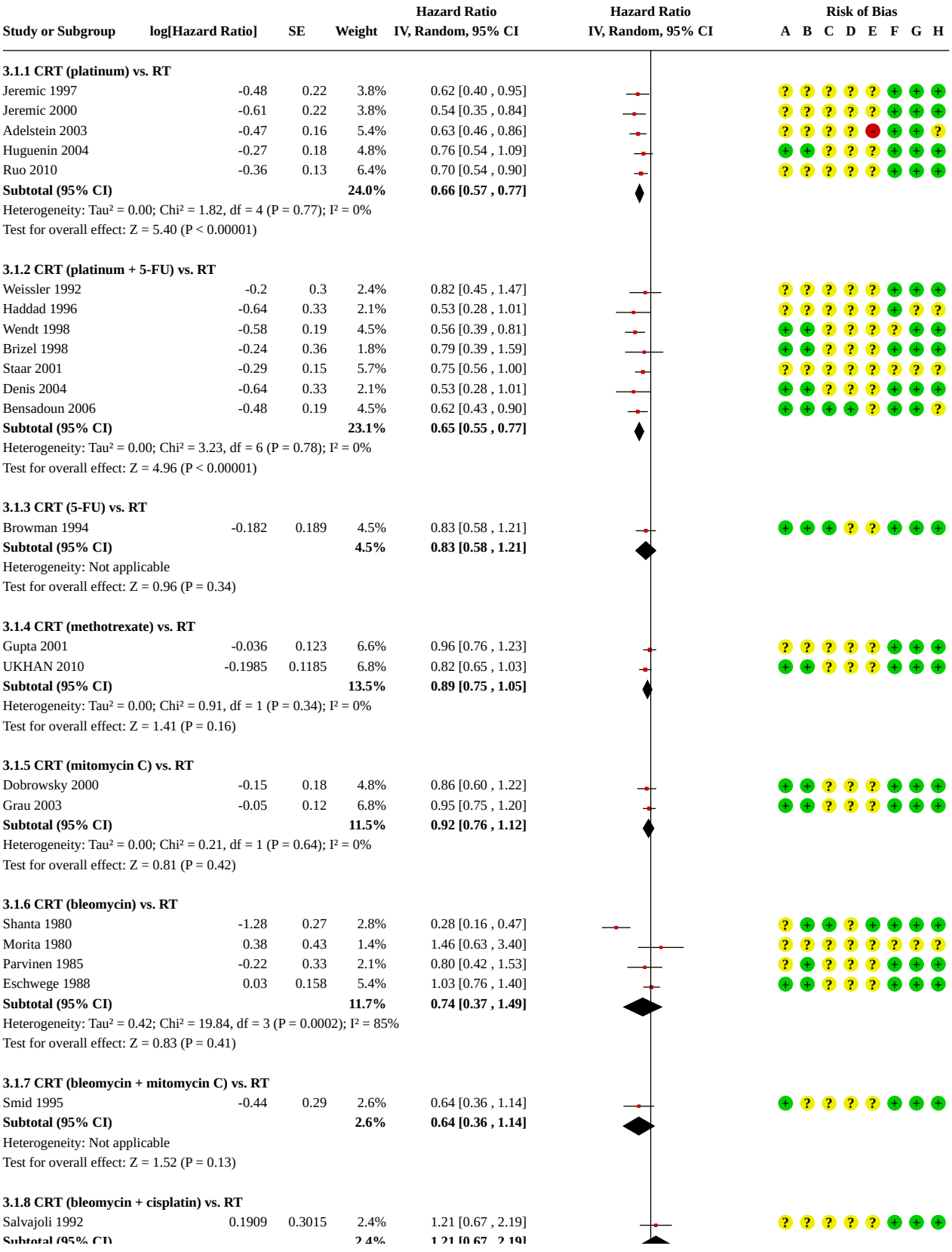
Comparison 3. Concurrent chemoradiotherapy versus radiotherapy alone (non-resectable)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Overall survival - concurrent chemoradiotherapy vs. radiotherapy	24		Hazard Ratio (IV, Random, 95% CI)	0.74 [0.67, 0.83]
3.1.1 CRT (platinum) vs. RT	5		Hazard Ratio (IV, Random, 95% CI)	0.66 [0.57, 0.77]
3.1.2 CRT (platinum + 5-FU) vs. RT	7		Hazard Ratio (IV, Random, 95% CI)	0.65 [0.55, 0.77]
3.1.3 CRT (5-FU) vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	0.83 [0.58, 1.21]
3.1.4 CRT (methotrexate) vs. RT	2		Hazard Ratio (IV, Random, 95% CI)	0.89 [0.75, 1.05]
3.1.5 CRT (mitomycin C) vs. RT	2		Hazard Ratio (IV, Random, 95% CI)	0.92 [0.76, 1.12]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1.6 CRT (bleomycin) vs. RT	4		Hazard Ratio (IV, Random, 95% CI)	0.74 [0.37, 1.49]
3.1.7 CRT (bleomycin + mitomycin C) vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	0.64 [0.36, 1.14]
3.1.8 CRT (bleomycin + cisplatin) vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	1.21 [0.67, 2.19]
3.1.9 CRT (5-FU + mitomycin C) with RT vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	0.77 [0.61, 0.98]
3.2 Overall survival - alternating chemotherapy + radiotherapy vs. radiotherapy	4		Risk Ratio (IV, Random, 95% CI)	0.85 [0.71, 1.01]
3.2.1 Alternating cisplatin + 5-FU with RT vs. RT	1		Risk Ratio (IV, Random, 95% CI)	0.76 [0.53, 1.09]
3.2.2 Alternating cisplatin + 5-FU with RT vs. altered fractionation RT	2		Risk Ratio (IV, Random, 95% CI)	0.75 [0.54, 1.05]
3.2.3 CRT (methotrexate or VBMF) + CT (methotrexate or VBMF) vs. RT + CT (methotrexate or VBMF)	1		Risk Ratio (IV, Random, 95% CI)	0.96 [0.74, 1.24]
3.3 Disease-free survival	15		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
3.3.1 CRT (daily carboplatin) vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	0.83 [0.68, 1.01]
3.3.2 CRT (cisplatin) vs. RT	2		Hazard Ratio (IV, Random, 95% CI)	0.84 [0.66, 1.08]
3.3.3 CRT (platinum + 5-FU) vs. RT	5		Hazard Ratio (IV, Random, 95% CI)	0.71 [0.60, 0.83]
3.3.4 CRT (methotrexate) vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	0.65 [0.43, 0.98]
3.3.5 CRT (5-FU) vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	0.79 [0.54, 1.14]
3.3.6 CRT (bleomycin + mitomycin C) vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	0.45 [0.22, 0.93]
3.3.7 CRT (methotrexate or 5-FU + bleomycin + methotrexate + vincristine) vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	0.72 [0.57, 0.91]
3.3.8 CRT (5-FU + mitomycin C) vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	0.60 [0.44, 0.83]

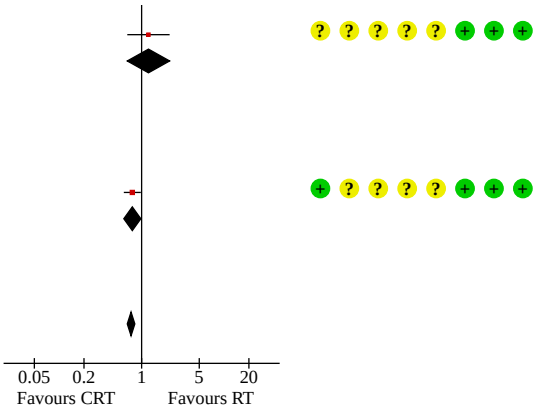
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3.9 Alternating cisplatin + 5-FU with RT vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	0.78 [0.55, 1.11]
3.3.10 Alternating cisplatin + 5-FU with RT vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	0.87 [0.58, 1.31]
3.4 Locoregional control	8		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
3.4.1 CRT (platinum + 5-FU) vs. RT	3		Hazard Ratio (IV, Random, 95% CI)	0.75 [0.61, 0.93]
3.4.2 CRT (methotrexate) vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	0.71 [0.49, 1.02]
3.4.3 CRT (daily carboplatin) vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	0.79 [0.64, 0.99]
3.4.4 CRT (5-FU + mitomycin C) vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	0.48 [0.33, 0.71]
3.4.5 CRT (cisplatin) vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	0.76 [0.54, 1.05]
3.4.6 Alternating cisplatin + 5-FU with RT vs. RT	1		Hazard Ratio (IV, Random, 95% CI)	0.35 [0.14, 0.87]
3.5 Locoregional control	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.5.1 CRT (mitomycin C) vs. RT	1	158	Risk Ratio (M-H, Random, 95% CI)	1.48 [1.00, 2.20]
3.5.2 CRT (bleomycin) vs. RT	1	46	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.45, 2.21]
3.5.3 CRT (gemcitabine) vs. RT	1	80	Risk Ratio (M-H, Random, 95% CI)	1.65 [1.17, 2.32]
3.5.4 CRT (pepleomycin) + RT vs. RT	1	101	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.47, 0.93]

Analysis 3.1. Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone (non-resectable), Outcome 1: Overall survival - concurrent chemoradiotherapy vs. radiotherapy



Analysis 3.1. (Continued)

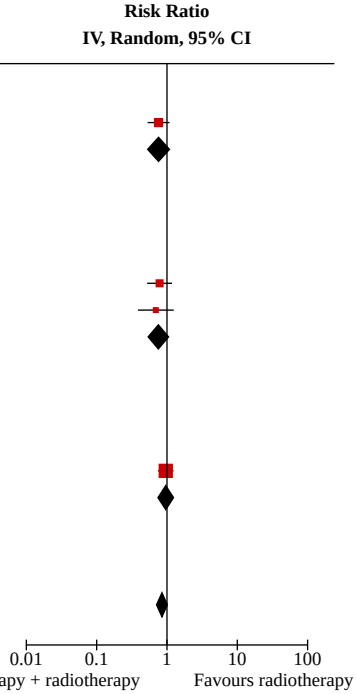
Salvajoli 1992	0.1909	0.3015	2.4%	1.21 [0.67 , 2.19]
Subtotal (95% CI)			**2.4%**	**1.21 [0.67 , 2.19]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.63 (P = 0.53)				
3.1.9 CRT (5-FU + mitomycin C) with RT vs. RT				
Budach 2005	-0.26	0.121	6.7%	0.77 [0.61 , 0.98]
Subtotal (95% CI)			**6.7%**	**0.77 [0.61 , 0.98]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.15 (P = 0.03)				
Total (95% CI)			**100.0%**	**0.74 [0.67 , 0.83]**
Heterogeneity: Tau² = 0.03; Chi² = 42.41, df = 23 (P = 0.008); I² = 46%				
Test for overall effect: Z = 5.50 (P < 0.00001)				
Test for subgroup differences: Chi² = 16.34, df = 8 (P = 0.04), I² = 51.1%				



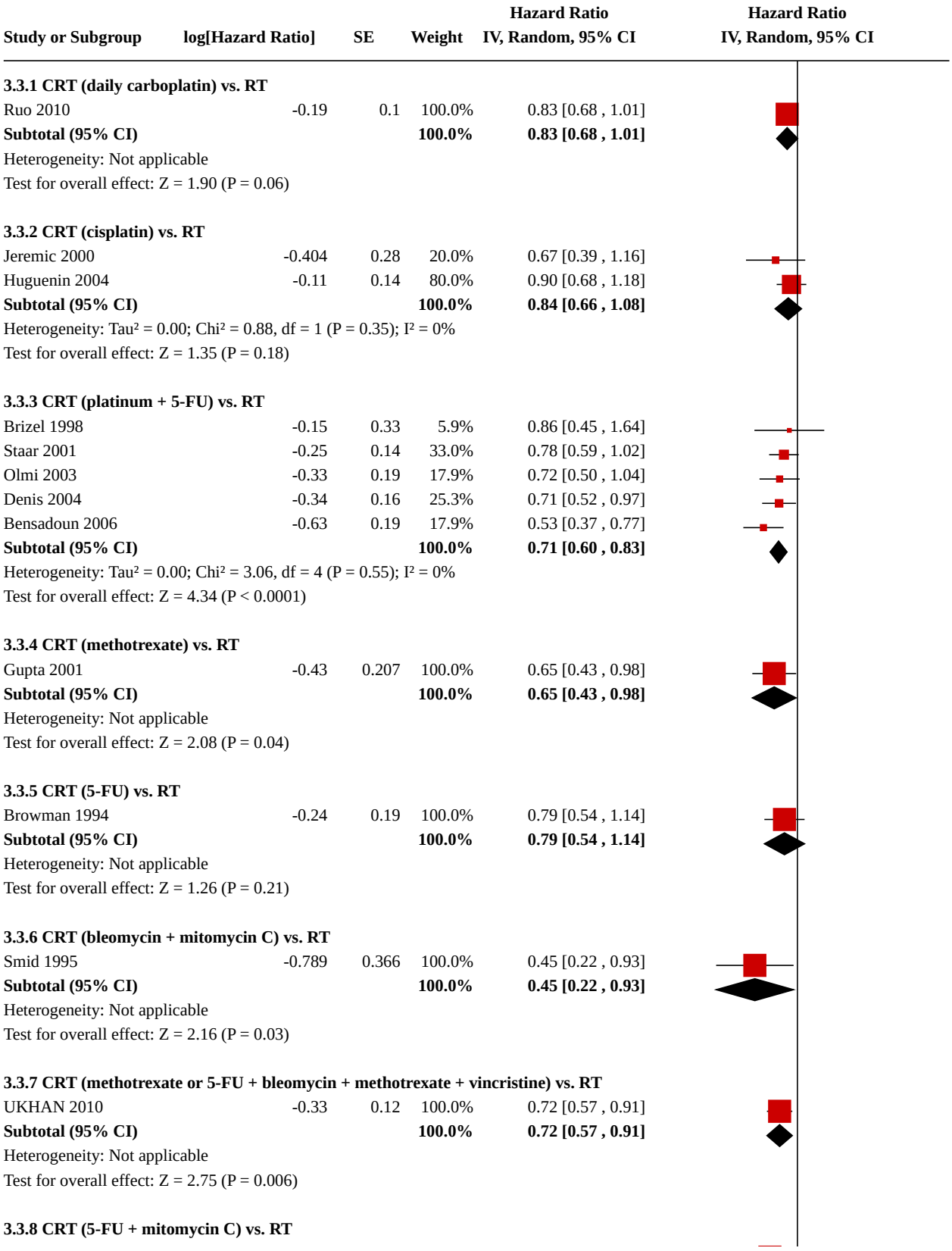
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants?
(D) Blinding of carers?
(E) Blinding of outcome assessors?
(F) Incomplete outcome data addressed?
(G) Free of selective reporting?
(H) Free of other bias?

Analysis 3.2. Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone (non-resectable), Outcome 2: Overall survival - alternating chemotherapy + radiotherapy vs. radiotherapy

Study or Subgroup	log[RR]	SE	Weight	Risk Ratio IV, Random, 95% CI
3.2.1 Alternating cisplatin + 5-FU with RT vs. RT				
Merlano 1992	-0.276	0.1826	24.3%	0.76 [0.53 , 1.09]
Subtotal (95% CI)			**24.3%**	**0.76 [0.53 , 1.09]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.51 (P = 0.13)				
3.2.2 Alternating cisplatin + 5-FU with RT vs. altered fractionation RT				
Corvo 2001	-0.242	0.208	18.7%	0.79 [0.52 , 1.18]
Giglio 1997	-0.366	0.2989	9.1%	0.69 [0.39 , 1.25]
Subtotal (95% CI)			**27.8%**	**0.75 [0.54 , 1.05]**
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.73); I² = 0%				
Test for overall effect: Z = 1.65 (P = 0.10)				
3.2.3 CRT (methotrexate or VBMF) + CT (methotrexate or VBMF) vs. RT + CT (methotrexate or VBMF)				
UKHAN 2010	-0.04	0.13	47.9%	0.96 [0.74 , 1.24]
Subtotal (95% CI)			**47.9%**	**0.96 [0.74 , 1.24]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.31 (P = 0.76)				
Total (95% CI)			**100.0%**	**0.85 [0.71 , 1.01]**
Heterogeneity: Tau² = 0.00; Chi² = 1.88, df = 3 (P = 0.60); I² = 0%				
Test for overall effect: Z = 1.83 (P = 0.07)				
Test for subgroup differences: Chi² = 1.77, df = 2 (P = 0.41), I² = 0%				

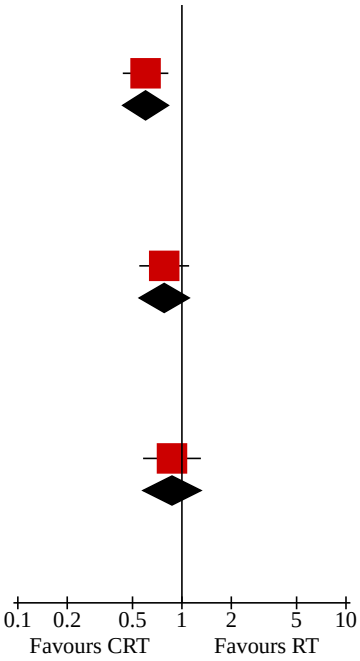


Analysis 3.3. Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone (non-resectable), Outcome 3: Disease-free survival

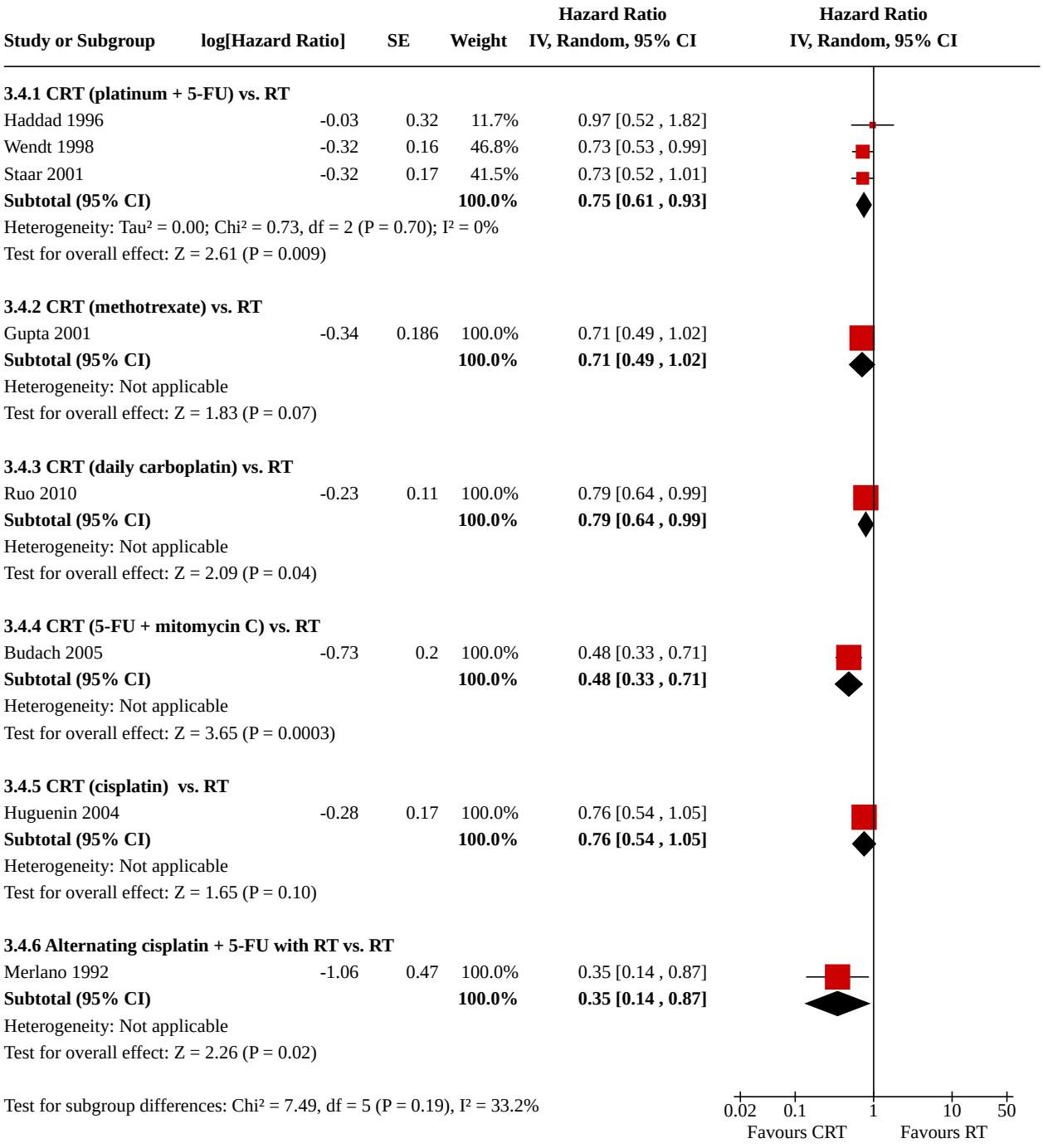


Analysis 3.3. (Continued)

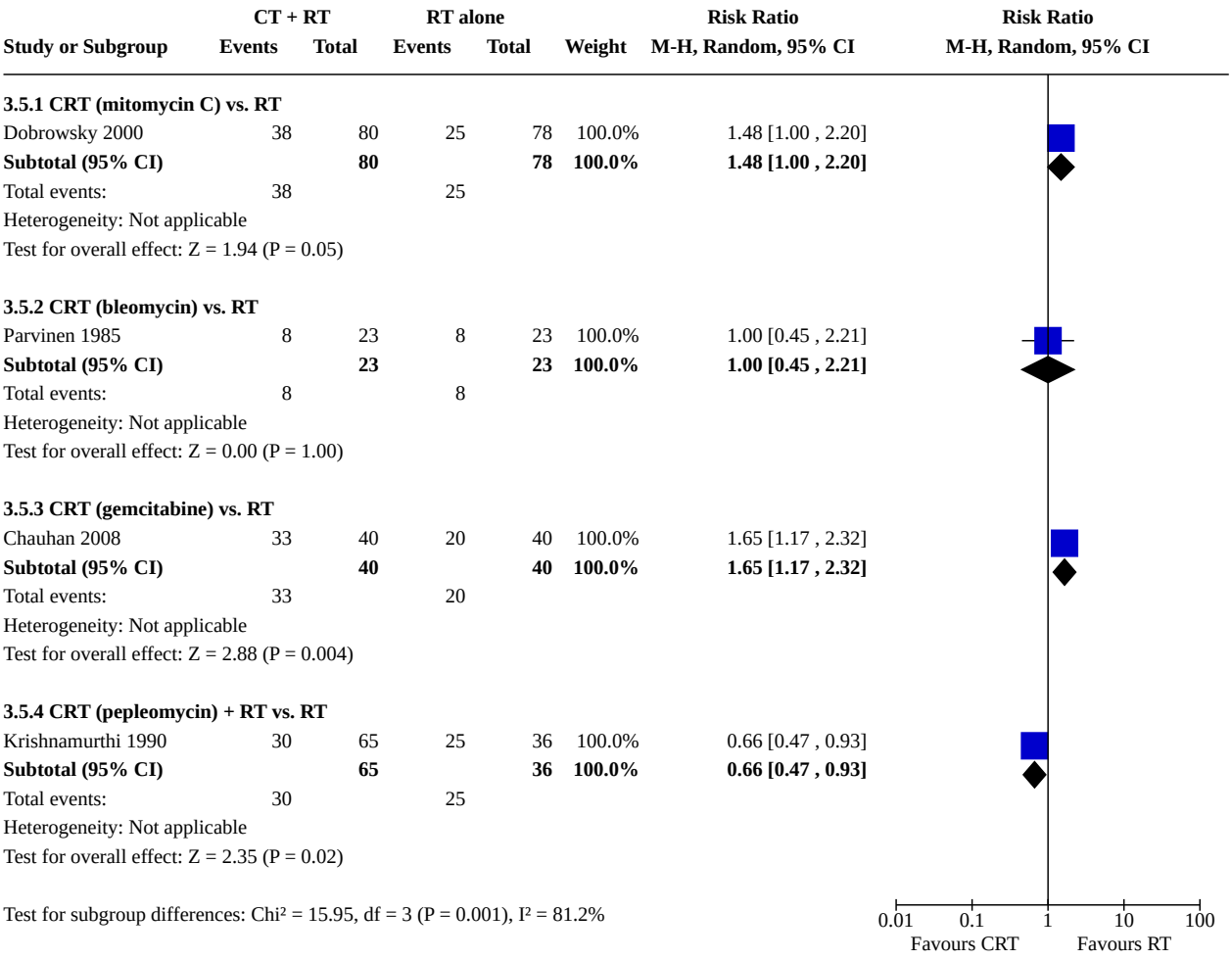
3.3.8 CRT (5-FU + mitomycin C) vs. RT				
Budach 2005	-0.51	0.163	100.0%	0.60 [0.44 , 0.83]
Subtotal (95% CI)			**100.0%**	**0.60 [0.44 , 0.83]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 3.13 (P = 0.002)				
3.3.9 Alternating cisplatin + 5-FU with RT vs. RT				
Merlano 1992	-0.2485	0.1783	100.0%	0.78 [0.55 , 1.11]
Subtotal (95% CI)			**100.0%**	**0.78 [0.55 , 1.11]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.39 (P = 0.16)				
3.3.10 Alternating cisplatin + 5-FU with RT vs. RT				
Corvo 2001	-0.1393	0.2069	100.0%	0.87 [0.58 , 1.31]
Subtotal (95% CI)			**100.0%**	**0.87 [0.58 , 1.31]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.67 (P = 0.50)				
Test for subgroup differences: Chi^2 = 7.36, df = 9 (P = 0.60), I^2 = 0%				



Analysis 3.4. Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone (non-resectable), Outcome 4: Locoregional control



Analysis 3.5. Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone (non-resectable), Outcome 5: Locoregional control



Comparison 4. Chemotherapy A (± LRT) versus chemotherapy B (± LRT)

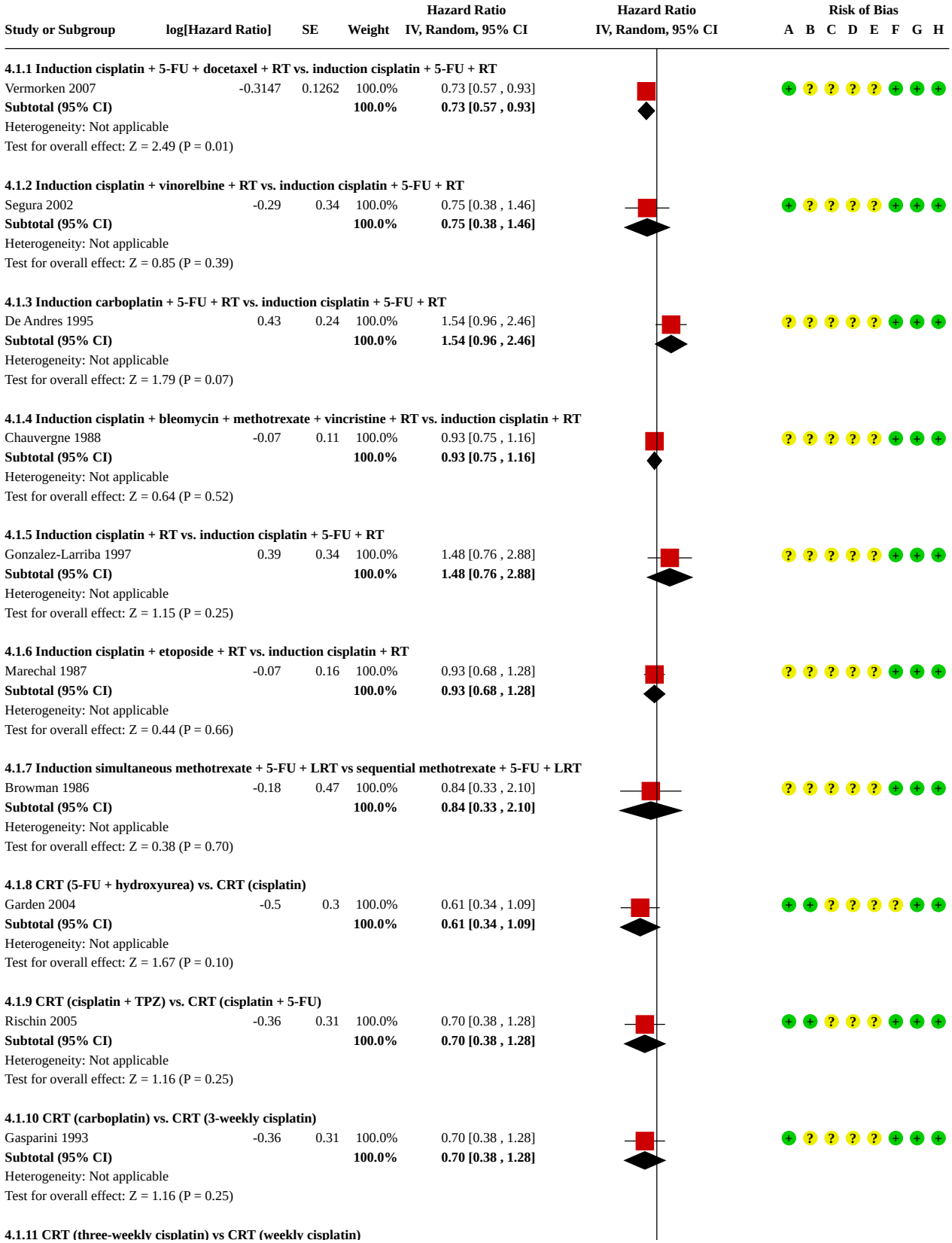
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Overall survival	16		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
4.1.1 Induction cisplatin + 5-FU + docetaxel + RT vs. induction cisplatin + 5-FU + RT	1		Hazard Ratio (IV, Random, 95% CI)	0.73 [0.57, 0.93]
4.1.2 Induction cisplatin + vinorelbine + RT vs. induction cisplatin + 5-FU + RT	1		Hazard Ratio (IV, Random, 95% CI)	0.75 [0.38, 1.46]
4.1.3 Induction carboplatin + 5-FU + RT vs. induction cisplatin + 5-FU + RT	1		Hazard Ratio (IV, Random, 95% CI)	1.54 [0.96, 2.46]
4.1.4 Induction cisplatin + bleomycin + methotrexate + vincristine + RT vs. induction cisplatin + RT	1		Hazard Ratio (IV, Random, 95% CI)	0.93 [0.75, 1.16]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1.5 Induction cisplatin + RT vs. induction cisplatin + 5-FU + RT	1		Hazard Ratio (IV, Random, 95% CI)	1.48 [0.76, 2.88]
4.1.6 Induction cisplatin + etoposide + RT vs. induction cisplatin + RT	1		Hazard Ratio (IV, Random, 95% CI)	0.93 [0.68, 1.28]
4.1.7 Induction simultaneous methotrexate + 5-FU + LRT vs sequential methotrexate + 5-FU + LRT	1		Hazard Ratio (IV, Random, 95% CI)	0.84 [0.33, 2.10]
4.1.8 CRT (5-FU + hydroxyurea) vs. CRT (cisplatin)	1		Hazard Ratio (IV, Random, 95% CI)	0.61 [0.34, 1.09]
4.1.9 CRT (cisplatin + TPZ) vs. CRT (cisplatin + 5-FU)	1		Hazard Ratio (IV, Random, 95% CI)	0.70 [0.38, 1.28]
4.1.10 CRT (carboplatin) vs. CRT (3-weekly cisplatin)	1		Hazard Ratio (IV, Random, 95% CI)	0.70 [0.38, 1.28]
4.1.11 CRT (three-weekly cisplatin) vs CRT (weekly cisplatin)	1		Hazard Ratio (IV, Random, 95% CI)	0.88 [0.61, 1.27]
4.1.12 CRT (cisplatin + TPZ) vs. CRT (cisplatin)	1		Hazard Ratio (IV, Random, 95% CI)	0.93 [0.75, 1.16]
4.1.13 CRT (cisplatin + paclitaxel) vs. CRT (cisplatin + 5-FU)	1		Hazard Ratio (IV, Random, 95% CI)	0.74 [0.45, 1.21]
4.1.14 CRT (cisplatin + paclitaxel) vs. CRT (5-FU + hydroxyurea)	1		Hazard Ratio (IV, Random, 95% CI)	0.78 [0.43, 1.40]
4.1.15 CRT (intra-arterial cisplatin) vs. CRT (intravenous cisplatin)	1		Hazard Ratio (IV, Random, 95% CI)	0.87 [0.62, 1.21]
4.1.16 Induction cisplatin + 5FU + TPZ + CRT (cisplatin + 5-FU + TPZ) vs. induction cisplatin + 5-FU + CRT (cisplatin + 5-FU)	1		Hazard Ratio (IV, Random, 95% CI)	0.45 [0.15, 1.29]
4.1.17 Induction cisplatin + 5-FU + docetaxel + CRT (carboplatin) vs. induction cisplatin + 5-FU + CRT (carboplatin)	1		Hazard Ratio (IV, Random, 95% CI)	0.70 [0.54, 0.91]
4.1.18 CRT (cisplatin + paclitaxel) with total RT dose 63.6 Gy vs. CRT (cisplatin + 5-FU) with total RT dose 70.6 Gray	1		Hazard Ratio (IV, Random, 95% CI)	0.82 [0.47, 1.44]
4.2 Disease-free survival	10		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
4.2.1 Induction cisplatin + RT vs. induction cisplatin + 5-FU + RT	1		Hazard Ratio (IV, Random, 95% CI)	1.16 [0.60, 2.26]
4.2.2 Induction cisplatin + 5-FU + docetaxel + RT vs. induction cisplatin + 5-FU + RT	1		Hazard Ratio (IV, Random, 95% CI)	0.72 [0.57, 0.91]

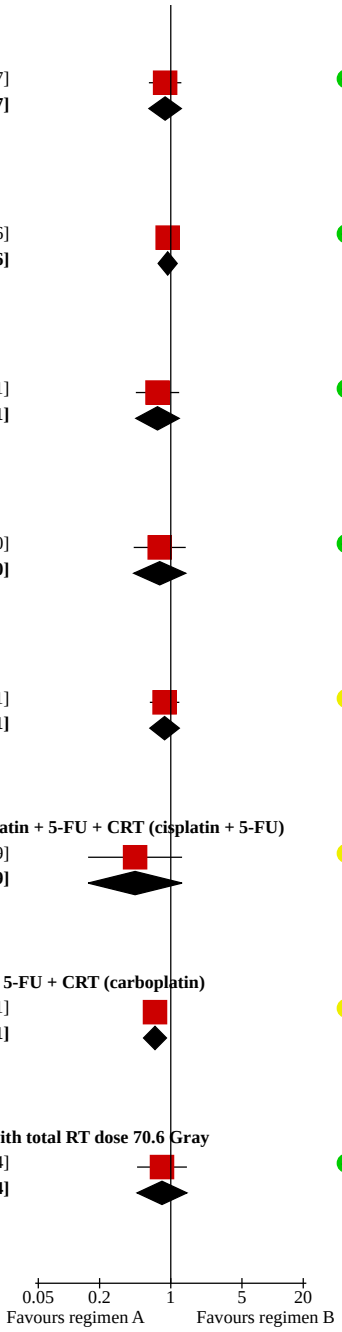
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2.3 CRT (cisplatin + TPZ) vs. CRT (cisplatin + 5-FU)	1		Hazard Ratio (IV, Random, 95% CI)	0.72 [0.42, 1.24]
4.2.4 CRT (cisplatin + TPZ) vs. CRT (cisplatin)	1		Hazard Ratio (IV, Random, 95% CI)	1.01 [0.83, 1.23]
4.2.5 CRT (carboplatin) vs. CRT (3-weekly cisplatin)	1		Hazard Ratio (IV, Random, 95% CI)	0.70 [0.32, 1.57]
4.2.6 CRT (intra-arterial cisplatin) vs. CRT (intravenous cisplatin)	1		Hazard Ratio (IV, Random, 95% CI)	1.15 [0.69, 1.91]
4.2.7 CRT (3-weekly cisplatin) vs. CRT (weekly cisplatin)	1		Hazard Ratio (IV, Random, 95% CI)	0.81 [0.59, 1.12]
4.2.8 Induction cisplatin + 5-FU + docetaxel + CRT (carboplatin) vs. induction cisplatin + 5-FU + CRT (carboplatin)	1		Hazard Ratio (IV, Random, 95% CI)	0.71 [0.56, 0.90]
4.2.9 Induction docetaxel + cisplatin + 5-FU (weekly x 9) + LRT vs. induction docetaxel + cisplatin + 5-FU (q3 week x 3) + LRT	1		Hazard Ratio (IV, Random, 95% CI)	1.82 [0.68, 4.87]
4.2.10 CRT (cisplatin + paclitaxel) with total RT dose 63.6 Gy vs. CRT (cisplatin + 5-FU) with total RT dose 70.6 Gy	1		Hazard Ratio (IV, Random, 95% CI)	0.82 [0.45, 1.48]
4.3 Locoregional control	3		Hazard Ratio (IV, Random, 95% CI)	Subtotals only
4.3.1 CRT (cisplatin + TPZ) vs. CRT (cisplatin +5-FU)	1		Hazard Ratio (IV, Random, 95% CI)	0.46 [0.21, 1.03]
4.3.2 CRT (intra-arterial cisplatin) vs. CRT (intravenous cisplatin)	1		Hazard Ratio (IV, Random, 95% CI)	0.95 [0.61, 1.49]
4.3.3 CRT (cisplatin + TPZ) vs. CRT (cisplatin)	1		Hazard Ratio (IV, Random, 95% CI)	0.89 [0.67, 1.17]
4.4 Overall survival	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.4.1 Induction bleomycin + methotrexate + cisplatin + vinorelbine + LRT vs. induction bleomycin + methotrexate + vinorelbine + LRT	1	38	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.30, 1.15]
4.5 Locoregional control	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.5.1 Induction bleomycin + methotrexate + cisplatin + vinorelbine + LRT vs induction bleomycin + methotrexate + vinorelbine + LRT	1	38	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.26, 0.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.5.2 Induction cisplatin + 5-FU + RT vs. induction cisplatin + etoposide + RT	1	197	Risk Ratio (M-H, Random, 95% CI)	1.48 [1.04, 2.11]
4.5.3 Induction intra-arterial bleomycin + LRT vs. induction intra-arterial methotrexate + LRT	1	85	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.19, 0.66]
4.5.4 Induction three-weekly paclitaxel + carboplatin + RT vs. induction weekly paclitaxel + carboplatin + RT	1	50	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.81, 2.20]
4.5.5 CRT (daily cisplatin) vs. CRT (weekly cisplatin)	1	48	Risk Ratio (M-H, Random, 95% CI)	1.42 [0.50, 4.02]
4.5.6 CRT (weekly cisplatin) vs. CRT (3-weekly cisplatin)	4	428	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.63, 1.89]
4.5.7 CRT (daily cisplatin) vs. CRT (3-weekly cisplatin)	1	34	Risk Ratio (M-H, Random, 95% CI)	1.64 [0.39, 6.89]
4.5.8 Induction docetaxel + cisplatin + 5-FU (weekly x 9) + LRT vs. induction docetaxel + cisplatin + 5-FU (q3week x 3) + LRT	1	82	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.79, 1.36]

Analysis 4.1. Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT), Outcome 1: Overall survival



Analysis 4.1. (Continued)



4.1.11 CRT (three-weekly cisplatin) vs CRT (weekly cisplatin)

Noronha 2018	-0.1278	0.1872	100.0%	0.88 [0.61 , 1.27]
Subtotal (95% CI)			**100.0%**	**0.88 [0.61 , 1.27]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.49)

4.1.12 CRT (cisplatin + TPZ) vs. CRT (cisplatin)

Rischin 2010	-0.07	0.11	100.0%	0.93 [0.75 , 1.16]
Subtotal (95% CI)			**100.0%**	**0.93 [0.75 , 1.16]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.64 (P = 0.52)

4.1.13 CRT (cisplatin + paclitaxel) vs. CRT (cisplatin + 5-FU)

Garden 2004	-0.3	0.25	100.0%	0.74 [0.45 , 1.21]
Subtotal (95% CI)			**100.0%**	**0.74 [0.45 , 1.21]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.20 (P = 0.23)

4.1.14 CRT (cisplatin + paclitaxel) vs. CRT (5-FU + hydroxyurea)

Garden 2004	-0.25	0.3	100.0%	0.78 [0.43 , 1.40]
Subtotal (95% CI)			**100.0%**	**0.78 [0.43 , 1.40]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.83 (P = 0.40)

4.1.15 CRT (intra-arterial cisplatin) vs. CRT (intravenous cisplatin)

Rasch 2010	-0.14	0.17	100.0%	0.87 [0.62 , 1.21]
Subtotal (95% CI)			**100.0%**	**0.87 [0.62 , 1.21]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.82 (P = 0.41)

4.1.16 Induction cisplatin + 5FU + TPZ + CRT (cisplatin + 5-FU + TPZ) vs. induction cisplatin + 5-FU + CRT (cisplatin + 5-FU)

Le 2006	-0.807	0.542	100.0%	0.45 [0.15 , 1.29]
Subtotal (95% CI)			**100.0%**	**0.45 [0.15 , 1.29]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.49 (P = 0.14)

4.1.17 Induction cisplatin + 5-FU + docetaxel + CRT (carboplatin) vs. induction cisplatin + 5-FU + CRT (carboplatin)

Posner 2007	-0.3567	0.1324	100.0%	0.70 [0.54 , 0.91]
Subtotal (95% CI)			**100.0%**	**0.70 [0.54 , 0.91]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.69 (P = 0.007)

4.1.18 CRT (cisplatin + paclitaxel) with total RT dose 63.6 Gy vs. CRT (cisplatin + 5-FU) with total RT dose 70.6 Gray

Fietkau 2020	-0.1985	0.2875	100.0%	0.82 [0.47 , 1.44]
Subtotal (95% CI)			**100.0%**	**0.82 [0.47 , 1.44]**

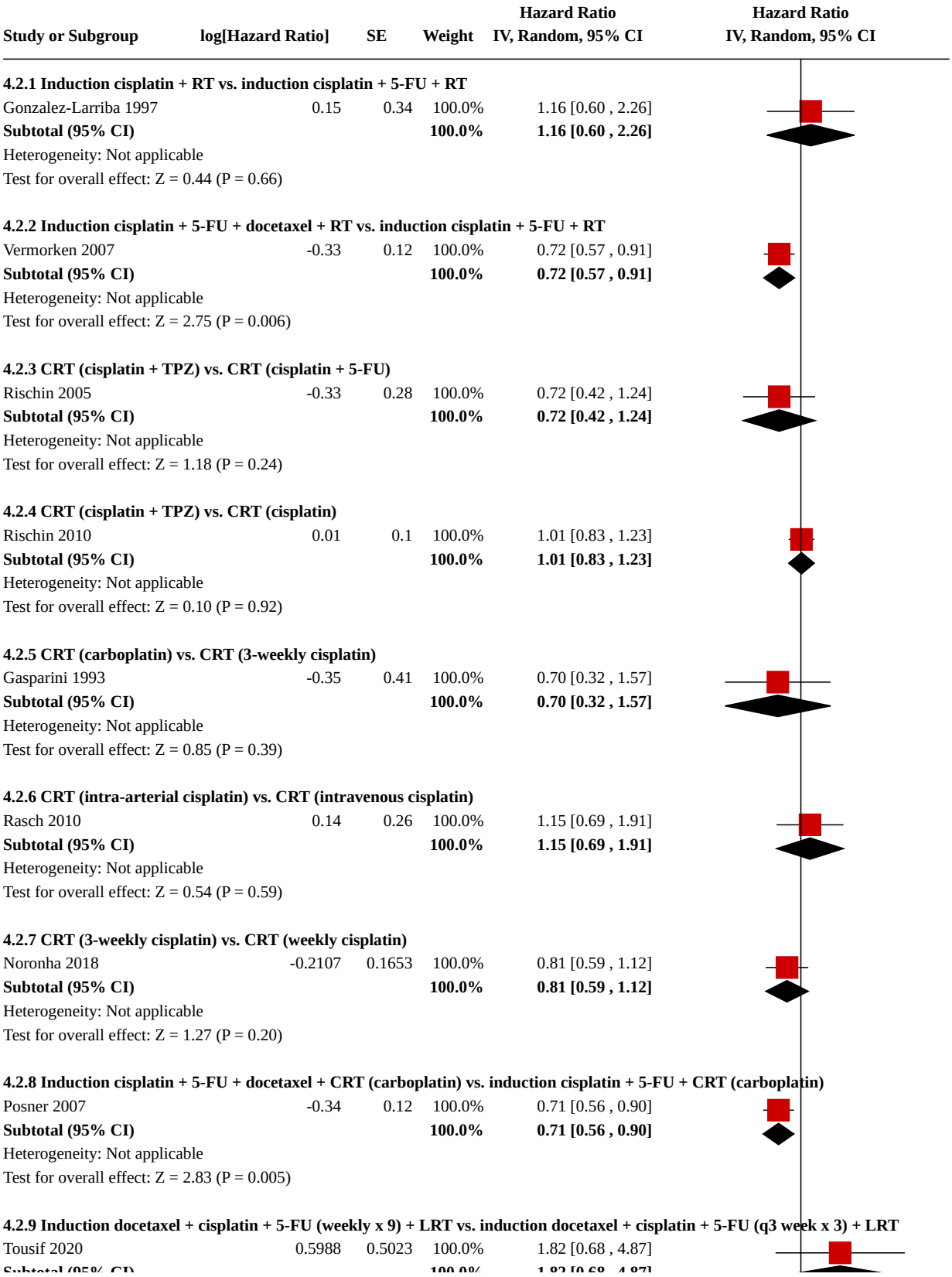
Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)

Test for subgroup differences: Chi² = 18.18, df = 17 (P = 0.38), I² = 6.5%

Risk of bias legend

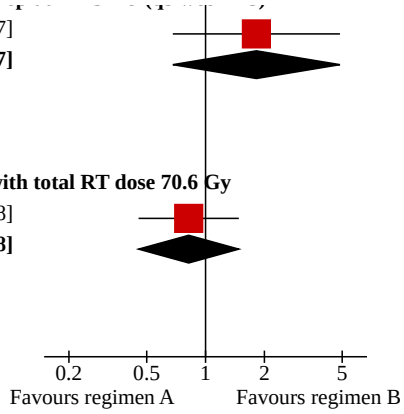
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants?
(D) Blinding of carers?
(E) Blinding of outcome assessors?
(F) Incomplete outcome data addressed?
(G) Free of selective reporting?
(H) Free of other bias?

Analysis 4.2. Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT), Outcome 2: Disease-free survival



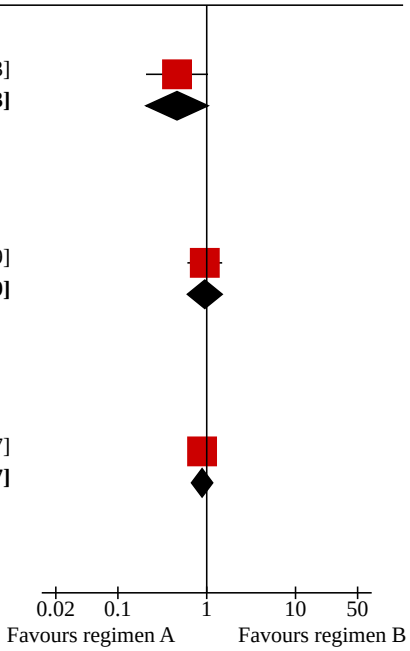
Analysis 4.2. (Continued)

Tousif 2020	0.5988	0.5023	100.0%	1.82 [0.68 , 4.87]
Subtotal (95% CI)			**100.0%**	**1.82 [0.68 , 4.87]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.19 (P = 0.23)				
4.2.10 CRT (cisplatin + paclitaxel) with total RT dose 63.6 Gy vs. CRT (cisplatin + 5-FU) with total RT dose 70.6 Gy				
Fietkau 2020	-0.1985	0.3012	100.0%	0.82 [0.45 , 1.48]
Subtotal (95% CI)			**100.0%**	**0.82 [0.45 , 1.48]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.66 (P = 0.51)				
Test for subgroup differences: Chi² = 12.26, df = 9 (P = 0.20), I² = 26.6%				

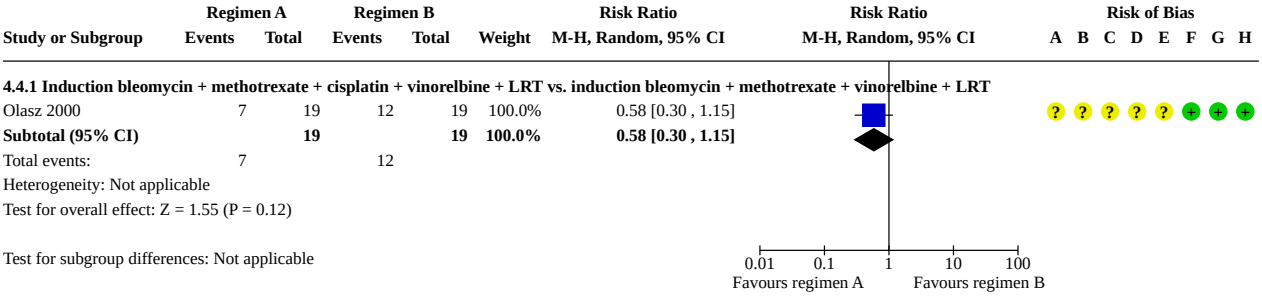


Analysis 4.3. Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT), Outcome 3: Locoregional control

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
4.3.1 CRT (cisplatin + TPZ) vs. CRT (cisplatin +5-FU)				
Rischin 2005	-0.77	0.41	100.0%	0.46 [0.21 , 1.03]
Subtotal (95% CI)			**100.0%**	**0.46 [0.21 , 1.03]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.88 (P = 0.06)				
4.3.2 CRT (intra-arterial cisplatin) vs. CRT (intravenous cisplatin)				
Rasch 2010	-0.05	0.23	100.0%	0.95 [0.61 , 1.49]
Subtotal (95% CI)			**100.0%**	**0.95 [0.61 , 1.49]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.22 (P = 0.83)				
4.3.3 CRT (cisplatin + TPZ) vs. CRT (cisplatin)				
Rischin 2010	-0.12	0.14	100.0%	0.89 [0.67 , 1.17]
Subtotal (95% CI)			**100.0%**	**0.89 [0.67 , 1.17]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.86 (P = 0.39)				
Test for subgroup differences: Chi² = 2.52, df = 2 (P = 0.28), I² = 20.7%				



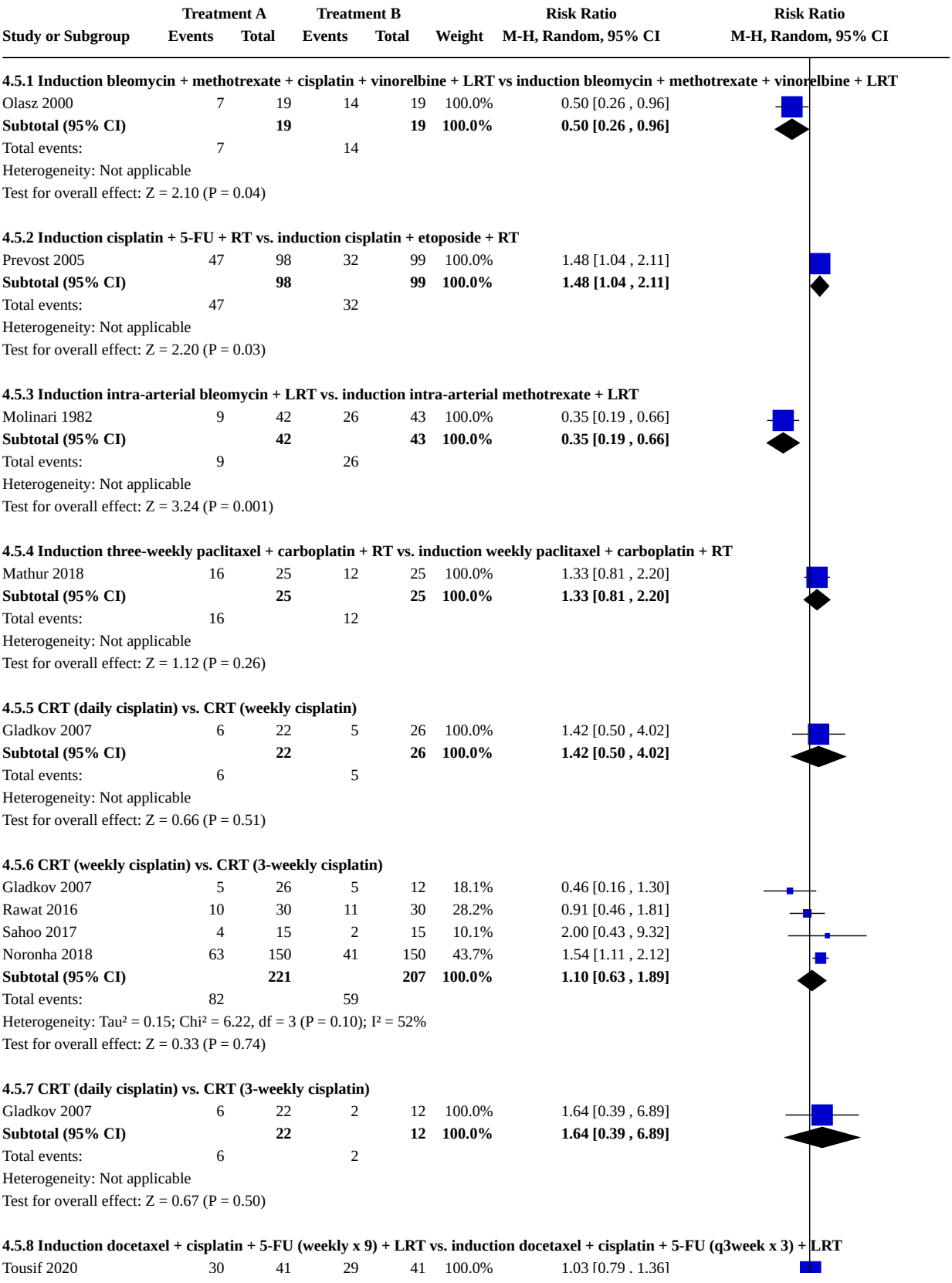
Analysis 4.4. Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT), Outcome 4: Overall survival



Risk of bias legend

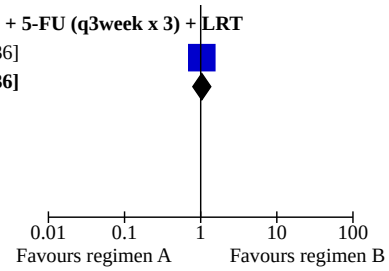
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants?
(D) Blinding of carers?
(E) Blinding of outcome assessors?
(F) Incomplete outcome data addressed?
(G) Free of selective reporting?
(H) Free of other bias?

Analysis 4.5. Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT), Outcome 5: Locoregional control



Analysis 4.5. (Continued)

4.5.8 Induction docetaxel + cisplatin + 5-FU (weekly x 9) + LRT vs. induction docetaxel + cisplatin + 5-FU (q3week x 3) + LRT						
Tousif 2020	30	41	29	41	100.0%	1.03 [0.79 , 1.36]
Subtotal (95% CI)		**41**		**41**	**100.0%**	**1.03 [0.79 , 1.36]**
Total events:	30		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.81)						
Test for subgroup differences: Chi^2 = 21.84, df = 7 (P = 0.003), I^2 = 67.9%						



ADDITIONAL TABLES

Table 1. Classification of chemotherapy agents

	Drugs included in review
ALKYLATING OR ALKYLATING-LIKE AGENTS - 'platins' - work by directly damaging DNA and preventing cancer cells from dividing	Cisplatin Carboplatin
ANTIMETABOLITES - interfere with DNA and RNA growth. Kill cancer cells in specific phase of cell division	5-FU, 5 fluorouracil 1-FU, 1 fluorouracil Etoposide Methotrexate Ftorafur (tegafur + uracil) UFT or uftoral
ANTITUMOUR ANTIBIOTICS - interfere with enzymes required for DNA replication	Bleomycin Mitomycin
VINCA ALKALOIDS - inhibit mitosis or inhibit enzymes from making proteins necessary for cell reproduction	Vinblastine Vincristine
TAXANES - diterpines from the genus Taxus. Inhibit mitosis by disrupting microtubule function	Paclitaxel Docetaxel
OTHER	Tirapazamine

Table 2. Proportion of participants with oral cavity or oropharyngeal cancer in the included studies

Trial ID	% oral cavity cancer	% oropharyngeal cancer	Total % OC/OP	Mortality data from Pignon meta-analyses
Bitter 1979	100%		100%	
Denis 2004		100%	100%	Pignon 2009

Table 2. Proportion of participants with oral cavity or oropharyngeal cancer in the included studies *(Continued)*

Domenge 2000		100%	100%	
Eschwege 1988		100%	100%	Pignon 2000
Gladkov 2007			100%	
Gupta 2009		100%	100%	
HNCProg 1987	100%		100%	
Krishnamurthi 1990	100%		100%	
Licitra 2003	100%		100%	
Luboinski 1985	100%		100%	
Mazeron 1992	37%	63%	100%	Pignon 2000
Mohr 1994			100%	
Molinari 1982	100%		100%	
Morita 1980*			100%	
Olmi 2003		100%	100%	Pignon 2009
Rao 1994	100%		100%	Pignon 2000
Richard 1974			100%	Pignon 2000
Richard 1991	100%		100%	Pignon 2000
Shanta 1980	100%		100%	Pignon 2000
Szabo 1999	100%		100%	
Szpirglas 1979	100%		100%	Pignon 2000
Szpirglas 1988			100%	Pignon 2000
Volling 1999*			100%	
Noronha 2018	87%	2%	89%	
Maipang 1995	76%	9%	85%	Pignon 2000
Chauhan 2008			84%	
Garden 2004	16%	67%	83%	
Adelstein 1993	48%	35%	83%	Pignon 2000
Nervi 1978	58%	25%	83%	
Smid 1995	16%	64%	80%	Pignon 2000

Table 2. Proportion of participants with oral cavity or oropharyngeal cancer in the included studies *(Continued)*

Fazekas 1980	23%	56%	79%	Pignon 2000
Parvinen 1985	71%	8%	79%	Pignon 2000
Rawat 2016	25%	53%	78%	
Grau 2003	48%	29%	77%	Pignon 2009
Salvajoli 1992	47%	30%	77%	Pignon 2000
Ghi 2017	19%	56%	75%	
Lewin 1997	41%	34%	75%	Pignon 2000
Rischin 2005	5%	70%	75%	
Brunin 1989	37%	37%	74%	Pignon 2000
Petrovich 1981	17%	57%	74%	
Staar 2001		74%	74%	Pignon 2009
Haddad 2013	18%	55%	73%	
Buffoli 1992			73%	
Dobrowsky 2000	29%	44%	73%	Pignon 2009
Paccagnella 1994	16%	57%	73%	Pignon 2000
Adelstein 2003	13%	59%	72%	Pignon 2009
Merlano 1991	25%	47%	72%	Pignon 2000
Bensadoun 2006	0%	75%	75%	
Rasch 2010	18%	63%	71%	
Merlano 1992	29%	42%	71%	Pignon 2000
Cooper 2004	27%	43%	70%	Pignon 2009
Paccagnella 2010	18%	54%	70%	
Cohen 2014	14%	58%	69%	
Le 2006	6%	63%	69%	
Pinnaro 1994	45%	24%	69%	
Gasparini 1993	28%	40%	68%	
Staar 2001		68%	68%	Pignon 2009
Schuller 1988	38%	30%	68%	Pignon 2000

Table 2. Proportion of participants with oral cavity or oropharyngeal cancer in the included studies *(Continued)*

Argiris 2008	35%	32%	67%	
Budach 2005	8%	59%	67%	Pignon 2009
Tejedor 1992	31%	36%	67%	Pignon 2000
Rischin 2010	13%	54%	67%	
Ruo 2010	17%	49%	66%	
Posner 2007	14%	52%	66%	
Kumar 1996	24%	42%	66%	Pignon 2009
Vermorken 2007	18%	46%	64%	
Browman 1986	64%		64%	
Haddad 1996	20%	43%	63%	
Tousif 2020	1%	62%	63%	
Fietkau 2020	14%	48%	62%	
Hitt 2014	19%	43%	62%	
Segura 2002	62%		62%	
Holoye 1985	28%	33%	61%	Pignon 2000
Depondt 1993	26%	35%	61%	Pignon 2000
Huguenin 2004	8%	53%	61%	Pignon 2009
Knowlton 1975	31%	30%	61%	
Prevost 2005	33%	26%	59%	
Chauvergne 1988			59%	
Jaulerry 1992	30%	28%	58%	Pignon 2000
Wendt 1998	38%	20%	58%	Pignon 2000
Jeremic 2000	21%	37%	58%	Pignon 2009
Sahoo 2017	3%	53%	57%	
Corvo 2001	19%	38%	57%	Pignon 2009
Bernier 2004	26%	30%	56%	Pignon 2009
De Andres 1995	16%	39%	55%	
Gupta 2001	22%	33%	55%	Pignon 2000

Table 2. Proportion of participants with oral cavity or oropharyngeal cancer in the included studies *(Continued)*

Marechal 1987	15%	40%	55%	
Rentschler 1987	33%	22%	55%	
Vokes 1990	12%	43%	55%	
Weissler 1992	16%	39%	55%	Pignon 2000
Browman 1994	12%	42%	54%	Pignon 2000
Giglio 1997	33%	20%	53%	Pignon 2009
Jeremic 1997	16%	37%	53%	Pignon 2000
Lam 2001	32%	21%	53%	
Laramore 1992	27%	25%	52%	Pignon 2000
UKHAN 2010	19%	33%	52%	
Gonzalez-Larriba 1997	12%	39%	51%	
Brizel 1998	5%	45%	50%	

*Oral cavity (OC) and/or oropharyngeal (OP) data available as a separate entity (in trial report or provided by author). i) OC/OP combined. ii) OC alone. iii) OP alone

Table 3. Summary of key results from comparison 1

Induction regimen	LRT	Number of trials	Overall survival (HR for death)	P value
Platinum + 5-fluorouracil	RT	5	HR 0.85 (95% CI 0.70 to 1.04)	0.11
Platinum + 5-fluorouracil	Surgery	1	HR 1.06 (95% CI 0.71 to 1.60)	0.77
Platinum + 5-fluorouracil	CRT	2	HR 0.71 (95% CI 0.37 to 1.35)	0.30
Platinum + 5-fluorouracil + docetaxel	CRT	3	HR 1.08 (95% CI 0.80 to 1.44)	0.63

CRT: concurrent chemoradiation
HR: hazard ratio
LRT: locoregional treatment
RT: radiation therapy
Platinum: either carboplatin or cisplatin

Table 4. Summary of key results from comparison 2

Regimen	Number of trials	Overall survival (HR for death)	P value
Adjuvant chemotherapy versus observation	5	HR 0.95 (95% CI 0.73 to 1.22)	0.67
Adjuvant concurrent chemoradiation versus radiotherapy	4	HR 0.84 (95% CI 0.72 to 0.98)	0.03

HR: hazard ratio

Table 5. Summary of key results from comparison 3

Regimen	Number of trials	Overall survival (HR for death)	P value
Concurrent chemotherapy (total)	24	HR 0.74 (95% CI 0.67 to 0.83)	P < 0.00001
Concurrent platinum	5	HR 0.66 (95% CI 0.57 to 0.77)	P < 0.00001
Concurrent platinum plus 5-fluorouracil	7	HR 0.66 (95% CI 0.55 to 0.77)	P < 0.00001

HR: hazard ratio
Platinum: either cisplatin or carboplatin

APPENDICES

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

Cochrane Oral Health's Trials Register is available via the Cochrane Register of Studies. For information on how the register is compiled, see https://oralhealth.cochrane.org/trials

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*) near5 (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 AND INREGISTER
8 MESH DESCRIPTOR Antineoplastic Agents EXPLODE ALL AND INREGISTER
9 (antineoplast* or antitumor* or anti-tumor* or anti-neoplast*) AND INREGISTER
10 MESH DESCRIPTOR Antineoplastic Combined Chemotherapy Protocols AND INREGISTER
11 MESH DESCRIPTOR Combined Modality Therapy EXPLODE ALL AND INREGISTER
12 MESH DESCRIPTOR Radiotherapy EXPLODE ALL AND INREGISTER
13 (radiotherap* or chemotherap* or chemoradiotherap* or chemo-radiotherap* or "radiation therap*" or bracytherap* or irradiat*) AND INREGISTER
14 (adjuvant or neo-adjuvant or "neo adjuvant") AND INREGISTER
15 (hyperfractionate* or hyper-fractionate*) AND INREGISTER
16 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 AND INREGISTER
17 #7 and #16 AND INREGISTER

Appendix 2. The Cochrane Central Register of Controlled Clinical 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*) near5 (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 Antineoplastic Agents EXPLODE ALL AND CENTRAL:TARGET
9 (antineoplast* or antitumor* or anti-tumor* or anti-neoplast*) AND CENTRAL:TARGET
10 MESH DESCRIPTOR Antineoplastic Combined Chemotherapy Protocols AND CENTRAL:TARGET
11 MESH DESCRIPTOR Combined Modality Therapy EXPLODE ALL AND CENTRAL:TARGET
12 MESH DESCRIPTOR Radiotherapy EXPLODE ALL AND CENTRAL:TARGET

13 (radiotherap* or chemotherap* or chemoradiotherap* or chemo-radiotherap* or "radiation therap*" or bracytherap* or irradiat*) AND CENTRAL:TARGET
14 (adjuvant or neo-adjuvant or "neo adjuvant") AND CENTRAL:TARGET
15 (hyperfractionate* or hyper-fractionate*) AND CENTRAL:TARGET
16 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
17 #7 and #16

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 Antineoplastic agents/
9. (antineoplast$ or antitumor$ or anti-tumor$ or anti-neoplast$).mp.
10. Antineoplastic combined chemotherapy protocols/
11. exp Combined Modality Therapy/
12. exp Radiotherapy/
13. (radiotherap$ or chemotherap$ or chemoradiotherap$ or chemo- radiotherap$ or "radiation therap$" or bracytherap$ or irradiat$).ti,ab.
14. (adjuvant or neo-adjuvant or "neo adjuvant").ti,ab.
15. (hyperfractionate$ or hyper-fractionate$).mp.
16. or/8-15
17. 7 and 16

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 Lefebvre 2020, box 3b.

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

Advanced search: “oral cancer”

Limited to interventional studies

Appendix 5. World Health Organization International Clinical Trials Registry Platform search strategy

Advanced search: oral cancer

Appendix 6. Search strategies used in previous versions of this review

Cochrane Oral Health Trials Register search strategy

((mouth or oral or intraoral or intra-oral or gingiva* or oropharyn* or cheek* or gum* or palat* or lip or tongue or “head and neck”) AND (tumour* or tumor* or cancer* or carcinoma* or neoplas* or malignan*))

Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 [mh ^"Head and neck neoplasms"]
#2 [mh ^"Mouth neoplasms"]

#3 [mh ^"Gingival neoplasms"]
#4 [mh ^"Palatal neoplasms"]
#5 [mh ^"Tongue neoplasms"]
#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"))
#7 (#1 or #2 or #3 or #4 or #5 or #6)
#8 [mh Radiotherapy]
#9 (radiotherap* or chemotherap* or chemoradiotherap* or chemo-radiotherap* or "radiation therap*" or bracytherap* or irradiat*)
#10 (adjuvant or neo-adjuvant or "neo adjuvant")
#11 (hyperfractionate* or hyper-fractionate*)
#12 [mh "Surgical procedures, operative"]
#13 (dissect* near/2 neck*)
#14 [mh ^"Lymph Node Excision"]
#15 (lymphadenectom* or glossectom*)
#16 [mh "Antineoplastic agents"]
#17 (antineoplast* or antitumor* or anti-tumor* or anti-neoplast*)
#18 (excision or excise or resect*)
#19 [mh ^"Antineoplastic combined chemotherapy protocol"]
#20 [mh "Combined Modality Therapy"]
#21 (#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20)
#22 (#7 and #21)

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 Radiotherapy/
9. (radiotherap$ or chemotherap$ or chemoradiotherap$ or chemo-radiotherap$ or "radiation therap$" or bracytherap$ or irradiat $).ti,ab.
10. (adjuvant or neo-adjuvant or "neo adjuvant").ti,ab.
11. (hyperfractionate$ or hyper-fractionate$).mp.
12. exp Surgical Procedures, Operative/
13. (dissect$ adj2 neck$).ti,ab.
14. (excision or excise or resect$).ti,ab.
15. Lymph Node Excision/
16. (lymphadenectom$ or glossectom$).ti,ab.
17. exp Antineoplastic agents/
18. (antineoplast$ or antitumor$ or anti-tumor$ or anti-neoplast$).mp.
19. Antineoplastic combined chemotherapy protocols/
20. exp Combined Modality Therapy/
21. or/8-20
22. 7 and 21

Embase 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 Radiotherapy/
9. (radiotherap$ or chemotherap$ or chemoradiotherap$ or chemo-radiotherap$ or "radiation therap$" or bracytherap$ or irradiat $).ti,ab.
10. (adjuvant or neo-adjuvant or "neo adjuvant").ti,ab.

11. (hyperfractionate$ or hyper-fractionate$).mp.
12. exp Surgical Procedures, Operative/
13. (dissect$ adj2 neck$).ti,ab.
14. (excision or excise or resect$).ti,ab.
15. Lymph Node Excision/
16. (lymphadenectom$ or glossectom$).ti,ab.
17. exp Antineoplastic agents/
18. (antineoplast$ or antitumor$ or anti-tumor$ or anti-neoplast$).mp.
19. Antineoplastic combined chemotherapy protocols/
20. exp Combined Modality Therapy/
21. or/8-20
22. 7 and 21

AMED Ovid search strategy

1. ((cancer$ or tumor$ or tumour$ or neoplasm$ or malignan$ or carcinoma$ or metasta$) adj5 (oral$ or intra-oral$ or gingiva$ or oropharyn$ or mouth$ or tongue$ or cheek or cheeks or gum or gums or palatal or palate or intraoral or (head adj2 neck))).mp. [mp=abstract, heading words, title]
2. (head and neck neoplasms).mp. [mp=abstract, heading words, title]
3. mouth neoplasms/
4. ((((gingiva$ adj4 neoplasm$) or tongue) adj4 neoplasm$) or ((palatal or palate) adj4 neoplasm$)).mp. [mp=abstract, heading words, title]
5. or/1-4
6. palliative care/
7. Palliative treatment/
8. chemotherapy.mp.
9. chemoradiotherap$.mp. [mp=abstract, heading words, title]
10. exp radiotherapy/
11. (radiotherap$ or chemotherap$ or brachytherap$).mp. [mp=abstract, heading words, title]
12. surg$.mp. [mp=abstract, heading words, title]
13. (neck adj1 dissection$).mp. [mp=abstract, heading words, title]
14. (adjuvant or neo-adjuvant).mp. [mp=abstract, heading words, title]
15. photodynamic.mp.
16. teletherap$.mp. [mp=abstract, heading words, title]
17. pleisiotherap$.mp. [mp=abstract, heading words, title]
18. (excision$ or excise$).mp. [mp=abstract, heading words, title]
19. (hyperfractionate$ or hyper-fractionate$).mp. [mp=abstract, heading words, title]
20. dahanca.mp. [mp=abstract, heading words, title]
21. arcon.mp.
22. (radiat$ or irradiat$).mp. [mp=abstract, heading words, title]
23. resect$.mp. [mp=abstract, heading words, title]
24. lymphadenectom$.mp. [mp=abstract, heading words, title]
25. curett$.mp. [mp=abstract, heading words, title]
26. neoadjuvant.mp. [mp=abstract, heading words, title]
27. glossectom$.mp. [mp=abstract, heading words, title]
28. antineoplas$.mp. [mp=abstract, heading words, title]
29. ((alternative or combined or gene or genetic or nutrition$) adj2 (therapy or therapies)).mp. [mp=abstract, heading words, title]
30. onyx-015.mp. [mp=abstract, heading words, title]
31. (fluorouracil$ or cisplatin$ or paclitaxel$ or vinblastine$ or bleomycin$).mp. [mp=abstract, heading words, title]
32. (adriamycin$ or doxorubicin$ or methotrexa$ or docetaxel$ or carboplatin$ or hydroxyurea).mp. [mp=abstract, heading words, title]
33. 5fu.mp. [mp=abstract, heading words, title]
34. ((vitamin or nutrition$) adj2 supplement$).mp. [mp=abstract, heading words, title]
35. (herb or herbs).mp. [mp=abstract, heading words, title]
36. herbal.mp. [mp=abstract, heading words, title]
37. (locoregional$ adj5 (recurren$ or control$ or treat$ or lymph$)).mp. [mp=abstract, heading words, title]
38. (aromatherap$ or homeopath$ or osteopath$ or naturopath$).mp. [mp=abstract, heading words, title]
39. (wholistic or holistic).mp. [mp=abstract, heading words, title]
40. reflexolog$.mp. [mp=abstract, heading words, title]
41. massage$.mp. [mp=abstract, heading words, title]
42. (essential adj1 oil$).mp. [mp=abstract, heading words, title]
43. exp antineoplastic agents/
44. surgery operative/
45. lymph node excision.mp.

46. exp antimetabolites/
47. exp nursing care/
48. exp terminal care/
49. perioperative care.mp. [mp=abstract, heading words, title]
50. combined modality therapy/
51. exp complementary therapies/
52. exp nutrition therapy/
53. rehabilitation.mp. [mp=abstract, heading words, title]
54. remission induction.mp.
55. salvage therapy.mp.
56. or/6-55
57. 5 and 56

ClinicalTrials.gov search strategy

Advanced search: “oral cancer”

Limited to interventional studies

WHO International Clinical Trials Registry Platform search strategy

Advanced search: oral cancer

Appendix 7. Embase 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 Antineoplastic agents/
9. (antineoplast$ or antitumor$ or anti-tumor$ or anti-neoplast$).mp.
10. Antineoplastic combined chemotherapy protocols/
11. exp Combined Modality Therapy/
12. exp Radiotherapy/
13. (radiotherap$ or chemotherap$ or chemoradiotherap$ or chemo- radiotherap$ or "radiation therap$" or bracytherap$ or irradiat $).ti,ab.
14. (adjuvant or neo-adjuvant or "neo adjuvant").ti,ab.
15. (hyperfractionate$ or hyper-fractionate$).mp.
16. or/8-15
17. 7 and 16

The above subject search was linked with the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials in Embase (as described in Lefebvre 2020, box 3e).

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 $1)).ti,ab.
15. (assigned or allocated).ti,ab.
16. (controlled adj7 (study or design or trial)).ti,ab.
17. (volunteer or volunteers).ti,ab.
18. human experiment/
19. trial.ti.
20. or/1-19
21. random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)
22. Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)
23. (((case adj control$) and random$) not randomi?ed controlled).ti,ab.
24. (Systematic review not (trial or study)).ti.
25. (nonrandom$ not random$).ti,ab.
26. "Random field$".ti,ab.
27. (random cluster adj3 sampl$).ti,ab.
28. (review.ab. and review.pt.) not trial.ti.
29. "we searched".ab. and (review.ti. or review.pt.)
30. "update review".ab.
31. (databases adj4 searched).ab.
32. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/
33. Animal experiment/ not (human experiment/ or human/)
34. or/21-33
35. 20 not 34

Appendix 8. Sensitivity analyses

Comparison 1: Induction chemotherapy plus locoregional treatment versus locoregional treatment alone

Sensitivity analysis - Overall survival

Sensitivity analyses were undertaken among the primary comparisons incorporating only those trials found to be at low risk of bias. For the comparison of induction chemotherapy with platinum plus 5-fluorouracil followed by radiotherapy, as compared to radiotherapy, the pooled estimate for total mortality based on the two trials (Domenge 2000; Paccagnella 1994) at low risk of bias was (HR 0.79, 95% CI 0.62 to 1.01, P = 0.06). This sensitivity analysis did not demonstrate any substantial difference in the difference in total mortality with this induction regimen. Similarly, no substantial difference in the primary outcome for platinum plus 5-fluorouracil induction chemotherapy prior to concurrent chemoradiation was noted with inclusion of only the low risk of bias study (Hitt 2014) (HR 0.91 (95% CI 0.69 to 1.20), P = 0.51).

For the comparison of induction chemotherapy with TPF prior to concurrent chemoradiation with cisplatin, all included studies above were found to be at low risk of bias.

Comparison 2: Surgery + adjuvant treatment A versus surgery + adjuvant treatment B

Sensitivity analysis - Overall survival

A sensitivity analysis was conducted including only trials assessed as being at low risk of bias for this outcome (Bernier 2004; Rao 1994; Rentschler 1987; UKHAN 2010). This did not change the conclusions for the comparison of adjuvant chemotherapy versus observation (HR 1.04, 95% CI 0.77 to 1.42, P = 0.78) (Rao 1994; Rentschler 1987). For the comparison of adjuvant chemoradiation versus radiotherapy, the effect of adjuvant concurrent chemoradiation on total mortality was no longer significant (HR 0.82, 95% CI 0.66 to 1.01, P = 0.06).

Comparison 3: Concurrent chemoradiotherapy versus radiotherapy alone

Sensitivity analysis - Overall survival

When the meta-analysis was based only on the nine trials assessed as being at low risk of bias with regard to total mortality (Brizel 1998; Corvo 2001; Denis 2004; Dobrowsky 2000; Eschwege 1988; Grau 2003; Huguenin 2004; Merlano 1992; UKHAN 2010), the pooled estimate for overall survival for any concurrent chemoradiation was HR 0.86 (95% CI 0.72 to 1.02, P = 0.09) with standard fractionation radiotherapy and HR 0.81 (95% CI 0.64 to 1.02, P = 0.08) with altered fractionation radiotherapy. Although the benefit for concurrent chemotherapy in these pooled estimates was lost, it is important to note the heterogeneity among the included chemotherapy regimens of platinum

plus 5-fluorouracil (Denis 2004), methotrexate (UKHAN 2010) and bleomycin (Eschwege 1988) for standard fractionation radiotherapy and platinum plus 5-fluorouracil (Brizel 1998), cisplatin (Huguenin 2004) and mitomycin C (Dobrowsky 2000).

WHAT'S NEW

Date	Event	Description
25 November 2021	New citation required and conclusions have changed	Eleven new trials included. There are no high-quality data to support use of induction chemotherapy prior to locoregional treatment or adjuvant chemotherapy following locoregional treatment.
15 September 2021	New search has been performed	Searches updated. Changes made to the way results are presented.

HISTORY

Protocol first published: Issue 1, 2007
Review first published: Issue 9, 2010

Date	Event	Description
28 February 2011	New citation required and conclusions have changed	Conclusions changed, summary of findings tables added, together with minor changes to the way results are presented.
28 February 2011	New search has been performed	Searches updated.

CONTRIBUTIONS OF AUTHORS

- Conceiving the review: Helen Worthington (HW), Jan Clarkson (JC), Anne-Marie Glenny (AMG), Richard Oliver (RO)
- Designing the review: HW, JC, AMG, RO, Sue Pavitt (SP), Michaelina Macluskey (MM), David Conway (DC)
- Co-ordinating the review: Susan Furness (SF), AMG, SP
- Data collection for the review: HW, JC, AMG, SF, RO, SP, MM, DC, Ambica Parmar (AP), Niall McGoldrick (NM)
- Designing search strategies: SP (in collaboration with the Trial Seach Co-ordinators)
- Undertaking searches: Trials Search Co-ordinators
- Screening search results: SF, HW, JC, AMG, RO, SP, MM, DC, AP, KC, NM
- Organising retrieval of papers: SP, SF
- Screening retrieved papers against eligibility criteria: SF, AMG, HW, JC, RO, SP, MM, DC, AP, NM
- Appraising risk of bias: HW, JC, AMG, RO, SP, MM, DC, SF, AP, NM
- Extracting data from papers: HW, SF, JC, AMG, RO, SP, MM, DC, AP, NM
- Writing to authors of papers for additional information: SP, SF
- Data management for the review: SF, AMG, HW, SP, AP
- Entering data into RevMan: SF, AMG, HW, SP, AP
- Analysis of data: HW, AMG, SF, AP
- Interpretation of data: SF, HW, AMG, JC, Kelvin Chan (KC), AP
- Assessing the certainty of evidence: AP, NMG, MM
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DECLARATIONS OF INTEREST

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Niall McGoldrick: I am a Director of the company Mouth Cancer Scotland Ltd (MCS Ltd), owned by the Scottish Charity Let's Talk About Mouth Cancer SC045100. MCS Ltd was set up to deliver the Global Oral Cancer Forum 2020 and received donations from the Henry Shein Cares Foundation and from the corporate giving arm of Bristol Myers Squibb.
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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of studies - as the primary outcome for this review is survival/mortality, we added a requirement that included studies have a minimum of six months of follow-up of participants after the end of treatment. Where participants in a trial have head and neck cancer in general, we have only included studies where at least 50% of the participants have either oral cavity or oropharyngeal cancer, or where data for the oral cavity and oropharyngeal patients only are available.

We excluded studies published only as abstracts although we had not explicitly stated our intention to do this in our original protocol. Where potentially eligible studies were abstracts only but had been conducted within the last 10 years, we categorised them as awaiting classification.

Types of outcomes - the primary outcome 'total mortality' was changed to 'overall survival or total mortality'.

The protocol for this review stated that quality of life would be a primary outcome for this review. Quality of life is an important outcome, for both people with oral cavity and oropharyngeal cancers and their doctors. In this deadly and disfiguring disease, searching for treatments that offer an improvement in both quantity and quality of life for patients motivates the large body of research into the management of this disease. The search for effective chemotherapies is motivated at least in part by the desire to avoid patients having to undergo radical disfiguring surgery with resultant loss of function.

However, as the review has progressed we have found the large quantity of research on chemotherapy focused on finding better treatments that prolong overall survival, disease-free survival and progression-free survival. Quality of life is inconsistently reported in trials which address a primary outcome of overall survival. Therefore, we have opted to transfer this outcome to the list of secondary outcomes to

be considered in future updates of this review as appropriate. Secondary outcome measures to be considered in future updates of this review include:

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

Search methods - we did not undertake a search of the Allied and Complementary Medicine Database (AMED) as these therapies are not eligible for inclusion in the current review.

INDEX TERMS

Medical Subject Headings (MeSH)

Chemoradiotherapy, Adjuvant; *Mouth Neoplasms [drug therapy]; Neoplasm Recurrence, Local; *Oropharyngeal Neoplasms [drug therapy]

MeSH check words

Humans