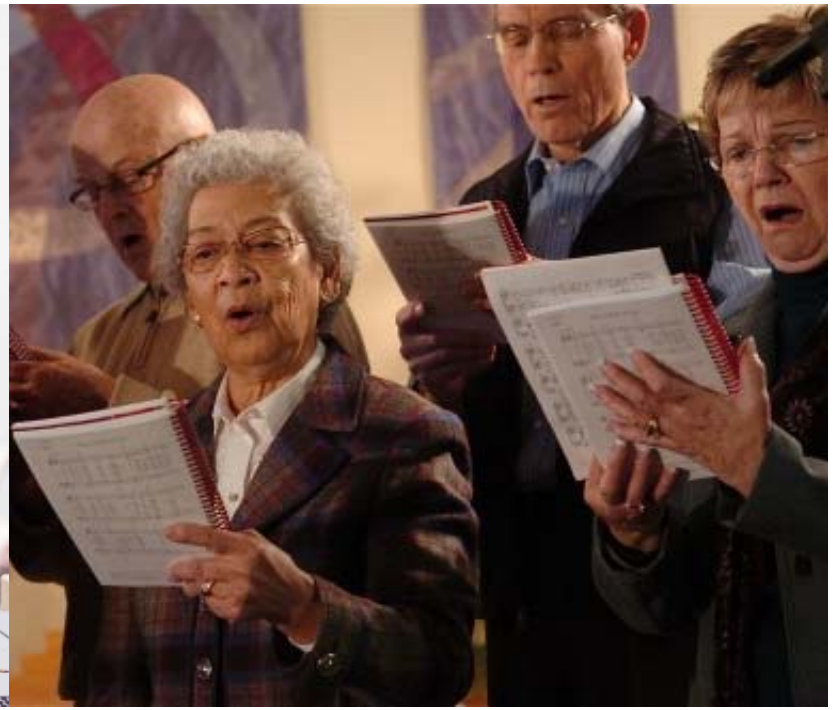
KCE REPORT 256

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

OROPHARYNGEAL, HYPOPHARYNGEAL AND LARYNGEAL CANCER: DIAGNOSIS, TREATMENT AND FOLLOW-UP



KCE REPORT 256
GOOD CLINICAL PRACTICE

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

OROPHARYNGEAL, HYPOPHARYNGEAL AND LARYNGEAL CANCER: DIAGNOSIS, TREATMENT AND FOLLOW-UP

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2015 www.kce.fgov.be

COLOPHON

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A grant, fees or funds for a member of staff or another form of compensation for the execution of research: Sandra Nuyts (FWO, VCK, Stichting tegen Kanker)

Consultancy or employment for a company, an association or an organisation that may gain or lose financially due to the results of this report: Jan Vermorken (Merck-Serono; Genetech)

Payments to speak, training remuneration, subsidised travel or payment for participation at a conference: Pierre Castadot (fees from Merck Serono for 2 presentations), Jean-François Daisne (payment from Merck to take part at the ICHNO congress 2013), Jan Vermorken (Merck-Serono), Dirk Van Gestel (occasional payments for communications from Accuray), Paul Clement (Merck Serono: teaching grants, payment for communications), Elisabeth Van Eycken (subsidised travels for RARECAREnet)

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- **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.**
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Publication date:	13 November 2015
Domain:	Good Clinical Practice (GCP)
MeSH:	Head and Neck Neoplasms; Laryngeal Neoplasms; Pharyngeal Neoplasms; Practice Guideline
NLM Classification:	WE 707
Language:	English
Format:	Adobe® PDF™ (A4)
Legal depot:	D/2015/10.273/105
ISSN:	2466-6459

How to refer to this document?

Grégoire V, Leroy R, Heus P, Hooft L, van de Wetering F, Spijker R, JPM Scholten R, Abeloos J, Carp L, Casselman J, Clement P, Deron P, Hamoir M, Lenssen O, Nuyts S, Van Laer C, Vermorken J, Vlayen J. Oropharyngeal, hypopharyngeal and laryngeal cancer: diagnosis, treatment and follow-up. Good Clinical Practice (GCP) Brussels: Belgian Health Care Knowledge Centre (KCE). 2015. KCE Reports 256. D/2015/10.273/105.

This document is available on the website of the Belgian Health Care Knowledge Centre.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
2D-EBRT	two-dimensional external beam radiotherapy
5-FU	five-fluorouracil
AJCC	American Joint Committee on Cancer
BCR	Belgian Cancer Registry
BSC	Best supportive care
CCO	Cancer Care Ontario
CEBAM	Belgian Centre for Evidence-Based Medicine
CE-PET/CT	Contrast enhanced positron emission tomography - computed tomography
C-HART	Chemotherapy and hyperfractionated accelerated radiation therapy
CI	Confidence interval
CND	Comprehensive neck dissection
CP	Cisplatin
CPG	Clinical practice guideline
cCR	Clinically assessed complete response
CRT	Chemoradiotherapy
CT	Computed tomography
DCC	Dutch Cochrane Centre
DFS	Disease free survival
DKG	Deutsche Krebsgesellschaft
DNA	Deoxyribonucleic acid
DTA	Diagnostic test accuracy
DW-MRI	Diffusion-weighted magnetic resonance imaging
EBRT	External beam radiotherapy
EGFR	Epidermal growth factor receptor
END	Elective neck dissection
ENT	Ear nose throat
FDG-PET/CT	Fluorodeoxyglucose Positron emission tomography - computed tomography
FISH	Fluorescence in situ hybridization

FNAC	Fine-needle aspiration cytology
GDG	Guideline Development Group
GIN	Guidelines International Network
GIV	Generic inverse variance
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Gy	Gray, International System of Units (SI) unit of absorbed radiation
HART	Hyperfractionated accelerated radiation therapy
HNSCC	Head & neck squamous cell carcinoma
HPV	Human papilloma virus
HR	Hazard ratio
HRQoL	Health-related Quality of Life
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
IMRT	Intensity-modulated radiotherapy
ISH	In situ hybridization
KCE	Belgian Health Care Knowledge Centre
LND	Lymph node dissection
M0	Free of metastases
MMC	Mitomycin
MRI	Magnetic resonance imaging
mRNA	Messenger Ribonucleic Acid
MRND	Modified radical neck dissection
NE-PET/CT	Non-enhanced PET/CT
RIZIV – INAMI (NIHDI)	Rijksinstituut voor ziekte- en invaliditeitsverzekering – Institut national d'assurance maladie-invalidité (National Institute for Health and Disability Insurance)
NPV	Negative predictive value
OIS	Optimal information size
OR	Odds ratio
OS	Overall survival

OTT	Overall treatment time
PCR	Polymerase chain reaction
PEG	Percutaneous endoscopic gastrostomy
PET	Positron emission tomography
PET-CT	Positron emission tomography - computed tomography
PICO	Participants–Interventions–Comparator–Outcomes
PF	Paclitaxel and fluorouracil (a chemotherapy regimen)
PFS	Progression-free survival
PPV	Positive predictive value
QoL	Quality of life
RCT	Randomised controlled trial
RNA	Ribonucleic acid
RND	Radical neck dissection
ROC	Receiver-operator curve
RR	Risk ratio / relative risk
RT	Radiotherapy
SCC	Squamous cell carcinoma(s)
Se	Sensitivity
SE	Standard error
SF-36	Short Form (36) Health Survey (a patient-reported survey of patient health)
SIGN	Scottish Intercollegiate Guidelines Network
SLNB	Sentinel lymph node biopsy
SMND	Submandibular neck dissection
SND	Selective neck dissection
SoF	Summary of Findings
SOND	Supraomohyoid neck dissection
Sp	Specificity

TNM Classification (of Malignant Tumours	T describes the size of the original (primary) tumour and whether it has invaded nearby tissue; N describes nearby (regional) lymph nodes that are involved; M describes distant metastasis (spread of cancer from one part of the body to another).
TLS	Transoral laser surgery
TORS	Transoral robotic surgery
TPF	Taxotere, paclitaxel, and fluorouracil (a chemotherapy regimen)
US	Ultrasound
WHO	World Health Organisation
WW	Watchful waiting
XQ	Xerostomia-related quality of life

SCIENTIFIC REPORT

1 INTRODUCTION

The development of clinical care pathways is one of the main actions described in the Belgian National Cancer Plan 2008-2010 and one of the assignments of the College of Oncology. For many years the Belgian Health Care Knowledge Centre (KCE) has collaborated with the College of Oncology. More precisely, it has provided scientific support in the development of clinical practice guidelines that can serve as a basis to develop care pathways. So far, this collaboration has resulted in the publication of clinical practice guidelines on breast cancer, colorectal cancer, testicular cancer, pancreatic cancer, upper gastrointestinal cancer, cervical cancer, prostate cancer and lung cancer.

1.1 Background

Head and neck cancer refers to a group of rare cancers arising in the upper aerodigestive tract, including the oral cavity, larynx, oropharynx, hypopharynx, and very rare tumours arising in nasal cavity and paranasal sinus, nasopharynx, middle ear, salivary glands and skull base. The majority of these cancers is squamous cell carcinomas (SCC) and is associated with a history of smoking and alcohol use. This is, however, not the case for cancers of the paranasal sinuses or salivary gland. In addition, tumours of the nose or paranasal sinuses have been linked with occupational and chemical exposures. Infection with human papilloma virus (HPV) is now also accepted as a contributing risk factor for the development of oropharyngeal cancers.

According to the 2008 – 2012 data of the Belgian Cancer Registry (BCR), the incidence of head and neck cancers (ICD-10 C00-C10, C12-C14, C30-32; nasopharynx excluded) fluctuated between 2 365 and 2 580 (Table 1). In 2011, they were the 4th most frequent cancer type in males. In the period 2004-2008, 5-year overall survival (OS) was 44.6% in males and 52.0% in females, while the 5-year relative survival was 50% and 57%, respectively (www.kankerregister.org).

Table 1 – Incidence of head and neck cancers (nasopharynx excluded) in Belgium between 2008 and 2012

Gender	2008	2009	2010	2011	2012
Males	1 894	1 902	1 774	1 939	1 879
Females	566	607	591	641	669
Total	2 460	2 509	2 365	2 580	2 548

Source: www.kankerregister.org

1.2 The need for a guideline

Head and neck cancer is a group of rare and complex cancers that require a specific approach. In 2014, the KCE published a report on the organisation of care for adults with a rare or complex cancer (KCE report 219). A concrete proposal for the organisation of care for patients with head and neck cancer is available on the KCE website (http://www.kcenet.be/files/KCE_219_proposal_cancer_head_and_neck.pdf). Independently of each other, a group of clinicians on the one hand and the College of Oncology on the other hand requested the KCE to develop a clinical practice guideline (CPG) for head and neck cancer.

1.3 Scope

During an initial scoping meeting on May 13, 2013 an overview was provided of the available recent high-quality guidelines. During this meeting it was decided to develop the CPG for head and neck cancer in 2 phases. The first part concerned the management of oral cavity cancer, and was published in 2014 (KCE report 227). This second part will deal with oropharyngeal, hypopharyngeal and laryngeal cancer.

The guideline focuses on the staging, treatment, follow-up and supportive care for patients with confirmed head and neck cancer. Screening for and prevention of head and neck cancer are out of scope.

1.4 Remit of the guideline

1.4.1 Overall objectives

This second part of the guideline provides recommendations based on current scientific evidence for the staging, treatment, follow-up and supportive care of patients with oropharyngeal, hypopharyngeal and laryngeal cancer. Clinicians are encouraged to interpret these recommendations in the context of the individual patient situation, values and preferences. The objective of the present CPG is to reduce the variability in clinical practice and to improve the communication between care providers and patients.

The guidelines are based on clinical evidence and may not always be in line with the current criteria for RIZIV – INAMI reimbursement of diagnostic and therapeutic interventions. The RIZIV – INAMI may consider adaptation of reimbursement/funding criteria based on these guidelines.

1.4.2 Target users of the guideline

This guideline is intended to be used by all care providers involved in the management of patients with oropharyngeal, hypopharyngeal and laryngeal cancer, including ear, nose, and throat surgeons, oral and maxillofacial surgeons, radiation oncologists, medical oncologists, pathologists, radiologists, nuclear medicine specialists, dentists, speech therapists, nutritional therapists, etc. It is also of interest for patients and their families, general practitioners, hospital managers and policy makers.

1.5 Statement of intent

Clinical Guidelines are designed to improve the quality of health care and decrease the use of unnecessary or harmful interventions. This guideline has been developed by clinicians and researchers for use within the Belgian healthcare context. It provides advice regarding the care and management of patients with oropharyngeal, hypopharyngeal and laryngeal cancer.

The recommendations are not intended to indicate an exclusive course of action or to serve as a standard of care. Standards of care are determined on the basis of all the available clinical data for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Variations, which take into account individual circumstances, clinical judgement and patient choice, may also be appropriate. The information in this guideline is not a substitute for proper diagnosis, treatment or the provision of advice by an appropriate health professional. It is advised, however, that significant deviations from the national guideline are fully documented in the patient's file at the time the relevant decision is taken.

1.6 Funding and declaration of interest

KCE is a federal institution funded for the largest part by INAMI/RIZIV, but also by the Federal Public Service of Health, Food chain Safety and Environment, and the Federal Public Service of Social Security. The development of clinical practice guidelines is part of the legal mission of the KCE. Although the development of guidelines is paid by KCE's budget, the sole mission of the KCE is providing scientifically valid information. KCE has no interest in companies (commercial or non-commercial i.e. hospitals and universities), associations (e.g. professional associations, unions), individuals or organisations (e.g. lobby groups) that could be positively or negatively affected (financially or in any other way) by the implementation of these guidelines. All clinicians involved in the Guideline Development Group (GDG) or the peer-review process completed a declaration of interest form. Information on potential conflicts of interest is published in the colophon of this report. All members of the KCE Expert Team make yearly declarations of interest and further details of these are available upon request.

2 METHODOLOGY

2.1 Introduction

The present guideline was developed using a standard methodology based on a systematic review of the evidence. Further details about KCE and the guideline development methodology are available at https://kce.fgov.be/content/kce-processes.

Several steps were followed to elaborate this guideline. Firstly, clinical questions were developed and the inclusion and exclusion criteria were defined in collaboration with members of the Guideline Development Group. Secondly, a literature review was conducted (including a search for recent, high-quality guidelines). Thirdly, on the basis of the results of the literature review, recommendations were formulated and graded according to the GRADE approach.

2.2 The Guideline Development Group

This guideline was developed as a result of a collaboration between multidisciplinary groups of practising clinicians and KCE experts. The composition of the GDG is documented in Appendix 1. Guideline development and literature review expertise, support, and facilitation were provided by the Dutch Cochrane Centre (DCC; subcontractor for literature searches for part of the research questions) and the KCE Expert Team.

The roles assigned to the GDG were:

- To define the clinical questions, in close collaboration with the KCE Expert Team and stakeholders;
- To identify critical and important outcomes;
- To provide feedback on the selection of studies and identify further relevant manuscripts which may have been missed;
- To provide feedback on the content of the guideline;
- To provide judgement about indirectness of evidence;
- To provide feedback on the draft recommendations;
- To address additional concerns to be reported under a section on 'other considerations'.

2.3 General approach and clinical research questions

First, a search was done to identify recent (i.e. published after 2010) high-quality guidelines addressing the topic. In addition to a search in OVID Medline, the National Guideline Clearinghouse and the GIN database (see Appendix 2.1 for search strategies) were searched to identify relevant guidelines. The search resulted in 359 hits, from which 18 potentially relevant guidelines were selected. These 18 guidelines were appraised with the AGREE II instrument by two researchers independently (see Appendix 3.2). Seven guidelines were found to be of sufficient quality (see Appendix 3.2). The results of this guideline search were discussed during a scoping meeting with the GDG and patient representatives on May 13, 2013. It was decided at that time to develop the guideline in two phases, with the first part focusing on oral cavity cancer, and this second part focusing on oropharyngeal, hypopharyngeal and laryngeal cancer. In contrast to the first part, the ADAPTE methodology was abandoned as no sufficiently good and recent guidelines were identified and several questions from the first part (on oral cavity cancer) had been elaborated in such a way that the identified evidence could be used for this second part too:

1. What is the clinical effectiveness of PET/CT in the staging of head and neck squamous cell carcinoma (HNSCC)?
2. What is the clinical effectiveness of HPV testing in patients with HNSCC?
3. What is the clinical effectiveness of PET or MRI in the detection of lymph node metastasis after chemoradiotherapy?
4. What is the clinical effectiveness of neck dissection after chemoradiotherapy in patients with HNSCC?
5. What is the clinical effectiveness of IMRT in patients with locally advanced HNSCC?
6. What is the clinical effectiveness of induction chemotherapy in patients with HNSCC?
7. What is the clinical effectiveness of primary chemoradiotherapy in patients with non-resectable M0 HNSCC?
8. What is the clinical effectiveness of treatment interventions in metastatic disease or recurrent disease not suitable for curative treatment?

In addition to these questions, the following questions (focusing on oropharyngeal, hypopharyngeal and laryngeal cancer) were proposed by the GDG during a scoping meeting on June 23, 2014:

9. What is the effectiveness of locoregional staging (i.e. T- and N-staging) with MRI versus CT in patients with laryngeal, hypopharyngeal and oropharyngeal cancer?
10. What is the clinical effectiveness of surgery in patients with early laryngeal, hypopharyngeal and oropharyngeal cancer?
    a. Surgery versus non-surgery
    b. Function-sparing surgery versus extensive surgery
11. What is the clinical effectiveness of surgery versus organ / function preservation strategies in patients with locally-advanced laryngeal, hypopharyngeal and oropharyngeal cancer?
12. What is the clinical effectiveness of postoperative (chemo)radiotherapy in patients with laryngeal, hypopharyngeal and oropharyngeal cancer?
    a. Postoperative (chemo)radiotherapy versus no (chemo)radiotherapy
    b. Postoperative radiotherapy versus chemoradiotherapy
13. What is the clinical effectiveness of neck dissection in patients with laryngeal, hypopharyngeal and oropharyngeal cancer?
    a. Neck dissection versus no neck dissection
    b. Type of neck dissection
14. What is the clinical effectiveness of salvage treatment in patients with second primaries or locoregional recurrence after curative treatment for laryngeal, hypopharyngeal and oropharyngeal cancer?

During the development process of this second part, an additional research question was formulated:

15. What is the clinical effectiveness of primary radiotherapy with altered fractionation versus conventional fractionation in patients with laryngeal, hypopharyngeal and oropharyngeal cancer?

For nine questions (question 5, 6, 8, 9, 10, 11, 12, 13 and 14) a literature search was done by the DCC. For the remaining six questions, the searches were done by the KCE.

2.4 Literature search and quality appraisal

Clinical questions were translated into in- and exclusion criteria using the PICO (Participants–Interventions–Comparator–Outcomes) framework. In general, studies were searched in Medline, Embase and the Cochrane Library, with the exception of the question on HPV testing (search limited to Medline and Embase). Detailed search strategies per database can be found in Appendix 2. For the diagnostic questions, systematic reviews, diagnostic accuracy studies and RCTs were searched; for the other research questions, systematic reviews, RCTs or comparative observational studies (in the absence of RCTs) were searched. Only articles published in Dutch, English and French were included. The results of the selection process are provided in the Appendix 3.3.

The quality appraisal was performed by at least one researcher:

- **Systematic reviews** were assessed using the AMSTAR checklist (http://amstar.ca/Amstar_Checklist.php);
- **RCTs and comparative observational studies** were assessed with the Cochrane Collaboration's tool for assessing risk of bias;
- **Diagnostic accuracy studies** were assessed with the QUADAS-2 checklist.

The tools used for the quality appraisal are reported in Appendix 3.1, while the results of the quality appraisal are available in Appendix 3.3.

2.5 Data extraction

For each systematic review, the search date, publication year, included studies and main results were extracted. For primary studies, the following data were extracted: publication year, study population, study intervention, and outcomes.

Data extraction was performed by at least one researcher and entered in evidence tables using standard KCE templates. All evidence tables are reported in Appendix 4.

2.6 Statistical analysis

For dichotomous outcomes the relative risk was used as the measure of treatment effect and for continuous outcomes the mean difference or – if applicable – the standardised mean difference. For time to event data, the log of the hazard ratio [log(HR)] and its standard error were used. For comparative observational studies the measure of treatment effect that has been adjusted for confounders was used. For observational Diagnostic Test Accuracy (DTA) studies analyses were based on the 2 by 2 Tables (sensitivity and specificity).

For all analyses the results of RCTs and comparative observational studies were analysed separately.[1] For each comparison (intervention vs. comparator) separate analyses were done and whenever applicable, subgroups were discriminated (e.g. for tumour localisation).

The meta-analyses of the included reviews were updated by the addition of newly retrieved primary studies. If the newly retrieved primary studies served for a new systematic review, meta-analyses of RCTs were performed according to the guidelines described in the Cochrane Handbook[2] and by the use of Review Manager software.[3]

Results of studies that were sufficiently clinically homogeneous, i.e. sufficiently similar with respect to the patients, interventions, outcomes and timing of the follow-up measurements (judged by the content experts) were combined by the use of a fixed-effect model. If the studies were statistically heterogeneous a random-effects model was used and – if sufficient studies were available – heterogeneity was explored by subgroup analyses. Statistical heterogeneity was assessed by a combination of visual inspection of the forest plots, the Chi-square test for homogeneity (p-value set at 0.1 to increase the power of this test) and the I^2 statistic. The latter two statistics were interpreted in the light of the size of the studies included in the meta-analysis (e.g. if many large studies were included that had clinically irrelevant different effect estimates, the Chi-square test would become significant (due to high power) and I^2 would approach 100%; in that case the results of the visual inspection dominated the judgment of heterogeneity).

For comparative observational studies the generic inverse variance (GIV) method was used for meta-analysis.[2] For each study the adjusted effect estimates (ORs or HRs) and their standard errors (SE) were entered in RevMan. If no SE was reported, the SE was derived from the 95%-

confidence interval of the adjusted effect estimate or from the reported p-value (if at least two decimals had been reported).

When single study results were available, no forest plots were made.

If possible, all analyses were performed according to the intention-to-treat (ITT) principle. If a study didn't report an ITT analysis or if it was unclear whether an ITT analysis was done, the results as reported in the paper were used. No imputations were carried out.

Meta-analyses of DTA studies were performed according to the guidelines described in the (draft) Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.[4] For the research questions on PET scan, Review Manager software was used to prepare forest plots of paired sensitivity and specificity of the included studies, the distribution of studies in the ROC-space and the graphical presentation of the results of the meta-analyses (see first part on oral cavity cancer[9]), whereas the actual meta-analyses were done by the use of Stata, module Metandi.[5] Metandi includes random effects methods for meta-analysis of DTA studies in which overall sensitivity and specificity are jointly estimated, whilst taking account of the existing covariance of those two parameters and the existing heterogeneity between studies, which is the rule rather than the exception in meta-analyses of DTA studies.[4]

Studies that were clinically heterogeneous or did not present the data in sufficient detail to enable statistical pooling were summarised qualitatively.

2.7 Grading evidence

For each recommendation, we provided its strength and the quality of the supporting evidence. According to GRADE, we classified the quality of evidence into 4 categories: high, moderate, low, and very low (Table 2 and Table 3). The quality of evidence reflects the extent to which a guideline panel's confidence in an estimate of the effect was adequate to support a particular recommendation.

GRADE for guidelines was used, meaning that the evidence across all outcomes and across studies for a particular recommendation was assessed. The following quality elements for intervention studies were evaluated: study limitations, inconsistency, indirectness, imprecision and publication bias.

The general principles used to downgrade the quality rating are summarized in Table 4. Decisions on downgrading with -1 or -2 points were based on the judgement of the assessors. Reasons for (no) downgrading were summarized in the GRADE profiles in Appendix 5. To create the GRADE profiles and SoF Tables the GRADEpro software (GRADEpro 2009) or the Guideline Development Tool (http://gdt.guidelinedevelopment.org/central_prod/_design/client/index.html) were used.

Table 2 – A summary of the GRADE approach to grading the quality of evidence for each outcome

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency 3. Indirectness 4. Imprecision 5. Publication bias	1. Large effect 2. Dose-response 3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	High (⊕⊕⊕⊕) Moderate (⊕⊕⊕⊖) Low (⊕⊕⊖⊖) Very low (⊕⊖⊖⊖)
Observational studies	Low			

Source: Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol. 2011;64(12):1311-6.

Table 3 – Levels of evidence according to the GRADE system

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

Source: Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.

Table 4 – Downgrading the quality rating of evidence using GRADE

Quality element	Reasons for downgrading
Limitations	For each study reporting the selected outcome, possible risk of bias introduced by lack of allocation concealment, lack of blinding, lack of intention-to-treat analysis, loss of follow-up and selective outcome reporting were assessed. Additionally, other limitations such as stopping early for benefit and use of unvalidated outcome measures were taken into consideration. Level of evidence was downgraded if studies were of sufficiently poor quality. Downgrading was omitted if studies with low risk of bias were available that lead to similar conclusions as the studies with a high risk of bias.
Inconsistency	Downgrading the level of evidence for inconsistency of results was considered in the following situations: point estimates vary widely across studies, confidence intervals show minimal or no overlap, the statistical test for heterogeneity shows a low p-value or the I^2 is large. If large variability in magnitude of effect remained unexplained, the quality of evidence was rated down.
Indirectness	Quality rating was downgraded for indirectness in case the trial population or the applied intervention differed significantly from the population or intervention of interest. Also, the use of surrogate outcomes could lead to downgrading. A third reason for downgrading for indirectness occurred when the studied interventions were not tested in a head-to-head comparison.
Imprecision	Evaluation of the imprecision of results was primarily based on examination of the 95%CI. Quality was rated down if clinical action would differ if the upper versus the lower boundary of the 95%CI represented the truth. In general, 95%CIs around relative effects were used for evaluation, except when the event rate was low in spite of a large sample size. To examine the 95%CIs, the clinical decision threshold (CDT) was defined. When the 95%CI crossed this clinical decision threshold, the quality level was rated down. A relative risk reduction (RRR) of 25% was defined as CDT by default and adapted if deemed appropriate e.g. in case of a low risk intervention. Even if 95%CIs appeared robust, level of evidence could be rated down because of fragility. To judge fragility of results, it is suggested to calculate the number of patients needed for an adequately powered (imaginary) single trial, also called the optimal information size (OIS). If the total number of patients included in a systematic review was less than the calculated OIS, rating down for imprecision was considered. For calculations, a RRR of 25% was used, unless otherwise stated. When the OIS could not be calculated, a minimum of 300 events for binary outcomes and a minimum of 400 participants for continuous outcomes were used as a rule of thumb.
Reporting bias	Quality rating was downgraded for reporting bias if publication bias was suggested by analysis using funnel plots or searching of trial registries. Publication bias was also suspected if results came from small, positive industry-sponsored trials only.

Source: Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.

2.7.1 Therapeutic research questions

For RCTs, quality rating was initially considered to be of high level for therapeutic questions (Table 2). The rating was then downgraded if needed based on the judgement of the different quality elements. Each quality element considered to have serious or very serious risk of bias was rated down -1 or -2 points respectively. Judgement of the overall confidence in the effect estimate was also taken into account. We considered confidence in estimates as a continuum and the final rating of confidence could differ from that suggested by each separate domain.[6]

Observational studies were by default considered low level of evidence for therapeutic questions (Table 2 and Table 3). However, the level of evidence of observational studies with no threats to validity can be upgraded for a number of reasons:

1. Large magnitude of effects: The larger the magnitude of effect, the stronger becomes the evidence. As a rule of thumb, the following criteria were proposed by GRADE:
   a. Large, i.e. RR >2 or <0.5 (based on consistent evidence from at least 2 studies, with no plausible confounders): upgrade 1 level
   b. Very large, i.e. RR >5 or <0.2 (based on direct evidence with no major threats to validity): upgrade 2 levels
2. All plausible confounders: all plausible confounding from observational studies or randomized trials may be working to reduce the demonstrated effect or increase the effect if no effect was observed
3. Dose-response gradient: The presence of a dose-response gradient may increase our confidence in the findings of observational studies and thereby increase the quality of evidence.

2.7.2 Diagnostic research questions

The methods for GRADEing the level of evidence for diagnostic studies are still under development as is software for preparing Summary of Findings Tables for Diagnostic Test Accuracy (DTA) studies. The methods described in 2008[7] and in a more recent draft paper by Schünemann et al. (Schünemann, personal communication) were applied. Clear guidance, however, regarding how to score the various domains of the GRADE profile is lacking. Wherever feasible, the criteria for scoring the overall results of RCTs were adapted to the scoring of DTA studies.

Sensitivity and specificity were by default considered to be high if at least 90%, moderate if between 80% and 90% and low if below 80%.

2.8 Formulation of recommendations

Based on the retrieved evidence, the first draft of recommendations was prepared by a small working group (researchers from KCE and Dutch Cochrane Centre). This first draft was, together with the evidence tables, circulated to the guideline development group 1 week prior to the face-to-face meetings (February 2, 2015; March 2, 2015; April 20, 2014; May 22, 2015). Based on the discussion meetings a second draft of recommendations was prepared and once more circulated to the guideline development group for final approval. No formal consensus procedure was used.

The strength of each recommendation was assigned using the GRADE system (Table 5). The strength of recommendations depends on a balance between all desirable and all undesirable effects of an intervention (i.e., net clinical benefit), quality of available evidence, values and preferences, and estimated cost (resource utilization). For this guideline, no formal cost-effectiveness study or search for economic literature was conducted (because of resource constraints), although studies identified through the literature searches for the medical questions were sometimes taken into account. Factors that influence the strength of a recommendation are reported in Table 6.

Table 5 – Strength of recommendations according to the GRADE system

Grade	Definition
Strong	The desirable effects of an intervention clearly outweigh the undesirable effects *(the intervention is to be put into practice)*, or the undesirable effects of an intervention clearly outweigh the desirable effects *(the intervention is not to be put into practice)*
Weak	The desirable effects of an intervention probably outweigh the undesirable effects *(the intervention probably is to be put into practice)*, or the undesirable effects of an intervention probably outweigh the desirable effects *(the intervention probably is not to be put into practice)*

Source: Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66(7):726-35.

Table 6 – Factors that influence the strength of a recommendation

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention, i.e. the greater the resources consumed, the lower the likelihood that a strong recommendation is warranted

Sources: Schünemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A et al. An Official ATS Statement: Grading the Quality of Evidence and Strength of Recommendations in ATS Guidelines and Recommendations. Am J Respir Crit Care Med 2006; 174:605–14.
Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B et al. Grading Strength of Recommendations and Quality of Evidence in Clinical Guidelines - Report From an American College of Chest Physicians Task Force. Chest 2006; 129:174-81.

A strong recommendation implies that most patients would want the recommended course of action. A weak recommendation implies that the majority of informed patients would want the intervention, but many would not.[8] Specifically, a strong negative recommendation means the harms of the recommended approach clearly exceed the benefits whereas a weak negative recommendation implies that the majority of patients would not want the intervention, but many would. In the case of a weak recommendation, clinicians are especially required to spend adequate time with patients to discuss patients' values and preferences. Such an in-depth discussion is necessary for the patient to make an informed decision. This may lead a significant proportion of patients to choose an alternative approach. Fully informed patients are in the best position to make decisions that are consistent with the best evidence and patients' values and preferences.

For policy-makers, a strong recommendation implies that variability in clinical practice between individuals or regions would likely be inappropriate whereas a weak recommendation implies that variability between individuals or regions may be appropriate, and use as a quality of care criterion is inappropriate.[8]

We offer the suggested interpretation of "strong" and "weak" recommendations in Table 7.

Table 7 – Interpretation of strong and conditional (weak)* recommendations

Implications	Strong recommendation	Weak recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

** the terms ''conditional'' and ''weak'' can be used synonymously*
Source: Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66(7):726-35.

2.9 External review

2.9.1 Healthcare professionals

The recommendations prepared by the guideline development group were circulated to relevant Professional Associations (Table 8). Each association was asked to assign one or two key representatives to act as external reviewers of the draft guideline. All expert referees made declarations of interest.

Globally, 7 external experts were involved in the evaluation of the clinical recommendations. All invited panellists received the scientific reports for all research questions and were asked to score each recommendation on a 5-point Likert scale indicating their level of agreement with the recommendation, with a score of '1' indicating 'completely disagree', '2' 'somewhat disagree', '3' 'unsure', '4' 'somewhat agree', and '5' 'completely agree' (the panellists were also able to answer 'not applicable' if they were not familiar with the underlying evidence). If panellists disagreed with the recommendation (score '1' or '2'), they were asked to provide an explanation supported by appropriate evidence. Scientific arguments reported by these experts were used to adapt the formulation or the strength of the clinical recommendations. This was discussed during a stakeholder meeting on September 11, 2015. In Appendix 7, an overview is provided of how their comments were taken into account. No formal consensus method was used.

Table 8 – List of Professional Associations invited

- Belgian Society of Medical Oncology - Belgische Vereniging voor Medische Oncologie - Société Belge d'Oncologie Médicale (BSMO)
- Belgische Vereniging voor Radiotherapie-Oncologie - Association Belge de Radiothérapie-Oncologie (BVRO - ABRO)
- Belgian Society of Radiology (BSR): no comments received
- Belgische Genootschap voor Nucleaire Geneeskunde - Société Belge de Médecine Nucléaire
- Belgian Society of Pathology - Belgische Vereniging Anatomopathologie - Société Belge d'Anatomopathologie
- Domus Medica
- Koninklijke Belgische Vereniging voor Oto-Rhino-Laryngologie, Gelaat- en Halschirurgie - Société Royale Belge d'ORL et de Chirurgie Cervico-faciale - Belgian ENT society
- Koninklijke Belgische Vereniging voor Stomatologie en Maxillo-Faciale Heelkunde - Société Royale Belge de Stomatologie et de Chirurgie Maxillo-Faciale
- Belgian Society of Surgical Oncology (BSSO): no representatives appointed
- Royal Belgian Society of Surgery: no representatives appointed
- Société Scientifique de Médecine Générale: no representatives appointed

2.9.2 Patient representatives

Associations of patient representatives were contacted to invite patient representatives to take part in stakeholder meetings (June 23, 2014; September 11, 2015). Their key role was to ensure that patient views and experiences informed the group's work. Patient representatives were asked the following questions:

- Have important considerations from a patients' perspective been missed in the formulation of our recommendations?
- Do we need to add information that could assist patients in making clear choices when doctors discuss treatment options with them?

For each recommendation where the patient representatives had a comment or suggestion, this was reported in the considerations, including the impact on the final recommendation.

2.10 Final validation

As part of the standard KCE procedures, an external scientific validation of the report was conducted prior to its publication. The scientific content was assessed by three validators on June 29, 2015 (cf. names in the colophon).

3 CLINICAL RECOMMENDATIONS

3.1 Diagnosis and staging

In the first part of the guideline on head and neck cancer – focusing on oral cavity cancer[9] – several general recommendations were formulated regarding diagnosis and staging, which are also applicable to oropharyngeal, hypopharyngeal and laryngeal cancer. An overview is provided in Table 9. The rest of this chapter focuses on specific topics that were discussed again by the GDG for this second part of the guideline.

Table 9 – Diagnosis and staging recommendations from oral cavity cancer guideline[9]

Recommendation	Strength of recommendation	Level of Evidence
Patient information		
The patient must be kept fully informed about his condition, the treatment options and consequences. Information should be complete and communicated in a clear and unambiguous way. Patient preferences should be taken into account when deciding on a treatment option.	Strong	Very low
Biopsy		
A biopsy should be taken from the most suspect part of the tumour. The pathologist should be provided with any clinically relevant information. If the result is inconclusive, or negative but the tumour is suspect, the biopsy should be repeated.	Strong	Very low
When a patient **…** is referred to another centre for work-up completion and treatment, and if no additional biopsies need to be performed in the reference centre, pathology specimens (slices and/or blocks) should be sent for revision to the reference laboratory for diagnosis confirmation upon request from the reference centre. Every uncommon tumour diagnosis beside classical SCC should be reviewed by an expert from a reference laboratory.	Strong	Very low
The biopsy report should include: tumour localization, tumour histology, tumour grade, depth of invasion (if assessable), lymphatic, vascular and perineural invasion. Some other prognostic factors, such as growing pattern (infiltrative vs. pushing border), can be considered.	Strong	Very low
Non-imaging staging		
To exclude synchronous secondary tumours in the head and neck area, all patients … should undergo clinical examination (including fiberoptic examination) of the upper aerodigestive tract. Endoscopy under general anaesthesia should be considered for better local staging of large tumours.	Strong	Very low
Patients … should be examined by a dedicated dental practitioner prior to commencing oncological treatment. The dentist should give preventive advice and perform necessary restorative work.	Strong	Very low

The parts focusing specifically on oral cavity cancer are deliberately left out.

3.1.1 Locoregional staging with MRI compared to CT

The detailed results of the literature search and assessment can be found in Appendix 2.3.1, Appendix 3.3.1, Appendix 3.3.2, Appendix 4.1, Appendix 5.1 and Appendix 6.1.

Larynx

No systematic reviews or RCTs were identified. The search for observational studies revealed two relevant studies in which the diagnostic test accuracy of MRI versus CT was compared for T-staging in patients with laryngeal cancer of the glottis, supraglottic, glotto-supraglottic, and glotto-subglottic region to select patients who are eligible for laryngeal conservative surgery.[10, 11] No studies were found for N-staging, so only indirect conclusions (based on evidence in patients with HNSCC) can be drawn about the diagnostic outcomes of MRI and CT in patients with laryngeal cancer.

The first study was a prospective cohort study in which adults suspected of laryngeal cancer of the glottis region based on indirect laryngoscopy and eligible for supracricoid laryngectomy or cordectomy by CO_2 laser were included (N=20) from August 2011 to November 2013.[10] Patients treated with radiotherapy were excluded (N=6). The results of MRI and CT were compared with each other and with the definitive pathological examination as reference standard. Risk of bias of this study was judged to be unclear, because the enrolment of patients and independent interpretation of the pathology results (without knowledge of imaging results) were not described. Also, it was unclear whether there was an appropriate interval between imaging and pathology, and not all patients were included in the analysis. The sensitivity (Se), specificity (Sp) and predictive values (PPV, NPV; see evidence tables) were calculated for MRI vs. CT for several T-staging locations (Table 10). This study suggests that MRI is more sensitive than CT in the preoperative T-staging of early glottic cancer, although these results are not significant (except for the location anterior commissure involvement).

In the second prospective cohort study patients undergoing microlaryngoscopy for laryngeal cancer underwent MRI, CT and endosonography.[11] Study period was not stated. Endosonography was performed in 84 patients, but only the 76 cases undergoing complete surgical excision of their tumours were included in the analyses where the results of endosonography were compared with those of CT and MRI. Risk of bias for this study was judged to be unclear, as there was no clear description about the enrolment of patients. Inappropriate exclusion of patients was not avoided, because not all patients in which endosonography (761 imaging criteria) was performed received MRI (150 imaging criteria) and CT (510 imaging criteria). It was unclear whether the pathology (i.e. the reference standard) was interpreted without knowledge of the results of MRI/CT imaging, and it was unclear whether there was an appropriate interval between MR/CT imaging and pathology. The diagnostic outcomes for all imaging criteria combined were calculated for MRI vs. CT for T-staging and showed similar results: Se 63% (95%CI: 51%-73%) vs. 68% (95%CI: 62%-74%); and Sp 89% (95%CI: 80%-94%) vs. 84% (95%CI: 80%-88%). The sensitivity (Se), specificity (Sp) and predictive values (PPV, NPV; see evidence tables) calculated for MRI vs. CT for several T-staging locations (Table 10).

Table 10 – Comparison of the diagnostic outcomes of T-staging of laryngeal cancer with MRI versus CT

Criteria	Allegra 2014 MRI vs. CT	Kraft 2013 MRI vs. CT
• **Paraglottic space involvement**	- **Se:** 1.00 (0.55-1.00) vs. 0.33 (0.10-0.70) - **Sp:** 1.00 (0.74-1.00) vs. 1.00 (0.74-1.00)	- **Se:** 0.00 (0.00-0.62) vs. 0.50 (0.29-0.71) - **Sp:** 0.92 (0.62-1.00) vs. 0.91 (0.76-0.98)
• **Thyroid cartilage invasion**	- **Se:** 1.00 (0.45-1.00) vs. 0.50 (0.12-0.77) - **Sp** 1.00 (0.77-1.00) vs. 1.00 (0.77-1.00)	- **Se:** 0.33 (0.06-0.80) vs. 0.57 (0.33-0.79) - **Sp:** 0.83 (0.54-0.96) vs. 0.95 (0.81-0.99)
• **Arytenoid cartilage invasion**	- **Se:** 1.00 (0.29-1.00) vs. 1.00 (0.29-1.00) - **Sp:** 1.00 (0.79-1.00) vs. 1.00 (0.79-1.00)	- **Se:** 0.60 (0.23-0.88) vs. 0.42 (0.19-0.68) - **Sp:** 1.00 (0.67-1.00) vs. 0.79 (0.64-0.89)
• **Midline crossing (anterior commissure involvement)**	- **Se** 1.00 (0.62-1.00) vs. 0.25 (0.07-0.60) - **Sp:** 0.83 (0.54-0.96) vs. 1.00 (0.71-1.00)	- **Se:** 0.73 (0.43-0.91) vs. 0.80 (0.66-0.90) - **Sp:** 0.75 (0.29-0.96) vs. 0.90 (0.57-1.00)
• **Cricoid cartilage invasion**	- **Se:** cannot be calculated since no patients had cricoid cartilage invasion - **Sp:** 1.00 (0.81-1.00) vs. 1.00 (0.81-1.00)	Not applicable
• **Vocal fold**	Not applicable	- **Se:** 0.91 (0.60-1,00) vs. 0.92 (0.78-0.98) - **Sp:** 1.00 (0.45-1.00) vs. 0.43 (0.22-0.67)
• **Ventricular fold**	Not applicable	- **Se:** 0.50 (0.24-0.76) vs. 0.63 (0.45-0.78) - **Sp:** 1.00 (0.51-1.00) vs. 0.71 (0.50-0.86)
• **Epiglottis**	Not applicable	- **Se:** 0.86 (0.46-0.99) vs 0.90 (0.80-1.00) - **Sp:** 0.88 (0.51-1.00) vs. 1.00 (0.86-1.00)
• **Preepiglottic**	Not applicable	- **Se:** 0.60 (0.23-0.88) vs. 0.67 (0.39-0.86) - **Sp:** 1.00 (0.67-1.00) vs. 0.95 (0.82-0.99)
• **Inner perichondrium**	Not applicable	- **Se:** 0.25 (0.04-0.71) vs. 0.47 (0.26-0.69) - **Sp:** 0.91 (0.60-1.00) vs. 0.94 (0.80-0.99)
• **Tumor diameter**	Not applicable	- **Se:** 0.64 (0.35-0.85) vs. 0.50 (0.34-0.66) - **Sp:** 0.25 (0.04-0.71) vs. 0.37 (0.19-0.59)

Hypopharynx

No systematic reviews, RCTs or comparative observational studies were identified. Therefore, no conclusions can be drawn about the clinical effectiveness of locoregional staging with MRI versus CT and only indirect conclusions (based on evidence in patients with HNSCC) can be drawn about the diagnostic outcomes of these modalities in patients with cancer of the hypopharynx.

Oropharynx

No systematic reviews comparing MRI with CT, RCTs or comparative observational studies were identified. Therefore, no conclusions can be drawn about the clinical effectiveness of locoregional staging with MRI versus CT and only indirect conclusions (based on evidence in patients with HNSCC) can be drawn about the diagnostic outcomes of these modalities in patients with cancer of the oropharynx.

Head and neck squamous cell carcinoma

One systematic review was included that compared the diagnostic outcomes of locoregional staging with MRI vs. CT in patients with HNSCC.[12] The search date was January 2011 and the overall risk of bias of this review was judged to be low. The review included 16 studies, including 10 studies with direct comparisons of MRI performance with CT for cervical lymph node status in 688 patients. The meta-analytical results suggested no major differences between MRI and CT: Se 67% (95%CI: 65%–70%) vs. 64% (95%CI: 61%–68%) and Sp 79% (95%CI: 77%–80%) vs. 75% (95%CI: 63%–80%), respectively. Unfortunately, not all diagnostic outcome results of the included primary studies were reported. Therefore, updating of the meta-analysis was not possible.

The update of the search identified two relevant studies published after January 2011.

The first study (design not reported by the authors) included previously untreated patients with HNSCC from May 2010 – April 2012.[13] Diffusion-Weighted (DW)-MRI was compared with CT Perfusion, but also with conventional CT images, for the preoperative diagnosis of cervical lymph node metastases, in 30 patients (N=65 lymph nodes). Risk of bias of this study was judged to be unclear. This study suggests that DW-MRI may be more accurate than CT for the preoperative diagnosis of cervical lymph node metastases: Se 90% (95%CI: 77%–96%) vs. 69% (95%CI: 55%–80%); and Sp 77% (95%CI: 52%–91%) vs. 53% (95%CI: 31%–74%).

The second study included a retrospective cohort of 114 previously untreated patients with HNSCC that underwent CT, MRI, US and PET/CT from January 2006 to September 2009 within three weeks prior to surgery with neck dissection.[14] Risk of bias for this study was judged to be low. There was no significant difference between the diagnostic outcomes of MRI vs CT: Se 66% (95%CI: 58%-74%) vs. 63% (95%CI: 55%-71%) and Sp 95% (95%CI: 93%-97%) vs. 94% (95%CI: 92%-96%). Both tests have similar results for Se and Sp in patients with HNSCC.

Conclusions

- No randomized or non-randomized comparative studies were identified that evaluated the clinical effectiveness of MRI vs. CT in patients with laryngeal, hypopharyngeal and oropharyngeal cancer.
- A difference in diagnostic accuracy between MRI and CT for staging cervical lymph node status in patients with HNSCC could neither be demonstrated nor refuted (very low level of evidence).
- A difference in diagnostic accuracy between MRI and CT for preoperative staging of the extension of the tumour in patients with laryngeal cancer at an early stage (I-II) in order to select patients who are eligible for laryngeal conservative surgery could not be demonstrated nor refuted (very low level of evidence).

3.1.2 PET scan

In the first part of the guideline on head and neck cancer – focusing on oral cavity cancer [9] – a search was done for studies evaluating the diagnostic value of FDG-PET and FDG-PET/CT in patients with head and neck cancer. The results of that search were used for the second part too, and are described below. Methodological information can be found in the appendix of the first part.

3.1.2.1 PET scan for nodal staging

Two recent systematic reviews were identified that evaluated the diagnostic value of FDG-PET and/or FDG-PET/CT for the nodal staging of patients with HNSCC.[15, 16] From these reviews, 16 primary studies were selected that met our inclusion criteria.[17-32] In addition, 6 primary studies were identified that were published since the search date of the systematic reviews.[33-38] The 22 primary studies included a total of 1 534 patients, of which about one third had non-oral cavity SCC. Eight studies had a prospective design. Many studies suffered from methodological drawbacks, such as differential verification, verification bias or absence of blinding.

FDG-PET

Nine studies evaluated FDG-PET.[17-19, 23, 24, 31, 33, 35, 36] Four studies (513 patients) reported a patient-based analysis.[18, 23, 24, 36] Pooled sensitivity was 78% (95%CI 71-84%) and pooled specificity 92% (95%CI 49-99%). Five studies reported a neck-side-based analysis.[17, 24, 31, 33, 35] Pooled sensitivity was 87% (95%CI 48-98%) and pooled specificity 88% (95%CI 68-96%). Finally, two studies reported a node-based analysis[17, 19] and found a sensitivity of 80% and 91%, respectively, and a specificity of 93% and 88%, respectively.

FDG-PET/CT

Fifteen studies evaluated FDG-PET/CT.[19-22, 25-30, 32-34, 37, 38] One study reported a patient-based analysis,[28] and found a sensitivity of 91% and a specificity of 87% for non-enhanced PET/CT. Four studies evaluated non-enhanced PET/CT using a neck-side-based analysis.[20, 29, 33, 38] Pooled sensitivity was 84% (95%CI 80-88%) and pooled specificity 85% (95%CI 77-90%). Ten studies evaluated non-enhanced PET/CT using a node-based analysis.[19, 20, 22, 25-29, 34, 37] Pooled sensitivity was 80% (95%CI 74-85%) and pooled specificity 96% (95%CI 94-98%). Three studies evaluated contrast-enhanced PET/CT using a neck-side-based analysis.[21, 30, 33] A moderate to high sensitivity was found (range 89-100%), while the reported specificities were heterogeneous (range 71-100%). Finally, two studies evaluated contrast-enhanced PET/CT using a node-based analysis[30, 32] and found a sensitivity of 81% and 96%, respectively, and a specificity of 98% and 99%, respectively.

Comparison with conventional imaging techniques

In 10 studies PET and/or PET/CT were directly compared with conventional imaging techniques (Table 11).[17, 19, 20, 25, 28, 30, 32-34, 37] Only in three studies PET[17] or PET/CT[20, 28] were found to have a superior sensitivity over MRI or CT/MRI, respectively. These concerned all node-based analyses. In none of the comparisons, PET or PET/CT was found to have a superior specificity.

Braams et al. found a significantly higher sensitivity with PET compared to MRI (91% vs. 36%) using a node-based analysis.[17] However, the statistical significance was not confirmed in their neck-side-based analysis (100% vs. 64%).

Kim et al. found a significantly higher sensitivity with non-enhanced PET/CT compared to CT/MRI (79% vs. 61%) using a node-based analysis[20] which was confirmed by Roh et al. (90% vs. 60%).[28] However, a third study (with a very low prevalence of 4%) found no difference in sensitivity between the two imaging modalities (0% vs. 0%)[25], and the statistical significance was also not confirmed using a patient-based (91% vs. 76%)[28] or neck-side-based analysis (83% vs. 71%).[20]

Four studies reporting a neck-side-based analysis were pooled.[17, 20, 30, 33] PET or PET/CT were found to have a better pooled sensitivity than conventional imaging (CT in 2 studies, MRI in 1 study, CT/MRI in 1 study), but the 95%CI were overlapping (96% [77-99%] vs. 82% [65-91%]). Pooled specificity was moderate for both interventions and the 95%CI were also found to overlap (83% [68-91%] vs. 84% [72-92%]).

Nine studies reporting a node-based analysis were pooled.[17, 19, 20, 25, 28, 30, 32, 34, 37] PET or PET/CT were found to have a better pooled sensitivity than conventional imaging (CT in 4 studies, CT/MRI in 3 studies, MRI in 1 study, CT/US in 1 study), but the 95%CI were again overlapping (83% [74-89%] vs. 68% [57-78%]). Pooled specificity was high for both interventions and the 95%CI were also found to overlap (96% [93-98%] vs. 98% [95-99%]). When only the 8 studies comparing PET/CT with conventional imaging were considered[19, 20, 25, 28, 30, 32, 34, 37] the difference in sensitivity decreased (82% [70-89%] vs. 72% [63-80%]). Furthermore, when only the 4 studies comparing PET/CT with CT were considered[19, 30, 32, 34] the difference in sensitivity was minimal (85% [70-94%] vs. 80% [71-87%]).

Table 11 – Comparison of PET or PET/CT with conventional imaging techniques for nodal staging: individual studies*

			Diagnostic accuracy (95%CI)			
Comparison	**Basis of analysis**	**N**	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
PET versus CT			**PET**		**CT**	
Haerle 2011b	Neck-side	36	93% (77-99%)	71% (29-96%)	97% (82-100%)	71% (29-96%)
Jeong 2007	Node	242	80% (68-89%)	93% (88-96%)	90% (80-96%)	94% (89-97%)
PET versus MRI			**PET**		**MRI**	
Braams 1995	Neck-side	24	100% (69-100%)	64% (35-87%)	64% (31-89%)	69% (39-91%)
Braams 1995	Node	199	***91% (71-99%)***	88% (82-92%)	36% (17-59%)	94% (90-97%)
NE-PET/CT versus CT			**NE-PET/CT**		**CT**	
Haerle 2011b	Neck-side	36	93% (77-99%)	71% (29-96%)	97% (82-100%)	71% (29-96%)
Hoshikawa 2012	Node	464	64% (51-76%)	99% (98-100%)	73% (60-84%)	100% (98-100%)
Jeong 2007	Node	242	92% (82-97%)	99% (96-100%)	90% (80-96%)	94% (89-97%)
NE-PET/CT versus CT/MRI			**NE-PET/CT**		**CT/MRI**	
Roh 2007	Patient	63	91% (76-98%)	87% (69-96%)	76% (58-89%)	83% (65-94%)
Kim 2011	Neck-side	228	83% (74-90%)	91% (85-95%)	71% (60-80%)	88% (82-93%)
Kim 2011	Node	899	***79% (72-85%)***	95% (93-97%)	61% (53-69%)	96% (94-97%)
Pentenero 2008	Node	79	0% (0-71%)	93% (85-98%)	0% (0-71%)	97% (91-100%)
Roh 2007	Node	324	***90% (79-96%)***	94% (90-96%)	60% (47-72%)	92% (88-95%)
NE-PET/CT versus CT/US			**NE-PET/CT**		**CT/US**	
Matsubara 2012	Node	498	77% (63-88%)	97% (95-99%)	73% (58-85%)	99% (97-100%)
CE-PET/CT versus CT			**CE-PET/CT**		**CT**	
Haerle 2011b	Neck-side	36	97% (82-100%)	71% (29-96%)	97% (82-100%)	71% (29-96%)
Schwartz 2005	Neck-side	26	100% (80-100%)	100% (66-100%)	82% (57-96%)	100% (66-100%)
Schwartz 2005	Node	96	96% (81-100%)	99% (92-100%)	78% (58-91%)	99% (92-100%)
Yoon 2009	Node	402	81% (70-89%)	98% (96-99%)	77% (66-86%)	99% (98-100%)
CE-PET/CT versus MRI			**CE-PET/CT**		**MRI**	
Yoon 2009	Node	402	81% (70-89%)	98% (96-99%)	77% (66-86%)	99% (98-100%)

* *Statistically significant differences are in bold and italic.*

3.1.2.2 PET scan for distant staging

Three recent systematic reviews were identified that evaluated the diagnostic value of FDG-PET and/or FDG-PET/CT for the distant staging of patients with HNSCC.[39-41] From these reviews, 4 primary studies were selected that met our inclusion criteria.[42-45] In addition, 4 primary studies were identified that were published since the search date of the systematic reviews.[35, 46-48] The 8 primary studies included a total of 972 patients, of which about two thirds had oral cavity or oropharyngeal SCC.

Detection of distant metastases or second primary tumours

Seven primary studies including 859 patients with HNSCC evaluated the diagnostic value of PET or PET/CT for the detection of distant metastases or second primary tumours.[35, 42-45, 47, 48] Pooled sensitivity was 88% (95%CI 79-94%) and pooled specificity 94% (95%CI 92-95%).

Three of these studies compared PET or PET/CT with conventional imaging (Table 12).[43, 44, 47] In only one study, a significantly higher specificity was found for PET compared with CT (93% vs. 63%).[43] However, this was not confirmed in the two other studies. Sensitivities did not differ significantly.

Table 12 – Comparison of PET or PET/CT with conventional imaging techniques for the detection of distant metastases or second primary tumours*

		Diagnostic accuracy (95%CI)			
Comparison	N	Sensitivity	Specificity	Sensitivity	Specificity
PET versus CT		**PET**		**CT**	
Krabbe 2009	149	92% (75-99%)	*93% (88-97%)*	74% (52-90%)	63% (49-75%)
Ng 2008	160	77% (56-91%)	94% (89-97%)	50% (30-70%)	98% (94-100%)
NE-PET/CT versus MRI		**NE-PET/CT**		**MRI**	
Chan 2011	103	83% (59-96%)	94% (87-98%)	67% (41-87%)	96% (90-99%)

* *Statistically significant differences are in italic.*

Bone metastases

One study compared the diagnostic value of non-enhanced FDG-PET/CT with that of MRI for the detection of bone metastases in 103 patients with oropharyngeal or hypopharyngeal SCC.[47] No significant differences were found in sensitivity (both 100%) or specificity (100% vs. 99%).

Bone marrow invasion

One study compared the diagnostic value of non-enhanced FDG-PET/CT with that of MRI for the detection of bone marrow invasion in 114 patients with oral cavity SCC.[46] No significant difference was found in sensitivity (78% vs. 97%), but the specificity was significantly higher with PET/CT (83% vs. 61%).

Lung metastases

Two studies evaluated the diagnostic value of non-enhanced PET/CT for the detection of lung metastases.[42, 47] Heterogeneous results were found for the sensitivity (50% and 100%, respectively), although the specificity was consistently high (99% and 96%, respectively). One of these studies compared the diagnostic value of PET/CT with that of MRI in 103 patients with oropharyngeal or hypopharyngeal SCC.[47] No significant differences were found in sensitivity (50% both) or specificity (99% both). The second study compared the diagnostic value of PET/CT with that of chest X-ray in 27 patients with HNSCC.[42] Again, no significant differences were found in sensitivity (100% vs. 67%) or specificity (96% vs. 100%).

Liver metastases

One study compared the diagnostic value of non-enhanced FDG-PET/CT with that of MRI for the detection of liver metastases in 103 patients with oropharyngeal or hypopharyngeal SCC.[47] No significant differences were found in sensitivity (100% vs. 0%) or specificity (100% both).

Head and neck metastases

One study compared the diagnostic value of non-enhanced FDG-PET/CT with that of MRI for the detection of head and neck metastases in 103 patients with oropharyngeal or hypopharyngeal SCC.[47] No significant differences were found in sensitivity (both 100%) or specificity (both 100%).

Distant lymph node metastases

One study compared the diagnostic value of non-enhanced FDG-PET/CT with that of MRI for the detection of distant lymph node metastases in 103 patients with oropharyngeal or hypopharyngeal SCC.[47] No significant differences were found in sensitivity (50% vs. 0%) or specificity (98% vs. 99%).

Other metastases of the aerodigestive tract

One study compared the diagnostic value of non-enhanced FDG-PET/CT with that of MRI for the detection of other metastases in the aerodigestive tract in 103 patients with oropharyngeal or hypopharyngeal SCC.[47] No significant differences were found in sensitivity (100% vs. 83%) or specificity (99% vs. 98%).

Conclusions: N-staging

- Evidence of moderate quality demonstrated that PET has a moderate sensitivity (pooled: 78%) to detect positive lymph nodes in patients with primary head and neck cancer. However, evidence of very low quality demonstrated that PET has a good specificity (pooled: 92%).
- Single-study evidence of low quality demonstrated that non-enhanced PET/CT has a good sensitivity (91%) and moderate specificity (87%) to detect positive lymph nodes in patients with primary head and neck cancer.
- Evidence of low quality demonstrated that contrast-enhanced PET/CT has a moderate to good sensitivity (range 81-100%) and specificity (range 71-100%) to detect positive lymph nodes in patients with primary head and neck cancer.
- Evidence of very low quality demonstrated that PET or PET/CT does not have a significantly superior diagnostic accuracy than conventional imaging techniques (CT and/or MRI) to detect positive lymph nodes in patients with primary head and neck cancer. This is particularly true when PET/CT is compared with CT.

Conclusions: M-staging

- Evidence of moderate quality demonstrated that PET or PET/CT has a moderate sensitivity (pooled: 88%) and good specificity (pooled: 94%) to detect distant metastases or second primary tumours in patients with primary head and neck cancer.
- PET or PET/CT does not seem to have a significantly superior diagnostic accuracy than conventional imaging techniques (CT and/or MRI) to detect distant metastases or second primary tumours in patients with primary head and neck cancer.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	• The evidence does not show a superiority of CT or MRI in the staging of HNSCC. • In general, PET/CT appears to have a moderate to good sensitivity and specificity to detect positive neck nodes in patients with head and neck cancer. However, in direct comparison with CT, PET/CT has no superior diagnostic accuracy. • In general, PET/CT has a moderate sensitivity and a good specificity to detect distant metastases or second primary tumours in patients with primary head and neck cancer. In direct comparison with CT or MRI, PET/CT has no statistically significantly better diagnostic accuracy, although the sensitivity consistently tends to be better.
Quality of evidence	Only (systematic reviews of) diagnostic accuracy studies are available. Many of these suffer from selection bias and/or differential verification. No evidence is available on the impact of MRI, CT or PET/CT on patient outcomes, such as survival. The evidence coming from diagnostic accuracy studies only provides indirect information about the impact on patient outcomes, and should therefore be downgraded for indirectness. Most of these studies are in stage III and IV patients.
Costs (resource allocation)	A Dutch cost-effectiveness study showed that the dominant strategy for the detection of distant metastases in patients at high risk was the combination of FDG-PET and CT, resulting in savings between € 203 and € 604 compared with chest CT alone or FDG-PET alone.[49] An American study reported that PET/CT is a more expensive test ($ 722 per patient versus $ 450 for traditional workup), but that it results in an overall cost saving by reducing the number of futile radical treatments.[50] Another American study found an ICER of $ 8718 per life year saved or $ 2505 per quality-adjusted life-year.[51]
Patients values and preferences	• Patient representatives considered it necessary to receive adequate information about the imaging and other diagnostic/staging techniques that were planned for their work-up. • No comments were received on the technical issues of and indications for PET scan. • The quality of an MRI of the larynx or hypopharynx is highly dependent on patient and radiologist factors. E.g. an MRI of the larynx can be disturbed by motion artifacts from swallowing, breathing, coughing, and carotid artery pulsations. If a good-quality MRI is impossible, a high-quality CT is preferable. E.g. for early (T1-2) hypopharyngeal tumours, a CT can be preferred because of the possibility to perform a Valsalva manoeuvre during the procedure to better assess the medial and lateral walls of the pyriform sinus.

Comments	• Multiparametric MRI may be useful to predict and assess the treatment response. However, studies are ongoing and the evidence is currently insufficient.
	• If PET/CT cannot be done for the metastatic work-up, a chest CT is recommended.
	• The following criteria are essential for a high-quality MRI of the oropharynx, hypopharynx and larynx in general:
	  o A dedicated neck-coil should be used;
	  o At least the following images should be available (with a slice thickness of maximum 3.5 mm and without gap between the slices):
	  ▪ Axial SE or TSE T2
	  ▪ Unenhanced SE or TSE axial T1
	  ▪ Axial gadolinium enhanced SE or TSE T1 images (preferably with Fat Suppression)
	  ▪ Coronal gadolinium enhanced SE or TSE T1 images

Factor	Comment
	▪ Axial diffusion Weighted Images of the complete neck (skull base to upper mediastinum) o Patient must repeatedly be instructed not to swallow and to breathe quietly through the nose during the measurements. • The following criteria are more specific for laryngeal studies, if the MRI equipment allows this: o Thinner slices through the larynx with a thickness of 2.5-3.0 mm without gap and smaller Field of View (FOV); o Keep the sequences shorter than 3 – 3,5 minutes, the longest time these patients are able to stop swallowing; o Use surface coils or even microscopic coils when the tumour is restricted to the vocal cords (when these coils are available). • Recommendations on high end MR – equipment: o Perfusion MR; o Intra Voxel Incoherent Motion (IVIM) diffusion images.

Recommendations	Strength of Recommendation	Level of Evidence
• **In patients with newly diagnosed oropharyngeal cancer, perform an MRI for primary T- and N-staging (i.e. before any treatment).**	Strong	Very low
• **In patients with newly diagnosed hypopharyngeal or laryngeal cancer, MRI is the preferred technique for primary T- and N-staging, but in these locations its quality is more dependent on patient and radiologist factors.**	Weak	Very low
• **In case (a good) MRI is technically impossible (e.g. pacemaker, cochlear implant, claustrophobia, etc.), likely to be distorted (e.g. anticipated motion artefacts, etc.) or not timely available, perform a contrast-enhanced CT for primary T- and N-staging in patients with oropharyngeal, hypopharyngeal or laryngeal cancer.**	Weak	Very low
• **In patients with stage I and II oropharyngeal, hypopharyngeal or laryngeal cancer and with low-risk features (e.g. no smoking), a whole-body FDG-PET/CT is not routinely recommended for the evaluation of metastatic spread and/or the detection of second primary tumours.**	Weak	Low

3.1.3 HPV testing

In the first part of the guideline on head and neck cancer – focusing on oral cavity cancer [9] – a search was done for studies evaluating the use of HPV testing in patients with head and neck cancer. One evidence-based guideline on the use of routine HPV testing in head and neck SCC was identified on the cancer care Ontario website.[52] A systematic review was performed to answer four research questions, of which the following three will be discussed below:

1. What is the relationship between HPV positivity and outcome in HNSCC?
2. In which head and neck subsites is the prevalence of HPV-associated squamous cell carcinoma high enough to justify routine testing of HPV positivity?
3. What is the optimal testing method for the identification of HPV positivity in HNSCC?

The review was judged to have a low risk of bias. Searches were up-to-date until March 2013.

3.1.3.1 Prevalence of HPV-associated SCC according to head and neck subsites

The Cancer Care Ontario guideline[52] identified five systematic reviews on the prevalence of HPV-associated SCC. Given the high number of observational studies, evidence summary was limited to the systematic reviews.

The most recent systematic review by Li et al.[53] focused on laryngeal cancer. The review was judged to be of high quality. The majority of studies addressed SSCs, other studies included laryngeal verrucous carcinoma and laryngeal carcinoma. The prevalence of HPV ranged from 0% to 79% with a summary estimate of 28.0% (95%CI 23.5%-32.9%). For Europe, HPV prevalence was estimated 26.8% (95%CI 20.5-34.2%). HPV DNA was detected more frequently in females, in cancers arising in the glottis region and when PCR-based methods were used.

Dayyani et al.[54] identified 34 articles that reported on HPV prevalence in oropharyngeal cancer published between 1980 and 2008. Overall, a HPV prevalence of 41% (95%CI 38-44%) in oropharyngeal cancer was found. All except one study used PCR to detect HPV DNA.

Termine et al.[55] collected studies published between January 1988 and January 2007 reporting on the prevalence of HPV DNA in head and neck SCC (without further specifications on subsites) or more specifically in oral SCC. Pooled prevalence of HPV in not site-specific HNSCC was 24.1% (95%CI 16.8-31.4%) and 38.1% (95%CI 30.0-46.2%) in oral SCC. PCR-based studies reported a higher prevalence rate than those that were ISH based (34.8%; 95%CI 27.8-41.7% versus 32.9%; 95%CI 19.5-46.3%).

Ragin et al.[56] searched for studies that investigated the influence of HPV on outcome in head and neck cancer. All retrieved studies used a PCR method to determine HPV status. Studies that reported an improved prognosis reported an overall HPV prevalence of 28%. Studies that reported no prognostic effect or a worse OS had a higher HPV prevalence of 42% and 44% respectively.

Kreimer et al.[57] searched for PCR-based studies with a minimum of 40 HNSCC tumours or 20 site specific SCC tumours. Overall, 26% of HNSCC biopsies were HPV positive, with a higher prevalence in oropharyngeal SCC (35.6%; 95%CI 32.6-38.7%) and a lower prevalence in oral cancer (23.5%; 95%CI 21.9-25.1%) and laryngeal SCC (24.0%; 95%CI 21.8-23.6%). Data were also analysed per region. For oropharyngeal cancer, HPV prevalence was significantly higher in North American populations (47%; 95%CI 41.1-53.0%) than in European populations (28.2%; 95%CI 24.2-32.2%).

3.1.3.2 Testing methods for the identification of HPV positivity

Thirteen recent studies compared the following diagnostic methods to evaluate HPV status of head and neck tumours: p16 immunohistochemistry (IHC), polymerase chain reaction (PCR) and in situ hybridization (ISH). Several different methods for RNA and DNA PCR and ISH are used. Also reference standard varies between studies.

Below, the results for sensitivity and specificity of p16 IHC compared to the respective reference standard are summarized. Prognostic value of p16 IHC was also summarized if data were available in the study.

Singhi et al.[58] performed p16 immunohistochemistry and HPV16 DNA in situ hybridisation on 256 HNSCC samples treated in their institution. Tumours that were p16 positive but HPV16 negative were further tested for 12 additional oncogenic HPV types using ISH. Overall, 69% of HNSCCs were HPV16 positive by ISH and 76% of the tumours had high p16 expression as detected by immunohistochemistry. There was a 93% correlation rate between the two tests. All HPV16 positive tumours exhibited strong and diffuse p16 staining. By using a more extended panel of ISH probes, high-risk HPV other than HPV16 was identified in 32% of discordant cases. The overall sensitivity of p16 expression as a surrogate marker of HPV infection was 100% and the overall specificity was 85%.

Schache et al.[59] analysed retrospectively all available samples of oropharyngeal SCC treated at their institution between 1988 and 2009. One hundred and eight samples were tested for p16 IHC, high-risk HPV ISH, HPV16 E6 DNA PCR and HPV16 E6 RNA PCR. RNA PCR was considered the gold standard, where only those positive in duplicate runs were deemed reliably diagnosed HPV16-driven SCC. Compared with this gold standard, p16 IHC had a sensitivity of 94% and a specificity of 82%.

Lewis et al.[60] identified all oropharyngeal SCC patients in the clinical database of Washington university that were treated between 1997 and 2008. P16 IHC, HPV ISH and DNA PCR were performed on 239 samples. Seventy-eight percent of the samples were positive for p16. Of the p16 positive patients, 48 out of 139 were HPV negative by ISH. Of these, an additional 19 were HPV positive by PCR. All three cohorts of p16 positive patients (whether HPV positive by ISH or PCR or HPV negative) had a better overall, disease-free and disease-specific survival than p16 negative, HPV negative SCC. Results were confirmed in multivariate analysis. Compared with the reference standard of combined ISH and PCR, calculated sensitivity was 97% and specificity 62%.

Jordan et al.[61] evaluated 235 tumours from consecutive patients diagnosed with oropharyngeal SCC and available biopsy. Samples were tested for HPV DNA and mRNA expression by PCR, p16 IHC and HPV16 ISH. Seventy percent of tumours stained p16 positive, with a high inter-rater agreement (κ>0.90). Compared with the gold standard of HPV16 E6/7 RNA PCR, p16 ICH had a sensitivity of 96.6% (95%CI 92.2-98.9%) and a specificity of 72.1% (95%CI 61.4-81.2%). Specificity improved to 83.8% (95%CI 73.4-91.3%) when compared with high-risk HPV oncogene expression (not limited to HPV16). Prognostic value of p16 IHC was not reported.

Evans et al.[62] identified 30 surgical pathology specimens from tonsillar tumours in their pathology archives. HPV genotyping using PCR, chromogenic ISH and p16 IHC were performed. Immunohistochemistry was positive in 22 out of 26 (84.6%) samples. Two p16 IHC positive samples were negative by PCR and two p16 IHC negative samples were positive by PCR. Compared with PCR, p16 IHC had a sensitivity of 91% and a specificity of 50%.

Agoston et al. tested biopsy specimens from patients with oropharyngeal cancer undergoing surgery at the Brigham and Women's Hospital, Boston. PCR (E7PCR and AGPCR) detection of HPV, IHC for p16 and in situ hybridization were performed. [63] All samples scoring positive for HPV by any of the methods were strongly positive for p16. Sensitivity of p16 was 100%, whereas specificity was 38%.

Kuo et al.[64] evaluated tissue blocks from 92 patients with primary tonsillar cancer. Seventy-five percent of cases were positive for HPV PCR (types 16, 18, 33, 35, 58, 66 and 69), only 49 out of 92 cases stained positive on p16 IHC. All cases with HPV genotypes 18, 33 and 66 were negative for ISH and p16 IHC. Tonsillar SCC with positive p16 immunostaining of high-risk ISH was associated with a favourable 5-year survival rate. Compared with DNA PCR, calculated sensitivity was 89%, specificity was 84%.

Smeets et al.[65] used tumour specimens from 48 patients with HNSCC who underwent surgical treatment. Detection of high-risk HPV DNA by PCR, detection of HPV16/18 DNA by fluorescence in situ hybridization (FISH), detection of HPV16 E6 mRNA by PCR and p16 immunohistochemical staining were performed. P16 IHC had a sensitivity of 100% and a specificity of 79% compared to the gold standard of tumours positive for both HPV DNA and mRNA PCR.

Klussmann et al.[66] collected data for 34 tonsillar tumours. P16 IHC was compared with HPV DNA PCR. Of the HPV-positive carcinomas, 89% showed diffuse p16 expression. Of the HPV-negative tumours, 94% lacked any p16 immunoreactivity. Using p16 immunoreactivity for stratification, revealed a statistically significant difference for disease-free survival between p16-positive versus p16-negative tumours. Analysis for OS reached neither significant differences for HPV status nor for p16 as

predictor. Compared with DNA PCR, calculated sensitivity of p16 staining was 89%, specificity was 94%.

Bishop et al.[67] collected 282 tumour blocks from patients with HNSCC treated at the Johns Hopkins Hospital. By the E6/E7 mRNA method, HPV was detected in 17% of HNSCCs. P16 expression was strongly associated with the presence of HPV E6/E7 mRNA. Ninety-four percent of HPV positive tumours had a high p16 expression versus nine percent of HPV negative tumours (p<0.0001). Compared with the E6/E7 mRNA method, p16 IHC had a calculated sensitivity of 94% and a specificity of 91%.

Hoffmann et al.[68] retrieved 78 tissue samples of head and neck squamous cell carcinomas. HPV analysis was carried out on fresh frozen tumour. Two PCR-based detection methods for HPV DNA were applied and compared with HPV E6 mRNA PCR and p16 immunohistochemistry. P16 overexpression was present in 45 of the 78 samples. The correlation between p16 staining patterns and HPV DNA status in combination with the E6 expression status was highly significant (p<0.0001). P16 expression did not show differences in OS but sample sizes were small. Compared with HPV DNA status, calculated sensitivity and specificity were 73% and 77% respectively.

Pannone et al.[69] evaluated 86 oral and oropharyngeal tumours. All oral cancer cases that were positive on PCR analysis were also p16 IHC positive with high and diffuse levels of p16 immunostaining, sensitivity was thus 100%. Specificity for oral cancer was 74%. Sensitivity of p16 IHC was also 100% in oropharyngeal cancer. Specificity was higher in oropharyngeal cancer, namely 93.5%.

Shi et al.[70] performed HPV16 E6 mRNA measurement using quantitative real-time PCR, HPV DNA detection using ISH en p16 immunohistochemistry on 111 tumour biopsies of patients with oropharyngeal SCC treated with curative intent, registered in a prospective database. P16 expression was positive in 65% of all samples, concordance with HPV16 ISH or E6 mRNA was 92% and 86% respectively. On univariate analysis p16 overexpression was significantly associated with improved OS (p=0.005) and disease-free survival (p=0.0006). Adjusted for age, stage and treatment however, p16 overexpression was only associated with superior disease-free survival. Sensitivity and specificity could not be calculated from available data.

Results were not pooled given the heterogeneity in patient groups, test methods and reference standard used. Despite this heterogeneity, overall, p16 immunohistochemistry has a consistently high sensitivity but low to moderate specificity to detect HPV in head and neck squamous cell carcinoma. The prognostic value of p16 IHC has been confirmed in several observational studies, in spite of its reduced specificity.

3.1.3.3 Relationship between HPV positivity and outcome in HNSCC

In the systematic review of the CCO, six randomized controlled trials (RCTs) were identified that evaluated tumour HPV status and clinical outcome. Only one study pre-specified the subgroup analysis according to HPV status, the other five studies performed a post hoc analysis. Two studies reported that patients for whom HPV status was available were more likely to have an operable tumour, a better performance status (PS), lower T categories and were less likely to be current smokers. Meta-analysis showed that overall, HPV positive patients have a survival benefit in terms of OS (HR 0.43; 95%CI 0.32-0.58), progression-free survival (HR 0.40; 95%CI 0.28-0.56) and disease-specific survival (HR 0.45; 95%CI 0.27-0.76).

A search for RCTs published since the search date of the Ontario review as performed in the first week of January 2014. No more recent RCTs were found. The six included RCTs were reviewed for the results according to HPV. Furthermore, adjustment for confounding was checked.

Oral cavity cancers were included in only one of the RCTs.[71] Twelve percent of the 794 patients had an oral cavity cancer, other patients had a laryngeal or (oro)pharyngeal cancer. HPV status was determined using p16 immunohistochemistry. P16-positivity was defined as strong, diffuse nuclear and cytoplasmatic staining in more than 10% of carcinoma cells. Fourteen percent of the oral cavity cancers were p16 positive. In the multivariate analysis, low tumour classification, negative lymph nodes, good performance status, positive HPV/p16-status and treatment with six fractions per week were independent prognostic factors for loco-regional failure. The trial compared accelerated radiotherapy (six fractions per week) with a standard schedule (five fractions per week) and showed an improved loco-regional tumour control with accelerated fractionation in both p16-positive as well as in p16-negative tumours.

Three trials included oropharyngeal cancer only.[72-74]

Ang et al.[73] performed a post hoc subgroup analysis in oropharyngeal cancer patients enrolled in a randomized trial comparing accelerated-fractionation radiotherapy with standard-fractionation therapy. HPV DNA was evaluated using in situ hybridization (ISH)-catalyzed signal-amplification method for biotinylated probes (GenPoint, Dako), first for HPV-16 and if negative for 12 additional oncogenic HPV types. HPV status was determined in 74.6% of oropharyngeal cancer patients. HPV DNA was detected in 63.8% of the tested tumours. Hazard ratio of death was 0.90 (95%CI 0.72-1.13) with a similar reduction in the subgroup of patients with HPV-positive cancer (HR 0.89; 95%CI 0.51-1.55) and in the subgroup with HPV-negative cancer (HR 0.91; 95%CI 0.69-1.19). In the multivariate analysis, HPV status, age, race, performance status, tumour stage, nodal stage and number of pack-years of tobacco-smoking were all significant determinants of overall and progression-free survival.

Rischin et al.[72] performed p16 immunohistochemistry, HPV chromogenic in situ hybridization for high risk HPV subtypes 16 and 18 and HPV polymerase chain reaction (PCR) on tissue samples from 206 oropharyngeal cancers for p16 testing, of which 172 were also tested for HPV. The trial compared radiation and cisplatin with or without tirapazamine. No statistically significant difference in OS, failure-free survival or time to locoregional failure between the two treatment arms was seen. The test for interaction between p16 and study arm was negative (p=0.95). On Cox regression analysis of OS, p16 status was the only significant prognostic factor. Assessment of HPV status by ISH demonstrated a large group of HPV-negative, p16-positive patients, representing 57% of the p16-positive patients. Results according to HPV status were not reported.

Posner et al.[74] evaluated HPV status using E6/E7 PCR for 111 of oropharyngeal cancer patients included in the TAX 324 study. The trial compared sequential therapy with docetaxel, cisplatin, and 5-fluorouracil in one group and sequential therapy with cisplatin and 5-fluorouracil in the other group. OS was improved for patients treated with triplet chemotherapy, but this effect was not confirmed in the subgroup analyses for HPV positive and HPV negative patients, probably due to small sample sizes. In univariate analysis, there was a 80% reduction in mortality in HPV-positive tumours compared to HPV-negative tumours. No adjustment for confounders was performed.

Fakhry et al.[75] reported on the ECOG 3299 protocol, investigating chemoradiation for organ preservation. All tumours were evaluated for HPV16 DNA using in situ hybridization. Furthermore, multiplex PCR for 37 HPV types was performed, tumours positive for an HPV type other than 16 were confirmed by in situ hybridization analysis. Additionally, the expression status of p16 was assessed by immunohistochemistry. Both oropharyngeal and laryngeal cancers were tested, but all HPV positive tumour were from oropharyngeal origin. HPV-positive tumours had higher response rates after induction chemotherapy. Tumour HPV status was independently associated with mortality after adjustment for age, tumour stage and ECOG performance status.

Lassen et al.[76] performed $p16^{INK4A}$ expression immunohistochemistry on 156 pharyngeal or supraglottic laryngeal cancers who were randomized into the placebo arm of the DAHANCA 5 protocol. Patients received primary conventional radiotherapy as the sole treatment. Twenty-two percent of the tumours expressed $p16^{INK4A}$. Patients with $p16^{INK4A}$-positive tumours were less likely to suffer from locoregional recurrence than were patients with $p16^{INK4A}$-negative tumours and had a lower disease-specific mortality and overall mortality. Cox proportional hazards analysis showed that low tumour classification, negative neck nodes and p16 expression were independently associated with locoregional failure, death from cancer and overall death.

Conclusions

- The prevalence of HPV in head and neck squamous cell carcinoma varies by geographical region, anatomical subsite and diagnostic technique used.
- HPV status is an independent prognostic factor in HNSCC.
- Overall, p16 immunohistochemistry has a high sensitivity but low to moderate specificity to detect HPV in head and neck squamous cell carcinoma.
- The prognostic value of p16 IHC has been confirmed in several observational studies, in spite of its reduced specificity.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	To date, there is no evidence from randomized trials that HPV status of a head and neck tumour can play a role in treatment decisions. RCTs investigating downscaling treatment strategies are ongoing. Hence, tests for HPV status are currently considered for prognostic information only. For this purpose, the cheapest and most easily available test, p16 immunohistochemistry, can be sufficient as a clear prognostic correlation between p16 results and oncologic outcomes is seen. However, the accuracy of p16 IHC to predict HPV status may be limited. Globally, HPV-related tumours, and thus p16 positive tumours are mainly seen in the oropharyngeal region. For Belgium, an observational study reported a prevalence of HPV positivity in oropharyngeal tumours of 24.8% (95%CI 19.9-30.4%).[77] Belgian data for oral cavity cancer are not available. The review of Kreimer et al.[57] reported a HPV prevalence of 16% (95%CI 13.4-18.8%) in Europe. Small studies (12 to 45 patients) from neighbouring countries (The Netherlands, France) included in the review reported a HPV prevalence in oral cancer between 4.4 and 54.3%. Based on these data, p16 IHC can be considered in oral cavity cancer for prognostic information, especially for tumours of the base of the tongue as differentiating with oropharyngeal tumours may clinically be difficult. The Canadian guidelines recommend to consider IHC staining for p16 positive when the following criteria are met: • Cytoplasmatic and nuclear staining • Staining is moderate to strong and diffuse • Staining is present in at least 50% of tumour cells Although a systematic review[57] found a 24% prevalence of HPV positivity in laryngeal SCC tumours, there is no evidence that it is a prognostic factor in these tumours.
Quality of evidence	No GRADEing performed (prognostic question)
Costs (resource allocation)	P16 immunohistochemistry is considered to be a low cost intervention. No formal cost analysis was performed.
Patients values and preferences	No comments were received from the patient representatives.

Recommendations	Strength of Recommendation	Level of Evidence
• **In patients with oropharyngeal cancer, p16 testing is recommended as it provides prognostic information. However, at present there is no evidence that it alters treatment decisions in these patients.**	Weak	No GRADE
• **Inclusion of p16-positive patients with oropharyngeal cancer in clinical trials should be encouraged.**	Weak	No GRADE
• **Due to insufficient evidence, routine p16 testing is not recommended in patients with hypopharyngeal or laryngeal cancer.**	Weak	No GRADE

3.2 Treatment of primary non-metastatic head and neck squamous cell carcinoma

In the first part of the guideline on head and neck cancer – focusing on oral cavity cancer[9] – a general recommendation was formulated regarding the multidisciplinary treatment, which is also applicable to oropharyngeal, hypopharyngeal and laryngeal cancer (Table 13). The rest of this chapter focuses on specific topics that were discussed again by the GDG for this second part of the guideline.

Table 13 – Multidisciplinary treatment recommendation from oral cavity cancer guideline [9]

Recommendation	Strength of recommendation	Level of Evidence
Head and neck squamous cell carcinoma must be treated on an interdisciplinary basis after upfront discussion of the case in question by a tumour board, comprising the specialist disciplines of … ENT, radiation oncology, medical oncology, pathology, radiology and nuclear medicine. The general practitioner, dentist and paramedical disciplines (e.g. speech therapist, nutritional therapist, and psychosocial worker) are recommended to be present. Continuity of care should be guaranteed through a cooperation between the hospital and the home care team.	Strong	Very low

3.2.1 Surgical treatment

3.2.1.1 Surgery vs. no surgery for early disease

The detailed results of the literature search and assessment can be found in Appendix 2.3.2, Appendix 3.3.1, Appendix 3.3.3, Appendix 4.2, Appendix 5.2 and Appendix 6.2. Early disease comprises stage I and II disease.

Oropharynx

Two systematic reviews were included that compared surgical treatment with nonsurgical treatment options.[78, 79]

The first review compared the clinical effectiveness of various surgical treatment modalities with each other or with other treatment modalities (such as radiotherapy, chemotherapy, immunotherapy/biotherapy with or without surgery) in patients with cancer of the oral cavity or oropharynx.[79] Patients with cancer of the hypopharynx, nasopharynx, larynx or lip were excluded. Only RCTs were searched and the search date was February 2011. The overall risk of bias of the review was judged to be low. The review included seven RCTs with a total of 669 patients, of whom 667 had cancer of the oral cavity. Only two patients with oropharyngeal cancer were included. Therefore, it must be concluded that in this systematic review no RCTs were identified that applied to patients with oropharyngeal cancer.

The other review intended to compare the effect of transoral robotic surgery (TORS) with intensity modulated radiotherapy (IMRT) for early T-stage oropharyngeal cancer.[78] The authors applied an extensive search strategy directed to any comparative study type. The search date was September 2012. The overall risk of bias of this review was considered as low, although no characteristics of included studies were reported. Only non-comparative observational studies were identified. Therefore, we conclude that there were no comparative studies regarding this comparison until the search dates of the review.

In the update of the search no RCTs were identified. One relevant observational study was found.[80] This study involved a multi-institutional study of a prospectively collected database of all new head and neck cancer patients (The Scottish Head and Neck Cancer Audit). Patients with T1-2

oropharyngeal squamous cell carcinoma were selected; 42 received surgical treatment and 30 radiotherapy (RT), chemotherapy or both. The risk of bias of this study was judged to be high. There were more patients with T2 in the nonsurgical group (p=0.54). Five-year OS rates were 60% and 50%, respectively. Local recurrences occurred in 4/42 vs. 4/30 and regional recurrences in 3/42 vs. 2/30. All patients with regional recurrence died of their disease. Disease-free survival (DFS), (local)regional control, quality of life and adverse events were not assessed. The differences between the groups did not appear to be significant.

Conclusions

- In adult patients with T1-2 oropharyngeal cancer a difference in recurrence rate or overall survival of surgery compared to nonsurgical interventions could neither be demonstrated nor refuted (very low level of evidence).
- No comparative studies were identified that addressed disease-free survival, (loco)regional control, quality of life or adverse events of surgery versus nonsurgical interventions in adult patients with T1-2 oropharyngeal cancer.

Hypopharynx

No systematic reviews, RCTs or comparative observational studies were identified. Therefore, no conclusions can be drawn about differences in effectiveness of surgery and nonsurgical interventions in patients with cancer of the hypopharynx.

Conclusions

- No comparative studies were identified that addressed disease-free survival, recurrence rate, (loco)regional control, overall survival, quality of life or adverse events of surgery versus nonsurgical interventions in adult patients with T1-2 hypopharyngeal cancer.

Larynx

Three systematic reviews were included that compared the clinical effectiveness of any type of surgery with non-surgical interventions in patients with early cancer of the glottic larynx.[81-83]

The first review compared radiotherapy, open surgery and endolaryngeal surgery (with or without laser) for early SCC of the glottic larynx (carcinoma in situ or invasive cancers confined to the vocal cords or with supraglottic or subglottic extension without cord fixation or nodal metastases (T1-T2, N0)).[81] The search was directed to RCTs and the search date was October 2009. The overall risk of bias of this review was judged to be low. Only one multicenter RCT was included that compared the effectiveness of open surgery with radiotherapy in 269 patients of whom 234 had glottic laryngeal cancer. Of those, 205 patients were evaluated. The risk of bias of this RCT was considered high. The 5-year DFS rate for T1 tumours was 100% vs. 71.1% (p-value not reported) and for T2 tumours 78.8% vs. 60.1% (one-sided p=0.036). The 5-year OS rates for T1 tumours were 100% vs. 91.7% and for T2 tumours 97.4% vs. 88.8% (both not statistically significant). Recurrence rates, (loco)regional control, quality of life and adverse events were not reported.

The second review compared transoral laser surgery (TLS) with radiotherapy in patients with T1a squamous cell carcinoma of the glottic larynx.[82] The search was directed to any head-to-head comparative study and the search date was February 2010. The overall risk of bias of this review was judged to be low. Only non-randomized comparative studies were identified, of which only one was prospective. The OR for local control of TLS vs. RT was 0.94 (95%CI 0.57 to 1.57 with significant heterogeneity). The OR for local control of TLS vs. RT >65 Gy (7 studies) was 0.63 (95%CI 0.42 to 0.96) and for TLS vs. RT ≤60 Gy (3 studies) 2.66 (95%CI 1.35 to 5.42). The OR for OS of TLS vs. RT (7 studies) was 1.22 (95%CI 0.89 to 1.66; p=0.21). There was significantly more preservation of the larynx after TLS (OR 3.11; 95%CI 1.16 to 8.34). No significant differences were observed for voice handicap index (VHI) and various acoustic parameters, except for fundamental frequency F0 (MD 13.89; 95%CI 9.64 to 18.13). DFS, recurrence rates and adverse events were not assessed.

The third review compared laser surgery with radiotherapy in patients with early glottic carcinoma (T1a and T2 tumours).[83] The search date of the review was September 2012 and the overall risk of bias of this review was considered low, although no characteristics of included studies were reported. Nineteen observational studies were included of which five compared laser surgery with RT. No statistical differences were found between laser surgery and radiotherapy using the COOP/Wonca questionnaire for the assessment of generic quality of life (one study). In the same study the mean voice handicap index (VHI) score[a] was significantly higher (18) in 40 patients of the RT group compared to a mean score of 12 in 52 laser-treated patients (no –p-value reported; 1 study). However, more invasive tumours were included in the RT group. No other outcomes were reported in this review.

No RCTs were identified in a search update. Eight comparative observational studies were included.[84-91]

The study of Luo was a retrospective chart review of patients who underwent either transoral laser microsurgery (TLM; N=18) or RT (N=24) for early glottic cancer (Tis-2, N0, M0).[86] The risk of bias of this study was judged to be high. None of the patients had tumour recurrences. There were no statistically significant differences between the groups with respect to the Voice Handicap Index (VHI-10) (4.5 vs 5.6; p=0.950) or Functional Assessment of Cancer Therapy (FACT-H&N) scale, except for the subscales Social/Family Well Being (23.25 vs 25.38; p=0.028) and Head and neck cancer-specific concerns (31.53 vs 28.61; p=0.041). DFS, (local)regional control, overall survival and adverse events were not assessed.

The study of Milovanovic involved patients with Tis and T1a glottic carcinoma treated with either transoral laser microsurgery (N=72), cordectomy through laryngofissure (N=75) or radiotherapy (N=74).[87] The risk of bias of this study was judged to be high. There were more patients with T0 in the transoral laser microsurgery group. Recurrence rates were 4.2%, 5.3% and 6.7%, respectively. The 5-, 6- and 8-year OS rates were almost identical and there were no statistically significant differences between the groups. This also applies to the occurrence of postoperative complications. With respect to voice quality, the various voice quality scores deteriorated in all groups. There were significant differences between the three treatment groups for fundamental frequency F0 (RT scoring worst), shimmer (transoral laser microsurgery scoring worst) and harmonic-to-noise ratio (cordectomy scoring worst) ($p < 0.01$) six months after treatment, but not for the other values. DFS, (local)regional control, quality of life measures other than voice quality and adverse events were not assessed.

The study of Remmelts compared laser surgery (direct microlaryngoscopy with complete resection of the lesion with CO_2 laser; N=89) with RT (4-MV or 6-MV photon linear accelerator; N=159) in patients with early stage (≤T2) glottic laryngeal cancer.[88] The risk of bias of this study was judged to be high. Tumour stage was higher in the RT group, which contained the majority of stage T1b and T2 patients. There were no statistically significant differences between the groups for local and regional recurrences, (loco)regional control, or 5-year OS, either overall or according to T stage. The 5-year larynx preservation percentage was higher in the laser surgery group (93% vs 83%; p=0.049). The mean score of the physical subscale of the VHI was significantly worse for the laser group than for the RT group (12.4 vs 8.3; p=0.005). Voice deficiency measured by a five-item questionnaire was also higher for the laser group (37% vs 23%; p=0.062). These differences were even stronger in patients with stage T1b. Adverse events were not assessed.

One retrospective observational cohort study using registry data from the Surveillance, Epidemiology, and End Results (SEER) Database involved 8721 patients diagnosed with stage 1 squamous cell carcinoma of the glottic larynx.[89] The aim of the study was to compare the occurrence of cerebrovascular accidents after surgery (N=1 484) or external beam radiation therapy (EBRT; N=7 237). The risk of bias of this study was judged to be low. The two groups were similar with respect to patient and demographic characteristics. However, no data regarding the distribution of T-stage or other prognostic characteristics at baseline were reported. There was no significant difference in OS between the groups (EBRT vs. surgery: HR =1.03, 95%CI 0.91 to 1.13). The HR for fatal stroke of RT vs. surgery, which was adjusted for patient and demographic characteristics, was 1.75 (95%CI 1.04 to 2.96; p=0.04). The adjusted HR for fatal heart disease was

[a] Range from 0 (no impairment) to 120 (maximal impairment)

0.91 (95%CI 0.77 to 1.09). DFS, recurrence rates, (local)regional control, quality of life and other adverse events were not assessed.

The study of Aydil involved a retrospective chart review of patients with T1 glottic SCC treated in a tertiary care centre and who had at least 12 months follow-up.[91] Patients were either treated with surgery (endolaryngeal laser surgery or open partial laryngectomy; N=26) or with RT (N=69). The risk of bias of this study was judged to be high. Baseline characteristics were not presented separately for each group. Three-year local recurrence rates were 10% vs 19.3% (p=0.220) and regional recurrence rates 5.6% vs 0% (p-value not reported). The 3-year OS rates were 92.3% and 92.2%, respectively (p-value not reported) and the 3-year laryngeal preservation percentages were 95.7% and 86.7%, respectively (p=0.220). For all these outcomes the 5-year rates were identical. DFS, (local)regional control and adverse events were not assessed.

Dinapoli and colleagues investigated 143 patients with T1 glottic carcinoma.[84] Seventy-three of them were treated with CO_2 laser surgery (from 1994 onwards) and 70 with RT (from 2001 onwards). The risk of bias of this study was judged to be high. There were no statistically significant differences between the groups with respect to five-year DFS (HR=0.93; 95%CI 0.30 to 2.88; log rank test: p=0.8979) and five-year OS (HR=1.11; 95%CI 0.40 to 3.30; log rank test: p=0.7983). Five-year DFS rates for T1a patients were 86.5% and 97.8% (HR=0.25; 95%CI 0.08 to 1.50) and for T1b 100% vs 53.3% (HR not calculable; p=0.07). RT patients scored significantly better on all domains of the Voice Handicap Index (VHI) (median VHI score 18 vs 4; p<0.0001). Recurrence rates, (local)regional control and adverse events were not assessed.

Jotic and colleagues prospectively investigated voice quality in 69 patients with TisN0 or T1N0 glottic carcinoma who underwent CO_2 laser surgery (N=19), cordectomy through laryngofissure (N=35) or RT (N=15).[85] The risk of bias of this study was judged to be high. Baseline characteristics of the included patients were not specified per intervention group. One month after treatment there were significant differences in favour of the RT group with respect to F0 values, jitter values, normalized noise energy (NNE) and other measures. Six and 12 months after treatment, there were few differences among the groups. DFS, recurrence rates, (local)regional control, OS, quality of life and adverse events were not objects of this study.

The last study involved male patients with T1aN0M0 glottic cancer.[90] Patients were either treated with endoscopic laser surgery (N=67) or with RT (N=39). The risk of bias of this study was judged to be high. The mean age was similar in both treatment groups and because of the strict inclusion criteria (same stage, only males) it was judged that no major imbalances were present. No significant differences between the groups were observed for local recurrences (RR=1.72; 95%CI 0.25 to 11.72) or larynx preservation (RR=0.95; 95%CI 0.88 to 1.02). Three months after treatment there was a significant difference between the groups with better scores for patients treated with laser surgery regarding jitter and shimmer (p=0.007 and 0.004, respectively) and higher fundamental frequency (p=0.000). At 6, 12 and 24 months there were no significant differences between the groups. DFS, (local)regional control, OS and adverse events were not assessed.

Conclusions

- In adult patients with T1-2 glottic cancer a difference in disease-free survival, recurrence rate, (loco)regional control, overall survival general quality of life and adverse effects of surgery compared to nonsurgical interventions could neither be demonstrated nor refuted (very low level of evidence).
- In adult patients with T1-2 glottic cancer conflicting results were found regarding voice quality of surgery compared to nonsurgical interventions (very low level of evidence).
- There is evidence of very low quality that in adult patients with T1-2 glottic cancer larynx preservation was better after surgery than after nonsurgical interventions.
- There is evidence of very low quality that in adult patients with T1-2 glottic cancer the incidence of fatal stroke after 15 years is higher in patients receiving RT compared to surgery.
- No comparative studies were found for patients with supraglottic cancer.

3.2.1.2 Function-sparing surgery versus extensive surgery

In the following paragraphs the available evidence on the effectiveness and safety of function-sparing surgery versus extensive surgery is discussed. Function-sparing surgery is defined as oncologically sound surgery intended to preserve the swallowing function in patients with oropharyngeal cancer, the swallowing function and speech in patients with hypopharyngeal cancer, and the voice in patients with laryngeal cancer.

The detailed results of the literature search and assessment can be found in Appendix 2.3.3, Appendix 3.3.1, Appendix 3.3.4, Appendix 4.3, Appendix 5.3 and Appendix 6.3.

Oropharynx

One systematic review was included that compared the clinical effectiveness of function sparing surgery with extensive surgery in patients with cancer of the oropharynx.[79] Only RCTs were searched and the search date was February 2011. The overall risk of bias of the review was judged to be low. The review included seven RCTs with a total of 669 patients, of whom 667 had cancer of the oral cavity. So, only two patients with oropharyngeal cancer were included. Therefore, it must be concluded that in this systematic review no RCTs were identified that applied to patients with oropharyngeal cancer.

The update of the search did not result in the inclusion of any RCT or relevant observational study. Therefore, no conclusions can be drawn for differences in effectiveness of function sparing surgery and extensive surgery in patients with cancer of the oropharynx.

Conclusions

- No comparative studies were identified that evaluated function-sparing surgery versus extensive surgery in adult patients with T1-2 oropharyngeal cancer.

Hypopharynx

No systematic reviews, RCTs or comparative observational studies were identified. Therefore, no conclusions can be drawn for differences in effectiveness of function sparing surgery and extensive surgery in patients with cancer of the hypopharynx.

Conclusions

- No comparative studies were identified that evaluated function-sparing surgery versus extensive surgery in adult patients with T1-2 hypopharyngeal cancer.

Larynx

One systematic review was included that compared radiotherapy, open surgery and endolaryngeal surgery (with or without laser) for early squamous cell cancer of the glottic larynx (T1-T2, N0).[81] The search was directed to RCTs and the search date was October 2009. The overall risk of bias of this review was judged to be low. No RCTs were identified that compared the effectiveness of open surgery with endolaryngeal surgery.

The update of the search resulted in the inclusion of one relevant observational study.[92] No RCTs were identified.

The only identified observational study compared the effectiveness of larynx preserving techniques transoral CO2 laser microsurgery (N=49) and horizontal laryngectomy (N=29) with total laryngectomy (N=23) in patients with pT1 or pT2/pN0 or cN0/M0 supraglottic carcinomas.[92] The risk of bias of this study was judged to be high. The proportion of patients with T2 was highest in the total laryngectomy group. No statistically significant differences were found for local control in T1 patients between transoral CO2 laser microsurgery and horizontal laryngectomy (p=0.924). The same was found for a comparison of the three types of surgery in T2 cases (p=0.143). Complications were found in 5/49 (10%) vs 7/29 (24%) vs 4/23 (17%). Major complications included postoperative bleeding, aspiration, fistula or granulation tissue formation, and dyspnoea. The incidence of complications was lower for transoral CO2 laser microsurgery compared with horizontal laryngectomy (p=0.09) and total laryngectomy (p=0.20). DFS, recurrence rates, overall survival and quality of life were not assessed.

Conclusions

- In adult patients with T1-2 laryngeal cancer a difference in local control or major complications of function-sparing surgery compared to extensive surgery interventions could neither be demonstrated nor refuted (very low level of evidence).
- No comparative studies were identified that addressed DFS, recurrence rate, overall survival or quality of life of function-sparing surgery versus extensive surgery in adult patients with T1-2 laryngeal cancer.

3.2.1.3 Surgery versus organ / function preservation strategies

Oropharynx

One systematic review was included that compared the clinical effectiveness of any type of surgery with organ or function preservation strategies in patients with cancer of the oropharynx.[79] The review compared various surgical treatment modalities with each other or with other treatment modalities (such as radiotherapy, chemotherapy, immunotherapy/biotherapy with or without surgery) in patients with cancer of the oral cavity or oropharynx. Patients with cancer of the hypopharynx, nasopharynx, larynx or lip were excluded. Only RCTs were searched and the search date was February 2011. The overall risk of bias of the review was judged to be low. The review included seven RCTs with a total of 669 patients, of whom 667 had cancer of the oral cavity. Only two patients with oropharyngeal cancer were included. Therefore, it must be concluded that in this systematic review no RCTs were identified that applied to patients with oropharyngeal cancer.

In the update of the search no RCTs were identified. Five relevant observational studies were found.[93-97]

The study of Boscolo-Rizzo was a cross-sectional evaluation of patients with previously untreated T3-4 oropharyngeal carcinoma who were treated either with surgery plus postoperative radiotherapy (N=26) or concurrent platinum-based chemoradiotherapy (N=31) between January 1998 and April 2006.[93] Risk of bias of this study was judged to be high. There were no statistically significant differences between the groups for disease-free survival (DFS) and OS (OS). Quality of life was assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the EORTC Quality of Life Questionnaire Head and Neck 35 (EORTC QLQ-H&N35). The scores for physical functioning, social functioning and global quality of life (EORTC QLQ-C30) were significantly better in the chemoradiation group. Surgical patients had more symptoms of pain and fatigue (21.8 vs. 8.6 [p=0.027] and 22.9 vs. 12.9 [p=0.047] respectively; EORTC QLQ-C30), swallowing, social eating and social contact (36.2 vs. 19.3 [p=0.042], 26.6 vs. 14.0 [p=0.038] and 14.9 vs. 4.7 [p=0.002] respectively; EORTC QLQ-H&N35). The chemoradiotherapy patients reported significantly more problems with teeth, open mouth, dry mouth and sticky saliva (20.5 vs. 39.8 [p=0.049], 14.1 vs. 32.2 [p=0.036], 38.5 vs. 58.1 [p=0.022] and 35.9 vs. 52.7 [p=0.044] respectively; EORTC QLQ-H&N35). Recurrence rate, (loco)regional control and adverse events were not assessed.

A matched-pair comparison between a prospective case series and a historical cohort was made by Boscolo-Rizzo.[94] Prospective cases with advanced oropharyngeal squamous cell carcinoma (SCC) (Stage III or IV) who were treated with concurrent induction platinum-based chemoradiotherapy (N=47) were matched with historical controls treated with surgery and postoperative radiotherapy (N=47). Risk of bias of this study was judged to be high. There were no statistically significant differences between study groups for recurrence or progression, 3-year actuarial rates of local control (79.5% vs. 79.3%, p=0.813), regional control (87.3% vs. 80.1% without planned neck dissection; 87.3% vs. 86.3% with planned neck dissection; p=0.549) and 3-year OS (HR 0.74; 95%CI 0.36 to 1.54). Numbers of patients with adverse events were presented for the chemoradiotherapy group: 25, 16 and 4 participants experienced grade 2, 3 and 4 toxicities, respectively. DFS and quality of life were not assessed.

In a retrospective chart review by Kuo et al. patients who were treated with primary surgery with or without adjuvant therapy (N=43) were compared to patients treated with radiotherapy/chemoradiotherapy (organ preservation group, N=62).[95] Patients with tonsillar SCC of all stages were included. However, results were presented separately for a subgroup of patients with T3-4 tumours (N=17 primary surgery group, N=23 organ preservation group). Risk of bias of this study was judged to be high. No significant differences were observed between the primary surgery and organ preservation groups in terms of local control (88.2% vs. 69.6%, p=0.256),

regional control (88.2% vs. 82.6%, p=0.978) and OS rates (46.3% vs. 51.5%, p=0.921). The rates of major complications (35.3% vs. 17.4%, p=0.274), long-term dependency on feeding tubes (35.3% vs. 21.7%, p=0.477), and tracheostomy (5.9% vs.18.2%, p=0.363) were also similar. DFS, recurrence rate and quality of life were not assessed.

The study of Mowry involved a cross-sectional evaluation of quality of life in stage II-IV oropharyngeal cancer patients treated 3–73 months before with either surgery followed by radiation (N=18) or primary chemoradiotherapy (N=17).[96] Risk of bias of this study was judged to be high, because of lack of blinding and missing information regarding initial study groups and the treatment they received. The only outcome that was presented was quality of life (University of Washington Quality of Life Questionnaire, version four [UW-QOL v.4]). For all functional domains there was no statistically significant difference between the two groups. The rating of quality of life in the week before the questionnaire was completed, was also similar for both study groups (p=0.47).

The fifth observational study was the study of O'Connell, a retrospective analysis of a prospectively collected population-based database.[97] Included were patients diagnosed with advanced (stage III-IV) oropharyngeal SCC that had received one of four treatment modalities: surgery with adjuvant chemotherapy and radiation (S-CRT, N=94), surgery with adjuvant radiotherapy (S-RT, N=131), concomitant chemoradiotherapy (CRT, N=56) or radiotherapy (RT, N=63). The RT group was excluded from survival analysis as a significant number were treated with palliative intent. Risk of bias of this study was judged to be high. In S-CRT, S-RT and CRT 2-year OS was 87.7%, 69.7% and 51.7%, respectively, and 5-year OS was 63.1%, 47.4% and 39.8%, respectively. Cox regression analysis revealed a significant association between survival and the treatment modality used. When compared to S-CRT, the hazard ratios were 1.974 (95%CI 1.170 to 3.330) for S-RT and 2.785 (95%CI 1.525 to 5.086) for CRT. It is unclear whether these results concern OS or DFS.

Conclusions

- In adult patients with resectable locally-advanced (M0, stage III-IV) oropharyngeal cancer a difference in disease-free survival, recurrence rate, (loco)regional control, overall survival or adverse effects of surgery compared to organ/function sparing strategies could neither be demonstrated nor refuted (very low level of evidence).
- There is evidence of very low quality from one observational study that organ/function sparing strategies compared to surgery result in better quality of life in adult patients with resectable locally-advanced (M0, stage III-IV) oropharyngeal cancer, although another observational study showed no significant difference.

Hypopharynx

No systematic reviews were identified. The search identified two RCTs regarding patients with hypopharyngeal carcinoma.[98-100]

In the first RCT 92 patients with T3-4, N0-3 resectable hypopharyngeal SCC first received three courses of neoadjuvant chemotherapy and were then randomized to surgery (total laryngopharyngectomy) plus postoperative radiotherapy (PORT) or radiotherapy (RT) with or without salvage surgery.[98] The risk of bias of this study was judged to be high for subjective outcomes and unclear for objective outcomes. Patient characteristics were well balanced between groups at baseline and the tumour was located in the pyriform sinus in all cases. Both 5-year local control and 5-year OS were significantly better in the surgery + PORT arm compared to the RT arm alone (5-year local control: 63% vs 39%, p<0.01; 5-year OS: 37% vs 19%, p=0.04). After a mean follow-up of 92 months 33/46 vs. 38/44 patients had died (RR=0.83; 95%CI 0.67 to 1.03). No significant differences between the two groups were found with respect to toxicity of chemotherapy (RR=1.00; 95%CI 0.67 to 1.48). The study did not report on DFS, recurrence rate and quality of life outcomes.

In the second RCT 202 patients with histologically proven SCC of the pyriform sinus or the hypopharyngeal aspect of the aryepiglottic fold were randomly assigned to immediate surgery (total laryngectomy with partial pharyngectomy and neck dissection) with PORT or induction chemotherapy (cisplatin 100 mg/m^2 day 1+ 5-FU 1000 mg/m^2 day 1–5) followed by RT for responders or by conventional surgery with PORT for nonresponders.[99, 100] The risk of bias of this study was judged to be high for subjective outcomes and unclear for objective outcomes. Patient characteristics were well balanced between groups at baseline. Three-year DFS was lower in the immediate-surgery + PORT arm compared to the induction-chemotherapy group (32% [95%CI 17% to 47%] vs. 43% [95%CI 28% to 58%]). For 5-year DFS, no differences were found (27% vs. 25%). Median DFS was 20 vs. 25 months. Both 5-year and 10-year event-free rates were lower in the immediate-surgery + PORT arm compared to the induction-chemotherapy arm (5-year: 26.4% [95%CI 17.5 to 35.4] vs. 31.7% [95%CI 22.5 to 40.9]; 10-year: 8.5% [95%CI 2.0 to 15.0] vs. 10.8% [95%CI 3.8 to 17.9]), as were the 3-year and 5-year OS rates (3-year OS: 43% [95%CI 27% to 59%] vs. 57% [95%CI 42% to 72%]; 5-year OS: 32.6% [95%CI 23.0 to 42.1] vs. 38.0% [95%CI 28.4 to 47.6]). The 10-year survival rates were 13.8% (95%CI 6.1 to 21.6) and 13.1% (95%CI 5.6 to 20.6), respectively. Median OS was 25 vs. 44 months. At 3 year the "observed dead hazard ratio" of the induction-chemotherapy arm vs. surgery was 0.86 (corrected 95%CI 0.50 to 1.48). No serious drug-related adverse events were found. The study did not report on recurrence rate, (loco)regional control and quality of life outcomes.

Conclusions

- In adult patients with resectable locally-advanced (M0, stage III-IV) hypopharyngeal cancer a difference in 3-, 5- or 10-year disease-free survival of surgery compared to organ/function sparing strategies could neither be demonstrated nor refuted (low level of evidence).
- There is evidence of low quality that surgery compared to organ/function sparing strategies results in better local control in adult patients with resectable locally-advanced (M0, stage III-IV) hypopharyngeal cancer.
- There is conflicting evidence of very low quality regarding the effect on overall survival of surgery compared to organ/function sparing strategies in adult patients with resectable locally-advanced (M0, stage III-IV) hypopharyngeal cancer.
- In adult patients with resectable locally-advanced (M0, stage III-IV) hypopharyngeal cancer a difference in adverse effects due to chemotherapy or surgery compared to organ/function sparing strategies could neither be demonstrated nor refuted (low level of evidence).
- No comparative studies were identified that addressed the effect on recurrence or quality of life of surgery compared to organ/function sparing strategies in adult patients with resectable locally-advanced (M0, stage III-IV) hypopharyngeal cancer.

Larynx

One systematic review was included that compared any treatment modality for laryngeal cancer with organ or function preservation strategies in patients with T4a laryngeal cancer.[101] The search was directed to any study design and the search date was April 2013. The overall risk of bias of this review was judged to be low, although no information of quality assessment of included studies was provided. However, only retrospective observational studies were identified (which will lead to low quality according to GRADE). For this chapter, only the surgical procedures neck dissection, supracricoid laryngectomy, salvage surgery, primary laryngectomy and transoral laser microsurgery will be considered. The review included seven relevant studies. Meta-analysis was not performed due to heterogeneity. Three studies compared primary laryngectomy (+ radiotherapy/chemotherapy if needed) with chemoradiation therapy. OS percentages at 2 years were 100% vs. 60% and 90% vs. <30% in two studies. In one study the OS was 55% vs. 25% after 5 years. Four studies compared primary laryngectomy (+ radiotherapy/chemotherapy if needed) with radiotherapy. OS percentages were all in favour of primary laryngectomy at 1 year (60% vs. 54.6%), 2 years (60% vs. 12% and 30% vs. 21.2%) and 5 years (49% vs. 5%, 10% vs. 9.1%, 41% vs. 11% and 58% vs. 32%). DFS, recurrence, (loco)regional control, quality of life and adverse effects were not addressed.

A search for RCTs resulted in two relevant studies regarding the treatment of patients with laryngeal carcinoma.[102-104]

In the first RCT 72 patients with resectable advanced supraglottic cancers were randomized to radical surgery (total laryngectomy, near-total laryngectomy or laryngo-pharyngectomy with or without modified nodal dissection) followed by PORT or radical radiation therapy (RRT) followed by salvage surgery.[102] The risk of bias of this study was judged to be high. Baseline patient characteristics were well balanced, although there were more T4 stages in the radical surgery + PORT group (20% vs. 7%). Both 5-year DFS and recurrence rate were significantly better in the radical surgery + PORT group compared to the RRT salvage surgery group (5-year DFS: 70% vs. 50%, p=0.04; recurrence rate: RR 0.83; 95%CI 0.17 to 0.88). No significant differences were found for loco-regional control (RR 1.0; 95%CI 0.70 to 1.43) and 5-year OS (73% vs. 77%, p=0.79). Eight patients of the radical surgery + PORT group had immediate post-operative complications compared to none in the RRT salvage surgery group. The study did not report on quality of life outcomes.

In the second RCT 332 previously untreated patients with stage III or IV SCC of the larynx were randomized to surgery and radiation therapy or three cycles of chemotherapy (cisplatin and fluorouracil) (CT) and radiation therapy.[103, 104] The risk of bias of this study was judged to be high. Patient characteristics were well balanced between groups at baseline. No significant differences between the groups were found for DFS (p=0.1195), recurrence rate (RR 0.83; 95%CI 0.57 to 1.14) or 2-year OS (68% [95%CI 60 to 75%] vs. 68% [95%CI 60 to 76%]; p=0.9846). For quality of life patients in the CT + RT group had significantly better scores on the SF-36 mental health domain than the surgery + RT group (76.0 vs. 63.0, p<.05) and better pain scores (81.3 vs. 64.3) on the University of Michigan Head and Neck Quality of Life (HNQOL) instrument. More patients in the surgery + RT group were depressed compared to the CT + RT group (28% vs. 15%). The study did not report on (loco)regional control and adverse events.

For most outcomes meta-analysis was not possible, except for recurrence: RR = 0.72 (95%CI 0.53 to 1.00) in favour of surgery.

Conclusions

- There is evidence of low quality that surgery compared to organ/function sparing strategies results in better DFS and lower recurrence rates in adult patients with resectable locally-advanced (M0, stage III-IV) laryngeal cancer.
- In adult patients with resectable locally-advanced (M0, stage III-IV) laryngeal cancer a difference in local control of surgery compared to organ/function sparing strategies could neither be demonstrated nor refuted (very low level of evidence).
- In adult patients with resectable locally-advanced (M0, stage III-IV) laryngeal cancer a difference in overall survival of surgery compared to organ/function sparing strategies could neither be demonstrated nor refuted (low level of evidence).
- There is evidence of low quality that organ/function sparing strategies compared to surgery result in better quality of life in adult patients with resectable locally-advanced (M0, stage III-IV) laryngeal cancer.
- No comparative studies were identified that addressed adverse effects surgery compared to organ/function sparing strategies in adult patients with resectable locally-advanced (M0, stage III-IV) laryngeal cancer.
- There is evidence of very low quality that surgery compared to organ/function sparing strategies results in better overall survival in adult patients with resectable locally-advanced stage T4a laryngeal cancer.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	• For early disease, surgery was not found to be superior to nonsurgical treatment, except for T1-2 laryngeal cancer, where final larynx preservation was better after surgery compared to nonsurgical interventions. Also for T1-2 laryngeal cancer, extensive surgery was not found to be superior to function-sparing surgery. Therefore, total laryngectomy is not recommended in patients with T1N0 laryngeal cancer. • For advanced disease, radical surgery was not clearly found to be superior to organ/function sparing strategies, although surgery resulted in a better local control than organ/function sparing strategies in patients with locally-advanced hypopharyngeal cancer (but no survival benefit, and worse function), and better DFS and lower recurrence rates in patients with locally-advanced laryngeal cancer (mix of T-stages included in RCTs). Specifically for T4a laryngeal cancer, a systematic review of observational studies found a better overall survival with surgery compared with organ/function sparing strategies.
Quality of evidence	Evidence is mainly of low to very low quality. Most of these studies were conducted 10-30 years ago: in the meantime, surgical and radiotherapeutic techniques are much improved.
Costs (resource allocation)	No cost issues were considered.
Patients values and preferences	The Liga voor Gelaryngectomeerden developed a care plan specifically for patients undergoing a total laryngectomy. Specific attention is given to: - the need for complete and understandable information; - the involvement of a speech therapist throughout the entire trajectory; - the availability of peer support.
Comments	• When two modalities have comparable treatment results, morbidity will play a crucial role in the choice of treatment. • If there is a high probability that adjuvant (chemo)radiotherapy will be needed after surgery or if a R1 resection cannot be achieved, primary surgery should be questioned.

Recommendations	Strength of Recommendation	Level of Evidence
• **The decision about treatment for early oropharyngeal, hypopharyngeal or laryngeal cancer should not only be based on efficacy, but also on the patient's general and functional status, age, morbidity, and on the tumour location.**	Weak	Very low
• **In patients with early (stage I or II) oropharyngeal, hypopharyngeal or laryngeal cancer a single-modality function-sparing approach (e.g. surgery, external radiotherapy) should be preferred.**	Weak	Very low
• **In patients with advanced oropharyngeal, hypopharyngeal or laryngeal cancer, organ and function-sparing procedures are recommended. However, in patients with T4a laryngeal cancer, total laryngectomy should be considered.**	Weak	Very low

3.2.2 Radiotherapy

3.2.2.1 Primary chemoradiotherapy versus radiotherapy for non-resectable non-metastatic HNSCC

In the first part of the guideline on head and neck cancer – focusing on oral cavity cancer [9] – a search was done for studies evaluating the effectiveness and safety of primary chemoradiotherapy versus radiotherapy in patients with non-resectable non-metastatic head and neck cancer. The results of that search were used for the second part too, and are described below. Methodological information can be found in the appendix of the first part.

Because no systematic reviews (published since 2008) were found that compared primary CRT with RT alone in patients with non-resectable (T4b) M0 HNSCC (or that allowed separating out the results for these patients), only primary studies were included. Two RCTs were included that fully fulfilled the research question.[105, 106] Another five RCTs which also involved patients with a stage lower than T4b were additionally included.[107-111]

The first RCT[105] compared chemotherapy (CP-5FU, three courses) and concurrent twice-daily RT with RT alone in 171 untreated, strictly unresectable squamous cell carcinoma of the oropharynx or hypopharynx. The risk of bias of this study was judged to be high for subjective outcomes and low for objective outcomes. Patient characteristics were evenly distributed between the two groups at baseline, as were patients within each investigating centre. However, small (non-significant) differences between groups for performance status at baseline were found. Significant differences in favour of primary CRT were found for OS (Kaplan Meier: 37.8% vs. 20.1%, p=0.038), disease-free survival (Kaplan Meier: 48.2% vs. 25.2%, p=0.002) and the rate of locoregional control (extrapolated by Kaplan-Meier method: 58.87% vs. 27.5%, p=0.0003). With regards to acute Grade 3-4 toxicities, only a significant difference was found for neutropenia in favour of RT alone (RR=13.67; 95%CI 3.36 to 55.59). No significant differences between groups for the remaining acute and late toxicities were found. Locoregional and distant tumour failure or uncontrolled disease was significantly lower in the CRT group compared to the RT group (RR=0.81; 95%CI 0.68 to 0.96). Quality of life outcomes were not assessed.

The second RCT[107] compared concurrent fluorouracil (FU) and mitomycin (MMC) chemotherapy and hyperfractionated accelerated radiation therapy (C-HART; 70.6 Gy) to hyperfractionated accelerated radiation therapy alone (HART; 77.6 Gy) in 384 stage III (6%) and IV (94%) head and neck cancer patients. The risk of bias of this study was judged to be high for subjective outcomes and unclear for objective outcomes. There were no statistically significant differences in patient baseline characteristics between both treatment groups. A significant difference in favour of primary CRT was found for OS at 2, 3 and 5 years (48.0 vs. 38.2, 37.5 vs. 28.6, 28.6 vs. 23.6, respectively, p=0.023). Also local control at 2, 3 and 5 years differed significantly between the two groups (57.7 vs. 42.4, 51.8 vs. 39.2, 49.9 vs. 37.4, respectively, p=0.001). With regard to acute toxicities, significant differences were found for erythema (RR=0.69 95%CI; 0.52 to 0.90) and moist desquamation (RR=0.65; 95%CI 0.49 to 0.86), both in favour of CRT. For late toxicities, no significant differences between the two groups were found. Disease-free survival, quality of life and recurrence rate were not assessed.

The third RCT[108] compared RT in combination with gemcitabine with RT alone in 80 patients with stage III or IV unresectable locally advanced and previously untreated HNSCC. Radiotherapy was administered once daily 5 days a week as a single 2 Gy fraction to a total dose of 64 Gy. Gemcitabine was administered intravenously over 30 minutes once weekly, 1 to 2 hours before radiation, during six consecutive weeks at a dose of 100 mg/m^2. The risk of bias of this study was judged to be high for subjective outcomes and unclear for objective outcomes. Performance status, tumour and nodal stages, and histology were balanced between the two study groups at baseline. Disease-free survival at three years was higher in the CRT group compared to the RT group: 63.3% vs. 20%. The authors stated that local control was good and none of the 19 patients with complete response developed relapse in the CRT group. Seven of the 13 patients with complete response in the radiation only group relapsed (three at primary site, three at nodal and one distant). No severe haematological toxicity was seen. However, for haemoglobin level significant differences between the two groups were found (Grade I toxicity: 80% vs. 47.5%, Grade II toxicity: 20% vs. 7.5%, p<0.05). Skin reactions were more severe in the chemoradiotherapy group (level 5: 50% vs. 7.5%; level 6: 7.5% vs. 2.5%; p<0.05). Significantly more patients in the chemoradiotherapy group experienced Grade 5 oral mucositis (67.5% vs.17.5% in the radiotherapy group, p<0.05). Two patients in the chemoradiotherapy group developed Grade 6 mucosal reactions. Only mild nausea and vomiting were seen.

There was significantly more weight loss in the CRT group (p<0.05) compared to the RT group during the second half of treatment. OS, quality of life and recurrence rate were not assessed.

The fourth RCT[110] compared nimotuzumab in combination with RT to placebo and RT in 106 patients with stage III or IV advanced HNSCC. The risk of bias of this study was judged to be unclear for both subjective and objective outcomes. Significant differences were found for global health status/quality of life questionnaire at baseline. Demographic and tumour characteristics at baseline were similar. For OS, no significant differences between the groups were found (RR=1.70; 95%CI 0.61 to 4.73). Differences in quality of life between the two groups were only found in relation to the general pain evaluation at month six. Patients treated with RT suffered less pain than patients treated with nimotuzumab and RT. The remaining parameters of the quality of life questionnaires did not show significant differences between the treatment groups at 3, 6, 9 and 12 months. No significant differences between the two groups were found with regards to overall adverse events (RR=1.22; 95%CI 0.91 to 1.63). Disease-free survival, local control and recurrence rate were not assessed.

The fifth RCT[106] compared RT combined with daily low-dose carboplatin to RT alone in 164 patients with biopsy-proven locally advanced and unresectable stage III or IV non-metastatic HNSCC. The risk of bias of this study was judged to be high for subjective outcomes and unclear for objective outcomes. There were no differences between the two treatment arms regarding age, sex, primary tumour site and staging at baseline. A significant difference was found in OS rates at 3, 5 and 10 years in favour of the CRT group (28.9%, 9% and 5.5% vs. 11.1%, 6.9% and 6.9%; p=0.02). The 3, 5 and 10-year disease-free survival rates of the CRT group (16%, 6.8% and 6.8%) were not significantly different compared to the RT group (9%, 5.5% and 5.5%) (p=0.09). In addition, the 3, 5 and 10-year locoregional recurrence-free survival rates were not significantly different between the two groups (21.7%, 15.1% and 15.1% vs. 15%, 10.7% and 10.7%; p=0.11). No significant differences were found for Grade 3-4 acute toxicities (haemoglobin: RR=6.74 [95%CI 0.35 to 128.38]; leukocytes: RR= 14.44 [95%CI 0.84 to 248.66]; thrombocytes: RR=3.00 [95%CI 0.12 to 72.56]; mucositis: RR=1.07 [95%CI 0.46 to 2.49]). The incidence of late toxicities did not differ significantly between the two groups. Quality of life outcomes and recurrence rate were not assessed.

The sixth RCT[111] compared RT combined with two cycles 5-fluorouracil and carboplatin on days 1–5 and 29–33 with RT alone in 264 patients with locoregionally advanced (stage III or IV) unresectable HNSCC. The two treatment groups were well balanced for tumour site, T- and N-stage, grading and pre-treatment haemoglobin levels at baseline. The risk of bias of this study was judged to be high for both subjective and objective outcomes. Patients in the CRT group had a statistically significant better 5-year OS compared with patients treated with RT alone (25.6% vs. 15.8%, p=0.016). In patients with an oropharyngeal tumour OS was significantly better for CRT compared to RT alone (26.1% vs. 13.0%, p=0.008). In patients with a hypopharyngeal tumour there was no difference in OS between treatment with CRT and treatment with RT alone (p=0.72). Five-year rates of survival with local control was significantly better in the CRT group than in RT group (22.7% vs. 12.6%, p=0.01). In a previously published paper of this study, Grade 3 and 4 acute toxicities were reported. A significant difference between the groups was found for Grade 3-4 mucositis (68% vs. 53%, p=0.01). Differences between the study groups for dermatitis, white blood cell count, platelets and anaemia were 30% vs. 28%, 18% vs. 0%, 5% vs. 0%, 0% vs. 1%, respectively. A difference in vomiting under therapy was seen with a higher percentage of patients in the CRT group compared to the RT group (8.2% vs. 1.6%, p=0.02). There were no significant differences between the groups regarding late toxicities. Disease-free survival, quality of life and recurrence rate were not assessed.

The seventh RCT[109] compared the addition of weekly cisplatin to daily RT with RT alone in 371 patients with stage III or IV unresectable squamous cell head-and-neck carcinoma. The risk of bias of this study was judged to be high for both subjective and objective outcomes. There were some imbalances between groups at baseline: a higher number of patients with age > 65, weight loss ≥ 10% in the previous 6 months, > 40 pack-years exposure to smoking, well or moderate cell differentiation, and non-nasopharyngeal primary tumours were found in the CRT group. No significant differences between the two groups were found for median survival in months (11.8 vs. 13.3, p=0.81). A multivariate analysis also did not demonstrate a significant treatment effect (p=0.60). With regards to acute adverse events, significant differences were found for the frequency and severity of nausea/vomiting (p<0.001) and of neurologic (p=0.002), renal (p<0.001), and hematologic toxicities (p<0.001) which were higher in

the CRT group. No significant differences for the remaining acute toxicities were found. For late toxicities, significant differences were found for oesophagus (9% vs. 3%, p=0.03) and larynx toxicities (11% vs. 4%, p=0.05).When each patient was classified by the worst grade of any type of toxicity, no significant differences between the treatment groups were found (p=0.21). Disease-free survival, quality of life, local control and recurrence rate were not assessed.

For the outcome acute Grade 3-4 toxicities results could be pooled for mucositis (pooled RR=1.05; 95%CI 0.95 to 1.16; Figure 87, Appendix 6.5 of first part), dermatitis (pooled RR=1.20; 95%CI 0.90 to 1.62; Figure 88, Appendix 6.5 of first part), anaemia (pooled RR=2.06; 95%CI 0.37 to 11.62; Figure 89, Appendix 6.5), leukopenia (pooled RR=29.62; 95%CI 4.15 to 211.63; Figure 90, Appendix 6.5 of first part) and thrombocytopenia (pooled RR=8.63; 95%CI 1.11 to 67.05; Figure 91, Appendix 6.5 of first part).

Conclusions

Primary CRT vs. primary RT

- There is evidence of low to very low quality that in adult patients with T4b M0 HNSCC overall survival is better with primary chemoradiotherapy compared to primary radiotherapy alone at 2 years (low) and at 3 and 5 years (very low), respectively.
- There is evidence of moderate quality that in adult patients with T4b M0 HNSCC primary chemoradiotherapy results in better disease-free survival at 2 years compared to primary radiotherapy. There is evidence of low quality that chemoradiotherapy results in better disease-free survival compared to primary radiotherapy at 3, 5 and 10 years.
- There is evidence of low to very low quality that in adult patients with T4b M0 HNSCC primary chemoradiotherapy results in better local control compared to radiotherapy alone at 2 and 10 years and at 3 and 5 years, respectively.
- In adult patients with T4b M0 HNSCC there is conflicting evidence of very low quality about the frequency and severity of acute toxicities. For Grade 3-4 acute toxicities, there is evidence of very low quality that primary chemoradiotherapy leads to less erythema and moist desquamation compared to primary radiotherapy.
- There is evidence of very low quality that in adult patients with T4b M0 HNSCC primary chemoradiotherapy results in more late toxicity of oesophagus and larynx compared to primary radiotherapy.
- There is evidence of very low quality that in adult patients with T4b M0 HNSCC primary chemoradiotherapy reduces locoregional and distant tumour failure, or uncontrolled disease compared to primary radiotherapy.
- None of the included studies, in which primary chemoradiotherapy was compared to primary radiotherapy in adult patients with T4b M0 HNSCC, studied quality of life.

Primary treatment with EGFR inhibitors combined with radiotherapy versus primary radiotherapy alone

- The available evidence of very low quality does not allow to draw conclusions about the effect of primary treatment with EGFR inhibitors combined with radiotherapy compared to primary radiotherapy alone on overall survival, quality of life and adverse events in adult patients with T4b M0 HNSCC.
- None of the included studies, in which primary treatment with combination of EGFR-inhibitors and radiotherapy was compared to primary radiotherapy, studied disease-free survival, local control and recurrence.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	• In patients with non-resectable M0 HNSCC primary chemoradiotherapy appears to be associated with a better overall and disease-free survival and local control than primary radiotherapy alone. The effect on adverse events is less straightforward. • No clear benefit was found for the combination of radiotherapy with EGFR-inhibitors.
Quality of evidence	Several RCTs were found. The evidence was generally of low to very low quality, although the effect on disease-free survival was based on evidence of moderate quality.
Costs (resource allocation)	No cost issues were considered.
Patients values and preferences	No comments were received from the patient representatives.
Comments	The combination of radiotherapy and cetuximab is an alternative for those patients who do not tolerate platinum-based chemoradiotherapy.

3.2.2.2 Primary radiotherapy with altered fractionation

The detailed results of the literature search and assessment can be found in Appendix 2.3.7, Appendix 3.3.8, Appendix 4.7, Appendix 5.7 and Appendix 6.7.

Four systematic reviews were identified evaluating the effectiveness of altered fractionation in patients with head and neck cancer.[112-115] The two Cochrane reviews are the most complete reviews and were both of good quality.[114, 115] Baujat et al. searched for RCTs comparing conventional radiotherapy with hyperfractionated or accelerated radiotherapy, or both, in patients with non-metastatic HNSCC and grouped trials into three pre-specified treatment categories: hyperfractionated, accelerated and accelerated with total dose reduction. Updated individual patient data (IPD) were used for meta-analysis. Glenny et al. only included RCTs with at least 50% of participants with primary tumours of the oral cavity or oropharynx. Where possible, the IPD of Bourhis et al. were used for meta-analysis. From these two Cochrane reviews, 18 relevant RCTs were available that compared primary (mono-)radiotherapy using altered fractionation with conventional fractionation in patients with previously untreated head and neck cancer.[116-133]

An update of the literature identified six additional RCTs.[134-139] Furthermore, two trials were updated with more recent data.[140, 141]

Hyperfractionation

Five RCTs (N=1524) compared hyperfractionation with conventional fractionation (Table 14).[116, 117, 120, 121, 139] Two studies only included patients with oropharyngeal cancer,[116, 117] while one study only included patients with T2 vocal cord cancer.[139] Fu et al. included a mixed population (60% oropharyngeal cancer), but stratified the treatment allocation by tumour site. Cummings et al. also included a mixed population (40% oropharyngeal cancer), but without stratified randomization.

Table 14 – Overview of included RCTs on hyperfractionation

Study ID	N	Hyperfractionation	Conventional fractionation	Comment
Cummings 2007 (PMHToronto)	331	58 Gy/40 fractions/4 weeks	51 Gy/20 fractions/4 weeks	
Fu 2000, Beitler 2014 (RTOG 9003)	531	81.6 Gy/68 fractions/7 weeks	70 Gy/35 fractions/7 weeks	
Horiot 1992 (EORTC 22791)	325	80.5 Gy/70 fractions/7 weeks	70 Gy/35 fractions/7 weeks	100% oropharynx
Pinto 1991 (RIO)	98	70.4 Gy/64 fractions/6.5 weeks	66 Gy/33 fractions/6.5 weeks	99% oropharynx
Trotti 2014 (RTOG 9512)	239	79.2 Gy/66 fractions/6.5 weeks	70 Gy/35 fractions/7 weeks	100% larynx

Overall survival

All five RCTs reported the effect of hyperfractionation on OS, of which four studies (N=1285) could be pooled.[116, 117, 120, 121] A significant effect on OS was found in favour of hyperfractionation (HR = 0.78; 95%CI 0.69 to 0.89). The fifth RCT (N=239) also found a survival benefit with hyperfractionation at 5 years, although the effect was not statistically significant (HR = 0.82; 72% vs. 63%; p=0.29).[139]

Locoregional control

All five RCTs reported the effect of hyperfractionation on locoregional control, of which four studies (N=1285) could be pooled.[116, 117, 120, 121] A significant effect on locoregional control was found in favour of hyperfractionation (HR = 0.77; 95%CI 0.66 to 0.89). The fifth RCT (N=239) also found a benefit with hyperfractionation at 5 years, although the effect was not statistically significant (HR = 0.77; 73% vs. 67%; p=0.26).[139]

Disease-free survival

Three RCTs reported the effect of hyperfractionation on disease-free survival, of which two studies (N=862) could be pooled.[120, 121] A borderline significant effect on disease-free survival was found in favour of hyperfractionation (HR = 0.86; 95%CI 0.73 to 1.00). The third RCT (N=239) also found a benefit with hyperfractionation at 5 years, although the effect was not statistically significant (HR = 0.79; 49% vs. 40%; p=0.13).[139]

Recurrence rate

One RCT (N=331) reported the effect of hyperfractionation on recurrence.[120] The 5-year probability of local relapse was lower in the hyperfractionation group, although the effect was not statistically significant (41% vs. 49%; p=0.082). No significant difference was found in 5-year regional lymph node relapse (33% vs. 29%; p=0.78) and 5-year distant relapse (11% vs. 8%; HR = 1.92; 95%CI 0.64-2.61).

Quality of life

No RCT reported the effect of hyperfractionation on quality of life.

Acute toxicity

Table 15 provides an overview of the pooled effects of hyperfractionation on acute toxicity. Hyperfractionation was associated with significantly more acute grade 3-4 mucositis (RR = 1.46; 95%CI 1.29 to 1.65) and skin reactions (RR = 1.53; 95%CI 1.05 to 2.24) than conventional fractionation. No significant effects were found for other acute toxicities.

Table 15 – Pooled effect estimates of hyperfractionation on acute toxicity

Acute toxicity	N studies	N patients	Pooled effect
Mucositis grade 3-4	5	1 498	RR = 1.46; 95%CI 1.29 to 1.65
Skin grade 3-4	4	1 178	RR = 1.53; 95%CI 1.05 to 2.24
Larynx / oedema grade 3-4	3	1 080	RR = 1.31; 95%CI 0.91 to 1.88
Salivary glands grade 3-4	2	770	RR = 2.98; 95%CI 0.12 to 72.31
Pharynx / oesophagus, grade 3-4	3	1 080	RR = 1.46; 95%CI 0.76 to 2.82
Upper gastrointestinal, grade 3-4	2	770	RR = 1.01; 95%CI 0.28 to 3.73

Late toxicity

Table 16 provides an overview of the pooled effects of hyperfractionation on late toxicity. For none of the reported late toxicities a significant effect of hyperfractionation was found.

Table 16 – Pooled effect estimates of hyperfractionation on late toxicity

Late toxicity	N studies	N patients	Pooled effect
Mucositis grade 3-4	4	1 328	RR = 1.39; 95%CI 0.84 to 2.31
Skin grade 3-4	3	1 075	RR = 0.85; 95%CI 0.41 to 1.78
Larynx grade 3-4	4	1 328	RR = 1.20; 95%CI 0.79 to 1.82
Salivary glands grade 3-4	3	1 075	RR = 0.85; 95%CI 0.29 to 2.50
Pharynx / oesophagus, grade 3-4	2	744	RR = 1.21; 95%CI 0.76 to 1.93

Conclusions

- There is evidence of moderate quality that hyperfractionated radiotherapy improves overall survival and locoregional control compared with conventional radiotherapy in patients with head and neck cancer.
- There is evidence of low quality that hyperfractionated radiotherapy improves disease-free survival compared with conventional radiotherapy in patients with head and neck cancer.
- There is evidence of moderate quality that hyperfractionated radiotherapy is associated with more acute grade 3-4 mucositis than conventional radiotherapy in patients with head and neck cancer.
- There is evidence of low quality that hyperfractionated radiotherapy is associated with more acute grade 3-4 toxicity of the skin than conventional radiotherapy in patients with head and neck cancer.
- The available evidence of very low quality does not allow to draw conclusions about the effect of hyperfractionated radiotherapy on acute grade 3-4 toxicity of the salivary glands, pharynx / oesophagus and upper gastrointestinal tract compared with conventional radiotherapy in patients with head and neck cancer.
- The available evidence of low to very low quality does not allow to draw conclusions about the effect of hyperfractionated radiotherapy on late grade 3-4 toxicity compared with conventional radiotherapy in patients with head and neck cancer.

Accelerated fractionation without total dose reduction

Twelve RCTs (N=6094) with thirteen comparisons compared accelerated fractionation without total dose reduction with conventional fractionation [Fu 2000, Ghoshal 2008, Hliniak 2002, Horiot 1997, Jackson 1997, Olmi 2003, Overgaard 2003, Skladowski 2000, Skladowski 2006, Moon 2014, Overgaard 2013, Zackrisson 2011, Yamazaki 2006] (Table 17).[121, 127-136, 138] Most RCTs included a mixed population. Hliniak et al. only included patients with T1-3 glottic or supraglottic cancer,[129] Moon et al. patients with T1-2 glottic cancer,[138] and Yamazaki et al. patients with T1 glottic cancer.[134] Olmi et al. only included patients with oropharyngeal cancer.[130] Three studies used a split-course regimen.[121, 127, 130]

Table 17 – Overview of included RCTs on accelerated fractionation without total dose reduction

Study ID	N	Accelerated fractionation	Conventional fractionation	Comment
Fu 2000 (RTOG 9003): split	542	67.2 Gy/42 fractions/6 weeks	70 Gy/35 fractions/7 weeks	Split-course
Fu 2000 (RTOG 9003): boost	536	72 Gy/42 fractions/6 weeks	70 Gy/35 fractions/7 weeks	
Ghoshal 2008	285	67.5 Gy/40 fractions/5 weeks	66 Gy/33 fractions/6.5 weeks	
Hliniak 2002 (KBN PO 79)	395	66 Gy/33 fractions/5.5 weeks	66 Gy/33 fractions/6.5 weeks	100% larynx, T1-3
Horiot 1997 (EORTC 22851)	500	72 Gy/45 fractions/5 weeks	70 Gy/35 fractions/7 weeks	Split-course
Jackson 1997 (BCCA 9113)	82	66 Gy/33 fractions/3.5 weeks	66 Gy/33 fractions/6.5 weeks	
Moon 2014 (KROG-0201)	156	63-67.5 Gy/28-30 fractions/5.5-6 weeks	66-70 Gy/33-35 fractions/6.5-7 weeks	100% glottis, T1-2
Olmi 2003, Fallai 2006 (ORO 93-01)	192	64-67.2 Gy/40-42 fractions/4 weeks	66-70 Gy/33-35 fractions/6.5-7 weeks	100% oropharynx; split-course
Overgaard 2003 (DAHANCA)	1 476	66-68 Gy/33-34 fractions/5.5 weeks	66-68 Gy/33-34 fractions/6.5 weeks	
Overgaard 2010 (IAEA-ACC)	900	66-70 Gy/33-35 fractions/5.5 weeks	66-70 Gy/33-35 fractions/6.5-7 weeks	
Skladowski 2000 & 2006 (CAIR)	100	66-70 Gy/33-36 fractions/4.5-5 weeks	66-70 Gy/33-36 fractions/6.5-7 weeks	
Yamazaki 2006	180	56.25-63 Gy/30-33 fractions/6-6.6 weeks	60-66 Gy/25-28 fractions/5-5.6 weeks	100% glottis, T1
Zackrisson 2011 (ARTSCAN)	750	68 Gy/22 fractions/4.5 weeks	68 Gy/34 fractions/7 weeks	

Overall survival

Eleven studies (twelve comparisons) reported the effect of accelerated fractionation without dose reduction on OS, of which nine studies (ten comparisons; N=5387) could be pooled.[121, 127-131, 133, 135, 136] Accelerated fractionation without dose reduction was found to have no significant effect on OS (HR = 0.93; 95%CI 0.81 to 1.08). Moon et al. also reported no significant effect on OS at 2 years (100% vs. 96%) and 5 years (87% vs. 83%)[138] as did Yamazaki et al. (5-year OS: 88% vs. 87%).[134]

Locoregional control

Twelve studies (thirteen comparisons) reported the effect of accelerated fractionation without dose reduction on locoregional control, of which eleven studies (twelve comparisons; N=5828) could be pooled.[121, 127-133, 135, 136, 138] Accelerated fractionation without dose reduction was found to have a significant effect on locoregional control (HR = 0.75; 95%CI 0.65 to 0.87). Yamazaki also reported a significantly better local control rate at 5 years with accelerated fractionation (92% vs. 77%; p=0.004).[134]

Disease-free survival

Six studies (seven comparisons) reported the effect of accelerated fractionation without dose reduction on disease-free survival, of which four studies (five comparisons; N=2363) could be pooled.[121, 132, 133, 135] Accelerated fractionation without dose reduction was found to have a significant beneficial effect on disease-free survival (HR = 0.67; 95%CI 0.51 to 0.89). Olmi et al. did not find a significant effect on 2-year disease-free survival (20% vs. 23%)[130] as did Hliniak et al. (78% vs. 75%).[129]

Quality of life

One RCT (N=750) evaluated the effect of accelerated fractionation without dose reduction on quality of life.[136] Global health status (measured with the EORTC QLQ-C30 and the QLQ-H&N35) was rated significantly lower ($p<0.05$) three months after radiotherapy for patients treated with accelerated fractionation. This difference was no longer detectable six months or later after treatment. Quantitative results were not provided.

Acute toxicity

Table 18 provides an overview of the pooled effects of accelerated fractionation without dose reduction on acute toxicity. Accelerated fractionation without dose reduction was associated with significantly more mucositis (confluent: RR = 1.84; 95%CI 1.50 to 2.26; grade 3-4: RR = 1.75; 95%CI 1.47 to 2.09), acute grade 3-4 toxicity of the pharynx / oesophagus (RR = 2.16; 95%CI 1.72 to 2.72) and need for tube feeding (RR = 1.16; 95%CI 1.01 to 1.33). No significant effects were found for other acute toxicities.

Table 18 – Pooled effect estimates of accelerated fractionation without total dose reduction on acute toxicity

Acute toxicity	N studies	N patients	Pooled effect
Confluent mucositis	6	3 490	RR = 1.84; 95%CI 1.50 to 2.26
Mucositis grade 3-4	6	1 805	RR = 1.75; 95%CI 1.47 to 2.09
Skin grade 3-4	7	2 685	RR = 1.23; 95%CI 0.77 to 1.95
Larynx grade 3-4	4	1 340	RR = 1.71; 95%CI 0.97 to 3.01
Pharynx / oesophagus, grade 3-4	4	1 469	RR = 2.16; 95%CI 1.72 to 2.72
Tube feeding	1	880	RR = 1.16; 95%CI 1.01 to 1.33
Salivary glands	1	106	RR = 3.11; 95%CI 0.13 to 74.74
Moderate to severe dysphagia	1	393	RR = 3.05; 95%CI 0.32 to 29.03

Late toxicity

Table 19 provides an overview of the pooled effects of accelerated fractionation without dose reduction on late toxicity. Only for grade 3-4 mucositis a significant effect of accelerated fractionation without dose reduction was found (RR = 2.24; 95%CI 1.53 to 3.29). For none of the other reported late toxicities a significant effect of accelerated fractionation without dose reduction was found.

Table 19 – Pooled effect estimates of accelerated fractionation without total dose reduction on late toxicity

Late toxicity	N studies	N patients	Pooled effect
Mucositis grade 3-4	6	1 737	RR = 2.24; 95%CI 1.53 to 3.29
Skin grade 3-4	6	2 092	RR = 0.92; 95%CI 0.48 to 1.76
Larynx grade 3-4	6	2 072	RR = 0.89; 95%CI 0.67 to 1.19
Xerostomia grade 3-4	2	824	RR = 0.98; 95%CI 0.84 to 1.14
Fibrosis grade 3-4	3	1 837	RR = 2.02; 95%CI 0.18 to 22.62
Moderate fibrosis	1	725	RR = 1.20; 95%CI 0.97 to 1.48
Salivary glands	1	72	RR = 1.89; 95%CI 0.37 to 9.69
Mandibula grade 3-4	1	100	RR = 4.81; 95%CI 0.24 to 97.68

Conclusions

- There is evidence of low quality that radiotherapy with accelerated fractionation without dose reduction has no significant effect on overall survival compared with conventional radiotherapy in patients with head and neck cancer.
- There is evidence of moderate quality that radiotherapy with accelerated fractionation without dose reduction improves disease-free survival and locoregional control compared with conventional radiotherapy in patients with head and neck cancer.
- There is evidence of moderate quality that radiotherapy with accelerated fractionation without dose reduction is associated with more acute grade 3-4 or confluent mucositis and grade 3-4 toxicity of the pharynx/oesophagus than conventional radiotherapy in patients with head and neck cancer.
- There is evidence of low quality that radiotherapy with accelerated fractionation without dose reduction is associated with more acute grade 3-4 toxicity of the larynx and more tube feeding than conventional radiotherapy in patients with head and neck cancer.
- The available evidence of very low quality does not allow to draw conclusions about the effect of radiotherapy with accelerated fractionation without dose reduction on acute grade 3-4 toxicity of the skin and salivary glands, and on moderate/severe dysphagia compared with conventional radiotherapy in patients with head and neck cancer.
- There is evidence of moderate quality that radiotherapy with accelerated fractionation without dose reduction is associated with more late grade 3-4 mucositis than conventional radiotherapy in patients with head and neck cancer.
- The available evidence of low to very low quality does not allow to draw conclusions about the effect of radiotherapy with accelerated fractionation without dose reduction on other late grade 3-4 toxicity compared with conventional radiotherapy in patients with head and neck cancer.

Accelerated fractionation with total dose reduction

Eight RCTs (N=2159) compared accelerated fractionation with total dose reduction with conventional fractionation (Table 20).[118, 119, 122-126, 137] Most RCTs included a mixed population. Marcial et al. only included patients with oropharyngeal cancer.[124] Two studies used a split-course regimen.[124, 137]

Table 20 – Overview of included RCTs on accelerated fractionation with total dose reduction

Study ID	N	Accelerated fractionation	Conventional fractionation	Comment
Bourhis 2006 (GORTEC 9402)	268	62-64 Gy/31-32 fractions/3 weeks	70 Gy/35 fractions/7 weeks	
Dische 1997 (CHART)	918	54 Gy/36 fractions/1.7 weeks	66 Gy/33 fractions/6.5 weeks	
Dobrowsky 2000 (Vienna)	159	55.3 Gy/33 fractions/2.5 weeks	70 Gy/35 fractions/7 weeks	
Marcial 1987 (RTOG 7913)	187	60 Gy/50 fractions/5 weeks	66-73.8 Gy/36 fractions/7 weeks	
Marcial 1993	137	60 Gy/20 fractions/4 weeks	60-66 Gy/30 fractions/6 weeks	Split-course, 100% oropharynx
Miszczyk 2014	76	64 Gy/40 fractions/3 weeks	72-74 Gy/36-37 fractions/7.5 weeks	Split-course
Poulsen 2001 (TROG 9101)	350	59.4 Gy/33 fractions/3.5 weeks	70 Gy/35 fractions/7 weeks	
Weissberg 1983	64	40-48 Gy/20-24 fractions/2-3 weeks	60-70 Gy/30-35 fractions/6-7 weeks	

Overall survival

Seven studies reported the effect of accelerated fractionation with dose reduction on OS, of which five studies (N=1033) could be pooled.[118, 119, 122, 123, 125] Accelerated fractionation with dose reduction was found to have no significant effect on OS (HR = 0.94; 95%CI 0.84 to 1.05). Marcial et al. also did not find a survival benefit with accelerated fractionation with dose reduction (5-year OS: 19% vs. 29%)[124] as did Miszczyk et al. (no quantitative data provided).[137]

Locoregional control

Six studies reported the effect of accelerated fractionation with dose reduction on locoregional control, of which five studies (N=1033) could be pooled.[118, 119, 122, 123, 125] Accelerated fractionation with dose reduction was found to have no significant effect on locoregional control (HR = 0.89; 95%CI 0.77 to 1.02). Marcial et al. also did not find a control benefit with accelerated fractionation with dose reduction (5-year locoregional control: 25% vs. 28%).[124]

Disease-free survival

Four studies reported the effect of accelerated fractionation with dose reduction on disease-free survival, of which three studies (N=1325) could be pooled.[118, 125, 126] Accelerated fractionation with dose reduction was found to have no significant effect on disease-free survival (HR = 0.93; 95%CI 0.81 to 1.07). Marcial et al. also did not find a disease-free survival benefit with accelerated fractionation with dose reduction in the subgroup of complete responders (5-year disease-free survival: 37% vs. 44%).[124]

Recurrence rate

Dobrowsky et al. found no significant difference in local recurrence (RR = 1.60; 95%CI 0.80 to 3.21) and regional recurrence (RR = 1.30; 95%CI 0.36 to 4.66) after complete response.[122]

Quality of life

Miszczyk et al. found a more deteriorated quality of life (measured with the EORTC QLQ-C30 and the QLQ-H&N35) with accelerated fractionation with dose reduction.[137] Poulsen et al. only found a temporarily deteriorated quality of life (measured on a 0-10 scale) in weeks 2-4 and in week 20 with accelerated fractionation with dose reduction.[125]

Acute toxicity

Table 21 provides an overview of the pooled effects of accelerated fractionation with dose reduction on acute toxicity. Accelerated fractionation with dose reduction was associated with significantly more mucositis (confluent: RR = 1.86; 95%CI 1.28 to 2.72; grade 3-4: RR = 1.75; 95%CI 1.47 to 2.09). No significant effects were found for other acute toxicities.

Table 21 – Pooled effect estimates of accelerated fractionation with total dose reduction on acute toxicity

Acute toxicity	N studies	N patients	Pooled effect
Confluent mucositis	3	1 453	RR = 1.86; 95%CI 1.28 to 2.72
Mucositis grade 3-4	2	453	RR = 1.75; 95%CI 1.45 to 2.11
Skin grade 3-4	1	187	RR = 0.87; 95%CI 0.30 to 2.48

Late toxicity

Table 22 provides an overview of the pooled effects of accelerated fractionation with dose reduction on late toxicity. Accelerated fractionation with dose reduction was associated with significantly less grade 3-4 toxicity of the skin (RR = 0.77; 95%CI 0.60 to 0.97), larynx (RR = 0.81; 95%CI 0.69 to 0.94) and dysphagia (RR = 0.80; 95%CI 0.65 to 0.98). More grade 3-4 mucositis and fibrosis was reported after accelerated fractionation with dose reduction, but the effect was not statistically significant.

Table 22 – Pooled effect estimates of accelerated fractionation with total dose reduction on acute toxicity

Late toxicity	N studies	N patients	Pooled effect
Mucositis grade 3-4	2	1 118	RR = 1.27; 95%CI 0.91 to 1.77
Skin grade 3-4	1	918	RR = 0.77; 95%CI 0.60 to 0.97
Larynx grade 3-4	2	1 118	RR = 0.81; 95%CI 0.69 to 0.94
Dysphagia grade 3-4	1	918	RR = 0.80; 95%CI 0.65 to 0.98
Fibrosis grade 3-4	1	200	RR = 1.92; 95%CI 0.96 to 3.82

Conclusions

- There is evidence of moderate quality that radiotherapy with accelerated fractionation with dose reduction has no significant effect on overall survival compared with conventional radiotherapy in patients with head and neck cancer.
- There is evidence of low quality that radiotherapy with accelerated fractionation with dose reduction has no significant effect on disease-free survival and locoregional control compared with conventional radiotherapy in patients with head and neck cancer.
- There is evidence of moderate quality that radiotherapy with accelerated fractionation with dose reduction is associated with more acute grade 3-4 or confluent mucositis than conventional radiotherapy in patients with head and neck cancer.
- The available evidence of very low quality does not allow to draw conclusions about the effect of radiotherapy with accelerated fractionation with dose reduction on acute grade 3-4 toxicity of the skin compared with conventional radiotherapy in patients with head and neck cancer.
- There is evidence of low quality that radiotherapy with accelerated fractionation with dose reduction is associated with more late grade 3-4 mucositis and fibrosis, but less grade 3-4 dysphagia and toxicity of the skin and larynx than conventional radiotherapy in patients with head and neck cancer.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	If single-modality radiotherapy is chosen as primary treatment, hyperfractionated radiotherapy is associated with better outcomes than conventionally fractionated radiotherapy. Accelerated radiotherapy is also associated with better outcomes, but only if the total dose is not reduced. However, both types of altered fractionation are associated with more adverse events.
Quality of evidence	Several RCTs were found, often with a high risk of bias. The evidence was of moderate to very low quality in general.
Costs (resource allocation)	No cost issues were considered.
Patients values and preferences	No comments were received from the patient representatives.

3.2.2.3 IMRT

In the first part of the guideline on head and neck cancer – focusing on oral cavity cancer [9] – a search was done for studies evaluating the effectiveness and safety of IMRT in patients with head and neck cancer. The results of that search were used for the second part too, and are described below. Methodological information can be found in the appendix of the first part.

One systematic review was included that compared IMRT with two-dimensional external beam radiotherapy (2D-EBRT) in the treatment of head and neck cancer.[142] The search date was March 2009 and the overall risk of bias of this review was judged to be low. The review served for a Canadian clinical guideline and included 15 studies. Of these, only one included RCT (abstract) and four included observational studies were found to be relevant (with some indirectness).

One included observational study did not find a significant difference between IMRT and 2D-RT with boost for local control rates at three years (95% vs. 85%, p=0.17).[142] No significant differences were found for overall survival at three years in one observational study (IMRT [N=41] 91% vs. 2D-RT with boost [N=71] 81%; p=0.10).[142]

With respect to adverse events, one RCT (published as abstract) and one observational study found significant differences for the presence of xerostomia at 1 year (IMRT 40% vs. 2-D EBRT 74%; p=0.005) and ≥20 months (IMRT [N=41] 12% vs. 2-D [N=71] 67%; p<0.002) in favour of IMRT.[142] For quality of life significant differences were found at 12 months in one observational study on the domain 'Eating' (IMRT 55.4 vs. 2-D EBRT 39.0; p=0.007), but not for the domains 'Speech' (83.2 vs. 74.3; p=0.059), 'Aestetics' (90.4 vs. 79.3; p=0.069) and 'Social disruption' (86.1 vs. 78.8; p=0.115).[142] In one observational study the score for xerostomia-related QoL (XQ) after a median follow-up of 31.2 months was in favour of IMRT (significance not reported).[142] In another observational study all post-therapy scores analysed simultaneously showed no significant difference (p=0.7), but at 12 months the median XQ scores of the standard RT patients were twice as high (worse) as the IMRT patients (67 [range 24–93] vs. 32 [range 5–79]).[142] After adjusting for baseline, the median XQ score of the standard RT patients at 12 months was 20 points higher than for the IMRT patients (p=0.2). This study also addressed Health-related Quality of Life (HRQoL). The median HRQOL summary score of the IMRT patients was 17 (range 2–67) compared with 68 (range 7–93) in the control group. After adjusting for baseline scores, the median standard RT group summary HRQoL score at 12 months was 19.2 higher (worse) than for the IMRT group (not statistically significant).

Based on all included studies the review authors concluded that there is insufficient evidence to recommend IMRT over two-dimensional EBRT if treatment-related outcomes are the main outcomes of interest. However, in case the reduction of xerostomia and improved quality of life are the main outcomes of interest, they recommend IMRT for all head and neck cancers where radiation of lymph node regions would result in damage to salivary function when 2-D EBRT would be used. They also state that "The data provided are applicable to locally advanced disease, but are equally applicable to early-stage disease and rare sites (e.g. salivary gland tumours) requiring radiotherapy that would otherwise damage these normal structures".

The update of the search resulted in the inclusion of eight additional relevant observational studies and two RCTs. These two RCTs also involved patients with TNM stage I and II, and therefore provide more indirect evidence.

The first RCT[151] compared IMRT with three-dimensional conformal radiotherapy (3D-CRT) with in curative-intent irradiation of HNSCC. Sixty-two previously untreated patients with biopsy-proven squamous carcinoma of the oropharynx, larynx, or hypopharynx (T1-3, N0-2b) were randomly assigned to either IMRT or 3D-CRT. The risk of bias of this study was judged to be high. There were no significant differences in the baseline patient, disease, and treatment characteristics between the two groups. Three-year Kaplan–Meier estimates were 68% (95%CI 51.2 to 84.8%) in the IMRT group and 80.5% (95%CI 66.1 to 94.9%) in the 3D-CRT group. Three-year Kaplan–Meier estimates for (loco) regional control were 70.6% (95%CI 53 to 88.2%) in the IMRT group and 88.2% (95%CI 75.4 to 100%) in the 3D-CRT group. With regards to adverse events, only significant differences were found for RTOG Grade 2 or worse acute salivary gland toxicity (RR=0.67; 95%CI 0.49 to 0.91) in favour of IMRT. Late morbidity, late xerostomia and subcutaneous fibrosis were significantly lesser with IMRT compared to 3D-CRT at most time points and there was significant recovery of salivary function over time in patients treated with IMRT (p-value for trend = 0.0036). For the remaining adverse events, no significant differences were

found. Disease-free survival, recurrence rate, secondary tumours and quality of life were not assessed.

The second RCT[152] compared parotid-sparing IMRT with conventional radiotherapy. Ninety-four patients with histologically confirmed pharyngeal squamous-cell carcinoma (T1–4, N0–3, M0) were randomly assigned to the two radiotherapy techniques. The risk of bias of this study was judged to be high. Baseline patient characteristics were balanced except for nodal stage and AJCC stage. No significant differences were found for OS between the two groups (HR=0.68; 95%CI 0.34 to 1.37). Two-year locoregional progression-free survival was 78% (95%CI 62 to 87) in the IMRT group and 80% (95%CI 65 to 90) in the conventional radiotherapy group (absolute difference 3%, 95%CI –15 to 20; HR=1.53, 95%CI 0.63 to 3.70). No significant differences were found for locoregional recurrences (RR=1.71; 95%CI 0.74 to 3.97). Mean changes in global health status from baseline to 12 months were 3.0 in the IMRT group compared to 1.1 in the conventional radiotherapy group (MD=1.90; 95%CI -16.13 to 19.93). At 24 months these changes were 8.3 in the IMRT group compared to -2.8 in the conventional radiotherapy group (MD=11.10; 95%CI -9.01 to 31.21). With regards to adverse events, only significant differences were found for xerostomia (Grade 2 to 4) (RR=0.77; 95%CI 0.63 to 0.95), dysphagia (Grade 2 to 4) (RR=0.87; 95%CI 0.77 to 0.99), salivary gland (RTOG late: Grade 2 to 4) (RR=0.82; 95%CI 0.67 to 1.00), rash (RR=0.84, 95%CI 0.71 to 1.00) and fatigue (RR=1.82; 95%CI 1.23 to 2.70 (the latter in favour of conventional RT). As for the remaining adverse events, no significant differences were found. Disease-free survival and secondary tumours were not assessed.

For two outcomes the results of the two RCTs could be pooled. For acute mucositis grade 2 or more the pooled RR was 0.91 (95%CI 0.83 to 1.00) (Appendix 6.3, Figure 82 of the first part). Dysphagia occurred significantly less frequently after IMRT (pooled RR= 0.86; 95%CI 0.74 to 0.99) (Appendix 6.3, Figure 83 of the first part).

The first observational study[143] performed a retrospective analysis of 49 patients with stage III and IV squamous cell carcinoma of the oral cavity who were treated with radical surgery followed by post-operative RT. The aim of this study was to assess the treatment results and toxicity profiles of post-operative IMRT and conventional radiotherapy. The type of conventional radiotherapy was not clearly described, but was assumedly 2D. Twenty-two patients received IMRT while 27 received conventional radiotherapy. The risk of bias of this study was judged to be high. There were more patients with buccal cancer in the IMRT group, and more tongue and alveolus cancer in the conventional radiotherapy group (p=0.001), but no (significant) differences were observed with respect to stage, number of positive lymph nodes, positive resection margins, mean dose of RT and chemotherapy. There were no statistically significant differences between the groups for 3-year DFS rates (64% vs. 66%, p=0.89; HR 1.19, 95%CI 0.45 to 3.13) and overall survival (67% vs. 77%, p=0.70). In a multivariate analysis (corrected for AJCC stage, extracapsular spread, positive resection margin, two or more positive lymph nodes, interval from surgery to start RT and total package time) the difference in DFS remained not significant (p=0.73). In addition, no significant differences were observed with respect to the recurrence rate (RR=0.98; 95%CI 0.47 to 2.06). As for secondary tumours, one patient in the conventional radiotherapy group developed secondary oesophageal cancer 2.5 years after diagnosis of his primary tongue cancer. There were no significant differences between the two groups with respect to acute toxicities. However, in terms of late toxicity, patients receiving IMRT had significantly less moderate to severe xerostomia and dysphagia than those receiving conventional radiotherapy (36% vs. 82%, p=0.01 for xerostomia and 21% vs. 59%, p=0.02 for dysphagia). Locoregional control and quality of life were not assessed.

The second retrospective study[144] compared the effect of IMRT (N=27) with conventional radiotherapy (N=24) in patients with squamous cell carcinoma of unknown primary origin involving the cervical lymph nodes. The risk of bias of this study was judged to be high. The groups were well balanced with respect to N-stage and initial Karnofsky performance status. The IMRT group included older patients, had less postoperative RT and more concurrent chemotherapy. OS was similar in both groups (87% vs. 86%; p=0.43). Loco-regional control was 92% in the IMRT group vs. 87% in the conventional RT group (p=0.44). The occurrence of grade 3+ acute mucositis was higher in the IMRT group (28% vs. 12%; p=0.01), but there were no significant differences between the groups for non-mucositis toxicities (oesophagitis, moist desquamation, laryngeal oedema with hoarseness and otitis media). Late grade 3+ toxicities of any kind occurred significantly less in the IMRT group (29% vs. 63%; p<0.001). The same applies to the occurrence of xerostomia (11% vs. 58%; p<0.001), the need for a liquid diet only (17% vs. 42%; p<0.001) and G-tube dependency at 6

months (11% vs. 42%; p<0.001) and at 1 year after treatment (0% vs. 33%; p<0.001). Oesophageal stricture percentages were similar in both groups (15% vs. 17%; p=0.55). Disease-free survival, recurrence rate, secondary tumours and quality of life were not assessed.

The third study[145] compared the long-term quality of life (measured by the University of Washington Quality of Life instrument) among patients treated with and without IMRT for locally advanced head-and-neck cancer. Eighty-four patients were treated with IMRT and 71 with 3-D conformal radiotherapy. The risk of bias of this study was judged to be high. The groups were well balanced with respect to primary tumour site, T stage, radiation modality, neck dissection, concurrent chemotherapy and age (including no significant differences between the groups). As for the domain-specific quality of life, the salivary domain was the only specific component in which significant differences were observed (mean scores at 1 year: 70.5 vs. 50.6; mean scores at 2 years: 77.3 vs. 53.0, p<0.001). The mean health-related quality of life scores were significantly higher in the IMRT group for both one year (62.0 vs. 50.9, p<0.001) and two years (78.7 vs. 55.3, p<0.001). The mean global quality of life scores were 67.5 and 80.1 for the IMRT patients at 1 and 2 years, respectively, compared with 55.4 and 57.0 for the 3D conformal radiotherapy patients, respectively (p<0.001). At 1 year after the completion of radiation therapy, the proportion of patients who rated their global quality of life (QoL) as “very good” or “outstanding” was 51% and 41% among patients treated by IMRT and 3D conformal radiotherapy, respectively (p=0.11). At 2 years, the corresponding percentages increased to 73% and 49%, respectively (p<0.001). In a multivariate analysis (corrected for sex, age, radiation intent [definitive vs. postoperative], radiation dose, T stage, primary site, use of concurrent chemotherapy, and neck dissection), 61/84 patients (73%) vs. 35/71 patients (49%) rated their global QoL at 2 years as “very good” or “outstanding”. Disease-free survival, OS, (loco) regional control, recurrence rate, secondary tumours and adverse events were not assessed.

The fourth study[146] performed a retrospective study which compared the toxicity and efficacy of simultaneous integrated boost using IMRT with conventional radiotherapy in patients treated with concomitant carboplatin and 5-fluorouracil for locally advanced oropharyngeal cancer. Between January 2000 and December 2007, 249 patients were treated with definitive chemoradiation. The risk of bias of this study was judged to be high. There were more patients with T3–4 disease (60% vs. 30%, p=0.001), fewer N2–3 (78% vs. 87%, p=0.063), more tongue cancer (51% vs. 39%), more neck dissection (28% vs. 20%, p=0.30) and more ‘positive pathology’ (not further specified by the authors) (36% vs. 15%, p=0.14) in the conventional radiotherapy group. Age, sex, overall AJCC stage (III vs. IVa vs. IVb, p=0.195), number of chemotherapy cycles and dose of RT were balanced. Three-year DFS, OS and locoregional control were 85.3% vs. 69.3% (p=0.001), 92.1% vs. 75.2% (p<0.001) and 95.1% vs. 84.4% (p=0.005) for IMRT and conventional radiotherapy, respectively. Cox multivariate analysis for DFS (corrected for T, AJCC stage and number of chemotherapy cycles received) resulted in a HR of 2.11 (95%CI 1.06 to 4.17). The HR for OS (corrected for T, AJCC stage and age) was 2.64 (95%CI 1.15 to 6.04) and for locoregional control (corrected for T and AJCC stage) 3.54 (95%CI 1.04 to 12.02). Except for less RTOG Grade 3-4 dermatitis (p=0.02) in the IMRT group, there were no significant differences with respect to acute toxicities. There was significantly less grade 2 xerostomia at 12 and 24 months (p<0.001) after treatment with IMRT and better subsequent weight gain at 36 months (p=0.03). There was no difference in other late complications. Recurrence rate, secondary tumours and quality of life were not assessed.

The fifth study[147] performed a retrospective review to assess the outcome and toxicity of Stage IVa and IVb HNSCC patients treated with concomitant chemotherapy and IMRT according to a hybrid fractionation schedule. Between 2006 and 2008, 42 patients who received RT according to a hybrid fractionation schedule consisting of 20 fractions of 2 Gy (once daily), followed by 20 fractions of 1.6 Gy (twice daily), to a total dose of 72 Gy were retrospectively compared with 55 previous patients who were treated according to the same schedule, but without intensity modulation. Chemotherapy (cisplatinum 100mg/m^2) was administered at the start of weeks 1 and 4. The risk of bias of this study was judged to be high. Age, gender, tumour grade and N classification were balanced between the groups. There were more T4a/b and stage IVB and less oropharyngeal cancer patients in the IMRT group, because IMRT was initially given to patients with large tumours and laryngeal and hypopharyngeal tumours, which resulted in a statistically significant difference for T classification (p=0.01) and tumour site (p=0.005) between the two groups. After 2 years, no significant differences in DFS (48% vs. 60%, p=0.18), OS (56% vs. 73%, p=0.29) and locoregional control (81% vs. 66%, p=0.38) were found

between the two groups. As for acute toxicity (assessed with the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0) differences between the groups were found for the incidence of acute grade 3 mucositis (54.7% vs. 72.7%, p=0.07), grade 2 or 3 nausea (4.8% vs. 20.0%, p=0.03), grade 2 or 3 xerostomia (81.0% vs. 92.7%, p=0.08) and grade 2 or 3 pain (47.6% vs. 83.6%, p<0.001). With respect to late toxicity (graded according to the RTOG/EORTC late radiation morbidity scoring schema) there was a significantly lower incidence of late subcutaneous tissue toxicity (p=0.02) and salivary glands toxicity (p<0.001) in favour of IMRT. No grade 4 or 5 toxicity was reported in the IMRT group, either acute or chronic. Recurrence rate, secondary tumours and quality of life were not assessed.

The sixth study[148] performed a retrospective chart review of patients of 65 years and older with high-risk locally advanced head and neck cancer. Radiation therapy consisted of 3D conformal radiotherapy or IMRT depending on patient's set up and availability of technology (patients with advanced neck disease where the parotid glands would not have been spared by IMRT were treated with 3D conformal radiotherapy).The study was judged as of high risk of bias. Group comparability at baseline was unclear as patient characteristics were not specified per treatment group. Patients receiving IMRT had a significantly higher rate of local control as compared to 3D conformal radiotherapy (94% vs. 68%, p=0.008). DFS, OS, recurrence rate, secondary tumours and quality of life were not assessed or not presented per intervention group.

The seventh study[149] performed a retrospective analysis of 245 patients with locally advanced HNSCC treated with primary (chemo)radiotherapy. Of these, 110 patients were treated with IMRT and 135 patients with a parotid-sparing 3D conformal radiotherapy technique. The study was judged as being of high risk of bias. Significant differences between the two groups at baseline were found for tumour location and N stage (less oro- and hypopharynx cancer and more N2c in the IMRT group). Age, gender, T stage, AJCC stage, prescribed dose, treatment time and concurrent treatment were balanced. No significant differences between the two groups were found for OS (64% vs. 61%, p=0.5) and regional control (70% vs. 71%, p=0.7). Adverse events (graded according to the CTCAE version 3.0) showed a significant difference for acute mucositis ≥ grade 3 (32% vs. 44%, p=0.03) in favour of the IMRT group. There were no significant differences in acute dysphagia and acute erythema ≥ grade 3 between the IMRT and 3D conformal radiotherapy groups. Significant differences six months after treatment were found for xerostomia (82% vs. 91%, p=0.03), severe xerostomia ≥ grade 2 (23% vs. 68%, p<0.001) and dysphagia at 24 months (11% vs. 21%, p=0.08) in favour of IMRT. DFS, recurrence rate, secondary tumours and quality of life were not assessed.

The eighth study[150] compared the results of IMRT with adjuvant conventional radiotherapy (2DRT) for patients with locally advanced hypopharyngeal cancer after resection and ileocolic free flap reconstruction. Five patients received IMRT and eight 2DRT. The risk of bias of this (very small) study was judged to be high. There were some differences in tumour stage, primary tumour stage and regional lymph node stage between the two groups at baseline. Two-year DFS was 80% versus 50%, and 2-year OS 80% versus 63%. The IMRT group showed less adverse effects (speech ability, ability to swallow, the occurrence of acute dermatitis and acute mucositis), but these differences were not statistically significant. Recurrence rate, secondary tumours and quality of life were not assessed.

In summary, in the observational studies no significant differences between IMRT and conventional radiotherapy were observed for DFS. From these observational studies, there are indications that IMRT results in better OS and local control, while the RCTs show no loss of efficacy with IMRT. Overall, QoL (various measures) and adverse effects are in favour of IMRT (which confirms the conclusions of the included systematic review). The update mainly included observational studies in which baseline differences between the intervention groups were present. Although some studies applied multivariate analyses to correct for those differences, there still appears to be a high risk of bias due to (rest) confounding by indication. Therefore, all studies have a high risk of bias and the results thereof should be interpreted cautiously. Also for this reason we did not attempt to perform meta-analyses for the observational evidence.

Conclusions

- The available evidence of very low quality does not allow to draw conclusions about the effect of IMRT compared to 2D-EBRT/3D-EBRT on overall and disease-free survival and (loco)regional control at 2 and 3 years in adult patients with locally-advanced HNSCC (TNM stage 3 and 4).
- The available evidence of very low quality does not allow to draw conclusions about the effect of IMRT compared to 2D-EBRT/3D-EBRT on recurrence rate, secondary tumours or xerostomia-related quality of life in adult patients with locally-advanced HNSCC (TNM stage 3 and 4).
- There is evidence of very low quality that in adult patients with locally-advanced HNSCC (TNM stage 3 and 4) IMRT results in a better health-related quality of life (median follow-up 1 to 2 years) and overall quality of life (median follow-up 2 years) compared to 2D-EBRT/3D-EBRT.
- There is evidence of very low quality that in adult patients with locally-advanced HNSCC (TNM stage 3 and 4) IMRT results in a reduction of xerostomia, mucositis, dysphagia, need for enteral feeding, need for liquid diet, grade 3+ late toxicity, acute grade 3-4 dermatitis, acute grade 2 or 3 nausea, acute grade 2 or 3 pain, late subcutaneous tissue toxicity and salivary glands toxicity compared to 2D-EBRT/3D-EBRT.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	IMRT is potentially associated with a better (loco)regional control and quality of life and less adverse events compared with EBRT. IMRT is a specific technique that should be performed in dedicated centres according to well-established procedures.
Quality of evidence	The direct evidence on IMRT is limited to observational studies with a high risk of bias. Two RCTs provide indirect evidence.
Costs (resource allocation)	No cost issues were considered.
Patients values and preferences	No comments were received from the patient representatives.

3.2.2.4 Postoperative (chemo)radiotherapy

Postoperative (chemo)radiotherapy versus no postoperative (chemo)radiotherapy

The detailed results of the literature search and assessment can be found in Appendix 2.3.4, Appendix 3.3.1, Appendix 3.3.5, Appendix 4.4, Appendix 5.4 and Appendix 6.4.

Mixed population of head-and-neck cancers

No systematic reviews were identified. One RCT was identified regarding a mixed population of patients with oropharyngeal, hypopharyngeal or glottis cancer.[153]

In this RCT 42 patients with advanced stage (III or IV) squamous cell carcinoma (SCC) of the head and neck, whose tumours had been completely removed, were randomized to receive either postoperative radiotherapy or not. Risk of bias for this study was judged to be high, as there was no blinding, a high risk of attrition bias and there were baseline imbalances in T-stage distribution between study groups. In stage III patients, recurrences were identified in 50% of the irradiated versus 80% of the non-irradiated patients. Corresponding results for stage IV patients were 84% versus 68%. However, p-values were not provided. Five-year disease-specific survival did not differ significantly between the study groups (35% vs. 35%; p=0.39 [log rank test]). The study did not report on disease-free survival, OS, quality of life and adverse events.

One observational study was found that included a mixed population of patients with head and neck cancer.[154]

Schmitz et al. performed a retrospective analysis of medical records in a population of head and neck cancer patients. The study included 163 patients with SCC of the larynx, hypopharynx, oropharynx or oral cavity who received surgery with or without postoperative radiotherapy. The risk of bias was high. Baseline characteristics were not reported separately for the study groups. No differences between treatments were found in the number of neck recurrences (pN0: 0 vs. 3/194; pN1: 2/21 vs. 1/18; pN2b: 1/16 vs. 0; p-values were not provided). The study did not report on disease-free survival, (loco)regional control, OS, quality of life and adverse events.

Conclusions

- In adult patients with head and neck cancer a difference between postoperative radiotherapy and no postoperative radiotherapy in recurrence rate and (loco)regional control could neither be demonstrated nor refuted (very low level of evidence).
- No comparative studies were identified that addressed disease-free survival, overall survival, quality of life and adverse events outcomes of postoperative (chemo)radiotherapy versus no postoperative (chemo)radiotherapy in adult patients with head and neck cancers.

Oropharynx

No systematic reviews and RCTs were identified. Six relevant comparative observational studies were found.[155-160]

The study of Bastos de Souza involved a retrospective chart review which assessed the effect of surgical treatment with or without postoperative radiotherapy in patients with clinical stage III or IV oropharyngeal SCC.[155] Two-hundred and fifty-six patients were included, of which 201 underwent surgery with postoperative radiotherapy and 55 surgery without postoperative radiotherapy. The risk of bias of this study was judged to be high. Baseline patient characteristics were not reported per treatment group. Significant differences between the two groups were found in favour of the postoperative radiotherapy group for disease-free survival at five years (57.4% vs. 43.3%, p=0.010) and OS at five years (45.8% vs. 32.8%, p=0.010). The study did not report on recurrence rate, (loco)regional control, quality of life and adverse events.

The study of Broglie involved a retrospective chart analysis and cross-sectional evaluation of quality of life in 98 long-term survivors treated for oropharyngeal SCC.[156] Thirty patients underwent surgery with postoperative radiotherapy and 13 surgery without postoperative radiotherapy. The risk of bias was judged to be high. Patients treated with postoperative radiotherapy had a higher nodal and tumour stage, but only univariate analyses were performed. No significant differences were found in both general (EORTC-QLQ-C30) and head-and-neck-specific (EORTC-QLQ-H&N35) quality of life between the two groups. Disease-free survival, recurrence rate, (loco)regional control, OS and adverse events were not addressed.

A study by Lim involved a retrospective analysis of 110 patients with histologically confirmed oropharyngeal SCC.[157] Of these, 84 underwent surgery with postoperative radiotherapy and 26 surgery without postoperative radiotherapy. The risk of bias in this study was high. Baseline characteristics were not presented for treatment groups separately. No differences in local (7% vs. 12%, p>0.05) and regional recurrence (20% vs. 8%, p>0.05) were found between patients receiving postoperative radiotherapy and patients with only surgery. Lower disease-specific survival was found for patients with postoperative radiotherapy (56% vs. 83%, p<0.05). Disease-free survival, (loco)regional control, OS, quality of life and adverse events were not reported.

Patel et al. performed a retrospective analysis of a database.[158] The study included 79 patients with SCC of the tonsil or tongue base. Thirty-eight patients received transoral laser microsurgery with postoperative radiotherapy and 41 transoral laser microsurgery alone. The study had a high risk of bias. The groups were comparable for sex, but there were baseline imbalances on age and tumour stage. The number of treatment failures was comparable between the groups (18% vs. 24%, p=0.41). However, three-year treatment failures for intermediate and high-risk patients were higher in the group that received postoperative radiotherapy (local: 0% vs. 21%, p=0.004; regional: 6% vs. 21.4%, p=0.08; locoregional: 6% vs. 32%, p=0.008; distant: 18.1% vs. 5.9%, p=0.33). The number of deaths was higher in the group with postoperative radiotherapy (16% vs. 7%), but there was no difference in three-year OS for intermediate or high-risk patients (93.8% vs. 94.1%, p=0.63). Disease-free survival,

(loco)regional control, quality of life and adverse events were not assessed in this study.

Röösli et al. published a retrospective chart review of 427 patients with SCC of the oropharynx.[159] The study included 159 patients that received surgery and postoperative radio(chemo)therapy, and 102 patients that received surgery only. The risk of bias of this study was high. Study groups were comparable for age and gender, but not for disease stage. More recurrences were reported in patients that did not receive postoperative radio(chemo)therapy (24.5 vs. 32%). Five-year overall and disease-specific survival were comparable (postoperative radio(chemo)therapy vs. surgery alone, OS: 66.6% vs. 70.3%; disease-specific survival: 78.9% vs. 76.5%). Disease-free survival, (loco)regional control, quality of life and adverse events were not reported.

Yokota et al. included 45 patients in a retrospective analysis of medical records.[160] Seventeen patients underwent primary tumour resection and/or neck dissection and radiotherapy, nine underwent primary tumour resection and/or neck dissection and chemoradiotherapy and 19 underwent primary tumour resection and/or neck dissection alone. The risk of bias in this study was judged to be high. There were differences between groups regarding age, and disease stage. Although multivariate analyses corrected for this, the small sample size may have impaired statistical significance of the results. No difference in disease-free and OS was found between postoperative radiotherapy and no postoperative radiotherapy (disease-free survival: HR 0.31, 95%CI 0.08 to 1.19, p=0.087; OS: HR 0.32, 95%CI 0.06 to 1.67, p=0.176). For the comparison between chemoradiotherapy and no chemoradiotherapy there was no difference in OS (HR 0.79, 95%CI 0.15 to 4.08). When postoperative radiotherapy and chemoradiotherapy groups together were compared to no postoperative (chemo)radiotherapy, no difference in disease-free survival was found (HR 3.02, 95%CI 0.80 to 11.3). Grade 3/4 mucositis, anorexia and grade 2 dysgeusia occurred more in patients treated with postoperative chemoradiotherapy and postoperative radiotherapy compared to patients treated with surgery alone (postoperative radiotherapy vs. postoperative chemoradiotherapy vs. surgery alone: mucositis: 4 (24%) vs. 4 (44%) vs. 0; anorexia: 3 (18%) vs. 2 (22%) vs. 0; dysgeusia: 6 (35%) vs. 5 (56%) vs. 0). The study did not report on recurrence rate, (loco)regional control, and quality of life.

Conclusions

- In adult patients with oropharyngeal cancer a difference between postoperative (chemo)radiotherapy and no postoperative (chemo)radiotherapy in disease-free survival could neither be demonstrated nor refuted (very low level of evidence).
- In adult patients with oropharyngeal cancer a difference between postoperative (chemo)radiotherapy and no postoperative (chemo)radiotherapy in recurrence could neither be demonstrated nor refuted (very low level of evidence). For intermediate or high risk patients there is evidence of very low quality that postoperative (chemo)radiotherapy leads to less local and locoregional recurrences than when no postoperative (chemo)radiotherapy is given.
- In adult patients with oropharyngeal cancer a difference between postoperative (chemo)radiotherapy and no postoperative (chemo)radiotherapy in overall survival could neither be demonstrated nor refuted (very low level of evidence).
- In adult patients with oropharyngeal cancer a difference between postoperative (chemo)radiotherapy and no postoperative (chemo)radiotherapy in quality of life could neither be demonstrated nor refuted (very low level of evidence).
- In adult patients with oropharyngeal cancer a difference between postoperative (chemo)radiotherapy and no postoperative (chemo)radiotherapy in adverse events could neither be demonstrated nor refuted (very low level of evidence).
- No comparative studies were identified that addressed (loco)regional control of postoperative (chemo)radiotherapy versus no postoperative (chemo)radiotherapy in adult patients with oropharyngeal cancers.

Hypopharynx

No systematic reviews and RCTs were identified. One relevant comparative observational study was found.[161]

Wang et al. performed a retrospective analysis of medical records.[162] The study included 41 patients with primary SCC at the pharyngoesophageal junction with simultaneous involvement of both the hypopharynx and cervical oesophagus. Twenty-seven patients received surgery and adjuvant radiotherapy (6 preoperative and 21 postoperative), and 14 patients received surgery alone. The risk of bias for this study was judged to be high. Baseline characteristics were not reported for separate treatment groups. A significantly better median, 1-year and 5-year survival was reported for the group receiving postoperative radiotherapy (median survival: 37.2 vs. 6.4 months; 1-year overall survival rate: 81.5% vs. 42.9%; 5-year OS rate: 48.2% vs. 0%, p<0.001), which remained significant when cases of hospital mortality were excluded from the analysis (p=0.003), and after adjusting for age, gender, tumour localization, tumour size and local invasion (Multivariate Cox regression analysis, HR=0.27; 95%CI 0.13 to 0.60; p=0.001). Disease-free survival, recurrence rate, (loco)regional control, quality of life and adverse events were not reported in this study.

Conclusions

- In adult patients with hypopharyngeal cancer there is evidence of very low quality that treatment with postoperative radiotherapy leads to better 5-year overall survival than treatment without postoperative radiotherapy.
- No comparative studies were identified that addressed disease-free survival, recurrence rate, (loco)regional control, quality of life or adverse events for postoperative (chemo)radiotherapy versus no postoperative (chemo)radiotherapy in adult patients with hypopharyngeal cancers.

Larynx

No systematic reviews and RCTs were identified. Eight relevant comparative observational studies were found.[163-170]

Gourin et al. performed a retrospective cross-sectional study of population-based registries.[168] Two-thousand three-hundred and seventy patients with larynx SCC were included, of which 1071 underwent surgery with postoperative radiation (including postoperative chemoradiation) and 271 surgery only. The risk of bias of this study was judged to be high. The groups were comparable with respect to age and gender. Tumour characteristics were not completely reported, but multivariate analyses were performed, correcting for possible imbalances. Patients whose initial treatment was surgery with postoperative radiation had improved survival, which remained significant after controlling for subsequent additional cancer-directed treatment (HR=0.66; 95%CI 0.52 to 0.84). Disease-free survival, recurrence rate, (loco)regional control, quality of life and adverse events were not addressed.

Ampil et al. retrospectively evaluated the effect of surgery with postoperative radiotherapy compared to surgery alone in 30 patients with resected T3-4 laryngeal cancer without adverse histopathology (metastatic involvement of cervical lymph nodes, extracapsular lymph node disease extension, or tumour positive resection margins and/or perineural invasion).[163] Eighteen received surgery with postoperative radiotherapy and 12 surgery alone. The risk of bias of this study was judged to be high. No significant differences between the two groups at baseline were found with respect to age, the occurrence of coexisting illnesses, number of recovered cervical nodes, T stage, or the presence of transglottic tumours. Relapse in the neck and OS at five years were not significantly different between the two groups (relapse in the neck: 0/16 (0%) vs. 3/12 (25%), p=0.07; OS at five years: 61% vs. 50%, p=0.63). Disease-free survival, (loco)regional control, quality of life and adverse events were not addressed.

Bindewald et al. performed a reanalysis of data of two multi-institutional cross-sectional studies.[164] The study included 205 patients with laryngeal carcinoma, of which 108 underwent laryngectomy and postoperative radiotherapy and 97 received laryngectomy alone. The risk of bias in this study was judged to be high. Almost half of the participants was excluded due to incomplete data and baseline characteristics were not comparable

between treatment groups. Patients receiving postoperative radiotherapy had a higher TNM-stage compared to patients that underwent surgery only. General quality of life (EORTC-QLQ-C30) was worse for patients receiving postoperative radiotherapy, significant differences were reported for role functioning and social functioning, but not for other aspects of functioning scales. In addition, patients receiving postoperative radiotherapy more often reported symptoms of fatigue and dyspnoea. In a multivariate model including operation mode, postoperative radiotherapy, disease stage groups, age, and time since operation, only age had a significant influence on EORTC-QLQ-C30. Head- and neck-specific quality of life (EORTC-QLQ-H&N35) was also better in the surgery only group. Patients that received postoperative radiotherapy more often reported swallowing problems, problems with taste, problems opening mouth, dry mouth and sticky saliva. In a multivariate model including operation mode, disease stage groups, age, and time since operation, radiotherapy had a significant influence on EORTC-QLQ-H&N35. Disease-free survival, recurrence rate, (loco)regional control, OS and adverse events were not addressed.

A retrospective review of medical records by Cho et al. included 114 patients with endolaryngeal cancer that underwent supracricoid laryngectomy.[165] Sixteen patients received postoperative (chemo)radiotherapy and 98 only supracricoid laryngectomy. The risk of bias was high. Baseline characteristics were not reported separately for treatment groups. No numerical results were presented in tables or text. However, significantly higher OS for patients receiving surgery only was reported in a figure by the authors. The study did not address recurrence rate, (loco)regional control, quality of life and adverse events.

Davis et al. performed a retrospective review of 26 patients with T1b or T2 SCC of the glottic larynx who underwent endoscopic vertical partial laryngectomy.[166] Thirteen patients received postoperative radiotherapy and 13 patients did not. The risk of bias was judged to be high. The treatment groups were comparable with regard to age and gender. However, radiotherapy was indicated for more advanced tumours. Higher rates of local control and OS were reported for the postoperative radiotherapy group than for the group receiving only surgery (local control: 84.5% vs. 100%; OS: 84.5 vs. 92.3%), however no information about statistical significance of these results was provided. Disease-free survival, recurrence rate, quality of life and adverse events were not addressed.

Dechaphunkul et al. retrospectively included 289 patients diagnosed with laryngeal cancer.[167] Of 106 patients with supraglottic cancer, 29 received surgery with postoperative radiotherapy and 3 surgery only. Of 180 patients with glottic cancer, 52 received postoperative radiotherapy and 12 surgery only. The risk of bias of this study was judged to be high. The groups were comparable for TNM-stage. Other baseline characteristics were not reported. A higher 5-year OS was reported for glottic cancer patients that received only surgery, compared to glottic cancer patients receiving postoperative radiotherapy (87.5% vs. 61.4%). OS in supraglottic cancer patients receiving postoperative radiotherapy was 52.2% but the number of patients receiving surgery only was too small to be analysed. Disease-free survival, recurrence rate, (loco)regional control, quality of life and adverse events were not addressed.

Olthoff et al. prospectively included 146 patients with laryngeal cancers.[169] Forty-four patients received surgery with postoperative radiotherapy and 102 surgery alone. The risk of bias was high in this study, and baseline characteristics were not separately presented for treatment groups. General quality of life was measured using the EORTC QLQ-C30 questionnaire. No differences between treatment groups were found on functional scales. Significantly lower QL scores were measured for irradiated patients on fatigue, pain, nausea and vomiting, appetite loss, constipation, dyspnoea and financial difficulties. The study did not address disease-free survival, recurrence rate, (loco)regional control, OS and adverse events.

Yilmaz et al. performed a retrospective analysis of medical records, which included 530 patients with laryngeal cancer.[170] Surgery and postoperative radiotherapy were given to 236 patients, and 294 patients received surgery alone. The risk of bias in this study was high. There seemed to be no baseline imbalances between treatment groups on age, sex and disease stage. Overall, the number of recurrences was comparable between the groups, except for regional recurrences that occurred more in the radiotherapy group (44/236 (19%) vs. 15/294 (5%)). Multivariate analyses revealed no difference in locoregional recurrence (HR 1.574, 95%CI 0.941 to 2.633). The study did not address disease-free survival, (loco)regional control, OS, quality of life and adverse events.

Conclusions

- In adult patients with laryngeal cancer a difference in recurrence rate between postoperative (chemo)radiotherapy and no postoperative (chemo)radiotherapy could neither be demonstrated nor refuted (very low level of evidence).
- In adult patients with laryngeal cancer a difference in local control between postoperative (chemo)radiotherapy and no postoperative (chemo)radiotherapy could neither be demonstrated nor refuted (very low level of evidence).
- In adult patients with laryngeal cancer there is conflicting evidence of a difference in overall survival between postoperative (chemo)radiotherapy and no postoperative (chemo)radiotherapy (very low level of evidence).
- In adult patients with laryngeal cancer a difference in quality of life outcomes between postoperative (chemo)radiotherapy and no postoperative (chemo)radiotherapy could neither be demonstrated nor refuted (very low level of evidence).
- No comparative studies were identified that addressed disease-free survival or adverse events for postoperative (chemo)radiotherapy versus no postoperative (chemo)radiotherapy in adult patients with laryngeal cancers.

Postoperative chemoradiotherapy versus postoperative radiotherapy

One systematic review was identified that studied chemotherapy in addition to radiotherapy and/or surgery.[171] The search date of this review was February 2011 and only RCTs with more than 50% of participants with oral cavity and/or oropharynx cancer were included. The overall risk of bias of the review was judged to be low. Eighty-nine trials met the inclusion criteria of the review, of which five RCTs (1621 participants) compared postoperative chemoradiotherapy with postoperative radiotherapy in the population of interest. All five RCTs studied a population of mostly advanced or high-risk head and neck cancer patients and were judged to be at unclear risk of bias for subjective outcomes by the review authors. For objective outcomes risk of bias of the trials was judged to be low (two trials) or unclear (three trials). OS was reported for all five trials. In four of the trials postoperative chemotherapy and radiotherapy were given concomitantly. The pooled results of these four trials show a significantly better survival for combined therapy compared to radiotherapy alone (pooled HR 0.84; 95%CI 0.72 to 0.98). In the fifth trial, in which postoperative chemotherapy and radiotherapy were not concomitant, no significant difference in survival was found (HR 0.91; 95%CI 0.73 to 1.13). Three trials reported on disease-free survival for postoperative concomitant chemoradiotherapy versus postoperative radiotherapy. There was no significant difference in disease-free survival (pooled HR 0.87, 95%CI 0.73 to 1.04). One trial reported a significantly lower rate of locoregional recurrence for postoperative concomitant chemoradiotherapy compared to postoperative radiotherapy alone (HR 0.61, 95%CI 0.41 to 0.91).

RCTs with less than 50% of participants with oral cavity and/or oropharynx cancer were excluded from the systematic review of Furness et al.[171]. Excluded studies and reasons for exclusion were well documented by the review authors. From the list of excluded studies we included five additional relevant RCTs.[172-176]

In the first RCT 88 patients who were referred for postoperative irradiation of a stage III or IV SCC of the head and neck and with histological evidence of extracapsular spread of tumour in lymph node metastases, were randomized to either concomitant postoperative radiotherapy and cisplatin infusion or radiotherapy alone.[172] Risk of bias for this study was judged to be high. There were some differences in the distribution of prognostic factors between the study groups at baseline. Besides, the number of included participants was much lower than the a priori calculated sample size of 200 participants. Mainly because of the growing use of neoadjuvant chemotherapy, the rate of inclusions decreased and enrolment was terminated. Both disease-free survival (DFS) and OS were significantly better in the postoperative chemoradiotherapy group compared to the postoperative radiotherapy group (5-year DFS: 45% vs. 23%, log rank test $p<0.01$; 5-year OS: 36% vs. 13%, log rank test $p<0.01$). Locoregional recurrence occurred in 23% and 41% of patients in chemoradiotherapy group and radiotherapy alone group, respectively (RR=0.56; 95%CI 0.29 to 1.11; p=0.08). There were more severe toxicities (>grade 3, RTOG/EORTC scale) in the chemoradiotherapy group compared to the radiotherapy group (acute severe toxicities: 16 vs. 7, RR=2.58; 95%CI 1.19 to 5.61; late severe toxicities: 6 vs. 4, RR=1.30; 95%CI 0.41 to 4.11). The study did not report on (loco)regional control and quality of life outcomes.

In the publication of Haffty et al., results of two consecutive RCTs from the same institution were presented.[173] Details of the first RCT were published before by Weissberg et al.[176] Eligibility criteria and study design of both trials were the same. Both trials included patients with histologically proven SCC of the head and neck who were treated with radiation therapy. Patients were stratified by intent of therapy into four groups: preoperative radiation, postoperative radiation without known residual disease, postoperative radiation therapy with residual disease, or exclusive radiation therapy. In the first trial (1980-1986) patients were randomized to either radiotherapy with concomitant mitomycin C or radiotherapy alone. In the second trial (1986-1992) dicoumarol was given in combination with radiotherapy and concomitant mitomycin C, and a comparison was made with radiotherapy alone. A total of 113 patients from both trials were treated in the postoperative setting and were included in the analysis. Risk of bias was judged to be high, due to lack of blinding and missing information on allocation concealment. Patients treated with radiotherapy and mitomycin C with or without dicoumarol (combined treatment group) were compared to patients treated with radiotherapy alone. There were no local recurrences in the combined treatment group compared to 12 in the radiotherapy group (RR=0.04; 95%CI 0.00 to 0.70). For regional and distant recurrences the numbers were 5 vs. 8 (RR=0.66; 95%CI 0.23 to 1.89) and 7 vs 9 (RR=0.82; 95%CI 0.33 to 2.05), respectively. Local and locoregional control were better in the combined treatment group (5-year actuarial local regional control rate: 87% vs. 67%, p<0.02; 5-year actuarial local control rate: 100% vs. 75%, p<0.01). There was a higher DFS in the combined treatment group (5-year actuarial DFS: 67 vs. 47, p<0.03). No significant differences were seen in OS for combined treatment vs. radiotherapy alone (56% vs. 41%). The major haematological toxicities that were seen, were leukopenia and thrombocytopenia. Moderate to severe leukopenia occurred in 18 of the 55 patients in the combined treatment group and in one of the 58 patients of the radiotherapy group (RR=18.98; 95%CI 2.62 to 137.42). Moderate, severe or life-threatening thrombocytopenia was observed in 12 patients of the combined treatment group compared to zero patients of the radiotherapy group (RR=26.34; 95%CI 1.60 to 434.42). The authors reported no significant differences between the study groups for non-haematological toxicities (including mucositis, epidermitis, and nausea/vomiting). Quality of life was not assessed. Results for locoregional and local control were also available for the comparison between postoperative radiotherapy with mitomycin C (without dicoumarol) and postoperative radiotherapy alone for the subgroups 'prophylactic treatment' and 'treatment of residual disease' separately (publication of Weissberg[176]). No significant differences were seen for 5-year actuarial local regional control rate for postoperative radiotherapy with mitomycin C vs. postoperative radiotherapy alone (prophylactic treatment: 93 vs. 75, p<0.07; treatment of residual disease: 83% vs. 60%, p<0.07). For 5-year actuarial local control rate the difference in the subgroup 'treatment of residual disease' was statistically significant in favour of postoperative radiotherapy with mitomycin C (prophylactic treatment intent: 100% vs. 83%, p<0.07; treatment of residual disease: 100% vs. 65%, p<0.02).

In the trial of Racadot et al. 144 patients with clinically T1-4 and N0-3 head and neck cancers and lymph node involvement were randomized to surgery followed by radiotherapy and concomitant carboplatin (N=72) or to surgery followed by radiotherapy alone (N=72).[174] Risk of bias for this study was judged to be high due to the lack of blinding. Patient characteristics were balanced between the study groups at baseline. The number of local and/or regional treatment failures for postoperative chemotherapy vs. postoperative radiotherapy were 19 vs. 26 (RR=0.73; 95%CI 0.45 to 1.20). Incorporating numbers for distant metastases as well, the numbers are 36 vs. 30 (RR=1.20; 95%CI 0.84 to 1.72). The 2-year locoregional control rate was 73% in the combined treatment group and 68% in the radiotherapy group (adjusted HR 0.77, 95%CI 0.40 to 1.48). OS did not differ significantly between groups (2-year OS for combined treatment vs. radiotherapy: 55% vs. 58%; adjusted HR=1.05; 95%CI 0.69 to 1.60). The incidence of acute (≤90 days after start of radiotherapy) or late treatment-related adverse events did not differ significantly between the study groups. DFS and quality of life were not assessed.

In the last RCT 114 patients with SCC of the head and neck were randomized to receive either postoperative chemoradiotherapy (N=59) or postoperative radiotherapy (N=55).[175] Risk of bias of this study was judged to be high due to lack of blinding and missing information about method of randomization. Baseline patient characteristics were well balanced between the study groups. For DFS no significant difference was found (postoperative chemoradiotherapy vs. postoperative radiotherapy: 76% vs. 60%, p=0.099). Local and/or regional recurrences with or without distant metastases were seen in 7/59 (12%) and 15/55 (27%) patients in

postoperative chemoradiotherapy and radiotherapy groups, respectively (RR=0.44; 95%CI 0.19 to 0.99). At two years, patients in the chemoradiotherapy group had better locoregional control than those in the radiotherapy group (86% vs. 69%; adjusted HR 2.82, 95%CI 1.12 to 7.09). 2-year OS was also better in the chemoradiotherapy group than in the radiotherapy group (74% vs. 62%; adjusted HR=0.503; 95%CI 0.256 to 0.990). Acute toxic effects that were assessed included mucositis, dermatitis and hematologic effects. A significant difference between both groups in degree of mucositis (Grade 4 vs. others) was found (chemoradiotherapy 17 vs. 41; radiotherapy 1 vs. 53; p<0.0001). No significant difference was found between the groups in the incidence of dermatitis and infection, nor in the degree of severe leukopenia, thrombocytopenia, and haemoglobin levels. More weight loss was seen in the chemoradiotherapy group compared to the radiotherapy group (7.5% vs. 3.3%, p=0.001). Quality of life was not assessed.

An update of the search identified no additional RCTs regarding chemoradiotherapy versus radiotherapy in the postoperative setting.

Two RCTs both reported 2-year OS and 2-year locoregional control and their results were pooled (see Appendix 6.4). No significant differences were seen between postoperative chemoradiotherapy and postoperative radiotherapy (OS: HR 0.86, 95%CI 0.60 to 1.22; locoregional control: HR 1.68, 95%CI 0.99 to 2.87).

The search for comparative observational studies revealed two relevant studies, both addressing patients with oropharyngeal cancer.

Röösli et al. described a retrospective chart review of 427 patients with SCC of the oropharynx.[159] The study included 159 patients that received surgery and postoperative radio(chemo)therapy, and 102 patients that received surgery only. The risk of bias of this study was high. The five-year overall and disease-specific survival for patients undergoing concurrent chemotherapy (N=26) compared with radiation only (N=133) was 45.7 compared to 38% (p=0.493). Disease-free survival, (loco)regional control, quality of life and adverse events were not addressed.

Yokota et al. included 45 patients in a retrospective analysis of medical records.[160] Seventeen patients underwent primary tumour resection and/or neck dissection and radiotherapy, nine primary tumour resection and/or neck dissection and chemoradiotherapy and 19 underwent primary tumour resection and/or neck dissection alone. The risk of bias in this study was judged to be high. There were differences between groups regarding age, and disease stage. Although multivariate analyses corrected for this, the small sample size may have impaired statistical significance of the results. No significant difference was seen in recurrence for chemoradiotherapy compared to treatment with radiotherapy alone (RR 1.06, p=0.971). The numbers of patients with ≥ grade 3 oral mucositis, dysphagia or dysgeusia were higher in the chemoradiotherapy group compared to the radiotherapy group (44% vs. 24%, 22% vs. 6 % and 56% vs. 35%, respectively). DFS and OS were not assessed for the comparison of interest. (Loco)regional control and quality of life were not addressed in this study.

Conclusions

- In adult patients with head and neck cancer a difference between postoperative chemoradiotherapy and postoperative radiotherapy in 2-year disease-free survival could neither be demonstrated nor refuted (low level of evidence).
- In adult patients with head and neck cancer there is evidence of moderate quality that postoperative chemoradiotherapy has better 5-year disease-free and overall survival than postoperative radiotherapy.
- In adult patients with head and neck cancer a difference between postoperative chemoradiotherapy and postoperative radiotherapy in 2-year locoregional control and 2-year overall survival could neither be demonstrated nor refuted (low level of evidence).
- In adult patients with head and neck cancer there is evidence of low quality that postoperative chemoradiotherapy has better local and locoregional control rates at 5 years than postoperative radiotherapy.
- In adult patients with head and neck cancer there is evidence of moderate quality that postoperative chemoradiotherapy leads to a lower rate of disease recurrence than postoperative radiotherapy.
- In adult patients with head and neck cancer there is evidence of low quality that postoperative chemoradiotherapy leads to more acute toxicities than postoperative radiotherapy. For late toxicities a difference between postoperative chemoradiotherapy and postoperative radiotherapy could neither be demonstrated nor refuted.

- No comparative studies were identified that addressed quality of life outcomes of postoperative chemoradiotherapy versus postoperative radiotherapy in adult patients with head and neck cancers.
- No comparative studies were identified that addressed disease-free survival, (loco)regional control or quality of life outcomes of postoperative chemoradiotherapy versus postoperative radiotherapy in adult patients with oropharyngeal cancers.
- No RCTs or comparative studies were identified that addressed disease-free survival, recurrence rate, (loco)regional control, overall survival, quality of life or adverse events of postoperative chemoradiotherapy versus postoperative radiotherapy in adult patients with hypopharyngeal or laryngeal cancers.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	• No clear differences were found between postoperative (chemo)radiotherapy versus no postoperative (chemo)radiotherapy, except for recurrence rate in patients with oropharyngeal cancer. • Postoperative chemoradiotherapy was found to be associated with better outcomes (DFS, locoregional control, recurrence) than postoperative radiotherapy, but with more acute toxicity.
Quality of evidence	• The evidence comparing postoperative (chemo)radiotherapy to no (chemo)radiotherapy is mainly based on observational studies. • For the comparison between postoperative (chemo)radiotherapy and postoperative radiotherapy several RCTs were found.
Costs (resource allocation)	No cost issues were considered.
Patients values and preferences	No comments were received from the patient representatives.
Comments	• In concurrent primary chemoradiotherapy, radiotherapy should be given up to a total dose of 70 Gy (2 Gy per fraction, 5-6 days per week, 6-7 weeks) and chemotherapy should be platinum-based. • No recommendation on the combination of cetuximab and radiotherapy was added, because no formal literature search was done.

3.2.2.5 Radiotherapy: recommendations

In the first part of the guideline on head and neck cancer – focusing on oral cavity cancer [9] – several recommendations were formulated regarding radiotherapy, which are also applicable to oropharyngeal, hypopharyngeal and laryngeal cancer. An overview is provided in Table 23.

Table 23 – Selected radiotherapy recommendations from oral cavity cancer guideline [9]

Recommendation	Strength of recommendation	Level of Evidence
Interruption of radiotherapy will be detrimental to tumour control and should be avoided.	Strong	Adapted recommendation
Chemoradiotherapy should only be performed at facilities in which radiotherapy- or chemotherapy-induced acute toxicities can be adequately managed.	Strong	Adapted recommendation

Based on the evidence and other considerations reported above the following recommendations can be formulated in addition:

Recommendations	Strength of Recommendation	Level of Evidence
• **In medically fit patients with locally-advanced (stage III and IV) non-metastatic oropharyngeal, hypopharyngeal or laryngeal cancer, primary concomitant platinum-based chemoradiotherapy is recommended (except in patients with T4a laryngeal cancer).**	Weak	Very low
• **IMRT is recommended in patients with advanced oropharyngeal, hypopharyngeal or laryngeal cancer.**	Strong	Very low
• **In patients with stage II oropharyngeal, hypopharyngeal or laryngeal cancer primary radiotherapy with altered fractionation (hyperfractionation or accelerated fractionation without dose reduction) is recommended.**	Strong	Low
• **In patients with locally-advanced (stage III and IV) oropharyngeal, hypopharyngeal or laryngeal cancer in whom a non-surgical approach is chosen and in whom concomitant chemoradiotherapy is not an option, primary radiotherapy with hyperfractionation or accelerated fractionation without dose reduction can be considered.**	Weak	Low
• **Primary radiotherapy with accelerated fractionation with dose reduction is not recommended in patients with head and neck cancer.**	Strong	Low
• **Postoperative (chemo)radiotherapy should be performed for advanced pT categories (T3 and T4) and lymph node involvement (> pN1). It should be considered for peri-neural extension or lymphatic vessels infiltration. In high-risk patients (i.e. close or positive resection margins, extracapsular spread) postoperative chemoradiotherapy is recommended.**	Strong	Low
• **Postoperative radiotherapy should be fractionated conventionally (e.g. 60-66 Gy in 6 to 6.5 weeks, 2 Gy per day, 5 times a week).**	Weak	Low
• **Postoperative (chemo)radiotherapy should be commenced as early as possible, i.e. within 6 weeks after surgery, and should be completed within 11-13 weeks after surgery.**	Strong	Low
• **In concurrent postoperative chemoradiotherapy, radiotherapy should be fractionated conventionally (i.e. 2 Gy per fraction, 5 days per week, total dose 64-66 Gy) and chemotherapy should be platinum-based (100 mg/m² 3-weekly).**	Weak	Low

3.2.3 Induction chemotherapy

In the first part of the guideline on head and neck cancer – focusing on oral cavity cancer [9] – a search was done for studies evaluating the effectiveness and safety of induction chemotherapy in patients with head and neck cancer. The results of that search were used for the second part too, and are described below. Methodological information can be found in the appendix of the first part.

Two systematic reviews were included that examined the evidence for the effect of induction chemotherapy before locoregional therapy (i.e. RT, CRT or surgery) compared to no induction chemotherapy (but identical locoregional therapy) in adult patients (≥18 years of age) diagnosed with stage 3 and 4 HNSCC.[171, 177]

In the systematic review of Furness et al. induction chemotherapy followed by locoregional treatment was compared to locoregional treatment alone in patients with oral cavity or oropharyngeal cancer.[171] The search date was December 2010 and the overall risk of bias of this review was judged to be low. The review included 89 RCTs, of which 26 RCTs addressed the relevant comparison. Four of the included RCTs had a low risk of bias, 10 a high risk of bias and 12 an unclear risk of bias. Results of 25 RCTs were combined for total mortality. A borderline non-significant difference was found for induction chemotherapy plus locoregional treatment versus locoregional treatment alone (HR=0.92; 95%CI 0.84 to 1.00). Sensitivity analysis of four low risk of bias trials showed a significant benefit for induction chemotherapy (HR=0.80; 95%CI 0.67 to 0.97). Eight RCTs provided evidence of a significant benefit for disease-free survival in favour of induction chemotherapy (HR=0.78; 95%CI 0.67 to 0.90).

In the systematic review of Ma et al. several interventions and comparisons were studied, of which two were relevant: induction chemotherapy followed by locoregional treatment versus locoregional treatment alone and induction chemotherapy followed by concomitant chemotherapy and radiotherapy versus concomitant chemotherapy and radiotherapy alone.[177] The search for this review was performed in 2011 and the overall risk of bias of this review was judged to be low. The review included 40 RCTs studying induction chemotherapy in patients with head and neck squamous cell carcinoma without distant metastasis. In 28 studies induction chemotherapy followed by locoregional treatment was compared with locoregional treatment alone. Eighteen studies that were included in the meta-analysis of Furness et al. were included in this meta-analysis as well.

No significant difference was found for OS (HR=0.94; 95%CI 0.87 to 1.01). Looking at subgroups, no significant difference was found for resectable/unresectable tumours at diagnosis, but for the specific induction chemotherapy protocol with cisplatin and 5-fluorouracil (10 RCTs) there was a benefit for induction chemotherapy followed by locoregional treatment compared to locoregional treatment alone (HR=0.87; 95%CI 0.78 to 0.97). In two studies a difference for 2-year and 5-year locoregional recurrence rate was presented; there were no significant differences (2-year: RD=-2%, 95%CI -11% to 8%; 5-year: RD=-1%, 95%CI -14% to 13%). In two studies induction chemotherapy followed by concomitant chemotherapy and radiotherapy was compared with concomitant chemotherapy and radiotherapy alone. No significant difference was found for OS (HR=0.96; 95%CI 0.71 to 1.30) or for progression-free survival (HR=0.99; 95%CI 0.53 to 1.87).

The update of the search (from January 2011 onwards) to identify primary studies published after the search date of the included reviews[171, 177] resulted in the inclusion of five additional relevant studies.

The first study[178] performed a randomized controlled trial with a Zelen's design (in which patients are randomized to either the treatment or control group before giving informed consent) in which 547 patients with stage III and IV squamous cell carcinoma of the supraglottic or glottic larynx were studied. Participants were allocated to one of the three study groups: induction chemotherapy (cisplatin and 5FU) followed by radiotherapy for responders (and surgery for non-responders), radiotherapy with concomitant chemotherapy or radiotherapy alone. As only the comparison induction chemotherapy followed by radiotherapy versus radiotherapy alone is relevant to the research question, only the results of this comparison will be discussed. The risk of bias of this study was judged to be high. Patient characteristics were well balanced between groups at baseline. Ten-year OS did not significantly differ between the two groups of interest (HR=0.87; 95%CI 0.68 to 1.12). As for quality of life outcomes, impaired speech or voice quality ("moderate difficulty saying some words, and cannot use the phone; only family and/or friends can understand me; or cannot be understood") was reported during years 2 to 5 in 3% to 9% of patients in the induction group and 5% to 8.5% of patients who received RT alone.

Swallowing dysfunction ("can only swallow soft foods" or worse) was reported during years 2 to 5 in 13% to 14% of patients in the induction group versus 10% to 17% of patients receiving RT alone. These results were not statistically tested. No significant differences between the two groups of interest were found for disease-free survival at ten years (HR=0.79; 95%CI 0.63 to 1.00) and local control at ten years (HR=0.85; 95%CI 0.63 to 1.15). With regard to adverse events, only significant differences between the two groups were found for grade 3 to 5 adverse events other than hematologic toxicity, toxicity of skin, mucous membrane/stomatitis, subcutaneous tissue, salivary gland, pharynx/oesophagus, larynx, upper gastrointestinal genitourinary/renal, spinal cord, neurologic, bone and joint (RR=0.29; 95%CI 0.10 to 0.87). No significant differences between the two groups were found for post-treatment mortality (deaths caused by complications of protocol treatment: RR=1.78; 95%CI 0.61 to 5.20). The study did not report on recurrence rate.

The second study[179] describes the PARADIGM study in which the use of docetaxel, cisplatin, and fluorouracil (TPF) induction chemotherapy followed by concurrent chemoradiotherapy was compared with cisplatin-based concurrent chemoradiotherapy alone in patients with locally-advanced head and neck cancer. One hundred and forty-five adult patients with previously untreated, non-metastatic, newly diagnosed head and neck cancer were randomly assigned to receive either induction chemotherapy with three cycles of TPF followed by concurrent chemoradiotherapy with either docetaxel or carboplatin or concurrent chemoradiotherapy alone with two cycles of bolus cisplatin. The risk of bias of this study was judged to be high. Patient characteristics were well balanced between groups at baseline. No significant differences between the two groups were found for 3-year OS, which was 73% (95%CI 60–82) in the induction therapy followed by chemoradiotherapy group and 78% (95%CI 66–86) in the chemoradiotherapy alone group (HR=1.09; 95%CI 0.59 to 2.03). Also total local or regional failure did not show significant differences between the groups (RR=1.07; 95%CI 0.50 to 2.31). With regard to adverse events, more patients had febrile neutropenia in the induction chemotherapy followed by chemoradiotherapy group (16/70) than in the chemoradiotherapy alone group (1/75) (RR=17.14; 95%CI 2.33 to 125.90). No significant differences between groups were found for the remaining adverse events. The authors stated that no treatment-related deaths occurred on this study. Quality of life, disease-free survival and recurrence rate were not assessed.

The third study[100] reports the 10-year results of the EORTC trial 24891 comparing a larynx-preservation approach to immediate surgery in hypopharynx and lateral epilarynx squamous cell carcinoma. Two hundred and two patients were randomized to either the surgical approach (total laryngectomy with partial pharyngectomy and neck dissection, followed by irradiation) or to the chemotherapy arm (up to three cycles of induction chemotherapy (cisplatin 100 mg/m^2 day 1 + 5-FU 1000 mg/m^2 day 1–5) followed by irradiation in complete responders and by surgery in the other patients). The risk of bias of this study was judged to be low. Patient characteristics were well balanced between groups at baseline. Only the results for the induction chemotherapy arm vs. surgery arm are discussed (results for the exact comparison: induction chemotherapy + surgery + radiotherapy versus immediate surgery + radiotherapy are not reported separately). No significant differences in 10-year OS (HR=0.88; 95%CI 0.65 to 1.19), local control (local failure: RR=0.94; 95%CI 0.37 to 2.40; locoregional failure: RR=2.26; 95%CI 0.83 to 6.16; regional failure: RR=0.75; 95%CI 0.37 to 1.52 and distant failure: RR=1.05; 95%CI 0.73 to 1.52) and post-treatment mortality (deaths caused by induction chemotherapy related toxicity and postoperative deaths: RR=4.70; 95%CI 0.23 to 96.70) between the induction chemotherapy arm and the surgery arm were found. The 5- and 10-year rates of survival with preserved larynx were 21.9% (95%CI 13.7% to 30.0%) and 8.7% (95%CI 2.5% to 16.1%), respectively. Quality of life, disease-free survival, recurrence rate and adverse events were not assessed.

The fourth study[180] assessed the efficacy of induction chemotherapy followed by radiotherapy in advanced head and neck cancer. One hundred and eighty patients were randomized to either the chemotherapy-radiotherapy (CT-RT) arm or the control arm which received external radiotherapy only. The risk of bias of this study was judged to be high. The two arms were found to be comparable in respect of site, stage of disease, age and sex of patients at baseline. Five-year survival, which was calculated by Kaplan-Meier method, was higher in the CT-RT arm but did not reach statistical significance (21% vs. 16%, p>0.05 by log rank test). With regards to adverse events, no significant differences between the two groups were found, except for upper gastrointestinal tract (RR=1.07; 95%CI 1.01 to 1.13).

The study did not report on quality of life, disease-free survival, local control, recurrence rate and mortality.

The fifth study[181] evaluated induction chemotherapy with docetaxel, cisplatin, and fluorouracil (TPF) followed by surgery and postoperative radiotherapy compared to up-front surgery and postoperative radiotherapy in patients with locally advanced resectable oral squamous cell carcinoma. Two hundred and fifty-six patients received either two cycles of TPF induction chemotherapy followed by radical surgery and postoperative radiotherapy or up-front radical surgery and postoperative radiotherapy. The risk of bias of this study was judged to be high. Patient characteristics were well balanced between groups at baseline. There was no significant difference in OS after two years (HR=0.977; 95%CI 0.634 to 1.507), disease-free survival (HR = 0.974; 95%CI, 0.654 to 1.45) and locoregional recurrence (HR = 1.019; 95%CI 0.618 to 1.524) between patients treated with and without TPF induction. The authors stated that there were no unexpected toxicities, and no significant differences in adverse events between the two groups were found. With regards to post treatment mortality, the authors reported that no chemotherapy-, surgery-, or radiotherapy-related deaths occurred. Quality of life and local control were either not assessed or presented.

Meta-analyses for the outcomes 'OS' and 'disease-free survival' from the two SRs were combined and updated with the results from the RCTs identified by the update of the search. In the included reviews results were separately reported according to chemotherapy regimen, on which the GRADE profiles were based. However, overall meta-analyses for the comparison induction chemotherapy (regardless of regimen) with locoregional therapy vs. identical locoregional therapy for the outcomes 'OS' and 'disease-free survival' were also performed (Figure 84, Appendix 6.4 and Figure 85, Appendix 6.4 of first part). The overall pooled result for 'OS' indicated a statistically significant difference between the two treatment groups in favour of induction chemotherapy before locoregional therapy (HR=0.93; 95%CI 0.87 to 0.99). For 'disease-free survival' the overall pooled result was also in favour of induction chemotherapy (HR=0.79; 95%CI 0.70 to 0.90).

With regard to subgroup analyses according to chemotherapy regimen, statistically significant differences were only found in favour of cisplatin and 5-fluorouracil (PF) for 'OS' (HR=0.87; 95%CI 0.79 to 0.95) and 'disease-free survival' (HR=0.76; 95%CI 0.66 to 0.87). The pooled results of two RCTs for the outcome post-treatment mortality[100, 178] was not significant: RR=2.11 (95%CI 0.75 to 5.92) (Figure 86, Appendix 6.4 of first part).

In summary, significant differences between induction chemotherapy followed by locoregional therapy vs. locoregional therapy were found for 'OS' and 'disease-free survival'. These favourable results for induction chemotherapy given before locoregional therapy seem to be mainly at the impact of the subgroup induction chemotherapy with cisplatin and 5-fluorouracil (PF) where significant differences for both outcomes were found. A difference in quality of life, local control, recurrence rate and post treatment mortality could neither be demonstrated nor refuted. With regard to radiotherapy related adverse events, a significant difference was found for mucositis, febrile neutropenia (induction chemotherapy with platin-containing combinations other than cisplatin and 5-fluorouracil followed by locoregional therapy versus locoregional therapy) and for the category 'other adverse events' (induction chemotherapy with cisplatin and 5-fluorouracil followed by locoregional therapy versus locoregional therapy). However, when interpreting the results it should be kept in mind that patients receiving chemotherapy could additionally suffer from chemotherapy-related adverse events. These adverse events effects are not included in the conclusions section.

Conclusions

Cisplatin and 5-fluorouracil chemotherapy

- There is evidence of moderate quality that in adult patients with locally-advanced HNSCC (TNM stage 3 and 4) induction chemotherapy with cisplatin and 5-fluorouracil followed by locoregional treatment results in better overall survival compared to locoregional treatment alone.
- There is evidence of high quality that in adult patients with locally-advanced HNSCC (TNM stage 3 and 4) induction chemotherapy with cisplatin and 5-fluorouracil followed by locoregional treatment results in better disease-free survival compared to locoregional treatment alone.
- The available evidence of low to very low quality does not allow to draw conclusions about the effect of induction chemotherapy with cisplatin and 5-fluorouracil followed by locoregional treatment compared to locoregional treatment alone on quality of life, local control, post-treatment mortality and grade III acute adverse events (skin, mucous membrane, larynx, upper gastrointestinal and leukopenia) in adult patients with locally-advanced HNSCC (TNM stage 3 and 4).
- The available evidence of low to very low quality does not allow to draw conclusions about the effect of induction chemotherapy with cisplatin and 5-fluorouracil followed by locoregional treatment compared to locoregional treatment alone on grade III+ late adverse events (hematologic, skin, mucous membrane/stomatitis, subcutaneous tissue, salivary gland, pharynx/esophagus, larynx, upper gastrointestinal, genitourinary/renal, spinal cord, neurologic, bone, joint) in adult patients with locally-advanced HNSCC (TNM stage 3 and 4), except for the category 'other', for which there are indications of a difference in favour of induction chemotherapy.

Other platin-containing combinations of chemotherapy

- The available evidence of moderate quality does not allow to draw conclusions about the effect of induction chemotherapy with platin-containing combinations other than cisplatin and 5 fluorouracil followed by locoregional treatment compared with locoregional treatment alone on overall survival in adult patients with locally-advanced HNSCC (TNM stage 3 and 4).
- The available evidence of low quality does not allow to draw conclusions about the effect of induction chemotherapy with platin-containing combinations other than cisplatin and 5 fluorouracil followed by locoregional treatment compared with locoregional treatment alone on disease-free survival, recurrence rate, post-treatment control and the need for a PEG tube in adult patients with locally-advanced HNSCC (TNM stage 3 and 4).
- The available evidence of very low quality does not allow to draw conclusions about the effect of induction chemotherapy with platin-containing combinations other than cisplatin and 5 fluorouracil followed by locoregional treatment compared with locoregional treatment alone on local control in adult patients with locally-advanced HNSCC (TNM stage 3 and 4).
- The available evidence of very low quality does not allow to draw conclusions about the effect of induction chemotherapy with platin-containing combinations other than cisplatin and 5 fluorouracil followed by locoregional treatment compared with locoregional treatment alone on grade III+ late adverse events (mucositis, febrile neutropenia, pain, xerostomia, neuropathy, trismus, dermatitis, dysphagia and odynophagia) in adult patients with locally-advanced HNSCC (TNM stage 3 and 4). However, for mucositis and febrile neutropenia there are indications of a difference in favour of induction chemotherapy.

Multi-agent induction chemotherapy

- The available evidence of low quality does not allow to draw conclusions about the effect of multi-agent induction chemotherapy without platin followed by locoregional treatment compared with locoregional treatment alone on overall survival and disease-free survival in adult patients with locally-advanced HNSCC (TNM stage 3 and 4).

Single-agent induction chemotherapy (methotrexate)

- The available evidence of moderate quality does not allow to draw conclusions about the effect of single-agent induction chemotherapy (methotrexate) followed by locoregional treatment compared with locoregional treatment alone on overall survival in adult patients with locally-advanced HNSCC (TNM stage 3 and 4).

Other considerations

Factor	Comment
Balance between clinical benefits and harms	• The meta-analysis by Ma et al. (3 studies) and the studies of Lefebvre 2012 and Forastière 2013 showed that a larynx-preserving strategy with induction chemotherapy can be used without compromising survival in patients with laryngeal or hypopharyngeal cancer. Most experience is available with the combination of cisplatin, 5FU and docetaxel. Induction chemotherapy appears to be less toxic. • The survival benefit of induction chemotherapy for patients with oropharyngeal cancer is only modest. • When induction chemotherapy is used within the context of strategies other than organ preservation (e.g. followed by concurrent CRT), the survival benefit is not convincing, as was shown in the meta-analysis by Ma et al. and confirmed by two more recent trials published after August 2013 (Cohen, JCO 2014; Hitt, Ann Oncol 2014).
Quality of evidence	Several RCTs are available, but many suffer from methodological shortcomings.
Costs (resource allocation)	No cost issues were considered.
Patients values and preferences	No comments were received from the patient representatives.

Recommendations	Strength of Recommendation	Level of Evidence
• **In patients with locally-advanced hypopharyngeal or laryngeal cancer, induction chemotherapy – followed by radiotherapy in responders and surgery in non-responders – is a valid option within the context of a function-sparing treatment strategy. The preferred induction chemotherapy is TPF.**	Strong	Low
• **In patients with oropharyngeal cancer, the evidence is insufficient to recommend induction chemotherapy yet.**	Weak	Low
• **In strategies other than function-sparing, induction chemotherapy is not recommended as a standard treatment.**	Strong	Low

3.2.4 Management of the neck lymph nodes

The detailed results of the literature search and assessment can be found in Appendix 2.3.5, Appendix 3.3.1, Appendix 3.3.6, Appendix 4.5, Appendix 5.5 and Appendix 6.5.

3.2.4.1 Neck dissection versus no neck dissection

Mixed study population

Two observational studies were identified that included a mixed study population and did not specify the result according to primary tumour sites.[182, 183]

The study of Liu et al. is a retrospective study in which previously untreated patients with N2/3 SCC of the supraglottis (N=54) or hypopharynx (N=31) were included who had undergone neck dissection before chemoradiation (N=46) or had not received neck dissection in a chemoradiation protocol (N=39). Salvage surgery was used for local or cervical node residual tumour or recurrence after chemoradiotherapy. Risk of bias was judged to be high as a result of non-concurrency of study groups and lack of blinding, and uncertainty about comparability of study groups as well as unclear risk of attrition and reporting bias. There were 16 (34.8%) recurrences in the neck dissection group compared to 15 (38.5%) in the group that did not undergo neck dissection. The 5-year control rate of neck nodes was better for neck dissection compared to no neck dissection (86.3% vs. 65.9%, p=0.02). Five-year overall survival rate was 46.6% and 35.1% for neck dissection versus no neck dissection. No major postoperative complications were seen in the neck dissection group compared to 7/15 major complications in the no neck dissection group (probably applying to patients that underwent salvage surgery). Disease-free survival and quality of life were not addressed.

Psychogios et al. retrospectively compared the effect of elective neck dissection (N=101) with observation (N=123) in previously untreated head and neck SCC with definitive surgical treatment as a monotherapy. Primary tumour site was the oral cavity in 72 (32.1%) patients, the oropharynx in 63 (28.2%) patients, the hypopharynx in 17 (7.6%) patients and the supraglottic region in 72 (32.1%) patients. Risk of bias of this study was judged to be high. Patients who were treated between 1980 and 2010 were included and the intervention and comparator group are likely to be non-concurrent. As details on patient characteristics were not reported per treatment group, the comparability between the two groups is unclear. No significant differences were found in five-year regional control (96.0% vs 90.3%, p=0.07) and five-year OS (72.4% vs. 67.4%, p=0.197). The study did not assess disease-free survival, recurrence rate, quality of life and adverse events.

Oropharynx

One systematic review was included that compared the clinical effectiveness of neck dissection with other treatment options in patients with cancer of the oropharynx.[79] This review compared various surgical treatment modalities with each other or with other treatment modalities (such as radiotherapy, chemotherapy, immunotherapy/biotherapy with or without surgery) in patients with cancer of the oral cavity or oropharynx. Patients with cancer of the hypopharynx, nasopharynx, larynx or lip were excluded. The search date was February 2011 and the overall risk of bias of this review was judged to be low. The review included seven RCTs with a total of 669 patients, of whom 667 had cancer of the oral cavity. So, only two patients with oropharyngeal cancer were included. Therefore, it must be concluded that in this systematic review no RCTs were identified that applied to patients with oropharyngeal cancer.

The update of the search identified no RCTs.

Five relevant comparative observational studies were identified.[184-188] In addition one other observational study addressed a mixed study population (described above), amongst which patients with oropharyngeal cancer.[183]

In the study of Böscke et al., a retrospective chart review, patients were included with previously untreated histologically proven oropharyngeal SCC and clinically negative neck lymph node involvement (cN0), undergoing surgical treatment of the primary lesion with elective neck dissection (END) or without elective neck dissection (OBS) between 1986 and 2004.[184] Risk of bias for this study was judged to be high. Decision-making for or against a therapeutic procedure did not follow a standardized protocol. Furthermore, the retrospective structure of the study did not allow for the incorporation of known confounders. Although study groups seem quite comparable, there are relatively small numbers of participants in the groups. Ten percent of the patients in the END group and 24% of the patients in the OBS group developed local and/or regional recurrence. Three- and five-year disease-free survival for END vs. OBS was 87 % vs. 76 % and 78 % vs. 67 %, respectively (HR 1.79, 95%CI 0.57 to 5.56). Three- and five-year OS was

93% vs. 82% and 82% vs. 76%, respectively (HR 1.01, 95%CI 0.44 to 2.27) and three- and five year disease-specific survival 97% vs. 88% and 97% vs. 81%, respectively (HR 2.22, 95%CI 0.49 to 10). (Loco)regional control, quality of life and adverse events were not addressed.

The study of Donatelli et al. was a prospective cohort study in which patients with newly diagnosed, stage IV oropharyngeal cancer, treated with chemoradiation, were enrolled from 2003.[185] Patients treated with chemoradiotherapy with (N=38) and without (N=65) neck dissection were compared. Risk of bias of this study was judged to be high as there is considerable risk of selection and detection bias and uncertainty about attrition, concurrency and comparability of the study groups under comparison. Quality of life, measured with SF-36 and Head and Neck Quality of Life Instrument, was the only outcome that was assessed. Only in the body pain domain of the SF-36 the groups differed significantly in change scores from baseline to one year (-2.2 vs. 8.0, p=0.041).

In a retrospective cohort study by Lanzer et al. patients with SCC of the oral cavity or oropharynx with contralateral clinically negative neck, who had undergone operative resection of primary with or without adjacent adjuvant radiotherapy, were included.[186] Elective contralateral neck dissection (N=24) was compared with observation (N=128). Risk of bias for this study was judged to be high. Patients who were treated between 1999 and 2009 were included and the intervention and comparator group might be non-concurrent. As it is not stated whether enrolment was consecutively and whether patients were left out of the analyses, risk of attrition bias is unclear. Local recurrences occurred in 5 (20.8%) patients in the neck dissection group and in 14 (10.9%) in the observation group. For lymph node recurrences the numbers were 1 (4.2%) and 11 (8.6%), respectively. Neither the five-year recurrence-free survival rate (59% vs. 66%, p=?), the five-year loco-regional survival rate (90% vs. 89%, p=0.452), nor the OS rate (72.5% vs. 70%, p=0.971) differed significantly between the groups. The study did not assess disease-free survival, quality of life and adverse events.

In a retrospective chart review by Sakashita et al. the effect of initial neck dissection (ND) (N=93) was compared to a “wait-and-see” policy (N=109) in patients with node-positive oropharyngeal SCC.[187] Risk of bias of this study was judged to be high. Patients who were treated between April 2005 and March 2007 were included. As it is not stated whether enrolment was consecutively and whether patients were left out of the analyses, risk of attrition bias is unclear. Recurrence occurred in 17 of 93 patients in the ND group and in 40 of 109 in the wait-and-see group. No significant differences between the two groups were found in four-year regional control rate (84.9% vs. 77.6%, p=0.2382) and four-year OS rate (78.7% vs. 74.0%, p=0.34). As for four-year regional control rates according to N classification, only significant differences were found for N2a (100% vs 62.5%, p=0.02). No significant differences were found for four-year OS rates according to N classification. The study did not assess disease-free survival, quality of life and adverse events.

In a retrospective chart review by Suzuki et al. the effect of neck dissection (ND, N=36) was compared to observation (N=48) in oro- and hypopharyngeal SCC patients with N2–3 disease treated with chemoradiotherapy.[188] There were 59 patients with oropharyngeal cancer (ND N=27, observation N=32). Risk of bias of this study was judged to be high. Patients who were treated between 1995 and 2006 were included and the intervention and comparator group might be non-concurrent. As it is not stated whether enrolment was consecutively and whether patients were left out of the analyses, risk of attrition bias is unclear. Patient characteristics were not reported per treatment group, which is why the comparability between the two groups is unclear. Five-year regional control (RC) and five-year OS were reported stratified by tumour site and did not differ between the study groups for oropharyngeal cancer patients (ND vs. observation, adjusted by age, sex, tumour and nodal classification, for RC: HR 0.17, 95%CI 0.02 to1.86 and for OS: HR 0.73, 95%CI 0.23 to 2.31). Relapses and adverse events were presented for oro- and hypopharyngeal patients together. Relapse occurred in 14 of 36 (38.9%) patients of the ND group and 20 of 48 (41.7%) of the observation group. As for adverse events, nine patients (25.0%) experienced postoperative complications from ND, 3 for laryngeal oedema, 3 for lymph fluid leaks, 2 for dysphagia, and 1 for lingual nerve paralysis. No patients died as a result of ND. The study did not assess disease-free survival and quality of life.

Conclusions

- In adult patients with various stages of oropharyngeal cancer with varying degrees of nodal involvement a difference in disease-free survival, recurrence, (loco)regional control, overall survival, quality of life or adverse effects of neck dissection versus no neck dissection could neither be demonstrated nor refuted (very low level of evidence).

Hypopharynx

No systematic reviews or RCTs were identified that compared neck dissection with no neck dissection in patients with cancer of the hypopharynx.

Two relevant observational studies were included.[188, 189] In addition two other observational studies addressed a mixed study population (described above), amongst which patients with hypopharyngeal cancer.[182, 183]

Al-Mamgani et al. analysed institutional data of 135 consecutive, previously untreated patients with node-positive hypopharyngeal cancer treated with curative intent from January 1996 to November 2010.[189] Up-front neck dissection (ND, N=32) was compared to no up-front ND (N=103). Risk of bias for this study was judged to be high. Groups differed significantly for T-stage and the number of patients treated with chemoradiation. No differences between ND and no ND groups were seen for disease-free survival (64% vs. 45%, p=0.06), local control (84% vs. 72%, p=0.15) and regional control (92% vs. 87%, p=0.37). Three-year OS was significantly higher in the ND group (66% vs. 42%, p=0.04). Differences between groups for quality of life assessment (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)) and EORTC Head and Neck 35 (EORTC H&N35) were statistically not significant. Regarding adverse events there were significant differences between ND group and no ND group for incidence of grade 3 acute toxicity (50% vs. 72%, p=0.02) and incidence of feeding tube dependency (grade 3 dysphagia; 22% vs. 46%, p=0.02). As more patients in the no ND group had T3 or T4 tumours, larger radiation fields were needed, increasing the chance of development of serious acute toxicity. For late toxicity no differences between groups were found. Recurrence rate was not assessed.

In a retrospective chart review by Suzuki et al. the effect of neck dissection (ND, N=36) was compared to observation (N=48) in oro- and hypopharyngeal SCC patients with N2–3 disease treated with chemoradiotherapy.[188] There were 25 patients with hypopharyngeal cancer (ND N=9, observation N=16). Risk of bias of this study was judged to be high. Patients who were treated between 1995 and 2006 were included and the intervention and comparator group might be non-concurrent. As it is not stated whether enrolment was consecutively and whether patients were left out of the analyses, risk of attrition bias is unclear. Patient characteristics were not reported per treatment group, which is why the comparability between the two groups is unclear. Five-year regional control (RC) and five-year OS were reported stratified by tumour site and did not differ between the study groups for hypopharyngeal cancer patients (ND vs. observation, adjusted by age, sex, tumour and nodal classification, for RC: HR 0.32, 95%CI 0.02 to 5.93 and for OS: HR 7.76, 95%CI 0.58 to 103.83). Relapses and adverse events were presented for oro- and hypopharyngeal patients together. Relapse occurred in 14 of 36 (38.9%) patients of the ND group and 20 of 48 (41.7%) of the observation group. As for adverse events, nine patients (25.0%) experienced postoperative complications from ND, 3 for laryngeal oedema, 3 for lymph fluid leaks, 2 for dysphagia, and 1 for lingual nerve paralysis. No patients died as a result of ND. The study did not assess disease-free survival and quality of life.

Conclusions

- In adult patients with node-positive hypopharyngeal cancer (all stages) a difference in disease-free survival of neck dissection versus no neck dissection could neither be demonstrated nor refuted (very low level of evidence).
- In adult patients with node-positive hypopharyngeal cancer (all stages) a difference in regional recurrence, (loco)regional control, overall survival or quality of life of neck dissection versus no neck dissection could neither be demonstrated nor refuted (very low level of evidence).
- In adult patients with node-positive hypopharyngeal cancer (all stages) a difference in adverse events of neck dissection versus no neck dissection could neither be demonstrated nor refuted (very low level of evidence).

Larynx

One systematic review was included that compared the clinical effectiveness of neck dissection with other treatment options in patients with cancer of the supraglottic larynx.[190]

This review compared neck dissection with radiotherapy, neck dissection plus preoperative and/or postoperative radiotherapy, or a 'wait and see' policy (conservative management) in patients with clinically neck negative supraglottic laryngeal SCC. The search date was December 2006 and the overall risk of bias of this review was judged to be low, but the results of the quality assessment were not reported for the individual studies. No RCTs were identified, but the review included seven comparative observational retrospective studies. A total of 792 patients were included (neck dissection = 259, radiotherapy = 272, combined therapy = 142 and 'wait and see' = 119). The majority of the tumours in the studies (75%) were stage T1/T2. Three studies provided data regarding the location of the primary carcinoma; the most frequent sites were epiglottis (67%), ventricular bands (30%), arytenoidepiglottis folds (10%) and ventricle (5%). No meta-analysis was performed due to clinical heterogeneity. OS (1 study, 115 patients) of neck dissection versus neck radiotherapy was 55% (95%CI 31 to 79) vs. 71% (95%CI 61 to 81) (p=0.4). DFS (four studies, 648 patients) did not differ significantly between the groups. OS (2 studies, 95 patients) of neck dissection versus a wait and see policy was 64% vs. 50% ($p < 0.05$) in one study and 46.4% vs. 50% (RD = -3.6%, 95%CI -34.9 to +28.2) in another study. The DFS (three studies: N unclear) did not differ significantly between the groups. Recurrence rate, (loco)regional control, quality of life and adverse events were not addressed.

The update of the search identified no RCTs.

Four relevant comparative observational studies were included.[191-194] In addition, two other observational studies addressed a mixed study population (described above), amongst which patients with laryngeal cancer.[182, 183]

The study of Bohannon et al. is a retrospective review of patients with N0 necks who underwent salvage laryngectomy with (N=38) or without (N=33) neck dissection between January 2001 and December 2007.[191] Risk of bias for this study was judged to be high. Although study groups seemed quite comparable, there were relatively small numbers of participants in the groups. No differences were seen for recurrence between patients with and without neck dissection (local recurrence: 10.5% vs.15%; regional recurrence: 7.9% vs. 15%, p=0.5). Survival rate at 2 years did not differ between the study groups (52% (neck dissection) vs. 48% (no neck dissection), p=0.48). Significantly more complications occurred in the neck dissection group compared to the group without neck dissection (16/38 (42.2 %) vs. 7/33 (21.3%), p=0.04). Disease-free survival, (loco)regional control and quality of life were not addressed..

Another retrospective chart review was presented by Gallo et al.[192] Consecutive cN0 laryngeal cancer patients who underwent surgical treatment between January 1978 and December 2003 were included in the study. Elective neck dissection (N=759) was compared to wait-and-see policy (N=1448). Elective neck dissection was either a radical neck dissection (RND, N=128), functional neck dissection (FND, N=403) or selective jugular node dissection (JND/SND, N=228). Risk of bias for this study was judged to be high. Analyses of this retrospective study at risk for selection bias were unadjusted for patient or disease characteristics. The five-year neck recurrence rate was 65/795 (8.5%) and 225/1448 15.5% for neck dissection group and the wait-and-see group, respectively. The study did not address disease-free survival, (loco)regional control, OS, quality of life and adverse events for the comparison between elective neck dissection and wait-and-see policy.

Jin et al. retrospectively analysed consecutive patients with biopsy proven, previously untreated, SCC of the supraglottic larynx who were treated with surgery (N=37) or radiotherapy (N=18), or received no treatment (N=46) for a clinically negative neck.[193] Risk of bias for this study was judged to be high. Details on patient characteristics and treatment were not specified for the three study groups. Five-year rates for neck disease-free survival (NDFS), local-regional control (LRC) and OS did not differ significantly between groups (NDFS: 78.5% vs. 83.3% vs. 87.3%, p=0.455; LRC: 74.3% vs. 65.7% vs. 74.0%, p=0.998; OS 65.8% vs. 83.3% vs. 72.4%, p=0.298 for surgery vs. radiotherapy vs. no treatment groups, respectively). Recurrence rate, quality of life and adverse events were not addressed.

The study of Pantel et al. retrospectively assessed the effect of elective neck dissection (N=35) compared to no neck dissection (N=38) in patients identified as having newly diagnosed glottic SCC with TNM stage pT2cN0M0 who were primarily treated by surgical means.[194] Risk of bias of

this study was judged to be high. Patients who were treated between 1996 and 2005 were included and the intervention and comparator group might be non-concurrent. No significant differences between the two groups were found in recurrence-free survival rates at 5 years (42.6% vs 76.9%, p=0.072). Five-year OS was 48.0% in the ND group compared to 64.5% in the no ND group. The study did not assess disease-free survival, (loco)regional control, quality of life and adverse events.

Conclusions

- In adult patients with clinically neck negative laryngeal cancer a difference in disease-free survival, (loco)regional control or overall survival of neck dissection versus no neck dissection could neither be demonstrated nor refuted (very low level of evidence).
- In adult patients with clinically neck negative laryngeal cancer there is evidence of very low quality that neck dissection leads to less recurrences than no neck dissection.
- In adult patients with clinically neck negative laryngeal cancer there is evidence of very low quality that neck dissection leads to more complications compared to no neck dissection.
- In adult patients with N2-3 supraglottic or hypopharyngeal carcinoma there is evidence of very low quality that neck dissection leads to better local control and less postoperative complications compared to no neck dissection.
- In adult patients with N2-3 supraglottic or hypopharyngeal carcinoma a difference in recurrence rate or overall survival of neck dissection versus no neck dissection could neither be demonstrated nor refuted (very low level of evidence).

3.2.4.2 Type of neck dissection

Oropharynx

One systematic review was included that compared the clinical effectiveness of neck dissection with other treatment options in patients with cancer of the oropharynx.[79]

This review compared various surgical treatment modalities with each other or with other treatment modalities (such as radiotherapy, chemotherapy, immunotherapy/biotherapy with or without surgery) in patients with cancer of the oral cavity or oropharynx. Patients with cancer of the hypopharynx, nasopharynx, larynx or lip were excluded. The search date was February 2011 and the overall risk of bias of this review was judged to be low. The review included seven RCTs with a total of 669 patients, of whom 667 had cancer of the oral cavity. Only two patients with oropharyngeal cancer were included. Therefore, it must be concluded that in this systematic review no RCTs were identified that applied to patients with oropharyngeal cancer.

The update of the search identified no RCTs.

The search for comparative observational studies revealed two relevant studies.[185, 195]

The first study was a prospective cohort study in which patients with newly diagnosed, stage IV oropharyngeal cancer treated with chemoradiation were enrolled from 2003.[185] One of the comparisons made in this study was between selective neck dissection (N=22) and modified radical neck dissection (N=16). Risk of bias of this study was judged to be high as there is considerable risk of selection and detection bias and uncertainty about attrition, concurrency and comparability of the study groups under comparison. Quality of life, measured with SF-36 and Head and Neck Quality of Life Instrument (HNQoL), was the only outcome that was assessed. Only in the mental health domain of the SF-36 the groups differed significantly in change scores from baseline to one year (13.6 vs. -0.3, p=0.029) in favour of selective neck dissection.

In the second study medical records were reviewed of patients treated with planned post–primary chemoradiation treatment (CRT) for histologically confirmed locoregionally advanced oropharyngeal squamous cell carcinoma (SCC) between 2001 and 2007.[195] All 41 patients who had undergone neck dissection had stage IVa disease. They were treated with either

comprehensive neck dissection (CND, N=23 dissections) or selective neck dissection (SND, N=25 dissections). Risk of bias for this study was judged to be high, as there may be selection bias and multivariable analyses were not possible due to small sample sizes. There was no significant association between type of neck dissection and regional failure: three-year regional disease control rate was 100% and 94% for SND and CND, respectively. There were no significant differences between SND and CND regarding three-year rates of overall survival (95% vs. 89%) and disease-specific survival (72% vs. 81%). Postoperative complications were seen in two (8%) patients in the SND group and six (26%) patients in the CND group (p=0.15). Disease-free survival, recurrence rate and quality of life were not addressed in this study.

Conclusions

- In patients with oropharyngeal cancer, no randomized study evaluated the clinical effectiveness of neck dissection. Two observational studies compared selective neck dissection with (modified) radical neck dissection, but these were limited to patients with stage IV disease pre-treated with chemoradiotherapy.
- In adult patients with stage IVa oropharyngeal cancer a difference in regional control, overall survival or adverse effects of selective neck dissection versus (modified) radical neck dissection could neither be demonstrated nor refuted (very low level of evidence).
- In adult patients with stage IV oropharyngeal cancer a difference in quality of life between selective and (modified) radical neck dissection could neither be demonstrated nor refuted (very low level of evidence).
- No comparative studies were identified that addressed disease-free survival or recurrence rate after selective neck dissection versus (modified) radical neck dissection in adult patients with oropharyngeal cancer.

Hypopharynx

No systematic reviews, RCTs or comparative observational studies were identified. Therefore, no conclusions can be drawn about the effectiveness of neck dissection in patients with cancer of the hypopharynx.

Conclusions

- No comparative studies were identified that addressed disease-free survival, recurrence, (loco)regional control, overall survival, quality of life or adverse effects of (1) neck dissection versus no neck dissection or (2) selective neck dissection versus (modified) radical neck dissection in adult patients with hypopharyngeal cancer.

Larynx

No systematic review was included in which different types of neck dissection were compared in patients with laryngeal cancer.

The search for RCTs identified one relevant study.[196] In this RCT 132 patients with previously untreated T2–T4 N0 M0 supraglottic or transglottic SCC were randomized to type III modified radical neck dissection or lateral neck dissection. The risk of bias of this study was judged to be unclear, mainly because of the lack of details provided about method of randomization and blinding. Patient characteristics were well balanced between groups at baseline. No significant differences between the two groups were found for recurrence rate (RR=0.86; 95%CI 0.46 to 1.61), 5-year actuarial OS rates (72.3% vs. 62.4%, log-rank test: p=0.312), disease-specific survival rates (81.3% vs.81.0%, p=0.778) and “significant complications” (RR=1.07; 95%CI 0.75 to 1.54). The study did not report on disease-free survival, (loco)regional control and quality of life outcomes.

Three relevant comparative observational studies were identified in which different types of neck dissection were compared in patients with various stages of laryngeal cancer.[192, 197, 198]

The first study was a retrospective chart review of patients with moderately advanced/advanced (T3-4 N0) SCC of the larynx, who underwent primary surgical treatment between 1981 and 2000.[197] The objective was to assess the efficacy of selective neck dissection with or without adjuvant radiotherapy (SND with or without RT, N=603) versus modified radical neck dissection with adjuvant radiotherapy (MRND, N=51). Risk of bias for this

study was judged to be high, because of a high risk of selection bias and reporting bias, and uncertainty whether the (unadjusted) analyses were performed on patient level or neck dissection level. Regional recurrence was 3% in the SND group and 11.7% in the MRND group, and this difference was statistically significant (p=0.005). Five-year regional control rates for pN0-patients were 96.8% (SND+/-RT) vs. 82.2% (MRND) (p=0.0003) and for pN+ patients 97.4% (SND+/-RT) vs. 95.3% (MRND) (p=0.50). OS was not reported. However, rates for five- and 10-year disease-specific survival (DSS) were presented. For SND+RT, SND-RT and MRND five-year DSS was 81%, 77% and 56.5%, respectively, and 10-year DSS was 29%, 74% and: 0% (p=0.04, unadjusted), respectively. Disease-free survival, quality of life and adverse events were not addressed in this study. The interpretation of the results is further complicated by the fact that some patients didn't receive radiotherapy.

Another retrospective chart review was published by Gallo et al.[192] Consecutive cN0 laryngeal cancer patients who underwent surgical treatment between January 1978 and December 2003 were included in the study. A comparison was made between patients who underwent either radical neck dissection (RND, N=128), functional neck dissection (FND, N=403) or selective jugular node dissection (JND/SND, N=228). A fourth study group was a wait-and-see group (N=1448). Risk of bias for this study was judged to be high. Analyses of this retrospective study at risk for selection bias were unadjusted for patient or disease characteristics. The 5-year neck recurrence rate did not significantly differ between the RND, FND and JND groups (p=0.178). Compared to the more extensive neck dissections (Group 1+2) JND (group 3) did not show statistically significant differences with respect to neck control (p=0.233). In the wait-and-see group 225 cN0 laryngeal cancer patients experienced neck relapse in the undissected neck(s) (15.5%), while 84.5% of the remainder were disease-free in the neck. No statistical significant differences were observed for the survival curves (p=0.222). The study did not address disease-free survival, quality of life and adverse events.

The third study is a retrospective chart review of patients who underwent surgery for T1-T2 supraglottic SCC and who had undergone either ipsilateral functional neck dissection (IFND, N=48) or bilateral functional neck dissections (BFND, N=60).[198] Risk of bias for this study was judged to be high. The patients who received an ipsilateral functional neck dissection were treated before 1992, whereas the patients who received bilateral functional neck dissections were treated between 1992 and 1998. Although study groups seem quite comparable, except for age, there are relatively small numbers of events (recurrences) in the groups. Regional recurrence developed in 17% and 13% of patients in the IFND and BFND groups (p=0.78), respectively. OS was not assessed. However, five-year disease-specific survival (81% vs. 73%; p=0.51) was reported. Disease-free survival, quality of life and adverse events were not assessed. Results for (loco)regional control were not specified for the study groups.

Conclusions

- In adult patients with resectable supraglottic or transglottic laryngeal cancer a difference in recurrence rate, overall survival or adverse effects of modified radical neck dissection versus lateral neck dissection could neither be demonstrated nor refuted (low to very low level of evidence).
- In adult patients with moderately advanced (T3-4 N0) squamous cell cancer of the larynx there is evidence of very low quality that selective neck dissection with or without adjuvant RT has lower regional recurrence rates and better 5-year regional control than modified radical neck dissection plus adjuvant RT.
- In adult patients with cN0 laryngeal cancer a difference in recurrence rate, local control or overall survival between (modified) radical and selective jugular neck dissection could neither be demonstrated nor refuted (very low level of evidence).
- In adult patients with T1-T2 supraglottic squamous cell carcinoma a difference in regional recurrence between ipsilateral and bilateral (modified) radical neck dissection could neither be demonstrated nor refuted (very low level of evidence).

Other considerations

Factor	Comment
Balance between clinical benefits and harms	• The evidence does not allow to draw firm conclusions about the effectiveness and safety of neck dissection. • In patients with a clinically node negative neck, the risk of having nodal involvement is estimated to be 0-15% for glottic cancer, 8-30% for supraglottic cancer and >50% for oropharyngeal and hypopharyngeal cancer.[199] According to SIGN, neck treatment should be offered if the risk for occult nodal metastases is >20%. • Also according to SIGN, active neck treatment is required when there is clinical or radiological evidence of neck disease.
Quality of evidence	The evidence is mainly limited to observational studies with a high risk of bias.
Costs (resource allocation)	No cost issues were considered.
Patients values and preferences	No comments were received from the patient representatives.
Comments	In case of a T1 tumour of the lateral wall of the pyriform sinus and early tonsil fossa (T1-2) tumours not invading the soft palate nor the glossotonsillar sulcus, unilateral neck dissection will be sufficient.

Recommendations	Strength of Recommendation	Level of Evidence
• **Management of the neck lymph nodes should follow the same treatment principles as those applied for the primary tumour (e.g. if the primary tumour is surgically treated, a neck dissection should be performed).**	Weak	Very low
• **In patients with oropharyngeal, hypopharyngeal or laryngeal cancer, bilateral selective neck treatment is recommended. However, in small lateralised cancers, unilateral neck treatment can be considered.**	Weak	Very low
• **In patients with early (stage I or II) glottic cancer, neck treatment can be omitted, with the exception of supraglottic extension.**	Weak	Very low

3.2.4.3 Neck dissection after chemoradiotherapy

In the first part of the guideline on head and neck cancer – focusing on oral cavity cancer[9] – a search was done for studies evaluating neck dissection after chemoradiotherapy. The results of that search were used for the second part too, and are described below. Methodological information can be found in the appendix of the first part.

Evaluation of neck disease after chemoradiotherapy

FDG-PET and/or FDG-PET/CT

Two recent systematic reviews were identified that evaluated the diagnostic value of FDG-PET and/or FDG-PET/CT in the decision of neck dissection after (at least) chemoradiotherapy in patients with head and neck squamous cell carcinoma.[200, 201] From these reviews, 15 primary studies were selected that met our inclusion criteria.[202-216] In addition, 6 primary studies were identified that were published since the search date of the systematic reviews.[217-222] The 21 primary studies included a total of 963 patients, of which 43 (4%) had oral cavity SCC.

Table 24 – Diagnostic accuracy of PET/CT or PET for decision of neck dissection after (at least) chemoradiotherapy: individual studies

Study	N	N Oral cavity SCC	Diagnostic accuracy (95%CI) Sensitivity	Specificity
PET/CT, patient-based				
Chen 2006	30	0	1.00 (0.40, 1.00)	0.73 (0.52, 0.88)
Gourin 2009	32	0	0.60 (0.26, 0.88)	0.36 (0.17, 0.59)
Gupta 2010	57	0	0.63 (0.24, 0.91)	0.98 (0.89, 1.00)
Moeller 2009	75	0	0.75 (0.35, 0.97)	0.76 (0.64, 0.86)
Prestwich 2012	41	0	1.00 (0.48, 1.00)	0.92 (0.78, 0.98)
Rabalais 2009	52	6	1.00 (0.40, 1.00)	0.88 (0.75, 0.95)
Zundel 2011	52	3	Not estimable	1.00 (0.93, 1.00)
PET/CT, hemineck-based				
Lyford-Pike 2009	37	0	0.57 (0.29, 0.82)	0.74 (0.52, 0.90)
Ong 2008	82	0	0.71 (0.29, 0.96)	0.89 (0.80, 0.95)
PET/CT, node-based				
None				
PET, patient-based				
Hanasono 1999	22	0	0.86 (0.42, 1.00)	0.73 (0.45, 0.92)
Kitagawa 2003	23	23	Not estimable	0.74 (0.52, 0.90)
Loo 2011	34	0	Not estimable	0.97 (0.85, 1.00)
McCollum 2004	24	2	0.67 (0.30, 0.93)	0.53 (0.27, 0.79)
Mori 2011	49	3	0.50 (0.01, 0.99)	0.70 (0.55, 0.83)
Porceddu 2011	112	0	1.00 (0.16, 1.00)	0.94 (0.87, 0.97)
Wang 2009	44	3	1.00 (0.69, 1.00)	0.97 (0.85, 1.00)
PET, hemineck-based				
Brkovich 2006	21	0	0.75 (0.19, 0.99)	0.65 (0.38, 0.86)
Inohara 2009	55	0	0.69 (0.39, 0.91)	0.88 (0.74, 0.96)
Yao 2005	70	0	1.00 (0.29, 1.00)	0.94 (0.85, 0.98)
Yao 2007	24	1	1.00 (0.48, 1.00)	0.68 (0.43, 0.87)
PET, node-based				
Kishino 2012	27	1	1.00 (0.48, 1.00)	0.64 (0.41, 0.83)
TOTAL	**963**	**43**		

PET/CT

Nine studies evaluated FDG-PET/CT.[203-205, 209, 211-213, 221, 222] Seven studies (339 patients, of whom 9 with oral cavity SCC) reported a patient-based analysis.[203-205, 211, 213, 221, 222] Six studies could be included in the meta-analysis, as Zundel 2011[222] had no true positives and no false negatives. The pooled sensitivity was 78% (95%CI 61-89%) and the pooled specificity 83% (95%CI 63-93%) (Table 25).

Only two studies reported a hemi-neck-based analysis (Lyford-Pike 2009[209] and Ong 2008[212]). As a consequence, it was not possible to pool the accuracy estimates of the individual studies (which are reported in Table 24). The sensitivity ranged between 57-71% and the specificity between 74-89% (Table 25).

No studies reported a node-based analysis.

PET

Twelve studies evaluated FDG-PET.[202, 206-208, 210, 214-220] Seven studies (308 patients, of whom 31 with OCSCC) reported a patient-based analysis.[206, 208, 210, 214, 218-220] However, it was not possible to calculate a pooled estimate, because the model did not converge. The sensitivity ranged between 50-100% and the specificity between 53-97% (Table 25).

Four studies reported a hemi-neck-based analysis.[202, 207, 215, 216] The pooled sensitivity was 81% (95%CI 59-92%) and the pooled specificity 83% (95%CI 67-92%) (Table 25). One study (Kishino 2012[217]) evaluated the value of FDG-PET on a node-based analysis (Table 24); the sensitivity was 100% and the specificity 64% (Table 25).

PET/CT and PET combined

When the seven studies that reported a patient-based analysis with FDG-PET/CT[203-205, 209, 211-213, 221, 222] and the seven studies that reported a patient-based analysis with FDG-PET[206, 208, 210, 214, 218-220] were combined, the pooled sensitivity was 82% (95%CI 68-91%) and the pooled specificity 83% (95%CI 70-91%). Similarly, when the studies on FDG-PET/CT[209, 212] and FDG-PET[202, 207, 215, 216] that performed a hemi-neck based analysis were combined, the pooled sensitivity was 72% (95%CI 57-83%) and the pooled specificity 84% (95%CI 73-91%).

Table 25 – Diagnostic accuracy of PET/CT or PET for decision of neck dissection after (at least) chemoradiotherapy: pooled analyses

	Sensitivity						Specificity					
		Range		Meta-analysis			Range		Meta-analysis			
	N studies	Low	High	Point estimate	95%CI		Low	High	Point estimate	95%CI	
PET/CT												
Patient-based	6/7*	60%	100%	78%	61%	89%	36%	100%	83%	63%	93%
Hemi-neck based	2	57%	71%	not possible			74%	89%	not possible		
Node-based	0			not possible					not possible		
PET												
Patient-based	7	50%	100%	not possible			53%	97%	not possible		
Hemi-neck based	4	69%	100%	81%	59%	92%	65%	94%	83%	67%	92%
Node-based	1		100%	not possible				64%	not possible		

** 6 studies were included for the calculation of the pooled sensitivity and 7 for the specificity*

Conclusions

- There is evidence of low quality that PET/CT has moderate sensitivity and specificity to detect residual disease in lymph nodes after (at least) CRT in patients with HNSCC.
- There is evidence of low to very low quality that PET has moderate sensitivity and specificity to detect residual disease in lymph nodes after (at least) CRT in patients with HNSCC.

MRI

No systematic reviews evaluated the diagnostic value of MRI in the decision of neck dissection after (at least) chemoradiotherapy in patients with head and neck squamous cell carcinoma. One retrospective study was finally included.[223]

Lin et al.[223] reported on 38 patients with SCC of the aerodigestive tract who underwent primary chemoradiation. Sixteen patients had findings of residual disease on MRI and underwent neck dissections. Only three neck dissection specimens contained residual tumour on final pathology (PPV 19%). For the calculations, findings on histopathology and during follow-up were taken as reference standard. Two out of twenty-two patients with a negative MRI were diagnosed with recurrence after 18 months and 26 months respectively. Considering these two patients had recurrence, a 100% sensitivity (95%CI 29-100%), 63% (95%CI 45-79%) specificity and a 100% NPV for residual disease was achieved.

Conclusions

- There is evidence of very low quality that MRI has a high sensitivity to detect residual disease in lymph nodes after CRT in patients with HNSCC.
- There is evidence of low quality that MRI has a low specificity to detect residual disease in lymph nodes after CRT in patients with HNSCC.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	In general, PET(/CT) appears to have a moderate sensitivity and specificity to detect residual disease in lymph nodes after (at least) CRT in patients with head and neck cancer. PET/CT, MRI and CT share a high negative predictive value to detect lymph node metastases after CRT. Therefore, the most important reason for additional imaging is to defer patients without lymph node metastasis after CRT from further neck dissection.
Quality of evidence	All PET(/CT) studies suffer from differential verification; in some studies selection bias is present. No evidence is available on the impact of PET(/CT) on patient outcomes, such as survival. Timing of PET(/CT) is critical, as many studies have shown that sensitivity and specificity change a lot depending on the time of imaging. However, in the present overview it was not feasible to stratify based on timing of PET(/CT) after (at least) CRT since the timing was reported in different ways (mean, median, range). Furthermore, in order to exclude the evaluation of recurrent disease, studies were excluded if the evaluation with PET(/CT) was not done within (a me(di)an of) 6 months after CRT.
Costs (resource allocation)	Possible sources of information: Sher DJ, Tishler RB, Annino D, Punglia RS. Cost-effectiveness of CT and PET-CT for determining the need for adjuvant neck dissection in locally advanced head and neck cancer. Ann Oncol. 2010;21(5):1072-7. Pryor DI, Porceddu SV, Scuffham PA, Whitty JA, Thomas PA, Burmeister BH. Economic analysis of FDG-PET-guided management of the neck after primary chemoradiotherapy for node-positive head and neck squamous cell carcinoma. Head Neck. 2013 Sep;35(9):1287-94.
Patients values and preferences	No comments were received from the patient representatives.

Recommendations	Strength of Recommendation	Level of Evidence
• **In node-positive patients treated with primary (chemo)radiotherapy, a diagnostic evaluation of the neck with PET/CT or DW-MRI should be performed not earlier than three months after completion of primary (chemo)radiotherapy.**	Weak	Very low

Neck dissection after chemoradiotherapy

No systematic reviews on the topic were identified. Only observational studies were obtained; for this review only comparative studies were included. The details of the literature search can be found in Appendix 2.2.7, Appendix 3.3.6, Appendix 4.6 and Appendix 5.6 of the first part.[9]

Disease-free survival

Brizel et al.[224] concluded that N2-N3 HNSCC patients (N=43) who had a neck dissection after complete clinical response to CRT benefited from an increased 4-year disease-free survival rate compared to those who did not have neck surgery (75% vs.53%, p=0.08), although the difference was statistically not significant. In addition, the study also suffered from serious methodological shortcomings and the subgroups were very small.

Progression-free survival

Goguen et al.[225] offered 20 HNSCC patients induction chemotherapy followed by concurrent CRT. Median progression-free survival after neck dissection was 43.2 months or longer and after watchful waiting 37.9 months or longer. It was not reported whether this difference was statistically significant. The results should be cautiously interpreted since the mean follow-up period was different for both groups (46.4 months in the neck dissection group and 40.6 months in the watchful waiting group), the sample size very small and the study had serious methodological flaws.

Overall survival

Cannady et al. demonstrated no benefit with regard to 3-year OS in 210 patients with HNSCC who had a lymph node dissection after CRT (86% vs. 85.2%, p>0.05).[226] However, major methodological shortcomings, careless reporting of data (confusing mix up of results assessed at patient and at neck level) and the fact that it is unclear whether intervention and control patients were comparable, compel careful interpretation of the results. Brizel et al. reported contradictory results: N2-N3 HNSCC patients who had a neck dissection after cCR to CRT benefited from a higher 4-year OS rate compared to those who did not have neck surgery (77% vs. 50%, p=0.04).[224] However, the results of both studies should be interpreted with caution.

Two studies reported the 5-year OS rate and found no difference between neck dissection after cCR to CRT versus watchful waiting (Cannady: 78.6% vs. 77.7%, p> 0.05; Grabenbauer: 44% vs. 42%, p=0.9).[226, 227] Grabenbauer et al. also reported no statistically significant difference in 10-year OS between intervention and control groups (35% vs. 20%, p=0.9).[226, 227] However, both studies had serious methodological flaws, hence the results should be cautiously interpreted.

Regional recurrence rate

Five primary studies evaluated the difference in regional recurrence rate.[225, 227-230] Soltys et al.[228] treated 56 HNSCC patients with sequential CRT, Goguen et al.[225] offered 20 HNSCC patients induction chemotherapy followed by concurrent CRT and Forest[229] and McHam[230] treated 126 and 65 HNSCC patients respectively with concurrent CRT. They all come to comparable results[225, 228-230] the regional recurrence rate was higher in the watchful waiting group, but the differences with the dissection group were statistically not significant (Soltys: 0% vs. 10%; Goguen: 0% vs. 8%; Forest: 0% vs. 5%; McHam: 3% vs. 12%). Seemingly contradictory results were obtained by Grabenbauer et al.[227] in the watchful waiting group the recurrence rate was lower than in the dissection group (ND: 16% vs. WW: 10%, p=0.367), but the difference was statistically not significant. As was discussed above, the results of all these studies should be interpreted with caution since they all had major methodological shortcomings. Because of the major methodological shortcomings no pooling of data was performed.

Regional control

Grabenbauer et al. also evaluated the impact of neck dissection vs. watchful waiting on regional tumour control rate and concluded that the difference was statistically not significant (80% vs. 85%, p=0.47).[227] Again, the serious methodological problems should be taken into account when interpreting these results.

Recurrence-free survival

Cannady et al. found no benefit with regard to 3-year or 5-year recurrence-free survival for patients with HNSCC (N=210) who had a lymph node dissection after clinically assessed complete response (cCR) to chemoradiotherapy (CRT) (at 3 years: 80% vs. 81.6%; at 5 years 72.6% vs. 78.1%, both p>0.05).[226] However, major methodological shortcomings,

careless reporting of data (confusing mix up of results assessed at patient and at neck level) and the fact that it is unclear whether intervention and control patients were comparable, compel careful interpretation of the results.

Quality of life

Donatelli-Lassig et al. assessed the effect of neck dissection after CRT on quality of life in 103 patients with stage IV HNSCC (65 patients underwent CRT alone and 38 patients had selective or modified radical ND after CRT).[185] Only the pain index of the SF-36[b] showed a significant difference between groups (p=0.04) with the neck dissection group reporting more pain. This study also suffered from serious shortcomings: a higher proportion of ND patients were N3 (selection bias) and the indications for ND changed during the study period, which resulted in a heterogeneous ND group.

Conclusions

- There is no sound scientific evidence that neck dissection after chemoradiotherapy results in better disease free, recurrence free or overall survival in patients with N2-3 head and neck squamous cell carcinoma (very low level of evidence).
- There is no sound scientific evidence that neck dissection after chemoradiotherapy results in a lower recurrence rate in patients with N2-3 head and neck squamous cell carcinoma (very low level of evidence).
- There is evidence of very low quality that neck dissection after chemoradiotherapy results in significantly more pain than watchful waiting as assessed by the SF-36 pain index 1 year after neck dissection.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	It is suggested that neck dissection after chemoradiotherapy results in significantly more pain than watchful waiting (1 year after neck dissection), while there is no sound evidence that neck dissection after chemoradiotherapy results in better disease free, recurrence free, overall survival or in a lower recurrence rate.
Quality of evidence	The results of all retrieved studies should be interpreted with caution since they all had major methodological shortcomings.
Costs (resource allocation)	No cost issues were considered.
Patients values and preferences	No comments were received from the patient representatives.

Recommendation	Strength of Recommendation	Level of Evidence
• **In patients with oropharyngeal, hypopharyngeal or laryngeal cancer (N1-3) and complete response to chemoradiotherapy (assessed by FDG-PET/CT or DW-MRI), there are no data to support an additional lymph node dissection.**	Weak	Very low

[b] The Short Form (36) Health Survey is a validated patient-reported survey of patient health.

3.3 Histopathology

In the first part of the guideline on head and neck cancer – focusing on oral cavity cancer [9] – several recommendations were formulated regarding histopathology, which are also applicable to oropharyngeal, hypopharyngeal and laryngeal cancer. An overview is provided in Table 26.

Table 26 – Histopathology recommendations from oral cavity cancer guideline [9]

Recommendation	Strength of recommendation	Level of Evidence
To avoid a positive resection margin (which is associated with a poorer prognosis), frozen sections taken intraoperatively may be useful.	Weak	Very low
A distance of at least 10 mm from the palpable tumour margin, whenever technically or anatomically possible, should be taken as a guide for resection to allow a minimal distance of 3-5 mm from the margin of the resected tissue to the primary tumour in the formalin-fixed specimen.	Weak	Very low
For discussion with the clinician, the histopathological findings must describe the exact localization of any existing R+ status. The anatomical topography must be clearly indicated when sending the tumour specimen to the pathologist. This may be done with suture markers or colour-coding. The histopathological result must include: tumour localization, macroscopic tumour size, histological tumour type, histological tumour grade, depth of invasion, lymphatic, vascular and perineural invasion, locally infiltrated structures, pT classification, details of affected areas and infiltrated structures, R status and p16 (if not done on biopsy).	Strong	Low
The histopathological findings from a neck dissection specimen must describe the anatomical topography, the side of the neck, type of neck dissection, eliminated levels, total number of lymph nodes plus number of lymph nodes affected, number of lymph nodes per level, level of the affected lymph nodes, diameter of the largest tumour deposit, additionally removed structures and, if present, extracapsular spread.	Strong	Low

3.4 Treatment of metastatic or recurrent disease not suitable for curative treatment

In the first part of the guideline on head and neck cancer – focusing on oral cavity cancer [9] – a search was done for studies evaluating treatment of metastatic or recurrent disease not suitable for curative treatment. The results of that search were used for the second part too, and are described below. Methodological information can be found in the appendix of the first part.

No systematic reviews were found that assessed the following treatment interventions for patients with metastatic disease or recurrent disease not suitable for curative treatment: chemotherapy, targeted therapy (EGFR inhibitors), radiotherapy (for recurrent disease), surgery (for recurrent disease). Only three primary studies were included, two observational studies[231, 232] in which treatment was assigned based on the patient's profile (confounding by indication) and one RCT.[233]

The included RCT[233] compared zalutumumab monotherapy and best supportive care (BSC) in 286 patients with incurable HNSCC. Patients assigned to best supportive care could receive methotrexate up to a maximum dose of 50 mg/m² per week. In the BSC group 72% received methotrexate from the start and a further 6% started using it during the study. Of the zalutumumab group only 8% started the use of methotrexate during the study. The risk of bias of this study was judged to be high for both subjective and objective outcomes. Baseline characteristics of the patients were similar between groups. Data for quality of life outcomes (measured with QLQ 30 and H&N 35) were not shown. However, the authors state that the quality of life assessment indicated that adding zalutumumab to best supportive care did not adversely affect quality of life. With regards to adverse events (Grade 3-4), significant differences between groups were only found for rash (RR=39.4; 95%CI 2.45 to 634.01) and neutropenia (RR=0.10; 95%CI 0.01 to 0.84). The most common serious adverse events were tumour haemorrhage, pneumonia and dysphagia, but these differences were not significant. The median OS (in months) did not significantly differ between the two groups (6.7 vs. 5.2; p=0.065). The HR for death (stratified by WHO performance status) was 0.77 (95%CI 0.57 to 1.05).

One retrospective study[231] analysed clinical records from 151 patients with recurrent and metastatic HNSCC treated with first-line platinum-based chemotherapy. After progression of the tumour on first-line platinum-based chemotherapy, all second-line treatments were assessed, including chemotherapy (N=43), radiotherapy (N=25), chemoradiotherapy (N=15) or best supportive care (N=68). The risk of bias of this study was judged to be high. Baseline characteristics were not specified per treatment group and patient comparability could thus not be assessed. As only the comparisons of second-line treatments with best supportive care are of interest for this research question (and not various second-line treatments compared with each other), only the results of these comparisons are reported. Significant differences were found for OS in favour of chemoradiotherapy versus best supportive care (Kaplan Meier estimates 12 months: 6.7% [95%CI 0.0 to 19.3] vs. 0%, p=0.0001). The median survival was 212 days (95%CI 154 to 274) in the chemoradiotherapy group and 56.5 days (95%CI 46 to 67) in the best supportive care group. Also, chemotherapy versus best supportive care showed significant differences in favour of chemotherapy for OS (12 months: 2.3% [95%CI 0.0 to 6.8] vs. 0%, p=0.0011), with 107 days (95%CI 83 to 135) of median survival for the chemotherapy group and 56.5 days (95%CI 46 to 67) for the best supportive care group. Finally, also significant differences in favour of radiotherapy were found (12-month survival: 12% [95%CI 0.0 to 24.7] vs. 0%, p=0.0001) with 188 days (95%CI 139 to 280) of median survival for the radiotherapy group and 56.5 days (95%CI 46 to 67) for the BSC group. Quality of life outcomes and adverse events were not assessed.

The second observational study[232] retrospectively reviewed 168 patients with locally recurrent squamous cell carcinoma of the oropharynx who underwent salvage surgery, reirradiation or brachytherapy, palliative chemotherapy, or supportive care. As the study was designed to assess functional outcomes and prognostic factors in patients who underwent salvage surgery, not all outcomes of interest were reported for the other treatment interventions (reirradiation or brachytherapy, palliative chemotherapy or supportive care). The risk of bias of this study was judged to be high. Baseline characteristics were not specified for all treatment groups of interest and patient comparability could thus not be assessed. Significant differences in 1-year OS between palliative chemotherapy and supportive care were found (1-year OS 32% vs. 13%; p=0.04). These differences became smaller at 3- and 5-years (3-year OS: 4% vs. 5%; 5-

year OS 0% vs. 0%) (differences not statistically tested). For the patients who underwent salvage surgery the 3- and 5-year OS was higher compared to patients receiving supportive care (3-year OS: 42% vs. 5%, 5-year OS: 28% vs. 0%) (difference not statistically tested). For the patients who received reirradiation or brachytherapy (with or without chemotherapy) 3- and 5 year OS was higher compared to the patients who received supportive care (3-year OS: 32% and 5%; 5-year OS: 32% vs. 0% (differences not statistically tested). Quality of life outcomes and adverse events were only presented for the salvage surgery group.

Conclusions

Chemoradiotherapy versus best supportive care

- There is evidence of very low quality that in adult patients (≥18 years of age) with locally recurrent HNSCC chemoradiotherapy results in a better 1-year overall survival and median survival compared to best supportive care.

Chemotherapy versus best supportive care

- There is evidence of very low quality that in adult patients (≥18 years of age) with (a) metastatic HNSCC or (b) locally recurrent HNSCC chemotherapy results in a better 1-year, 3-year and 5-year overall survival and median survival compared to best supportive care.

Radiotherapy versus best supportive care

- There is evidence of very low quality that in adult patients (≥18 years of age) with locally recurrent HNSCC radiotherapy results in a better 1-year, 3-year and 5-year overall survival and median survival compared to best supportive care.

Salvage surgery versus supportive care

- There is evidence of very low quality that in adult patients (≥18 years of age) with locally recurrent HNSCC salvage surgery results in a better 3-year and 5-year overall survival compared to best supportive care.

EGFR inhibitors plus best supportive care versus best supportive care only

- The available evidence of low quality does not allow to draw conclusions about the effect of EGFR inhibitors plus BSC compared to BSC alone on quality of life in adult patients (≥18 years of age) with metastatic HNSCC or locally recurrent HNSCC.
- There is evidence of low quality that in adult patients (≥18 years of age) with metastatic HNSCC or locally recurrent HNSCC treatment with EGFR inhibitors plus BSC results in more Grade 3-4 rash and less neutropenia compared to BSC alone. A difference for other Grade 3-4 adverse events could neither be demonstrated nor refuted.
- The available evidence of low quality does not allow to draw conclusions about the effect of EGFR inhibitors plus BSC compared to BSC alone on median survival in adult patients (≥18 years of age) with metastatic HNSCC or locally recurrent HNSCC.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Compared to best supportive treatment, most interventions appear to have a survival benefit. However, the available evidence is limited.
Quality of evidence	Only one RCT with a high risk of bias was found comparing EGFR inhibitors and best supportive care versus best supportive care alone. For the other comparisons, only observational studies were found.
Costs (resource allocation)	EGFR-inhibitors are not reimbursed in Belgium for this indication.
Patients values and preferences	No comments were received from the patient representatives.

Recommendation	Strength of Recommendation	Level of Evidence
• **In patients with metastatic HNSCC or recurrent disease that is not eligible for curative treatment, palliative chemotherapy or targeted therapies should be considered after discussion with the patient.**	Strong	Very low

3.5 Salvage treatment

The detailed results of the literature search and assessment can be found in Appendix 2.3.6, Appendix 3.3.1, Appendix 3.3.7, Appendix 4.6, Appendix 5.6 and Appendix 6.6.

Four observational studies [232, 234-236] were found that assessed the role of salvage treatment in patients with second primaries or locoregional recurrence after curative treatment for laryngeal, hypopharyngeal and oropharyngeal cancer.

The study of Kano [234] involved a retrospective chart review which assessed the role of salvage surgery for patients with oropharyngeal cancer who failed initial chemoradiotherapy. Thirty-five patients with local recurrence or residual disease were included. Of these, 11 patients received salvage surgery (open surgery, requiring microvascular free flap reconstruction or transoral surgery) and 24 patients received nonsurgical treatment (including re-irradiation, chemotherapy and best supportive care). The risk of bias of this study was judged to be high. Significant differences between the two groups at baseline were found for patient age and the presence of a simultaneous regional recurrence. Patients who had more aggressive initial disease and developed distant metastasis tended to belong to the nonsurgical treatment group. Overall survival was significantly higher for patients treated with salvage surgery compared with patients treated without salvage surgery (p=0.04). Three- and five-year OS rates for patients who underwent salvage surgery were 61.8% and 49.1%, respectively. For patients receiving nonsurgical treatment these rates were 24.4% and 16.3%, respectively. No perioperative deaths were reported among the patients who received salvage surgery. As for adverse events of surgical salvage, six patients needed oral feeding, five patients required tube-feeding support and three patients required removal of their larynxes. Disease-free survival, recurrence rate, (loco)regional control and quality of life were not reported.

The study of Lim [235] retrospectively evaluated the effect of salvage treatment for isolated neck recurrence after primary curative surgery for HNSCC. Two hundred thirty-six patients who developed a recurrence after primary curative surgery with or without radiotherapy for HNSCC were included. Of these, 61 patients (26%) developed an isolated neck recurrence of which 49 received salvage treatment (surgical salvage or nonsurgical salvage) and 12 supportive care. The risk of bias of this study was judged to be high. Baseline patient characteristics were not reported per treatment group. Yet,

it is likely that characteristics between the two groups differed as indications for treatment are different. Three-year OS was 36% in the surgical salvage group and 12% in the nonsurgical salvage group. None of the patients receiving supportive care survived. Disease-free survival, recurrence rate, (loco)regional control, quality of life and adverse events were not reported.

The study of Yasumatsu[236] retrospectively studied the effect of salvage treatment for recurrent hypopharyngeal SCC after primary curative treatment. Forty-nine patients who were treated for recurrent hypopharyngeal SCC were reviewed. Twenty-three patients underwent salvage surgery followed by chemotherapy and/or radiotherapy and 26 patients received chemotherapy and/or radiotherapy. The risk of bias of this study was judged to be high. Patient characteristics were not reported per treatment group. However, it is likely that characteristics between the two groups differed as indications for treatment were different. One- and three-year tumour-free actuarial survival rates were 96% and 79%, respectively, for patients who received salvage surgery followed by chemotherapy and/or radiotherapy. There was no three-year survivor in the chemotherapy and/or radiotherapy only group. Mean survival of patients without surgical salvage was 9 months (range 1 to 33 months). Disease-free survival, recurrence rate, (loco)regional control, quality of life and adverse events were not reported.

The study of Zafereo[232] involved a retrospective chart review which assessed the effect of salvage surgery for locally recurrent SCC of the oropharynx, after initial radiotherapy. One-hundred and sixty-eight patients with locally recurrent or residual SCC of the oropharynx who completed definitive therapy for their primary tumour were included. Forty-one patients underwent salvage surgery, 18 patients received reirradiation or brachytherapy, 70 palliative chemotherapy and 39 patients supportive care. The risk of bias of this study was judged to be high. Significant differences between groups at baseline were found with respect to comorbidity (diabetes), tumour classification, treatment (surgery to primary site and chemotherapy), disease status (residual/recurrent) and overall disease stage. Three-year OS rates were 48.7%, 31.6%, 3.7% and 5.1% for patients who received salvage surgery, reirradiation, palliative chemotherapy or supportive care, respectively, and five-year OS rates were 28%, 32%, 0% and 0%, respectively. Disease-free survival, recurrence and quality of life outcomes were only reported for the surgical salvage group and no comparisons were made. Nineteen of 41 patients experienced postoperative complications. (Loco)regional control was not addressed.

Conclusions

- In adult patients with second primaries or locoregional recurrence after curative treatment of laryngeal, hypopharyngeal or oropharyngeal cancer a difference in overall survival of salvage treatment compared to no or other treatment could not be demonstrated nor refuted (very low level of evidence).
- No comparative studies were identified that addressed disease-free survival, recurrence rate, (loco)regional control, quality of life or adverse events of salvage treatment versus no or other treatment in adult patients with second primaries or locoregional recurrence after curative treatment of laryngeal, hypopharyngeal or oropharyngeal cancer.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	The evidence does not allow to draw firm conclusions about the effectiveness of salvage treatment.
Quality of evidence	The evidence is limited to observational studies with a high risk of bias.
Costs (resource allocation)	No cost issues were considered.
Patients values and preferences	No comments were received from the patient representatives.

Recommendations	Strength of Recommendation	Level of Evidence
• **In patients with a resectable locoregional recurrence after primary treatment with curative intent, salvage surgery should be considered. The procedure should only be performed by an experienced surgical team.**	Weak	Very low
• **In patients with a non-resectable locoregional recurrence after primary treatment with curative intent, re-irradiation, possibly with curative intent, should be considered. Irradiation should only take place in facilities with adequate expertise.**	Weak	Very low

3.6 Follow-up

In the first part of the guideline on head and neck cancer – focusing on oral cavity cancer [9] – a recommendation was formulated regarding follow-up, which is also applicable to oropharyngeal, hypopharyngeal and laryngeal cancer (Table 27).

Table 27 – Follow-up recommendations from oral cavity cancer guideline [9]

Recommendation	Strength of recommendation	Level of Evidence
An individually structured follow-up schedule should be devised for each patient. The quality of life, side effects of treatment, nutritional status, speech, dental status, thyroid function, smoking and alcohol consumption, etc. should be surveyed periodically. There is no evidence to support routine use of imaging techniques for the detection of locoregional or metastatic recurrence during follow-up. Follow-up frequency, even in symptom-free patients, should be at least every 3 months in the first and second year, 6 months in the third to fifth year, and annually afterwards.	Weak	Very low

3.7 Rehabilitation and supportive treatment

In the first part of the guideline on head and neck cancer – focusing on oral cavity cancer[9] – several recommendations were formulated regarding rehabilitation and supportive treatment, which are also applicable to oropharyngeal, hypopharyngeal and laryngeal cancer (Table 28). Patients should receive the necessary information about the access to specialised supporting interventions and techniques. For example, patients undergoing total laryngectomy should receive information about voice restoration (tracheoesophageal voice prosthesis, oesophageal speech, electrolarynx, etc).

Table 28 – Rehabilitation and supportive treatment recommendations from oral cavity cancer guideline [9]

Recommendation	Strength of recommendation	Level of Evidence
Dental rehabilitation		
In patients having undergone surgery and/or irradiation of the mouth for head and neck cancer, the masticatory function should be restored with the help of functional masticatory rehabilitation, using conventional prosthetics and/or implants. Surgical interventions (e.g. extractions) should be performed by professionals with experience in treating patients with head and neck cancer. The patients should undergo routine dental check-ups at a frequency depending on the individual patient case (usually every 4-6 months).	Strong	Very low
Infected osteoradionecrosis of the jaw is a serious treatment complication that should be managed in specialized centres.	Strong	Very low
Speech and swallowing rehabilitation		
Patients with chewing, speaking and swallowing problems should be timely provided with appropriate functional therapy. The patients should be introduced to suitably qualified therapists prior to commencing treatment if the scheduled surgical or conservative procedures (e.g. radiotherapy) are likely to cause problems with chewing, swallowing and/or speech.	Strong	Low
Patients with dysphagia should undergo appropriate diagnostic procedures, e.g. clinical exam by the speech therapist, videofluoroscopy or fiber-optic endoscopy.	Strong	Low
Patients having eating and speaking problems due to head and neck cancer and/or its management should have access to speech therapists and nutritional therapists with experience of such pathologies before, during and after treatment.	Strong	Low
Nutritional therapy		
Patients should be regularly screened for malnutrition due to head and neck cancer or its treatment. Patients at risk for malnutrition should receive timely and ongoing professional dietary counselling and nutritional therapy.	Strong	Low
Psychosocial counselling and support		
Patients with head and neck cancer (and their family, carers) should be offered dedicated psychosocial support on a continuous basis within the context of a multidisciplinary team.	Strong	Very low

4 IMPLEMENTATION AND UPDATING OF THE GUIDELINE

4.1 Implementation

4.1.1 Multidisciplinary approach

In this report we focused on the effectiveness of specific (medical) interventions, without taking into account the organization of health services. In clinical practice, a multidisciplinary approach by different health care professionals should be encouraged. This approach should not only cover the medical needs of the patient but also their psychosocial needs.

4.1.2 Patient-centered care

The choice of a treatment should not only consider medical aspects but also patient preferences. Patients should be well and timely informed about all treatment options and the advantages and disadvantages they offer. Indeed, patients and patient representatives involved in the development of this report emphasized the need for patient information. This information should be clear and repeated over time. Also more emphasis should be put on potential adverse events related to each treatment. Importantly, it was stressed that patients also have the right to be not informed.

4.1.3 Barriers and facilitators for implementation of this guideline

During the stakeholders meeting, the potential barriers and facilitators related to the use of this guideline were discussed.

The following barriers for implementation were identified:

- Most recommendations are based on evidence of low to very low quality, and clinicians may be reluctant to implement such recommendations.
- The recommendations concerning imaging with PET/CT or MRI do not take into account potential waiting times.
- Treatment with IMRT is not available in all radiotherapy centres in Belgium.
- Some recommendations stress the need for treatment at facilities with adequate expertise. However, at present the care for patients with head and neck cancer is not centralised, and no formal evaluation of the quality of care for these patients is organised.
- In some centres treating patients with head and neck cancer, dedicated dentists, nutritional therapists, speech therapists, etc. may not be available.

The identification of potential barriers and facilitators related to the use of this guideline is limited to a discussion held during the stakeholders meeting. More sophisticated methods could be used, but this would go beyond the scope of this project. More information on the identification of barriers and facilitators in guidelines implementation can be found in a recent KCE report (see KCE website).

4.1.4 Actors of the implementation of this guideline

Clinical guidelines provide a tool for physicians to consult at different stages of the patient management pathway: screening, diagnosis, treatment and follow-up. They are developed according to highly codified principles, based on scientific information regularly updated from the international literature. KCE formulates recommendations addressed to specific audiences (clinicians, decision-makers, sickness funds, NIHDI, professional organizations, hospital managers…). KCE is not involved in the decision making process itself, or in the execution of the decisions.

The implementation of this guideline will be facilitated / conducted by the College of Oncology and the professional associations involved in this guideline (see Table 8, page 18). An online implementation tool similar to the tools accompanying previous guidelines will be developed (www.collegeoncologie.be). The scientific material of this guideline is intended to be disseminated by scientific and professional organisations. They can transform this material into attractive and user-friendly tools tailored to caregivers groups. They will also play a key role by a dissemination that makes use of diverse channels such as websites or sessions of continuing education.

4.2 Monitoring the quality of care

This guideline could be considered as a starting point to develop quality improvement programs that target all caregivers concerned.

It can be used as a tool to support health policies to improve the quality of care, e.g. through the support of actions to increase caregivers' awareness and to improve their practice, or through the development (or revision) of sets of process and outcome quality indicators. The development of quality indicators is foreseen after the publication of this second part of the guideline on head and neck cancer.

KCE previously recommended to set up an integrative quality system in oncology, covering the development and implementation of clinical practice guidelines, the monitoring of the quality of care with quality indicators, feedback to health care providers and organizations and targeted actions to improve the quality if needed.

4.3 Guideline update

In view of the rapidly evolving evidence, this guideline should be updated every 5 years. If, in the meantime, important new evidence would become available, this should be taken into consideration.

The KCE processes foresee that the relevance of an update would be yearly assessed for each published guideline by the authors. Decisions are made on the basis of new scientific publications on a specific topic (e.g. Cochrane reviews, RCTs on medications or interventions). Potential interest for groups of health practitioners is also considered in this process.

This appraisal leads to a decision on whether to update or not a guideline or specific parts of it to ensure the recommendations stay in line with the latest scientific developments.

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