Interventions for the treatment of oral cavity and oropharyngeal cancer

Furness, Susan; Glenny, Anne-Marie; Worthington, Helen V.; Pavitt, Sue; Oliver, Richard; Clarkson, Jan E.

Published in:
Cochrane Database of Systematic Reviews

DOI:
10.1002/14651858.CD006386.pub3

Publication date:
2011

Document Version
Publisher's PDF, also known as Version of record

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

Furness S, Glenny AM, Worthington HV, Pavitt S, Oliver R, Clarkson JE, Macluskey M, Chan KKW, Conway DI

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2011, Issue 4

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

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

Susan Furness[1], Anne-Marie Glenny[1], Helen V Worthington[1], Sue Pavitt[2], Richard Oliver[3], Jan E Clarkson[4], Michaelina Macluskey[5], Kelvin KW Chan[6], David I Conway[7]

[1]Cochrane Oral Health Group, School of Dentistry, The University of Manchester, Manchester, UK. [2]Leeds Institute of Health Sciences, University of Leeds, Leeds, UK. [3]RED (Research and Education in Dentistry), Shrewsbury, UK. [4]Dental Health Services & Research Unit, University of Dundee, Dundee, UK. [5]Unit of Oral Surgery and Medicine, University of Dundee, Dundee, UK. [6]Princess Margaret Hospital, Toronto, Canada. [7]Glasgow Dental School, University of Glasgow, Glasgow, UK

Contact address: Susan Furness, Cochrane Oral Health Group, School of Dentistry, The University of Manchester, Coupland III Building, Oxford Rd, Manchester, M13 9PL, UK. Susan.Furness@manchester.ac.uk. suefurness@gmail.com.

Editorial group: Cochrane Oral Health Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 4, 2011.
Review content assessed as up-to-date: 27 February 2011.

Citation: Furness S, Glenny AM, Worthington HV, Pavitt S, Oliver R, Clarkson JE, Macluskey M, Chan KKW, Conway DI. Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy. *Cochrane Database of Systematic Reviews* 2011, Issue 4. Art. No.: CD006386. DOI: 10.1002/14651858.CD006386.pub3.

ABSTRACT

Background

Oral cavity and oropharyngeal cancers are frequently described as part of a group of oral cancers or head and neck cancer. 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, notably impaired ability to eat, drink and talk. 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.

Objectives

To determine whether chemotherapy, in addition to radiotherapy and/or surgery for oral cavity and oropharyngeal cancer results in improved survival, disease free survival, progression free survival, locoregional control and reduced recurrence of disease. To determine which regimen and time of administration (induction, concomitant or adjuvant) is associated with better outcomes.

Search methods

Electronic searches of the Cochrane Oral Health Group's Trials Register, CENTRAL, MEDLINE, EMBASE, AMED were undertaken on 1st December 2010. Reference lists of recent reviews and included studies were also searched to identify further trials.

Selection criteria

Randomised controlled trials where more than 50% of participants had primary tumours in the oral cavity or oropharynx, and which compared the addition of chemotherapy to other treatments such as radiotherapy and/or surgery, or compared two or more chemotherapy regimens or modes of administration, were included.

Data collection and analysis

Eighty-nine trials which met the inclusion criteria were assessed for risk of bias and data were extracted by two or more review authors. The primary outcome was total mortality. Trial authors were contacted for additional information or for clarification.

Main results

There is evidence of a small increase in overall survival associated with induction chemotherapy compared to locoregional treatment alone (25 trials), hazard ratio (HR) of mortality 0.92 (95% confidence interval (CI) 0.84 to 1.00, P = 0.06). Post-surgery adjuvant chemotherapy is associated with improved overall survival compared to surgery ± radiotherapy alone (10 trials), HR of mortality 0.88 (95% CI 0.79 to 0.99, P = 0.03), and there is some evidence that this improvement may be greater with concomitant adjuvant chemoradiotherapy (4 trials), HR of mortality 0.84 (95% CI 0.72 to 0.98, P = 0.03). In patients with unresectable tumours, there is evidence that concomitant or alternating chemoradiotherapy is associated with improved survival compared to radiotherapy alone (26 trials), HR of mortality 0.78 (95% CI 0.73 to 0.83, P < 0.00001). These findings are confirmed by sensitivity analyses based on studies assessed at low risk of bias. There is insufficient evidence to identify which agent(s) and/or regimen(s) are the most effective. The additional toxicity attributable to chemotherapy in the combined regimens remains unquantified.

Authors' conclusions

Chemotherapy, in addition to radiotherapy and surgery, is associated with improved overall survival in patients with oral cavity and oropharyngeal cancers. Induction chemotherapy may prolong survival by 8 to 20% and adjuvant concomitant chemoradiotherapy may prolong survival by up to 16%. In patients with unresectable tumours, concomitant or alternating chemoradiotherapy may prolong survival by 10 to 22%. There is insufficient evidence as to which agent or regimen is most effective and the additional toxicity associated with chemotherapy given in addition to radiotherapy and/or surgery cannot be quantified.

PLAIN LANGUAGE SUMMARY

Chemotherapy for mouth and throat cancer

Oral cavity (mouth) cancer is usually detected earlier and treated with surgery and radiotherapy. Oropharyngeal (throat) cancer may be advanced when it is found and is treated with radiotherapy. Both treatments may be associated with disfigurement and decreased ability to eat, drink and talk. Treatment with chemotherapy (drugs which kill cancer cells), in addition to radiotherapy (and surgery where possible) offers prolonged survival. Chemotherapy given at the same time as radiotherapy, is more effective than chemotherapy given before radiotherapy, and may reduce the need for surgery. The improvement in overall survival with the use of chemotherapy is estimated to be between 8% and 22%. The additional side effects of combined chemoradiotherapy (nausea, vomiting, diarrhoea, hair loss, and infections) were not measured.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Induction chemotherapy plus Locoregional treatment (LRT) versus LRT alone for the treatment of oral cavity and oropharyngeal cancer

Patient or population: patients with oral cavity and oropharyngeal cancer
Settings: hospital
Intervention: induction chemotherapy plus locoregional treatment (LRT)
Comparison: locoregional treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	locoregional treatment	induction chemotherapy plus locoregional treatment (LRT)				
Total Mortality Hazard Ratio Follow-up: 3-8 years	**Low risk population**[1]		**HR 0.92** (0.84 to 1)[2]	4051 (25 studies)	⊕○○○ **very low**[3,4]	
	200 per 1000	**186 per 1000** (171 to 200)				
	Medium risk population[1]					
	500 per 1000	**471 per 1000** (441 to 500)				
	High risk population[1]					
	700 per 1000	**670 per 1000** (636 to 700)				
Total Mortality Follow-up: 3-8 years	**Low risk population**[1]		**HR 0.80** (0.67 to 0.97)[5]	968 (4 studies)	⊕⊕⊕○ **moderate**[4]	

	200 per 1000	**163 per 1000** (139 to 195)
	Medium risk population[1]	
	500 per 1000	**426 per 1000** (371 to 489)
	High risk population[1]	
	700 per 1000	**618 per 1000** (554 to 689)

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

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

[1] Control risk based on 5 year mortality data in McGurk 2005
[2] Analysis conducted on all included studies
[3] Four studies at low risk of bias, 12 are unclear and 9 are at high risk of bias
[4] Studies included patients with other head and neck cancers
[5] Analysis conducted on included studies at low risk of bias

BACKGROUND

Description of the condition

Oral cancers are a significant disease group globally with more than 404,000 new cases worldwide in 2002 (Parkin 2005; Warnakulasuriya 2009). Oral cancers are the sixth most common cancer worldwide, accounting for an estimated 4% of all cancers. The incidence and mortality from oral cancers varies geographically; the highest age standardised rates of oral cancers are reported in parts of Europe (France, Hungary), Botswana and south central Asia (Sri Lanka, Pakistan, Banglasdesh and India) (Parkin 2005). There is overwhelming evidence that tobacco use, alcohol consumption and betel quid chewing are the main risk factors in the aetiology of intraoral cancer (La Vecchia 1997; Macfarlane 1995). There is also strong evidence that low socio-economic status is associated with a higher incidence and poorer survival of oral cancers (Faggiano 1997). There is a higher incidence of oral cancers in men (Freedman 2007) that is generally attributed to a greater exposure to the known risk factors and vast majority of cases occur in men over 50 (Warnakulasuriya 2009) and among low socio-economic groups (Conway 2008). However, the ratio of males to females diagnosed with oral cancers has declined from approximately 5:1 in the 1960s to less than 2:1 in 2002 (Parkin 2005). Another recent trend is the increasing incidence of oral cavity and oropharyngeal cancers in younger adults in the European Union and the United States (Warnakulasuriya 2009).

The epidemiological data concerning 'oral cancer' obscures the fact that 'oral cancer' includes both oral cavity and oropharyngeal cancers which have clinically different aetiology, are generally diagnosed at different stages and managed in different ways. Patients with oral cavity cancers generally present with early stage disease and the primary treatment is surgery or radiotherapy or both. However, 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 where HPV infection is found in 40% to 60% of patients (D'Souza 2007), and HPV is thought to be associated with the increased incidence of oropharyngeal cancer (Hammarstedt 2006). The link between oncogenic HPV and oropharyngeal cancer is strong and has been documented in numerous studies, fufilling the epidemiological criteria for disease causality, especially in the development of oropharyngeal cancer in non-smokers (Sturgis 2007). The proportion of patients with oropharyngeal cancer who are HPV positive has increased dramatically over recent years (Attner 2010; Ryerson 2008) but it is interesting to note that this group of patients have significantly improved rates of both overall survival and disease free survival (Fakhry 2006; Fakhry 2008; Licitra 2006).

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

Description of the intervention

The primary treatment modality for oral cavity cancer in most countries has been surgery, whereas oropharyngeal cancer, which is often diagnosed at a more advanced stage, may be inoperable and is more commonly treated with radiation or chemoradiation. Postoperative radiotherapy is added for late stage disease but chemotherapy has historically been used in a relatively small proportion of cases (Funk 2002). Surgery for oral cancers can be disfiguring and both surgery and radiotherapy have significant functional side effects, notably impaired ability to eat, drink and talk. As a consequence there has been considerable research into non-surgical treatment modalities such as chemotherapy and radiotherapy. A major determination of survival in the treatment of oral cancer is that it commonly spreads to the lymph nodes of the neck (cervical lymph nodes) (Haddadin 2000; Hughes 1993; Partridge 2000; Pentenero 2005; Shah 1990). In low volume disease, chemotherapy may have an important role to play in the control/treatment of metastatic disease, and may be equally as effective as radiotherapy and surgery (Fanucchi 2006; Harari 2005).

Chemotherapy is the administration of anticancer or 'cytotoxic' drugs. These drugs work by attacking rapidly dividing cancer cells, disrupting the growth of the cancer cells and destroying them. The drugs used in chemotherapy affect the life cycle of the cancer cells, most commonly by damaging the deoxyribonucleic acid (DNA) of the cells so that they can no longer reproduce. Because the drugs enter the body's circulatory system their effect is systemic and therefore this offers greater applicability in higher stage tumours where there is a higher risk of metastases to other parts of the body. Different types of chemotherapeutic agents interrupt the life cycle of cancer cells at different stages; thus combining two or three different agents into a chemotherapy regimen may produce a greater and/or longer lasting effect on the tumour than single agent chemotherapy. However as well as increased benefits, combinations of chemotherapeutic agents may also be associated with increased toxicity, effects which may be exacerbated by the simultaneous used of radiotherapy.

How the intervention might work

Chemotherapy agents can be classified into groups according to their mode of action (Additional Table 1). It is common to give two or more chemotherapy drugs together and this is commonly

referred to as 'combinational therapy'. A commonly used standard chemotherapy regimen for oral cancer, for the past 20 years has been a combination of cisplatin and 5 fluorouracil (Specenier 2007). Most chemotherapy drugs are administered directly into the bloodstream but other modes, including oral, intramuscular or intratumoural administration may also be used. The timing of chemotherapy can vary. It may be given as 'induction' therapy, early treatment in order to shrink a tumour prior to surgery or radiotherapy, concurrently with radiotherapy (concomitant, concurrent or synchronous chemoradiotherapy), or may be provided following treatment with surgery or radiotherapy (adjuvant) (Pignon 2009). Sequential therapy usually refers to induction chemotherapy followed by concurrent chemoradiotherapy.

Chemotherapy regimens are cycles of treatment, with drugs administered daily for one or more days, followed by rest days, depending on the combination of agents and dosages used. Chemotherapy is often associated with adverse effects, which are usually temporary, but may be quite severe, and are the result of the chemotherapy drugs targetting all dividing cells in the body: normal cells as well as cancer cells. Adverse effects vary amongst patients and treatment type, but can include tiredness, anaemia, nausea/vomiting, diarrhoea or constipation, hair loss, mucositis and susceptibility to infections. The rest days included in chemotherapy regimens allow time for adverse events to resolve before the next treatment cycle begins.

Why it is important to do this review

The management of advanced oral cavity and oropharyngeal cancers is problematic and has traditionally relied on surgery and radiotherapy, both of which are associated with substantial adverse effects. Although there have been new treatments developed there has been limited improvement in survival over the past 3 decades (Warnakulasuriya 2009). Oropharyngeal cancers have relatively 'silent' symptoms which may not be present during the early stages of the disease, which is a possible explanation for the fact that stage of disease at diagnosis has not altered in the past 40 years despite public education (McGurk 2005). Tumour recurrence and the development of multiple primary tumours are the major causes of treatment failure (Day 1992; Partridge 2000; Woolgar 2003). Surgical treatment may be disfiguring and result in a substantially reduced quality of life as patients are socially isolated, due to difficulties with altered appearance, speech, eating and drinking. The development of new chemotherapy agents, new combinations of agents and changes in the relative timing of treatments may bring about increases in both survival and quality of life.

This review of chemotherapy will attempt 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 undertaken as part of a series of Cochrane reviews looking at the treatment modalities of oral cavity and oropharyngeal cancers categorised into four intervention groups: surgery (Oliver 2007), chemotherapy, radiotherapy (Glenny 2010) and immunotherapy/biotherapy (Pavitt 2007).

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

OBJECTIVES

Primary objective

To determine whether chemotherapy, in addition to radiotherapy and/or surgery for oral cavity and oropharyngeal cancer, results in increased overall survival, disease free survival, progression free survival, locoregional control and reduced recurrence.

Secondary objective

To determine which chemotherapeutic agents, and which treatment regimen(s) (induction, concomitant or adjuvant) are associated with the best outcome in terms of overall survival, disease free survival, progression free survival, recurrent disease and quality of life

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials comparing chemotherapy treatment, with either chemotherapy combined with locoregional treatment (radiotherapy or surgery), a different chemotherapy regimen, or chemotherapy given at different times relative to locoregional treatment (either induction, concomitant or adjuvant chemotherapy) will be included in the review provided there is a minimum follow-up of 6 months. It is anticipated that there will be no studies comparing chemotherapy with placebo (although if there are such studies they will be included).

Types of participants

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

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

Types of interventions

Chemotherapy 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 the cancer cells preventing the development or spread of the cancer.

Patients may be randomised to treatment with chemotherapy plus other treatments (such as surgery, radiotherapy or other medical therapies) but the comparison must be either between chemotherapy and other treatments (no chemotherapy), or chemotherapy A compared with chemotherapy B (different agent, timing or mode of administration). The treatments received and compared must be the primary treatment for the tumour and patients should not have received any prior intervention other than diagnostic biopsy, or surgery. Therefore trials where participants present with recurrent or metastatic disease will be excluded.

Trials where all participants receive the same chemotherapy regimen and are randomised to other treatments such Chinese herbal medicine, a radiosensitiser (for example amifostine) and/or a chemosensitiser (for example leucovorin or vitamins), where these 'other treatments' are the intervention being compared (i.e. they are the only difference in intervention between the experimental and control groups) will be excluded.

Trials of targeted therapies, or monoclonal antibodies will be evaluated in a separate review which will evaluate immunotherapies and targeted therapies.

Types of outcome measures

Primary outcome measures will be:

- Total mortality (either a hazard ratio for death, or where this is not estimable, the numbers of deaths per treatment group at a specific time point)
- Disease free survival
- Progression free survival or time to recurrence
- Locoregional control
- Locoregional recurrence.

Search methods for identification of studies

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

- MEDLINE via OVID (1950 to 1st December 2010) (Appendix 1)
- The Cochrane Oral Health Group's Trials Register (to 1st December 2010) (Appendix 2)
- The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 4) (Appendix 3)
- EMBASE via OVID (1980 to 1st December 2010) (Appendix 4)
- Allied and Complementary Medicine Database (AMED) via OVID (1985 to 1st December 2010) (Appendix 5).

Current Controlled trials (www.controlled-trials.com) was searched for oral cancer or oropharyngeal cancer on 25th January 2010.

Because studies involving oral cancer are often included with those of the head and neck, a broad search was undertaken to include all possible studies. The searches attempted to identify all relevant trials irrespective of language. The reference list of related re-

view articles and articles considered to be potentially relevant were checked for further trials. Authors of identified trials and known specialists in the field were contacted in an attempt to identify any additional published or unpublished trials.

Sensitive search strategies were developed for each database using a combination of free text and MeSH terms; these were based on the search strategy developed for MEDLINE (Appendix 1) but revised appropriately for each database. The search strategy combined the subject search with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity maximising version (2009 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions* version 5.0.2 (updated September 2009) (Higgins 2009). Handsearching was done as part of the Cochrane Collaboration's worldwide handsearching programme, *see* the Cochrane Master List of journals being searched for more information.

The reference lists of related reviews and all articles obtained were checked for further trials. Authors of trial reports and specialists in the field known to the review authors were written to concerning further published and unpublished trials.

The original search strategy was deployed for all four reviews at the same time i.e. encompassing all the oral cancer treatment modalities and combinations of treatment with identified papers being then classified into subsets of treatment modalities: surgery, chemotherapy, radiotherapy and immunotherapy/biotherapy.

Data collection and analysis

Selection of studies

The titles and abstracts (when available) of all reports identified through the electronic searches were scanned independently by two review authors for eligibility for the oral cancer reviews. 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. 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 table, 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) where greater 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 the following data were recorded:

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

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 six domains for each included study: sequence generation, allocation concealment, blinding (of patient, carer, outcome assessor), completeness of outcome data, risk of selective outcome reporting and risk of other potential sources of bias. An overall risk of bias assessment was also made.

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

- Sequence generation: use of a random number table, use of a computerised system, central randomisation by statistical co-ordinating centre, randomisation by an independent service using minimisation technique, permuted block allocation or Zelan technique. If the paper merely stated randomised or randomly allocated with no further information this was assessed as being unclear.
- Allocation concealment: centralised allocation including access by telephone call or fax, or pharmacy-controlled randomisation, sequentially numbered, sealed, opaque envelopes.

- Blinding: in most of the included studies blinding of patients 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 it was assumed that blinding of patients, clinical staff and outcome assessors did not occur.
- Outcome data: outcome data were considered complete if all patients randomised were included in the analysis of the outcome(s). However, in trials of treatment for cancer this is rarely the case. Trials where less than 10% of those randomised were excluded from the analysis, and where reasons for exclusions were described for each group, and where both numbers and reasons were similar in each group, were assessed as being at low risk of bias due to incomplete outcome assessment. Where post-randomisation exclusions were greater than 10%, or reasons were not given for exclusions from each group, or where rates and reasons were different for each group, the risk of bias due to (in)complete outcome data was assessed as unclear.
- Selective outcome reporting: a trial was assessed as being at low risk of bias due to selective outcome reporting if the outcomes of interest described in the methods section, were systematically reported in the results section. Where reported outcomes did not include those outcomes specified or expected in trials of treatments for oral cancer, or where additional analyses were reported this domain was assessed as unclear.
- Other bias: imbalance in potentially important prognostic factors between the treatment groups at baseline, or the use of a co-intervention in only one group (for example nasogastric feeding) are examples of potential sources of bias noted.

Data synthesis

The primary outcome is total mortality expressed as hazard ratio of death. These data were entered into the meta-analysis using the inverse variance method. If hazard ratios were not quoted in studies, but there were Kaplan-Meier estimates and the numbers at risk over a range of time intervals were reported, we then calculated the log hazard ratio and the standard error (SE) from the available summary statistics (observed events, expected events, variance, confidence intervals, P values or Kaplan-Meier estimates - survival curves) according to the methods proposed by Parmar et al (Parmar 1998), or these data were requested from authors. Where possible we have presented total mortality as log hazard ratios, either calculated from Kaplan-Meier graphs, or from data presented in the MACH-NC meta-analyses (Pignon 2000 or Pignon 2009). For dichotomous outcomes, the estimates of effect of an intervention were expressed as risk ratios together with 95% confidence intervals. Total mortality at a specific timepoint, disease free survival and progression free survival were analysed in two ways depending on the data presented in study reports, or obtained from authors. 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 '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.

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. Meta-analyses were conducted only if there were studies of similar comparisons reporting the same outcome measures. Risk ratios were combined for dichotomous data, and hazard ratios for survival data, using fixed-effect models, unless there were more than four trials to be combined, when random-effects were used. Where the same meta-analysis contained subgroups with varying numbers of trials, a decision as to whether to use a fixed-effect or random-effects model was based on the degree of heterogeneity of the larger subgroups of studies. In this situation where heterogeneity was low a fixed-effect model was chosen. The significance of any discrepancies in the estimates of the treatment effects from the different trials was assessed by means of Cochran's test for heterogeneity and the I^2 statistic, and any heterogeneity investigated.

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

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

There were some 5000 papers identified from the search strategy. 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 89 included trials (many with multiple publications) were identified. Some of the included studies had 100% of participants with oral cavity or oropharyngeal cancer and others included participants with primary tumours in other sites (Additional Table 2).

There were 89 trials included in this review. Trials were undertaken all over the world with 17 based in the USA, 15 in France, 12 in Italy, 6 in Germany, 6 in India, 4 in Spain, 2 each in Canada, UK, South America and Scandinavia, 1 trial in Russia, 1 trial in Australasia, 3 conducted worldwide,13 multicentre trials in Europe and 3 multicentre trials in Asia. A total of 16,767 patients were randomly allocated to treatments and individual trials varied in size between 23 and 966 participants. Participants were recruited over periods ranging between 1 and 10 years, with the first study starting recruitment in 1965 (Richard 1974) and the most recent

completing recruitment in 2007 (Gladkov 2007; Gupta 2009). Fifty trials described the stage of cancer of patients eligible for inclusion (6 trials included patient with stages 2-4, 44 stages 3-4) and 23 trials described cancer stage using the more specific TNM system (Patel 2005) (3 trials included patients with T2-T4 tumours and a further 3 with T1-T4 tumours). The remaining 16 trials did not specify the disease stage(s) in their inclusion criteria. The clinical heterogeneity of the included studies is substantial, and one of the strengths of this review lies in presenting an overall summary of the results of this body of research undertaken across the world over the past 45 years.

Twenty-eight of the included studies 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 total mortality from these meta-analyses, because they are from individual patient data from the included trials (details of the data source for total mortality 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.

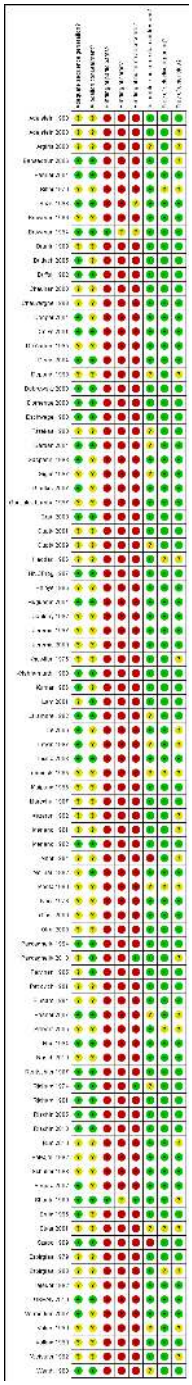
Only 23 of the included trials restricted inclusion to patients with oral cavity and oropharyngeal cancer. In the remainder of trials included in this review at least 50% of included participants had either oral cavity or oropharyngeal cancer (for details *see* Additional Table 2).

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 six domains described in the methods section. All of the included studies are described as randomised with the method of sequence generation described as either adequate or unclear.

In most studies of chemotherapy, blinding of patients and clinicians would be difficult and possibly unethical. Where blinding of patients, carers or outcome assessors is not mentioned in the text, we have assumed that there was no blinding. We have taken a pragmatic approach and assumed that where outcomes are objective (e.g. mortality, overall survival) the lack of blinding in the included studies is unlikely to result in bias. However, it is acknowledged that for outcomes which may be seen as more subjective, such as progression free survival, disease free survival or recurrence, the absence of blinding of trial personnel, especially of those assessing these outcomes may represent a potential risk of bias. Only three of the included studies used blinding of either patients or outcome assessors (Figure 1).

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Assessment of possible selective reporting was based on the printed paper and it is acknowledged that even when the planned outcomes are listed in the methods section and reported in the results section of a paper, selective outcome reporting may still be a risk. However, in most cases, the only information available to us was that included in the published article so assessment was based on this information unless otherwise stated. Eight 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.

In 15 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.

Various other potential sources of bias were identified in 20 trials. Eight trials presented so little information it was not possible to make a clear assessment. In seven trials there was a degree of imbalance between the randomised groups at baseline which may have introduced a bias to the results. Two trials gave inconsistent descriptions of methods used, and another three trials included a co-intervention which may result in bias (*see* 'Risk of bias' tables in the Characteristics of included studies on each study for details, and summary in Figure 1).

We have described our assessment of the risk of bias of the studies included for each comparison under the heading Effects of interventions (below). Overall 21 of the 89 included trials were assessed as being at low risk of bias for the outcome of total mortality.

Effects of interventions

See: **Summary of findings for the main comparison** Induction chemotherapy plus Locoregional treatment (LRT) versus LRT alone for the treatment of oral cavity and oropharyngeal cancer; **Summary of findings 2** Surgery +/- RT + chemotherapy compared to surgery +/- RT alone for oral cavity and oropharyngeal cancer; **Summary of findings 3** Concomitant chemoradiotherapy compared to radiotherapy alone for oral cavity and oropharyngeal cancer

The searches revealed two published meta-analyses of individual patient data (IPD) (Pignon 2000; Pignon 2009) which gave log hazard ratios and standard errors for total mortality and some data were pertinent to this systematic review; these data were included providing the trials met our own inclusion criteria. As the Pignon data were calculated from IPD we considered these data to be more precise than figures we calculated from the often scant data presented in trial manuscripts. Therefore these Pignon 2000 and 2009 data take precedence over our data where both types of data were available. We contacted Pignon for relevant site-specific data; however his team were unable to provide these until they were able to finalise their own publications - their IPD data were protected under strict agreement by those contributing data for their use and distribution.

As described in the methods section, the primary outcome of this review is total mortality expressed as hazard ratio for death. For obvious reasons clinicians prefer to use the more positive term overall survival when communicating information about treatment effectiveness with patients, but the data from the trials is based on deaths. We have used the positive term overall survival in the interpretation of the hazard ratios for mortality. However, where hazard ratios cannot be estimated from the data presented in each trial, any dichotomous data available from the trials for numbers of deaths per treatment group at a specified time point, these data have been presented in the meta-analysis.

Additional Table 2 records the percentages of patients included in each trial, who have oral cavity cancer, oropharyngeal cancer and the combined percentage. Where data from one of the meta-analyses published by Pignon has been used this is also recorded.

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

Comparison 2: Surgery ± radiotherapy + chemotherapy versus surgery ± radiotherapy alone.

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

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

The structure of the text for each comparison varies according to the nature of the individuals trials included, but follows the same order as the meta-analyses.

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

There are 26 randomised controlled trials (Brunin 1989; Depondt 1993; Domenge 2000; Fazekas 1980; Giglio 1997; Holoye 1985; Jaulerry 1992; Knowlton 1975; Lewin 1997; Licitra 2003; Luboinski 1985; Maipang 1995; Mazeron 1992; Mohr 1994; Nervi 1978; Olmi 2003; Paccagnella 1994; Petrovich 1981; Richard 1974; Richard 1991; Salvajoli 1992; Schuller 1988; Szabo 1999; Szpirglas 1988; Tejedor 1992; Volling 1999) included in this comparison, under eight outcome subgroups. Each trial compares the addition of induction chemotherapy to locoregional treatment (either radiotherapy or surgery or both) with locoregional treatment alone. All of the trials in this group provided data for analysis of total mortality, eight trials (Brunin 1989; Domenge 2000; Holoye 1985; Olmi 2003; Paccagnella 1994; Richard 1991; Tejedor 1992; Volling 1999) for disease free survival, two trials (Domenge 2000; Olmi 2003) provided data for analysis of pro-

gression free survival and four trials (Knowlton 1975; Licitra 2003; Richard 1974; Szabo 1999) reported the dichotomous outcome of overall survival at either 1 or 5 years of follow-up. One trial (Licitra 2003) also reported the dichotomous outcomes of disease free survival and disease related mortality after 5 years of follow-up.

Cisplatin is the most common chemotherapy agent, used in 14 trials, either alone, or in combination with other chemotherapeutic agents:

- cisplatin alone (Mohr 1994)
- cisplatin plus 5 fluorouracil (5-FU) (Domenge 2000; Lewin 1997; Licitra 2003; Paccagnella 1994)
- cisplatin plus 5-FU plus folinic acid (Giglio 1997)
- cisplatin plus 5-FU plus vindesine (Jaulerry 1992)
- cisplatin plus 5-FU plus bleomycin and methotrexate (Mazeron 1992)
- cisplatin plus bleomycin, vinblastine plus mitomycin C (Salvajoli 1992)
- cisplatin plus bleomycin, vindesine plus mitomycin C (Brunin 1989)
- cisplatin plus bleomycin, vincristine plus adriamycin (Szpirglas 1988)
- cisplatin plus bleomycin, vincristine plus methotrexate (Schuller 1988)
- cisplatin plus bleomycin plus methotrexate (Maipang 1995)
- cisplatin plus epirubicin (Szabo 1999).

The other 'platin' used in these trials is carboplatin, used either in combination with 5-FU (Depondt 1993; Olmi 2003; Volling 1999) or with ftorafur (Tejedor 1992).

Methotrexate was the next most frequently studied component of induction chemotherapy in the 26 included trials in Comparison 1. Methotrexate was administered as a single agent in four trials, either intravenously (Fazekas 1980; Knowlton 1975) or intra-arterially (directly to the target area) (Nervi 1978; Richard 1974) or in the following combinations:

- methotrexate plus cisplatin, bleomycin and vincristine (Schuller 1988), *see* above
- methotrexate plus cisplatin and bleomycin (Maipang 1995), *see* above
- methotrexate plus vincristine (Petrovich 1981)
- methotrexate plus bleomycin, 5-FU and cyclophosphamide (Holoye 1985).

The remaining two trials in Comparison 1 used a combination of bleomycin and vincristine, administered intra-arterially (Luboinski 1985; Richard 1991).

Risk of bias

None of the 26 trials incorporated blinding of patients or clinicians and only one (Richard 1974) used blinded outcome assessment. The lack of blinding is unlikely to have influenced the objective outcomes of total mortality, but may have had an effect on the assessment of the more subjective outcomes such as disease free survival, progression free survival, locoregional control and disease recurrence. Only seven trials had information indicating adequate sequence generation and allocation concealment (Domenge 2000; HNCProg 1987; Licitra 2003; Paccagnella 1994; Richard 1974; Szabo 1999; UKHAN 2010) but two of these had incomplete outcome assessment (Richard 1974; Szabo 1999).

Therefore our assessment is that:

- four studies had low risk of bias with regard to total mortality (Domenge 2000; Licitra 2003; Paccagnella 1994; Richard 1991), no blinding but adequate with regard to the other five domains of the assessment;
- ten studies had high risk of bias with regard to all outcomes reported (Depondt 1993; Fazekas 1980; Giglio 1997; Knowlton 1975; Lewin 1997; Mazeron 1992; Mohr 1994; Richard 1974; Szabo 1999; Szpirglas 1988) (no blinding, unclear sequence generation and allocation concealment and a problem in at least one of the other domains assessed);
- twelve had unclear risk of bias with regard to total mortality (no blinding and insufficient information provided on sequence generation and allocation concealment) and moderate to high risk of bias for the outcomes of disease free survival, progression free survival, locoregional control and disease recurrence (Brunin 1989; Holoye 1985; Jaulerry 1992; Luboinski 1985; Maipang 1995; Nervi 1978; Olmi 2003; Petrovich 1981; Salvajoli 1992; Schuller 1988; Tejedor 1992; Volling 1999).

Total mortality

- One trial by Mohr 1994 compared pre-operative chemoradiotherapy with concomitant low dose cisplatin followed by surgery to surgery alone. This trial is included in this comparison because the chemotherapy is the first treatment used in these patients, but the trial is not truly a trial of induction chemotherapy versus none, and should be considered as a separate subgroup. In this trial, 377 patients were randomly allocated to chemoradiotherapy treatment followed by surgery or surgery alone, but only 268 patients were included in the outcome data. An additional 25 patients randomised to pre-operative chemoradiotherapy subsequently refused surgery (these patients had larger tumours than the group average), 23 patients were not evaluated due to 'protocol violations' and a further 61 randomised patients are not accounted for in the outcome. Sequence generation and allocation concealment are unclear from the information given in the paper. Although the results from this trial showed a statistically significant reduction in total mortality in favour of the chemoradiotherapy group, the results from this trial must be interpreted with caution as there is a high risk of bias, and missing data from 29% of randomised patients could potentially alter the conclusions from this trial. This trial has not been included in the meta-analysis.

The remaining 25 trials in this group compared induction chemotherapy plus locoregional treatment with locoregional treatment alone Analysis 1.1.

None of the seven trials (Depondt 1993; Domenge 2000; Olmi 2003 (oropharyngeal cancer only); Lewin 1997; Licitra 2003 (primary tumour in oral cavity only); Paccagnella 1994; Volling 1999) that compared platin chemotherapy (either cisplatin or carboplatin) plus 5-FU plus radiotherapy, to radiotherapy alone, found a statistically significant reduction in total mortality due to the addition of this chemotherapy regimen (Comparisons 1.1.1). The trial by Lewin 1997 was the only trial in this group which provided data for the outcome of total mortality for patients with oral cavity cancers only, and these data showed no difference between induction chemotherapy with cisplatin/5-FU plus LRT compared to LRT alone (Analysis 1.1, Comparison 1.1.1). The pooled estimate showed no strong evidence of a difference between induction therapy with a platin plus locoregional treatment and locoregional treatment alone (hazard ratio (HR) 0.90, 95% confidence interval (CI) 0.80 to 1.02, P = 0.09).

There were four trials of induction chemotherapy with methotrexate alone (Fazekas 1980; Knowlton 1975; Nervi 1978; Richard 1974). Two of these used intra-arterial administration of methotrexate and three trials provided outcome data for patients with oral cavity and oropharyngeal cancer (Fazekas 1980; Nervi 1978; Richard 1974). Nervi 1978 showed a reduction in total mortality which just attained statistical significance, favouring the group who received induction therapy with methotrexate plus radiotherapy compared to those who received radiotherapy alone (Analysis 1.1, Comparison 1.1.12). The overall pooled estimate for total mortality in the four trials of induction chemotherapy with methotrexate alone showed no evidence of a difference (HR 0.90, 95% CI 0.72 to 1.14, P = 0.38) (Analysis 1.1, Comparison 1.1.13).

Four trials compared methotrexate in combination with other chemotherapy agents (Schuller 1988; Maipang 1995; Petrovich 1981; Holoye 1985 - two of these trials are included in the cisplatin group above), and none showed evidence of any benefit.

There were two trials that used a combination of bleomycin and vincristine, administered intra-arterially to patients with a primary tumour in the oral cavity (Luboinski 1985; Richard 1991). Pooling the data from both trials (total of 342 randomised patients evaluated) shows a statistically significant benefit in favour of intra-arterial induction chemotherapy with bleomycin and vincristine (HR 0.67, 95% CI 0.50 to 0.91, P = 0.01) (Analysis 1.1, Comparison 1.1.15).

Summary of results of Comparison 1: Induction chemotherapy plus LRT versus LRT alone

Induction regimen	No of trials	Total mortality (HR for death)	P value
Either cisplatin or carboplatin plus 5FU	7	HR 0.94, (95% CI 0.86 to 1.04)	P = 0.09
Containing cisplatin or carboplatin	10	Not applicable	
Methotrexate alone	4	HR 0.90, (95% CI 0.72 to 1.14)	P = 0.38
Containing methotrexate,	2	Not applicable	
Bleomycin + vincristine	2	HR 0.67, (95% CI 0.50 to 0.91)	P = 0.01
Overall*	25	HR 0.92, (95% CI 0.84 to 1.00)	P = 0.06

* Data from Mohr 1994 is not included in this summary.

Overall, the 25 included trials of induction chemotherapy plus locoregional treatment versus locoregional treatment alone showed some evidence of a small benefit for overall survival (HR 0.92, 95% CI 0.84 to 1.00, P = 0.06).

Sensitivity Analysis - Total Mortality

A sensitivity analysis was undertaken incorporating only the four trials assessed as being at low risk of bias (Domenge 2000; Licitra 2003; Paccagnella 1994; Richard 1991). The pooled estimate for total mortality based on these four trials is (HR 0.80, 95% CI 0.67 to 0.97, P = 0.02) (analysis not shown) which suggests that

induction chemotherapy may have a benefit (up to 20%) for overall survival.

Disease free survival

Two of the three trials which compared induction chemotherapy with carboplatin and 5-FU plus LRT to LRT alone (Olmi 2003; Volling 1999), reported the outcome of disease free survival (Analysis 1.2). When combined by meta-analysis these two trials (total of 332 patients) provided evidence of a benefit for disease free survival in favour of induction chemotherapy with carboplatin and 5-FU (HR 0.66, 95% CI 0.48 to 0.89, P = 0.007).

Likewise the two trials that compared induction chemotherapy with cisplatin and fluorouracil plus LRT to LRT alone (Domenge 2000; Paccagnella 1994) individually showed no difference in disease free survival, but when data were pooled (total of 655 patients) there was a statistically significant benefit in favour of induction chemotherapy (Comparison 1.2.3) (HR 0.78, 95% CI 0.62 to 0.97, P = 0.03).

There was no evidence of a difference in disease free survival between groups treated with induction chemotherapy comprising carboplatin/ftorafur (Tejedor 1992), cisplatin/bleomycin/vindesine/mitomycin C combination (Brunin 1989), bleomycin/vincristine (Richard 1991) or bleomycin/cyclophosphamide/methotrexate/5-FU (Holoye 1985) (Comparisons 1.2.2, 1.2.4, 1.2.5, 1.2.6).

Pooling the data on disease free survival from all of the eight trials of different chemotherapy regimens showed evidence of an overall benefit favouring induction chemotherapy (HR 0.78, 95% CI 0.67 to 0.90, P = 0.001).

Progression free survival

Progression free survival was reported by Domenge 2000 and Olmi 2003 (Analysis 1.3), and the estimate from pooling these data showed some evidence of a benefit favouring induction chemotherapy (HR 0.80, 95% CI 0.64 to 1.00, P = 0.05).

Disease free survival and recurrent disease after 5 years of follow-up

Licitra 2003 reported disease free survival at 5 years (Comparison 1.4.1), and locoregional recurrence (Comparison 1.5.1). There was no evidence of a difference between groups treated with induction chemotherapy plus LRT compared to LRT alone for either of these outcomes.

Comparison 2: Surgery ± radiotherapy + chemotherapy versus surgery ± radiotherapy alone

There are 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 patients included in the trials in this comparison had surgical resection with curative intent. Following surgery patients were randomised to post-operative (adjuvant) chemotherapy ± radiotherapy or surgery ± radiotherapy In this comparison, 10 of the 11 studies reported the outcome of total mortality. For the HNCProg 1987 a publication of the subset analysis of the oral cavity and oropharyngeal patients provided data for analysis for the outcome of disease free survival. Disease free survival is reported in a total of eight trials in this comparison (Argiris 2008; Bitter 1979; Cooper 2004; HNCProg 1987; Laramore 1992; Rao 1994; Rentschler 1987; UKHAN 2010) and two reported progression free survival (Bernier 2004; UKHAN 2010). Locoregional control was reported by one trial (Cooper 2004).

Risk of bias

In Comparison 2, none of the trials incorporated blinding of patients, carers or those assessing outcomes. We consider that absence of blinding is unlikely to have influenced the estimation of the objective outcomes of total mortality. Therefore our assessment of risk of bias with regard to total mortality is;

- five studies are at low risk of bias for total mortality (Bernier 2004; HNCProg 1987; Rao 1994; Rentschler 1987; UKHAN 2010) as these have adequate sequence generation and allocation concealment and no other threats to validity in the domains assessed;
- Argiris 2008; Bitter 1979; Cooper 2004; Lam 2001; Laramore 1992; Szpirglas 1979 are at unclear risk of bias for total mortality due to inadequate information presented on sequence generation, allocation concealment, incomplete outcome data and/or other issues.
- no trials in this comparison were assessed as high risk of bias for the outcome of total mortality

However with regard to the more subjective outcomes of disease free survival, progression free survival, locoregional control and disease recurrence our assessment is that risk of bias is unclear for all trials in this comparison.

Effects of interventions

As the trials in this comparison evaluate a range of chemotherapy regimens in patients who also undergo surgery, the results below are presented in five subgroups for all of the reported outcomes in the table below, summarising total mortality in the 10 trials that reported this outcome.

Interventions in this comparison included:

- post-surgery chemotherapy (MTX) versus post-operative radiotherapy (Bitter 1979)
- pre- and post-surgery chemotherapy (levamisole/UFT) versus surgery alone (Lam 2001) (no radiotherapy)
- post-surgery chemotherapy (MTX) verus surgery alone (Rao 1994) (no radiotherapy)

- surgery ± radiotherapy + chemotherapy (MTX/BLM/citrovorum) versus surgery ± radiotherapy (Szpirglas 1979)
- post-surgery chemotherapy (cis/5-FU) then radiotherapy versus post-surgery radiotherapy alone (Laramore 1992)
- pre- and post-surgery chemotherapy (MTX) then radiotherapy versus post-surgery radiotherapy alone (Rentschler 1987)
- post-surgery concomitant chemoradiotherapy (cisplatin) versus post-surgery radiotherapy alone (Bernier 2004; Cooper 2004)
- post-surgery concomitant chemoradiotherapy (carboplatin) versus post-surgery radiotherapy alone (Argiris 2008)
- post-surgery concomitant chemoradiotherapy (MTX or VBMF) versus post-surgery radiotherapy alone (UKHAN 2010)
- pre-surgery chemotherapy, then surgery + radiotherapy then chemotherapy versus post-surgery radiotherapy alone (HNCProg 1987) (no data for total mortality).

Total mortality

One small trial (Bitter 1979) compared post-surgery chemotherapy with post-operative radiotherapy in 33 patients who had undergone surgery, and found no difference between the two treatments with regard to total mortality or disease free survival (Analysis 2.1 and Analysis 2.2 respectively).

Two trials compared surgery plus post-operative chemotherapy with surgery alone (no patients in these trials had radiotherapy). Rao 1994(participants with primary tumour in the oral cavity) randomised 116 post-operative patients to receive either methotrexate or no further treatment and in Lam 2001, 65 patients who had been given levamisole prior to surgery, were randomised to post-surgery UFT (oral formulation of tegafur and uracil) plus levamisole or no further treatment. Both of these studies showed no statistically significant difference between surgery plus chemotherapy and surgery alone with regard to total mortality (total mortality data for Rao 1994 from Pignon 2000). However, Rao 1994 showed a statistically significant difference in favour of adjuvant methotrexate chemotherapy in post-surgery patients with regard to the outcomes of disease free survival (Analysis 2.2, HR 0.47, 95% CI 0.26 to 0.87, P = 0.02), and disease recurrence at 2 years (Analysis 2.5, risk ratio (RR) 0.62, 95% CI 0.4 to 0.97).

Szpirglas 1979 randomised patients with primary tumours in the oral cavity, who had undergone standard therapy (surgery ± radiotherapy) to either chemotherapy with a combination of methotrexate/bleomycin/leucovorin or no further treatment. There was no statistically significant difference between the groups in this trial for total mortality (Analysis 2.1, Comparison 2.1.4).

Rentschler 1987 randomly allocated patients to adjuvant chemotherapy versus standard treatment of surgery and radiotherapy alone. The chemotherapy group received methotrexate once a week for 4 weeks pre-operatively, followed by surgery, then weekly methotrexate for 4 weeks, followed by a course of radiotherapy followed by a final eight doses of weekly methotrexate. The comparison group received surgery followed by radiotherapy. There was no statistically significant difference between the groups in this trial for either total mortality or disease free survival (Analysis 2.1, Comparison 2.1.5; Analysis 2.2, Comparison 2.2.3).

Another trial, Laramore 1992 randomly allocated post-surgery patients to either three cycles of cisplatin/5-FU followed by radiotherapy or post-surgery radiotherapy alone. There was no statistically significant difference between the groups compared with regard to total mortality (Analysis 2.1, Comparison 2.1.6), or disease free survival (Analysis 2.2, Comparison 2.2.4).

Post-surgery concomitant chemoradiotherapy was compared with post-surgery radiotherapy alone in four trials. Two trials (Bernier 2004; Cooper 2004) with 334 and 459 patients respectively, compared concomitant cisplatin plus radiotherapy with radiotherapy alone. Another smaller trial with 72 patients randomised patients to concomitant carboplatin plus radiotherapy or radiotherapy alone (Argiris 2008) and the large UKHAN 2010 study which included both patients with unresectable tumours and a post-operative group of 253 patients, randomly allocated the latter group of patients to either concomitant chemoradiotherapy (either methotrexate alone or vincristine/bleomycin/methotrexate/fluorouracil) or radiotherapy alone.

In the trial by Bernier 2004, 56% of the included patients had oral cavity or oropharyngeal cancer and in Cooper 2004, 70% of the patients included had oral cavity or oropharyngeal cancer and also two 'high risk factors' (any two of histological evidence of invasion of at least two lymph nodes, extracapsular extension of nodal disease, microscopically involved mucosal margins of resection). These two trials evaluated the same interventions and when data from these two studies are pooled, the overall effect estimate shows a reduction in total mortality favouring chemoradiotherapy with cisplatin (HR 0.80, 95% CI 0.66 to 0.97, Comparison 2.1.7). The trial by Cooper 2004 also showed a statistically significant benefit favouring cisplatin chemoradiotherapy in disease free survival (HR 0.78, 95% CI 0.62 to 0.99, Comparison 2.2.5) and locoregional recurrence (HR 0.61, 95% CI 0.41 to 0.91, Comparison 2.4.1). There was also a statistically significant difference between the groups in favour of cisplatin plus radiotherapy with regard to progression free survival in Bernier 2004 (HR 0.75, 95% CI 0.57 to 0.99, Comparison 2.3.1).

Argiris 2008 found no statistically significant difference between concomitant carboplatin plus radiotherapy and radiotherapy alone for the outcomes of either total mortality or disease free survival.

The post-surgery patients (n = 253) in the UKHAN 2010 trial were randomised to post-surgery chemotherapy with methotrexate or VBMF (vincristine/bleomycin/methotrexate/fluorouracil) or post-surgery radiotherapy alone. There was no statistically significant difference between these two groups in total mortality (Analysis 2.1, Comparison 2.1.9), disease free survival (Analysis 2.2, Comparison 2.2.7) or in progression free survival (Analysis 2.3, Comparison 2.3.2).

However, the combined estimate of total mortality from the pooled data from any concomitant chemoradiotherapy regimen versus radiotherapy alone in post-operative patients (four trials Argiris 2008; Bernier 2004; Cooper 2004; UKHAN 2010) shows evidence of a reduction in total mortality in favour of concomitant chemoradiotherapy (HR 0.84, 95% CI 0.72 to 0.98, P = 0.03 Analysis 2.1 Comparisons 2.1.7 to 2.1.9).

Summary of results of Comparison 2: Surgery ± radiotherapy + chemotherapy versus surgery ± radiotherapy alone

Regimen	No of trials	Total mortality (HR for death)	P value
Post-surgery chemotherapy versus post-surgery radiotherapy	1	HR 0.32, (95% CI 0.08 to 1.35)	P = 0.12
Post-surgery chemotherapy versus surgery alone (no radiotherapy)	2	HR 0.84, (95% CI 0.50 to 1.39)	P = 0.49
Post-surgery chemotherapy (± radiotherapy) versus surgery alone (± radiotherapy)	1	HR 1.01, (95% CI 0.50 to 2.05)	P = 0.98
Post-surgery chemotherapy + radiotherapy versus post-surgery radiotherapy alone	2	HR 0.95, (95% CI 0.79 to 1.14)	P = 0.56
Post-surgery concomitant chemoradiotherapy versus post-surgery radiotherapy alone	4	HR 0.84, (95% CI 0.72 to 0.98)	P = 0.03
Overall	10	HR 0.88, (95% CI 0.79 to 0.99)	P = 0.03

The overall pooled estimate based on the ten trials in this comparison, shows some evidence of a reduction in total mortality favouring adjuvant chemotherapy, (HR 0.88, 95% CI 0.79 to 0.99, P = 0.03).

Sensitivity Analysis - Total Mortality

When only trials assessed as being at low risk of bias for this outcome (Bernier 2004; Rentschler 1987; Rao 1994; UKHAN 2010) are included in the meta analysis, the pooled estimate for total mortality is (HR 0.88, 95% CI 0.74 to 1.05, P = 0.16), the same estimate as when all the trials are included but with a reduction in precision.

Disease Free Survival

Disease free survival was reported by eight trials in this comparison, and all evaluated different agents, administered either prior to radiotherapy or concomitantly. Rao 1994 was the only trial that showed a difference in disease free survival between the groups, favouring adjuvant methotrexate compared to surgery alone.

The three trials (Argiris 2008; Cooper 2004; UKHAN 2010) reported disease free survival for *concomitant* adjuvant chemoradiotherapy, and the pooled estimate for these trials shows no evidence of a difference in disease free survival, (HR 0.87, 95% CI 0.73 to 1.04, P = 0.12 Analysis 2.2 estimate not shown on forest plot).

The remaining trial in Comparison 2 reported data for disease free survival only. The HNCProg 1987 trial randomly allocated 462

patients to one of three treatment regimens: either A, standard therapy (surgery plus radiotherapy), or B, 5 days of induction chemotherapy with cisplatin and bleomycin, followed by surgery and radiotherapy, or C, 5 days of induction chemotherapy with cisplatin and bleomycin, followed by surgery and radiotherapy, plus adjuvant cisplatin (subsequent chemotherapy). We extracted data from a published subgroup analysis of the oral cavity and oropharyngeal cancer patients (n = 192) (HNCProg 1987). Group C is compared to Group A in Analysis 2.2 (Comparison 2.2.8) which found no statistically significant difference between these groups with regard to disease free survival.

Overall there is weak evidence from meta-analysis of these trials of a possible improvement in disease free survival as a result of adjuvant chemotherapy (HR 0.89, 95% CI 0.78 to 1.01, P = 0.06).

Comparison 3: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)

This category included 29 trials (Adelstein 2003; Bensadoun 2006; Brizel 1998; Browman 1994; Budach 2005; Chauhan 2008; Corvo 2001; Denis 2004; Dobrowsky 2000; Eschwege 1988; Grau 2003; Gupta 2001; Haddad 1996; Huguenin 2004; Jeremic 1997; Jeremic 2000; Krishnamurthi 1990; Kumar 1996; Merlano 1992; Morita 1980; Parvinen 1985; Ruo 2010; Salvajoli 1992; Shanta 1980; Smid 1995; Staar 2001; UKHAN 2010; Weissler 1992; Wendt 1998).

Two trials evaluated a combination of induction and concomitant chemoradiotherapy (Kumar 1996; Shanta 1980), and two evaluated alternating chemo/radiotherapy (Corvo 2001; Merlano 1992). These trials are presented separately from the trials that describe concomitant chemoradiotherapy alone. Within this review we have used the term concomitant chemoradiotherapy to describe chemotherapy and radiotherapy that is administered at the same time, usually on the same days. Other publications use the terms concurrent or combined and radiochemotherapy, RCT or CRT to refer to this type of treatment.

Risk of bias

Only two of the trials clearly include blinding of patients and/or outcome assessors (Browman 1994; Shanta 1980). Browman 1994 is assessed as unclear risk of bias for total mortality due to a lack of information about the method of sequence generation and allocation concealment, but in Shanta 1980 there were inconsistencies between the groups at baseline, with an unclear effect of the risk of bias in this trial. Overall the risk of bias for the outcome of total mortality was assessed as follows;

- Low risk of bias; 9 trials (Brizel 1998; Corvo 2001; Denis 2004; Dobrowsky 2000; Eschwege 1988; Grau 2003; Huguenin 2004; Merlano 1992; UKHAN 2010);
- Unclear risk of bias; the remaining 20 trials assessed as unclear due to insufficient information being provided for one or more of the domains assessed;
- High risk of bias; none of the trials in this comparison was assessed as being at high risk of bias for total mortality.

Effects of interventions

Three trials included patients with cancer of the oral cavity only (Krishnamurthi 1990; Morita 1980; Shanta 1980); two included patients with cancer of the oropharynx only (Denis 2004; Eschwege 1988); two included patients with cancer of either the oropharynx or hypopharynx (Bensadoun 2006; Staar 2001). The remaining trials included mixed head and neck cancer patients, of whom more than 50% were patients with cancer of the oral cavity or oropharynx.

Fourteen trials recruited patients with non-resectable tumours only (Adelstein 2003; Bensadoun 2006; Brizel 1998; Budach 2005; Chauhan 2008; Haddad 1996; Jeremic 1997; Jeremic 2000; Kumar 1996; Merlano 1992; Salvajoli 1992; Smid 1995; Staar 2001; Wendt 1998).

Staging was presented in two main ways: UICC staging or TNM. Of the 17 trials reporting UICC staging, 14 recruited patients with Stage 3 to 4. Twelve trials reported the TNM classification; tumours ranged from T1 to T4.

Data presented in this section are either from the published paper or from a previously published meta-analysis (Pignon 2000) based on individual patient data (data supplied to Pignon by the investigators of the included trials). Trials in this comparison are in three subgroups, and each outcome is described in turn:

- induction plus concomitant chemoradiotherapy 2 trials (Kumar 1996; Shanta 1980)
- concomitant chemoradiotherapy 26 trials* (only 24 provided data for hazard ratio for total mortality)
- alternating chemo and radiotherapy 2 trials (Corvo 2001; Merlano 1992).

*Shanta 1980 is also included in this group.

Induction plus concomitant chemoradiotherapy

- Cyclophosphamide + MTX plus concomitant chemoradiotherapy (5-FU) (Kumar 1996).
- Bleomycin (IM) (Shanta 1980).

Two trials evaluated the combination of induction and concomitant chemotherapy (Kumar 1996; Shanta 1980). Data on total mortality were available for both trials. No data on disease free survival, locoregional control or progression free survival were available for either trial. The data from these two trials are not included in the forest plots because it was felt that induction plus concomitant chemoradiotherapy was a sufficiently different intervention from concomitant chemoradiotherapy alone and combining these could skew the estimates inappropriately.

One trial, conducted in India (Kumar 1996), compared treatment with induction cyclophosphamide and MTX followed by concomitant 5-FU, to radiotherapy alone in 38 participants with previously untreated inoperable primary malignancy of the oral cavity, oropharynx and laryngopharynx. No statistically significant difference was shown between the combined chemoradiotherapy group and radiotherapy alone with regard to total mortality (Kumar 1996 (data from Pignon 2009)) (Analysis not shown).
A trial of 157 patients with histologically proven squamous cell carcinoma of the buccal mucosa was undertaken by Shanta 1980. It evaluated the administration of bleomycin and radiotherapy versus radiotherapy alone. Bleomycin was administered intra-arterially (IA) (n = 42), intravenously (IV) (n = 22) or intramuscularly (IM) (n = 20). IA and IV cases received bleomycin and radiotherapy concomitantly, and results from these groups are described below. The group who received IM bleomycin commenced chemotherapy 2 weeks prior to the radiotherapy, and continued during radiotherapy (Analysis 3.1, Comparison 3.1.2). Based on data presented in Pignon 2000, for trial coded WIA-OC5c there was no evidence of a benefit with regard to total mortality for IM bleomycin plus radiotherapy compared to radiotherapy alone (Shanta 1980). (Analysis not shown).

Concomitant chemoradiotherapy

Twenty-six trials evaluated chemotherapy in combination with radiotherapy versus radiotherapy alone. Thirteen trials evaluated a platin (either alone or in combination with other chemotherapy agents) plus radiotherapy, compared to radiotherapy alone:

- cisplatin (Adelstein 2003; Huguenin 2004*; Jeremic 2000*)
- cisplatin or carboplatin (Jeremic 1997*; Ruo 2010)
- cisplatin + 5-FU (Adelstein 2003; Bensadoun 2006; Brizel 1998*; Haddad 1996; Weissler 1992)
- carboplatin + 5-FU (Staar 2001*; Denis 2004)
- cisplatin + 5-FU + CA-foliant (Wendt 1998)
- cisplatin + bleomycin (Salvajoli 1992)
- 1-FU (Browman 1994)
- MTX (Gupta 2001)
- MTX +/- vincristine, bleomycin, 5-FU (UKHAN 2010)
- gemcitabine (Chauhan 2008)
- mitomycin (Dobrowsky 2000*; Grau 2003)
- mitomycin + bleomycin (Smid 1995)
- mitomycin + 5-FU (Budach 2005*)
- bleomycin (Eschwege 1988; Morita 1980; Parvinen 1985; Shanta 1980)
- pepleomycin (Krishnamurthi 1990)

(*studies with hyperfractionated radiotherapy).
Trials presented data on total mortality, disease free survival, locoregional control or progression free survival.

Total mortality

Total mortality data was available from 24 of the trials in this group (all except Chauhan 2008 and Krishnamurthi 1990). Five trials compared concomitant chemoradiotherapy with a platin, to radiotherapy alone. (Adelstein 2003 (data from Pignon 2009 Int 0126a); Huguenin 2004 (data from Pignon 2009); Jeremic 1997; Jeremic 2000 (data from Pignon 2009) and Ruo 2010).
One trial compared either cisplatin or carboplatin plus standard fraction radiotherapy with radiotherapy alone (n = 159) (Jeremic 1997) and one compared carboplatin plus radiotherapy to radiotherapy alone in 164 patients (Ruo 2010). Participants recruited were those with histologically confirmed locally advanced, non-metastatic, unresectable squamous cell carcinoma (SCC) of the head and neck. The other three trials in this group recruited patients with SCC of the head and neck and randomised them to cisplatin plus radiotherapy or radiotherapy alone (Adelstein 2003 (n = 182); Huguenin 2004 (n = 224); Jeremic 2000 (n = 130)). Two trials in this group used hyperfractionated radiotherapy (Huguenin 2004; Jeremic 1997) and the other three used standard fractionation. When the estimates from all five trials of a platin plus radiotherapy versus radiotherapy alone were combined by meta-analysis, a hazard ratio for total mortality of 0.66 (95% CI 0.57 to 0.77) was calculated, in favour of the combined chemoradiotherapy arm. (*See* summary of results table below.) No statistical heterogeneity was identified (P = 0.77, I^2 = 0%).
Eight trials evaluated the effect of a platin plus 5-FU administered concomitantly to radiotherapy (Adelstein 2003; Bensadoun 2006; Brizel 1998; Denis 2004; Haddad 1996; Staar 2001; Weissler 1992; Wendt 1998). In two trials the intervention was carboplatin + 5-FU (Denis 2004 (data from Pignon 2009); Staar 2001 (oropharyngeal cancer only)) . The remaining six trials evaluated concomitant chemotherapy with cisplatin + 5-FU (Adelstein 2003 (data from Pignon 2009 Int 0126b); Bensadoun 2006 (oropharyngeal cancer only); Brizel 1998 (IPD data for oral cavity and oropharyngeal cancer patients supplied by authors); Haddad 1996; Weissler 1992; Wendt 1998). The participants in all six trials had similar diagnoses, predominantly unresectable, Stage III/IV SCC of the head and neck. It should be noted that the trial by Wendt 1998 also administered CA-foliant along with the cisplatin and radiotherapy. For the eight trials of concomitant platin (either cisplatin or carboplatin) + 5-FU, the pooled estimate shows evidence of a reduction in total mortality (HR 0.71, 95% CI 0.62 to 0.81, P < 0.00001) with no significant heterogeneity (I^2 = 0%, P = 0.77) (Analysis 3.1, Comparison 3.1.2).
One trial compared a combination of cisplatin and bleomycin plus radiotherapy with radiotherapy alone in 90 patients with head and neck cancer in Brazil. No statistically significant difference was shown in terms of total mortality between the chemoradiotherapy group and radiotherapy alone (Salvajoli 1992) (Analysis 3.1, Comparison 3.1.3).
Browman 1994 compared chemoradiotherapy with concomitant 1-FU to radiotherapy alone. The trial recruited 175 participants with histologically confirmed SCC of the head and neck (Stage III

or IV). Data from Pignon 2000 showed no statistically significant difference between 1-FU plus radiotherapy and radiotherapy alone (Analysis 3.1, Comparison 3.1.4).

A trial of FU and mitomycin plus radiotherapy showed a statistically significant reduction in total mortality compared to radiotherapy alone (Analysis 3.1, Comparison 3.1.5) (Budach 2005 (data from Pignon 2009)). This trial recruited 386 patients with unresectable, Stage III/IV SCC of the head and neck and used hyperfractionated radiotherapy.

No statistically significant difference was shown in total mortality when methotrexate was used as a single agent chemotherapy combined with radiotherapy compared to radiotherapy alone in one trial (Analysis 3.1, Comparison 3.1.6) (Gupta 2001 (data from Pignon 2000)).

A large multicentre trial of patients with locally advanced squamous cell carcinoma of the head and neck, judged suitable for radical radiotherapy as either initial treatment or following surgery, used a factorial design (UKHAN 2010). The chemotherapy regimen used was either methotrexate alone or methotrexate in combination with vincristine, bleomycin and 5-FU. Chemotherapy started on either days 1-14 concurrent with radiotherapy (SIM) or 14 and 28 days after completing radiotherapy (SUB). Neither the concomitant (SIM) regimen, nor the concomitant plus subsequent (SIM + SUB) regimen showed a statistically significant difference between the chemotherapy plus radiotherapy arm compared to radiotherapy alone (Comparisons 3.1.7 and 3.1.8 respectively).

Bleomycin as single agent chemotherapy concomitant with radiotherapy was compared to radiotherapy alone in four trials (Eschwege 1988; Morita 1980; Parvinen 1985; Shanta 1980 (all data from Pignon 2000)), all undertaken in the 1980s. In these trials primary tumours were located in oropharynx only (Eschwege 1988), tongue only (Morita 1980), buccal mucosa (Shanta 1980) and both oral cavity and oropharynx (Parvinen 1985) and the dose of bleomycin varied between 5 and 15 mg/dose, delivered between 2 & 5 times weekly to a total of 60-150 mg. Three of these trials found no difference between bleomycin plus radiotherapy and radiotherapy alone. In the trial by Shanta 1980, 157 patients were randomised to either bleomycin and radiotherapy or radiotherapy alone. Bleomycin was administered intra-arterially (IA) (n = 42), intravenously (IV) (n = 22) or intramuscularly (IM) (n = 20) compared to radiotherapy alone (n = 73), and the IA and IV groups received bleomycin and radiotherapy concomitantly. (The IM group in this trial received bleomycin for 2 weeks before starting radiotherapy and also during radiotherapy - results reported above). There is some discrepancy between the numbers of patients in each subgroup in the original paper compared to the numbers per group in the data presented in Pignon 2000. The data included in Comparison 3.1.9 is from Pignon 2000 WIA OC5b from the IV + IA bleomycin groups combined (n = 38) versus radiotherapy alone (n = 41), and shows a significant benefit associated with bleomycin plus radiotherapy in this study. Overall these four trials show considerable clinical and statistical heterogeneity (I^2 = 85%, P = 0.0002) which suggests that these data should not be pooled.

Bleomycin and mitomycin were combined with radiotherapy in one trial (Smid 1995) of patients with inoperable head and neck cancer. There was no difference between the groups with regard to total mortality in this trial (Comparison 3.1.10).

Mitomycin C as single agent plus concomitant radiotherapy was compared to radiotherapy alone in two large trials with 558 and 239 patients with head and neck cancer respectively (Dobrowsky 2000; Grau 2003 (data from Pignon 2000)). There was no difference between chemoradiotherapy with Mitomycin C and radiotherapy alone (HR 0.92, 95% CI 0.76 to 1.12) in the pooled data from these two trials.

Summary of results of Comparison 3: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)

Regimen	No of trials	Total mortality (HR for death)	P value
Concomitant platin	5*	HR 0.66, (95% CI 0.57 to 0.77)	P < 0.00001
Concomitant platin + 5-FU	8*	HR 0.71, (95% CI 0.62 to 0.81)	P < 0.00001
Concomitant bleomycin	4	Data not pooled due to considerable heterogeneity	
Concomitant mitomycin	2	HR 0.92, (95% CI 0.76 to 1.12)	P = 0.42
Concomitant other	6	Not applicable	

(*Continued*)

Alternating chemoradiotherapy	2	HR 0.69, (95% CI 0.53 to 0.90)	P = 0.006
Concomitant chemoradiotherapy**	24	HR 0.79, (95% CI 0.74 to 0.84)	P < 0.00001
Concomitant + alternating CRT***	26	HR 0.78, (95% CI 0.73 to 0.83)	P < 0.00001

Note: Multiarm trials may be included in more than one subgroup in this table.

* Adelstein 2003 included in both these subgroups (different comparisons).

** 24 trials of 'truly concomitant' regimens are included in this estimate (Analysis 3.1.1 to 3.1.11).

*** 26 trials of 'truly concomitant' or alternating regimens are included in this estimate (Analysis 3.1.1 to 3.1.12).

Combining the data from the 24 trials of concomitant chemoradiotherapy shows evidence of a 21% reduction in total mortality with concomitant chemoradiotherapy compared to radiotherapy alone (HR 0.79, 95% CI 0.74 to 0.84, P < 0.00001).

Alternating chemo and radiotherapy

Two trials assessed alternating chemo and radiotherapy versus radiotherapy alone (Corvo 2001; Merlano 1992). Both used a combination of cisplatin + 5-FU, but each used different radiotherapy regimens. Merlano 1992 recruited 157 patients with biopsy-confirmed, unresectable SCC of the head and neck. Patients were randomised to receive either cisplatin and 5-FU, alternating with standard fraction radiotherapy (2 Gy per day, 5 days per week), or radiotherapy alone. Corvo 2001 randomised 136 patients, with stage II-IV SCC of the head and neck to either cisplatin and 5-FU, alternating with three 2-week courses of standard fraction radiotherapy, or radiotherapy alone. The radiotherapy alone group received high dose, partly accelerated radiotherapy (PA-RT), with a final second course using concomitant boost technique. No statistically significant difference was shown between the two treatment groups (data from Pignon 2009), but this trial was stopped early due to low accrual. Despite the differences in the radiotherapy regimens in the control arms of these two studies, the pooled data show some evidence of a benefit in favour of alternating chemoradiotherapy (HR 0.69, 95% CI 0.53 to 0.90, P = 0.006) (Comparison 3.1.12).

In Merlano 1992, which compared a chemoradiotherapy regimen comprising cisplatin and 5-FU alternated with radiotherapy to radiotherapy alone, there was a statistically significant increase in locoregional control in favour of the chemoradiotherapy group (Comparison 3.3.7) and no difference between the groups with regard to disease free survival (Comparison 3.2.4).

When the alternating regimens are combined with the concomitant trials, there is a statistically significant, 22% reduction in total mortality associated with treatment with concomitant chemoradiotherapy in 26 trials of patients with non-resectable head and neck cancer where more than 50% of patients have a primary tumour in either oral cavity or oropharynx (HR 0.78, 95% CI 0.73 to 0.83, P < 0.00001).

Sensitivity Analysis - Total Mortality

When the meta-analysis is based only on the seven trials of truly concomitant regimens assessed as being at low risk of bias with regard to total mortality, (Brizel 1998; Denis 2004; Dobrowsky 2000; Eschwege 1988; Grau 2003; Huguenin 2004; UKHAN 2010) the pooled estimate for total mortality is (HR 0.90, 95% CI 0.81 to 0.99, P = 0.03).

The hazard ratio for total mortality for *either* concomitant or alternating chemotherapy, based on studies at low risk of bias (n = 9) is HR 0.87 (95% CI 0.79 to 0.95, P = 0.003) (both Corvo 2001; Merlano 1992 are assessed as being at low risk of bias for this outcome).

These sensitivity analyses suggests that the finding of a benefit associated with concomitant or alternating chemoradiotherapy is robust, and the size of the benefit is somewhere between 10% and 22%.

Disease free survival

Analysis 3.2. Nine trials of concomitant chemoradiotherapy also reported the outcome of disease free survival.

Four trials evaluated a combination of a platin (either cisplatin or carboplatin) plus 5-FU. Brizel 1998 and Bensadoun 2006 compared concomitant cisplatin + 5-FU plus radiotherapy versus radiotherapy alone. In a trial of 122 patients with cancer of the head and neck (Brizel 1998), there was no statistically significant difference in disease free survival between the chemoradiotherapy group and radiotherapy alone. However, in a trial of 123 patients with cancer of the oropharynx alone (Bensadoun 2006), a statistically significant difference in favour of combined chemoradiotherapy was shown for disease free survival. Denis 2004 and Staar 2001 both compared carboplatin + 5-FU plus radiotherapy versus radiotherapy alone in 222 and 263 patients respectively, and

both found a benefit for disease free survival in favour of concomitant chemoradiotherapy that attained statistical significance in the larger trial (Staar 2001). Staar 2001 also reported disease free survival for those patients with primary tumours of the oropharynx (HR 0.69, 95% CI 0.52 to 0.91, these data not shown on forest plot).The pooled estimate from the four trials of concomitant chemoradiotherapy with a platin plus 5-FU showed evidence of a benefit for concomitant chemoradiotherapy (HR 0.70, 95% CI 0.59 to 0.84, P < 0.0001) with little heterogeneity (I^2 = 2%, P = 0.38) (Analysis 3.2).

A trial of 164 patients randomised to either concomitant carboplatin and radiotherapy or radiotherapy alone found no statistically significant difference in disease free survival (Ruo 2010).

The trial by Gupta 2001 presented data for disease free survival separately for oral cavity cancer and oropharyngeal cancer. There was a statistically significant benefit in disease free survival for patients with oral cavity or oropharyngeal cancers favouring methotrexate administered concomitant to radiotherapy compared to radiotherapy alone (Gupta 2001) (Analysis 3.2, Comparison 3.2.4).

In a small trial of 64 patients with non-resectable cancer of the head and neck (Smid 1995) compared a combination of bleomycin and mitomycin C, plus concomitant radiotherapy, to radiotherapy alone. A statistically significant difference in disease free survival was found overall (Analysis 3.2, Comparison 3.2.5).

In the UKHAN multicentre trial of either methotrexate (MTX) alone or MTX in combination with vincristine, bleomycin and 5-FU, there was a statistically significant increase in disease free survival when the chemotherapy was given concomitantly to radiotherapy (UKHAN 2010) (Analysis 3.2, Comparison 3.2.6). No statistically significant difference was shown when the chemotherapy was given both simultaneously and subsequently (SIM + SUB) to radiotherapy (Analysis 3.2, Comparison 3.2.7).

Overall in the eight trials, there was evidence of a benefit for disease free survival in favour of concomitant chemoradiotherapy (HR 0.77, 95% CI 0.70 to 0.84, P < 0.00001) with a little heterogeneity (I^2 = 18.6%, P = 0.29) Analysis 3.2

Locoregional control

Analysis 3.3.

Seven trials of concomitant chemoradiotherapy presented data for this outcome (Budach 2005; Gupta 2001; Haddad 1996; Huguenin 2004; Ruo 2010; Staar 2001; Wendt 1998).

Only one of four trials evaluating the effect of cisplatin as single agent chemotherapy given concomitantly to radiotherapy assessed locoregional control (Huguenin 2004). Hyperfractionated radiotherapy was used in the trial of 224 patients with SCC of the head and neck. No statistically significant difference was found between treatment groups. Ruo 2010 reported locoregional control as the primary outcome measure in this trial which compared carboplatin plus radiotherapy with radiotherapy alone, and found a difference favouring concomitant chemoradiotherapy that just attained statistical significance. The pooled estimate of concomitant platin plus radiotherapy showed some evidence of a benefit favouring concomitant chemoradiotherapy (HR 0.78, 95% CI 0.65 to 0.94, P = 0.008) (Analysis 3.3, Comparison 3.3.1).

Three of the seven trials that compared a platin + 5-FU + radiotherapy to radiotherapy alone, presented data on locoregional control (Haddad 1996; Staar 2001; Wendt 1998). Haddad 1996 and Wendt 1998 both administered cisplatin plus 5-FU concomitantly with radiotherapy (Wendt 1998 also administered CA-folinat along with the cisplatin and radiotherapy). There was some evidence of a benefit in locoregional control in favour of concomitant platin plus 5-FU when these trials were pooled (HR 0.75, 95% CI 0.61 to 0.93, P = 0.009) (Analysis 3.3, Comparison 3.3.2).

No statistically significant difference was shown in locoregional control between concomitant methotrexate plus radiotherapy compared with radiotherapy alone (Gupta 2001), in the group of patients with a primary tumour in either the oral cavity or oropharynx (Analysis 3.3, Comparison 3.3.3).

Budach 2005 combined mitomycin and 5-FU with hyperfractionated radiotherapy. A statistically significant increase in locoregional control was found for concomitant mitomycin+ 5-FU+ radiotherapy compared to hyperfractionated radiotherapy alone in this study (Analysis 3.3, Comparison 3.3.4).

Overall the pooled estimate from these seven trials showed evidence of a benefit for locoregional control associated with concomitant chemoradiotherapy (HR 0.73, 95% CI 0.64 to 0.82, P = 0.02) with some heterogeneity (I^2 = 39.7%, P = 0.17) (Data not shown on forest plot).

Progression free survival

Analysis 3.4.

Four trials of concomitant chemoradiotherapy presented data for the outcome of progression free survival for concomitant chemoradiotherapy compared to radiotherapy alone, and a further two evaluated alternating regimens.

Two trials compared cisplatin plus radiotherapy with radiotherapy alone (Huguenin 2004; Jeremic 2000). Both trials used hyperfractionated radiotherapy. Pooling of data from these trials showed no evidence of a difference for progression free survival between the combined chemoradiotherapy group and radiotherapy alone (HR 0.84, 95% CI 0.66 to 1.08, P = 0.18).

Browman 1994 found no difference between concomitant chemoradiotherapy with 1-FU and radiotherapy alone with regard to progression free survival (Analysis 3.4, Comparison 3.4.2).

In the trial by Budach 2005 comparing concomitant mitomycin and 5-FU and hyperfractionated radiotherapy, to hyperfractionated radiotherapy alone, there was a statistically significant benefit in terms of progression free survival (Analysis 3.4, Comparison 3.4.3).

Overall these four trials showed a statistically significant benefit for progression free survival in favour of concomitant chemora-

diotherapy (HR 0.75, 95% CI 0.63 to 0.89, P = 0.001) with little heterogeneity (I^2 = 19%, P = 0.30) .

Alternating Regimens

Both trials which compared alternating chemoradiotherapy with radiotherapy alone (Corvo 2001; Merlano 1992) presented data on progression free survival. However, the pooled estimate from these two trials found no evidence for a difference in progression free survival between concomitant chemoradiotherapy and radiotherapy alone (HR 0.82, 95% CI 0.62 to 1.07, P = 0.14).

When the alternating and concomitant regimens were combined the pooled estimate for progression free survival based on all 6 trials showed evidence of a benefit favouring concomitant chemoradiotherapy (HR 0.77, 95% CI 0.67 to 0.89, P = 0.0004)

Locoregional control (complete response to treatment)

Analysis 3.5.

Four trials reported complete response to treatment (Chauhan 2008; Dobrowsky 2000; Krishnamurthi 1990; Parvinen 1985). No statistically significant difference was seen in complete response rate for patients with head and neck cancer treated with mitomycin and hyperfractionated radiotherapy compared to hyperfractionated radiotherapy alone (Dobrowsky 2000) (Comparison 3.5.1) or bleomycin and radiotherapy compared to radiotherapy alone (Parvinen 1985) (Comparison 3.5.2). A single study compared gemcitabine plus concomitant radiotherapy with radiotherapy alone (Chauhan 2008) and found a statistically significant improvement in complete response rate in favour of chemoradiotherapy (Comparison 3.5.3). Krishnamurthi 1990 compared radiotherapy with pepleomycin alone, radiotherapy plus pepleomycin plus hyperthermia, and radiotherapy plus hyperthermia alone and evaluated patients for complete tumour response. The pepleomycin plus radiotherapy group combined had a higher complete response rate compared to radiotherapy and hyperthermia alone (Analysis 3.5, Comparison 3.5.4). However, no post-treatment follow-up is reported in this paper so it is unknown whether this initial tumour response was followed by a difference in survival for these patients.

Due to the substantial clinical and statistical heterogeneity between these four trials, data were not pooled.

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

This comparison includes a total of 28 trials in which two chemotherapy regimens are compared head to head. Chemotherapy regimens in these trials differ in terms of agents used and timing relative to radiotherapy. There are also comparisons between sequential chemotherapy followed by radiotherapy and concomitant chemoradiotherapy. They are grouped into five subsections:

- Induction chemotherapy; Regimen A versus Regimen B
- Induction chemotherapy followed by sequential chemoradiotherapy
- Concomitant chemoradiotherapy; Regimen A versus Regimen B
- Induction chemotherapy followed by radiotherapy versus concomitant chemoradiotherapy
- Comparisons between other chemotherapy regimens.

Data has been extracted for analysis with regard to the outcomes of total mortality in 20 trials (Adelstein 1993; Browman 1986; Chauvergne 1988; De Andres 1995; Garden 2004; Gasparini 1993; Gonzalez-Larriba 1997; Gupta 2009; Le 2006; Marechal 1987; Merlano 1991; Paccagnella 2010; Pinnaro 1994; Posner 2007; Rasch 2010; Rischin 2005; Rischin 2010; Segura 2002; UKHAN 2010; Vermorken 2007), disease free survival (Gasparini 1993; Gupta 2009; HNCProg 1987; Merlano 1991; Rasch 2010; Rischin 2005; Rischin 2010), progression free survival (Adelstein 1993; Gonzalez-Larriba 1997; Paccagnella 2010; Pinnaro 1994; Posner 2007; UKHAN 2010; Vermorken 2007), locoregional control (Rasch 2010; Rischin 2005; Rischin 2010), and the dichotomous outcomes of total mortality at 2-5 years (Olasz 2000), disease free survival at 5 years (De Andres 1995), locoregional control (Buffoli 1992; Gladkov 2007; Merlano 1991; Molinari 1982; Prevost 2005; Vermorken 2007) and locoregional recurrence (Olasz 2000). It was not possible to extract data in a form suitable to include in these analyses from Vokes 1990.

Risk of bias

None of the trials in this comparison include blinding of patients, carers or outcome assessors. Five trials describe adequate sequence generation and allocation concealment methods, with no additional risks in the other domains assessed and can be considered at low risk of bias for objective outcomes of total mortality (Buffoli 1992; HNCProg 1987; Rischin 2005; Rischin 2010; UKHAN 2010), with an increased risk of bias for the more subjective outcomes. The remaining 23 trials are assessed as being at unclear risk of bias due to insufficient information available for assessment in one or more domains risk of bias (Adelstein 1993; Browman 1986; Chauvergne 1988; De Andres 1995; Garden 2004; Gasparini 1993; Gladkov 2007; Gonzalez-Larriba 1997; Gupta 2009; Le 2006; Marechal 1987; Merlano 1991; Molinari 1982; Olasz 2000; Paccagnella 2010; Pinnaro 1994; Posner 2007; Prevost 2005; Rasch 2010; Segura 2002; Szpirglas 1979; Vermorken 2007; Vokes 1990).

Effects of interventions

The treatment regimens being compared vary with regard to the chemotherapeutic agents used, the timing of the chemotherapy relative to radiotherapy and surgery, and the use of subsequent therapy (either further chemotherapy or concomitant chemoradiotherapy) after the initial regimen is completed. This group are described below under five subheadings.

Induction chemotherapy: Regimen A versus Regimen B

The first group of nine trials included in this comparison (Browman 1986; Chauvergne 1988; De Andres 1995; Gonzalez-Larriba 1997; HNCProg 1987; Marechal 1987; Olasz 2000; Segura 2002; Vermorken 2007), randomised patients with inoperable oral cancer to one of two different regimens of chemotherapy administered as first line (induction) therapy, and all except HNCProg 1987 and Olasz 2000 provided data to estimate the hazard ratios for total mortality.

Four of these trials compared cisplatin followed by 5-FU as a 120 hour continuous infusion (PF), with the following:

- cisplatin and UFT (oral formulation of tegafur and uracil) (Gonzalez-Larriba 1997)
- carboplatin and 5-FU (De Andres 1995)
- cisplatin and vinorelbine (Segura 2002)
- cisplatin and 5-FU and docetaxel (TPF regimen) - in Vermorken 2007 (TAX 323 study).

Cisplatin alone was compared with either cisplatin plus etoposide (Marechal 1987) or cisplatin/methotrexate/bleomycin/vincristine combination (Chauvergne 1988). Browman 1986 compared methotrexate and 5-FU given simultaneously to the same drugs given sequentially. In the HNCProg 1987 induction chemotherapy with cisplatin plus bleomycin was compared with the same induction chemotherapy regimen plus adjuvant cisplatin as subsequent chemotherapy, and the main outcome reported was disease free survival. Vermorken 2007 in the TAX 323 study compared cisplatin and 5-FU (PF) with cisplatin plus docetaxel plus 5-FU (TPF).

In six of these trials patients went on to receive radiotherapy, and in two studies (Browman 1986; Chauvergne 1988) there was no mention of planned subsequent radiotherapy, but this may have taken place, outside of the clinical trial, as part of usual clinical practice in these centres.

A further small study in Hungary randomised patients to induction chemotherapy with either bleomycin, vincristine, cisplatin and methotrexate or bleomycin, vincristine and methotrexate (Olasz 2000). Three weeks after the end of chemotherapy patients had surgery for lymph node excision. After 2 years follow-up the locoregional recurrence rate was significantly lower in the BVCM group (RR 0.50, 95% CI 0.26 to 0.96) (Analysis 4.8) and there was no difference in total mortality (RR 0.58, 95% CI 0.30 to 1.15) (Analysis 4.5).

The TAX 323 trial (Vermorken 2007) was the only trial to find a statistically significant difference in total mortality between the induction regimens compared. There was a reduction in total mortality favouring the TPF regimen used as induction (HR 0.73, 95% CI 0.57 to 0.95) (Analysis 4.1, Comparison 4.1.7) and also an increase in progression free survival (HR 0.72, 95% CI 0.57 to 0.91) (Analysis 4.3, Comparison 4.3.2).

There was no difference between the regimens compared with regard to the outcome of disease free survival (reported by one trial (HNCProg 1987) (Analysis 4.2)). None of these nine trials reported data on disease free survival at 5 years or the hazard ratio for locoregional control.

Disease free survival after 5 years follow-up in the trial by De Andres 1995 showed a statistically significant benefit in favour of cisplatin/5-FU (HR 0.51, 95% CI 0.28 to 0.92) (Analysis 4.6).

Induction chemotherapy followed by sequential chemoradiotherapy

Two trials compared different agents used in induction chemotherapy followed by concomitant chemoradiotherapy (Le 2006; Posner 2007).

Le 2006 randomly allocated 62 patients to either two cycles of cisplatin plus 5-FU, followed by concomitant chemoradiotherapy with cisplatin, 5-FU and radiotherapy 5 times per week or two cycles of cisplatin, 5-FU and tirapazamine followed by concomitant chemoradiotherapy. Posner 2007, in the TAX 324 trial, a much larger study of 501 patients, compared three cycles of induction chemotherapy with cisplatin/FU followed by concomitant chemoradiotherapy (weekly carboplatin and radiotherapy 5 tiimes weekly for 7 weeks), with a different induction regimen, cisplatin, docetaxel and 5-FU (TPF) also followed by the same concomitant chemoradiotherapy with weekly carboplatin.

There was no difference between the two groups in Le 2006, but the TAX 324 trial (Posner 2007) found that the group who received cisplatin/5-FU/docetaxel showed a statistically significant reduction in total mortality (HR 0.70, 95% CI 0.54 to 0.90, Analysis 4.1) and increase in progression free survival (HR 0.71, 95% CI 0.56 to 0.90, Analysis 4.3) compared to the cisplatin/5-FU (PF) group.

Concomitant chemoradiotherapy: Regimen A versus Regimen B

Concomitant chemoradiotherapy regimens were compared in seven randomised controlled trials (Garden 2004; Gasparini 1993; Gladkov 2007; Rasch 2010; Rischin 2005; Rischin 2010; UKHAN 2010). Data were presented with regard to the outcomes of total mortality (Garden 2004; Gasparini 1993; Rasch 2010; Rischin 2005; Rischin 2010; UKHAN 2010), disease free survival (Gasparini 1993; Rasch 2010; Rischin 2005; Rischin 2010), progression free survival (UKHAN 2010) and locoregional control (Gladkov 2007; Rasch 2010; Rischin 2005; Rischin 2010).

Gasparini 1993 compared two concomitant chemoradiotherapy regimens in 63 patients who received three cycles of chemotherapy starting on days 1, 21 and 42 of radiotherapy. One group received cisplatin and the other carboplatin. This trial showed no difference between the two regimens in either total mortality (Analysis 4.1) or disease free survival (Analysis 4.2) and commented that there were differences in the spectra of toxicities associated with the two regimens, but a similar severity.

Garden 2004 randomised 242 patients to one of three chemoradiotherapy regimens; either radiotherapy with weekly concomi-

tant cisplatin plus FU for 7 weeks, radiotherapy with concomitant hydroxyurea plus FU every alternate week for 13 weeks, or radiotherapy with concomitant cisplatin plus paclitaxel weekly for 7 weeks. There was no statistically significant difference between any of the regimens with regard to total mortality (Comparisons 4.1.13 to 4.1.15 in Analysis 4.1).

In a small trial Gladkov 2007 compared different frequency of concomitant chemoradiotherapy. All 64 patients received daily radiotherapy, 2 Gy 5 times a week together with either daily cisplatin (n = 22), weekly cisplatin (n = 26) or cisplatin once every 3 weeks (n = 12). No statistically significant difference between any of the groups was found with regard to locoregional control (Analysis 4.7).

Rasch 2010 compared intra-arterial chemoradiotherapy with intravenous chemoradiotherapy in 239 patients with unresectable tumours. Patients randomised to the intra-arterial group had arteriography prior to the start of treatment to determine whether intra-arterial chemotherapy was feasible. Ten patients in the intra-arterial group for whom intra-arterial chemotherapy was not feasible were treated according to the intravenous protocol. After a median follow-up of 33 months this study found no difference between the groups with regard to the primary outcome locoregional control (Analysis 4.4), or total mortality (Analysis 4.1), or disease free survival (Analysis 4.2).

Rischin 2005 reported a trial of 122 patients randomly allocated to chemoradiotherapy with either concomitant cisplatin and FU (chemoboost), or cisplatin and tirapazamine (TPZ). There was no statistically significant difference between the two regimens with regard to total mortality (Analysis 4.1), disease free survival (Analysis 4.2) and locoregional control (Analysis 4.4).

Rischin 2010, in a large a large international trial of 861 patients with low risk of bias, compared concomitant chemoradiotherapy with cisplatin plus tirapazamine to concomitant chemoradiotherapy with cisplatin alone and found no difference between the two arms with regard to total mortality (Analysis 4.1), disease free survival (Analysis 4.2) or locoregional control (Analysis 4.4).

The UKHAN 2010 trial used a factorial design for a total of 966 patients, 253 who had undergone surgery and a further 713 untreated patients whose tumours were considered unresectable. Non-surgical patients were randomised to either radiotherapy alone or one of three chemoradiotherapy regimens: concomitant chemoradiotherapy (SIM), radiotherapy followed by chemotherapy (SUB) or concomitant chemoradiotherapy followed by chemotherapy (BOTH); post-operative patients were randomised to either concomitant chemoradiotherapy (SIM) or radiotherapy alone.

UKHAN is a multicentre trial (34 centres) and each participating centre nominated one, or both of two chemotherapy protocols, either single agent methotrexate (24 centres, 433 randomised to this treatment, 417 received treatment), or a multiagent combination of vincristine, bleomycin, methotrexate and fluorouracil (12 centres, 165 randomised to this treatment and 153 received treatment). In comparing the three chemoradiotherapy regimens against each other, data from both the single and multiagent chemotherapy regimens are combined, to give an overall comparison of concomitant chemoradiotherapy, chemotherapy with subsequent radiotherapy and both concomitant and subsequent chemoradiotherapy. UKHAN 2010 found the concomitant regimens showed a statistically significant reduction in total mortality compared to radiotherapy followed by chemotherapy (SUB regimen) (Comparison 4.1.17), and a larger benefit in favour of concomitant chemoradiotherapy on progression free survival (Comparison 4.3.4), compared to the radiotherapy followed by chemotherapy (SUB) regimens.

Induction chemotherapy followed by radiotherapy versus concomitant chemoradiotherapy

Two trials (Adelstein 1993; Pinnaro 1994) compared a regimen of chemotherapy followed by radiotherapy, with a concomitant chemoradiotherapy regimen in previously untreated patients. Adelstein 1993 (data for total mortality from Pignon 2000) compared three cycles of induction cisplatin and 5-FU, then surgery followed by 7 weeks of radiotherapy 5 times per week for 7 weeks, with a cycle of the same chemotherapy regimen given concomitantly with 3 weeks of radiotherapy, 5 times per week, followed by a second chemotherapy cycle starting 5-7 weeks after the first cycle followed by surgery. Pinnaro 1994 randomly allocated patients to three cycles of cisplatin/5-FU induction chemotherapy followed by up to 7 weeks of radiotherapy, (5 times per week) or cisplatin once every 3 weeks during a 7-week course of radiotherapy. Broadly these two trials compare induction chemotherapy with concomitant chemoradiotherapy and although neither show a statistically significant difference in total mortality, when estimates from them are pooled there is a reduction in total mortality favouring induction chemotherapy (HR 0.68, 95% CI 0.47 to 0.97). (Data not shown.)

Gupta 2009 compared induction chemotherapy with cisplatin + 5-FU (PF regimen) followed by concomitant chemoradiotherapy (weekly low dose cisplatin) with concomitant chemoradiotherapy alone in patients with oropharyngeal cancer. Paccagnella 2010 compared induction chemotherapy with cisplatin +5-FU + docetaxel (TPF regimen) followed by chemoradiotherapy (cisplatin + 5-FU in weeks 1 and 6 of radiotherapy) with chemoradiotherapy alone. Pooling the data from these two trials which broadly compare induction chemotherapy plus chemoradiotherapy with chemoradiotherapy alone shows no difference with regard to total mortality (HR 0.66, 95% CI 0.35 to 1.24). (Data not shown.)

None of these four trials showed any statistically significant difference between the regimens compared. All four trials presented data for total mortality (Analysis 4.1), one (Gupta 2009) for disease free survival (no difference between groups) and three trials reported progression free survival (Adelstein 1993; Paccagnella 2010; Pinnaro 1994) but showed no statistically significant differ-

ence between the regimens compared (Analysis 4.3, Comparisons 4.3.7 to 4.3.9).

The next two trials compared induction chemotherapy followed by radiotherapy with an alternating chemoradiotherapy regimen. Merlano 1991 compared chemotherapy with bleomycin, methotrexate, vinblastine and leucovorin, followed by 7 weeks of radiotherapy 5 times per week, with a regimen that alternated chemotherapy and radiotherapy. Buffoli 1992, in a similar approach, compared four cycles of induction chemotherapy with bleomycin, methotrexate and hydroxyurea, followed by a total of 60 Gy of radiotherapy, with a regimen whereby patients had 20 Gy radiotherapy, then four cycles of chemotherapy over 4 weeks, followed by the remaining 40 Gy of radiotherapy.

Merlano 1991 found a statistically significant difference in total mortality between the two treatments in favour of alternating chemoradiotherapy (Analysis 4.1 comparison 4.1.24), but no difference in the dichotomous outcome of tumour response at the end of treatment (Analysis 4.7 comparison 4.7.1). Buffoli 1992 reported 5-year disease free survival, and locoregional control at the end of treatment and found no difference between the sequential and alternating chemoradiotherapy regimens (Analysis 4.6). Total mortality was reported in this trial but data were not presented according to the intervention patients received.

Comparisons between other chemotherapy regimens

There are three other trials included in this comparison although none of these contributed total mortality data to the analyses.

Vokes 1990 described a small trial of 29 patients, 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 and 5-FU. After induction chemotherapy locoregional therapy was planned but 32% of Arm A and 15% of Arm B did not receive LRT 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 patients were randomised, the study was stopped early. There were changes to the planned treatment protocol in the small number of patients included make it difficult to draw valid conclusions from this trial.

Prevost 2005 is a trial of 197 patients who were allocated to induction chemotherapy with either cisplatin plus 5-FU or cisplatin and etoposide, to be followed by radiotherapy. Data are given for tumour response, although it is not clear as to the timing of this evaluation (likely to be at the completion of chemotherapy). There is a 48% increase in tumour response in the cisplatin etoposide group (RR 1.48, 95%CI 1.04 to 2.11) (Analysis 4.7) which is statistically significant. The paper states that there was no difference in survival between the two groups.

Molinari 1982 randomised 85 patients to either 500 mg methotrexate as intra-arterial infusion over 10 days or 95 mg of bleomycin as intra-arterial infusion over 13 days. Patients were evaluated for tumour response 10-15 days after the end of treatment and greater than 50% tumour regression was found in 21% of the patients in the methotrexate group and 60% of the bleomycin group, a statistically significant difference favouring bleomycin (RR 0.35, 95% CI 0.19 to 0.66) (Analysis 4.7). However, the trial did not look at any longer term outcomes such as total mortality.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Surgery +/- RT + chemotherapy compared to surgery +/- RT alone for oral cavity and oropharyngeal cancer

Patient or population: patients with oral cavity and oropharyngeal cancer
Settings: hospital
Intervention: surgery +/- RT + chemotherapy
Comparison: surgery +/- RT alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	surgery +/- RT alone	surgery +/- RT + chemotherapy				
Total Mortality Hazard Ratio Follow-up: 3-8 years	**Low risk population**[1]		**HR 0.88** (0.79 to 0.99)	2017 (10 studies)	⊕⊕◯◯ **low**[2,3]	
	200 per 1000	**178 per 1000** (162 to 198)				
	Medium risk population[1]					
	500 per 1000	**457 per 1000** (422 to 497)				
	High risk population[1]					
	700 per 1000	**653 per 1000** (614 to 696)				
Total Mortality Follow-up: 3-8 years	**Low risk population**[1]		**HR 0.88** (0.74 to 1.05)[4]	758 (4 studies)	⊕⊕⊕◯ **moderate**[3]	
	200 per 1000	**178 per 1000** (152 to 209)				

	Medium risk population[1]	
	500 per 1000	**457 per 1000** (401 to 517)
	High risk population[1]	
	700 per 1000	**653 per 1000** (590 to 718)

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

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

[1] Based on 5-year mortality data in McGurk 2005
[2] Four studies are at low risk of bias and 6 are at unclear risk of bias
[3] Studies included patients with other head and neck cancers
[4] Analysis conducted on included studies at low risk of bias

Concomitant chemoradiotherapy compared to radiotherapy alone for oral cavity and oropharyngeal cancer

Patient or population: patients with oral cavity and oropharyngeal cancer
Settings: hospital
Intervention: concomitant chemoradiotherapy
Comparison: radiotherapy alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	radiotherapy alone	concomitant chemoradiotherapy				
Total Mortality Hazard Ratio Follow-up: 3-8 years	**Low risk population**[1]		**HR 0.78** (0.73 to 0.83)[2]	4734 (26 studies)	⊕⊕◯◯ **low**[3,4]	
	200 per 1000	**160 per 1000** (150 to 169)				
	Medium risk population[1]					
	500 per 1000	**418 per 1000** (397 to 437)				
	High risk population[1]					
	700 per 1000	**609 per 1000** (585 to 632)				
Total Mortality Hazard Ratio Follow-up: 3-8 years	**Low risk population**[1]		**HR 0.87** (0.79 to 0.95)[5]	2266 (9 studies)	⊕⊕⊕◯ **moderate**[4]	
	200 per 1000	**176 per 1000** (162 to 191)				
	Medium risk population[1]					

	500 per 1000	**453 per 1000** (422 to 482)
	High risk population[1]	
	700 per 1000	**649 per 1000** (614 to 681)

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

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

[1] Based on 5-year mortality data in McGurk 2005
[2] Analysis based on all included studies
[3] Nine trials are at low risk of bias, and remaining 17 at unclear risk of bias
[4] Trials include patients with other head and neck cancers
[5] Analysis based on included studies at low risk of bias

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 are evaluated in the 89 randomised controlled trials included in this systematic review. Only 21 of the included studies can be considered at low risk of bias with regard to the outcome of total mortality. A total of 16,767 patients were randomly allocated to treatments in trials where at least 50% of the patients with head and neck cancers had primary tumours in either the oral cavity or oropharynx.

We have divided the included trials into four major comparisons, according to the type of regimens, and stage of disease of the participants. Our primary outcome is total mortality as measured by hazard ratio for mortality. A reduction in the hazard ratio for mortality can be interpreted as an improvement in overall survival.

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

The first comparison concerned the addition of induction chemotherapy to locoregional treatment (either radiotherapy or surgery or both) 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-FU, either as single agents, or more commonly as combinations of two or more agents. The pooled estimate from seven trials of induction chemotherapy with a regimen including either cisplatin or carboplatin plus 5-FU showed no evidence of a difference in overall survival between the induction chemotherapy arm and locoregional treatment alone. Likewise four trials of methotrexate alone showed no evidence of a difference in overall survival between those who had induction chemotherapy and those who had locoregional treatment alone. However the two trials of induction therapy with bleomycin plus vincristine did show evidence of improvement in overall survival (hazard ratio (HR) 0.67, 95% confidence interval (CI) 0.50 to 0.91, P = 0.01). Overall, meta-analysis of 25 trials of induction chemotherapy plus locoregional treatment versus locoregional treatment alone showed some evidence of a small improvement in overall survival (HR 0.92, 95% CI 0.84 to 1.00, P = 0.06). A sensitivity analysis based on pooling data from the four studies assessed as being at low risk of bias for this outcome showed HR 0.80, 95% CI 0.67 to 0.97, P = 0.02, which suggests that induction therapy may be associated with a benefit (up to 20%) for overall survival.

Comparison 2: Surgery ± radiotherapy + chemotherapy versus surgery ± radiotherapy alone

There were 11 trials in this comparison, involving a range of chemotherapeutic agents, with most regimens including either methotrexate or a platin (either cisplatin or carboplatin). Overall, in the 10 trials that reported total mortality, there was some evidence of a benefit in overall survival associated with the addition of chemotherapy to radiotherapy after surgery (HR 0.88, 95% CI 0.79 to 0.99, P = 0.03). Sensitivity analysis based on four of these studies assessed as being at low risk of bias, showed the same point estimate (HR 0.88, 95% CI 0.74 to 1.05, P = 0.16) confirming the size of the benefit, but indicating reduced precision.

However it appears that timing of post-operative chemotherapy, relative to post-operative radiotherapy, may be important. In the four trials that evaluated concomitant chemoradiotherapy after surgery there was evidence of a benefit in overall survival in favour of concomitant chemoradiotherapy after surgery compared to radiotherapy alone (HR 0.84, 95% CI 0.72 to 0.98, P = 0.03).

Comparison 3: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)

Of the 29 trials included in this comparison two evaluated a combination of induction and concomitant chemotherapy, 26 evaluated concomitant chemoradiotherapy and a further two evaluated alternating chemotherapy and radiotherapy regimens.

The induction plus concomitant trials used different agents and regimens and neither found a statistically significant benefit associated with chemotherapy over radiotherapy alone. These trials combined included less than 200 patients and had an unclear risk of bias.

The two trials of alternating chemoradiotherapy were both assessed as being at low risk of bias and both used cisplatin/5-FU, but used different radiotherapy alone regimens as controls. The pooled estimate shows evidence of a reduction in total mortality favouring the alternating regimens (HR 0.69, 95% CI 0.53 to 0.90, P = 0.006)

The remaining 26 trials in this comparison evaluated concomitant chemoradiotherapy regimens compared to radiotherapy alone, and 24 provided data for calculation of a hazard ratio for total mortality. More than half of the trials used a chemotherapy regimen which included either cisplatin or carboplatin. From these 24 trials, there is evidence of a reduction of total mortality (improvement in overall survival) in the order of 20% (HR 0.79, 95% CI 0.74 to 0.84, P < 0.00001). Senstivity analysis based on the 7 studies at low risk of bias confirmed this finding (HR 0.90, 95% CI 0.81 to 0.99, P = 0.03) albeit with a reduced magnitude of effect (10% benefit).

Pooling data from 26 trials of either alternating or concomitant chemoradiotherapy showed a benefit in overall survival favouring chemoradiotherapy (HR 0.78, 95% CI 0.73 to 0.83, P < 0.00001). Sensitivity analysis based on the 9 studies at low risk of bias con-

firmed this finding (HR 0.87, 95% CI 0.79 to 0.95, P = 0.003) suggesting that concomitant or alternating chemoradiotherapy is associated with a benefit in overall survival of 10 to 22%.

Summary of results for Comparisons 1-3 (Induction chemotherapy, adjuvant chemotherapy and concomitant chemoradiotherapy)

Timing of chemotherapy regimen	No of trials	Total mortality (HR for death)	P value
Induction chemotherapy	25	HR 0.92, (95% CI 0.84 to 1.00)	P = 0.06
Adjuvant chemotherapy	10	HR 0.88, (95% CI 0.79 to 0.99)	P = 0.03
Concomitant chemoradiotherapy or alternating chemoradiotherapy	26	HR 0.78, (95% CI 0.73 to 0.83)	P < 0.00001

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

Comparison four included 28 trials which directly compared different chemotherapeutic agents, different regimens, and different timing relative to locoregional treatment. The analyses show that many of the regimens compared showed no statistically significant differences in the outcomes evaluated. Those that showed a statistically significant difference between the regimens compared are summarised below.

In a large trial with direct comparisons (UKHAN 2010) concomitant chemoradiotherapy resulted in improved overall survival compared to either radiotherapy alone, radiotherapy followed by chemotherapy or concomitant chemoradiotherapy followed by chemotherapy, in patients who had not undergone surgery. However, in the post-operative group (adjuvant setting) there was no difference in mortality between concomitant chemoradiotherapy and radiotherapy alone in this trial.

Docetaxel was the new chemotherapy agent added to the commonly used cisplatin/5-FU (PF) regimen in both the TAX 324 and TAX 323 trials (Posner 2007; Vermorken 2007) in the induction setting. Both these trials showed a statistically significant increase in overall survival (43% and 36% respectively) associated with the TPF regimen (docetaxel/cisplatin/5-FU). Vermorken 2007 (n = 358) compared induction chemotherapy with TPF to PF followed by radiotherapy, whereas Posner 2007 (n = 539) compared TPF induction with PF induction and then followed both arms with chemoradiotherapy using carboplatin. Following these results, the trial by Paccagnella 2010 (n = 101) compared TPF induction regimen followed by cisplatin/5-FU (PF) chemoradiotherapy versus PF concomitant chemoradiotherapy alone, and found no statistically significant difference in total mortality or progression free survival associated with the addition of induction chemotherapy. It may be that Paccagnella 2010 lacked power to detect a difference as this trial included fewer participants compared to TAX 323 or TAX 324, or perhaps the delay in the start of concomitant chemoradiotherapy associated with the prior induction chemotherapy regimen is the reason for the poorer outcome. All three of these trials included a similar proportion of oral cavity and oropharyngeal cancer patients (64% to 70%). There is not clear evidence as to which regimen of chemotherapy is the most effective.

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 randomised controlled trials concerning harms associated with treatment, and almost all data were in a form unsuitable for analysis. Toxicities and adverse events were often reported as numbers of events rather than numbers of patients with adverse events, and there was considerable variation in the way harms were reported (e.g. all adverse events, moderate to severe adverse events, those

requiring treatment interruption/cessation, causes of death).
We have therefore reluctantly modified the original protocol for this systematic review and have reported only the benefits associated with chemotherapy, in terms of survival and response to treatment. However we acknowledge that the addition of chemotherapy to radiotherapy and/or surgery is 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 other issue that we have encountered in this systematic review is that the majority of the research trials have specified squamous cell carcinoma of the head and neck in the inclusion criteria. Only 11 of the included trials specifically recruited participants with oral cavity cancer only and a further five included only those with oropharyngeal cancer. The authors of three trials provide us with separate data (*see* Additional Table 2 for details). In the remaining 68 trials included in this systematic review at least 50% of participants had either oral cavity or oropharyngeal cancer. We have included these trials because we believe that they contribute important information concerning the effectiveness of chemotherapy in oral cavity and oropharyngeal cancers, in the absence of separate data in the research literature. However, we acknowledge that trials on the two specific cancer sites, or combined trials where the data are reported separately by primary tumour site, would yield much better information to guide clinical practice in these two conditions which have imported differences in aetiology, presentation and management. We look forward to trials on oral cavity or oropharyngeal cancer alone being available for inclusion in future updates of this review.

Quality of the evidence

Only three of the trials included in this systematic review used blinding of either the participants (Browman 1994) or the outcome assessors (Richard 1974; Shanta 1980). It is recognised 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. It is likely that many outcome assessments are performed by the clinicians treating the patients. However blinded outcome assessment would be a pragmatic step to reduce the risk of bias for the more subjective outcomes.
For objective outcomes such as total mortality, trials assessed as adequate with regard to the domains of sequence generation, allocation concealment, complete outcome data and absence of selective reporting, have been assessed as being at low risk of bias. Only 21 of the 89 included studies (24%) meet these criteria, and can be considered at low risk of bias. The more recent trials are more likely to have low risk of bias.

Agreements and disagreements with other studies or reviews

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, and found a statistically significant benefit in favour of concomitant chemoradiotherapy. Pignon 2009 calculated an overall hazard ratio for death and showed that the addition of chemotherapy to locoregional therapies was associated with an absolute benefit of 4.5% at 5 years. A significant interaction between timing of chemotherapy and treatment was noted. We have not calculated an overall estimate in this way. Our inclusion criteria specified that at least 50% of the participants in included trials in this systematic review had a primary tumour of the oral cavity or oropharynx and we assessed risk of bias for each of the included trials. The overall findings of this Cochrane systematic review that

- induction chemotherapy was not associated with a statistically significant improvement in overall survival compared to locoregional treatment alone;
- post-surgery adjuvant chemotherapy improved overall survival compared to surgery ± radiotherapy alone, and there was an additional benefit of adjuvant concomitant chemoradiotherapy compared to sequential chemotherapy and radiotherapy;
- concomitant chemoradiotherapy was associated with a statistically significant improvement overall survival compared to radiotherapy alone in patients whose tumours were considered unresectable;
- in direct comparisons
    - the addition of docetaxel to the frequently used chemotherapy regimen of cisplatin and 5-FU may be associated with a decrease in mortality,
    - concomitant chemoradiotherapy reduces mortality compared to the same regimen given prior to radiotherapy

support the conclusions reached in the MACH-NC meta-analysis Pignon 2009, and a recent review of series of trials of taxanes (either docetaxel or paclitaxel) being added to chemotherapy regimens for treatment of head and neck cancers (Specenier 2007). It is possible that the observed improvement in survival in oropharyngeal cancer over time may partly be explained by an increasing proportion of HPV-related oropharyngeal cancer, rather than purely explained by improvement in treatments (Licitra 2006).

AUTHORS' CONCLUSIONS

Implications for practice

There is some evidence that induction chemotherapy results in a small increase in overall survival compared to locoregional treatment alone, which is confirmed by a sensitivity analysis of trials at low risk of bias. There is evidence that adjuvant chemoradiotherapy, and specifically concomitant adjuvant chemotherapy, improves overall survival compared to these treatments given sequentially. In patients with unresectable tumours, there is evidence that concomitant chemoradiotherapy is associated with an improvement in overall survival of between 10 and 22%. The additional toxicity associated with the combined regimens remains unquantified. While the addition of docetaxel to cisplatin and 5-FU during induction chemotherapy appears to improve overall survival further, it remains unclear whether the combination of induction chemotherapy (with or without docetaxel) plus concomitant chemoradiotherapy improves overall survival.

Implications for research

Further research on the use of other taxanes, such as paclitaxel, in addition to the standard regimen of cisplatin/5-FU is currently underway in patients with advanced head and neck cancers. Trials of chemotherapy regimens in single cancer sites are desirable to identify differences in response between oral cavity and oropharyngeal tumours. This will require multicentre collaborations in order to conduct trials of sufficient size and statistical power. Research to identify the high risk subgroups most likely to benefit from post-operative concomitant chemoradiotherapy is desirable because these regimens are associated with substantial toxicities.

Given the substantial toxicities associated with chemotherapy it would also be desirable for future trials to report toxicities per patient treated, rather than summarising the most common toxicities experienced. This would enable patients and their doctors to better estimate the benefits and harms of treatment so that individuals could make more informed treatment plans.

ACKNOWLEDGEMENTS

We would like to acknowledge the work of the CSROC (Cochrane Systematic Reviews in Oral Cancer) Expert Panel who played a substantial role in the design of the original protocols for this series of reviews and provided comments and advice on the early drafts. The CSROC Expert Panel comprised Bertrand Baujat, Gerry Humphris, Iain Hutchison, Jean-Pierre Pignon, Gerry Robertson, Simon Rogers, Jatin Shah, Nick Slevin, Phil Sloan, David Soutar, Erich Sturgis, Jan Vermorken, Steve Wardell, Saman Warnakulasuriya and Keith Webster.

Thanks to:

- May Wong for her statistical input during data extraction
- Emma Tavender for her contribution to the drafting of the original protocol for this review, and helping to secure funding for the review
- Sylvia Bickley and Anne Littlewood - Cochrane Oral Health Group, Trials Search Co-ordinators
- Phil Riley - retrieval of papers
- Brian Bonner - input into risk of bias assessments
- Chris O'Brien for his contribution to the CSROC Expert Panel.

Thanks to the following for their translation of published papers into English:

- Toru Naito - translated Tsukuda 1994, Yoshino 1991 and Yoshino 1994 from Japanese
- Anette Bluemle - translated Muncker 2000, Von Heyden 1982, Von Heyden 1984, Von Heyden 1984, and Bitter 1979 from German
- J-H Vergnes translated Haddad 1996 from French
- Prof V Vlassov and Dr Oleg Borisenko translated Gladkov 2007 from Russian
- Daniel Bereczki translated Olasz 2000 from Hungarian
- Luisa Fernandez-Mauleffinch translated Giglio 1997 and Segura 2002 from Spanish
- Dr Nicoletta Bobola translated Buffoli 1992 from Italian.

REFERENCES

References to studies included in this review

Adelstein 1993 *{published data only}*

* Adelstein DJ, Sharan VM, Earle AS, et al.Long-term follow-up of a prospective randomized trial comparing simultaneous and sequential chemoradiotherapy for squamous cell head and neck cancer. In: Salmon SE editor (s). *Adjuvant Therapy of Cancer*. Vol. **vii**, Philadelphia: Lippincott Company, 1993:82–91.

Adelstein DJ, Sharan VM, Earle AS, Shah AC, Vlastou C, Haria CD, et al.Simultaneous versus sequential combined technique therapy for squamous cell head and neck cancer. Cancer 1990; Vol. 65, issue 8:1685–91.

Adelstein 2003 *{published data only}*

Adelstein DJ, Li Y, Adams GL, Wagner H Jr, Kish JA, Ensley JF, et al.An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *Journal of Clinical Oncology* 2003;**21**(1):92–8.

Argiris 2008 *{published data only}*

* Argiris A, Karamouzis MV, Johnson JT, Heron DE, Myers E, Eibling D, et al.Long-term results of a phase III randomized trial of postoperative radiotherapy with or without carboplatin in patients with high-risk head and neck cancer. Laryngoscope 2008; Vol. 118, issue 3:444–9.

Johnson JT, Agarwala SS, Karamouzis MV, Heron DE, Eibling DE, Cano E, et al.Phase III randomized trial of postoperative radiotherapy (RT) with or without carboplatin (Cb) in patients (pts) with head and neck squamous cell carcinoma (HNSCC). Journal of Clinical Oncology 2007; Vol. 25, issue 18S.

Bensadoun 2006 *{published data only}*

* Bensadoun RJ, Benezery K, Dassonville O, Magne N, Poissonnet G, Ramaioli A, et al.French multicenter phase III randomized study testing concurrent twice-a-day radiotherapy and cisplatin/5-fluorouracil chemotherapy (BiRCF) in unresectable pharyngeal carcinoma: Results at 2 years (FNCLCC-GORTEC). International Journal of Radiation Oncology, Biology, Physics 2006; Vol. 64, issue 4:983–94.

Bensadoun RJ, Dassonville O, Ramaioli A, Magne N, Benezery K, Marcy P, et al.Phase III multicenter randomized study of concurrent twice-a-day radiotherapy with and without cisplatin (BiRCF) in unresectable pharyngeal carcinoma. Results at 18 months (FNCLCC-GORTEC): 5504. *Journal of Clinical Oncology* 2004;**22 Suppl 14**:489S.

Bernier 2004 *{published data only}*

* Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefebvre JL, Greiner RH, et al.Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *New England Journal of Medicine* 2004;**350**(19):1945–52.

Bernier J, Ozsahin M, Greiner R, Glanzmann C, van Glabbeke M, Kirkpatrick A. Results of EORTC phase III trial 22931 comparing, in post-operative setting, radiotherapy (RT) and radiotherapy combined to cisplatin (RT-CT) in locally advanced head and neck (H&N) squamous cell carcinomas (SCC). Strahlentherapie Und Onkologie 2002; Vol. 178:116.

Bernier J, van Glabbeke M, Domenge C, Wibault P, Ozsahin M, et al.Results of EORTC phase III trial 22931 comparing postoperatively , radiotherapy (RT) to concurrent chemo-radiotherapy (RT-CT) with high dose cisplatin in locally advanced head and neck (H&N) carcinomas (SCC). *European Journal of Cancer* 2001;**37 Suppl 6**:S267.

Bitter 1979 *{published data only}*

* Bitter K. Comparison of a post-operative chemotherapy with post-operative Co-60 radiotherapy in patients with advanced oral cavity carcinomas. Report of a randomised study. *Deutsche Zeitschrift fur Mund, Kiefer und Gesichtschirurgie* 1979;**3**:55S–58S.

Bitter K. Postoperative chemotherapy versus postoperative cobalt 60 radiation in patients with advanced oral carcinoma. Report on a randomized study. *Head and Neck Surgery* 1981;**3**:264.

Brizel 1998 *{published data only}*

* Brizel DM, Albers ME, Fisher SR, Scher RL, Richtsmeier WJ, Hars V, et al.Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. *New England Journal of Medicine* 1998; **338**(25):1798–804.

Kasibhatla M, Prosnitz LR, Fisher SR, Scher RL, Clough R, Brizel DM. Hyperfractionated radiotherapy versus hyperfractionated radiotherapy and concomitant chemotherapy in locally advanced head and neck cancer. International Journal of Radiation Oncology, Biology, Physics 2007; Vol. 69, issue 3 Suppl 1:S11–2.

Browman 1986 *{published data only}*

Browman GP, Levine MN, Russell R, Young JE, Archibald SD. Survival results from a phase III study of simultaneous versus 1-hour sequential methotrexate-5-fluorouracil chemotherapy in head and neck cancer. *Head & Neck Surgery* 1986;**8**(3):146–52.

Browman 1994 *{published data only}*

* Browman GP, Cripps C, Hodson DI, Eapen L, Sathya J, Levine MN. Placebo-controlled randomized trial of infusional fluorouracil during standard radiotherapy in locally advanced head and neck cancer. *Journal of Clinical Oncology* 1994;**12**(12):2648–53.

Browman GP, Levine MN, Hodson DI, Sathya J, Russell R, Skingley P, et al.The Head and Neck Radiotherapy Questionnaire: a morbidity/quality-of-life instrument for clinical trials of radiation therapy in locally advanced head and neck cancer. *Journal of Clinical Oncology* 1993;**11**(5): 863–72.

Brunin 1989 *{published data only}*

* Brunin F, Rodriguez J, Jaulerry C, Jouve M, Pontvert D, Point D, et al.Induction chemotherapy in advanced head

and neck cancer. Preliminary results of a randomized study. *Acta Oncologica* 1989;**28**(1):61–5.
Brunin F, Rodriguez J, Jaulerry C, Jouve M, Pontvert D, Point D, et al.Induction chemotherapy in advanced head and neck cancer. Preliminary results of a randomized study. Oncologia (Madrid) 1990; Vol. 13, issue 6.
Brunin F, Rodriguez J, Jaulerry C, Mosseri V, Jouve M, Point D, et al.Role of neoadjuvant chemotherapy in the treatment of advanced head and neck tumors. Results of two randomized therapeutical trials conducted at the Institut Curie on 208 patients. *Bulletin du Cancer* 1992;**79**(9):893–904.

Budach 2005 ***{published data only}***
Budach V, Geismar D, Lammert I, Stuschke M, et al.Accelerated hyperfractionated radiation therapy to 70.6 Gy plus 5-FU/MMC (c-HART) is more effective than HART to 77.6 Gy alone for locally advanced head and neck cancer. Four year results of the German ARO 95-6 trial in 384 patients. Proceedings of the 45th annual ASTRO meeting (Abstract 49). 2003.
* Budach V, Stuschke M, Budach W, Baumann M, Geismar D, Grabenbauer G, et al.Hyperfractionated accelerated chemoradiation with concurrent fluorouracil-mitomycin is more effective than dose-escalated hyperfractionated accelerated radiation therapy alone in locally advanced head and neck cancer: final results of the radiotherapy cooperative clinical trials group of the German Cancer Society 95-06 Prospective Randomized Trial. Journal of Clinical Oncology 2005; Vol. 23, issue 6:1125–35.
Budach VGF, Poettgen C, Baumann M, Budach W, et al.Mitomycin-C and 5-fluoro-uracil containing chemotherapy with concurrent hyperfractionated accelerated radiotherapy (C-HART) of 70.6 Gy is more effective than dose escalated HART of 77.6 Gy alone - 10 year results of the German multi centre phase III randomised trial (ARO 95-06). *International Journal of Radiation Oncology Biology Physics* 2007;**69**(3):S11.

Buffoli 1992 ***{published data only}***
Buffoli A, Morrica B, Frata P, La FB. Chemo-radiotherapy in advanced head and neck tumors. Personal experience. Radiologia Medica 1992; Vol. 83, issue 5:636–40.

Chauhan 2008 ***{published data only}***
Chauhan A, Singh H, Sharma T, Manocha KK. Gemcitabine concurrent with radiation therapy for locally advanced head and neck carcinomas. African Health Sciences 2008; Vol. 8, issue 3:149–55.

Chauvergne 1988 ***{published data only}***
Chauvergne J, Cappelaere P, Clavel B, David M, Fargeot P, Meeus L, et al.Randomized trial of initial chemotherapy with cisplatin alone or in combination in 241 advanced carcinomas of the upper respiratory and digestive tract. *Annales d Oto-Laryngologie et de Chirurgie Cervico-Faciale* 1988;**105**(8):581–9.
Chauvergne J, Cappelaere P, Fargeot P, Meeus L, Gary-Bobo J, Klein T, et al.A randomized study comparing cisplatin alone or combined in the palliative treatment of carcinoma of the head and neck. Analysis of a series of 209 patients. *Bulletin du Cancer* 1988;**75**(1):9–22.

Cooper 2004 ***{published data only}***
Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al.Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *New England Journal of Medicine* 2004;**350**(19):1937–44.

Corvo 2001 ***{published data only}***
Corvo R, Benasso M, Sanguineti G, Lionetto R, Bacigalupo A, Margarino G, et al.Alternating chemoradiotherapy versus partly accelerated radiotherapy in locally advanced squamous cell carcinoma of the head and neck: results from a phase III randomized trial. *Cancer* 2001;**92**(11):2856–67.

De Andres 1995 ***{published data only}***
De Andres L, Brunet J, Lopez-Pousa A, Burgues J, Vega M, Tabernero JM, et al.Randomized trial of neoadjuvant cisplatin and fluorouracil versus carboplatin and fluorouracil in patients with stage IV-M0 head and neck cancer. *Journal of Clinical oncology* 1995;**13**(6):1493–1500.

Denis 2004 ***{published data only}***
Bourhis J, Calais G, Lapeyre M, Tortochaux J, Alfonsi M, Sire C, et al.Concomitant radiochemotherapy or accelerated radiotherapy: analysis of two randomized trials of the French Head and Neck Cancer Group (GORTEC). *Seminars in Oncology* 2004;**31**(6):822–6.
Calais, G, Alfonsi, M, Bardet, E, et al.Randomised study comparing radiation alone (RT) versus RT with concomitatnt chemotherapy (CT) in stages III and IV oropharynx carcinoma (ARCORO). Preliminary results of the 94.01 study from the French group of radiation oncology for head and cancer (GORTEC). Proceedings of ASCO. 1998; Vol. 17:385a.
Calais G, Alfonsi M, Bardet E, Sire C, Bourgeois C, Bergerot P, et al.Radiation alone (RT) versus RT with concomitant chemotherapy (CT) in stages III and IV oropharynx carcinoma. Results of the 94.01 randomised study from the French group of radiation oncology for head and neck cancer (GORTEC). 'Management.of Head and Neck Tumors: What are the challenges for the third millennium?'. *Acta Otorhinolaryngologica Belgica* 1999;**53**:166.
Calais G, Alfonsi M, Bardet E, Sire C, Germain T, Bergerot C, et al.Radiation alone (RT) versus RT with concomitant chemotherapy (CT) in stages III and IV oropharynx carcinoma. Final results of the 94-01 Gortec Randomized Study. *International Journal of Radiation Oncology, Biology, Physics* 2001;**51**:1–2.
Calais G, Alfonsi M, Bardet E, Sire C, Germain T, Bergerot P, et al.Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. *Journal of the National Cancer Institute* 1999;**91**(24):2081–6.
Calais G, Alfonsi M, Bardet E, Sire C, Germain T, Bergerot P, et al.Stage III and IV cancers of the oropharynx: results of a randomized study of Gortec comparing radiotherapy

alone with concomitant chemotherapy. *Bulletin du Cancer* 2000;**87 Spec No**:48–53.
Calais G, Alfonsi M, et al.Radiation alone (RT) versus RT with concomitant chemotherapy (CT) in stages III and IV oropharynx carcinoma. Results of the 94.01 randomized study from the French Group of Radiation Oncology for Head and Neck Cancer (GORTEC). *Radiotherapy and Oncology* 1998;**48 Suppl 1**:S78.
Denis F, Alfonsi M, Bardet E, Sire C, Germain T, Bergerot P, et al.Late toxicity results of randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced stage oropharynx carcinoma (GORTEC 94-01). International Journal of Radiation Oncology, Biology, Physics 2001; Vol. 51:39.
* Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, et al.Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. *Journal of Clinical Oncology* 2004;**22**(1):69–76.
Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, et al.Late toxicity results of the GORTEC 94-01 randomized trial comparing radiotherapy with concomitant radiochemotherapy for advanced-stage oropharynx carcinoma: comparison of LENT/SOMA, RTOG/EORTC, and NCI-CTC scoring systems. *International Journal of Radiation Oncology, Biology, Physics* 2003;**55**(1):93–8.
Ezra P, Noel G, Mazeron JJ. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. *Cancer Radiotherapie* 2000;**4**(4):324–5.

Depondt 1993 ***{published data only}***
* Depondt J, Gehanno P, Martin M, Lelievre G, Guerrier B, Peytral C, et al.Neoadjuvant chemotherapy with carboplatin/5-fluorouracil in head and neck cancer. *Oncology* 1993;**50 Suppl 2**:23–7.
Martin M, Depondt J, Gehanno P, Lelievre P, Guerrier B, Peytral C, et al.A phase III study comparing induction chemotherapy by Carboplatin (CBDCA) and 5 Fluorouracil (5 FU) before locoregional treatment (LRT) versus locoregional treatment alone in head and neck carcinomas. European Journal of Cancer 1993; Vol. 29 Suppl 6:S139.

Dobrowsky 2000 ***{published data only}***
* Dobrowsky W, Naude J. Continuous hyperfractionated accelerated radiotherapy with/without mitomycin C in head and neck cancers. *Radiotherapy and Oncology* 2000;**57**(2):119–24.
Dobrowsky W, Naude J, Widder J, Dobrowsky E, Millesi W, Pavelka R, et al.Continuous hyperfractionated accelerated radiotherapy with/without mitomycin C in head and neck cancer. *International Journal of Radiation Oncology, Biology, Physics* 1998;**42**(4):803–6.

Domenge 2000 ***{published data only}***
* Domenge C, Hill C, Lefebvre JL, De Raucourt D, Rhein B, Wibault P, et al.Randomized trial of neoadjuvant chemotherapy in oropharyngeal carcinoma. French Groupe d'Etude des Tumeurs de la Tete et du Cou (GETTEC). *British Journal of Cancer* 2000;**83**(12):1594–8.
Domenge C, Lancar R, Coche DB, et al.Induction chemotherapy before radiotherapy in oropharyngeal carcinoma. *European Journal of Cancer* 1995;**31A**(5):s86.

Eschwege 1988 ***{published data only}***
Cachin Y, Jortay A, Sancho H, Eschwege F, Madelain M, Desaulty A, et al.Preliminary results of a randomized E.O.R.T.C. study comparing radiotherapy and concomitant bleomycin to radiotherapy alone in epidermoid carcinomas of the oropharynx. *European Journal of Cancer* 1977;**13**(12):1389–95.
* Eschwege F, Sancho-Garnier H, Gerard JP, et al.Ten-year results of a randomized trial comparing radiotherapy and concomitant bleomycin to radiotherapy alone in epidermoid carcinomas of the oropharynx: experience of the European Organization for Research and Treatment of Cancer. *National Cancer Institute Monograph* 1988;**6**:275–8.

Fazekas 1980 ***{published data only}***
Fazekas, JT, Pajak, TF, Marcial, VA, et al.RTOG randomized trial - 79-15: Misonizadole adjuvant to radiotherapy in advanced head and neck squamous cancers. American Society of Clinical Oncology 20th Annual Meeting 1984, issue C719:185.
* Fazekas JT, Sommer C, Kramer S. Adjuvant intravenous methotrexate or definitive radiotherapy alone for advanced squamous cancers of the oral cavity, oropharynx, supraglottic larynx or hypopharynx. *International Journal of Radiation Oncology, Biology, Physics* 1980;**6**(5):533–41.
Fazekas JT, Sommer C, Kramer S. Tumor regression and other prognosticators in advanced head and neck cancers: a sequel to the RTOG methotrexate study. *International Journal of Radiation Oncology, Biology, Physics* 1983;**9**(7):957–64.
Kramer S. Methotrexate and radiation therapy in the treatment of advanced squamous cell carcinoma of the oral cavity, oropharynx, supraglottic larynx, and hypopharynx. (Preliminary report of a controlled clinical trial of the Radiation Therapy Oncology Group). *Canadian Journal of Otolaryngology* 1975;**Supplement**:213–8.

Garden 2004 ***{published data only}***
Garden AS, Harris J, Vokes EE, Forastiere AA, Ridge JA, Jones C, et al.Preliminary results of Radiation Therapy Oncology Group 97-03: a randomized phase ii trial of concurrent radiation and chemotherapy for advanced squamous cell carcinomas of the head and neck. Journal of Clinical Oncology 2004; Vol. 22, issue 14:2856–64.
Garden AS, Harris J, Vokes EE, Forastiere AA, Ridge JA, Jones CU, et al.Results of Radiation Therapy Oncology Group 97-03 - A randomized phase II trial of concurrent radiation and chemotherapy for advanced squamous cell carcinomas of the head and neck: long term results and late toxicities. International Journal of Radiation Oncology, Biology, Physics 2006; Vol. 66, issue 3 Suppl 1:S411.

Gasparini 1993 *{published data only}*

* Gasparini G, Testolin A, Maluta S, Cristoferi V, Pozza F. Treatment of locally advanced squamous-cell carcinoma of the head and neck with concurrent radio-chemotherapy: Randomized comparison of cisplatin versus carboplatin. International Journal of Oncology 1993; Vol. 2, issue 2: 185–90.

Testolin A. Cisplatin (CDDP) versus Carboplatin (CRP) and concomitant radiotherapy (RT) in stage III-IV squamous cell carcinomas (SCC) of head and neck (H&N): preliminary results of a randomized trial. European Journal of Cancer 1991; Vol. 27, issue Suppl 2:S146.

Testolin A, Bolzicco GP, Panizzoni GA, Recher G, Padula E, Squaquara R, et al.Cisplatin (CDDP) versus carboplatin (CRP) and concomitant radiotherapy in stage III - IV squamous cell carcinomas (SCC) of head and neck (HN): Preliminary results of a randomized trial. Folia Oncologica 1992; Vol. 15, issue 2:147.

Giglio 1997 *{published data only}*

* Giglio R, Mickiewicz E, Pradier R, Roth B, Gatica G, Califano L, et al.Chemotherapy + alternating hyperfractionated radiotherapy vs. hyperfractionated radiotherapy alone in patients with inoperable stage III and IV epidermoid carcinoma. Prensa Medica Argentina 1997; Vol. 84, issue 5.

Giglio R, Mickiewicz E, Pradier R, Roth B, Gatica G, Califano L, et al.No recurrences beyond the second year of follow up in inoperable stage III and IV squamous cell carcinoma of the head and neck patients (IOHN). Final report of a randomized trial of alternating chemotherapy (CT) + hyperfractionated radiotherapy (RT) vs RT alone. Amercian Society of Clinical Oncology 1999; Vol. 15:317.

Giglio R, Mickiewicz E, Pradier R, Roth B, Gatica G, et al.Alternating chemotherapy (CT) + hyperfractionated radiotherapy (rt) vs RT alone in inoperable Stage III and IV squamous cell carcinoma of head and neck (IOHN) a randomized trial. American Society of Clinical Oncology 1996.

Gladkov 2007 *{published data only}*

Gladkov OA, Vazhenin AV, Sharabura TM, Kandakova E, Galiatova Iu V, Sychev VI, et al.Effectiveness of different regimes of combined treatment (cisplatin+ radiotherapy) for intraoral and oropharyngeal cancer. *Voprosy Onkologii* 2007;**53**(5):575–7.

Gonzalez-Larriba 1997 *{published data only}*

* Gonzalez-Larriba JL, Garcia Carbonero I, Sastre Valera J, Perez Ssegura P, Diaz-Rubio E. Neoadjuvant therapy with cisplatin/fluorouracil vs cisplatin/UFT in locally advanced squamous cell head and neck cancer. *Oncology* 1997;**11**(9 Suppl 10):90–7.

Valverde JJ, Gonzalez JL, Dominguez S, Lopez PM, Alonso MC, Adrover E, et al.Neoadjuvant chemotherapy (CT) with cisplatin (CDDP) and 5-fluorouracil (5FU) vs cisplatin and ftorafur-uracil (UFT) in advanced squamous head and neck cancer (SHNC) (909). Proceedings of the Annual Meeting of the American Society of Clinical Oncology. 1993; Vol. 12.

Grau 2003 *{published data only}*

Grau C, Agarwal J, Jabeen K, Jayatilake R, Khan A, et al.Radiotherapy combined with mitomycin C in the treatment of locally advanced head and neck cancer. First report from the IAEA-CRP E3.30.13 randomised multicentre study. *Radiotherapy and Oncology* 2001;**58 Suppl 1**:S16.

Grau C, Agarwal J, Jabeen K, Jayatilake R, Khan A, et al.Radiotherapy with or without mitomycin C in the treatment of locally advanced head and neck cancer. Results from the IAEA multicentre randomised trial. *European Journal of Cancer* 2001;**37 Suppl 6**:S38.

* Grau C, Prakash AJ, Jabeen K, Rab KA, Abeyakoon S, Hadjieva T, et al.Radiotherapy with or without mitomycin c in the treatment of locally advanced head and neck cancer: results of the IAEA multicentre randomised trial. *Radiotherapy and Oncology* 2003;**67**(1):17–26.

Gupta 2001 *{published data only}*

Gupta NK, Pointon RC, Wilkinson PM. A randomised clinical trial to contrast radiotherapy with radiotherapy and methotrexate given synchronously in head and neck cancer. *Clinical Radiology* 1987;**38**(6):575–81.

* Gupta NK, Swindell R. Concomitant methotrexate and radiotherapy in advanced head and neck cancer: 15-year follow-up of a randomized clinical trial. *Clinical Oncology* 2001;**13**(5):339–44.

Gupta 2009 *{published data only}*

Gupta D, Shukla P, Bisht S, Dhawan A, Pant M, Bhatt M, et al.A prospective comparison of sequential chemoradiation vs concurrent chemoradiation in locally advanced oropharyngeal carcinoma. Cancer Biology & Therapy 2009; Vol. 8, issue 3:213–7.

Haddad 1996 *{published data only}*

Haddad E, Mazeron JJ, Martin M, Vergnes L, Brun B, Piedbois P, et al.Comparison of concomitant radiotherapy and chemotherapy with radiotherapy alone in advanced cancers of the head and neck: results of a randomized trial. *Bulletin du Cancer. Radiotherapie* 1996;**83**(2):97–103.

HNCProg 1987 *{published data only}*

Anonymous. Adjuvant chemotherapy for advanced head and neck squamous carcinoma: final report of the head and neck contracts program. *Cancer* 1987;**60**:301–11.

Endicott JN, Jensen R, Lyman G. Adjuvant chemotherapy for advanced head and neck squamous carcinoma. Final report of the head and neck contracts program. Cancer 1987; Vol. 60, issue 3.

* Jacobs C, Makuch R. Efficacy of adjuvant chemotherapy for patients with resectable head and neck cancer: a subset analysis of the Head and Neck Contracts Program. Journal of Clinical Oncology 1990; Vol. 8, issue 5:838–47.

Holoye 1985 *{published data only}*

* Holoye PY, Grossman TW, Toohill RJ, Kun LE, Byhardt RW, Duncavage JA, et al.Randomized study of adjuvant

chemotherapy for head and neck cancer. *Otolaryngology - Head and Neck Surgery* 1985;**93**(6):712–7.

Holoye PY, Kun L, Toohill R, Byherdt R, et al.Prospective, randomized trial of adjuvant chemotherapy in head and neck (H/N) cancer. Proceedings of American Society of Clinical Oncology. 1984; Vol. Supplement:183 (Abs No C712).

Kun LE, Toohill RJ, Holoye PY, Duncavage JA, Byhardt RW, Ritch PS, et al.A randomized study of adjuvant chemotherapy for cancer of the upper aerodigestive tract. International Journal of Radiation Oncology, Biology, Physics 1986; Vol. 12, issue 2:173–8.

Toohill RJ, Duncavage JA, Grossmam TW, Malin TC, Teplin RW, Wilson JF, et al.The effects of delay in standard treatment due to induction chemotherapy in two randomized prospective studies. Laryngoscope 1987; Vol. 97, issue 4:407–12.

Huguenin 2004 ***{published data only}***

Huguenin P, Beer K, Allal A, Bernier J, Schmitz SF, Rufibach K, et al.Hyperfractionated radiation therapy with or without simultaneous cisplatin (DDP) in patients with stage III and IV carcinomas of the head and neck. A phase III randomized trial of the Swiss Group for Clinical Cancer Research (SAKK). Annals of Oncology 2002; Vol. 13 Suppl 5:127.

* Huguenin P, Beer KT, Allal A, Rufibach K, Friedli C, Davis JB, et al.Concomitant cisplatin significantly improves locoregional control in advanced head and neck cancers treated with hyperfractionated radiotherapy. *Journal of Clinical Oncology* 2004;**22**(23):4665–73.

Huguenin P, Glanzmann C, Taussky D, Lutolf UM, Schmid S, Moe K. Hyperfractionated radiotherapy and simultaneous cisplatin for stage-III and -IV carcinomas of the head and neck. Long-term results including functional outcome. Strahlentherapie und Onkologie 1998; Vol. 174, issue 8:397–402.

Jaulerry 1992 ***{published data only}***

Jaulerry C, Rodriguez J, Brunin F, Jouve M, Mosseri V, Point D, et al.Induction chemotherapy in advanced head and neck tumors: results of two randomized trials. *International Journal of Radiation Oncology, Biology, Physics* 1992;**23**(3):483–9.

Jeremic 1997 ***{published data only}***

Jeremic B, Milicic B, Dagovic A, Vaskovic Z, Tadic L. Radiation therapy with or without concurrent low-dose daily chemotherapy in locally advanced, nonmetastatic squamous cell carcinoma of the head and neck. *Journal of Clinical Oncology* 2004;**22**(17):3540–8.

* Jeremic B, Shibamoto Y, Stanisavljevic B, Milojevic L, Milicic B, Nikolic N. Radiation therapy alone or with concurrent low-dose daily either cisplatin or carboplatin in locally advanced unresectable squamous cell carcinoma of the head and neck: a prospective randomized trial. *Radiotherapy and Oncology* 1997;**43**(1):29–37.

Jeremic 2000 ***{published data only}***

Jeremic B, Milicic B, Dagovic A, Vaskovic Z, Tadic L. Radiation therapy with or without concurrent low-dose daily chemotherapy in locally advanced, nonmetastatic squamous cell carcinoma of the head and neck. *Journal of Clinical Oncology* 2004;**22**(17):3540–8.

Jeremic B, Shibamoto Y, Igrutinovic I. Absence of cervical radiation myelitis after hyperfractionated radiation therapy with and without concurrent chemotherapy for locally advanced, unresectable, nonmetastatic squamous cell carcinoma of the head and neck. *Journal of Cancer Research & Clinical Oncology* 2001;**127**(11):687–91.

Jeremic B, Shibamoto Y, Milicic B, Nikolic N, Dagovic A. Hyperfractionated radiotherapy (Hfx RT) with or without concurrent low dose daily cisplatin (CDDP) in locally advanced unresectable squamous cell carcinoma of the head and neck (SCC H&N). A prospective randomized trial. Head and Neck 1999:S163.

* Jeremic B, Shibamoto Y, Milicic B, Nikolic N, Dagovic A, Aleksandrovic J, et al.Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial. *Journal of Clinical Oncology* 2000;**18**(7):1458–64.

Knowlton 1975 ***{published data only}***

Knowlton AH, Percarpio B, Bobrow S, Fischer JJ. Methotrexate and radiation therapy in the treatment of advanced head and neck tumors. *Radiology* 1975;**116**(3): 709–12.

Krishnamurthi 1990 ***{published data only}***

Krishnamurthi S, Shanta V, Vasanthan A, Balakrishnan IS, Jayaraman R. Radiation, pepleomycin and hyperthermia in the therapy of locally advanced squamous cell carcinomas of the buccal mucosa. *Clinical Oncology* 1990;**2**(1):10–3.

Kumar 1996 ***{published data only}***

Kumar S, Datta NR, Ahuja RC, Mali HR, Agarwal GN, Ayyagari S. Feasibility of non-cisplatin-based induction chemotherapy and concurrent chemoradiotherapy in advanced head and neck cancer. *Acta Oncologica* 1996;**35** (6):721–5.

Lam 2001 ***{published data only}***

Lam P, Yuen AP, Ho CM, Ho WK, Wei WI. Prospective randomized study of post-operative chemotherapy with levamisole and UFT for head and neck carcinoma. *European Journal of Surgical Oncology* 2001;**27**(8):750–3.

Laramore 1992 ***{published data only}***

Al-Sarraf M, Pjak T, Laramore G, Jacobs J, Ensley J, Ahmad S, et al.Radiotherapy (RT) vs. chemotherapy (CT) followed by RT in resected and negative-margins head and neck cancers (HNC). Intergroup Study 0034: final analysis. Journal of Clinical Oncology 1997; Vol. 16:392a (Abs No 1399).

Aref A, Berkey BA, Schwade JG, Ensley J, Schuller DE, Haselow RE, et al.The influence of beam energy on the outcome of postoperative radiotherapy in head and neck cancer patients: secondary analysis of RTOG 85-03. *International Journal of Radiation Oncology, Biology, Physics* 2000;**47**(2):389–94.

Hong WK. Adjuvant chemotherapy for resectable squamous cell carcinoma of the head and neck. Report on Intergroup

Study 0034. *International Journal of Radiation Oncology, Biology, Physics* 1992;**23**(4):885–6.
Jacobs JR, Casiano RR, Schuller DE, Pajak TF, Laramore GE, al-Sarraf M. Chemotherapy as predictor of compliance. *Journal of Surgical Oncology* 1994;**55**(3):143–8.
Laramore GE. Adjuvant chemotherapy for resectable squamous cell carcinomas of the head and neck: report on intergroup study 0034. International Journal of Radiation Oncology, Biology, Physics 1991; Vol. 21, issue S1:190.
* Laramore GE, Scott CB, al-Sarraf M, Haselow RE, Ervin TJ, Wheeler R, et al.Adjuvant chemotherapy for resectable squamous cell carcinomas of the head and neck: report on Intergroup Study 0034. *International Journal of Radiation Oncology, Biology, Physics* 1992;**23**(4):705–13.

Le 2006 ***{published data only}***
* Le QT, Taira A, Budenz S, Dorie MJ, Goffinet DR, Fee WE, et al.Mature results from a randomized phase II trial of cisplatin plus 5-fluorouracil and radiotherapy with or without tirapazamine in patients with resectable stage IV head and neck squamous cell carcinomas. *Cancer* 2006;**106**(9):1940–9.
Le QX, Pinto HA, Tate DJ, Terris DJ, Gabalski E, Goffinet DR. A randomized phase II trial of tirpazamine in advanced squamous cell carcinoma of the head and neck: A preliminary report of radiation related toxicity. Radiology 1998; Vol. 209P:1522.
Pinto H, Le Q, Terris D, et al.Randomized trial of tirapazamine/cisplatin/fluorouracil versus cisplatin/fluorouracil for organ preservation in advanced resectable head and neck cancer. Proceedings of ASCO. 2002 (Abs No 904).

Lewin 1997 ***{published data only}***
Lewin F, Damber L, Jonsson H, Andersson T, Berthelsen A, Biorklund A, et al.Neoadjuvant chemotherapy with cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the head and neck: a randomized phase III study. *Radiotherapy and Oncology* 1997;**43**(1):23–8.

Licitra 2003 ***{published data only}***
Grandi C, Licitra L, Cavina R, Guzzo M, Mariani L, Colli S, et al.Surgery vrs primary chemotherapy and surgery in cancer of the oral cavity: Preliminary report of final results of a randomised study. 5th International Conference on Head and Neck Cancer. San Francisco, California, USA, 29 July - 2 August. 2000:141 (Abs No 297).
Grandi C, Molinari R, Bonadonna G, Licitra L, Cavina R, Guzzo M, et al.Surgery versus primary chemotherapy plus surgery in squamous cell carcinoma of the oral cavity: preliminary report of a randomized study. European Journal of Cancer 1993; Vol. 29Y:S145.
Licitra L, Grandi C, Cavina R, Guzzo M, Mariani L, Lo Vullo S, et al.Primary chemotherapy (pCT) for patients with operable oral cavity cancer: Results of a randomized study. Proceedings of the American Society of Clinical Oncology (ASCO). 2001; Vol. 20 (Abs No 890).
* Licitra L, Grandi C, Guzzo M, Mariani L, Lo VS, Valvo F, et al.Primary chemotherapy in resectable oral cavity squamous cell cancer: a randomized controlled trial. Journal of Clinical Oncology 2003; Vol. 21, issue 2:327–33.

Luboinski 1985 ***{published data only}***
* Luboinski B. Preliminary results of a randomized study on preoperative intra-arterial chemotherapy combined with surgery and irradiation for carcinomas of the floor of the mouth. *Progress in Clinical & Biological Research* 1985;**201**:199–203.
Mamelle G, Luboinski B, Domenge C, Saravane D. Induction chemotherapy in the treatment of squamous carcinomas of the tongue and floor of mouth. Clinical Otolaryngology 1989; Vol. 14:465–6.

Maipang 1995 ***{published data only}***
Maipang T, Maipang M, Geater A, Panjapiyakul C, Watanaarepornchai S, Punperk S. Combination chemotherapy as induction therapy for advanced resectable head and neck cancer. *Journal of Surgical Oncology* 1995;**59**(2):80–5.

Marechal 1987 ***{published data only}***
Marechal F, Coninx P, Legros M, Nasca S, Jezekova D, Vins C, et al.Preliminary report of a prospective randomised trial of cisplatin vs cisplatin-etoposide for advanced head and neck squamous cell cancer. Cancer Chemotherapy and Pharmacology 1985; Vol. 14, issue Suppl 1:S44.
* Marechal F, Nasca S, Morel M, Jezekova D, Coninx P, Legros M, et al.A phase III of cisplatinum versus cisplatinum-etoposide for previously untreated squamous cell carcinoma of the head and neck. *Anticancer Research* 1987;**7**(3 Pt B):455–8.

Mazeron 1992 ***{published data only}***
Mazeron JJ, Martin M, Brun B, Grimard L, Lelievre G, Vergnes L, et al.Induction chemotherapy in head and neck cancer: results of a phase III trial. *Head & Neck* 1992;**14**(2):85–91.

Merlano 1991 ***{published data only}***
Benasso M, Bonelli L, Numico G, Corvo R, Sanguineti G, Rosso R, et al.Treatment with cisplatin and fluorouracil alternating with radiation favourably affects prognosis of inoperable squamous cell carcinoma of the head and neck: results of a multivariate analysis on 273 patients. Annals of Oncology 1997; Vol. 8, issue 8:773–9.
Corvo R. Sequential vs alternative chemo-radiotherapy in advanced head and neck tumors. Report on a randomized study. International Journal of Radiation Oncology, Biology, Physics 1990; Vol. 19, issue S1:226.
Corvo R, Merlano M, Scarpati D, Grimaldi A, Benasso M, Franzone P, et al.Sequential or alternate chemo-radiotherapy in the treatment of advanced head and neck tumors. Results of a randomized study. *Radiologia Medica* 1988;**75**(6):653–9.
* Merlano M, Corvo R, Margarino G, Benasso M, Rosso R, Sertoli MR, et al.Combined chemotherapy and radiation therapy in advanced inoperable squamous cell carcinoma of the head and neck. The final report of a randomized trial. *Cancer* 1991;**67**(4):915–21.
Merlano M, Rosso R, Sertoli MR, Benasso M, Bacigalupo A, Ardizzoni A, et al.Randomized comparison of two

chemotherapy, radiotherapy schemes for stage III and IV unresectable squamous cell carcinoma of the head and neck. *Laryngoscope* 1990;**100**(5):531–5.

Merlano M, Rosso R, Sertoli MR, Bonelli L, Margarino G, Grimaldi A, et al.Sequential versus alternating chemotherapy and radiotherapy in stage III-IV squamous cell carcinoma of the head and neck: a phase III study. *Journal of Clinical Oncology* 1988;**6**(4):627–32.

Merlano 1992 *{published data only}*

Benasso M, Bonelli L, Numico G, Corvo R, Sanguineti G, Rosso R, et al.Treatment with cisplatin and fluorouracil alternating with radiation favourably affects prognosis of inoperable squamous cell carcinoma of the head and neck: results of a multivariate analysis on 273 patients. Annals of Oncology 1997; Vol. 8, issue 8:773–9.

Merlano M, Benasso M, Corvo R, Rosso R, Vitale V, Blengio F, et al.Five-year update of a randomized trial of alternating radiotherapy and chemotherapy compared with radiotherapy alone in treatment of unresectable squamous cell carcinoma of the head and neck. *Journal of the National Cancer Institute* 1996;**88**(9):583–9.

Merlano M, Corvo R, Brema F, Benasso M, Bacigalupo A, Toma S, et al.Alternating chemotherapy and radiotherapy in advanced squamous cell carcinoma of the head and neck. A randomized trial. Proceedings of the Annual Meeting of the American Society of Clinical Oncology. 1989:175 (Abs No 682).

Merlano M, Grimaldi A, Sertoli MR, Gardin G, Scala M, Corvo R, et al.Alternating chemotherapy (CT) and radiotherapy (RT) vs neo adjuvant CT in advanced head and neck cancer. Cancer Chemotherapy and Pharmacology 1986; Vol. 18, issue Suppl 1:A49.

* Merlano M, Vitale V, Rosso R, Benasso M, Corvo R, Cavallari M, et al.Treatment of advanced squamous-cell carcinoma of the head and neck with alternating chemotherapy and radiotherapy. *New England Journal of Medicine* 1992;**327**(16):1115–21.

Mohr 1994 *{published data only}*

Mohr C, Bohndorf W, Carstens J, Harle F, Hausamen JE, Hirche H, et al.Preoperative radiochemotherapy and radical surgery in comparison with radical surgery alone. A prospective, multicentric, randomized DOSAK study of advanced squamous cell carcinoma of the oral cavity and the oropharynx (a 3-year follow-up). *International Journal of Oral & Maxillofacial Surgery* 1994;**23**(3):140–8.

Molinari 1982 *{published data only}*

Molinari R, Jortay A, Sancho-Garnier H, Brugere J, Demard M, Desaulty A, et al.A randomized EORTC trial comparing intra-arterial infusion with methotrexate vs bleomycin as initial therapy in carcinoma of the oral cavity. European Journal of Cancer & Clinical Oncology 1982; Vol. 18, issue 9:807–12.

Morita 1980 *{published data only}*

Morita K. Clinical significance of radiation therapy combined with chemotherapy. *Strahlentherapie* 1980;**156**(4):228–33.

Nervi 1978 *{published data only}*

Arcangeli G, Nervi C, Righini R, Creton G, Mirri MA Guerra A. Combined radiation and drugs: the effect of intra-arterial chemotherapy followed by radiotherapy in head and neck cancer. *Radiotherapy and Oncology* 1983;**1**(2):101–7.

* Nervi C, Arcangeli G, Badaracco G, Cortese M, Morelli M, Starace G. The relevance of tumour size and cell kinetics as predictors of radiation response in head and neck cancer. *Cancer* 1978;**41**(3):900–6.

Olasz 2000 *{published data only}*

Olasz L, Nemeth A, Nyarady Z, Tornoczky T, Kiralyfalvi L. Randomized study of cisplatin-based combination chemotherapy for the treatment of planocellular cancer of the head and neck region. *Orvosi Hetilap* 2000;**141**(45):2433–7.

Olasz L, Nemeth A, Nyarady Z, Tornoczky T, Kiralyfalvi L. Results and failures with or without cisplatin containing induction chemotherapy in the treatment of squamous cell carcinoma of the head and neck. Cancer Detection & Prevention 2004; Vol. 28, issue 1:65–71.

Olmi 2003 *{published data only}*

Crispino SP, Olmi C, Fallai F, Rossi S, Marsoni A, Tinazzi M. Conventional radiotherapy (RT) versus accelerated hyperfractionated RT versus conventional RT and concomitant chemotherapy in locally advanced oropharyngeal carcinoma (ORO-93/01). Proceedings of the Annual Meeting of the American Society of Clinical Oncology. 1997 (Abs No 1423).

Fallai C, Bolner A, Signor M, Gava A, Franchin G, Ponticelli P, et al.Long-term results of conventional radiotherapy versus accelerated hyperfractionated radiotherapy versus concomitant radiotherapy and chemotherapy in locoregionally advanced carcinoma of the oropharynx. Tumori 2006; Vol. 92, issue 1:41–54.

* Olmi P, Crispino S, Fallai C, Torri V, Rossi F, Bolner A, et al.Locoregionally advanced carcinoma of the oropharynx: conventional radiotherapy vs. accelerated hyperfractionated radiotherapy vs. concomitant radiotherapy and chemotherapy--a multicenter randomized trial. *International Journal of Radiation Oncology, Biology, Physics* 2003;**55**(1):78–92.

Olmi P, Fallai C, Rossi F, Crispino S, Marsoni S, Torri V, et al.Conventional radiotherapy versus accelerated hyperfractionated radiotherapy versus conventional radiotherapy and concomitant chemotherapy in advanced oropharyngeal carcinoma: a randomized clinical trial. *European Journal of Cancer* 1995;**31Y**:S91.

Paccagnella 1994 *{published data only}*

* Paccagnella A, Orlando A, Marchiori C, Zorat PL, Cavaniglia G, Sileni VC, et al.Phase III trial of initial chemotherapy in stage III or IV head and neck cancers: a study by the Gruppo di Studio sui Tumori della Testa e del Collo. *Journal of the National Cancer Institute* 1994;**86**(4):265–72.

Zorat P, Paccagnella A, Cavaniglia G, Gava A, Baili M, et al.Chemotherapy (CT) plus loco-regional treatment (LRT)

versus LRT alone in stage III-IV head and neck cancer. European Journal of Cancer 1991; Vol. 27, issue Suppl 2: S209 (Abs No 1273).

Zorat PL, Loreggian L, Paccagnella A, Gava A, Mione CA, Bordin F, et al.Randomized phase III trial of neoadjuvant chemotherapy (CT) in head and neck (H&N) cancer patients: An update based on 10 years' follow up. Proceedings of the Annual Meeting of the American Society of Clinical Oncology. 2004:494.

Zorat PL, Paccagnella A, Cavaniglia G, Loreggian L, Gava A, Mione CA, et al.Randomized phase III trial of neoadjuvant chemotherapy in head and neck cancer: 10-year follow-up. *Journal of the National Cancer Institute* 2004;**96**(22):1714–7.

Paccagnella 2010 *{published data only}*

Ghi M, Paccagnella A, Buffoli A, Koussis H, et al.Concomitant chemoradiotherapy (CT/RT) vs induction chemotherapy with docetaxel/cisplatin/5fluorouracil (TPF) followed by CT/RT in locally advanced head and neck cancer. Final results of phase II study. Annals of Oncology 2008; Vol. 19, issue Suppl 8.

Ghi M, Paccagnella A, Koussis H, Mastromauro C, Morandini G, et al.Randomized Phase II-III trial of concomitant CT/RT versus TPF followed by concomitant CT/RT in locally advanced squamous cell carcinoma of head & neck (LASCCHN). Results of the phase II part of the study. Annals of Oncology 2006; Vol. 17, issue Suppl 9:179.

Paccagnella A, Buffoli A, Koussis H, D'Amanzo L, Loreggian A, Bonetti A, et al.Randomized phase II trial of concomitant CT/RT versus TPF followed by concomitant CT/RT in locally advanced squamous cell carcinoma of the head and neck (LASCCHN). Journal of Clinical Oncology, 2006 ASCO Annual Meeting Proceedings Part I 2006; Vol. 24:18S (Abs No 5518).

Paccagnella A, Buffoli A, Koussis H, Gava A, Franceschi T, Gardani G, et al.Concomitant chemoradiotherapy (CT/RT) vs neoadjuvant chemotherapy with docetaxel/cisplatin/5-fluorouracil (TPF) followed by CT/RT in locally advanced head and neck cancer. Final results of a phase II randomized study. Journal of Clinical Oncology 2008; Vol. 26, issue Suppl:(Abs No 6000).

* Paccagnella A, Ghi MG, Loreggian A, Buffoli A, Koussis H, Mione CA, et al.Concomitant chemoradiotherapy versus induction docetaxel, cisplatin and 5 fluorouracil (TPF) followed by concomitant chemoradiotherapy in locally advanced head and neck cancer: a phase II randomized study. *Annals of Oncology* 2010;**21**(7):1515–22.

Turcato G, Buffoli A, Loreggian L, Gava A, Campostrini F, Gardani G, et al.Randomized phase II trial of concomitant chemoradiotherapy (CT/RT) versus docetaxel, cisplatin and 5-fluorouracil (TPF) followed by concomitant CT/RT in locally advanced head and neck squamous cell carcinoma (HNSCC). International Journal of Radiation Oncology, Biology, Physics 2006; Vol. 66, issue 3 Suppl 1:S192.

Parvinen 1985 *{published data only}*

Parvinen LM, Parvinen M, Nordman E, Kortekangas AE. Combined bleomycin treatment and radiation therapy in squamous cell carcinoma of the head and neck region. *Acta Radiologica - Oncology* 1985;**24**(6):487–9.

Petrovich 1981 *{published data only}*

* Petrovich Z, Block J, Kuisk H, Mackintosh R, Casciato D, Jose L, et al.A randomized comparison of radiotherapy with a radiotherapy--chemotherapy combination in stage IV carcinoma of the head and neck. *Cancer* 1981;**47**(9): 2259–64.

Petrovich Z, Block M, Barton R. Randomized comparison of radiotherapy (RT) and radiotherapy-chemotherapy (RT + CT) combination in stage IV carcinoma of the head and neck. *International Journal of Radiation Oncology, Biology, Physics* 1979;**6 Suppl 1**:18.

Pinnaro 1994 *{published data only}*

Cognetti F. Randomized trial of sequential versus simultaneous chemo and radiotherapy (CT-xRT) in patients (PTS) with locally advanced unresectable squamous cell carcinoma of the head and neck (LAU-SCCHN). European Journal of Cancer 1991; Vol. 27 Suppl 2:S138.

* Pinnaro P, Cercato MC, Giannarelli D, Carlini P, Del Vecchio MR, Impiombato FA, et al.A randomized phase II study comparing sequential versus simultaneous chemo-radiotherapy in patients with unresectable locally advanced squamous cell cancer of the head and neck. *Annals of Oncology* 1994;**5**(6):513–9.

Posner 2007 *{published data only}*

Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winquist E, Gorbounova V, et al.Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *New England Journal of Medicine* 2007;**357**(17):1705–15.

Prevost 2005 *{published data only}*

Prévost A, Mérol JC, Aimé P, Moutel K, Roger-Liautaud F, Nasca S, et al.A randomized trial between two neoadjuvant chemotherapy protocols: CDDP + 5-FU versus CDDP + VP16 in advanced cancer of the head and neck. *Oncology Reports* 2005;**14**(3):771–6.

Rao 1994 *{published data only}*

Rao RS, Parikh DM, Parikh HK, Bhansali MB, Deshmane VH, Fakih AR. Perioperative chemotherapy in patients with oral cancer. *American Journal of Surgery* 1994;**168**(3): 262–7.

* Rao RS, Parikh DM, Parikh HK, Bhansali MB, Fakih AR. Perioperative chemotherapy in oral cancer. *Journal of Surgical Oncology* 1991;**47**(1):21–6.

Rasch 2010 *{published data only}*

Ackerstaff AH, Balm AJM, Rasch CRN, De Boer JP, Wiggenraad R, Rietveld DHF, et al.First-year quality of life assessment of an intraarterial (radplat) versus intravenous chemoradiation phase III trial. Head and Neck 2009; Vol. 31, issue 1:77–84.

Rasch C, Salverda G, Schornagel J, Kroger R, Wiggenraud R, et al.Intra-arterial versus intravenous chemoradiation for advanced head and neck cancer, early results of a multi-

institutional trial. Proceedings of the 48th Annual Meeting of ASTRO. 2006:S1.
Rasch CRN, Hauptmann M, Schnoragel J, Wijers O, Buter J, Gregor T, et al.Intra-arterial versus intravenous chemoradiation for advanced head and neck cancer: Results of a randomized phase 3 trial. *Cancer* 2010;**116**(9): 2068–70.

Rentschler 1987 *{published data only}*
Rentschler RE, Wilbur DW, Petti GH, Chonkich GD, Hilliard DA, Camacho ES, et al.Adjuvant methotrexate escalated to toxicity for resectable stage III and IV squamous head and neck carcinomas--a prospective, randomized study. *Journal of Clinical Oncology* 1987;**5**(2):278–85.

Richard 1974 *{published data only}*
Richard JM, Sancho H, Brugere J, Vandenbrouck C. Intra-arterial methotrexate in head and neck tumors. *European Journal of Cancer* 1973;**9**(11-12):847–51.
* Richard JM, Sancho H, Lepintre Y, Rodary J, Pierquin B. Intra-arterial methotrexate chemotherapy and telecobalt therapy in cancer of the oral cavity and oropharynx. *Cancer* 1974;**34**(3):491–6.

Richard 1991 *{published data only}*
Richard J, Sancho GH. Intraarterial infusion. An adjuvant to surgery of oral carcinoma. A randomized EORTC study. *Journal Europeen de Radiotherapie* 1983;**4**:81–6.
* Richard JM, Kramar A, Molinari R, Lefebvre JL, Blanchet F, Jortay A, et al.Randomised EORTC head and neck cooperative group trial of preoperative intra-arterial chemotherapy in oral cavity and oropharynx carcinoma. *European Journal of Cancer* 1991;**27**(7):821–7.

Rischin 2005 *{published data only}*
Rischin, D, Peters, L, Smith, J, et al.Preliminary results of TROG 98.02 - a randomized phase II study of 5-fluorouracil, cisplatin and radiation versus tirapazamine, cisplatin and radiation for advanced squamous cell carcinoma of the head and neck. *Proceedings of the American Society of Clinical Oncology* 2003;**22**:(Abs No 1992).
* Rischin D, Peters L, Fisher R, Macann A, Denham J, Poulsen M, et al.Tirapazamine, Cisplatin, and Radiation versus Fluorouracil, Cisplatin, and Radiation in patients with locally advanced head and neck cancer: a randomized phase II trial of the Trans-Tasman Radiation Oncology Group (TROG 98.02). *Journal of Clinical Oncology* 2005; **23**(1):79–87.

Rischin 2010 *{published data only}*
Rischin D, Peters LJ, O'Sullivan B, Giralt J, Fisher R, Yuen K, et al.Tirapazamine, cisplatin, and radiation versus cisplatin and radiation for advanced squamous cell carcinoma of the head and neck (TROG 02.02, HeadSTART): a phase III trial of the Trans-Tasman Radiation Oncology Group. *Journal of Clinical Oncology* 2010;**28**(18):2989–95.

Ruo 2010 *{published data only}*
Ruo Redda MG, Ragona R, Ricardi U, Beltramo G, Rampino M, Gabriele P, et al.Radiotherapy alone or with concomitant daily low-dose carboplatin in locally advanced, unresectable head and neck cancer: definitive results of a phase III study with a follow-up period of up to ten years. *Tumori* 2010;**96**(2):246–53.

Salvajoli 1992 *{published data only}*
Salvajoli JV, Morioka H, Trippe N, Kowalski LP. A randomized trial of neoadjuvant vs concomitant chemotherapy vs radiotherapy alone in the treatment of stage IV head and neck squamous cell carcinoma. *European Archives of Oto-Rhino-Laryngology* 1992;**249**(4):211–5.

Schuller 1988 *{published data only}*
* Schuller DE, Metch B, Stein DW, Mattox D, McCracken JD. Preoperative chemotherapy in advanced resectable head and neck cancer: final report of the Southwest Oncology Group. *Laryngoscope* 1988;**98**(11):1205–11.
Schuller DE, Stein DW, Metch B. Analysis of treatment failure patterns. A Southwest Oncology Group Study. *Archives of Otolaryngology - Head & Neck Surgery* 1989;**115** (7):834–6.

Segura 2002 *{published data only}*
Segura A, Pastor M, Santaballa A, Yuste A, Garcera S, Oltra A, et al.Cisplatin plus 5-fluorouracil vs cisplatin plus vinorelbine as neoadjuvant treatment in locally advanced head and neck cancer. Preliminary results of a randomized trial. European Journal of Cancer 1999; Vol. 35, issue Suppl 2:S61.
* Segura A, Yuste A, Pastor M, Lopez-Tendero P, Perez-Fidalgo J, Girones R, et al.Cisplatino-5fluorouracilo versus cisplatino- vinorrelbina como tratamiento de los carcinomas epidermoid de cabeza y cuello localmente avanzados. *Oncologia* 2002;**25**:466–71.

Shanta 1980 *{published data only}*
* Shanta V, Krishnamurthi S. Combined bleomycin and radiotherapy in oral cancer. *Clinical Radiology* 1980;**31**(5): 617–20.
Shanta V, Krishnamurthi S. Combined therapy of oral cancer bleomycin and radiation: a clinical trial. Clinical Radiology 1977; Vol. 28, issue 4:427–9.

Smid 1995 *{published data only}*
* Smid L, Lesnicar H, Zakotnik B, Soba E, Budihna M, Furlan L, et al.Radiotherapy, combined with simultaneous chemotherapy with mitomycin C and bleomycin for inoperable head and neck cancer--preliminary report. *International Journal of Radiation Oncology, Biology, Physics* 1995;**32**(3):769–75.
Zakotnik B, Budihna M, Smid L, Soba E, Zargi M, et al.Concomitant radiotherapy and chemotherapy of inoperable head and neck squamous cell carcinomas. *European Journal of Cancer* 1993;**Suppl 6**:S226.
Zakotnik B, Smid L, Budihna M, Lesnicar H, Soba E, Furlan L, et al.Concomitant radiotherapy and mitomycin C with bleomycin in inoperable head and neck cancer. *Radiology and Oncology* 1997;**31**:173–7.
Zakotnik B, Smid L, Budihna M, Lesnicar H, Soba E, Furlan L, et al.Concomitant radiotherapy with mitomycin C and bleomycin compared with radiotherapy alone in inoperable head and neck cancer: final report. *International*

Journal of Radiation Oncology, Biology, Physics 1998;**41**(5): 1121–7.

Zakotnik B, Smid L, Lesnicar H, Soba E, Budihna M, Furlan L, et al.Concomitant radiotherapy and mitomycin C with bleomycin in inoperable head and neck cancer. Annals of Oncology 1994; Vol. 5 Suppl 8:121.

Staar 2001 *{published data only}*

Semrau R, Mueller RP, Stuetzer H, Staar S, Schroeder U, Guntinas-Lichius O, et al.Efficacy of intensified hyperfractionated and accelerated radiotherapy and concurrent chemotherapy with carboplatin and 5-fluorouracil: Updated results of a randomized multicentric trial in advanced head-and-neck cancer. *International Journal of Radiation Oncology, Biology, Physics* 2006;**64**(5): 1308–16.

Staar, S, Rudat, V, Dietz, A, et al.Hyperfractionated (HF) accelerated (ACC) radiochemotherapy (RCT) versus HF/ACC radiotherapy (RT) in advanced head and neck (HN) cancer. Proceedings of ASCO. 2000; Vol. 19:411a.

Staar S, Eckel HE, Rudat V, Dietz A, Flentje M, Schroeder M, et al.Benefits and toxicities of accelerated radiochemo- versus accelerated radiotherapy in advanced head and neck cancer - Results of a German randomized study. European Journal of Cancer 2001; Vol. 37, issue Suppl 6:38 (Abs No 126).

Staar S, Rudat V, Stuetzer H, Dietz A, Volling P, Schroeder M, et al.Erratum: Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy. Results of a multicentric randomized German trial in advanced head-and-neck cancer (International Journal of Radiation Oncology Biology Physics 2001; 50: (1161-1171)). International Journal of Radiation Oncology, Biology, Physics 2001; Vol. 51, issue 2:1.

* Staar S, Rudat V, Stuetzer H, Dietz A, Volling P, Schroeder M, et al.Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy--results of a multicentric randomized German trial in advanced head-and-neck cancer. *International Journal of Radiation Oncology, Biology, Physics* 2001;**50**(5):1161–71.

Staar S, Rudat V, Stuetzer H, Dietz A, Volling P, Schroeder M, et al.Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy--results of a multicentric randomized German trial in advanced head-and-neck cancer. International Journal of Radiation Oncology, Biology, Physics 2002; Vol. 54:300.

Szabo 1999 *{published data only}*

Szabo G, Kreidler J, Hollmann K, Kovacs A, Nemeth G, Nemeth Z, et al.Intra-arterial preoperative cytostatic treatment versus preoperative irradiation: A prospective, randomized study of lingual and sublingual carcinomas. *Cancer* 1999;**86**(8):1381–6.

Szpirglas 1979 *{published data only}*

Szpirglas H, Chastang C, Bertrand JC. Adjuvant treatment of tongue and floor of the mouth cancers. *Recent Results in Cancer Research* 1978;**68**:309–17.

* Szpirglas H, Chastang Cl, Bertrand JCh. Adjuvant treatment of tongue and floor of the mouth cancers. In: Bonadonna G, Mathé G, Salmon SE editor(s). *Adjuvant Therapies and Markers of Post-Surgical Minimal Residual Disease II. Adjuvant Therapies of the Various Primary Tumors*. Berlin: Springer Verlag, 1979:309–17.

Szpirglas 1988 *{published data only}*

Szpirglas H, Nizri D, Marneur M. Neoadjuvant chemotherapy. A randomized trial before radiotherapy in oral and oropharyngeal carcinomas: end results. Proceedings of the 2nd International Head and Neck Oncology Research Conference. 1988:261–4.

Tejedor 1992 *{published data only}*

Tejedor M, Murias A, Soria P, Aguiar J, Salinas J, Hernandez MA, et al.Induction chemotherapy with carboplatin and ftorafur in advanced head and neck cancer. A randomized study. *American Journal of Clinical Oncology* 1992;**15**(5): 417–21.

UKHAN 2010 *{published and unpublished data}*

Monson K, Meadows H, Houghton J, Tobias JS. Combined modality treatment in head and neck cancer: an update on the UKHAN trial. *Clinical Oncology* 1996;**8**(5):340.

Tobias J, Monson K, Gupta N, MacDougall H, Glaholm J, Peto J, et al.Does chemotherapy have a role in the management of patients with advanced head and neck cancer? Early results from the UK head and neck (UKHAN) trial. Proceedings of the American Society of Clinical Oncology. 2001; Vol. 20:(Abs No 888).

* Tobias JS, Monson K, Gupta N, Macdougall H, Glaholm J, Hutchison I, et al.Chemoradiotherapy for locally advanced head and neck cancer: 10-year follow-up of the UK Head and Neck (UKHAN1) trial. Lancet Oncology 2010; Vol. 11, issue 1:66–74.

Tobias JS, Monson KM, Glaholm J, MacDougall RH, Gupta NK, et al.UKHAN 1: a prospective multi-centre randomised trial investigating chemotherapy as part of initial management in advanced head and neck cancer. *Radiotherapy and Oncology* 2001;**58 Suppl 1**:S16.

Tobias JS, Monson KM Glaholm J, MacDougall RH, Gupta NK, Peto J, et al.Early results from the UK head and neck (UKHAN) trial: the role of chemotherapy in primary management of advanced head and neck cancer. *British Journal of Cancer* 2001;**85 Suppl 1**:20.

Vermorken 2007 *{published data only}*

Bernier J, Coens C, Remenar E, Van Herpen C, Germa Lluch J, Stewart S, et al.Impact on quality of life (QoL) of the addition of docetaxel (T) to neoadjuvant cisplatin plus 5-fluorouracil treatment in patients with locally advanced unresectable squamous cell carcinoma of the head and neck (SCCHN): EORTC study 24971. Journal of Clinical Oncology 2006; Vol. 24, issue 18S.

Biakhov M, Betka J, Shah P, Julka P, et al.Results of a randomized phase 2 trial of docetaxel (TXT) with cisplatin (CDDP) or TXT with 5-fluorouracil (5FU) in patients (pts) with unresectable locally advanced squamous cell carcinoma

of the head and neck (SCCHN). *Annals of Oncology* 2000; **11 Suppl 4**:92.

Biakhov M, Shah P, Betka J, Doval D, Garin A, et al.A randomized phase II trial of taxotere (TXT) with cisplatin (CDDP) or TXT with 5-fluorouracil (5FU) in patients (PTS) with unresectable locally advanced squamous cell carcinoma of the head and neck. Proceedings of the American Society of Clinical Oncology. 2000:(Abs No 1657).

Remenar E, Van Herpen C, Germa Lluch J, Stewart S, Gorlia T, Degardin M, et al.A randomized phase III multicenter trial of neoadjuvant docetaxel plus cisplatin and 5-fluorouracil (TPF) versus neoadjuvant PF in patients with locally advanced unresectable squamous cell carcinoma of the head and neck (SCCHN). Final analysis of EORTC 24971. Journal of Clinical Oncology 2006; Vol. 24, issue 18S.

Vermorken J, Remenar E, Van Herpen C, Germa Lluch J, Stewart S, Gorlia T, et al.Standard cisplatin/infusional 5-fluorouracil (PF) vs docetaxel (T) plus PF (TPF) as neoadjuvant chemotherapy for nonresectable locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN): A phase III trial of the EORTC Head and Neck Cancer Group (EORTC #24971). Journal of Clinical Oncology 2004; Vol. 22:14S (Abs No 5508).

* Vermorken JB, Remenar E, van Herpen C, Gorlia T, Mesia R, Degardin M, et al.Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. New England Journal of Medicine 2007; Vol. 357, issue 17:1695–704.

Vokes 1990 *{published data only}*

Vokes EE, Panje WR, Mick R, Kozloff MF, Moran WJ, Sutton HG, et al.A randomized study comparing two regimens of neoadjuvant and adjuvant chemotherapy in multimodal therapy for locally advanced head and neck cancer. Cancer 1990; Vol. 66, issue 2:206–13.

Volling 1999 *{published data only}*

Schroder M, Muller RP, Knufermann H, Volling P. Improved survival after neoadjuvant Carboplatin/5 FU in resectable stage II and III squamous cell carcinomas of the oral cavity and tonsil. European Journal of Cancer 1993; Vol. 29Y:S144.

Volling P, Ebeling O, Schroder M. Results of a prospective randomized trial with induction chemotherapy for cancer of the oral cavity and tonsil. European Archives of Oto-Rhino-Laryngology 1999; Vol. 256, issue 1:45.

Volling P, Schroder M. Carboplatin/5-FU + operation + radiotherapy versus operation + radiotherapy by primary operable head and neck carcinomas: 4-year results. European Archives of Oto-Rhino-Laryngology 1993; Vol. Suppl II:175.

Volling P, Schroder M. Preliminary results of a prospective randomized study of primary chemotherapy in carcinoma of the oral cavity and pharynx. *HNO* 1995;**43**(2):58–64.

* Volling P, Schroder M, Eckel H, Ebeling O, Stennert E. Results of a prospective randomized trial with induction chemotherapy for cancer of the oral cavity and tonsils. *HNO* 1999;**47**(10):899–906.

Volling P, Schroder M, Muller RP, Ebeling O, Quirin R, Stennert E. Induction chemotherapy in primary resectable head and neck tumors: A prospective randomized trial. *International Journal of Oncology* 1994;**4**:909–14.

Weissler 1992 *{published data only}*

Keegan P, Pillsbury H, Weissler M. Simultaneous cisplatinum -5FU and radiotherapy versus radiotherapy alone in advanced carcinoma of the head and neck. Proceedings of the American Society of Clinical Oncology. 1988; Vol. 7:157.

* Weissler MC, Melin S, Sailer SL, Qaqish F, Rosenman JG, Pillsbury HC. Simultaneous chemoradiation in the treatment of advanced head and neck cancer. *Archives of Otolaryngology - Head & Neck Surgery* 1992;**118**(8):806–10.

Wendt 1998 *{published data only}*

Wendt T, Grabenbauer GG, Thiel HJ, et al.Simultaneous radiation therapy and chemotherapy versus radiation therapy alone in stage III and IV carcinoma of the head and neck: Results of a randomized trial. 81st Scientific Assembly and Annual Meeting of the Radiological Society of North America. 1995.

* Wendt TG, Grabenbauer GG, Rodel CM, Thiel HJ, Aydin H, Rohloff R, et al.Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: a randomized multicenter study. *Journal of Clinical Oncology* 1998;**16**(4):1318–24.

References to studies excluded from this review

Abele 1984 *{published data only}*

Abele R, Honegger HP, Grossenbacher R, Kaplan E, et al.Randomized trial of methotrexate (M), bleomycin (B) hydroxyurea (HU) with versus without cisplatin in advanced squamous cell carcinoma of head and neck. Proceedings of the American Society of Clinical Oncology. 1984:186 (Abs No C724).

Abele 1985 *{published data only}*

Abele R, Honegger HP, Wolfensberger M, Grossenbacher R, Mermillod B, Cavalli F. Methotrexate (M), bleomycin (B), hydroxyurea (HU) versus M+B+HU and cisplatin (C) in stage III-IV squamous cell carcinoma of the head and neck: a randomized study. Cancer Chemotherapy and Pharmacology 1985; Vol. 14, issue Suppl 1:S1.

Adelstein 1997 *{published data only}*

Adelstein DJ, Saxton JP, Lavertu P, Tuason L, Wood BG, Wanamaker JR, et al.A phase III randomized trial comparing concurrent chemotherapy and radiotherapy with radiotherapy alone in resectable stage III and IV squamous cell head and neck cancer: preliminary results. Head & Neck 1997; Vol. 19, issue 7:567–75.

Adelstein 2000 *{published data only}*

Adelstein DJ, Lavertu P, Saxton JP, Secic M, Wood BG, Wanamaker JR, et al.Mature results of a phase III randomized trial comparing concurrent chemoradiotherapy with radiation therapy alone in patients with stage III and

IV squamous cell carcinoma of the head and neck. *Cancer* 2000;**88**(4):876–83.

Amichetti 1989 ***{published data only}***

Amichetti M, Valentini A. Comparative study of two neoadjuvant protocols (VBM and DDP-BLM) combined with radiation therapy in advanced head and neck cancer. Journal of Chemotherapy 1989; Vol. 1, issue 1:68–71.

Andreadis 1999 ***{published data only}***

Andreadis C, Sidiropoulos J, Vahtsevanos K, Thomaidis J, et al.A phase III study of concurrent radiotherapy with carboplatin or weekly paclitaxel in patients with advanced squamous cell head and neck cancer (SCHNC). *European Journal of Cancer* 1999;**35 Suppl 4**:S172.

Anonymous 1976 ***{published data only}***

Anonymous. Bleomycin in advanced squamous cell carcinoma: a random controlled trial. Report of Medical Research Council Working Party on Bleomycin. *BMJ* 1976; **1**(6003):188–90.

Ansfield 1970 ***{published data only}***

Ansfield FJ, Ramirez G, Davis HL Jr, Korbitz BC, Vermund H, et al.Treatment of advanced cancer of the head and neck. *Cancer* 1970;**25**:78–82.

Antanadou 2002 ***{published data only}***

Antonadou D, Pepelassi M, Synodinou M, Puglisi M, Throuvalas N. Prophylactic use of amifostine to prevent radiochemotherapy-induced mucositis and xerostomia in head-and-neck cancer. International Journal of Radiation Oncology, Biology, Physics 2002; Vol. 52, issue 3:739–47.

Asif 2003 ***{published data only}***

Asif R, Chandra K, Chopra V, Bhatt. Concurrent cisplatin and radiotherapy in advanced head and neck cancer. Indian Journal of Otolaryngology and Head and Neck Surgery 2003; Vol. 55, issue 2:94–6.

Auersperg 1977 ***{published data only}***

Auersperg M, Soba E, Vraspir PO. Intravenous chemotherapy with syndronization in advanced cancer of oral cavity and oropharynx. Zeitschrift fur Krebsforschung und Klinische Onkologie 1977; Vol. 90:149–59.

Bachaud 1996 ***{published data only}***

* Bachaud JM, Cohen-Jonathan E, Alzieu C, David JM, Serrano E, ly-Schveitzer N. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial. *International Journal of Radiation Oncology, Biology, Physics* 1996;**36**(5):999–1004.
Bachaud JM, David JM, Boussin G, Daly N. Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced squamous cell carcinoma of the head and neck: preliminary report of a randomized trial. International Journal of Radiation Oncology, Biology, Physics 1991; Vol. 20, issue 2:243–6.

Bakowski 1978 ***{published data only}***

Bakowski MT, Macdonald E, Mould RF, Cawte P, Sloggem J, Barrett A, et al.Double blind controlled clinical trial of radiation plus razoxane (ICRF 159) versus radiation plus placebo in the treatment of head and neck cancer. *International Journal of Radiation Oncology, Biology, Physics* 1978;**4**(1-2):115–9.

Berger 1995 ***{published data only}***

Berger C, Chapet S, Calais G, Reynaud-Bougnoux A, Garand G, le FO. Concomitant radiochemotherapy with cisplatin (CDDP), 5-fluorouracil (5-FU) and mitomycin C (MMC) in locally advanced carcinoma of the oropharynx. Results of a phase II trial. *Bulletin du Cancer* 1995;**82**(12): 1044–51.

Bezwoda 1979 ***{published data only}***

Bezwoda WR, de Moor NG, Derman DP. Treatment of advanced head and neck cancer by means of radiation therapy plus chemotherapy--a randomised trial. *Medical & Pediatric Oncology* 1979;**6**(4):353–8.

Bier 1986 ***{published data only}***

Bier J. Prospective randomized clinical trial for squamous cell carcinomas of the oral cavity: preoperative chemotherapy versus postoperative chemotherapy versus surgery alone. Journal of Cancer Research & Clinical Oncology 1986; Vol. 111:S121.

Boidi 1991 ***{published data only}***

Boidi TA, Rovea P, Gabriele AM, Tseroni V, Fracchia F, Raiteri M, et al.Simultaneous treatment with c-DPP and radiation therapy for advanced head and neck tumors. A randomized study. *Radiologia Medica* 1991;**82**(4):504–7.

Bolla 1994 ***{published data only}***

Bolla M, Lefur R, Ton Van J, Domenge C, Badet JM, Koskas Y, et al.Prevention of second primary tumours with etretinate in squamous cell carcinoma of the oral cavity and oropharynx. Results of a multicentric double-blind randomised study. *European Journal of Cancer* 1994;**30A**: 767–72.

Bonner 2006 ***{published data only}***

Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, et al.Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *New England Journal of Medicine* 2006;**354**(6):567–78.

Bradley 1982 ***{published data only}***

Bradley PJ, Stell PM, Dalby JA, Fraser G, Strickland P. Does the addition of chemotherapy to radiotherapy improve survival in advanced head and neck cancer. *Clinical Otolaryngology* 1982;**7**:284.

Brigham 1998 ***{published data only}***

Brigham BA, Fisher RJ, Stewart J, Fong T, Mead K. Role of folinic acid in methotrexate treatment of head and neck squamous cancers. Proceedings of the American Society of Clinical Oncology. 1998:(Abs No 1518).

Browman 1983 ***{published data only}***

* Browman GP, Archibald SD, Young JE, Hryniuk WM, Russell R, Kiehl K, et al.Prospective randomized trial of one-hour sequential versus simultaneous methotrexate plus 5-fluorouracil in advanced and recurrent squamous cell

head and neck cancer. *Journal of Clinical Oncology* 1983;**1** (12):787–92.

Browman GP, Levine MN, Russell R, Young JE, Archibald SD. Survival results from a phase III study of simultaneous versus 1-hour sequential methotrexate-5-fluorouracil chemotherapy in head and neck cancer. *Head & Neck Surgery* 1986;**8**(3):146–52.

Browman GP, Young JEM, Archibald SD, Kiehl K, et al.Prospective randomised trial of i-hour sequential versus simultaneous methotrexate (MTX) + 5 fluorouracil (5FU) in squamous cell carcinoma of the head and neck (SCHN). Proceedings of the American Society of Clinical Oncology. 1983:158 (Abs No C-616).

Browman 1988 ***{published data only}***

Browman GP, Levine MN, Goodyear MD, Russell R, Archibald SD, Jackson BS, et al.Methotrexate/fluorouracil scheduling influences normal tissue toxicity but not antitumor effects in patients with squamous cell head and neck cancer: results from a randomized trial. *Journal of Clinical Oncology* 1988;**6**(6):963–8.

Browman 1990 ***{published data only}***

Browman GP, Goodyear MD, Levine MN, Russell R, Archibald SD, Young JE. Modulation of the antitumor effect of methotrexate by low-dose leucovorin in squamous cell head and neck cancer: a randomized placebo-controlled clinical trial. *Journal of Clinical Oncology* 1990;**8**(2):203–8.

Buentzel 2006 ***{published data only}***

* Buentzel J, Micke O, Adamietz IA, Monnier A, Glatzel M, De Vries A. Intravenous amifostine during chemoradiotherapy for head-and-neck cancer: A randomized placebo-controlled phase III study. *International Journal of Radiation Oncology, Biology, Physics* 2006;**64**(3):684–91.

Buentzel J, Monier A, Ammon G, Schmitt N, et al.Phase III randomized double blind placebo controlled trial of carboplatin and radiation therapy ± Amifostine in patients with head and neck cancer. Proceedings of the 43rd Annual Meeting of ASTRO. 2001; Vol. Suppl:85 (Abs No 151).

Buntzel 1998 ***{published data only}***

Buntzel J, Glatzel M, Kuttner K, Weinaug R, Frohlich D. Amifostine in simultaneous radiochemotherapy of advanced head and neck cancer. *Seminars in Radiation Oncology* 2002; **12**(1 Suppl 1):4–13.

* Buntzel J, Schuth J, Kuttner K, Glatzel M. Radiochemotherapy with amifostine cytoprotection for head and neck cancer. *Supportive Care in Cancer* 1998;**6**(2): 155–60.

Buntzel 1998a ***{published data only}***

Buntzel J, Glatzel M, Schuth J, Weinaug R, Kuttner K, Frohlich D. Clinical experiences with amifostine in the radiochemotherapy of head neck cancer. Journal of Cancer Research & Clinical Oncology 1998; Vol. 124 Suppl 1: R113.

* Buntzel J, Kuttner K, Frohlich D, Glatzel M. Selective cytoprotection with amifostine in concurrent radiochemotherapy for head and neck cancer. *Annals of Oncology* 1998;**9**(5):505–9.

Buntzel J, Schuth J, Weinaug R, Glatzel M, Frohlich D, Kuttner K. Cytoprotection with amifostine (A) as the base for intensification of radiochemotherapy in head and neck cancer. *Annals of Hematology* 1998;**77 Suppl 2**:S197.

Campbell 1987 ***{published data only}***

Campbell JB, Dorman EB, McCormick M, Miles J, Morton RP, Rugman F, et al.A randomized phase III trial of cisplatinum, methotrexate, cisplatinum + methotrexate, and cisplatinum + 5-fluoro-uracil in end-stage head and neck cancer. Acta Oto-Laryngologica 1987; Vol. 103, issue 5–6: 519–28.

Caponigro 2002 ***{published data only}***

Caponigro F, De Rosa P, Rosati G, Avallons A, De Lucia L, Morrica B, et al.A phase 2 randomised study of cisplatin (CDDP) raltitrexed (TOM) levofolinic acid (LFA) and 5-fluoruracil (5-FU) or CDDP, methotrexate (MTX) LFA and 5-FU in locally advanced (LAD) or metastatic (M) head and neck cancer (HNC). *Head and Neck Cancer* 2001;**37**: S105–6.

* Caponigro F, Rosati G, De Rosa P, Avallone A, De Rosa V, De Lucia L, et al.Cisplatin, raltitrexed, levofolinic acid and 5-fluorouracil in locally advanced or metastatic squamous cell carcinoma of the head and neck: a phase II randomized study. *Oncology* 2002;**63**(3):232–8.

Cappelaere 1981 ***{published data only}***

Cappelaere P, Chauvergne J, Klein T, Gary-Bobo J, Guerrin J, Meeus L. Randomized trial of vincristin-methotrexate-bleomycin and cis-platin or detorubicin for advanced head and neck cancer (author's transl). *Bulletin du Cancer* 1981; **68**(5):422–7.

Cappelaere 1990 ***{published data only}***

Cappelaere P, Vignoud J, Fargeot P, Metz R, Chauvergne J, Meeus L, et al.Palliative chemotherapy of epidermoid carcinoma of the upper respiratory and digestive tracts with a combination of carboplatin and 5-fluorouracil. *Bulletin du Cancer* 1990;**77**(11):1099–105.

Carugati 1988 ***{published data only}***

Carugati A, Pradier R, de la Torre A. Combination chemotherapy preradical treatment for head and neck squamous cell carcinoma. Proceedings of the American Society of Clinical Oncology. 1988; Vol. 7:152.

Clavel 1987 ***{published data only}***

* Clavel M, Cognetti F, Dodion P, Wildiers J, Rosso R, Rossi A, et al.Combination chemotherapy with methotrexate, bleomycin, and vincristine with or without cisplatin in advanced squamous cell carcinoma of the head and neck. *Cancer* 1987;**60**(6):1173–7.

Clavel M, Dodion P, Cognetti F, Van Rymenant M, Wildiers J, Rossi A, et al.Randomized trial of cisplatin (C), methotrexate (A), bleomycin (B) and vincristine (O) vs ABO in advanced squamous cell cancer of the head and neck. Cancer Chemotherapy and Pharmacology 1985; Vol. 14 Suppl 1:S14.

Coates 1984 *{published data only}*

Coates AS, Tattersall MH, Swanson C, Hedley D, Fox RM, Raghavan D. Combination therapy with methotrexate and 5-fluorouracil: a prospective randomized clinical trial of order of administration. *Journal of Clinical Oncology* 1984; **2**(7):756–61.

Coninx 1986 *{published data only}*

Coninx P, Nasca S, Jezekova D, Marechal F, Garbe E, Legros M, et al.Sequential trials in initial chemotherapy of advanced tumors of the upper aero-digestive system. Cis-diamminedichloroplatinum (DDP) versus DDP-etoposide (VP16). *Bulletin du Cancer* 1986;**73**(1):85–8.

Coninx 1988 *{published data only}*

Coninx P, Nasca S, Lebrun D, Panis X, Lucas P, Garbe E, et al.Sequential trial of initial chemotherapy for advanced cancer of the head and neck. DDP versus DDP + 5-fluorouracil. *Cancer* 1988;**62**(9):1888–92.

Corvo 1997 *{published data only}*

Corvo R, Giaretti W, Sanguineti G, Geido E, Bacigalupo A, Orecchia R, et al.Chemoradiotherapy as an alternative to radiotherapy alone in fast proliferating head and neck squamous cell carcinomas. *Clinical Cancer Research* 1997;**3** (11):1993–7.

Cruz 1997 *{published data only}*

Cruz JJ, Fonseca E, Rodriguez CA, Gomez A, Martin G, Sanchez P, et al.Randomized trial of cisplatin (P) plus 5-fluorouracil (F) with or without folinic acid in locally advanced head and neck cancer (LAHNC). European Journal of Cancer 1997; Vol. 33:854.

Cummings 2007 *{published data only}*

Cummings B, Keane T, Pintilie M, Warde P, Waldron J, Payne D, et al.Five year results of a randomized trial comparing hyperfractionated to conventional radiotherapy over four weeks in locally advanced head and neck cancer. *Radiotherapy and Oncology* 2007;**85**(1):7–16.

Dalley 1995 *{published data only}*

Dalley D, Beller E, Aroney R, Dewar J, Page J, Philip R, et al.The value of chemotherapy (CT) prior to definitive local therapy (DLT) in patients with locally advanced squamous cell carcinoma (SCC) of the head and neck (HN). Proceedings of American Society of Clinical Oncology. 1995; Vol. 14:297.

De la Torre 1991 *{published data only}*

De la Torre A, Aragon G, Valcarcel F, Magallon R, Cardenes H, Vazquez G, et al.A randomized study of radiotherapy treatment of advanced head and neck cancer, with vs without tegafur. European Journal of Cancer 1991; Vol. 27 Suppl 2:S143.

DeConti 1981 *{published data only}*

DeConti RC, Schoenfeld D. A randomized prospective comparison of intermittent methotrexate, methotrexate with leucovorin, and a methotrexate combination in head and neck cancer. *Cancer* 1981;**48**(5):1061–72.

Deka 1983 *{published data only}*

Deka AC, Deka BC, Kalghatgi RR, Patil RB. Combination treatment in moderately advanced head & neck cancer. Indian Journal of Medical Research 1983; Vol. 78 Suppl: 74–80.

Di Blasio 1994 *{published data only}*

Di Blasio B, Barbieri W, Bozzetti A, Iotti C, Di Sarra S, Cocconi G. A prospective randomized trial in resectable head and neck carcinoma: loco-regional treatment with and without neoadjuvant chemotherapy. Proceedings of the American Society of Clinical Oncology. 1994; Vol. 13:279.

Dobrowsky 1996 *{published data only}*

Dobrowsky W, Dobrowsky E, Naude J, Millesi W, Pavelka R, Kautzky M, et al.Conventional vs accelerated fractionation in head and neck cancer. British Journal of Cancer 1996; Vol. 27:S279–81.

Domenge 1987 *{published data only}*

Domenge C, Marands P, Douillard JY, Peuvrel P, Prevost B, Lefebvre J, et al.Post surgical adjuvant chemotherapy in extracapsular spread invaded lymph node (N+ R+) of epidermoid carcinoma of the head and neck. A randomized multicentric trial. Proceedings of the European Conference on Clinical Oncology. 1987; Vol. 4:242.

Domenge 1988 *{published data only}*

Domenge C, Marandas P, Vignoud J, et al.Post-surgical adjuvant chemotherapy in extracapsular spread invaded lymph node (N+R+) of epidermoid carcinoma of the head and neck: a randomized multicentric trial. 2nd International Conference on Head and Neck Cancer. Boston. American Society of Head & Neck Surgery. 1988; Vol. 74.

Drelichman 1983 *{published data only}*

Drelichman A, Cummings G, al Sarraf M. A randomized trial of the combination of cis-platinum, oncovin and bleomycin (COB) versus methotrexate in patients with advanced squamous cell carcinoma of the head and neck. Cancer 1983; Vol. 52, issue 3:399–403.

Ebeling 1994 *{published data only}*

Ebeling O, Eckel HE, Volling P, Heitmann K, Vossing M. Cisplatin/5FU versus carboplatin/5FU. 5 year follow up. *Head and Neck Oncology* 1994;**42**(10):629–35.

Eschwege 1997 *{published data only}*

Chassagne D, Charreau I, Sancho-Garnier H, Eschwege F, Malaise EP. First analysis of tumor regression for the European randomized trial of etanidazole combined with radiotherapy in head and neck carcinomas. *International Journal of Radiation Oncology, Biology, Physics* 1992;**22**(3): 581–4.

* Eschwege F, Sancho-Garnier H, Chassagne D, Brisgand D, Guerra M, Malaise EP, et al.Results of a European randomized trial of Etanidazole combined with radiotherapy in head and neck carcinomas. *International Journal of Radiation Oncology, Biology, Physics* 1997;**39**(2):275–81.

Ezzat 2005 *{published data only}*

Ezzat M, Shouman T, Zaza K, Safwat A, El-Khoudary A, El-Senosi M, et al.A randomized study of accelerated fractionation radiotherapy with and without mitomycin C in the treatment of locally advanced head and neck cancer.

Journal of the Egyptian National Cancer Institute 2005; Vol. 17, issue 2:85–92.

Fety 1994 *{published data only}*
Fety R, Rolland F, Barberi-Heyob M, Merlin JL, Conroy T, Hardouin A, et al.Clinical randomized study of 5FU monitoring versus standard dose in patients with head and neck cancer: preliminary results. *Anticancer Research* 1994; **14**(6A):2347–52.

Fety 1998 *{published data only}*
Fety R, Rolland F, Barberi-Heyob M, Hardouin A, Campion L, Conroy T, et al.Clinical impact of pharmacokinetically-guided dose adaptation of 5-fluorouracil: results from a multicentric randomized trial in patients with locally advanced head and neck carcinomas. *Clinical Cancer Research* 1998;**4**(9):2039–45.

Fonseca 1997 *{published data only}*
Fonseca E, Cruz JJ, Rodriguez CA, Gomez-Bernal A, Martin G, Sanchez P, et al.Randomized trial of neoadjuvant chemotherapy with cisplatin plus 5-fluorouracil, with or without leucovorin, in locally advanced head and neck cancer. Annals of Oncology 1997; Vol. 8, issue 7:713–4.

Fonseca 2005 *{published data only}*
Cruz JJ, Fonseca E, Gomez JG, Rueda A, et al.Randomized phase II trial of induction chemotherapy in patients with locally advanced head and neck carcinoma (LA-HNC) Docetaxel plus cisplatin (DP) versus cisplatin plus 5-FU (PF): interim results. Proceedings of the American Society of Clinical Oncology. 2002:(Abs No 920).
* Fonseca E, Grau JJ, Sastre J, Garcia-Gomez JM, Rueda A, Pastor M, et al.Induction chemotherapy with cisplatin/docetaxel versus cisplatin/5-fluorouracil for locally advanced squamous cell carcinoma of the head and neck: a randomised phase II study. *European Journal of Cancer* 2005;**41**(9):1254–60.

Forastiere 2001 *{published data only}*
Forastiere AA, Leong T, Rowinsky E, Murphy BA, Vlock DR, DeConti RC, et al.Phase III comparison of high-dose paclitaxel + cisplatin + granulocyte colony-stimulating factor versus low-dose paclitaxel + cisplatin in advanced head and neck cancer: Eastern Cooperative Oncology Group Study E1393. *Journal of Clinical Oncology* 2001;**19**(4):1088–95.

Fountzalis 2004 *{published data only}*
Fountzilas, G, Ciuleanu E, Theophanopoulou M, Kalogera-Fountzila A, et al.A randomised study of concomitant radiotherapy with cisplatin or carboplatin versus radiotherapy alone in patients with locally advanced non-nasopharyngeal head and neck cancer. A Hellenic cooperative oncology group phase III study. Proceedings of the American Society of Clinical Oncology. 2003:495 (Abs No 1991).
* Fountzilas G, Ciuleanu E, Dafni U, Plataniotis G, et al.Concomitant radiochemotherapy vs radiotherapy alone in patients with head and neck cancer. *Medical Oncology* 2004;**21**(2):95–107.

Fu 1987 *{published data only}*
Fu KK, Phillips TL, Silverberg IJ, Friedman MA, et al.Combined radiotherapy and chemotherapy with bleomycin and methotrexate for advanced head and neck cancer: interim report of NCOG randomized trial. Proceedings of the American Society of Clinical Oncology. 1983:159 (Abs No C-622).
* Fu KK, Phillips TL, Silverberg IJ, Jacobs C, Goffinet DR, Chun C, et al.Combined radiotherapy and chemotherapy with bleomycin and methotrexate for advanced inoperable head and neck cancer: update of a Northern California Oncology Group randomized trial. *Journal of Clinical Oncology* 1987;**5**(9):1410–8.

Fujii 1996 *{published data only}*
Fujii M, Ohno Y, Tokumaru Y, Imanishi Y, Kanke M. Combination chemotherapy with 5-FU and CDDP or CDDP analog for head and neck cancer. *Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy]* 1996;**23** (13):1740–6.

Fujii 1999 *{published data only}*
Fujii M, Kanke M, Tomita T. Low-dose CDDP and 5-FU for head and neck cancer patients. *Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy]* 1999;**26**(11): 1542–7.

Furukawa 1994 *{published data only}*
Furukawa S, Tsukuda M, Mochimatsu I, Kokatsu T, Satoh H, Sakumoto M. Modified combination chemotherapy of cisplatin and 5-fluorouracil in squamous cell carcinomas of the head and neck. *Auris, Nasus, Larynx* 1994;**21**(3):181–5.

Gabriele 1994 *{published data only (unpublished sought but not used)}*
Gabriele P, Orrechia R, Ragona R, Airoldi M, Ciambellotti E, et al.A cooperative AIRO/PIEMONTE randomized clinical trial of carboplatin as an adjunct to radiotherapy in head and neck cancer. *Radiotherapy and Oncology* 1994;**32 Suppl 1**:S93.

Gabriele 1996 *{published data only}*
Gabriele P, Gandolfo S, Solazzo L, Gallesio C, Ragona R, Beltramo G, et al.A phase III study of radiotherapy alone versus radiotherapy plus carboplatin in stage III-IV head and neck cancers. An analysis on oral cavity cancer. Journal of Cranio Maxillo Facial Surgery 1996; Vol. 24 Suppl 1:18.

Gasparini 1992 *{published data only}*
Gasparini G, Recher G, Testolin A, Dal FS, Panizzoni GA, Cristoferi V, et al.Synchronous radiotherapy and chemotherapy with cisplatin in the management of locally advanced or recurrent head and neck cancer. *American Journal of Clinical Oncology: Cancer Clinical Trials* 1992;**15** (3):242–9.

Gedouin 1986 *{published data only}*
Gedouin D, Desprez P, Perron JJ, Fleury F, Leclech G, Miglianico L, et al.Cancers of the base of the tongue and hypopharynx: results of a multicenter randomized trial of chemotherapy prior to locoregional treatment. *Bulletin du Cancer Radiotherapie* 1986;**83**(2):104–7.

Gedouin 1996 *{published data only}*

Gedouin D, Desprez P, Perron JJ, Fleury F, Leclech G, Miglianico L, et al.Cancers of the base of the tongue and hypopharynx: results of a multicenter randomized trial of chemotherapy prior to locoregional treatment. *Bulletin du Cancer Radiotherapie* 1996;**83**(2):104–7.

Gehanno 1992 *{published data only}*

Gehanno P, Depondt J, Peynegre R, Peytral C, Martin M, Baillet F, et al.Neoadjuvant combination of carboplatin and 5-FU in head and neck cancer: a randomized study. *Annals of Oncology* 1992;**3 Suppl 3**:43–6.

Gibson 2005 *{published data only}*

Gibson MK, Li Y, Murphy B, Hussain MHA, DeConti RC, Ensley J, et al.Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. *Journal of Clinical Oncology* 2005;**23**(15):3562–7.

Gollin 1972 *{published data only}*

* Gollin FF, Ansfield FJ, Brandenburg JH, Ramirez G, Vermund H. Combined therapy in advanced head and neck cancer: a randomized study. *American Journal of Roentgenology, Radium Therapy & Nuclear Medicine* 1972; **114**(1):83–8.

Lo TC, Wiley AL Jr, Ansfield FJ, Brandenburg JH, Davis HL, Jr, Gollin FF, et al.Combined radiation therapy and 5-fluorouracil for advanced squamous cell carcinoma of the oral cavity and oropharynx: a randomized study. *American Journal of Roentgenology* 1976;**126**(2):229–35.

Grose 1985 *{published data only}*

Grose WE, Lehane DE, Dixon DO, Fletcher WS, Stuckey WJ. Comparison of methotrexate and cisplatin for patients with advanced squamous cell carcinoma of the head and neck region: a Southwest Oncology Group Study. Cancer Treatment Reports 1985; Vol. 69, issue 6:577–81.

Haas 1985 *{published data only}*

Haas C, Byhardt R, Cox J, Duncovage J, Grossman T, Haas J, et al.Randomized study of 5-fluorouracil (F) and cis-platinum (P) as initial therapy of locally advanced squamous carcinoma of the head and neck (LASCHN): a preliminary analysis. Proceedings of the American Society of Clinical Oncology. 1985; Vol. 4:143.

Haas 1986 *{published data only}*

* Haas C, Anderson T, Byhardt R, Cox J, Duncavage J, Grossman T, et al.Randomized neo-adjuvant study of 5-fluorouracil and cis-platinum for patients with advanced resectable head and neck squamous cancer. Proceedings of the American Association for Cancer Research (AACR). 1986; Vol. 27:185.

Haas C, Byhardt R, Cox J, Duncovage J, Grossman T, Haas J, et al.Randomized study of 5-fluorouracil (F) and cis-platinum (P) as initial therapy of locally advanced squamous carcinoma of the head and neck (LASCHN): a preliminary analysis. Proceedings of the American Society of Clinical Oncology. 1985; Vol. 4:143.

Haffty 1993 *{published data only}*

Haffty BG, Son YH, Sasaki CT, Papac R, Fischer D, Rockwell S, et al.Mitomycin C as an adjunct to postoperative radiation therapy in squamous cell carcinoma of the head and neck: results from two randomized clinical trials. *International Journal of Radiation Oncology, Biology, Physics* 1993;**27**(2):241–50.

Haffty 1997 *{published data only}*

* Haffty BG, Son YH, Papac R, Sasaki CT, Weissberg JB, Fischer D, et al.Chemotherapy as an adjunct to radiation in the treatment of squamous cell carcinoma of the head and neck: results of the Yale Mitomycin Randomized Trials. *Journal of Clinical Oncology* 1997;**15**(1):268–76.

Hafty BG, Son YH, Papac R, Sasaki CT, Fischer D, Rockwell S, et al.chemotherapy as an adjunct to radiation therapy 9RT) in the treatment of squamous cell carcinoma, a (SCC) of the head and neck (H and N): results of the Yale mitomycin C (MC) randomized trials. Proceedings of the American Society of Clinical Oncology. 1996:(Abs No 893).

Haffty 1997a *{published data only}*

Haffty BG, Son YH, Wilson LD, Papac R, Fischer D, Rockwell S, et al.Bioreductive alkylating agent porfiromycin in combination with radiation therapy for the management of squamous cell carcinoma of the head and neck. *Radiation Oncology Investigations* 1997;**5**(5):235–45.

Haffty 2005 *{published data only}*

Haffty B, Son YH, Wilson LD, Cho EI, Papac RJ, et al.Concurrent chemo-radiotherapy with mitomycin C compared with porfiromycin in squamous cell cancer of the head and neck: Final results of a randomized clinical trial. International Journal of Radiation Oncology, Biology, Physics 2003; Vol. 57 Suppl 2:S246.

Haffty BG, Son Y, Papac R, Wilson L, et al.The bioreductive alkylating agent mitomycin-C (MC) or porfiromycin (PORF) with radiation therapy (RT) in squamous cell carcinoma of the head and neck (SCCHN): Results of a randomized clinical trial. Proceedings of the American Society of Clinical Oncology. 2001; Vol. 20:(Abs No 901).

* Haffty BG, Wilson LD, Son YH, Cho EI, Papac RJ, Fischer DB, et al.Concurrent chemo-radiotherapy with mitomycin C compared with porfiromycin in squamous cell cancer of the head and neck: final results of a randomized clinical trial. *International Journal of Radiation Oncology, Biology, Physics* 2005;**61**(1):119–28.

Handa 1980 *{published data only}*

Handa K, Edoliya TN, Pandey RP, Agarwal YC, Sinha N. A radiotherapeutic clinical trial of twice per week vs. five times per week in oral cancer. *Strahlentherapie* 1980;**156**(9): 626–31.

Hasegawa 1996 *{published data only}*

Hasegawa Y, Matsuura H, Fukushima M, Kano M, Shimozato K. Potential suppression of distant and node metastasis by neoadjuvant chemotherapy in advanced head and neck cancer: result of a randomized trial. Proceedings of the American Society of Clinical Oncology. 1996; Vol. 15:318.

Haselow 1990 *{published data only}*

Haselow RE, Warshaw ME, Oken MM, Adams GL, Aughey JL, Cooper JS, et al.Radiation alone versus radiation with weekly low dose cis-platinum in unresectable cancer of the head and neck. In: Fee WR Jr, Goepfert H, Johns ME, et al. editor(s). *Head and Neck Cancer*. Vol. **II**, Philadelphia: B C Decker, 1990:279–81.

Henk 1984 *{published data only}*

Henk JM, Adams GE, Ash D. A study of the effect of misonidazole in conjunction with radiotherapy for the treatment of head and neck cancer. *British Journal of Radiology* 1984;**57**(679):585–95.

Hitt 2005 *{published data only}*

Hitt R, Grau J, Lopez-Pousa A, Berrocal A, Garcia-Giron C, Belon J, et al.Randomized phase II/III clinical trial of induction chemotherapy (ICT) with either cisplatin/5-fluorouracil (PF) or docetaxel/cisplatin/5-fluorouracil (TPF) followed by chemoradiotherapy (CRT) vs. CRT alone for patients (pts) with unresectable locally advanced head and neck cancer (LAHNC). Journal of Clinical Oncology 2006; Vol. 24, issue 18S (Abs No 5515).

Hitt R, Grau J, Lopez-Pousa A, Berrocal A, Sastre J, Belon J, et al.Phase II/III Trial of Induction Chemotherapy(ICT) with Cisplatin/5-Fluorouracil (PF) vs. Docetaxel (T) plus PF (TPF) followed by Chemoradiotherapy (CRT) vs. CRT for Unresectable Locally Advanced Head and Neck Cancer (LAHNC). Journal of Clinical Oncology 2005; Vol. 23: 519 (Abs No 5578).

* Hitt R, Lopez-Pousa A, Martinez-Trufero J, Escrig V, Carles J, Rizo A, et al.Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. *Journal of Clinical Oncology* 2005;**23**(34):8636–45.

Homma 2004 *{published data only}*

Homma A, Shirato H, Furuta Y, Nishioka T, Oridate N, Tsuchiya K, et al.Randomized phase II trial of concomitant chemoradiotherapy using weekly carboplatin or daily low-dose cisplatin for squamous cell carcinoma of the head and neck. *Cancer Journal* 2004;**10**(5):326–32.

Hussey 1975 *{published data only}*

Hussey DH, Abrams JP. Combined therapy in advanced head and neck cancer: hydroxyurea and radiotherapy. *Progress in Clinical Cancer* 1975;**6**:79–86.

Jain 1979 *{published data only}*

Jain SP, Pandey UC, Tandon US. Methotrexate vs bleomycin experiences in advanced oral malignancies. *Indian Journal of Cancer* 1979;**16**:3–4.

Jones 1992 *{published data only}*

Jones AS, Phillips DE, Field JK. A phase II study of cisplatinum versus cisplatinum + nifedipine in end-stage carcinoma of the head and neck. *Clinical Otolaryngology & Allied Sciences* 1992;**17**(6):501–4.

Jortay 1990 *{published data only}*

Jortay A, Demard F, Dalesio O, Blanchet C, Desaulty A, Gehanno C, et al.A randomized EORTC study on the effect of preoperative polychemotherapy in pyriform sinus carcinoma treated by pharyngolaryngectomy and irradiation. Results from 5 to 10 years. *Acta Chirurgica Belgica* 1990;**90**(3):115–22.

Kamioner 1994 *{published data only}*

Kamioner D, Haddad E, Rocher MA. Carboplatin-radiotherapy versus cisplatin-radiotherapy according to a concurrent schedule in advanced head and neck cancer: results of a randomized study. Annals of Oncology 1994; Vol. 5 Suppl 8:115.

Kaneda 1987 *{published data only}*

Kaneda T, Kawabe Y. Primary clinical effects of chemotherapy mainly with cisplatin, peplomycin (PP therapy) against head and neck cancer--the multi-institutional joint research in Tokai district. *Nippon Gan Chiryo Gakkai Shi [Journal of Japanese Society for Cancer Therapy]* 1987;**22**(7):1385–98.

Kapstad 1978 *{published data only}*

Kapstad B, Bang G, Rennaes S, Dahler A. Combined preoperative treatment with cobalt and bleomycin in patients with head and neck carcinoma--a controlled clinical study. *International Journal of Radiation Oncology, Biology, Physics* 1978;**4**(1-2):85–9.

Kapstad 1979 *{published data only}*

Kapstad B. Cobalt and bleomycin against carcinomas of head and neck. A controlled clinical study. *Acta Oto Laryngologica* 1979;**360**(Suppl):171–3.

Katori 2007 *{published data only}*

* Katori H, Tsukuda M, Watai K. Comparison of hyperfractionation and conventional fractionation radiotherapy with concurrent docetaxel, cisplatin and 5-fluorouracil (TPF) chemotherapy in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN). *Cancer Chemotherapy & Pharmacology* 2007;**60** (3):399–406.

* Katori K, Tsukuda M, Ishitoya J, Kimura M, Hirose S, Takahashi M, et al.Comparison of induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil (TPF) followed by radiation versus concurrent chemoradiotherapy with TPF in patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN). Journal of Clinical Oncology 2005; Vol. 23:16S.

Klima 1988 *{published data only}*

Klima A, Bergmann I, Szepesi S. Multimodality treatment in stage IV squamous cell carcinoma of the head and neck. A long-term follow-up. *Journal of Laryngology & Otology* 1992;**106**(3):234–7.

* Klima A, Klippstein TH, Bergmann L, Szepesi S, Ilberg CV. Adjuvant chemotherapy in stage III and IV squamous cell carcinoma of the head and neck. *Journal of Laryngology & Otology* 1988;**102**:337–40.

Klima A, von Ilberg C, Bergmann L, Klippstein T, Zoubek A, Mitrou PS, et al.The effect of radio- and chemotherapy on

survival in advanced head and neck tumors. *Strahlentherapie und Onkologie* 1987;**163**(5):297–300.

Klima A, von Ilberg C, Bergmann L, Zoubek A, Klippstein T, Mitrou PS, et al.Chemotherapy or chemotherapy and radiotherapy in advanced head and neck tumors. A prospective, randomized study comparing the 2 therapeutic modalities. *Head & Neck Oncology (HNO)* 1987;**35**(2): 78–83.

Klima A, von Ilberg C, Klippstein T, Szepesi S. Chemotherapy of advanced head and neck tumors. A prospective randomized study comparing the effectiveness of chemotherapy alone to a chemo-radiotherapy procedure. *Laryngologie, Rhinologie, Otologie* 1987;**66**(4):205–10.

Kotani 1994 *{published data only}*

Kotani A, Sunada O, Tamura M, Takaku S, Kobayashi A, Asakura A, et al.Multiple cooperative study of UFT-adjuvant chemotherapy for malignant tumor in the jaw and oral cavities. The Oral Surgery Malignant Tumor Research Association in Kanto Kohshinetsu District. *Gan To Kagaku Ryoho* 1994;**21**(7):987–92.

Laccourreye 1983 *{published data only}*

Laccourreye H, Beutter P, Brasnu D, Lacau-Saint-Guily J, Bassot V, Garabedian N, et al.Comparative study of 2 chemotherapy induction protocols. Cisplatinum-methotrexate-bleomycin and oncovin-methotrexate-bleomycin. *Annales d'Oto-Laryngologie et de Chirurgie Cervico-Faciale* 1983;**100**(4):269–74.

Lavertu 1998 *{published data only}*

Lavertu P, Bonafede JP, Adelstein DJ, Saxton JP, Strome M, Wanamaker JR, et al.Comparison of surgical complications after organ-preservation therapy in patients with stage III or IV squamous cell head and neck cancer. *Archives of Otolaryngology - Head & Neck Surgery* 1998;**124**(4):401–6.

Le 1998 *{published data only}*

Le QX, Pinto HA, Tate DJ, et al.Randomized phase II trial of tirpazamine in advanced squamous cell carcinoma of the head and neck: A preliminary report of radiation related toxicity. 84th Annual Meeting of the Scientific Assembly of the Radiological Society of North America. 1998.

Lee 1989 *{published data only}*

Lee DJ, Pajak TF, Stetz J, Order SE, Weissberg JB, Fischer JJ. A phase I/II study of the hypoxic cell sensitizer misonidazole as an adjunct to high fractional dose radiotherapy in patients with unresectable squamous cell carcinoma of the head and neck: a RTOG randomized study (#79-04). *International Journal of Radiation Oncology, Biology, Physics* 1989;**16**(2): 465–70.

Lippman 1988 *{published data only}*

Lippman SM, Kessler JF, al Sarraf M, Alberts DS, Itri LM, Mattox D, et al.Treatment of advanced squamous cell carcinoma of the head and neck with isotretinoin: a phase II randomized trial. *Investigational New Drugs* 1988;**6**(1): 51–6.

Liverpool HNOG 1990 *{published data only}*

Liverpool Head and Neck Oncology Group. A phase III randomised trial of cisplatinum, methotrextate, cisplatinum + methotrexate and cisplatinum + 5-FU in end stage squamous carcinoma of the head and neck. Liverpool Head and Neck Oncology Group. *British Journal of Cancer* 1990; **61**(2):311–5.

Lopes 1991 *{published data only}*

Lopes M, Morais R, Viterbo L, et al.Induction chemotherapy in advanced head and neck cancer. *European Journal of Cancer* 1991;**27 Suppl 2**:S147.

Magno 1994 *{published data only}*

Magno L, Terraneo F, Bertoni F, Tordiglione M, Bardelli D, Rosignoli MT, et al.Double-blind randomized study of lonidamine and radiotherapy in head and neck cancer. *International Journal of Radiation Oncology, Biology, Physics* 1994;**29**(1):45–55.

Manocha 2006 *{published data only}*

Manocha S, Suhag V, Sunita B, Hooda H, Singh S. Comparison of sequential chemoradiation with radiation alone in the treatment of advanced head and neck cancers. Indian Journal of Otolaryngology 2006; Vol. 58, issue 1: 57–60.

Mantovani 1998 *{published data only}*

Mantovani G, Gebbia V, Airoldi M, Bumma C, Contu P, Bianchi A, et al.Neo-adjuvant chemo-(immuno-)therapy of advanced squamous-cell head and neck carcinoma: a multicenter, phase III, randomized study comparing cisplatin + 5-fluorouracil (5-FU) with cisplatin + 5-FU + recombinant interleukin 2. *Cancer Immunology & Immunotherapy* 1998;**47**(3):149–56.

Martin 1994 *{published data only}*

Martin M, Hazan A, Vergnes L, Peytral C, Mazeron JJ, Senechaut JP, et al.Randomized study of 5 fluorouracil and cis platin as neoadjuvant therapy in head and neck cancer: a preliminary report. *International Journal of Radiation Oncology, Biology, Physics* 1990;**19**(4):973–5.

* Martin M, Vergnes L, Lelièvre G, et al.A randomized study of CDDP and 5-FU as neoadjuvant chemotherapy in head and neck cancer: an interim analysis. In: Banzet P, Holland JF, Khayat D, Weil M editor(s). *Cancer Treatment: An Update*. Paris: Springer-Verlag, 1994:214–8.

Mechl 1987 *{published data only}*

Mechl Z, Kerpel-Fronius S, Decker A, Gorbunova VA, Gurtler R, Hindy I, et al.Comparative evaluation of two administration schedules of cis-dichlorodiammineplatinum (DDP) in ovarian and head and neck cancers: a CMEA chemotherapy group study. *Neoplasma* 1987;**34**(1):37–43.

Moro 1994 *{published data only}*

Moro G, Orrechia R, Tseroni V, Munoz Argenta A, Melano A, Ragona R, et al.Concomitant carboplatin and radiotherapy versus standard irradiation in advanced head and neck cancer: preliminary results of a cooperative randomized trial. Annals of Oncology 1994; Vol. 5 Suppl 8:116.

Morton 1985 *{published data only}*

Morton RP, Rugman F, Dorman EB, Stoney PJ, Wilson JA, McCormick M, et al.Cisplatinum and bleomycin for advanced or recurrent squamous cell carcinoma of the head

and neck: a randomised factorial phase III controlled trial. *Cancer Chemotherapy & Pharmacology* 1985;**15**(3):283–9.

Morton 1987 ***{published data only}***

Morton RP, Rugman F, Dorman EB, Stoney PJ, Wilson JA, McCormick M, et al.Cisplatin and bleomycin in the treatment of advanced or recurrent squamous cell carcinoma of the head and neck. A randomized facultative Phase III controlled study. *Sonderbande zur Strahlentherapie und Onkologie* 1987;**81**:141–50.

Nissenbaum 1984 ***{published data only}***

Nissenbaum M, Browde S, Bezwoda WR, de Moor NG, Derman DP. Treatment of advanced head and neck cancer: multiple daily dose fractionated radiation therapy and sequential multimodal treatment approach. *Medical & Pediatric Oncology* 1984;**12**(3):204–8.

O'Connor 1979 ***{published data only}***

O'Connor AD, Clifford P, Dalley VM, Durden Smith DJ, Edwards WG, Hollis BA. Advanced head and neck cancer treated by combined radiotherapy and VBM cytotoxic regimen--four-year results. *Clinical Otolaryngology and Allied Sciences* 1979;**4**(5):329–37.

Olasz 2004 ***{published data only}***

Olasz L, Nemeth A, Nyarady Z, Tornoczky T, Kiralyfalvi L. Results and failures with or without cisplatin containing induction chemotherapy in the treatment of squamous cell carcinoma of the head and neck. *Cancer Detection & Prevention* 2004;**28**(1):65–71.

Panis 1984 ***{published data only}***

Panis X, Nguyen TD, Froissart D, Demange L. Hyperfractionated radiotherapy with or without misonidazole: results of a prospective randomized study in stage III-IV squamous cell carcinoma of the head and neck. *International Journal of Radiation Oncology, Biology, Physics* 1984;**10**(10):1845–9.

Pant 1973 ***{published data only}***

Pant GC, Sanyal B, Khanna NN, Rastogi BL. Sequential treatment of advanced oral carcinoma by methotrexate and radiotherapy. Indian Journal of Medical Research 1973; Vol. 61, issue 6:848–55.

Papac 1978 ***{published data only}***

Papac R, Minor DR, Rudnick S, Solomon LR, Capizzi RL. Controlled trial of methotrexate and Bacillus Calmette-Guerin therapy for advanced head and neck cancer. *Cancer Research* 1978;**38**(10):3150–3.

Pearlman 1985 ***{published data only}***

* Pearlman NW, Johnson FB, Braun TJ, Kennaugh RC, Spofford BF, Borlase BC, et al.A prospective study of preoperative chemotherapy and split-course irradiation for locally advanced or recurrent oral/pharyngeal squamous carcinoma. *American Journal of Clinical Oncology* 1985;**8**(6):490–6.

Pearlman NW, Meyers AD, Johnson FB, DiBella NJ. Preoperative chemo-radiotherapy in advanced head and neck cancer. Head & Neck Surgery 1982; Vol. 5, issue 1: 10–4.

Peng 2007 ***{published data only}***

Peng JW, Liang HL, Zhang JK, Xiao JJ, Zhang CZ. Clinical effect of nedaplatin in treatment of advanced head and neck cancer. Chinese Journal of Cancer Prevention & Treatment 2007; Vol. 14, issue 10:779–81.

Phillips 1980 ***{published data only}***

Phillips TL, Silverberg IJ, Fu KK, Friedman MA, Torti F, Kohler M, et al.Interim report on a phase III study of Bleomycin and Methotrexate with radiotherapy in the treatment of inoperable head and neck cancer. *International Journal of Radiation Oncology, Biology, Physics* 1980;**6**(10): 1447.

Platzer 1990 ***{published data only}***

Platzer E, Sendler A, Iro H, Gramatzki M, Waitz G, Nitsche NC, et al.Recombinant human granulocyte colony-stimulating factor in chemotherapy for advanced head and neck carcinoma. *Journal of Cancer Research & Clinical Oncology* 1990;**116**(Suppl):700.

Price 1978 ***{published data only}***

Price LA, Hill BT, Calvert AH, Dalley M, Levene A, Busby ER, et al.Improved results in combination chemotherapy of head and neck cancer using a kinetically-based approach: a randomised study with and without adriamycin. *Oncology* 1978;**35**(1):26–8.

Proto 1993 ***{published data only}***

Proto E, Puxeddu P, Curreli L, Bianchi A, Puxeddu R, Mantovani G. Combined modality therapy (chemoimmunotherapy + radiotherapy +/- surgery) in advanced neoplasias of the head and neck. Otorinolaringologia 1993; Vol. 43, issue 4:165–9.

Racadot 2008 ***{published data only}***

Racadot S, Mercier M, Dussart S, Dessard-Diana B, Bensadoun RJ, Martin M, et al.Randomized clinical trial of post-operative radiotherapy versus concomitant carboplatin and radiotherapy for head and neck cancers with lymph node involvement. *Radiotherapy and Oncology* 2008;**87**(2): 164–72.

Rodrigo 2004 ***{published data only}***

Rodrigo JP, Maseda E, Maldonado M, Aldama P, Puente M, Llorente JL, et al.Efficacy of postoperative radiation therapy for squamous cell carcinoma of the head and neck: results of a prospective randomised clinical trial. *Acta Otorrinolaringologica Espanola* 2004;**55**(9):415–9.

Rosen 2003 ***{published data only}***

Rosen FR, Haraf DJ, Kies MS, Stenson K, Portugal L, List MA, et al.Multicenter randomized Phase II study of paclitaxel (1-hour infusion), fluorouracil, hydroxyurea, and concomitant twice daily radiation with or without erythropoietin for advanced head and neck cancer. Clinical Cancer Research 2003; Vol. 9, issue 5:1689–97.

Sanchiz 1990 ***{published data only}***

Sanchiz F, Milla A, Torner J, Bonet F, Artola N, Carreno L, et al.Single fraction per day versus two fractions per day versus radiochemotherapy in the treatment of head and neck cancer. *International Journal of Radiation Oncology, Biology, Physics* 1990;**19**(6):1347–50.

Sanguineti 1999 *{published data only}*

Sanguineti G, Corvo R, Sormani MP, Benasso M, Numico G, Bacigalupo A, et al.Chemotherapy alternated with radiotherapy in the treatment of advanced head and neck carcinoma: predictive factors of outcome. *International Journal of Radiation Oncology, Biology, Physics* 1999;**44**(1): 139–47.

Sarkar 2008 *{published data only}*

Sarkar SK, Patra NB, Goswami J, Basu S. Comparative study of efficacy and toxicities of cisplatin vs vinorelbine as radiosensitisers in locally advanced head and neck cancer. Journal of Laryngology & Otology 2008; Vol. 122, issue 2: 188–92.

Schildhauer 2005 *{published data only}*

Schildhauer S, Pecher G, Pollmann D, Wernecke KD, Possinger K, Luftner D. Liposomal formulated cisplatin (lipoplatin) in the treatment of squamous cell carcinoma of the head and neck (SCCHN): First safety results of a randomized phase III study. *Onkologie* 2005;**28 Suppl 3**: 48.

Schildhauer S, Pollmann D, Pecher G, Wernecke K-D, Possinger K, Luftner D. Randomized phase III study in squamous cell carcinoma of the head & neck (SCCHN) using Lipoplatin: First safety results of a multicentre trial. *European Journal of Cancer* 2005;**3**(2):S286.

Schuller 1989 *{published data only}*

Schuller DE, Laramore G, al Sarraf M, Jacobs J, Pajak TF. Combined therapy for resectable head and neck cancer. A phase 3 intergroup study. *Archives of Otolaryngology -- Head & Neck Surgery* 1989;**115**(3):364–8.

Sealy 1978 *{published data only}*

Sealy R. A preliminary clinical study in the use of misonidazole in cancer of the head and neck. *British Journal of Cancer* 1978;**37**(3):314–7.

SECOG 1986 *{published data only}*

Clifford P, O'Connor AD, Carter RL, Dalley VM, Darby AJ, Deutsch G, et al.Combination treatment in advanced head and neck cancer. *Lancet* 1982;**2**(8300):708–9.

* South-East Co-operative Oncology Group. A randomized trial of combined multidrug chemotherapy and radiotherapy in advanced squamous cell carcinoma of the head and neck. An interim report from the SECOG participants. South-East Co-operative Oncology Group. *European Journal of Surgical Oncology* 1986;**12**(3):289–95.

Tobias JS, Edwards WG, Grant HR, Monson KM, Houghton J. Combined radiotherapy and chemotherapy in the treatment of squamous cell carcinoma of the oral cavity: results from two randomized trials. *Clinical Oncology* 1994; **6**:61.

Shaw 1978 *{published data only}*

Shaw HJ, Price LA, Hill BT, Calvert AH, Dalley VM, Levene A. A randomized combination chemotherapy trial, with and without adriamycin, in squamous cell carcinoma of the head and neck. *Otolaryngology* 1978;**86**(6 Pt 1): ORL–50.

Shetty 1985 *{published data only}*

Shetty P, Mehta A, Shinde S, Mazumdar A, Hingorani C. Controlled study in squamous cell carcinoma of base of tongue using conventional radiation, radiation with single drug, and radiation with multiple drug chemotherapy. Proceedings of the Annual Meeting of the American Society of Clinical Oncology. 1985; Vol. 4:152.

Siodlak 1989 *{published data only}*

Siodlak MZ, Dalby JE, Bradley PJ, Campbell JB, Strickland P, Fraser JG, et al.Induction VBM plus radiotherapy, versus radiotherapy alone for advanced head and neck cancer: long-term results. *Clinical Otolaryngology & Allied Sciences* 1989;**14**(1):17–22.

Smid 2003 *{published data only}*

Smid L, Budihna M, Zakotnik B, Soba E, Strojan P, Fajdiga I, et al.Postoperative concomitant irradiation and chemotherapy with mitomycin C and bleomycin for advanced head-and-neck carcinoma. *International Journal of Radiation Oncology, Biology, Physics* 2003;**56**(4):1055–62.

Snow 1981 *{published data only}*

Snow JB, Gelber RD, Kramer S, Davis LW, Marcial VA, Lowry LD. Comparison of preoperative and postoperative radiation therapy for patients with carcinoma of the head and neck. Interim report. Acta Oto-Laryngologica 1981; Vol. 91, issue 5–6:611–26.

Soo 2005 *{published data only}*

Lim D, Tai B, Wee J, Tan E, Leong SS, et al.Randomised trial comparing surgery and adjuvant radiotherapy with concurrent chemoirradiation and salvage surgery in resectable stage III and IV squamous cell carcinoma of the head and neck. Proceedings of ASCO. 2003.

* Soo KC, Tan EH, Wee J, Lim D, Tai BC, Khoo ML, et al.Surgery and adjuvant radiotherapy vs concurrent chemoradiotherapy in stage III/IV nonmetastatic squamous cell head and neck cancer: a randomised comparison. *British Journal of Cancer* 2005;**93**(3):279–86.

Stefani 1971 *{published data only}*

Stefani S, Eells RW, Abbate J. Hydroxyurea and radiotherapy in head and neck cancer. Results of a prospective controlled study in 126 patients. *Radiology* 1971;**101**(2):391–6.

Stefani 1980 *{published data only}*

Stefani S, Chung TS. Hydroxyurea and radiotherapy in head and neck cancer. Long term results of a double blind randomized prospective study. *International Journal of Radiation Oncology, Biology, Physics* 1980;**6**(10):1398.

Stell 1983 *{published data only}*

Stell PM, Dalby JE, Strickland P, Fraser JG, Bradley PJ, Flood LM. Sequential chemotherapy and radiotherapy in advanced head and neck cancer. *Clinical Radiology* 1983;**34** (4):463–7.

Stell 1990 *{published data only}*

Stell PM, Allison RS, Campbell JB, Dalby JE, Dorman EB, Helliwell TR, et al.A phase III randomised trial of cisplatinum, methotrexate, cisplatinum + methotrexate and cisplatinum + 5-FU in end stage squamous carcinoma of the head and neck. *British Journal of Cancer* 1990;**61**(2):311–5.

Stolwijk 1985 *{published data only}*

Stolwijk C, Wagener DJ, Van den Broek P, Levendag PC, Kazem I, Bruaset I, et al.Randomized neo-adjuvant chemotherapy trial for advanced head and neck cancer. Netherlands Journal of Medicine 1985; Vol. 28, issue 9: 347–51.

Suwinski 2005 *{published data only}*

Suwinski R, Bankowska-Wozniak M, Majewski W, Sowa A, Idasiak A, Ziolkowska E, et al.Randomized clinical trial on continuous 7-days-a-week postoperative radiotherapy for high-risk squamous cell head-and-neck cancer: a report on acute normal tissue reactions. *Radiotherapy and Oncology* 2005;**77**(1):58–64.

Taylor 1979 *{published data only}*

Taylor SG, DeWys WD, Perlia CP, Wolter J, Slayton RE, Kosova LA, et al.A randomized comparison of two dosage schedules of methyl CCNU: three-week versus six-week treatments. *Cancer* 1979;**44**(3):824–30.

Taylor 1984 *{published data only}*

Taylor SG, McGuire WP, Hauck WW, Showel JL, Lad TE. A randomized comparison of high-dose infusion methotrexate versus standard-dose weekly therapy in head and neck squamous cancer. Journal of Clinical Oncology 1984; Vol. 2, issue 9:1006–11.

Taylor 1985 *{published data only}*

Corey JP, Caldarelli DD, Hutchinson JC Jr, Holinger LD, Taylor SG, Showel JL, et al.Surgical complications in patients with head and neck cancer receiving chemotherapy. *Archives of Otolaryngology - Head & Neck Surgery* 1986;**112**(4):437–9.

* Taylor SG, Applebaum E, Showel JL, Norusis M, Holinger LD, Hutchinson JC, et al.A randomized trial of adjuvant chemotherapy in head and neck cancer. Journal of Clinical Oncology 1985; Vol. 3, issue 5:672–9.

Taylor 1994 *{published data only}*

Taylor SG, Murthy AK, Vannetzel JM, Colin P, Dray M, Caldarelli DD, et al.Randomized comparison of neoadjuvant cisplatin and fluorouracil infusion followed by radiation versus concomitant treatment in advanced head and neck cancer. *Journal of Clinical Oncology* 1994;**12**(2): 385–95.

Taylor 1997 *{published data only}*

Griem K, Murthy A, Vannetzel J, Kies M, et al.The five year results of an randomized trial of sequential versus concomitant cisplatin and fluorouracil and radiation in advanced head and neck cancer. Proceedings of the 37th annual ASTRO meeting. 1995:(Abs No 105).

* Taylor SG, Murthy AK, Griem KL, Recine DC, Kiel K, Blendowski C, et al.Concomitant cisplatin/5FU infusion and radiotherapy in advanced head and neck cancer: 8-year analysis of results. *Head & Neck* 1997;**19**(8):684–91.

Toohill 1987 *{published data only}*

* Toohill RJ, Anderson T, Byhardt RW, Cox JD, Duncavage JA, Grossman TW, et al.Cisplatin and fluorouracil as neoadjuvant therapy in head and neck cancer. A preliminary report. *Archives of Otolaryngology - Head & Neck Surgery* 1987;**113**(7):758–61.

Toohill RJ, Anderson T, Byhardt RW, et al.Cisplatin/5FU as neoadjuvant therapy in head and neck cancer: a preliminary report. 5th Joint Meeting of the American Society for Head and Neck Surgery and Society of Head and Neck Surgeons. Dorado, Puerto Rico, 1985.

Tsukuda 1994 *{published data only}*

Tsukuda M, Ogasawara H, Kaneko S, Komiyama S, Horiuchi M, Inuyama Y, et al.A prospective randomized trial of adjuvant chemotherapy with UFT for head and neck carcinoma. Head and Neck UFT Study Group. *Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy]* 1994;**21**(8):1169–77.

Tsukuda 2005 *{published data only}*

Tsukuda M, Kida A, Fujii M, Kono N, Yoshihara T, Hasegawa Y, et al.Randomized scheduling feasibility study of S-1 for adjuvant chemotherapy in advanced head and neck cancer. *British Journal of Cancer* 2005;**93**(8):884–9.

Vega 1981 *{published data only}*

Vega MF, Scola B, Perez MG. Polychemotherapy in advanced tumors of head and neck. A randomized study. *Acta Otorrinolaringologica Espanola* 1981;**32**(5):700–6.

Venkatachalam 1998 *{published data only}*

Venkatachalam VP, Bhowmik KT. Comparative evaluation of chemoimmunoradiotherapy and chemoradiotherapy in the management of advanced head and neck cancer. Indian Journal of Otolaryngology 1998; Vol. 50, issue 4:345–8.

Vermund 1985 *{published data only}*

Vermund H, Kaalhus O, Winther F, Trausjo J, Thorud E, Harang R. Bleomycin and radiation therapy in squamous cell carcinoma of the upper aero-digestive tract: a phase III clinical trial. *International Journal of Radiation Oncology, Biology, Physics* 1985;**11**(11):1877–86.

Veronesi 1985 *{published data only}*

Veronesi A, Zagonel V, Tirelli U, Galligioni E, Tumolo S, Barzan L, et al.High-dose versus low-dose cisplatin in advanced head and neck squamous carcinoma: a randomized study. *Journal of Clinical Oncology* 1985;**3**(8): 1105–8.

Von Heyden 1984 *{published data only}*

Schroder M, Von Heyden HW, Scherpe A, Borghardt J, Beyer JH, Nagel GA, et al.2nd interim evaluation of a chemotherapy study on patients with squamous cell carcinomas of the head-neck area. A comparison of 2 therapy regimens: cis-diamminedichloroplatinum (II) and bleomycin versus methotrexate and vindesine. *Onkologie* 1983;**6**(3):114–7.

Von Heyden HW, Schroder M, Scherpe A. Chemotherapy of advanced squamous carcinoma of the head and neck region. A randomized trial between cis-dichlorodiamineplatinum-(II) (cis-DDP) and bleomycin (BLM) against methotrexate (MTX) and vindesine (VDS). *Onkologie* 1984;**7**:183–90.

Von Heyden HW, Schroder M, Scherpe A. Preoperative chemotherapy results of 44 patients with advanced

squamous cell carcinoma of the head and neck region. *Head and Neck Oncology (HNO)* 1984;**32**:454–9.

Von Heyden 1982 ***{published data only}***
Von Heyden HW. Multicentre crossover trial of cis-dichlorodiamine platinum (cDDP) and bleomycin (BL) versus methotrexate (MTX) and vindesine (VD) in advanced squamous cell carcinoma of the head and neck. *Journal of Cancer Research and Clinical Oncology* 1982;**103** (Suppl):A16.

Von Heyden 1984 ***{published data only}***
Von Heyden HW, Schroder M, Scherpe A. Preoperative chemotherapy results of 44 patients with advanced squamous cell carcinoma of the head and neck region. HNO 1984; Vol. 32, issue 11.

Von Heyden 1985 ***{published data only}***
Von Heyden H, Schroder M, Scherpe A, Beyer J, et al.Chemotherapy (CT) of advanced squamous cell carcinoma of the head and neck, a randomized crossover trial between cis-dichlorodiamineplatinum (cis-DDP) and bleomycin (BLM) versus methotrexate (MTX) and vindesine (VDS). Proceedings of the American Society of Clinical Oncology. 1984:178 (Abs No C-693).
Von Heyden HW, Schroder M, Scherpe A, Beyer JH, Kaboth U, Stennert E, et al.Cytostatic therapy of advanced squamous cell carcinoma of the head and neck. A randomized study comparing cis-dichlorodiammineplatinum(II) and bleomycin with methotrexate and vindesine. *Onkologie* 1984;**7**(3):183–90.
* Von Heyden HW, Schroder M, Scherpe A, Borghardt J, Beyer JH, Nagel GA, et al.Chemotherapy of squamous head and neck cancer: a prospective randomized trial comparing cis-platinum and bleomycin with methotrexate and vindesine. *Recent Results in Cancer Research* 1985;**98**: 148–52.

Weissberg 1989 ***{published data only}***
Weissberg, JB. Prospective randomized trial of radiation therapy (RT) versus RT plus mitomycin C (MC) in head and neck cancer. American Society for Therapeutic Radiology and Oncology 27th Annual Meeting. 1985.
Weissberg JB, Son YH, Papac R, Rockwell S, Kennedy KA, et al.Radiation therapy and mitomycin C in the treatment of head and neck cancer: prospective randomized trial. *International Journal of Radiation Oncology, Biology, Physics* 1981;**7**(9):1261.
Weissberg JB, Son YH, Papac RJ. Radiation therapy (RT) and mitomycin C (MC) in the treatment of head and neck cancer: Prospective randomized trial. Proceedings of the American Association for Cancer Research. 1985; Vol. 26: 675.
* Weissberg JB, Son YH, Papac RJ, Sasaki C, Fischer DB, Lawrence R, et al.Randomized clinical trial of mitomycin C as an adjunct to radiotherapy in head and neck cancer. *International Journal of Radiation Oncology, Biology, Physics* 1989;**17**(1):3–9.
Weissberg JB, Son YH, Papac RJ, Sasaki DB, Fischer DS, et al.Radiation therapy (RT) and mitomycin C (MC) in the treatment of head and neck cancer: prospective randomized trial. Proceedings of AACR. 1985:170.

Woods 1977 ***{published data only}***
Woods JE, DeSanto LW, Ritts RE Jr. A controlled study of combined methotrexate, BCG, and INH therapy for squamous cell carcinoma of the head and neck. *Surgical Clinics of North America* 1977;**57**(4):769–78.

Woods 1981 ***{published data only}***
Woods RL, Fox RM, Tattersall MH. Methotrexate treatment of advanced head and neck cancers: a dose response evaluation. Cancer Treatment Reports 1981; Vol. 65 Suppl 1:155–9.

Woods 1981a ***{published data only}***
Woods RL, Fox RM, Tattersall MH. Methotrexate treatment of squamous-cell head and neck cancers: dose-response evaluation. *British Medical Journal Clinical Research Ed* 1981;**282**(6264):600–2.

Woods 1984 ***{published data only}***
Woods RL, Gill PG, Levi JA. Chemotherapy (CT for advanced squamous cell carcinomas) (SCCs) of head and neck: A randomised comparison of high dose versus low dose cis platinum (CIS DDP) in combination with bleomycin and methotrexate. American Association for Cancer Research 75th Annual Meeting. 1984:(Abs No 764).

Yoshino 1991 ***{published data only}***
Yoshino K, Sato T, Nakai Y, Tanabe M, Matsunaga T, Kozuka T, et al.A comparative clinical study of adjuvant chemotherapy of tumors in the head and neck areas by means of HCFU. *Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy]* 1991;**18**(15):2581–8.

Yoshino 1994 ***{published data only}***
Yoshino K, Sato T, Nakai Y, Tanabe M, Matsunaga T, Kozuka T, et al.A comparative clinical study on the treatment of head and neck tumors by adjuvant chemotherapy with HCFU--Second Study by Kinki Head and Neck Tumor Study Group. *Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy]* 1994;**21**(6): 777–83.

References to studies awaiting assessment

Abdel Wahab 2006 ***{published data only}***
Abdel Wahab MMA, Ezz Alarab LR, Adly A, El Fiky LM. Radiotherapy versus concurrent chemotherapy followed by adjuvant chemotherapy in the treatment of locally advanced head and neck cancer. *Annals of Oncology* 2006;**17**(9 Suppl 9):179–80.

Bouillet 2007 ***{published data only}***
Bouillet T, Nizri D, Zawadi A, Herman D, Cupissol D, Demaux H, et al.A randomized phase II study of concomitant CT (docetaxel?cisplatin) and (RT) in first-line treatment of locally advanced head and neck cancer (LAHNC). Journal of Clinical Oncology 2007; Vol. 25, issue 18S.

Bourhis 2002 *{published data only}*

Bourhis J, Lapeyre M, Tortochaux J, Etassami A, et al.Preliminary results of the GORTEC 96-01 randomized trial, comparing very accelerated radiotherapy versus concomitant radio-chemotherapy for locally inoperable HNSCC. Proceedings of the American Society of Clinical Oncology. 2002; Vol. 21:(Abs No 905).

Bourhis J, Lapeyre M, Tortochaux J, Etessami A, et al.Very accelerated RT versus CDDP-5FU in unresectable HNSCC: results of the GORTEC 96-01 randomized trial. Radiation Oncology 2002; Vol. 64 Suppl 1:S118.

Datta 1991 *{published data only}*

Datta NR, Handa S, Bose AK. Concurrent radiotherapy and chemotherapy in the management of oral cancer. *Indian Journal of Radiology and Imaging* 1991;**1**:425–9.

Ghosh 2006 *{published data only}*

Ghosh S, Agarwal JP, Bhutani R, Vora A, Prabhash K, D'Cruz A, et al.Randomized trial of conventional fractionated RT (CFRT) vs. concomitant chemo radiotherapy (CTRT) and accelerated radiotherapy (ACRT) in patients with advanced, non nasopharyngeal, squamous cell cancers of the head and neck region. International Journal of Radiation Oncology, Biology, Physics 2006; Vol. 66, issue 3 Suppl 1:S191.

Hitt 2009 *{published data only}*

Hitt R, Grau JJ, Lopez-Pousa A, Berrocal A, Garcia Giron C, Irigoyen A. Final results of a randomized phase III trial comparing induction chemotherapy with cisplatin/5-FU or docetaxel/cisplatin/5-FU follow by chemoradiotherapy (CRT) versus CRT alone as first-line treatment of unresectable locally advanced head and neck cancer (LAHNC). Journal of Clinical Oncology 2009; Vol. 27:15S (Abs No 6009).

Rapoport 1991 *{published data only}*

Rapoport A, Kowalski LP, Carvalho MBD, Fava AS, Gois F, Chagas JFS, et al.Induction intra-arterial chemotherapy in cancer of the tongue and floor of the mouth: end results of clinical trial. *Revista do Colégio Brasileiro de Cirurgioes* 1991; **18**:167–72.

Saber 2005 *{published data only}*

Saber RA, Mohamad SS. Use of chemotherapy in combination with radiotherapy in the treatment of locally advanced head and neck cancer patients. Journal of Clinical Oncology 2005; Vol. 23.

Sharma 2007 *{published data only}*

Sharma A, Mohanti BK, Thakar A, Bahadur S, Bhasker S, Bahl A. Concomitant chemoradiation versus radiotherapy in advanced squamous cell carcinoma of oropharynx and nasopharynx using weekly cisplatin: Final result of a phase III trial. Journal of Clinical Oncology 2007; Vol. 25:18S.

Tepmongkol 1989 *{published data only}*

Tepmongkol P, Thansakul A, Jirapanuwat S. Neo-adjuvant chemotherapy by using methotrexate prior to radiation therapy in the treatment of advanced oral cancers. *Siriraj Hospital Gazette* 1989;**41**:277–84.

Additional references

Attner 2010

Attner P, Du J, Nasman A, Hammarstedt L, et al.The role of human papillomavirus in the increased incidence of base of tongue cancer. *International Journal of Cancer* 2010;**126**: 2879–84.

Conway 2008

Conway DI, Petticrew M, Marlborough H, Berthiller J, Mia Hashibe M, Macpherson LMD. Socioeconomic inequalities and oral cancer risk: A systematic review and meta-analysis of case-control studies. *International Journal of Cancer* 2008;**122**(12):2811–9.

D'Souza 2007

D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, et al.Case-control study of human papillomavirus and oropharyngeal cancer. New England Journal of Medicine 2007; Vol. 356, issue 19:1944–56.

Day 1992

Day GL, Blot WJ. Second primary tumors in patients with oral cancer. *Cancer* 1992;**70**(1):14–9.

Faggiano 1997

Faggiano F, Partanen T, Kogevinas M, Boffetta P. Socioeconomic differences in cancer incidence and mortality. In: Kogevinas M, Pearce N, Susser M, Boffetta P editor(s). *Social Inequalities and Cancer*. Lyon: IARC Scientific Publications No 138. International Agency for Research in Cancer, 1997.

Fakhry 2006

Fakhry C, Gillison ML. Clinical implications of human papillomavirus in head and neck cancers. *Journal of Clinical Oncology* 2006;**24**(17):2606–11.

Fakhry 2008

Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, et al.Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. Journal of the National Cancer Institute 2008; Vol. 100, issue 4:261–9.

Fanucchi 2006

Fanucchi M, Khuri FD, Shin D, Johnstone PAS, Chen A. Update in the management of head and neck cancer. *Update on Cancer Therapeutics* 2006;**1**(2):211–9.

Freedman 2007

Freedman ND, Abnet CC, Leitzmann MF, Hollenbeck AR, Schatzkin A. Prospective investigation of the cigarette smoking-head and neck cancer association by sex. Cancer 2007; Vol. 110, issue 7:1593–601.

Funk 2002

Funk GF, Karnell LH, Robinson RA, Zhen WK, Trask DK, Hoffman HT. Presentation, treatment, and outcome of oral cavity cancer: a National Cancer Data Base report. *Head & Neck* 2002;**24**(2):165–80.

Glenny 2010

Glenny AM, Furness S, Worthington HV, Conway DI, Oliver R, Clarkson JE, Macluskey M, Pavitt S, Chan KKW,

Brocklehurst P, The CSROC Expert Panel. Interventions for the treatment of oral cavity and oropharyngeal cancer: radiotherapy. *Cochrane Database of Systematic Reviews* 2010, Issue 12. [DOI: 10.1002/14651858.CD006387]

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

Hammarstedt 2006
Hammarstedt L, Lindquist D, Dahlstrand H, Romanitan M, Dahlgren LO, Joneberg J, et al.Human papillomavirus as a risk factor for the increase in incidence of tonsillar cancer. International Journal of Cancer 2006; Vol. 119, issue 11:2620–3.

Harari 2005
Harari PM. Promising new advances in head and neck radiotherapy. *Annals of Oncology* 2005;**16 Suppl 6**: vi13–vi19.

Higgins 2009
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions version 5.0.2 (updated September 2009). The Cochrane Collaboration, 2009. Available from www.cochrane-handbook.org.

Hughes 1993
Hughes CJ, Gallo O, Spiro RH, Shah JP. Management of occult neck metastases in oral cavity squamous carcinoma. *American Journal of Surgery* 1993;**166**(4):380–3.

La Vecchia 1997
La Vecchia C, Tavani A, Franceschi S, Levi F, Corrao G, Negri E. Epidemiology and prevention of oral cancer. *Oral Oncology* 1997;**33**(5):302–12.

Licitra 2006
Licitra L, Perrone F, Bossi P, Suardi S, Mariani L, Artusi R, et al.High-risk human papillomavirus affects prognosis in patients with surgically treated oropharyngeal squamous cell carcinoma. Journal of Clinical Oncology 2006; Vol. 24, issue 36:5630–6.

Macfarlane 1995
Macfarlane GJ, Zheng T, Marshall JR, Boffetta P, Niu S, Brasure J, et al.Alcohol, tobacco, diet and the risk of oral cancer: a pooled analysis of three case-control studies. *Oral Oncology* 1995;**31B**(3):181–7.

McGurk 2005
McGurk M, Chan C, Jones J, O'Regan E, Sherriff M. Delay in diagnosis and its effect on outcome in head and neck cancer. *British Journal of Oral and Maxillofacial Surgery* 2005;**43**(4):281–4.

Oliver 2007
Oliver R, Clarkson JE, Conway D, Glenny AM, Macluskey M, Pavitt S, Sloan P, The CSROC Expert Panel, Worthington HV. Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment. *Cochrane Database of Systematic Reviews* 2007, Issue 4. [DOI: 10.1002/14651858.CD006205.pub2]

Parkin 2001
Parkin DM. Global cancer statistics in the year 2000. *Lancet Oncology* 2001;**2**(9):533–43.

Parkin 2005
Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA: a Cancer Journal for Clinicians 2005; Vol. 55, issue 2:74–108.

Parmar 1998
Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analysis of the published literature for survival endpoints. *Statistics in Medicine* 1998;**17**(24): 2815–34.

Partridge 2000
Partridge M, Li SR, Pateromichelakis S, Francis R, Phillips E, Huang XH, et al.Detection of minimal residual cancer to investigate why oral tumors recur despite seemingly adequate treatment. *Clinical Cancer Research* 2000;**6**(7): 2718–25.

Patel 2005
Patel SG, Shah JP. TNM Staging of Cancers of the Head and Neck: Striving for Uniformity Among Diversity. *CA: a Cancer Journal for Clinicians* 2005;**55**(4):242–58.

Pavitt 2007
Pavitt S, Clarkson JE, Conway D, Glenny AM, Macluskey M, Oliver R, Sloan P, The CSROC Expert Panel, Warnakulasuriya S, Worthington HV. Interventions for the treatment of oral and oropharyngeal cancers: immunotherapy/biotherapy. *Cochrane Database of Systematic Reviews* 2007, Issue 4. [DOI: 10.1002/14651858.CD006845]

Pentenero 2005
Pentenero M, Gandolfo S, Carrozzo M. Importance of tumor thickness and depth of invasion in nodal involvement and prognosis of oral squamous cell carcinoma: a review of the literature. *Head & Neck* 2005;**27**(12):1080–91.

Pignon 2000
Pignon JP, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *The Lancet* 2000;**355**(9208):949–55.

Pignon 2009
Pignon JP, le Maitre A, Maillard E, Bourhis J, Group M-NC. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiotherapy & Oncology 2009; Vol. 92, issue 1:4–14.

Ryerson 2008
Ryerson AB, Peters ES, Coughlin SS, Chen VW, Gillison ML, Reichman ME, et al.Burden of potentially human papillomavirus-associated cancers of the oropharynx and oral cavity in the US, 1998-2003. *Cancer* 2008;**113**(10 Suppl):2901–9.

Shah 1990

Shah J. Cervical lymph node metastases--diagnostic, therapeutic, and prognostic implications. *Oncology* 1990;**4** (10):61–9.

Specenier 2007

Specenier P, Vermorken JB. The role of taxanes and targeted therapies in locally advanced head and neck cancer. *Current Opinion in Oncology* 2007;**19**(3):195–201.

Sturgis 2007

Sturgis EM, Cinciripini PM. Trends in head and neck cancer incidence in relation to smoking prevalence. *Cancer* 2007;**110**(7):1429–35.

Warnakulasuriya 2009

Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncology 2009; Vol. 45, issue 4–5:309–16.

WHO 1992

WHO. *ICD-O. International Statistical Classification of Diseases and Related Health Problems, 1989 Revision*. Geneva: World Health Organization, 1992.

Woolgar 2003

Woolgar JA, Rogers SN, Lowe D, Brown JS, Vaughan ED. Cervical lymph node metastasis in oral cancer: the importance of even microscopic extracapsular spread. *Oral Oncology* 2003;**39**(2):130–7.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Adelstein 1993

Methods	Randomised controlled trial conducted in: Cleveland USA Number of centres: 1 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 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** 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 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

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information on sequence generation given
Allocation concealment?	Unclear	No information given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All those randomised accounted for in analysis

Adelstein 1993 (*Continued*)

Free of selective reporting?	Yes	Planned outcomes described and reported
Free of other bias?	Yes	

Adelstein 2003

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 (non-resectable)** 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 30-40Gy 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	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?	Unclear	No information given

Adelstein 2003 (*Continued*)

Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	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 7, 10 and 7 patients from groups A, B &C respectively were either ineligible or had no data)
Free of selective reporting?	Yes	Planned outcomes described and reported
Free of other bias?	Unclear	In toxicity results (table 4, p 95) data from ineligible patients are included. ?ineligible patients are included in other outcome data

Argiris 2008

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 ± radiotherapy + chemotherapy versus surgery ± radiotherapy alone** Gr A (n = 36): radiotherapy 1.8 Gy /day, 5x 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, 5x 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%

Argiris 2008 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	"Randomly assigned, no stratification factors". No information on sequence generation provided
Allocation concealment?	Unclear	No information on allocation concealment provided
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Unclear	4/76 subsequently found to be ineligible and 2 refused treatment. Not stated which groups these were from
Free of selective reporting?	Yes	Planned outcomes of DFS, OS, patterns of relapse and toxicity reported
Free of other bias?	Unclear	There is some imbalance between groups at baseline - Gr A has 80% of larynx cancer patients and Gr B has 70% of oral cavity cancer patients. Details of high risk features of Gr A largely unknown (table 1)

Bensadoun 2006

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: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)**

Bensadoun 2006 (*Continued*)

	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 = 40.8Gy. 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 (ie 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Carried out centrally by independent service using a minimisation technique with stratification according to location of primary tumour
Allocation concealment?	Yes	No other information given but likely to have been concealed
Blinding of participants?	No	Open label
Blinding of carers?	No	Open label
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	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?	Yes	Primary and secondary outcomes clearly stated and results presented
Free of other bias?	Unclear	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

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 year
Interventions	**Comparison 2: Surgery ± radiotherapy + chemotherapy versus surgery ± radiotherapy alone** 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) 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 includes 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

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation performed centrally by EORTC DATA co-ordinating centre. Randomisation was by Pocock minimisation technique stratified by

Bernier 2004 (*Continued*)

		centre, site and T stage (T1-T3 vs T4)
Allocation concealment?	Yes	Allocation was revealed by telephone call or internet connection to randomisation centre
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Insufficient information provided
Incomplete outcome data addressed?	Yes	All randomised participants accounted for and included in analysis
Free of selective reporting?	Yes	Primary and secondary outcomes clearly stated and results reported
Free of other bias?	Yes	

Bitter 1979

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 ± radiotherapy + chemotherapy versus surgery ± radiotherapy alone** Gr A (n = 16): received post-operative chemotherapy methotrexate, bleomycin and vincristine (dosages and regimen not stated) Gr B (n = 17): received post-operative 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No information on sequence generation given

Bitter 1979 (*Continued*)

Allocation concealment?	Unclear	No information on allocation concealment given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All 33 patients randomised to treatment are included in the analysis of outcomes at 2 years
Free of selective reporting?	Unclear	No primary or secondary outcomes specified
Free of other bias?	Unclear	Numbers of patients from each hospital are different in Groups A & B - potentially this could mean that the groups varied with respect to extent of disease at baseline

Brizel 1998

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 *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: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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

Brizel 1998 (*Continued*)

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

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Strategy designed by biostatistics unit. PI telephone 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?	Yes	Third party allocation by biostatistics unit
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	Unclear	Insufficient information given
Incomplete outcome data addressed?	Yes	All randomised participants accounted for and included in analysis
Free of selective reporting?	Yes	Primary and secondary outcomes clearly stated and results presented
Free of other bias?	Yes	No additional threats to validity

Browman 1986

Methods	Randomised controlled trial conducted in: Canada Number of centres: multicentre Recruitment period: October 1980 - September1982 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

Browman 1986 (*Continued*)

	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 are included in this review. Data for this subgroup are available. 35 participants in this trial have recurrent disease and 32 of these had prior treatment

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Insufficient information given
Allocation concealment?	Unclear	Insufficient information given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All randomised participants accounted for and included in analysis
Free of selective reporting?	Yes	Primary outcomes clearly stated and results reported
Free of other bias?	Yes	No additional threats to validity

Browman 1994

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. Withdrawls and drop outs accounted for
Interventions	**Comparison 3: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	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?	Yes	Treatment centres contacted a central randomisation office to obtain allocation
Blinding of participants?	Yes	Patients randomised to receive either radiotherapy + 1-FU or radiotherapy + placebo

Browman 1994 (*Continued*)

Blinding of carers?	Unclear	Insufficient information provided
Blinding of outcome assessors?	Unclear	Insufficient information provided
Incomplete outcome data addressed?	Yes	All randomised participants accounted for and included in analysis
Free of selective reporting?	Yes	Primary and secondary outcomes clearly stated and results presented
Free of other bias?	Yes	No additional threats to validity

Brunin 1989

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 i.v. on day 1; mitomycin C 10 mg/day given given by i.v. 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

Brunin 1989 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Insufficient information given
Allocation concealment?	Unclear	Insufficient information given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All randomised participants accounted for and included in analysis
Free of selective reporting?	Yes	Primary and secondary outcomes clearly stated and results presented
Free of other bias?	Yes	No additional threats to validity identified

Budach 2005

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: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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 6MV photons with up to 36-40 Gy when the posterior neck was blocked to

	shield the spinal cord max of 45Gy 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 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 are given at 2, 3 and 5 years follow-up Hazard ratios are given Data for total mortality taken from Pignon 2009
Notes	NOTE: RADIOTHERAPY DIFFERS 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"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?	Unclear	No information given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	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, non-compliance or death (total 20% in C-HART & 10% in HART) intention-to-treat, available for therapy and per protocol populations analysed

Budach 2005 (*Continued*)

Free of selective reporting?	Yes	Outcomes clearly described and reported
Free of other bias?	Yes	

Buffoli 1992

Methods	Randomised controlled trial conducted in: Brescia, Italy Number of centres: 1 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 $\geq$ 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 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** 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} 6Mv 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Sequence generation was by means of random numbers generated by computer. Allocations were placed in sealed envelopes

Buffoli 1992 (*Continued*)

Allocation concealment?	Yes	Sealed envelopes were distributed by Insitute secretary as each patient was included in the study
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All randomised patients included in evaluation of survival, tumour response and toxicities
Free of selective reporting?	Yes	Planned outcomes of OS, DFS at 5 years and tumour response reported
Free of other bias?	Yes	No additional threats to validity identified

Chauhan 2008

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 $\leq$ 70% (sic), adequate liver function, bone marrow reserve and renal function 80 randomised 40 in each group, 84% oral or oropharyngeal cancer
Interventions	**Comparison 3: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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	

Chauhan 2008 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	"Prospectively randomised", no details of sequence generation methods given
Allocation concealment?	Unclear	No information on allocation concealment given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All randomised patients included in toxicity and locoregional control outcomes
Free of selective reporting?	Yes	Planned outcomes of toxicity and locoregional control reported
Free of other bias?	Yes	Groups appear well balanced at baseline

Chauvergne 1988

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

Item	Authors' judgement	Description

Chauvergne 1988 (*Continued*)

Adequate sequence generation?	Unclear	"Randomly assigned", no details of sequence generation given
Allocation concealment?	Unclear	Insufficient information given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	2 post-randomisation exclusions in each group - unlikely to bias results
Free of selective reporting?	Yes	Total mortality, relapse free survival and toxicity planned and reported
Free of other bias?	Yes	No significant differences between the groups at baseline

Cooper 2004

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 characteristic, (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 ± radiotherapy + chemotherapy versus surgery ± radiotherapy alone** Both groups underwent total surgical resection of all visible and palpable disease Gr A (n = 228): surgery plus post-operative concomitant RCT (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 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	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 balanced by institution and then according to patient factors
Allocation concealment?	Unclear	No details given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	Reasons for post-randomisation exclusions clearly described and similar in both groups
Free of selective reporting?	Yes	Pre-specified outcomes described and reported
Free of other bias?	Yes	

Corvo 2001

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 drop outs accounted for Patients were adults aged < 75 years
Interventions	**Comparison 3: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** Gr A (n = 70): alternating CT and RT. Treatment consisted of 4 cycles of iv cisplatin (20 mg/ 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) 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 DIFFERS BETWEEN TWO GROUPS

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"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?	Yes	Maintained by central office, accessed by telephone
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned

Corvo 2001 (*Continued*)

Incomplete outcome data addressed?	Yes	Analysis by intention-to-treat. Exclusions, withdrawals and discontinuation clearly described for each group
Free of selective reporting?	Yes	
Free of other bias?	Yes	

De Andres 1995

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)** 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 antiemetic 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No information on sequence generation given
Allocation concealment?	Unclear	No information given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned

De Andres 1995 (*Continued*)

Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	1 patient randomised withdrew consent prior to start of treatment but other 95 patients included in evaluation. 2 patients lost to follow-up after treatment completion
Free of selective reporting?	Yes	Planned outcomes of response and toxicity were reported
Free of other bias?	Yes	

Denis 2004

Methods	Randomised controlled trial conducted pan-France Multicentre centre (8 institutions) Recruitment period: July 1994 - September 1997. Funding source: government - French Ministry of Health Trial identification number: GORTEC study ('Groupe d'Oncolgie Radiothérape Tête et Cou - GORTEC) 9401
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: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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

Denis 2004 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"Randomly assigned to a treatment group by a central office ..... Randomisation balanced by institution and clinical stage"
Allocation concealment?	Yes	Performed centrally
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	Withdrawals clearly described in each group
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Depondt 1993

Methods	Randomised controlled trial conducted in France 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 receive RT some receive surgery) Gr B (n = 150): radiotherapy (all receive RT some receive 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,

Depondt 1993 (*Continued*)

	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

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No details given
Allocation concealment?	Unclear	No details given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Unclear	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?	Yes	Planned outcomes described and reported
Free of other bias?	Unclear	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

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: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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 is included in the analysis (3.1.15) ln (HR)= -0.15, SE = 0.18 However OS estimate calculated from Fig 1, p 122 of paper gives ln (HR)= -0.35, Se ln(HR) = 0.19 (non significant difference)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	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?	Yes	Patients were allocated to treatment groups by means of a phone call from investigator to randomisation centre

Dobrowsky 2000 (*Continued*)

Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All 239 randomised patients are included in the outcome assessment
Free of selective reporting?	Yes	Primary outcome is overall survival and tumour response and toxicity also reported
Free of other bias?	Yes	4 patients were randomised twice but second randomisation was discarded

Domenge 2000

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) 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 bilateral superior cervical areas, and 50 Gy to the inferior cervical areas with a boost of 15 Gy in the case of extracapsular spread

Domenge 2000 (*Continued*)

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 are 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

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"Patients were randomised by telephone .... randomisation was stratified by centre and local treatment (surgery +/- Radiotherapy or radiotherapy alone)"
Allocation concealment?	Yes	Randomisation performed centrally, allocated by telephone
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	Withdrawals and drop outs accounted for
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Eschwege 1988

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 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

Eschwege 1988 (*Continued*)

	of nodal statusT2-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: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"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?	Yes	Generation of randomisation sequence and concealment performed by statistical unit
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	"25 patients were excluded for different reasons; these patients were well balanced within the two treatment groups"
Free of selective reporting?	Yes	Primary and secondary outcomes clearly stated and results presented

Eschwege 1988 (*Continued*)

Free of other bias?	Yes	2/15 centres were excluded from the analysis because they each only randomised one patient. This is unlikely to have influenced the results of the trial

Fazekas 1980

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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomisation stratified by primary site, stage and institution. Generation of randomisation sequence unclear
Allocation concealment?	Unclear	No details given

Fazekas 1980 (*Continued*)

Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Unclear	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 states 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?	Yes	Planned outcomes described and reported
Free of other bias?	Yes	

Garden 2004

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: Regimen A versus Regimen B versus Regimen C** 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 R
Outcomes	Tolerance, toxicity, locoregional control, disease free survival, overall survival
Notes	HR for total mortality calculated from Kaplan-Meier curves

Garden 2004 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	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
Allocation concealment?	Yes	Patients were enrolled and randomised by a telephone call to the RTOG centre
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Unclear	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?	Yes	Many outcomes described and reported
Free of other bias?	Yes	

Gasparini 1993

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 $\geq$ 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

Gasparini 1993 (*Continued*)

	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

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	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?	Unclear	No details given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All patients assigned to treatment groups were included in analyses of DFS & OS
Free of selective reporting?	Yes	Primary and secondary outcomes described and reported
Free of other bias?	Yes	

Giglio 1997

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 1: Induction chemotherapy plus Locoregional treatment (LRT) versus LRT 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

Giglio 1997 (*Continued*)

	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 hours intervals on weeks 5&6, and 8&9 to total dose of 80 Gy 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

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	"Rrandomised". No information on sequence generation given. Planned 2:1 ratio GrA: GrB
Allocation concealment?	Unclear	No information given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Unclear	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?	Yes	Planned outcomes - response, toxicity, survival, time to progression reported
Free of other bias?	Yes	Groups appear similar at baseline

Gladkov 2007

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)

Gladkov 2007 (*Continued*)

	Gr B (n = 26): radiotherapy + cisplatin (40 mg/m^2 IV once per week) + NaCl (up to 2500 ml intravenously) 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 is 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

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

Gonzalez-Larriba 1997

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 $\geq$ 70%, no previous treatment, evaluable/measurable tumour lesions, adequate renal & liver function, no previous neoplasia

Gonzalez-Larriba 1997 (*Continued*)

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. 4x 21-day cycles Gr B (n = 33): cisplatin 100 mg/m^2 on day 1+ uracil 300 mg/m^2/day in 3 doses on days 2-20. 4x 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	"Randomly assigned" - no further details given
Allocation concealment?	Unclear	No information given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All randomised patients included in the analyses
Free of selective reporting?	Yes	Primary and secondary outcomes described and reported
Free of other bias?	Yes	

Grau 2003

Methods	Randomised controlled trial conducted pan-world (Bulgaria, India, Malaysia, Pakistan, Sri Lanka and Turkey) Multicentre centre (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 centres. Patients had stage III (n = 223) or stage IV (n = 255), (T1-T2, T3-T4; N0, N1-N3>) SCC oral cavity n = 230 (48%) oropharynx n = 140 (29%) combined OC/OP = 77%
Interventions	**Comparison 3: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	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-

Grau 2003 (*Continued*)

		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?	Yes	The randomisation results were returned to the investigator with a working day by fax
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	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
Free of selective reporting?	Yes	Planned outcomes described and reported
Free of other bias?	Yes	

Gupta 2001

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: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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

Gupta 2001 (*Continued*)

	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

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	"Randomly allocated" - stratified for both site of disease and stage of disease
Allocation concealment?	Unclear	Insufficient information given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	No withdrawals/drop outs - all patients randomised accounted for and included in the analyses
Free of selective reporting?	Yes	Primary and secondary outcomes described and reported
Free of other bias?	Yes	

Gupta 2009

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/

Gupta 2009 (*Continued*)

	mm^3, platelets > 100,000/mm^3, total bilirubin < 1.25 x upper limit of normal, creatinine clearance > 50 ml/min Eclusion: ECOG performance status > 2, treatment protocol changed during study, previous chemotherapy or radiotherapy, any abnormal organ function 105 randomised
Interventions	**Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** 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 fraction/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 fraction/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

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Stratified by age, stage, ECOG performance status then 'randomised'. No details of sequence generation method described
Allocation concealment?	Unclear	Allocation concealment not described
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Unclear	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?	Yes	Appears that planned outcomes were reported
Free of other bias?	Yes	

Haddad 1996

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: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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, 5x/week to total dose of 70 Gy + 2-hour infusion cisplatin 50 mg/m^2 + 5 mg/kg 5-FU IM 3x/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

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	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?	Unclear	No details given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	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

Haddad 1996 (*Continued*)

Free of selective reporting?	Unclear	Little information available
Free of other bias?	Unclear	Little information available

HNCProg 1987

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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Stratified by institution, primary tumour site and stage and randomised to treatment at a central site
Allocation concealment?	Yes	Randomisation was done by a phone call to a central office
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned

HNCProg 1987 (*Continued*)

Incomplete outcome data addressed?	Yes	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 are from Jacobs 1990, a subset analysis
Free of selective reporting?	Yes	Planned outcomes clearly defined and analyses presented
Free of other bias?	Yes	

Holoye 1985

Methods	Randomised controlled trial conducted in: USA Number of centres: 3 hospitals Recruitment period: July 1979 to September 1982 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 (edema, 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 i.v. over 8 hours for 12 doses over 4 days; cytoxan 200 mg/m^2/day i.v. for 5 consecutive days; methotrexate 30 mg/m^2/day in 50 ml of 5% dextrose in water i.v. over no more than 5 mins on days 1 and 5; 5-FU 400 mg/m^2/day i.v. for 5 consecutive days Patients showing tumour regression underwent second round of CT after 3-week interval Gr B (n = 40): RT (pre-operative 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	

Holoye 1985 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information given
Allocation concealment?	Unclear	No information given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All randomised patients included in analysis
Free of selective reporting?	Yes	Planned outcomes described and reported
Free of other bias?	Yes	

Huguenin 2004

Methods	Randomised controlled trial conducted in: Switzerland & Italy Number of centres: 12 Recruitment period: July 1994 to July 2000 Funding source: not stated. States 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: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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 interfraction interval of 6 hours, 5x/week to a median dose of 74.4 Gy Gr B (n = 112): RT Hfx RT (1.2 Gy twice daily with interfraction interval of 6 hours, 5x/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)

Huguenin 2004 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"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?	Yes	Randomisation performed centrally
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	4 withdrawals Gr A, protocol violations described in detail for each group, intention-to-treat analysis
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Jaulerry 1992

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

Jaulerry 1992 (*Continued*)

	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 Presents 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 states that trial design was same in both studies

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Insufficient information given
Allocation concealment?	Unclear	Insufficient information given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All randomised patients included in the outcome data used from Pignon 2000
Free of selective reporting?	Yes	Tumour response, toxicity and overall survival planned and reported
Free of other bias?	Yes	

Jeremic 1997

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

Jeremic 1997 (*Continued*)

	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: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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) 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

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	"Patients were randomised" - no further details given
Allocation concealment?	Unclear	No details given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All patients randomised are accounted for and included in analysis
Free of selective reporting?	Yes	Planned outcomes clearly described and reported

Jeremic 1997 (*Continued*)

Free of other bias?	Yes	

Jeremic 2000

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 154 patients recruited, 130 randomised (27/130 patients with OC 21% and 48/130 patients with OP, 37% combined OC/OP = 58%) (Withdrawals and drop outs accounted for). Patients aged 39-70 years, median 60 years
Interventions	**Comparison 3: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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 interfraction interval of 4.5-6 hours Gr B (n = 65): hyperfractionated radiotherapy alone 2 daily fractions of 1.1 Gy with interfraction 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

Jeremic 2000 (*Continued*)

	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

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	"Randomised" - no details given
Allocation concealment?	Unclear	No information given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All randomised participants included in the analyses
Free of selective reporting?	Yes	Planned outcomes described and reported
Free of other bias?	Yes	

Knowlton 1975

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/

Knowlton 1975 (*Continued*)

	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 shows difference between groups for phase 2 toxicity

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	"Patients were randomised" no details given
Allocation concealment?	Unclear	No details given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All randomised participants included in the analysis
Free of selective reporting?	Yes	
Free of other bias?	Unclear	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

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

Krishnamurthi 1990 (*Continued*)

	Exclusion: distant metastases, total trismus 114 randomised, 101 evaluated
Interventions	**Comparison 3: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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 42º 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"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?	Yes	Allocation was concealed in sealed envelopes
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	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?	Yes	Planned outcomes described and reported
Free of other bias?	Yes	

Kumar 1996

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 3: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** Gr A (n = 21): induction CT (cyclophosphamide 600 mg/m^2 and methotrexate 60 mg/m^2 i.v. bolus on days 1 and 14, followed by concomitant 5-FU 600 mg/m^2 i.v. 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 Adverse events: deaths due to treatment (Gr A n = 7; Gr B n = 0)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"Randomised using a table of random digits"
Allocation concealment?	Unclear	Not described
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All randomised patients accounted for in analysis
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Lam 2001

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 ± radiotherapy + chemotherapy versus surgery ± radiotherapy alone** 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 post-operative 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.
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

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Randomisation is stratified by tumour site, stage & prior radiotherapy. Generation of allocation sequence is unclear
Allocation concealment?	Yes	Allocation was revealed by drawing sealed envelopes
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	2 patients (6%) from Gr A excluded from analysis due to post-operative death
Free of selective reporting?	Yes	Survival outcome planned and reported

Lam 2001 (*Continued*)

Free of other bias?	Yes	

Laramore 1992

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%
Interventions	**Comparison 2: Surgery ± radiotherapy + chemotherapy versus surgery ± radiotherapy alone** 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 post-operative treatment started within 4 weeks of surgery Gr A (n = 223): post-operative 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 - post-operative 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)

Laramore 1992 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Patients were stratified by tumour location, pathological staging and surgical margins. Then randomisation was performed by headquarters office. Generation of allocation sequence is adequate (author personal communication)
Allocation concealment?	Yes	Allocation concealment is adequate (author personal communication)
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Unclear	Of the 51 randomised patients excluded from the analyses, reasons are given for 42 but paper does 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?	Yes	Tumour response, overall survival, patterns of recurrence described and reported
Free of other bias?	Yes	No additional threats to validity identified

Le 2006

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). Next 4 patients received 330 mg/m^2 TPZ induction and 260 mg/m^2 concomitant (Level 2). 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	**IP 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 endpoint 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 patient would yield 80% power to detect a 32% improvement rate with TPZ with a 2-sided level of significance = 0.05"

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Stratified by tumour site, nodal status (N0 vs N2-3), mean tumour oxygen tension (</= 12 mm vs > 12mm). Randomisation used permuted block procedure
Allocation concealment?	Unclear	No information given

Le 2006 (*Continued*)

Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Nnot mentioned
Incomplete outcome data addressed?	Yes	All randomised participants (except one who withdrew prior to any treatment) were included in analyses
Free of selective reporting?	Yes	Primary outcome of lymph node response and secondary outcome of survival and toxicity planned and reported
Free of other bias?	Unclear	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)

Lewin 1997

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 is 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, combine 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** 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

Lewin 1997 (*Continued*)

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

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

Licitra 2003

Methods	Randomised controlled trial performed in Italy Multicentre trial (4 centres) Recruitment period: June 1989-December 1999 Funding source: external but source unknown
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 $\geq$ 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 post-operative 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 note that "the lack of statistical significance was not because of low power"

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"Randomly assigned ... after stratification by institution and nodal stage (N0 vs N1-3)"
Allocation concealment?	Yes	Randomisation was performed on the phone by central operations office in accordance with stratified lists from permuted blocks of

Licitra 2003 (*Continued*)

		length 4
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	Post-randomisation withdrawals and exclusions clearly described for each group. 96% of those randomised are evaluable
Free of selective reporting?	Yes	Planned outcomes clearly described and reported
Free of other bias?	Yes	

Luboinski 1985

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 post-operative radiotherapy (determined by the quality of the margins and extension to cervical nodes) Gr B (n = 62): control - surgery alone or with post-operative 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 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 post-operatively determined by the quality of the margins and extension to cervical nodes (data not presented by +/- radiotherapy treatment)

Luboinski 1985 (*Continued*)

Outcomes	Overall survival
Notes	Radiotherapy is an optional treatment for non-responders

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No details given
Allocation concealment?	Unclear	No information given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Unclear	74% of those randomised actually received IA chemotherapy. Not clear how many participants were included in the outcome assessments
Free of selective reporting?	Unclear	Preliminary results only reported. Unclear as to which were planned primary or secondary outcome measures
Free of other bias?	Unclear	Considerable variation in the treatment within each group

Maipang 1995

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%

Maipang 1995 (*Continued*)

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 post-operative 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 post-operative 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

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	"Randomly allocated" - no details given
Allocation concealment?	Unclear	No information given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All randomised patients included in analyses
Free of selective reporting?	Yes	Tumour response and survival outcomes planned and reported
Free of other bias?	Yes	

Marechal 1987

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 205 superiority of Group b (cisplatin-etoposide) compared to Group A (cisplatin alone) giving and 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"

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	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?	Unclear	No information given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	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

Marechal 1987 (*Continued*)

Free of selective reporting?	Yes	Tumour response, toxicity, and overall survival reported
Free of other bias?	Yes	No other threats to validity identified

Mazeron 1992

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) 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

Item	Authors' judgement	Description

Mazeron 1992 (*Continued*)

Adequate sequence generation?	Unclear	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?	Unclear	No information given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	Reasons and numbers for post randomisation exclusions described and are similar in each group
Free of selective reporting?	Yes	Planned outcomes described and reported
Free of other bias?	Unclear	"Patients with unresectable disease were assigned to external radiotherapy alone" (p 86) - not sure if these patients are included in the control group

Merlano 1991

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 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, hear, bone marrow, lung or kidney 116 were randomised (29/116, 25% with oral cavity and 55/116, 47% with oropharynx equivalent to 72% oral cavity/oropharynx cancer patients)
Interventions	**Comparison 4: Induction chemotherapy + RT versus alternating CT + RT** 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

Merlano 1991 (*Continued*)

	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 forth 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 wrong way round but results favour alternating therapy group)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	"Prospectively randomised" and stratified by T and N status
Allocation concealment?	Unclear	No details given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	No withdrawals or drop outs - all patients evaluable for survival
Free of selective reporting?	Yes	Planned outcomes described and reported
Free of other bias?	Unclear	Little information available

Merlano 1992

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

Merlano 1992 (*Continued*)

	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: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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 GrA, 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	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?	Yes	Allocation was obtained by a phone call to central trial centre
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned

Merlano 1992 (*Continued*)

Incomplete outcome data addressed?	Yes	No withdrawals or drop outs. All patients assigned to treatment groups were included in analysis of PFS and survival
Free of selective reporting?	Yes	Planned outcomes described and reported
Free of other bias?	Yes	

Mohr 1994

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 states 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): pre-operative RT conventional fractionated irradiation on the primary and regional nodes, (5 x 2 Gy per week) to a total dose of 36 Gy and pre-operative 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Stratified by primary site of tumour, depth of infiltration, stage of lymph node disease and age of patient; generated 17 TPI subgroups similarly distributed between arms of study. No information on sequence generation given
Allocation concealment?	Unclear	No details given
Blinding of participants?	No	Not mentioned

Mohr 1994 (*Continued*)

Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	No	109/377 = 29% of those randomised are 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 remainder "incomplete files" but allocated treatment group not stated
Free of selective reporting?	Yes	L/R recurrence, mortality, survival planned and reported
Free of other bias?	Unclear	Baseline comparability for TPI and stage, but no information as to how many of those randomised are included in these figures

Molinari 1982

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) Intrarterial** 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	
Risk of bias	

Molinari 1982 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	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?	Yes	Randomisation and pairing performed by central office and accessed by telephone
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All 72 patients randomised are included in the tumour regression analysis
Free of selective reporting?	Yes	Planned outcomes of tumour regression and toxicity reported
Free of other bias?	Yes	

Morita 1980

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: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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 them offered Phase 2 treatment with interstitial radium needles
Outcomes	Overall survival
Notes	Data from Pignon 2000

Morita 1980 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	No details on method of randomisation given
Allocation concealment?	Unclear	No details given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Unclear	Unclear how many patients are included in the outcomes assessment
Free of selective reporting?	Unclear	Unclear outcome reporting
Free of other bias?	Unclear	Authors provide insufficient detail concerning methods used to enable reader to evaluate sources of bias

Nervi 1978

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 (intrarterial)** 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 intraoral 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 intraoral tumours
Outcomes	Overall survival
Notes	Data from Arcangeli 1983

Nervi 1978 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Patients were stratified by site of cancer and then randomised
Allocation concealment?	Unclear	No details given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All patients included in analyses
Free of selective reporting?	Yes	Planned outcomes described and reported
Free of other bias?	Yes	

Olasz 2000

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 is increased by 25%, methotrexate dose is 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 is increased by 25%, methotrexate dose is increased by 100% and cisplatin dose in increased by 50%. Weeks 3 & 4 no chemotherapy, & Week 5 Cycle 3 at the increased doses 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

Olasz 2000 (*Continued*)

Notes	From translation by Daniel Bereczki	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomisation was not stratified, details of sequence generation not given
Allocation concealment?	Unclear	No details given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All randomised patients are included in the the outcome assessments
Free of selective reporting?	Yes	Outcomes lo local control, overall survival, time to recurrence and site of recurrence planned and reported
Free of other bias?	Yes	Groups appear similar at baseline

Olmi 2003

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 1: Induction chemotherapy plus Locoregional treatment (LRT) versus LRT alone** 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

Olmi 2003 (*Continued*)

	Gr B (n= 65): 64-67.2 - 2 fractions of 1.6 Gy daily, 4-6 hours apart, 5x/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

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	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?	Unclear	Allocation concealment not described
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	Missing data and exclusions described (2, 4 4 excluded in Gr A, B, C respectively), numbers similar in each group
Free of selective reporting?	Yes	Long term follow-up in Fallai 2006
Free of other bias?	Yes	Groups similar at baseline

Paccagnella 1994

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

Paccagnella 1994 (*Continued*)

	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 60-Co 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

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	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?	Yes	Allocation obtained by telephone call to trial office at Padua general hospital
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned

Paccagnella 1994 (*Continued*)

Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All randomised patients included in analysis
Free of selective reporting?	Yes	Outcomes of overall survival, tumour response and time to relapse planned and reported
Free of other bias?	Yes	No other threat to validity identified

Paccagnella 2010

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 4: Induction CT then concomitant CRT versus concomitant CRT 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, 5x/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, 5x/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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Registration and randomisation carried out centrally but no information on sequence generation provided

Paccagnella 2010 (*Continued*)

Allocation concealment?	Yes	Treatment allocation obtained by phone or fax to centre
Blinding of participants?	No	Open study
Blinding of carers?	No	Open study
Blinding of outcome assessors?	Yes	"Radiologic responses in our study were centrally reviewed by an internal committee in a blinded fashion to minimise possible bias"
Incomplete outcome data addressed?	Yes	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 pre-treatment, 1 early progression, 1 withdrew consent, 1 had no imaging). ITT undertaken for PFS and OS
Free of selective reporting?	Yes	Progression free survival, overall survival, toxicity reported
Free of other bias?	Unclear	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

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: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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

Parvinen 1985 (*Continued*)

	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

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Envelope method - no details about sequence generation
Allocation concealment?	Yes	Envelope method
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All randomised patients included in analyses
Free of selective reporting?	Yes	Planned outcomes described and reported
Free of other bias?	Yes	Similar numbers in each group underwent surgery post-RT

Petrovich 1981

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

Petrovich 1981 (*Continued*)

	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

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	"Prospectively randomised" no further information given
Allocation concealment?	Unclear	Not described
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	Reasons for protocol violations described, and numbers similar in both groups
Free of selective reporting?	Yes	Planned outcomes reported
Free of other bias?	Yes	

Pinnaro 1994

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: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** 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

Pinnaro 1994 (*Continued*)

Outcomes	Response, toxicity, progression free survival, overall survival, time to progression, time to metastases
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Patients were stratified by performance status, primary site, T stage, N stage and then randomised. No details of sequence generation given
Allocation concealment?	Unclear	No information given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	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?	Yes	Planned outcomes described and reported
Free of other bias?	Yes	

Posner 2007

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

Posner 2007 (*Continued*)

	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 5x/week radiotherapy to a total dose of 70-74 Gy, followed by surgery 6-13 weeks later
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

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation performed centrally with biased coin minimisation technique. Randomisation was stratified by site of primary tumour, N0-N1 vs N2-N3, institution
Allocation concealment?	Yes	Not described, but considered to
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Unclear	539 patients enrolled but 38 (8%) excluded due to computer randomisation error, allocated groups not given
Free of selective reporting?	Yes	Primary and secondary outcomes clearly described and reported

Free of other bias?	Unclear	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 TPF regimen. However fewer TPF patients, compared to PF, did not complete induction chemotherapy due to progressive disease

Prevost 2005

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)** 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Patients paired by tumour sites and UICC stage through "sequential closed plans". The first patient in each pair was allocated centrally by statistician, and the second patient in the pair received the alternate treatment
Allocation concealment?	Unclear	No information provided on allocation concealment
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned

Prevost 2005 (*Continued*)

Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All randomised patients are included in outcomes of tumour response and toxicity
Free of selective reporting?	Unclear	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	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

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 $\geq$ 80%, no residual disease and clear margins after surgery 135 patients recruited, 116 evaluable patients 100% OC
Interventions	**Comparison 2: Surgery ± radiotherapy + chemotherapy versus surgery ± radiotherapy alone** Gr A (n = 65): adjuvant chemotherapy - methotrexate 50 mg/m^2, 3 IV bolus doses on days 3, 10 and 17 post-operative. If leukopenia or low platelet count or severe mucositis injection deferred for 1 week (evaluable n = 54) Gr B (n = 70): control - post-operative 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 use 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

Rao 1994 (*Continued*)

Notes	Very specific oral cancer location i.e. alveolobuccal complex *Some data supplied from Pignon 2000.

Risk of bias

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

Rasch 2010

Methods	Randomised controlled trial conducted in: Netherlands & New Zealand Number of centres: 5 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 35x 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 35x 2 Gy fractions of radiotherapy to total dose of 70 Gy Patients randomised to the intra-arterial group underwent arteriography prior to treatment.

Rasch 2010 (*Continued*)

	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, would require 100 events in each arm to give 80% power

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomisation was stratified by centre, T classification, N classification and site of primary tumour. No information about the method of sequence generation is provided
Allocation concealment?	Unclear	Not described
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	2 patients were excluded post-randomisation. Authors state that ITT analysis was used but outcomes are reported as percentages only. Compliance is described for 224/237 patients
Free of selective reporting?	Yes	Primary outcome is locoregional control and secondary are disease free survival, overall survival, quality of life and toxicity
Free of other bias?	Yes	Groups appear similar at baseline. Intra-arterial treatment was not feasible in10 patients randomised to this group and they were then treated by intravenous therapy but analysed in the intra-arterial group (ITT)

Rentschler 1987

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 $\geq$ 4000, platelets $\geq$ 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 ± radiotherapy + chemotherapy versus surgery ± radiotherapy alone** Patients were randomised to receive LRT + CT (methotrexate) or LRT alone Gr A (n = 28): chemotherapy - escalating dose methotrexate (weekly x4) then surgery then post-operative methotrexate (weekly x4) then radiotherapy then methotrexate (weekly x8) Gr B (n = 27): control - surgery plus post-operative radiotherapy For patients with primary tumours in oral cavity, oropharynx, hypopharynx, pyriform sinus or larynx, LRT comprised both standard surgery (radical neck dissection) and post-operative 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, 5x/week continuous course with all fields treated with 60 Co 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

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	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

Rentschler 1987 (*Continued*)

Allocation concealment?	Yes	Assignment was conveyed by envelopes (presumed sealed)
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	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 drop outs accounted for)
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Richard 1974

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 psycho-social 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

Richard 1974 (*Continued*)

	advantage over radiotherapy alone

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random allocation of treatments into groups had been prepared by the statistician
Allocation concealment?	Yes	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?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	Yes	3 independent outcome assessors evaluated each patient at each assessment visit. Comparsion of observers described in table 4 p 494
Incomplete outcome data addressed?	Unclear	Not clear how many patients were included in the outcomes assessments at each point
Free of selective reporting?	Yes	Primary and secondary outcomes clearly stated and reported
Free of other bias?	Yes	No other threats to validity identified

Richard 1991

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: Chemotherapy plus surgery versus surgery** 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

Richard 1991 (*Continued*)

	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

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	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?	Yes	Assignment was conveyed by sealed envelopes
Blinding of participants?	No	Not possible
Blinding of carers?	No	Not possible
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	5 post-randomisation exclusions (3 surgery only arm and 2 in CT + surgery arm)
Free of selective reporting?	Yes	Primary and secondary outcomes clearly stated and reported
Free of other bias?	Yes	Some differences between the groups at baseline (p 822) but these were adjusted for in the analysis

Rischin 2005

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 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomisation charts were prepared at trial centre (based on adaptive biased-coin method), in ratio 1:1
Allocation concealment?	Yes	Allocation was obtained by a telephone call to trial centre following patient recruitment and registration
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	1 post-randomisation exclusion, no losses to follow-up
Free of selective reporting?	Yes	
Free of other bias?	Yes	Although treatment varied depending on individual requirement, the paper claims 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

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: Concomitant CIS/TPZ + RT versus concomitant CIS +RT** 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

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	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?	Yes	Centralised assignment
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	5/430 and 3/431 were excluded from primary analysis due to incorrect diagnosis or early withdrawal
Free of selective reporting?	Yes	Primary outcome is 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?	Yes	Groups similar at baseline, and chemotherapy and radiotherapy delivery was similar in both arms

Ruo 2010

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 Exclusion: metastatic disease, multiple primary tumours OC = 17%, OP = 49%, OC + OP = 66% M/F: 129/16
Interventions	**Comparison 3: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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 of 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 drop outs"

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	"Randomised" - no further information provided
Allocation concealment?	Unclear	No information provided
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned

Ruo 2010 (*Continued*)

Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	In CRT group 2/82 developed distant metastases and were withdrawn and further 7 died during treatment, and in RT group 5 did not receive treatment and further 5 died during treatment leaving 73 & 72 patients evaluated in each group respectively
Free of selective reporting?	Yes	Primary outcome locoregional recurrence free survival, and secondary outcomes of disease free survival, overall survival, response rate and toxicity
Free of other bias?	Unclear	More patients in CRT arm had ECOG performance status of 0 compared to RT group

Salvajoli 1992

Methods	Randomised controlled trial conducted in: Brazil Number of centres: 1 Recruitment period: January 1983 to December 1986 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: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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

Salvajoli 1992 (*Continued*)

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

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	"Randomised" - no further details given
Allocation concealment?	Unclear	No details given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All randomised participants accounted for and included in analysis
Free of selective reporting?	Yes	Primary and secondary outcomes clearly described and reported
Free of other bias?	Yes	

Schuller 1988

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 post-operative 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 post-operative radiotherapy (n = 76) Common treatment: assessment for surgery and extent of surgical resection was determined

Schuller 1988 (*Continued*)

	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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "Patients were randomly assigned..."
Allocation concealment?	Unclear	Insufficient information
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	175 entered into study but 158 eligible. Unclear if all 17 patients excluded at this stage had been randomised or not, but suggests they did not receive treatment. IPD data used in analysis
Free of selective reporting?	Yes	Relevant outcome data presented
Free of other bias?	Yes	No reported threats to validity

Segura 2002

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

Segura 2002 (*Continued*)

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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomised using a list of random numbers generated by computer
Allocation concealment?	Unclear	No details given
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	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
Free of selective reporting?	Yes	Planned outcome measures - tumour response, toxicity and survival are reported
Free of other bias?	Yes	No other risks to validity identified

Shanta 1980

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: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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 do 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

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Generation of randomisation sequence took place in the tumour registry
Allocation concealment?	Yes	Sealed envelope technique from central tumour registry

Shanta 1980 (*Continued*)

Blinding of participants?	Yes	Not mentioned but it is likely that patients were blinded as placebo infusions were used
Blinding of carers?	Unclear	Not mentioned
Blinding of outcome assessors?	Yes	Outcome assessment was conducted by head and neck surgical group who were unaware of type of treatment each patient received
Incomplete outcome data addressed?	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Unclear	Some imbalance between groups at baseline - BLM group had higher rate of mandibular invasion and control group more extensive nodal involvement

Smid 1995

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. Withdrawls and drop outs accounted for
Interventions	**Comparison 3: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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 **Some data supplied from Pignon 2000.Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000

Smid 1995 (*Continued*)

	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

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"Randomisation used was permuted blocks and stratified by primary site and whether tumour was inoperable locally, regionally, or both"
Allocation concealment?	Unclear	Not described
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All patients entering study had evaluable data
Free of selective reporting?	Yes	
Free of other bias?	Yes	

Staar 2001

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: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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

Staar 2001 (*Continued*)

	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 does not take into account other metastases Adverse events: mucositis, dermatitis, WBC, anaemia, platelets, feeding problems/tube feeding

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method of randomisation not described
Allocation concealment?	Unclear	Method of allocation concealment not described
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Unclear	Post-randomisation exclusions not described by group. Some randomised to RT actually received RCT and viceversa. 4 patients randomised to RCT received RT alone and one patient randomised to RT received RCT (n = 113 in received RCT & n = 127 received RT)
Free of selective reporting?	Unclear	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	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

Methods	Randomised controlled trial conducted in Europe (Hungary, Germany and Austria) Multicentre (4 institutes) Recruitment period: 1986-1991 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): pre-operative 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): pre-operative 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 pre-operative treatment. Surgery was performed as early feasible following completion of pre-treatment - 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

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Generation of randomisation sequence performed by Central Operations Office at University of Vienna, using a computer-assisted procedure
Allocation concealment?	Yes	Allocation by statistics centre - telephone notification

Szabo 1999 (*Continued*)

Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	No	36/131 (27%) patients randomised are not included in evaluation. Reasons and treatment allocation are not given
Free of selective reporting?	Yes	Primary outcomes specified and reported
Free of other bias?	Yes	

Szpirglas 1979

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 ± radiotherapy + chemotherapy versus surgery ± radiotherapy alone** Randomised after surgery (+/- radiotherapy) when patient regarded as in remission of 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)

Szpirglas 1979 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Quote: "randomized into three groups"
Allocation concealment?	Unclear	Insufficent detail
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All participants accounted for, and IPD data used within review
Free of selective reporting?	Yes	
Free of other bias?	Yes	No reported threats to validity

Szpirglas 1988

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 (D1 Adriamycin 60 mg IV over 6 hours, D2 vincristine 2 mg IV+ bleomycin 15 mg IM, D3 & 4 bleomycin 15 mg IM, D5 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

Szpirglas 1988 (*Continued*)

Notes	*Data supplied from Pignon 2000. Total mortality: log [hazard ratio] SE calculated from data provided from Pignon 2000

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Radiotherapy "randomised in three arms", patients randomised to CT + RT or RT alone - no further details given
Allocation concealment?	Unclear	Not mentioned
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	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	Little information available
Free of other bias?	Unclear	Distribution of prognostic factors in each group at baseline not presented

Tejedor 1992

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 were 67%) 42 randomised, 36 evaluable

Tejedor 1992 (*Continued*)

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 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 was 50 Gy 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomised but method not described
Allocation concealment?	Unclear	Not described
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	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 possibly influence results. However, IPD data used within the review
Free of selective reporting?	Yes	
Free of other bias?	Yes	Groups comparable at baseline

UKHAN 2010

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 966 patients randomised, 966 patients evaluable 187 oral cavity (19%) & 315 oropharynx (33%) total OC/OP = 52%
Interventions	**Comparison 2: Surgery ± radiotherapy + chemotherapy versus surgery ± radiotherapy alone** **Comparison 3: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** **Comparison 4: Chemotherapy A (± LRT) versus chemotherapy B (± LRT)** 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 post-operatively 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 hour before RT and dose 2 on day 14 of RT. Folinic acid rescue was given if serum MTX levels >0.4 μmol/L24 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.

UKHAN 2010 (*Continued*)

	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 are 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	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
Allocation concealment?	Yes	Random number lists generated at co-ordinating centre, each centre obtained randomisation by phone call to co-ordinating centre, who assigned treatment allocation after recording eligibility and stratification factors
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	All randomised patients are included in the analysis (ITT)
Free of selective reporting?	Yes	Primary and secondary outcomes clearly described, defined and reported
Free of other bias?	Yes	No other sources of bias identified

Vermorken 2007

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 $\leq$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)"

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation was balanced according to primary tumour site (OC/OP/HP/L) and centre with the use of variance minimisation method
Allocation concealment?	Unclear	Not described
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	Reasons for small number of post-randomisation exclusions and withdrawals clearly described (Fig 1) and similar in each group. Efficacy analysis is by intention-to-treat

Free of selective reporting?	Yes	Primary and secondary endpoints clearly stated and reported
Free of other bias?	Yes	No other threats to validity detected

Vokes 1990

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 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Pre-randomisation stratification based on T, N stage and performance status. No details given on method of randomisation
Allocation concealment?	Unclear	No information given

Vokes 1990 (*Continued*)

Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Unclear	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?	Yes	Planned outcomes described and reported
Free of other bias?	Unclear	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

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 144 randomised 140 patients evaluable (withdrawals and drop outs 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

Volling 1999 (*Continued*)

	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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	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?	Unclear	Insufficient information
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Yes	1 patient in each group died post-operatively 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 drop outs given and similar in each group
Free of selective reporting?	Yes	Tumour response and overall survival outcomes planned and reported
Free of other bias?	Yes	No other threats to validity identified

Weissler 1992

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: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** 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 via 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 via 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

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	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

Weissler 1992 (*Continued*)

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

Wendt 1998

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: Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)** Gr A (n = 130): concomitant RCT: 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^2/24hours as continuous infusion from day 2 to 5 of each cycle. Cycle repeated on days 22 and

Wendt 1998 (*Continued*)

	44. RT given with CT 15 fractions, each 1.8 Gy given twice daily with 6-hour interfraction 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 interfraction 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
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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"By telephone randomisation at an independent organisation (Algora, Munich Germany) ". Stratified by centre, tumour site and nodal stage
Allocation concealment?	Yes	
Blinding of participants?	No	Not mentioned
Blinding of carers?	No	Not mentioned
Blinding of outcome assessors?	No	Not mentioned
Incomplete outcome data addressed?	Unclear	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?	Yes	Planned outcomes reported
Free of other bias?	Yes	Groups comparable at baseline

AF = accelerated fraction; BLM = bleomycin; Carb = carboplatin; CF = conventional fraction; Cis = Cisplatin; CR = complete response; CT = chemotherapy; CRT = chemoradiotherapy; CYC = cyclophosphamide; Gr = group; H&N = head and neck; Hfx = hyperfractionation; IA= intra-arterially; IL-2 = interleukin-2; IM = intramuscularly; IPD = individual patient data; IV = intravenously; LRT = locoregional treatment; LV= leucovorin; MMC = mitomycin C; MTX = methotrexate; OC/OP = oral cancer/oropharyngeal

cancer; PORT = post-operative radiotherapy; RT = radiotherapy; SCC = squamous cell carcinoma; SE = standard error; vin = vincristine; 5-FU = 5-fluorouracil.

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

Study	Reason for exclusion
Abele 1984	Abstract only includes patients with recurrent disease and a low proportion of oral cavity/oropharyngeal cancer
Abele 1985	Abstract only includes patients with recurrent disease and a low proportion of oral cavity/oropharyngeal cancer
Adelstein 1997	Less than 50% of participants had oral cavity/oropharynx cancers
Adelstein 2000	Less than 50% of participants had oral cavity/oropharynx cancers
Amichetti 1989	Non-randomised study
Andreadis 1999	Abstract only, and no subsequent publication found September 09
Anonymous 1976	Less than 50% oral cavity cancer
Ansfield 1970	Non-randomised study
Antanadou 2002	Patients are randomised to receive amifostine or not
Asif 2003	Unclear percentage of oral cavity and oropharyngeal cancer, and it is likely that duration of follow-up for published outcomes is 3 months
Auersperg 1977	Non-randomised study including patients with recurrent disease
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
Berger 1995	Non-randomised study
Bezwoda 1979	Concern as to validity of the data from this study published in 1979. Unable to verify data
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 have metastatic disease
Bolla 1994	Etretinate is not a chemotherapy agent

(*Continued*)

Bonner 2006	This trial deals 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
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	Includes patients with recurrent disease
Browman 1988	Includes patients with recurrent disease
Browman 1990	Includes patients with recurrent disease
Buentzel 2006	Patients randomised to amifostine or none
Buntzel 1998	Less than 50% of participants had oral cavity/oropharynx cancers
Buntzel 1998a	Less than 50% of participants had oral cavity/oropharynx cancers
Campbell 1987	Less than 50% of patients had oral cavity/oropharyngeal cancer. Includes 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 is tumour response published in an abstract (Caponigro 2001)
Cappelaere 1981	Less than 50% of patients had oral cavity/oropharyngeal cancer
Cappelaere 1990	Includes patients who have undergone prior treatment for oral cancer
Carugati 1988	Abstract only; insufficient information available
Clavel 1987	Includes patients with recurrent disease
Coates 1984	Study includes patients with recurrent disease
Coninx 1986	Quasi-randomised study
Coninx 1988	Study includes patients with metastatic disease
Corvo 1997	Pilot clinical trial with no relevant outcomes
Cruz 1997	Abstract only - no subsequent publication found October 09

(*Continued*)

Cummings 2007	Less than 50% of participants in trial have oral cavity or oropharyngeal cancer
Dalley 1995	Abstract only; insufficient information available
De la Torre 1991	1991 abstract - no subsequent publication identified. Unclear what proportion of patients in this study had oral cavity/oropharyngeal cancer
DeConti 1981	Less than 50% of patients have oral cavity cancer and some have recurrent disease
Deka 1983	Methodology concerning randomisation unclear - alternation?
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 have nasopharyngeal cancer
Drelichman 1983	Includes patients with recurrent disease
Ebeling 1994	Non-randomised study
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 have oral cavity or oropharyngeal cancer
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 is the addition of folinic acid to chemotherapy
Fonseca 2005	Less than 50% of participants have oral cavity or oropharyngeal cancer
Forastiere 2001	Includes 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
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

(*Continued*)

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
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
Gibson 2005	Includes patients with recurrent disease
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
Grose 1985	Includes patients with metastatic disease
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
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

(*Continued*)

Hussey 1975	Less than 50% participants had oral cavity/oropharynx cancers
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
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 includes 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
Klima 1988	Trial includes patients with metastatic disease
Kotani 1994	Based on translation by Toru Naito it appears that the included patients had a variety of primary treatments before being allocated to subsequent chemotherapy or not
Laccourreye 1983	Less than 50% participants had oral cavity/oropharynx cancers
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	Includes patients with recurrent disease
Lippman 1988	Less than 50% or particpants have oral cavity cancer
Liverpool HNOG 1990	Includes patients with recurrent disease
Lopes 1991	Abstract only, less than 50% oral cavity/oropharynx cancer patients included, and no subsequent publication found September 09
Magno 1994	Less than 50% participants had oral cavity/oropharynx cancers
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 is same in both groups - patients randomised to immunotherapy or not

(*Continued*)

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
Mechl 1987	Less than 50% of participants have oral cavity cancer
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
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
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 have oral cavity cancer
Pearlman 1985	Includes 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 are 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
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 have oral cavity or oropharyngeal cancer
Rodrigo 2004	Less than 50% of participants had oral cavity/oropharynx cancers
Rosen 2003	Randomised comparison of erythropoietin versus no erythropoietin, therefore does not meet intervention inclusion criteria for this review

(*Continued*)

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 have oral cavity or oropharyngeal cancer
Schildhauer 2005	Patients have primary metastatic or recurrent disease
Schuller 1989	Less than 50% of participants had oral cavity/oropharynx cancers
Sealy 1978	Unclear concerning proportion of patients with oral cavity/oropharyngeal cancer. Unclear methodology concerning randomisation
SECOG 1986	43% oral cavity cancers 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
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 have oral cavity or oropharyngeal cancer
Stefani 1971	Includes participants with metastatic disease. Linked to Stefani 1980
Stefani 1980	Includes 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
Suwinski 2005	Less than 50% of participants have oral cavity or oropharyngeal cancer
Taylor 1979	Includes patients who had prior treatment
Taylor 1984	Includes 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

(*Continued*)

Taylor 1994	9% of included patients have recurrent disease and only 51% of patients have oral cavity/oropharynx disease. It is likely that less than 50% of patients included have 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
Toohill 1987	50% participants had oral cavity/oropharynx cancers, interim report
Tsukuda 1994	Less than 50% of participants have oral cavity or oropharyngeal cancer
Tsukuda 2005	Less than 50% of participants have oral cavity or oropharyngeal cancer
Vega 1981	[Spanish] Some patients in this study have recurrent or metastatic disease and less than 50% have oral cavity/oropharynx primary tumours
Venkatachalam 1998	Chemotherapy is 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 have undergone previous treatment and 19% have metastatic disease. Requested data on participants without prior treatment - no response received
Von Heyden 1984	Cross-over design. Onkologie reference gives results of patients without pre-treatment but 4 and 9 patients from each group received both chemotherapy regimens
Von Heyden 1982	Cross-over study included 23/52 patients who had undergone previous surgery or radiotherapy, and patients with no response to allocated treatment then received the alternative treatment
Von Heyden 1984	Cross-over study
Von Heyden 1985	Cross-over study - (n = 79) some patients had prior treatment
Weissberg 1989	Less than 50% oral cavity and oropharynx cancer. Data in Pignon 2000 is for all the included patients. No separate data for oral cavity and oropharyngeal cancer patients available
Woods 1977	Less than 50% oral cavity or oropharyngeal cancer and includes patients with recurrent disease
Woods 1981	Includes 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
Yoshino 1991	Less than 50% of participants have oral cavity or oropharyngeal cancer
Yoshino 1994	Less than 50% of participants have oral cavity or oropharyngeal cancer

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

Abdel Wahab 2006

Methods	Randomised controlled trial conducted in: Egypt Number of centres: ?one Recruitment period: January 2000 to December 2005 Funding source: not stated
Participants	Patients with locally advanced squamous cell carcinoma of head and neck
Interventions	Group A (n = 35) chemoradiotherapy. 70 Gy over 7 weeks using standard portals and techniques of radiotherapy + concomitant cisplatin (30 mg/m^2 weekly from week 1-7 followed by 3 cycles adjuvant cisplatin (20 mg/m^2) on days 1-4 and fluorouracil (1000 mg/m^2) on days 1-4 on weeks 11,15 &19 Group B (n = 36) radiotherapy alone, 70 Gy over 7 weeks using standard portals and techniques of radiotherapy
Outcomes	Tumour response, 2 & 3 yr OS, 2 & 3 yr PFS, ITT, f/up 29 months
Notes	Abstract, no full publication found August 2010

Bouillet 2007

Methods	
Participants	Patients with inoperable locally advanced head and neck cancer, T3/T4, PS <2, buccal cavity 38% oro-hypopharynx 47%, larynx 11% - unclear percentage of oral cavity/oropharynx
Interventions	Group A (n = 35) 7 cycles weekly docetaxel 20 mg/m^2 before radiotherapy and cisplatin 20 mg/m^2 D1-3 every 3 weeks (3 cycles) + 70 Gy radiotherapy over 7 weeks Group B (n = 47) 7 cycles weekly docetaxel 20 mg/m^2 before radiotherapy (70 Gy over 7 weeks) Both groups offered G-CSF secondary prophylaxis and ciprofloxacin
Outcomes	ITT ORR, median TTP, median OS Docetaxel/cisplatin arm discontinued for insufficient efficacy
Notes	Abstract, no full publication found August 2010

Bourhis 2002

Methods	Randomised controlled trial conducted in: France Number of centres: multi Recruitment period: 1996-2000 GORTEC 96-01
Participants	109 participants

Bourhis 2002 (*Continued*)

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	Locorregional control, distant metyastases, 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)

Datta 1991

Methods	
Participants	
Interventions	
Outcomes	
Notes	Unclear whether this is an RCT. Waiting to obtain paper copy August 2010

Ghosh 2006

Methods	Randomised controlled trial conducted in: Mumbai, India Number of centres: 1 Recruitment period: April 2000 to December 2004
Participants	Stage III & IV non-nasopharyngeal squamous cancers of the head and neck region. Randomisation stratified by tumour site and stage
Interventions	Group A conventional fractionated radiotherapy 66-70 Gy in 6-7 weeks @ 5 fractions/week Group B conventional fractionated radiotherapy 66-70 Gy in 6-7 weeks @ 5 fractions/week + concomitant weekly inj cisplatin 30 mg/m^2 Grroup C accelerated fractionated radiotherapy 66-70 Gy in 6.5 weeks @ 6 fractions/week (6th fraction used reduced fields) 150 randomised
Outcomes	Tumour response, toxicity
Notes	Abstract, no full publication found August 2010

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
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 evenets
Notes	Unclear percentage of oral cavity + oropharyngeal cancers. No subsequent publication found August 2010

Rapoport 1991

Methods	
Participants	
Interventions	
Outcomes	
Notes	Unclear whether this is an RCT. Waiting to obtain paper copy August 2010

Saber 2005

Methods	Recruitment period: August 2001 to July 2004
Participants	Locally advanced squamous cell carcinoma of head and neck
Interventions	Group A conventional radiotherapy alone (60-70 Gy over 6-7 weeks) Group B concomitant chemoradiotherapy - conventional radiotherapy + cisplatin 30 mg/m^2 weekly on day 1 of chemo then weekly till the end of radiotherapy
Outcomes	Tumour response, toxicity
Notes	Abstract, no full publication found August 2010

Sharma 2007

Methods	Randomised controlled trial conducted in: India
Participants	Previously untreated stage II-IV oropharyngeal and nasopharyngeal cancer
Interventions	Group A radiotherapy 70 Gy in 35 fractions over 7 weeks Group B cisplatin 40 mg/m^2 weekly for 6 doses beginning on day 1 of radiotherapy total 70 Gy in 35 fractions over 7 weeks 153 randomised, 137 evaluated
Outcomes	Response, toxicity and overall survival
Notes	Abstract, no full publication found August 2010. Imbalance at baseline - 83% of nasopharyngeal cancer patients in Group B (combined therapy)

Tepmongkol 1989

Methods	
Participants	
Interventions	
Outcomes	
Notes	Unclear whether this is an RCT. Waiting to obtain translation paper copy January 2011

RCT = randomised controlled trial

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 Total mortality	25		Hazard Ratio (Random, 95% CI)	0.92 [0.84, 1.00]
1.1 Cisplatin or carboplatin + 5-FU + RT ± surgery vs RT ± surgery	7		Hazard Ratio (Random, 95% CI)	0.90 [0.80, 1.02]
1.2 Carboplatin and ftorofur + RT vs RT alone	1		Hazard Ratio (Random, 95% CI)	0.45 [0.19, 1.08]
1.3 Cisplatin + 5-FU + folinic acid + RT vs RT alone	1		Hazard Ratio (Random, 95% CI)	0.69 [0.39, 1.25]
1.4 Cisplatin + 5-FU + vindesine + RT vs RT alone	1		Hazard Ratio (Random, 95% CI)	1.09 [0.69, 1.70]
1.5 Cisplatin + 5-FU + bleomycin + methotrexate + RT vs RT alone	1		Hazard Ratio (Random, 95% CI)	1.46 [0.93, 2.29]
1.6 Cisplatin + bleomycin + vinblastine + mitomycin C + RT vs RT alone	1		Hazard Ratio (Random, 95% CI)	1.04 [0.57, 1.87]
1.7 Cisplatin + bleomycin + vindesine + mitomycin C + RT vs RT alone	1		Hazard Ratio (Random, 95% CI)	1.13 [0.74, 1.72]
1.8 Cisplatin + bleomycin + vincristine + adriamycin + RT vs RT alone	1		Hazard Ratio (Random, 95% CI)	0.92 [0.62, 1.37]
1.9 Cisplatin + bleomycin + vincristine + methotrexate + RT + surgery vs RT + surgery	1		Hazard Ratio (Random, 95% CI)	1.07 [0.77, 1.49]
1.10 Cisplatin + bleomycin + methotrexate + surgery + RT vs surgery + RT	1		Hazard Ratio (Random, 95% CI)	1.07 [0.56, 2.05]
1.11 Cisplatin + epirubicin + surgery vs RT plus surgery (5 years)	1		Hazard Ratio (Random, 95% CI)	0.88 [0.56, 1.38]
1.12 Methotrexate + RT vs RT alone	4		Hazard Ratio (Random, 95% CI)	0.90 [0.72, 1.14]
1.13 Methotrexate + vincristine + RT vs RT alone	1		Hazard Ratio (Random, 95% CI)	0.57 [0.24, 1.34]
1.14 Methotrexate + bleomycin + 5-FU + cyclophosphamide + RT ± surgery vs RT ± surgery	1		Hazard Ratio (Random, 95% CI)	1.48 [0.91, 2.42]
1.15 Bleomycin + vincristine + surgery ± RT vs surgery ± RT	2		Hazard Ratio (Random, 95% CI)	0.67 [0.50, 0.91]
2 Disease free survival	8		Hazard Ratio (Random, 95% CI)	0.78 [0.67, 0.90]

2.1 Carboplatin + 5-FU + RT + surgery vs RT + surgery	2	Hazard Ratio (Random, 95% CI)	0.66 [0.48, 0.89]
2.2 Carboplatin + ftorafur + RT vs RT alone	1	Hazard Ratio (Random, 95% CI)	0.86 [0.34, 2.21]
2.3 Cisplatin + fluorouracil + RT + surgery vs RT + surgery (5 years)	2	Hazard Ratio (Random, 95% CI)	0.78 [0.62, 0.97]
2.4 Cisplatin + bleomycin + vindesine + mitomycin C + RT vs RT alone	1	Hazard Ratio (Random, 95% CI)	0.93 [0.58, 1.49]
2.5 Bleomycin + vincristine + surgery vs surgery (floor of mouth)	1	Hazard Ratio (Random, 95% CI)	0.86 [0.56, 1.32]
2.6 Bleomycin + cyclophosphamide + MTX + 5-FU plus RT ± surgery versus RT ± surgery	1	Hazard Ratio (Random, 95% CI)	0.92 [0.48, 1.76]
3 Progression free survival	2	Hazard Ratio (Fixed, 95% CI)	0.80 [0.64, 1.00]
3.1 Cisplatin + 5-FU + RT + surgery vs RT + surgery	1	Hazard Ratio (Fixed, 95% CI)	0.83 [0.63, 1.09]
3.2 Carboplatin + 5-FU + RT + surgery vs RT + surgery	1	Hazard Ratio (Fixed, 95% CI)	0.76 [0.52, 1.10]
4 Disease free survival	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4.1 Cisplatin + 5-FU + surgery vs surgery alone (5 years)	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Recurrent disease - Locoregional	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Cisplatin + 5-FU + surgery vs surgery alone (5 years)	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 2. Surgery ± radiotherapy + chemotherapy versus surgery ± radiotherapy alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total mortality	10		Hazard Ratio (Fixed, 95% CI)	0.88 [0.79, 0.99]
1.1 Surgery + CT (methotrexate/ bleomycin/ vincristine) vs surgery + RT	1		Hazard Ratio (Fixed, 95% CI)	0.32 [0.08, 1.35]
1.2 Surgery + CT (methotrexate) vs surgery alone	1		Hazard Ratio (Fixed, 95% CI)	1.07 [0.48, 2.38]
1.3 Surgery + CT (levamisole/ UFT) vs surgery alone	1		Hazard Ratio (Fixed, 95% CI)	0.70 [0.36, 1.37]
1.4 Surgery ± RT + CT (methotrexate/bleomycin/ leucovorin) vs surgery ± RT	1		Hazard Ratio (Fixed, 95% CI)	1.01 [0.50, 2.05]
1.5 Surgery + RT + CT (methotrexate) vs surgery + RT alone	1		Hazard Ratio (Fixed, 95% CI)	1.04 [0.75, 1.45]

1.6 Surgery +CT (cisplatin/ 5-FU) + RT vs surgery + RT alone	1	Hazard Ratio (Fixed, 95% CI)	0.91 [0.73, 1.13]
1.7 Surgery + RT + CT (concom cisplatin) vs surgery + RT alone	2	Hazard Ratio (Fixed, 95% CI)	0.80 [0.66, 0.97]
1.8 Surgery + RT + CT (concom carboplatin) vs surgery + RT alone	1	Hazard Ratio (Fixed, 95% CI)	0.90 [0.42, 1.92]
1.9 Surgery + RT + CT (concom MTX or VBMF) vs surgery + RT alone	1	Hazard Ratio (Fixed, 95% CI)	0.94 [0.70, 1.26]
2 Disease free survival	8	Hazard Ratio (Fixed, 95% CI)	0.89 [0.78, 1.01]
2.1 Surgery + CT (methotrexate/ bleomycin/ vincristine) vs surgery + RT	1	Hazard Ratio (Fixed, 95% CI)	0.90 [0.19, 4.21]
2.2 Surgery + CT (methotrexate) vs surgery alone	1	Hazard Ratio (Fixed, 95% CI)	0.47 [0.26, 0.87]
2.3 Surgery + RT + CT (methotrexate) vs surgery + RT alone	1	Hazard Ratio (Fixed, 95% CI)	0.84 [0.38, 1.83]
2.4 Surgery +CT (cisplatin/ 5-FU) + RT vs surgery + RT alone	1	Hazard Ratio (Fixed, 95% CI)	0.90 [0.72, 1.14]
2.5 Surgery + RT + CT (concom cisplatin) vs surgery + RT alone	1	Hazard Ratio (Fixed, 95% CI)	0.78 [0.62, 0.99]
2.6 Surgery + RT + CT (concom carboplatin) vs surgery + RT alone	1	Hazard Ratio (Fixed, 95% CI)	0.82 [0.40, 1.66]
2.7 Surgery + RT + CT (concom MTX or VBMF) vs surgery + RT alone	1	Hazard Ratio (Fixed, 95% CI)	1.03 [0.78, 1.36]
2.8 Induction cis/BLM + surgery + RT + adjuvant cisplatin versus surgery + RT alone	1	Hazard Ratio (Fixed, 95% CI)	1.55 [0.93, 2.58]
3 Progression free survival	2	Hazard Ratio (Fixed, 95% CI)	0.88 [0.72, 1.07]
3.1 Surgery + RT + CT (concom cisplatin) vs surgery + RT alone	1	Hazard Ratio (Fixed, 95% CI)	0.75 [0.57, 0.99]
3.2 Surgery + RT + CT (concom MTX or VBMF) vs surgery + RT alone	1	Hazard Ratio (Fixed, 95% CI)	1.03 [0.78, 1.36]
4 Locoregional recurrence	1	Hazard Ratio (Fixed, 95% CI)	Totals not selected
4.1 Surgery + RT + CT (cisplatin) vs surgery + RT alone	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
5 Recurrent disease (overall)	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

5.1 Surgery + RT + CT (methotrexate) vs surgery + RT alone (2 years)	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total mortality	26		Hazard Ratio (Fixed, 95% CI)	0.78 [0.73, 0.83]
1.1 Cisplatin or carboplatin + RT vs RT alone	5		Hazard Ratio (Fixed, 95% CI)	0.66 [0.57, 0.77]
1.2 Cisplatin or carboplatin + 5-FU + RT vs RT alone	8		Hazard Ratio (Fixed, 95% CI)	0.71 [0.62, 0.81]
1.3 Cisplatin + bleomycin + RT vs RT alone	1		Hazard Ratio (Fixed, 95% CI)	1.21 [0.67, 2.19]
1.4 1-FU+ RT vs RT alone	1		Hazard Ratio (Fixed, 95% CI)	0.83 [0.58, 1.21]
1.5 Mitomycin + 5-FU + RT vs RT alone	1		Hazard Ratio (Fixed, 95% CI)	0.77 [0.61, 0.98]
1.6 Methotrexate + RT vs RT alone	1		Hazard Ratio (Fixed, 95% CI)	0.96 [0.76, 1.23]
1.7 Sim CRT (MTX or VBMF) versus RT alone	1		Hazard Ratio (Fixed, 95% CI)	0.82 [0.65, 1.04]
1.8 Sim CRT (MTX or VBMF) + Sub CT (MTX or VBMF) vs RT alone	1		Hazard Ratio (Fixed, 95% CI)	1.06 [0.84, 1.34]
1.9 Bleomycin + RT vs RT alone	4		Hazard Ratio (Fixed, 95% CI)	0.79 [0.62, 1.00]
1.10 Bleomycin + mitomycin + RT vs RT alone	1		Hazard Ratio (Fixed, 95% CI)	0.64 [0.36, 1.14]
1.11 Mitomycin + RT versus RT alone	2		Hazard Ratio (Fixed, 95% CI)	0.92 [0.76, 1.12]
1.12 Cisplatin + 5-FU alternating with RT vs RT alone	2		Hazard Ratio (Fixed, 95% CI)	0.69 [0.53, 0.90]
2 Disease free survival	9		Hazard Ratio (Fixed, 95% CI)	0.77 [0.70, 0.84]
2.1 Cisplatin or carboplatin + 5-FU + RT versus RT alone	4		Hazard Ratio (Fixed, 95% CI)	0.70 [0.59, 0.84]
2.2 Carboplatin + RT versus RT alone	1		Hazard Ratio (Fixed, 95% CI)	0.83 [0.68, 1.01]
2.3 Cisplatin + 5-FU alternating with RT vs RT alone	1		Hazard Ratio (Fixed, 95% CI)	0.78 [0.55, 1.11]
2.4 MTX + RT versus RT alone	1		Hazard Ratio (Fixed, 95% CI)	0.65 [0.43, 0.98]
2.5 Bleomycin + mitomycin + RT versus RT alone	1		Hazard Ratio (Fixed, 95% CI)	0.45 [0.22, 0.93]
2.6 Sim CRT (MTX or VBMF) versus RT alone	1		Hazard Ratio (Fixed, 95% CI)	0.72 [0.57, 0.91]

2.7 Sim CRT (MTX or VBMF) + Sub CT (MTX or VBMF) vs RT alone	1	Hazard Ratio (Fixed, 95% CI)	0.92 [0.74, 1.15]
3 Locoregional control	8	Hazard Ratio (Fixed, 95% CI)	0.72 [0.64, 0.81]
3.1 Cisplatin or carboplatin + RT vs RT alone	2	Hazard Ratio (Fixed, 95% CI)	0.78 [0.65, 0.94]
3.2 Cisplatin or carboplatin + 5-FU + RT ± surgery vs RT alone	3	Hazard Ratio (Fixed, 95% CI)	0.75 [0.61, 0.93]
3.3 Methotrexate + RT vs RT alone	1	Hazard Ratio (Fixed, 95% CI)	0.71 [0.49, 1.02]
3.4 Mitomycin + 5-FU + RT vs RT alone	1	Hazard Ratio (Fixed, 95% CI)	0.48 [0.33, 0.71]
3.5 Cisplatin +5-FU alternating with RT	1	Hazard Ratio (Fixed, 95% CI)	0.35 [0.14, 0.87]
4 Progression free survival	6	Hazard Ratio (Fixed, 95% CI)	0.77 [0.67, 0.89]
4.1 Cisplatin + post-op RT vs post-op RT	2	Hazard Ratio (Fixed, 95% CI)	0.84 [0.66, 1.08]
4.2 1-FU + RT vs RT alone	1	Hazard Ratio (Fixed, 95% CI)	0.79 [0.54, 1.14]
4.3 Mitomycin + 5-FU + RT vs RT alone	1	Hazard Ratio (Fixed, 95% CI)	0.60 [0.44, 0.83]
4.4 Alternating cisplatin + 5-FU + RT	2	Hazard Ratio (Fixed, 95% CI)	0.82 [0.62, 1.07]
5 Locoregional control	4	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Mitomycin + HFxAcc RT versus HFxAcc RT alone (median 4 years)	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.2 Bleomycin + LRT versus LRT	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.3 Gemcitabine + RT versus RT alone	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.4 Pepleomycin + RT ± hyperthermia vs RT + hyperthermia	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total mortality	20		Hazard Ratio (Fixed, 95% CI)	Totals not selected
1.1 Induction cisplatin + UFT versus induction cisplatin + 5-FU	1		Hazard Ratio (Fixed, 95% CI)	Not estimable
1.2 Induction carboplatin + 5-FU versus induction cisplatin + 5-FU	1		Hazard Ratio (Fixed, 95% CI)	Not estimable

1.3 Induction cisplatin + vinorelbine ± LRT versus induction cisplatin + 5-FU ± LRT	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
1.4 Induction cisplatin + etoposide + RT versus induction cisplatin + RT	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
1.5 Induction cisplatin + methotrexate + bleomycin + vincristine versus induction cisplatin	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
1.6 Induction simultaneous MTX + 5-FU versus sequential MTX + 5-FU	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
1.7 Induction cisplatin + docetaxel + 5-FU (TPF) ± RT versus induction cisplatin + 5-FU (PF) ±RT	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
1.8 Induction TPF + CRT ± surg versus induction PF + CRT + surg	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
1.9 Induction CT(cis/5-FU/TPZ) then CRT(cis/5-FU/TPZ/RT) versus induction CT (PF) then CRT (PF+RT)	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
1.10 Concomitant CRT (carboplatin) versus concomitant CRT (cisplatin)	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
1.11 Concomitant CRT(cis/TPZ) versus concomitant CRT (cis/5-FU)	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
1.12 Concomitant CRT (cis/TPZ) versus concomitant CRT (cis)	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
1.13 Concomitant CRT(HU/5-FU) versus concomitant CRT (cis/FU)	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
1.14 Concomitant CRT (cis/paclitaxel) versus concomitant CRT (cis/FU)	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
1.15 Concomitant CRT (cis/paclitaxel) versus concomitant CRT (HU/5-FU)	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
1.16 Concomitant intra-arterial CRT vs concomitant intravenous CRT	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
1.17 Concomitant CRT (MTX or VBMF) versus RT then CT (MTX or VBMF)	1	Hazard Ratio (Fixed, 95% CI)	Not estimable

1.18 Concomitant CRT (MTX or VBMF) then CT versus RT then CT (MTX or VBMF)	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
1.19 Concomitant CRT (MTX or VBMF) then CT versus concomitant CRT (MTX or VBMF)	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
1.20 Induction CT (PF) then RT vs concomitant CRT + maint CT (PF)	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
1.21 Induction sequential cisplatin then RT versus concomitant CRT (cis/5-FU)	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
1.22 Induction CT (PF) then concomitant CRT versus concomitant CRT (PF)	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
1.23 Induction CT (TPF) then CRT versus CRT alone	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
1.24 Induction CT (BLM/MTX/VINB) then RT vs alternating CRT	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
2 Disease free survival	7	Hazard ratio (Fixed, 95% CI)	Totals not selected
2.1 Induction CT(cis/BLM) then surg/RT then CT (cis) vs induction CT (cis/BLM) then surg/RT	1	Hazard ratio (Fixed, 95% CI)	Not estimable
2.2 Induction CT (cis/5-FU) then concomitant CRT versus concomitant CRT (cisplatin + 5-FU)	1	Hazard ratio (Fixed, 95% CI)	Not estimable
2.3 Concomitant CRT (cis/TPZ) versus concomitant CRT (cis/5-FU)	1	Hazard ratio (Fixed, 95% CI)	Not estimable
2.4 Concomitant CRT (cis/TPZ) versus concomitant CRT (cis)	1	Hazard ratio (Fixed, 95% CI)	Not estimable
2.5 Concomitant CRT (carboplatin) versus concomitant CRT (cisplatin)	1	Hazard ratio (Fixed, 95% CI)	Not estimable
2.6 Concomitant intra-arterial CRT vs concomitant intravenous CRT	1	Hazard ratio (Fixed, 95% CI)	Not estimable
2.7 Induction CT (BLM/MTX/VINB/Leucov) then RT vs alternating CRT	1	Hazard ratio (Fixed, 95% CI)	Not estimable
3 Progression free survival	7	Hazard Ratio (Fixed, 95% CI)	Totals not selected
3.1 Induction cisplatin + UFT versus induction cisplatin + 5-FU	1	Hazard Ratio (Fixed, 95% CI)	Not estimable

3.2 Induction cisplatin + docetaxel + 5-FU (TPF) ± RT versus induction cisplatin + 5-FU (PF) ± RT induction cisplatin + FU ±RT versus induction cisplatin + docetaxel + 5FU ± RT	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
3.3 Induction (TPF) versus induction (PF)	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
3.4 Concomitant CRT (MTX or VBMF) versus RT then CT (MTX or VBMF)	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
3.5 Concomitant CRT (MTX or VBMF) then CT versus RT then CT (MTX or VBMF)	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
3.6 Concomitant CRT (MTX or VBMF) then CT versus neo concomitant CRT (MTX or VBMF)	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
3.7 Induction CT (PF) then RT versus concomitant CRT + maint CT (PF)	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
3.8 Induction sequential cisplatin then RT versus concomitant CRT (cis/5-FU)	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
3.9 Induction CT (TPF) then CRT versus CRT alone	1	Hazard Ratio (Fixed, 95% CI)	Not estimable
4 Locoregional control	3	hazard ratio (Fixed, 95% CI)	Totals not selected
4.1 Neo concomitant CRT (cis/TPZ) versus neo concomitant CRT (cis/5-FU)	1	hazard ratio (Fixed, 95% CI)	Not estimable
4.2 Concomitant intra-arterial CRT vs concomitant intravenous CRT	1	hazard ratio (Fixed, 95% CI)	Not estimable
4.3 Concomitant CRT (cis/TPZ) versus concomitant CRT (cis)	1	hazard ratio (Fixed, 95% CI)	Not estimable
5 Total mortality (2-5 years)	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Induction CT (BVCM) + surgery vs induction CT (BVM) + surgery	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 Disease free survival (5 years)	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Induction carboplatin + 5-FU versus induction cisplatin + 5-FU	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Locoregional control	5	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Induction CT (BLM/MTX/VINB/Leucov) then RT vs alternating CRT	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

7.2 Induction CT (BLM/MTX/HU) then RT versus alternating CR	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.3 Induction cisplatin + 5-FU + RT versus induction cisplatin + etoposide + RT	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.4 Induction methotrexate (intra-arterial) versus bleomycin (intra-arterial)	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.5 Concomitant cisplatin (daily) + RT versus concomitant cisplatin (weekly) + RT	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.6 Concomitant cisplatin (weekly) + RT versus concomitant cisplatin (once/3 weeks) + RT	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.7 Concomitant cisplatin (daily) + RT versus concomitant cisplatin (once/3weeks) + RT	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8 Locoregional recurrence (2 years)	1	Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 Induction CT (BVCM) + surgery vs induction CT (BVM)	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 1.1. Comparison 1 Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone, Outcome 1 Total mortality.

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

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

Outcome: 1 Total mortality

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
1 Cisplatin or carboplatin + 5-FU + RT surgery vs RT surgery				
Depondt 1993 (1)	-0.178 (0.147)		6.7 %	0.84 [0.63, 1.12]
Paccagnella 1994 (2)	-0.18 (0.146)		6.8 %	0.84 [0.63, 1.11]
Lewin 1997 (3)	0.046 (0.104)		10.3 %	1.05 [0.85, 1.28]
Volling 1999 (4)	-0.3 (0.29)		2.2 %	0.74 [0.42, 1.31]
Domenge 2000	-0.41 (0.25)		2.9 %	0.66 [0.41, 1.08]
Licitra 2003 (5)	-0.01 (0.23)		3.3 %	0.99 [0.63, 1.55]
Olmi 2003 (6)	-0.193 (0.214)		3.8 %	0.82 [0.54, 1.25]
Subtotal (95% CI) (8) Intra-arterial			**36.0 %**	**0.90 [0.80, 1.02]**

(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
Heterogeneity: Tau² = 0.0; Chi² = 4.90, df = 6 (P = 0.56); I² =0.0%				
Test for overall effect: Z = 1.69 (P = 0.091)				
2 Carboplatin and ftorofur + RT vs RT alone				
Tejedor 1992	-0.8 (0.4472)		1.0 %	0.45 [0.19, 1.08]
Subtotal (95% CI)			**1.0 %**	**0.45 [0.19, 1.08]**
Heterogeneity: not applicable				
Test for overall effect: Z = 1.79 (P = 0.074)				
3 Cisplatin + 5-FU + folinic acid + RT vs RT alone				
Giglio 1997	-0.366 (0.299)		2.1 %	0.69 [0.39, 1.25]
Subtotal (95% CI)			**2.1 %**	**0.69 [0.39, 1.25]**
Heterogeneity: not applicable				
Test for overall effect: Z = 1.22 (P = 0.22)				
4 Cisplatin + 5-FU + vindesine + RT vs RT alone				
Jaulerry 1992	0.084 (0.229)		3.4 %	1.09 [0.69, 1.70]
Subtotal (95% CI)			**3.4 %**	**1.09 [0.69, 1.70]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.37 (P = 0.71)				
5 Cisplatin + 5-FU + bleomycin + methotrexate + RT vs RT alone				
Mazeron 1992	0.3789 (0.2294)		3.4 %	1.46 [0.93, 2.29]
Subtotal (95% CI)			**3.4 %**	**1.46 [0.93, 2.29]**
Heterogeneity: not applicable				
Test for overall effect: Z = 1.65 (P = 0.099)				
6 Cisplatin + bleomycin + vinblastine + mitomycin C + RT vs RT alone				
Salvajoli 1992	0.036 (0.302)		2.1 %	1.04 [0.57, 1.87]
Subtotal (95% CI)			**2.1 %**	**1.04 [0.57, 1.87]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.12 (P = 0.91)				
7 Cisplatin + bleomycin + vindesine + mitomycin C + RT vs RT alone				
Brunin 1989	0.123 (0.213)		3.8 %	1.13 [0.74, 1.72]
Subtotal (95% CI)			**3.8 %**	**1.13 [0.74, 1.72]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.58 (P = 0.56)				
8 Cisplatin + bleomycin + vincristine + adriamycin + RT vs RT alone				
Szpirglas 1988	-0.08 (0.2)		4.2 %	0.92 [0.62, 1.37]
Subtotal (95% CI)			**4.2 %**	**0.92 [0.62, 1.37]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.40 (P = 0.69)				
9 Cisplatin + bleomycin + vincristine + methotrexate + RT + surgery vs RT + surgery				
Schuller 1988	0.072 (0.167)		5.6 %	1.07 [0.77, 1.49]
Subtotal (95% CI)			**5.6 %**	**1.07 [0.77, 1.49]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.43 (P = 0.67)				
10 Cisplatin + bleomycin + methotrexate + surgery + RT vs surgery + RT				
(8) Intra-arterial				

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
Maipang 1995	0.067 (0.333)		1.7 %	1.07 [0.56, 2.05]
Subtotal (95% CI)			**1.7 %**	**1.07 [0.56, 2.05]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.20 (P = 0.84)				
11 Cisplatin + epirubicin + surgery vs RT plus surgery (5 years)				
Szabo 1999	-0.13 (0.23)		3.3 %	0.88 [0.56, 1.38]
Subtotal (95% CI)			**3.3 %**	**0.88 [0.56, 1.38]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.57 (P = 0.57)				
12 Methotrexate + RT vs RT alone				
Richard 1974	-0.37 (0.31)		2.0 %	0.69 [0.38, 1.27]
Knowlton 1975	0.15 (0.21)		3.9 %	1.16 [0.77, 1.75]
Nervi 1978	-0.38 (0.19)		4.6 %	0.68 [0.47, 0.99]
Fazekas 1980	-0.0064 (0.0894)		11.9 %	0.99 [0.83, 1.18]
Subtotal (95% CI)			**22.4 %**	**0.90 [0.72, 1.14]**
Heterogeneity: Tau^2 = 0.02; Chi^2 = 5.19, df = 3 (P = 0.16); I^2 =42%				
Test for overall effect: Z = 0.88 (P = 0.38)				
13 Methotrexate + vincristine + RT vs RT alone				
Petrovich 1981	-0.559 (0.436)		1.0 %	0.57 [0.24, 1.34]
Subtotal (95% CI)			**1.0 %**	**0.57 [0.24, 1.34]**
Heterogeneity: not applicable				
Test for overall effect: Z = 1.28 (P = 0.20)				
14 Methotrexate + bleomycin + 5-FU + cyclophosphamide + RT surgery vs RT surgery				
Holoye 1985	0.394 (0.25)		2.9 %	1.48 [0.91, 2.42]
Subtotal (95% CI)			**2.9 %**	**1.48 [0.91, 2.42]**
Heterogeneity: not applicable				
Test for overall effect: Z = 1.58 (P = 0.12)				
15 Bleomycin + vincristine + surgery RT vs surgery RT				
Luboinski 1985 (7)	-0.57 (0.28)		2.4 %	0.57 [0.33, 0.98]
Richard 1991 (8)	-0.317 (0.186)		4.7 %	0.73 [0.51, 1.05]
Subtotal (95% CI)			**7.1 %**	**0.67 [0.50, 0.91]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.57, df = 1 (P = 0.45); I^2 =0.0%				
Test for overall effect: Z = 2.55 (P = 0.011)				
Total (95% CI)			**100.0 %**	**0.92 [0.84, 1.00]**
Heterogeneity: Tau^2 = 0.01; Chi^2 = 29.91, df = 24 (P = 0.19); I^2 =20%				
Test for overall effect: Z = 1.87 (P = 0.061)				

(1) Carboplatin

(8) Intra-arterial

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
(2) Cisplatin				
(3) Cisplatin				
(4) Carboplatin				
(5) Cisplatin				
(6) Carboplatin				
(7) Intra-arterial				
(8) Intra-arterial				

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

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

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

Outcome: 2 Disease free survival

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
1 Carboplatin + 5-FU + RT + surgery vs RT + surgery				
Volling 1999	-0.6 (0.27)		8.0 %	0.55 [0.32, 0.93]
Olmi 2003	-0.33 (0.19)		16.1 %	0.72 [0.50, 1.04]
Subtotal (95% CI)			**24.1 %**	**0.66 [0.48, 0.89]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.67$, df = 1 (P = 0.41); $I^2 = 0.0\%$				
Test for overall effect: Z = 2.70 (P = 0.0069)				
2 Carboplatin + ftorafur + RT vs RT alone				
Tejedor 1992	-0.15 (0.48)		2.5 %	0.86 [0.34, 2.21]
Subtotal (95% CI)			**2.5 %**	**0.86 [0.34, 2.21]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.31 (P = 0.75)				
3 Cisplatin + fluorouracil + RT + surgery vs RT + surgery (5 years)				
Paccagnella 1994	-0.29 (0.19)		16.1 %	0.75 [0.52, 1.09]
Domenge 2000	-0.23 (0.14)		29.7 %	0.79 [0.60, 1.05]
Subtotal (95% CI)			**45.9 %**	**0.78 [0.62, 0.97]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.06$, df = 1 (P = 0.80); $I^2 = 0.0\%$				
Test for overall effect: Z = 2.23 (P = 0.026)				
4 Cisplatin + bleomycin + vindesine + mitomycin C + RT vs RT alone				

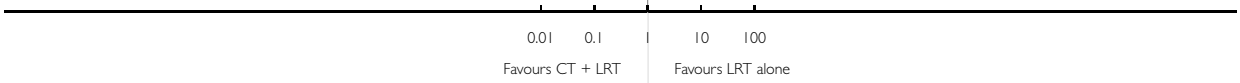
0.01 0.1 1 10 100

Favours CT + LRT Favours LRT alone

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
Brunin 1989	-0.07 (0.24)		10.1 %	0.93 [0.58, 1.49]
Subtotal (95% CI)			**10.1 %**	**0.93 [0.58, 1.49]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.29 (P = 0.77)				
5 Bleomycin + vincristine + surgery vs surgery (floor of mouth)				
Richard 1991	-0.15 (0.22)		12.0 %	0.86 [0.56, 1.32]
Subtotal (95% CI)			**12.0 %**	**0.86 [0.56, 1.32]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.68 (P = 0.50)				
6 Bleomycin + cyclophosphamide + MTX + 5-FU plus RT surgery versus RT surgery				
Holoye 1985	-0.08 (0.33)		5.3 %	0.92 [0.48, 1.76]
Subtotal (95% CI)			**5.3 %**	**0.92 [0.48, 1.76]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.24 (P = 0.81)				
Total (95% CI)			**100.0 %**	**0.78 [0.67, 0.90]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.00, df = 7 (P = 0.88); I^2 =0.0%				
Test for overall effect: Z = 3.27 (P = 0.0011)				

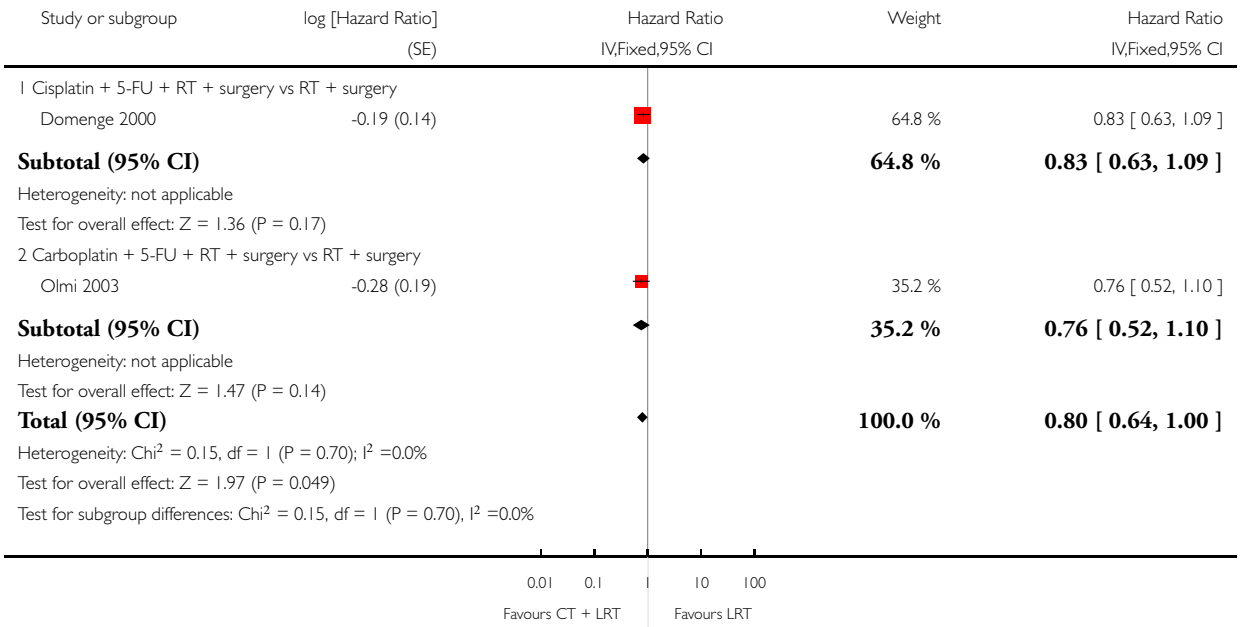


Analysis 1.3. Comparison 1 Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone, Outcome 3 Progression free survival.

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

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

Outcome: 3 Progression free survival

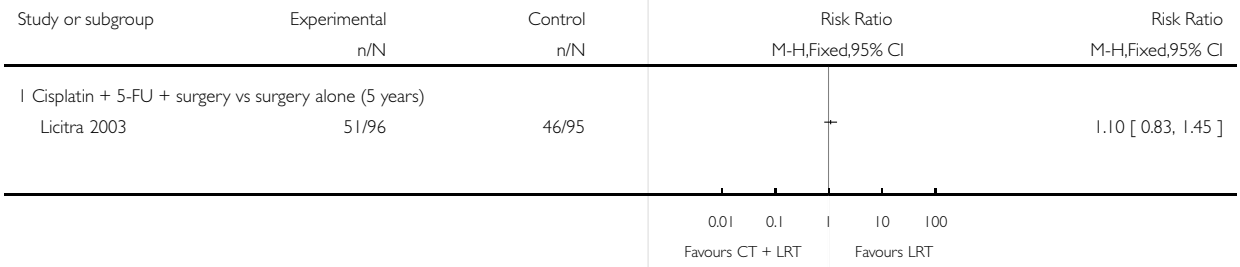


Analysis 1.4. Comparison 1 Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone, Outcome 4 Disease free survival.

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

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

Outcome: 4 Disease free survival

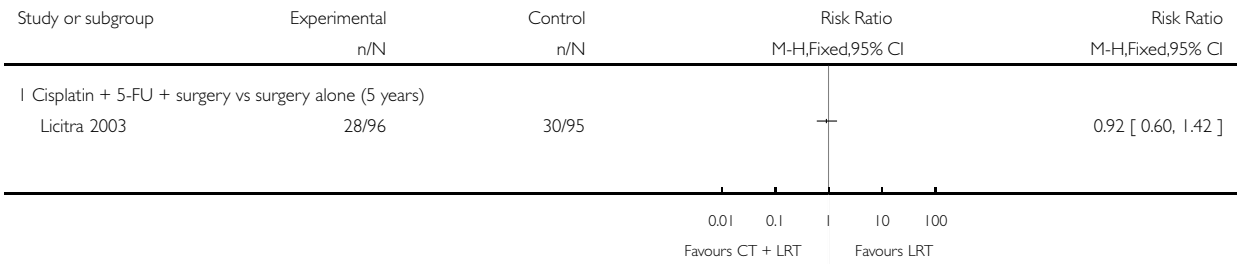


Analysis 1.5. Comparison 1 Induction chemotherapy plus locoregional treatment (LRT) versus LRT alone, Outcome 5 Recurrent disease - Locoregional.

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

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

Outcome: 5 Recurrent disease - Locoregional

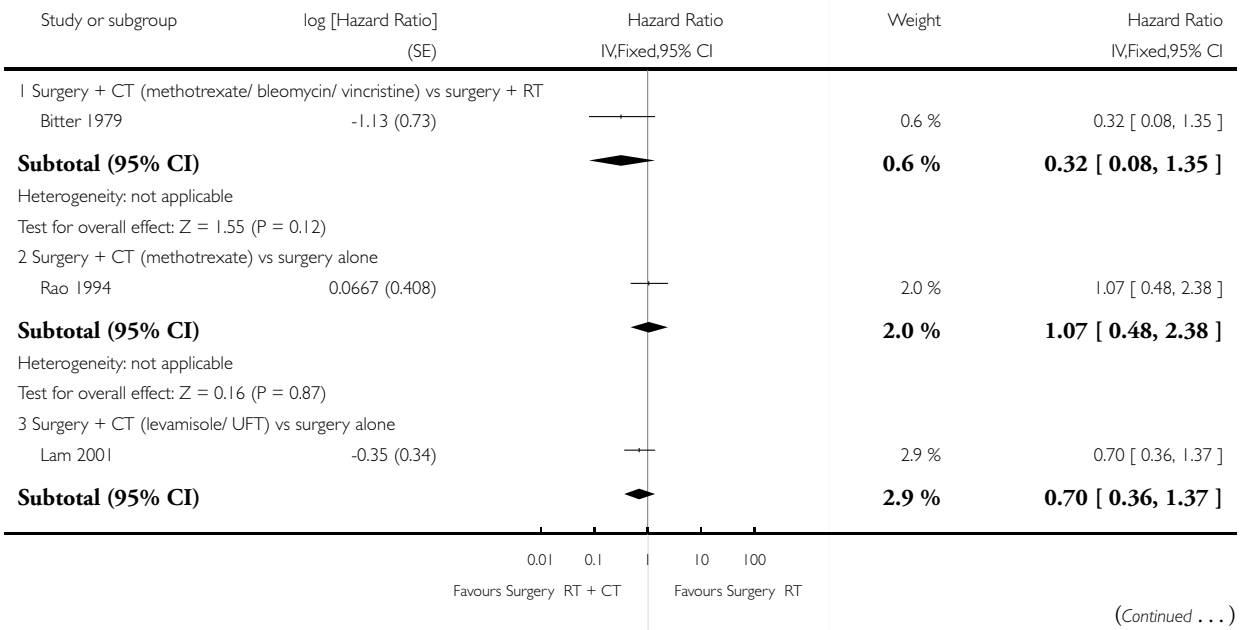


Analysis 2.1. Comparison 2 Surgery ± radiotherapy + chemotherapy versus surgery ± radiotherapy alone, Outcome 1 Total mortality.

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

Comparison: 2 Surgery radiotherapy + chemotherapy versus surgery radiotherapy alone

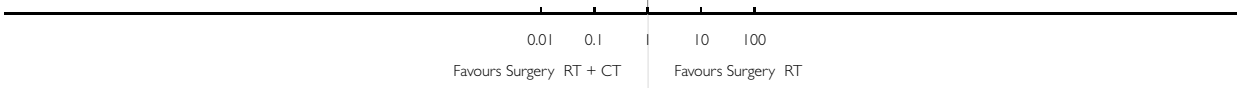
Outcome: 1 Total mortality



(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Heterogeneity: not applicable				
Test for overall effect: Z = 1.03 (P = 0.30)				
4 Surgery RT + CT (methotrexate/bleomycin/leucovorin) vs surgery RT				
Szpirglas 1979	0.01 (0.36)		2.6 %	1.01 [0.50, 2.05]
Subtotal (95% CI)			**2.6 %**	**1.01 [0.50, 2.05]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.03 (P = 0.98)				
5 Surgery + RT + CT (methotrexate) vs surgery + RT alone				
Rentschler 1987	0.04 (0.17)		11.6 %	1.04 [0.75, 1.45]
Subtotal (95% CI)			**11.6 %**	**1.04 [0.75, 1.45]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.24 (P = 0.81)				
6 Surgery +CT (cisplatin/ 5-FU) + RT vs surgery + RT alone				
Laramore 1992	-0.093 (0.11)		27.8 %	0.91 [0.73, 1.13]
Subtotal (95% CI)			**27.8 %**	**0.91 [0.73, 1.13]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.85 (P = 0.40)				
7 Surgery + RT + CT (concom cisplatin) vs surgery + RT alone				
Cooper 2004	-0.139 (0.127)		20.9 %	0.87 [0.68, 1.12]
Bernier 2004	-0.354 (0.153)		14.4 %	0.70 [0.52, 0.95]
Subtotal (95% CI)			**35.2 %**	**0.80 [0.66, 0.97]**
Heterogeneity: Chi^2 = 1.17, df = 1 (P = 0.28); I^2 =14%				
Test for overall effect: Z = 2.32 (P = 0.020)				
8 Surgery + RT + CT (concom carboplatin) vs surgery + RT alone				
Argiris 2008	-0.11 (0.39)		2.2 %	0.90 [0.42, 1.92]
Subtotal (95% CI)			**2.2 %**	**0.90 [0.42, 1.92]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.28 (P = 0.78)				
9 Surgery + RT + CT (concom MTX or VBMF) vs surgery + RT alone				
UKHAN 2010	-0.06 (0.15)		15.0 %	0.94 [0.70, 1.26]
Subtotal (95% CI)			**15.0 %**	**0.94 [0.70, 1.26]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.40 (P = 0.69)				
Total (95% CI)			**100.0 %**	**0.88 [0.79, 0.99]**
Heterogeneity: Chi^2 = 6.16, df = 9 (P = 0.72); I^2 =0.0%				
Test for overall effect: Z = 2.21 (P = 0.027)				
Test for subgroup differences: Chi^2 = 4.99, df = 8 (P = 0.76), I^2 =0.0%				

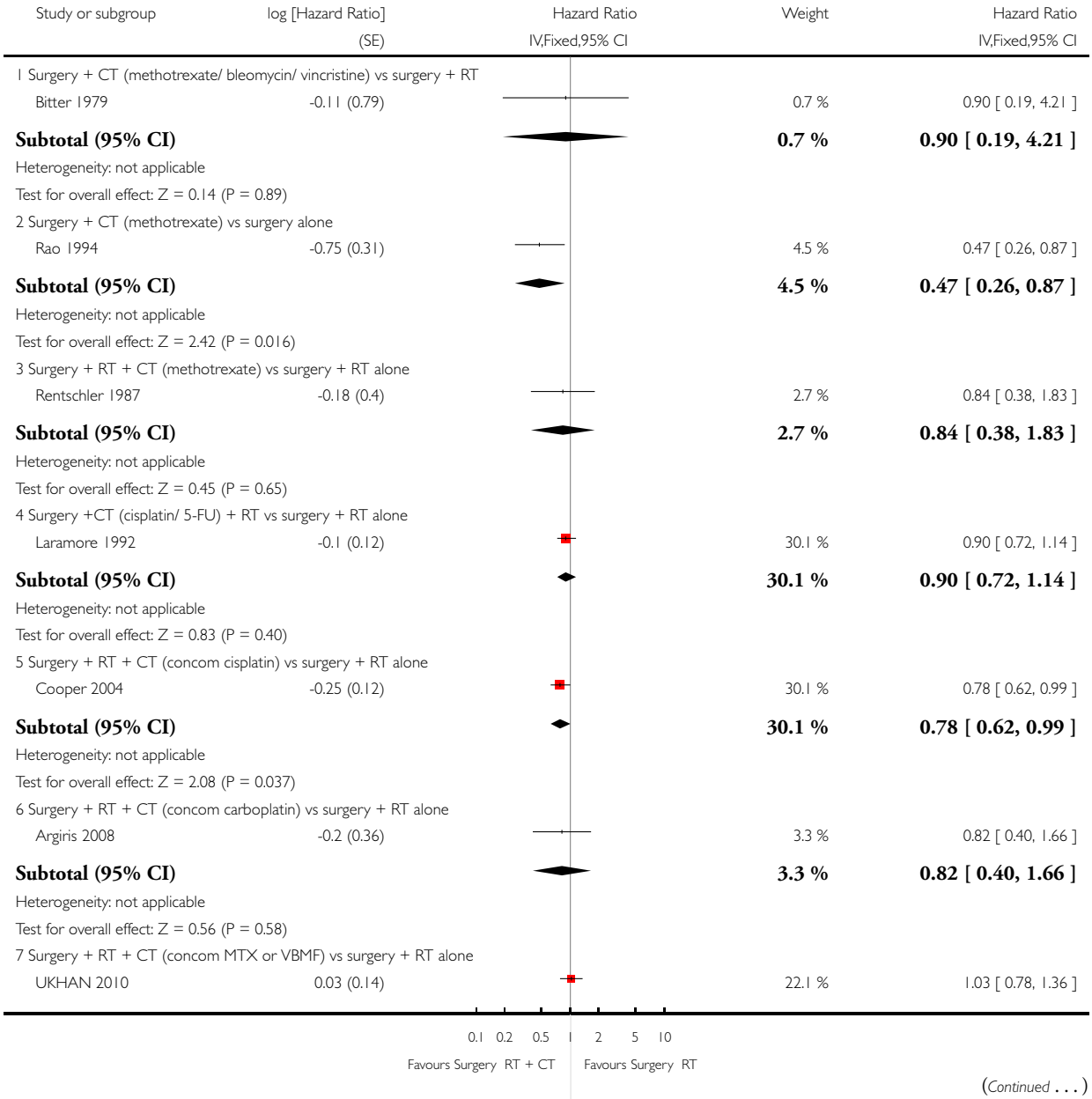


Analysis 2.2. Comparison 2 Surgery ± radiotherapy + chemotherapy versus surgery ± radiotherapy alone, Outcome 2 Disease free survival.

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

Comparison: 2 Surgery radiotherapy + chemotherapy versus surgery radiotherapy alone

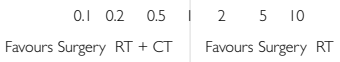
Outcome: 2 Disease free survival



(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Subtotal (95% CI)			**22.1 %**	**1.03 [0.78, 1.36]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.21 (P = 0.83)				
8 Induction cis/BLM + surgery + RT + adjuvant cisplatin versus surgery + RT alone				
HNCProg 1987	0.44 (0.26)		6.4 %	1.55 [0.93, 2.58]
Subtotal (95% CI)			**6.4 %**	**1.55 [0.93, 2.58]**
Heterogeneity: not applicable				
Test for overall effect: Z = 1.69 (P = 0.091)				
Total (95% CI)			**100.0 %**	**0.89 [0.78, 1.01]**
Heterogeneity: Chi^2 = 11.19, df = 7 (P = 0.13); I^2 =37%				
Test for overall effect: Z = 1.77 (P = 0.076)				
Test for subgroup differences: Chi^2 = 11.19, df = 7 (P = 0.13), I^2 =37%				



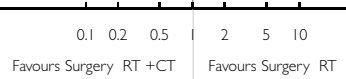
Analysis 2.3. Comparison 2 Surgery ± radiotherapy + chemotherapy versus surgery ± radiotherapy alone, Outcome 3 Progression free survival.

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

Comparison: 2 Surgery radiotherapy + chemotherapy versus surgery radiotherapy alone

Outcome: 3 Progression free survival

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
1 Surgery + RT + CT (concom cisplatin) vs surgery + RT alone				
Bernier 2004	-0.288 (0.143)		48.9 %	0.75 [0.57, 0.99]
Subtotal (95% CI)			**48.9 %**	**0.75 [0.57, 0.99]**
Heterogeneity: not applicable				
Test for overall effect: Z = 2.01 (P = 0.044)				
2 Surgery + RT + CT (concom MTX or VBMF) vs surgery + RT alone				
UKHAN 2010	0.03 (0.14)		51.1 %	1.03 [0.78, 1.36]
Subtotal (95% CI)			**51.1 %**	**1.03 [0.78, 1.36]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.21 (P = 0.83)				



(*Continued* . . .)

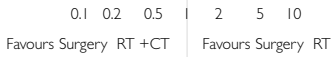
(. . . *Continued*)

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Total (95% CI)			**100.0 %**	**0.88 [0.72, 1.07]**

Heterogeneity: $Chi^2 = 2.53$, df = 1 (P = 0.11); I^2 =60%

Test for overall effect: Z = 1.26 (P = 0.21)

Test for subgroup differences: $Chi^2 = 2.53$, df = 1 (P = 0.11), I^2 =60%



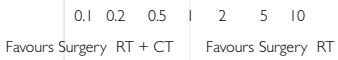
Analysis 2.4. Comparison 2 Surgery ± radiotherapy + chemotherapy versus surgery ± radiotherapy alone, Outcome 4 Locoregional recurrence.

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

Comparison: 2 Surgery radiotherapy + chemotherapy versus surgery radiotherapy alone

Outcome: 4 Locoregional recurrence

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Hazard Ratio IV,Fixed,95% CI
1 Surgery + RT + CT (cisplatin) vs surgery + RT alone			
Cooper 2004	-0.49 (0.2)		0.61 [0.41, 0.91]

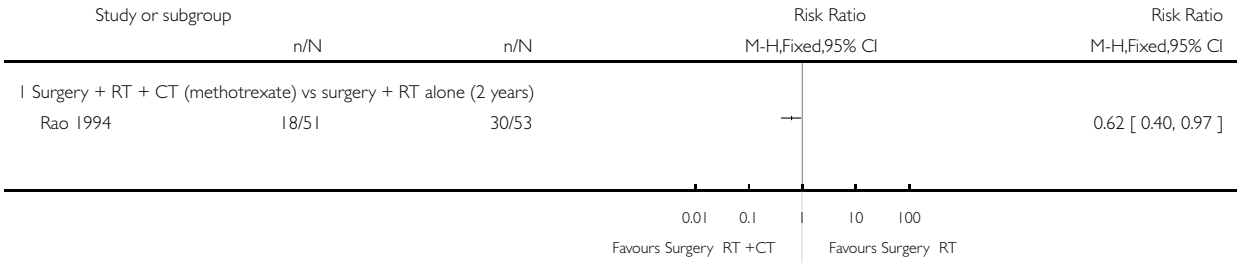


Analysis 2.5. Comparison 2 Surgery ± radiotherapy + chemotherapy versus surgery ± radiotherapy alone, Outcome 5 Recurrent disease (overall).

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

Comparison: 2 Surgery radiotherapy + chemotherapy versus surgery radiotherapy alone

Outcome: 5 Recurrent disease (overall)



Analysis 3.1. Comparison 3 Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable), Outcome 1 Total mortality.

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

Comparison: 3 Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)

Outcome: 1 Total mortality

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
1 Cisplatin or carboplatin + RT vs RT alone				
Jeremic 1997	-0.48 (0.22)		2.2 %	0.62 [0.40, 0.95]
Jeremic 2000	-0.61 (0.22)		2.2 %	0.54 [0.35, 0.84]
Adelstein 2003	-0.47 (0.16)		4.2 %	0.63 [0.46, 0.86]
Huguenin 2004	-0.27 (0.18)		3.3 %	0.76 [0.54, 1.09]
Ruo 2010	-0.36 (0.13)		6.3 %	0.70 [0.54, 0.90]
Subtotal (95% CI)			**18.3 %**	**0.66 [0.57, 0.77]**
Heterogeneity: Chi^2 = 1.82, df = 4 (P = 0.77); I^2 =0.0%				
Test for overall effect: Z = 5.40 (P < 0.00001)				
2 Cisplatin or carboplatin + 5-FU + RT vs RT alone				
Weissler 1992 (1)	-0.2 (0.3)		1.2 %	0.82 [0.45, 1.47]
Haddad 1996 (2)	-0.64 (0.33)		1.0 %	0.53 [0.28, 1.01]
Wendt 1998 (3)	-0.58 (0.19)		3.0 %	0.56 [0.39, 0.81]
(8) Cisplatin				

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Brizel 1998 (4)	-0.24 (0.36)		0.8 %	0.79 [0.39, 1.59]
Staar 2001 (5)	-0.29 (0.15)		4.8 %	0.75 [0.56, 1.00]
Adelstein 2003 (6)	-0.22 (0.15)		4.8 %	0.80 [0.60, 1.08]
Denis 2004 (7)	-0.3 (0.15)		4.8 %	0.74 [0.55, 0.99]
Bensadoun 2006 (8)	-0.48 (0.19)		3.0 %	0.62 [0.43, 0.90]
Subtotal (95% CI)			**23.2 %**	**0.71 [0.62, 0.81]**
Heterogeneity: Chi^2 = 4.07, df = 7 (P = 0.77); I^2 =0.0%				
Test for overall effect: Z = 5.12 (P < 0.00001)				
3 Cisplatin + bleomycin + RT vs RT alone				
Salvajoli 1992	0.1909 (0.3015)		1.2 %	1.21 [0.67, 2.19]
Subtotal (95% CI)			**1.2 %**	**1.21 [0.67, 2.19]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.63 (P = 0.53)				
4 1-FU+ RT vs RT alone				
Browman 1994	-0.182 (0.189)		3.0 %	0.83 [0.58, 1.21]
Subtotal (95% CI)			**3.0 %**	**0.83 [0.58, 1.21]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.96 (P = 0.34)				
5 Mitomycin + 5-FU + RT vs RT alone				
Budach 2005	-0.26 (0.121)		7.3 %	0.77 [0.61, 0.98]
Subtotal (95% CI)			**7.3 %**	**0.77 [0.61, 0.98]**
Heterogeneity: not applicable				
Test for overall effect: Z = 2.15 (P = 0.032)				
6 Methotrexate + RT vs RT alone				
Gupta 2001	-0.036 (0.123)		7.1 %	0.96 [0.76, 1.23]
Subtotal (95% CI)			**7.1 %**	**0.96 [0.76, 1.23]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.29 (P = 0.77)				
7 Sim CRT (MTX or VBMF) versus RT alone				
UKHAN 2010	-0.2 (0.12)		7.4 %	0.82 [0.65, 1.04]
Subtotal (95% CI)			**7.4 %**	**0.82 [0.65, 1.04]**
Heterogeneity: not applicable				
Test for overall effect: Z = 1.67 (P = 0.096)				
8 Sim CRT (MTX or VBMF) + Sub CT (MTX or VBMF) vs RT alone				
UKHAN 2010	0.06 (0.12)		7.4 %	1.06 [0.84, 1.34]
Subtotal (95% CI)			**7.4 %**	**1.06 [0.84, 1.34]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.50 (P = 0.62)				
9 Bleomycin + RT vs RT alone				
Shanta 1980	-1.28 (0.27)		1.5 %	0.28 [0.16, 0.47]
Morita 1980	0.38 (0.43)		0.6 %	1.46 [0.63, 3.40]
(8) Cisplatin				

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Parvinen 1985	-0.22 (0.33)		1.0 %	0.80 [0.42, 1.53]
Eschwege 1988	0.03 (0.158)		4.3 %	1.03 [0.76, 1.40]
Subtotal (95% CI)			**7.3 %**	**0.79 [0.62, 1.00]**
Heterogeneity: Chi² = 19.84, df = 3 (P = 0.00018); I² =85%				
Test for overall effect: Z = 1.97 (P = 0.048)				
10 Bleomycin + mitomycin + RT vs RT alone				
Smid 1995	-0.44 (0.29)		1.3 %	0.64 [0.36, 1.14]
Subtotal (95% CI)			**1.3 %**	**0.64 [0.36, 1.14]**
Heterogeneity: not applicable				
Test for overall effect: Z = 1.52 (P = 0.13)				
11 Mitomycin + RT versus RT alone				
Dobrowsky 2000	-0.15 (0.18)		3.3 %	0.86 [0.60, 1.22]
Grau 2003	-0.05 (0.12)		7.4 %	0.95 [0.75, 1.20]
Subtotal (95% CI)			**10.7 %**	**0.92 [0.76, 1.12]**
Heterogeneity: Chi² = 0.21, df = 1 (P = 0.64); I² =0.0%				
Test for overall effect: Z = 0.81 (P = 0.42)				
12 Cisplatin + 5-FU alternating with RT vs RT alone				
Merlano 1992	-0.4766 (0.1826)		3.2 %	0.62 [0.43, 0.89]
Corvo 2001	-0.242 (0.208)		2.5 %	0.79 [0.52, 1.18]
Subtotal (95% CI)			**5.7 %**	**0.69 [0.53, 0.90]**
Heterogeneity: Chi² = 0.72, df = 1 (P = 0.40); I² =0.0%				
Test for overall effect: Z = 2.73 (P = 0.0064)				
Total (95% CI)			**100.0 %**	**0.78 [0.73, 0.83]**
Heterogeneity: Chi² = 49.55, df = 27 (P = 0.01); I² =46%				
Test for overall effect: Z = 7.47 (P < 0.00001)				
Test for subgroup differences: Chi² = 22.89, df = 11 (P = 0.02), I² =52%				

(1) Cisplatin
(2) Cisplatin
(3) Cisplatin
(4) Cisplatin
(5) Carboplatin
(6) Cisplatin
(7) Carboplatin
(8) Cisplatin

Analysis 3.2. Comparison 3 Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable), Outcome 2 Disease free survival.

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

Comparison: 3 Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)

Outcome: 2 Disease free survival

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
1 Cisplatin or carboplatin + 5-FU + RT versus RT alone				
Brizel 1998 (1)	-0.15 (0.33)		2.1 %	0.86 [0.45, 1.64]
Staar 2001 (2)	-0.25 (0.14)		11.6 %	0.78 [0.59, 1.02]
Denis 2004 (3)	-0.34 (0.16)		8.9 %	0.71 [0.52, 0.97]
Bensadoun 2006 (4)	-0.63 (0.19)		6.3 %	0.53 [0.37, 0.77]
Subtotal (95% CI)			**28.8 %**	**0.70 [0.59, 0.84]**
Heterogeneity: Chi² = 3.05, df = 3 (P = 0.38); I² =2%				
Test for overall effect: Z = 3.98 (P = 0.000068)				
2 Carboplatin + RT versus RT alone				
Ruo 2010	-0.19 (0.1)		22.7 %	0.83 [0.68, 1.01]
Subtotal (95% CI)			**22.7 %**	**0.83 [0.68, 1.01]**
Heterogeneity: not applicable				
Test for overall effect: Z = 1.90 (P = 0.057)				
3 Cisplatin + 5-FU alternating with RT vs RT alone				
Merlano 1992	-0.25 (0.18)		7.0 %	0.78 [0.55, 1.11]
Subtotal (95% CI)			**7.0 %**	**0.78 [0.55, 1.11]**
Heterogeneity: not applicable				
Test for overall effect: Z = 1.39 (P = 0.16)				
4 MTX + RT versus RT alone				
Gupta 2001	-0.43 (0.207)		5.3 %	0.65 [0.43, 0.98]
Subtotal (95% CI)			**5.3 %**	**0.65 [0.43, 0.98]**
Heterogeneity: not applicable				
Test for overall effect: Z = 2.08 (P = 0.038)				
5 Bleomycin + mitomycin + RT versus RT alone				
Smid 1995	-0.789 (0.366)		1.7 %	0.45 [0.22, 0.93]
Subtotal (95% CI)			**1.7 %**	**0.45 [0.22, 0.93]**
Heterogeneity: not applicable				
Test for overall effect: Z = 2.16 (P = 0.031)				
6 Sim CRT (MTX or VBMF) versus RT alone				
UKHAN 2010	-0.33 (0.12)		15.8 %	0.72 [0.57, 0.91]
Subtotal (95% CI)			**15.8 %**	**0.72 [0.57, 0.91]**
Heterogeneity: not applicable				
Test for overall effect: Z = 2.75 (P = 0.0060)				
7 Sim CRT (MTX or VBMF) + Sub CT (MTX or VBMF) vs RT alone				
(4) Cisplatin				

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
UKHAN 2010	-0.08 (0.11)		18.8 %	0.92 [0.74, 1.15]
Subtotal (95% CI)			**18.8 %**	**0.92 [0.74, 1.15]**
Heterogeneity: not applicable				
Test for overall effect: Z = 0.73 (P = 0.47)				
Total (95% CI)			**100.0 %**	**0.77 [0.70, 0.84]**
Heterogeneity: Chi² = 10.42, df = 9 (P = 0.32); I² =14%				
Test for overall effect: Z = 5.57 (P < 0.00001)				
Test for subgroup differences: Chi² = 7.37, df = 6 (P = 0.29), I² =19%				

(1) Cisplatin
(2) Carboplatin
(3) Carboplatin
(4) Cisplatin

Analysis 3.3. Comparison 3 Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable), Outcome 3 Locoregional control.

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

Comparison: 3 Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)

Outcome: 3 Locoregional control

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
1 Cisplatin or carboplatin + RT vs RT alone				
Huguenin 2004	-0.28 (0.17)		13.4 %	0.76 [0.54, 1.05]
Ruo 2010 (1)	-0.23 (0.11)		31.9 %	0.79 [0.64, 0.99]
Subtotal (95% CI)			**45.2 %**	**0.78 [0.65, 0.94]**
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² =0.0%				
Test for overall effect: Z = 2.65 (P = 0.0080)				
2 Cisplatin or carboplatin + 5-FU + RT surgery vs RT alone				
Haddad 1996 (2)	-0.03 (0.32)		3.8 %	0.97 [0.52, 1.82]
Wendt 1998 (3)	-0.32 (0.16)		15.1 %	0.73 [0.53, 0.99]
Staar 2001 (4)	-0.32 (0.17)		13.4 %	0.73 [0.52, 1.01]
Subtotal (95% CI)			**32.2 %**	**0.75 [0.61, 0.93]**
(4) Carboplatin				

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Heterogeneity: Chi² = 0.73, df = 2 (P = 0.70); I² =0.0%				
Test for overall effect: Z = 2.61 (P = 0.0090)				
3 Methotrexate + RT vs RT alone				
Gupta 2001	-0.34 (0.186)		11.2 %	0.71 [0.49, 1.02]
Subtotal (95% CI)			**11.2 %**	**0.71 [0.49, 1.02]**
Heterogeneity: not applicable				
Test for overall effect: Z = 1.83 (P = 0.068)				
4 Mitomycin + 5-FU + RT vs RT alone				
Budach 2005	-0.73 (0.2)		9.6 %	0.48 [0.33, 0.71]
Subtotal (95% CI)			**9.6 %**	**0.48 [0.33, 0.71]**
Heterogeneity: not applicable				
Test for overall effect: Z = 3.65 (P = 0.00026)				
5 Cisplatin +5-FU alternating with RT				
Merlano 1992	-1.06 (0.47)		1.7 %	0.35 [0.14, 0.87]
Subtotal (95% CI)			**1.7 %**	**0.35 [0.14, 0.87]**
Heterogeneity: not applicable				
Test for overall effect: Z = 2.26 (P = 0.024)				
Total (95% CI)			**100.0 %**	**0.72 [0.64, 0.81]**
Heterogeneity: Chi² = 8.21, df = 7 (P = 0.31); I² =15%				
Test for overall effect: Z = 5.31 (P < 0.00001)				
Test for subgroup differences: Chi² = 7.43, df = 4 (P = 0.11), I² =46%				

(1) Carboplatin

(2) Cisplatin

(3) Cisplatin

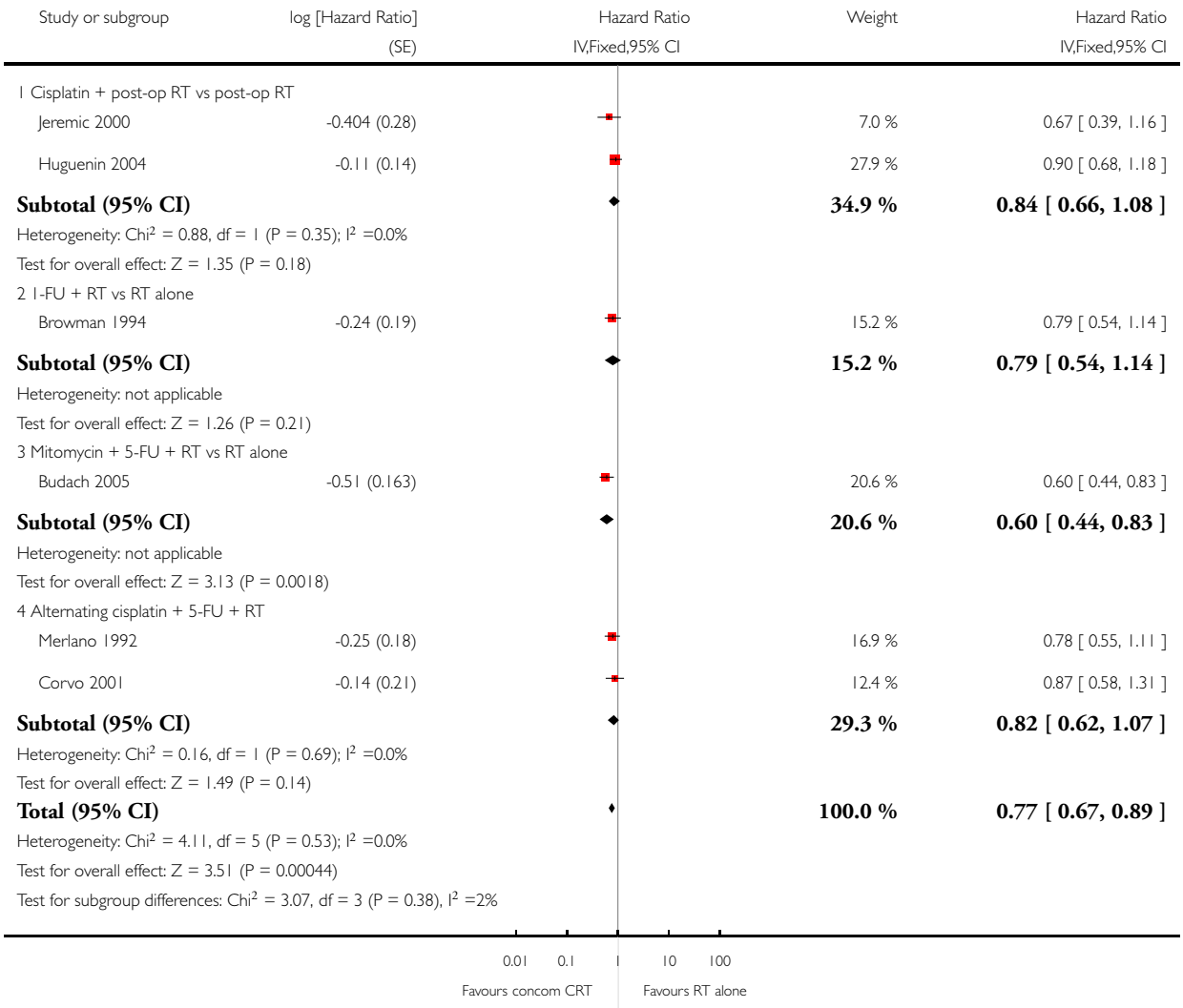
(4) Carboplatin

Analysis 3.4. Comparison 3 Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable), Outcome 4 Progression free survival.

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

Comparison: 3 Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)

Outcome: 4 Progression free survival



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

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

Comparison: 3 Concomitant chemoradiotherapy versus radiotherapy alone (non-resectable)

Outcome: 5 Locoregional control

Study or subgroup	CT + RT n/N	RT alone n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Mitomycin + HFxAcc RT versus HFxAcc RT alone (median 4 years)				
Dobrowsky 2000	38/80	25/78		1.48 [1.00, 2.20]
2 Bleomycin + LRT versus LRT				
Parvinen 1985	8/23	8/23		1.00 [0.45, 2.21]
3 Gemcitabine + RT versus RT alone				
Chauhan 2008	33/40	20/40		1.65 [1.17, 2.32]
4 Pepleomycin + RT hyperthermia vs RT + hyperthermia				
Krishnamurthi 1990	30/65	25/36		0.66 [0.47, 0.93]

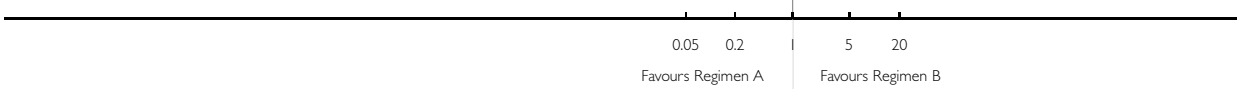
Analysis 4.1. Comparison 4 Chemotherapy A (± LRT) versus chemotherapy B (± LRT), Outcome 1 Total mortality.

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

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

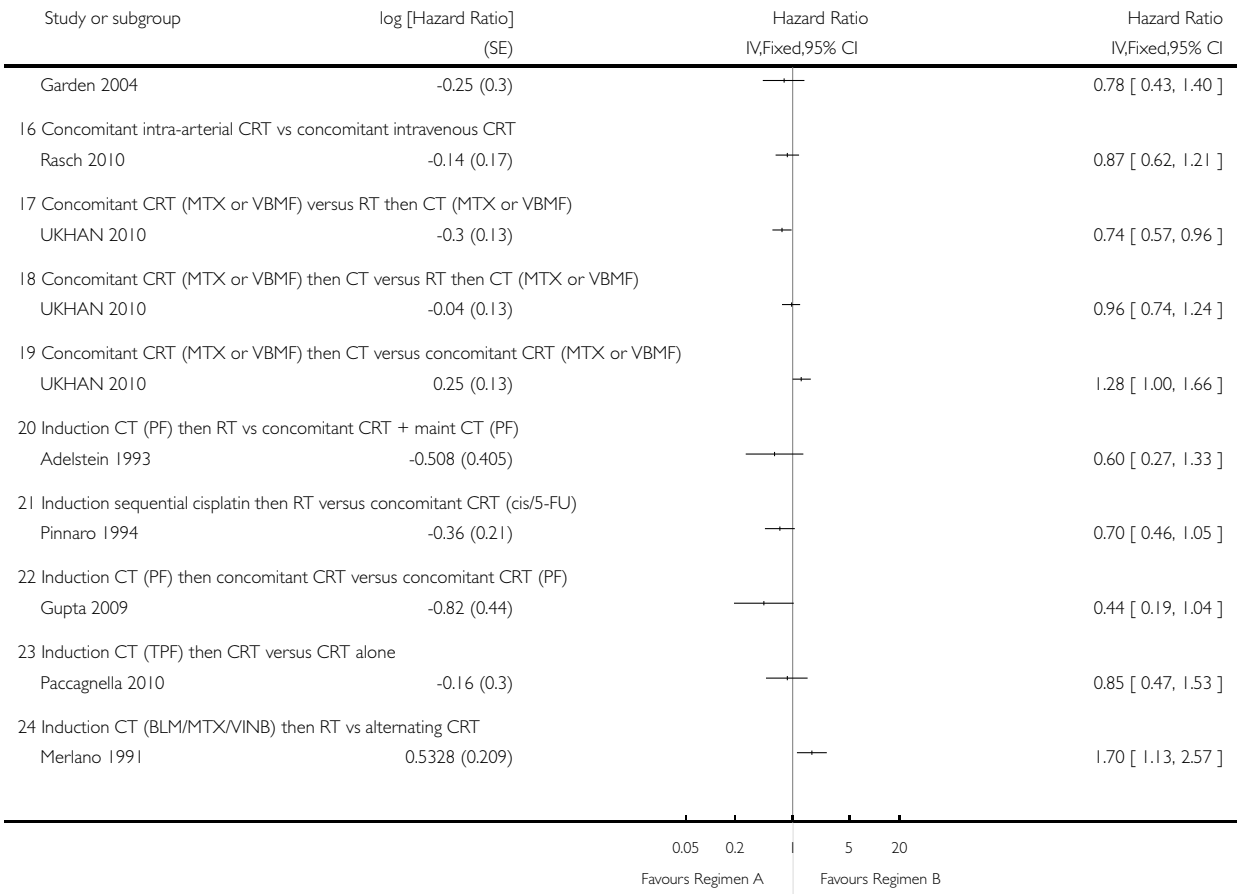
Outcome: 1 Total mortality

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Hazard Ratio IV,Fixed,95% CI
1 Induction cisplatin + UFT versus induction cisplatin + 5-FU			
Gonzalez-Larriba 1997	0.39 (0.34)		1.48 [0.76, 2.88]
2 Induction carboplatin + 5-FU versus induction cisplatin + 5-FU			
De Andres 1995	0.43 (0.24)		1.54 [0.96, 2.46]
3 Induction cisplatin + vinorelbine LRT versus induction cisplatin + 5-FU LRT			
Segura 2002	-0.29 (0.34)		0.75 [0.38, 1.46]
4 Induction cisplatin + etoposide + RT versus induction cisplatin + RT			
Marechal 1987	-0.07 (0.16)		0.93 [0.68, 1.28]
5 Induction cisplatin + methotrexate + bleomycin + vincristine versus induction cisplatin			
Chauvergne 1988	-0.07 (0.11)		0.93 [0.75, 1.16]
6 Induction simultaneous MTX + 5-FU versus sequential MTX + 5-FU			
Browman 1986	-0.18 (0.47)		0.84 [0.33, 2.10]
7 Induction cisplatin + docetaxel + 5-FU (TPF) RT versus induction cisplatin + 5-FU (PF) RT			
Vermorken 2007	-0.31 (0.13)		0.73 [0.57, 0.95]
8 Induction TPF + CRT surg versus induction PF + CRT + surg			
Posner 2007	-0.36 (0.13)		0.70 [0.54, 0.90]
9 Induction CT(cis/5-FU/TPZ) then CRT(cis/5-FU/TPZ/RT) versus induction CT (PF) then CRT (PF+RT)			
Le 2006	-0.807 (0.542)		0.45 [0.15, 1.29]
10 Concomitant CRT (carboplatin) versus concomitant CRT (cisplatin)			
Gasparini 1993	-0.36 (0.31)		0.70 [0.38, 1.28]
11 Concomitant CRT(cis/TPZ) versus concomitant CRT (cis/5-FU)			
Rischin 2005	-0.36 (0.31)		0.70 [0.38, 1.28]
12 Concomitant CRT (cis/TPZ) versus concomitant CRT (cis)			
Rischin 2010	-0.07 (0.11)		0.93 [0.75, 1.16]
13 Concomitant CRT(HU/5-FU) versus concomitant CRT (cis/FU)			
Garden 2004	-0.5 (0.3)		0.61 [0.34, 1.09]
14 Concomitant CRT (cis/paclitaxel) versus concomitant CRT (cis/FU)			
Garden 2004	-0.3 (0.25)		0.74 [0.45, 1.21]
15 Concomitant CRT (cis/paclitaxel) versus concomitant CRT (HU/5-FU)			



(*Continued* . . .)

(. . . *Continued*)

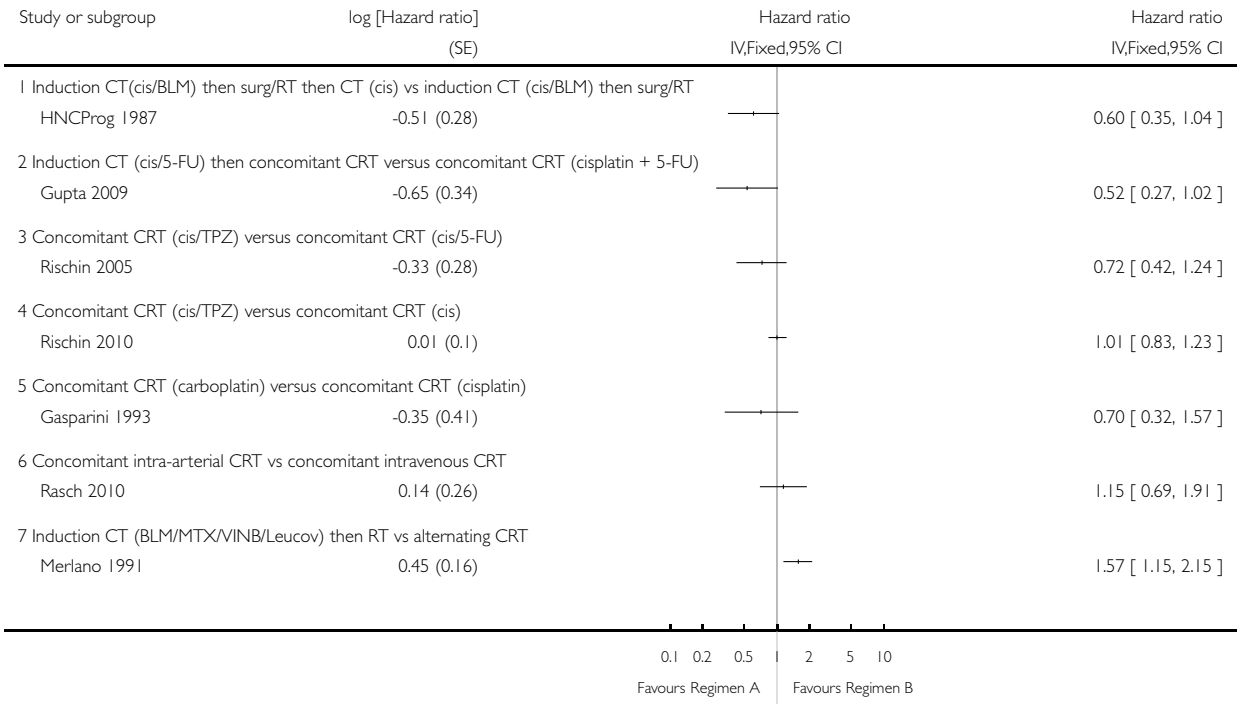


Analysis 4.2. Comparison 4 Chemotherapy A (± LRT) versus chemotherapy B (± LRT), Outcome 2 Disease free survival.

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

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

Outcome: 2 Disease free survival

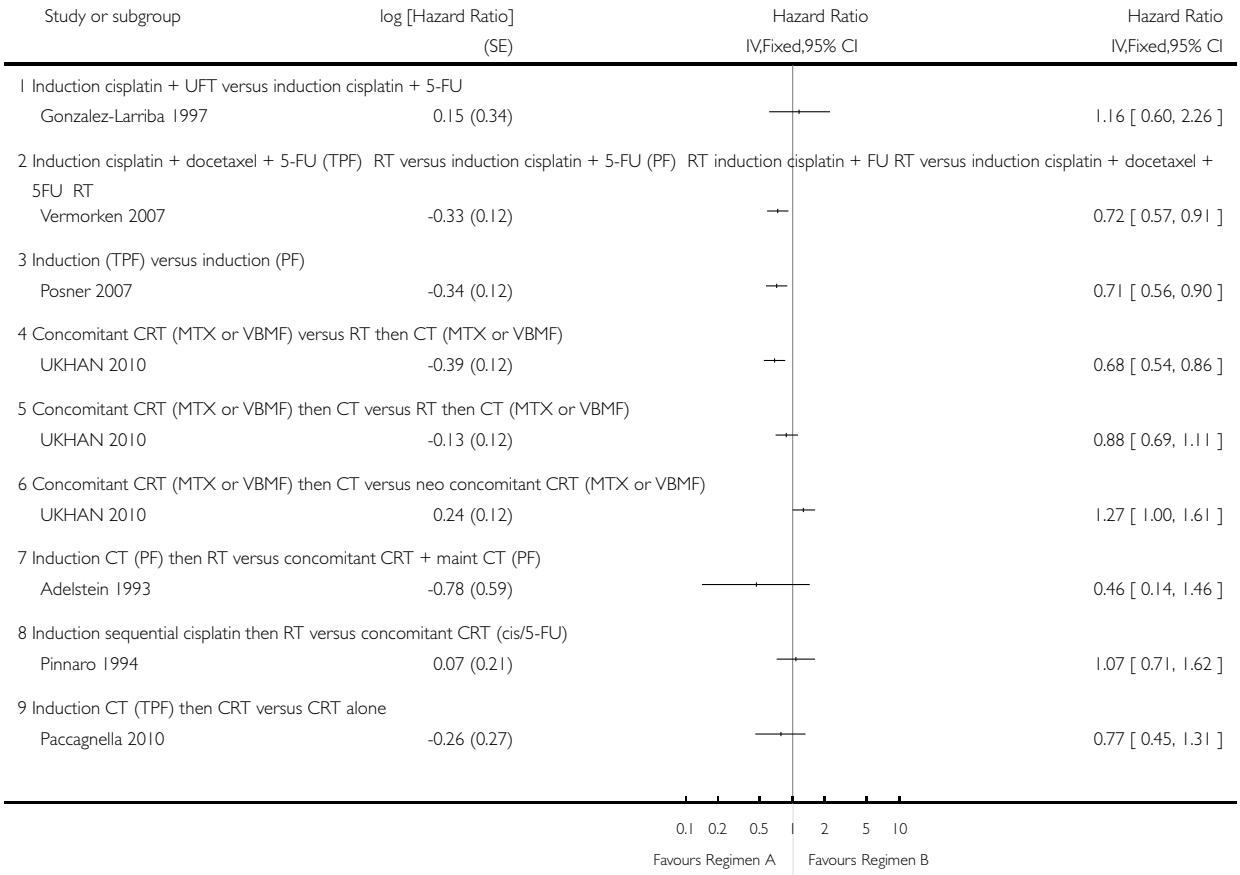


Analysis 4.3. Comparison 4 Chemotherapy A (± LRT) versus chemotherapy B (± LRT), Outcome 3 Progression free survival.

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

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

Outcome: 3 Progression free survival

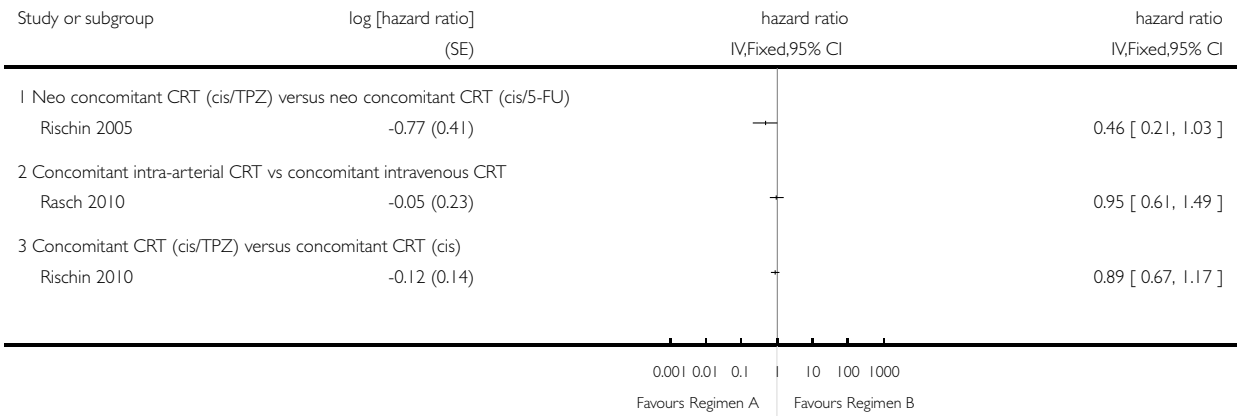


Analysis 4.4. Comparison 4 Chemotherapy A (± LRT) versus chemotherapy B (± LRT), Outcome 4 Locoregional control.

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

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

Outcome: 4 Locoregional control

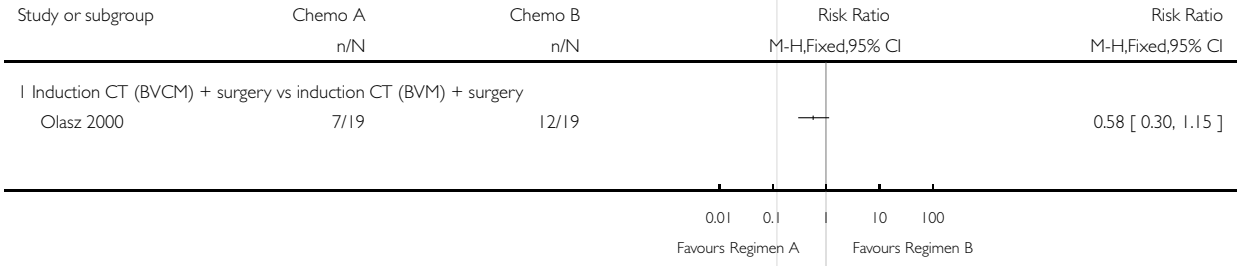


Analysis 4.5. Comparison 4 Chemotherapy A (± LRT) versus chemotherapy B (± LRT), Outcome 5 Total mortality (2-5 years).

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

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

Outcome: 5 Total mortality (2-5 years)



Analysis 4.6. Comparison 4 Chemotherapy A (± LRT) versus chemotherapy B (± LRT), Outcome 6 Disease free survival (5 years).

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

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

Outcome: 6 Disease free survival (5 years)

Study or subgroup	Treatment A n/N	Treatment B n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Induction carboplatin + 5-FU versus induction cisplatin + 5-FU				
De Andres 1995	11/46	23/49		0.51 [0.28, 0.92]

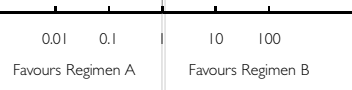
Analysis 4.7. Comparison 4 Chemotherapy A (± LRT) versus chemotherapy B (± LRT), Outcome 7 Locoregional control.

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

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

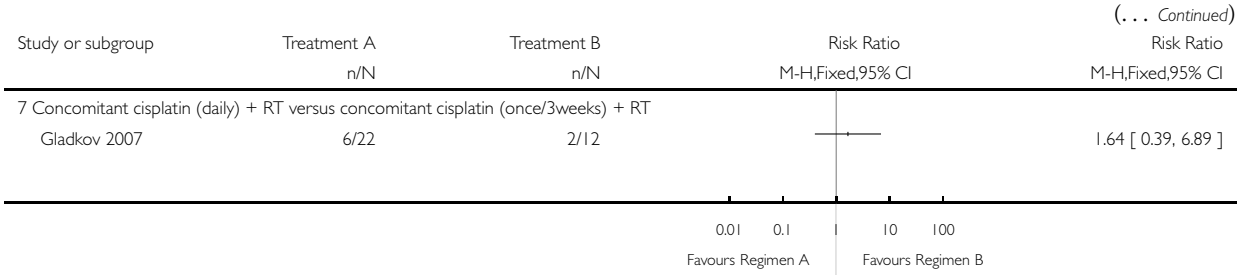
Outcome: 7 Locoregional control

Study or subgroup	Treatment A n/N	Treatment B n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Induction CT (BLM/MTX/VINB/Leucov) then RT vs alternating CRT				
Merlano 1991	37/57	25/48		1.25 [0.89, 1.74]
2 Induction CT (BLM/MTX/HU) then RT versus alternating CR				
Buffoli 1992	13/29	6/20		1.49 [0.68, 3.27]
3 Induction cisplatin + 5-FU + RT versus induction cisplatin + etoposide + RT				
Prevost 2005	47/98	32/99		1.48 [1.04, 2.11]
4 Induction methotrexate (intra-arterial) versus bleomycin (intra-arterial)				
Molinari 1982	9/42	26/43		0.35 [0.19, 0.66]
5 Concomitant cisplatin (daily) + RT versus concomitant cisplatin (weekly) + RT				
Gladkov 2007	6/22	5/26		1.42 [0.50, 4.02]
6 Concomitant cisplatin (weekly) + RT versus concomitant cisplatin (once/3 weeks) + RT				
Gladkov 2007	5/26	5/12		0.46 [0.16, 1.30]



(*Continued* . . .)

(. . . *Continued*)



Analysis 4.8. Comparison 4 Chemotherapy A (± LRT) versus chemotherapy B (± LRT), Outcome 8 Locoregional recurrence (2 years).

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

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

Outcome: 8 Locoregional recurrence (2 years)

ADDITIONAL TABLES

Table 1. Classification of chemotherapy agents

	Drugs included in review
ALKYLATING 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

Table 1. Classification of chemotherapy agents (*Continued*)

ANTITUMOUR ANTIBIOTICS - interfere with enzymes required for DNA replication	Bleomycin Mitomycin
VINCA ALKALOIDS - inhibit mitosis or 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 patients with oral cavity or oropharyngeal cancer in studies included in this review

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
Domenge 2000		100%	100%	
Eschwege 1988		100%	100%	Pignon 2000
Gladhov 2007			100%	
Gupta 2009		100%	100%	
HNC Prog 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

Table 2. Proportion of patients with oral cavity or oropharyngeal cancer in studies included in this review (*Continued*)

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%	
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
Fazekas 1980	23%	56%	79%	Pignon 2000
Parvinen 1985	71%	8%	79%	Pignon 2000
Grau 2003	48%	29%	77%	Pignon 2009
Salvajoli 1992	47%	30%	77%	Pignon 2000
Lewin 1997	41%	34%	75%	Pignon 2000
Rischin 2005	5%	70%	75%	
Brunin 1989	37%	37%	74%	Pignon 2000
Petrovich 1981	17%	57%	74%	
Starr 2001		74%	74%	Pignon 2009

Table 2. Proportion of patients with oral cavity or oropharyngeal cancer in studies included in this review (*Continued*)

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 2009	18%	54%	70%	
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
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%	

Table 2. Proportion of patients with oral cavity or oropharyngeal cancer in studies included in this review (*Continued*)

Browman 1986	64%		64%	
Haddad 1996	20%	43%	63%	
Segura 2002	62%		62%	
Holoye 1985	28%	33%	61%	Pignon 2000
Depondt 1993	26%	35%	61%	Pignon 2000
Hugenin 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
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
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

Table 2. Proportion of patients with oral cavity or oropharyngeal cancer in studies included in this review (*Continued*)

Lam 2001	32%	21%	53%	
Laramore 1992	27%	25%	52%	Pignon 2000
UKHAN 2009	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.

APPENDICES

Appendix 1. MEDLINE via OVID search strategy

1. "head and neck neoplasms"/ or mouth neoplasms/ or gingival neoplasms/ or palatal neoplasms/ or tongue neoplasms/
2. ((cancer$ or tumour$ or tumor$ or neoplas$ or malignan$ or carcinoma$ or metatasta$) adj5 (oral$ 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 and neck")).ti,ab.
3. or/1-2
4. chemoradiotherap$.ti,ab.
5. surg$.ti,ab.
6. radiotherap$.ti,ab.
7. chemotherap$.ti,ab.
8. (neck adj1 dissection$).ti,ab.
9. brachytherap$.ti,ab.
10. (adjuvant or neo-adjuvant).ti,ab.
11. photodynamic.ti,ab.
12. teletherap$.ti,ab.
13. plesiotherap$.ti,ab.
14. excision$.ti,ab.
15. excise$.ti,ab.
16. (hyperfractionate$ or hyper-fractionate$).ti,ab.
17. dahanca.ti,ab.
18. arcon.ti,ab.
19. radiat$.ti,ab.
20. irradiat$.ti,ab.
21. resect$.ti,ab.
22. lymphadenectom$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
23. curett$.ti,ab.
24. neoadjuvant.ti,ab.
25. glossectom$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
26. antineoplas$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
27. ((alternative or combined or gene or genetic) adj2 (therapy or therapies)).ti,ab.

28. (onyx-015 or amifostine$ or misonidazole$ or erythropoietin$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
29. fluorouracil$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
30. 5-fluorouracil$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
31. cisplatin$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
32. paclitaxel$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
33. vinblastine$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
34. bleomycin$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
35. 5fu.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
36. adriamycin$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
37. doxorubicin$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
38. methotrexa$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
39. docetaxel$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
40. carboplatin$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
41. hydroxyurea.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
42. ((vitamin or nutrition$) adj2 supplement$).ti,ab.
43. (herb or herbs or herbal).ti,ab.
44. cetuximab.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
45. (locoregional$ adj5 (recurren$ or control$ or treat$ or lymph$)).ti,ab.
46. surgery.mp. or surgical$.ti,ab. [mp=title, original title, abstract, name of substance word, subject heading word]
47. exp Radiotherapy/
48. exp Antineoplastic Agents/
49. exp surgical procedures, operative/ or lymph node excision/
50. exp Antimetabolites/
51. exp combined modality therapy/ or exp complementary therapies/
52. or/4-25
53. or/26-51
54. 52 or 53
55. 3 and 54

The above subject search was combined with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity maximising version (2009 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions* version 5.0.2 (updated September 2009):

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 2. Cochrane Oral Health Group's 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*))

Appendix 3. The Cochrane Central Register of Controlled Clinical Trials (CENTRAL) search strategy

#1 MeSH descriptor HEAD AND NECK NEOPLASMS this term only
#2 MeSH descriptor MOUTH NEOPLASMS this term only
#3 MeSH descriptor GINGIVAL NEOPLASMS this term only
#4 MeSH descriptor PALATAL NEOPLASMS this term only
#5 MeSH descriptor TONGUE NEOPLASMS this term only
#6 ((oral in Title, Abstract or Keywords near/6 cancer* in Title, Abstract or Keywords) or (oral in Title, Abstract or Keywords near/6 tumour* in Title, Abstract or Keywords) or (oral in Title, Abstract or Keywords near/6 tumor* in Title, Abstract or Keywords) or (oral in Title, Abstract or Keywords near/6 neoplas* in Title, Abstract or Keywords) or (oral in Title, Abstract or Keywords near/6 malignan* in Title, Abstract or Keywords) or (oral in Title, Abstract or Keywords near/6 carcinoma* in Title, Abstract or Keywords) or (oral in Title, Abstract or Keywords near/6 metastas* in Title, Abstract or Keywords) or (cancer* in Title, Abstract or Keywords near/6 intra-oral* in Title, Abstract or Keywords) or (intra-oral* in Title, Abstract or Keywords near/6 tumour* in Title, Abstract or Keywords) or (intra-oral* in Title, Abstract or Keywords near/6 tumor* in Title, Abstract or Keywords) or (intra-oral* in Title, Abstract or Keywords near/6 neoplas* in Title, Abstract or Keywords) or (intra-oral* in Title, Abstract or Keywords near/6 malignan* in Title, Abstract or Keywords) or (intra-oral* in Title, Abstract or Keywords near/6 carcinoma* in Title, Abstract or Keywords) or (intra-oral* in Title, Abstract or Keywords near/6 metastas* in Title, Abstract or Keywords) or (cancer* in Title, Abstract or Keywords near/6 intraoral* in Title, Abstract or Keywords) or (intraoral* in Title, Abstract or Keywords near/6 tumour* in Title, Abstract or Keywords) or (intraoral* in Title, Abstract or Keywords near/6 tumor* in Title, Abstract or Keywords) or (intraoral* in Title, Abstract or Keywords near/6 neoplas* in Title, Abstract or Keywords) or (intraoral* in Title, Abstract or Keywords near/6 malignan* in Title, Abstract or Keywords) or (intraoral* in Title, Abstract or Keywords near/6 carconoma* in Title, Abstract or Keywords) or (intraoral* in Title, Abstract or Keywords near/6 metasta* in Title, Abstract or Keywords) or (gingiva* in Title, Abstract or Keywords near/6 cancer* in Title, Abstract or Keywords) or (gingiva* in Title, Abstract or Keywords near/6 tumour* in Title, Abstract or Keywords) or (gingiva* in Title, Abstract or Keywords near/6 tumor* in Title, Abstract or Keywords) or (gingiva* in Title, Abstract or Keywords near/6 neoplas* in Title, Abstract or Keywords) or (gingiva* in Title, Abstract or Keywords near/6 malignan* in Title, Abstract or Keywords) or (gingiva* in Title, Abstract or Keywords near/6 carcinoma* in Title, Abstract or Keywords) or (gingiva* in Title, Abstract or Keywords near/6 metastas* in Title, Abstract or Keywords) or (oropharyn* in Title, Abstract or Keywords near/6 cancer* in Title, Abstract or Keywords) or (oropharyn* in Title, Abstract or Keywords near/6 tumour* in Title, Abstract or Keywords) or (oropharyn* in Title, Abstract or Keywords near/6 tumor* in Title, Abstract or Keywords) or (oropharyn* in Title, Abstract or Keywords near/6 neoplas* in Title, Abstract or Keywords) or (oropharyn* in Title, Abstract or Keywords near/6 malignan* in Title, Abstract or Keywords) or (oropharyn* in Title, Abstract or Keywords near/6 carcinoma* in Title, Abstract or Keywords) or (oropharyn* in Title, Abstract or Keywords near/6 metastas* in Title, Abstract or Keywords) or (mouth* in Title, Abstract or Keywords near/6 cancer* in Title, Abstract or Keywords) or (mouth* in Title, Abstract or Keywords near/6 tumour* in Title, Abstract or Keywords) or (mouth* in Title, Abstract or Keywords near/6 tumor* in Title, Abstract or Keywords) or (mouth* in Title, Abstract or Keywords near/6 neoplas* in Title, Abstract or Keywords) or (mouth* in Title, Abstract or Keywords near/6 malignan* in Title, Abstract or Keywords) or (mouth* in Title, Abstract or Keywords near/6 carcinoma* in Title, Abstract or Keywords) or (mouth* in Title, Abstract or Keywords near/6 metastas* in Title, Abstract or Keywords) or (tongue* in Title, Abstract or Keywords near/6 cancer* in Title, Abstract or Keywords) or (tongue* in Title, Abstract or Keywords near/6 tumour* in Title, Abstract or Keywords) or (tongue* in Title, Abstract or Keywords near/6 tumor* in Title, Abstract or Keywords) or (tongue* in Title, Abstract or Keywords near/6 neoplas* in Title, Abstract or Keywords) or (tongue* in Title, Abstract or Keywords near/6 malignan* in Title, Abstract or Keywords) or (tongue* in Title, Abstract or Keywords near/6 carcinoma* in Title, Abstract or Keywords) or (tongue* in Title, Abstract or Keywords near/6 metastas* in Title, Abstract or Keywords) or (cheek in Title, Abstract or Keywords near/6 cancer* in Title, Abstract or Keywords) or (cheek in Title, Abstract or Keywords near/6 tumour* in Title, Abstract or Keywords) or (cheek in Title, Abstract or Keywords near/6 tumor* in Title, Abstract or Keywords) or (cheek in Title, Abstract or Keywords near/6 neoplas* in Title, Abstract or Keywords) or (cheek in Title, Abstract or Keywords near/6 malignan* in Title, Abstract or Keywords) or (cheek in Title, Abstract or Keywords near/6 carcinoma* in Title, Abstract or Keywords) or (cheek in Title, Abstract or Keywords near/6 metastas* in Title, Abstract or Keywords) or (cheeks in Title, Abstract or Keywords near/6 cancer* in Title, Abstract or Keywords) or (cheeks in Title, Abstract or Keywords near/6 tumour* in Title, Abstract or Keywords)

or (cheeks in Title, Abstract or Keywords near/6 tumor* in Title, Abstract or Keywords) or (cheeks in Title, Abstract or Keywords near/6 neoplas* in Title, Abstract or Keywords) or (cheeks in Title, Abstract or Keywords near/6 malignan* in Title, Abstract or Keywords) or (cheeks in Title, Abstract or Keywords near/6 carcinoma* in Title, Abstract or Keywords) or (cheeks in Title, Abstract or Keywords near/6 metastas* in Title, Abstract or Keywords) or (gum in Title, Abstract or Keywords near/6 cancer* in Title, Abstract or Keywords) or (gum in Title, Abstract or Keywords near/6 tumour* in Title, Abstract or Keywords) or (gum in Title, Abstract or Keywords near/6 tumor* in Title, Abstract or Keywords) or (gum in Title, Abstract or Keywords near/6 neoplas* in Title, Abstract or Keywords) or (gum in Title, Abstract or Keywords near/6 malignan* in Title, Abstract or Keywords) or (gum in Title, Abstract or Keywords near/6 carcinoma* in Title, Abstract or Keywords) or (gum in Title, Abstract or Keywords near/6 metastas* in Title, Abstract or Keywords) or (gums in Title, Abstract or Keywords near/6 cancer* in Title, Abstract or Keywords) or (gums in Title, Abstract or Keywords near/6 tumour* in Title, Abstract or Keywords) or (gums in Title, Abstract or Keywords near/6 tumor* in Title, Abstract or Keywords) or (gums in Title, Abstract or Keywords near/6 neoplas* in Title, Abstract or Keywords) or (gums in Title, Abstract or Keywords near/6 malignan* in Title, Abstract or Keywords) or (gums in Title, Abstract or Keywords near/6 carcinoma* in Title, Abstract or Keywords) or (gums in Title, Abstract or Keywords near/6 metastas* in Title, Abstract or Keywords) or (palate in Title, Abstract or Keywords near/6 cancer* in Title, Abstract or Keywords) or (palate in Title, Abstract or Keywords near/6 tumour* in Title, Abstract or Keywords) or (palate in Title, Abstract or Keywords near/6 tumor* in Title, Abstract or Keywords) or (palate in Title, Abstract or Keywords near/6 neoplas* in Title, Abstract or Keywords) or (palate in Title, Abstract or Keywords near/6 malignan* in Title, Abstract or Keywords) or (palate in Title, Abstract or Keywords near/6 carcinoma* in Title, Abstract or Keywords) or (palate in Title, Abstract or Keywords near/6 metastas* in Title, Abstract or Keywords) or (palatal in Title, Abstract or Keywords near/6 cancer* in Title, Abstract or Keywords) or (palatal in Title, Abstract or Keywords near/6 tumour* in Title, Abstract or Keywords) or (palatal in Title, Abstract or Keywords near/6 tumor* in Title, Abstract or Keywords) or (palatal in Title, Abstract or Keywords near/6 neoplas* in Title, Abstract or Keywords) or (palatal in Title, Abstract or Keywords near/6 malignan* in Title, Abstract or Keywords) or (palatal in Title, Abstract or Keywords near/6 carcinoma* in Title, Abstract or Keywords) or (palatal in Title, Abstract or Keywords near/6 metastas* in Title, Abstract or Keywords) or ("head and neck" in Title, Abstract or Keywords near/6 cancer* in Title, Abstract or Keywords) or ("head and neck" in Title, Abstract or Keywords near/6 tumour* in Title, Abstract or Keywords) or ("head and neck" in Title, Abstract or Keywords near/6 tumor* in Title, Abstract or Keywords) or ("head and neck" in Title, Abstract or Keywords near/6 neoplas* in Title, Abstract or Keywords) or ("head and neck" in Title, Abstract or Keywords near/6 malignan* in Title, Abstract or Keywords) or ("head and neck" in Title, Abstract or Keywords near/6 carcinoma* in Title, Abstract or Keywords) or ("head and neck" in Title, Abstract or Keywords near/6 metastas* in Title, Abstract or Keywords))

#7 (#1 or #2 or #3 or #4 or #5 or #6)

#8 (chemotherap* in Record Title or chemoradiotherap* in Record Title or (surg* in Record Title and curett* in Record Title) or radiotherap* in Record Title or "neck dissection*" in Record Title or brachytherap* in Record Title or adjuvant in Record Title or neo-adjuvant in Record Title or neoadjuvant in Record Title or photodynamic in Record Title or teletherap* in Record Title or plesiotherap* in Record Title or excision* in Record Title or excise* in Record Title or hyperfractionate* in Record Title or hyper-fractionate* in Record Title or dahanca in Record Title or arcon in Record Title or radiat* in Record Title or irradiat* in Record Title or resect* in Record Title)

#9 (chemotherap* in Abstract or chemoradiotherap* in Abstract or (surg* in Abstract and curett* in Abstract) or radiotherap* in Abstract or "neck dissection*" in Abstract or brachytherap* in Abstract or adjuvant in Abstract or neo-adjuvant in Abstract or neoadjuvant in Abstract or photodynamic in Abstract or teletherap* in Abstract or plesiotherap* in Abstract or excision* in Abstract or excise* in Abstract or hyperfractionate* in Abstract or hyper-fractionate* in Abstract or dahanca in Abstract or arcon in Abstract or radiat* in Abstract or irradiat* in Abstract or resect* in Abstract)

#10 (lymphadenectom* in Title, Abstract or Keywords or glossectom* in Title, Abstract or Keywords)

#11 antineoplas* in Title, Abstract or Keywords

#12 ((alternative in Title, Abstract or Keywords near/6 therap* in Title, Abstract or Keywords) or (combined in Title, Abstract or Keywords near/6 therap* in Title, Abstract or Keywords) or (gene in Title, Abstract or Keywords near/6 therap* in Title, Abstract or Keywords) or (genetic in Title, Abstract or Keywords near/6 therap* in Title, Abstract or Keywords))

#13 (onyx-015 in Title, Abstract or Keywords or amifostine* in Title, Abstract or Keywords or misonidazole* in Title, Abstract or Keywords or erythropoietin* in Title, Abstract or Keywords)

#14 (fluorouracil* in Title, Abstract or Keywords or 5-fluorouracil* in Title, Abstract or Keywords or cisplatin* in Title, Abstract or Keywords or paclitaxel* in Title, Abstract or Keywords or vinblastine* in Title, Abstract or Keywords or bleomycin* in Title, Abstract or Keywords or "5fu" in Title, Abstract or Keywords or adriamycin* in Title, Abstract or Keywords or doxorubicin* in Title, Abstract or Keywords or methotrexa* in Title, Abstract or Keywords or docetaxel* in Title, Abstract or Keywords or carboplatin* in Title, Abstract or Keywords or hydroxyurea in Title, Abstract or Keywords)

#15 ("vitamin supplement*" in Title, Abstract or Keywords or "nutrition* supplement*" in Title, Abstract or Keywords)

#16 (herb in Title, Abstract or Keywords or herbs in Title, Abstract or Keywords or herbal in Title, Abstract or Keywords)
#17 cetuximab in Title, Abstract or Keywords
#18 ((locoregional* in Title, Abstract or Keywords near/6 recurren* in Title, Abstract or Keywords) or (loco-regional* in Title, Abstract or Keywords near/6 recurren* in Title, Abstract or Keywords) or (locoregional* in Title, Abstract or Keywords near/6 control* in Title, Abstract or Keywords) or (loco-regional* in Title, Abstract or Keywords near/6 control* in Title, Abstract or Keywords) or (locoregional* in Title, Abstract or Keywords near/6 treat* in Title, Abstract or Keywords) or (loco-regional* in Title, Abstract or Keywords near/6 treat* in Title, Abstract or Keywords) or (locoregional in Title, Abstract or Keywords near/6 lymph* in Title, Abstract or Keywords) or (loco-regional* in Title, Abstract or Keywords near/6 lymph in Title, Abstract or Keywords))
#19 MeSH descriptor RADIOTHERAPY explode all trees
#20 MeSH descriptor ANTINEOPLASTIC AGENTS explode all trees
#21 MeSH descriptor SURGICAL PROCEDURES, OPERATIVE explode all trees
#22 MeSH descriptor LYMPH NODE EXCISION explode all trees
#23 MeSH descriptor ANTIMETABOLITES explode all trees
#24 MeSH descriptor COMBINED MODALITY THERAPY explode all trees
#25 MeSH descriptor COMPLEMENTARY THERAPIES explode all trees
#26 (surgery in Record Title or surgical* in Record Title)
#27 (surgery in Abstract or surgical* in Abstract)
#28 (#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27)
#29 (#7 and #28)

Appendix 4. EMBASE via OVID search strategy

1. "head and neck neoplasms"/ or mouth neoplasms/ or gingival neoplasms/ or palatal neoplasms/ or tongue neoplasms/
2. ((cancer$ or tumour$ or tumor$ or neoplas$ or malignan$ or carcinoma$ or metatasta$) adj5 (oral$ 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 and neck")).ti,ab.
3. or/1-2
4. chemoradiotherap$.ti,ab.
5. surg$.ti,ab.
6. radiotherap$.ti,ab.
7. chemotherap$.ti,ab.
8. (neck adj1 dissection$).ti,ab.
9. brachytherap$.ti,ab.
10. (adjuvant or neo-adjuvant).ti,ab.
11. photodynamic.ti,ab.
12. teletherap$.ti,ab.
13. plesiotherap$.ti,ab.
14. excision$.ti,ab.
15. excise$.ti,ab.
16. (hyperfractionate$ or hyper-fractionate$).ti,ab.
17. dahanca.ti,ab.
18. arcon.ti,ab.
19. radiat$.ti,ab.
20. irradiat$.ti,ab.
21. resect$.ti,ab.
22. lymphadenectom$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
23. curett$.ti,ab.
24. neoadjuvant.ti,ab.
25. glossectom$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]

26. antineoplas$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
27. ((alternative or combined or gene or genetic) adj2 (therapy or therapies)).ti,ab.
28. (onyx-015 or amifostine$ or misonidazole$ or erythropoietin$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
29. fluorouracil$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
30. 5-fluorouracil$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
31. cisplatin$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
32. paclitaxel$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
33. vinblastine$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
34. bleomycin$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
35. 5fu.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
36. adriamycin$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
37. doxorubicin$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
38. methotrexa$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
39. docetaxel$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
40. carboplatin$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
41. hydroxyurea.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
42. ((vitamin or nutrition$) adj2 supplement$).ti,ab.
43. (herb or herbs or herbal).ti,ab.
44. cetuximab.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
45. (locoregional$ adj5 (recurren$ or control$ or treat$ or lymph$)).ti,ab.
46. surgery.mp. or surgical$.ti,ab. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
47. exp Radiotherapy/ or cancer radiotherapy/ or cancerchemotherapy/
48. exp Antineoplastic Agent/
49. lymphadenectomy.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
50. exp Antimetabolites/
51. multimodality cancer therapy/ or alternative medicine/
52. or/4-25
53. or/26-51
54. 52 or 53
55. 3 and 54

The above subject search was combined with the Cochrane Oral Health Group's RCT filter for searching EMBASE:

1. random$.ti,ab.
2. factorial$.ti,ab.
3. (crossover$ or cross over$ or cross-over$).ti,ab.
4. placebo$.ti,ab.

5. (doubl$ adj blind$).ti,ab.
6. (singl$ adj blind$).ti,ab.
7. assign$.ti,ab.
8. allocat$.ti,ab.
9. volunteer$.ti,ab.
10. CROSSOVER PROCEDURE.sh.
11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE BLIND PROCEDURE.sh.
14. or/1-13
15. ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/
16. HUMAN/
17. 16 and 15
18. 15 not 17
19. 14 not 18

Appendix 5. Allied and Complementary Medicine Database (AMED) via 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

The above subject search was combined with an RCT filter for searching AMED:

1. exp randomized controlled trials/
2. exp double blind method/
3. exp random allocation/
4. (random$ or control$ or placebo$ or factorial).mp. [mp=abstract, heading words, title]
5. (double adj blind).mp. [mp=abstract, heading words, title]
6. (single adj blind).mp. [mp=abstract, heading words, title]
7. exp comparative study/
8. or/1-7

WHAT'S NEW

Last assessed as up-to-date: 27 February 2011.

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.

HISTORY

Protocol first published: Issue 1, 2007

Review first published: Issue 9, 2010

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
- 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
- Organizing retrieval of papers: SP, SF
- Screening retrieved papers against eligibility criteria: SF, AMG, HW, JC, RO, SP, MM, DC
- Appraising risk of bias: HW, JC, AMG, RO, SP, MM, DC, SF
- Extracting data from papers: HW, SF, JC, AMG, RO, SP, MM, DC
- Writing to authors of papers for additional information: SP, SF
- Data management for the review: SF, AMG, HW, SP
- Entering data into RevMan: SF, AMG, HW, SP
- Analysis of data: HW, AMG, SF
- Interpretation of data: SF, HW, AMG, JC, Kelvin Chan (KC)
- Writing the review: SF, HW, AMG, JC, KC, SP

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- School of Dentistry, The University of Manchester, UK.
- Cochrane Oral Health Group, UK.
- The University of Dundee, UK.
- The University of Glasgow, UK.
- Manchester Academic Health Sciences Centre (MAHSC) and NIHR Manchester Biomedical Research Centre, UK.

External sources

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of studies - As the primary outcome for this review is total mortality we have added a requirement that included studies have a minimum of 6 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.

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 patients 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.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Combined Chemotherapy Protocols [adverse effects; *therapeutic use]; Carcinoma, Squamous Cell [*drug therapy; mortality; radiotherapy; surgery]; Combined Modality Therapy [methods; mortality]; Mouth Neoplasms [*drug therapy; mortality; radiotherapy; surgery]; Oropharyngeal Neoplasms [*drug therapy; mortality; radiotherapy; surgery]; Randomized Controlled Trials as Topic; Remission Induction; Survival Analysis

MeSH check words

Humans