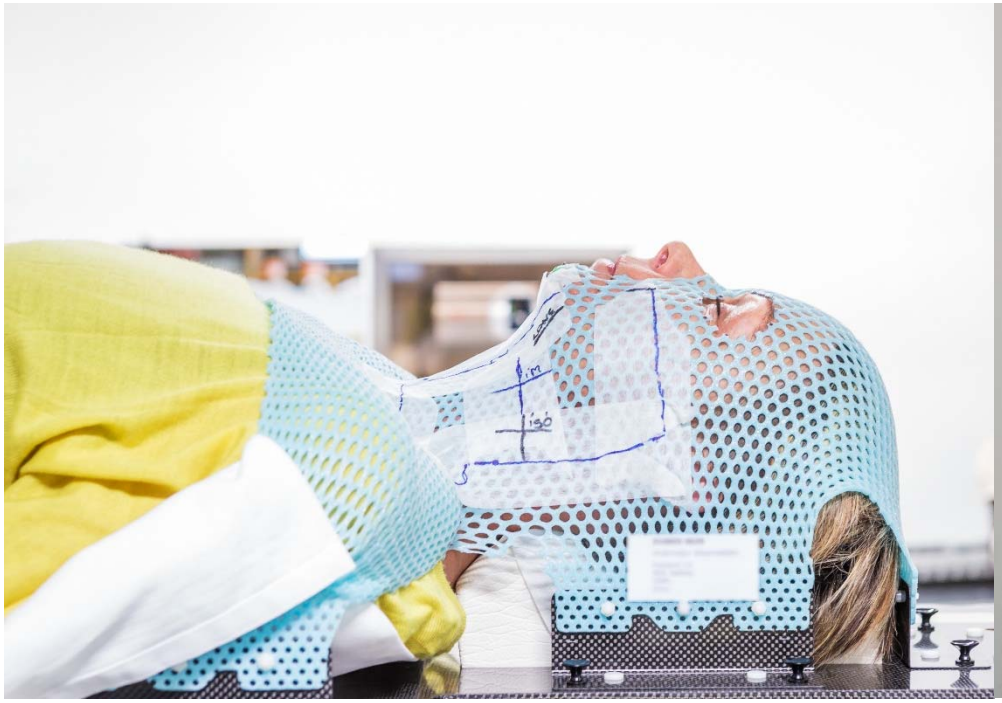
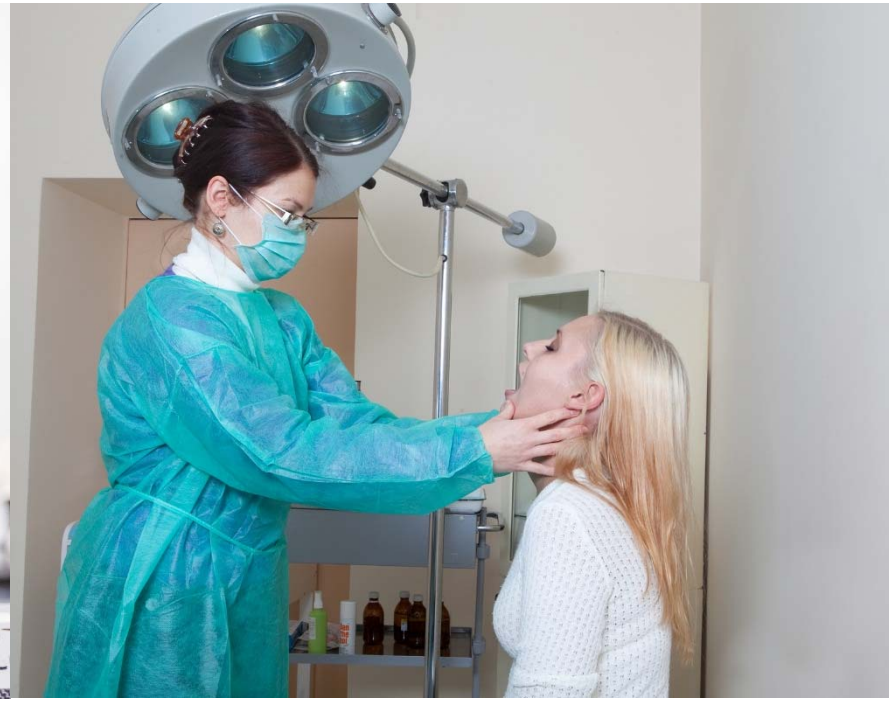
KCE REPORT 227

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

ORAL CAVITY CANCER: DIAGNOSIS, TREATMENT AND FOLLOW-UP





KCE REPORT 227
GOOD CLINICAL PRACTICE

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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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- **Finally, this report has been approved by common assent by the Executive Board.**
- **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE.**

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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
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
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
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	Mitochondrial 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
OR	Odds ratio
OS	Overall survival
OCSCC	Oral cavity squamous cell carcinoma
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
RR	Risk ratio / relative risk
RT	Radiotherapy
SCC	Squamous cell carcinoma(s)
SE	Standard error
SF-36	Short Form (36) Health Survey (a patient-reported survey of patient health)
SLNB	Sentinel lymph node biopsy
SMND	Submandibular neck dissection
SND	Selective neck dissection
SOND	Supraomohyoid neck dissection
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).
TPF	Taxotere, paclitaxel, and fluorouracil (a chemotherapy regimen)
US	Ultra sound
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 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 2008 and 2011 (Table 1). In 2011, they were the 4th most frequent cancer type in males. In the period 2004-2008, 5-year overall survival 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 2011

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

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. Recently, the KCE published a report on the organisation of care for adults with a rare or complex cancer. 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 (see chapter 2.3). During this meeting it was decided to develop the CPG for head and neck cancer in 2 phases. This first part concerns the management of oral cavity cancer, the second part will deal with oropharyngeal, hypopharyngeal and laryngeal cancer, and will be published in 2015.

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 first part of the guideline provides recommendations based on current scientific evidence for the staging, treatment, follow-up and supportive care of patients with oral cavity squamous cell 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 oral cavity squamous cell cancer, including oral and maxillofacial surgeons, ear, nose, and throat 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 oral cavity squamous cell 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, given the availability of the Deutsche Krebsgesellschaft (DKG) 2012 guideline that could serve as a basis for adaptation because of its quality, its comprehensiveness and its recent publication.[1]

The ADAPTE methodology generally includes three major phases (www.adapte.org):

1. **Set-up Phase:** In which an outline of the necessary tasks to be completed prior to beginning the adaptation process (e.g., identifying necessary skills and resources) is prepared.
2. **Adaptation Phase**: In which guideline developers move from the selection of a topic to the identification of specific clinical questions; search for and retrieve guidelines; assess the consistency of the evidence considered, its quality, validity, content and applicability; decide how to best adapt the evidence found; and prepare a draft of the adapted guideline.
3. **Finalization Phase**: Guides guideline developers through getting feedback on the document from stakeholders who will be impacted by the guideline, consulting with the source developers of guidelines used in the adaptation process, establishing a process for review and updating of the adapted guideline and the process of creating a final document.

Relevant recommendations were extracted from the DKG guideline to an Excel-file and the members of the GDG were asked to score their agreement with these recommendations using a 5-point scale. The scores were summarized and served as a basis for email discussion to define the clinical questions that would need an update of the literature searches done by the DKG. In addition to the clinical questions in the DKG 2012 guideline, the following 11 clinical questions were selected and submitted to a systematic review of the literature, because they were deemed out-of-date or insufficiently elaborated in the DKG guideline:

1. What is the clinical effectiveness of PET/CT in the staging of HNSCC?
2. What is the clinical effectiveness of HPV testing in patients with HNSCC?
3. What is the clinical effectiveness of elective lymph node dissection for patients with cN0 oral cavity cancer?
4. What is the clinical effectiveness of lymph node dissection for patients with cN+ oral cavity cancer?
5. What is the clinical effectiveness of elective lymph node dissection of the contralateral neck in patients with cN+ oral cavity cancer?
6. What is the clinical effectiveness of PET or MRI in the detection of lymph node metastasis after chemoradiotherapy?
7. What is the clinical effectiveness of neck dissection after chemoradiotherapy in patients with HNSCC?
8. What is the clinical effectiveness of IMRT for patients with locally advanced HNSCC?
9. What is the clinical effectiveness of induction chemotherapy in patients with HNSCC?
10. What is the clinical effectiveness of primary chemoradiotherapy for patients with non-resectable M0 HNSCC?
11. What is the clinical effectiveness of treatment interventions for metastatic disease or recurrent disease not suitable for curative treatment?

Some of these research questions were deliberately formulated in a general way, i.e. not focusing on oral cavity cancer alone, in order to be able to use the evidence for part two also. For six questions (question 3, 4, 8, 9, 10 and 11) a literature search was done by the DCC. For the remaining five questions, the searches were done by the KCE.

For the topics for which no literature update was performed, the original recommendations were discussed with the GDG using the evidence provided by the DKG 2012 guideline.[1] Three options were possible: acceptation without changes, acceptation with changes or omission. In case changes were proposed to the original formulation, these were not based on a systematic literature search but rather based on consensus.

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. Detailed search strategies per database can be found in Appendix 2.2. 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

2.6.1 Therapeutic interventions

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. If these were not reported, an attempt was made to estimate the log (HR) and its standard error using the methods of Parmar.[2]

For comparative observational studies the measure of treatment effect that has been adjusted for confounders was used. For dichotomous outcomes this was – in most cases – either the adjusted odds ratio (OR) or the adjusted hazard ratio (HR). The OR, however, lacks easy interpretation, but ORs were translated into absolute numbers in the Summary of Findings Tables (see below).

For all analyses the results of RCTs and comparative observational studies were analysed separately. If results of both RCTs and comparative observational studies were to be processed for the same comparison and outcome, the same measure of treatment effect were calculated for both study types to enable easy comparison of the results. Meta-analyses were presented in one forest plot by the use of subgroups according to study type.

For each comparison (intervention vs. comparator) separate analyses were done and whenever applicable, subgroups were distinguished.

The meta-analyses of the included reviews were updated by the addition of newly retrieved studies. This was only feasible if the required data in the review were readily available (i.e. the review reports the 2 by 2 Tables of the included RCTs or the for confounding factors adjusted effect estimates and

their standard errors for comparative observational studies). In case the required data were not available in the review, we went back to the original studies, if feasible. If this was not feasible, the results of the reviews and the newly identified studies were summarised separately and presented in Summary of Findings Tables. If the newly retrieved studies served for a new systematic review, meta-analyses were performed and the results were presented in Summary of Findings Tables.

Meta-analyses of RCTs were performed according to the guidelines described in the Cochrane Handbook and by the use of Review Manager software (Review Manager 2012). 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 (to be 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 have clinically irrelevant different effect estimates, the Chi-square test became significant (due to high power) and I^2 approached 100%; in that case the results of the visual inspection dominated the judgement of heterogeneity).

For comparative observational studies, the generic inverse variance (GIV) method was used for meta-analysis. For each study the for confounding factors 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 were reported).

If possible, all analyses were performed according to the intention-to-treat principle.

2.6.2 Diagnostic interventions

For diagnostic questions, a meta-analysis was performed when at least 4 primary studies were available. Meta-analyses were performed using the metandi command in Stata/MP version 12.1.

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.

For RCTs, quality rating was initially considered to be of high level (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.[3]

Observational studies were by default considered low level of evidence (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.

The general principles used to downgrade the quality rating are summarized in Table 4.

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.

Adapted recommendations were also graded using the GRADE system to some extent, taking into account the following limitations:

- Full-texts of the studies referenced by the DKG guideline were not assessed;
- Only information available in the DKG guideline was used.

No formal GRADE tables were produced. Where an overview of the original DKG recommendations was provided, the original levels of evidence (using the SIGN methodology) were also added.

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 (October 7, 2013; December 10, 2013; January 27, 2014; February 28, 2014). 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.[4] 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.[4]

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, 18 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 March 31, 2014. In Appendix 7, an overview is provided of how their comments were taken into account. Again, 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)
- 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 Médicine 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 (May 13, 2013; March 31, 2014) from the start of the project. A key role for patient representatives is to ensure that patient views and experiences inform the group's work.

During a separate meeting with the 3 patient representatives they 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. This validation was done in two phases. First, the content was evaluated by two clinicians on May 9, 2014. Second, the methodology was validated making use of the AGREE II checklist. This validation process was chaired by CEBAM on May 22, 2.

3 CLINICAL RECOMMENDATIONS

3.1 Diagnosis and staging

3.1.1 Patient information

The DKG guideline[1] included some general recommendations on the treatment of oral cavity cancer (Table 9). One of these addressed the provision of information to the patient.

Table 9 – General DKG recommendations on treatment of oral cavity cancer[1]

Original DKG recommendation	Original level of evidence	Decision
The patient must be kept fully informed about his condition, the treatment options and consequences.	Expert opinion	Accepted, but placed at the beginning of the guideline on the demand of the patient representatives. Also, changes were proposed by the patient representatives.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Information is considered a basic right of the (cancer) patient.
Quality of evidence	No evidence was referenced to support this recommendation.
Costs (resource allocation)	No cost issues were identified.
Patients values and preferences	Information to the patient was considered very important by the patient representatives. During the care trajectory, communication is often difficult from the patient's perspective (because of the aggressive treatment), and they should therefore be supported by any means. Information can be provided by means of leaflets.

Recommendation	Strength of Recommendation	Level of Evidence
• **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

3.1.2 Biopsy

For the recommendations on biopsy, the DKG guideline was used as a basis (Table 10).[1] However, for the present guideline a clear distinction was made between the biopsy (this chapter) and the resection specimen (see chapter 3.3).

Table 10 – DKG recommendations on biopsy for oral cavity cancer[1]

Original DKG recommendation	Original level of evidence	Decision
The tissue must be taken from the tumour margin, thus providing a representative sample. The pathologist must be provided with any clinically relevant information. If the result is inconclusive, the biopsy must be repeated. The pathologist should be consulted prior to repeating the biopsy.	Expert opinion	Biopsy should be taken in a viable and suspect part of the tumour. Biopsy should also be repeated if it was negative but the tumour is still suspect. Consulting the pathologist before repeating the biopsy is not always necessary. The recommendation was changed accordingly. A recommendation on revising the result in case of referral was felt necessary. A recommendation on the content of the biopsy result was felt necessary, similar to the recommendation on the histopathology report (see chapter 3.3).

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Having a histopathological confirmation of oral cavity cancer is necessary to guide further management. To avoid the need for repeating the biopsy, it should be representative and taken from the most suspect part of the tumour. However, in case of doubt, the benefits outweigh the harms, and the biopsy should be repeated. Not all centres provide treatment for patients with oral cavity cancer, and a recommendation on revising the result in case of referral was felt necessary. This recommendation was adopted from a recent KCE report on rare cancers (KCE report 219). Finally, similar to the reporting of the resection specimen, the biopsy report should contain minimal information about prognostic factors.
Quality of evidence	The DKG guideline did not provide evidence to support this particular recommendation, and it should therefore be considered consensus-based. Two consensus-based recommendations were added, although the recommendation about the biopsy report is supported by many prognostic studies that are referenced by the DKG guideline (as supporting evidence for the histopathology report, see chapter 3.3).
Costs (resource allocation)	No cost issues were identified.
Patients values and preferences	The patient representatives considered it necessary to receive adequate information about the imaging and other diagnostic/staging techniques that were planned for their work-up. Since patient information is a right that is also

Factor	Comment
	applicable to treatment and follow-up, a general recommendation was added to the beginning of this guideline (see chapter 3.1.1). No comments were received on the technical issues of and indications for biopsy.

Recommendations	Strength of Recommendation	Level of Evidence
• **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 with a diagnosis of oral SCC 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

3.1.3 Conventional imaging techniques

For the recommendations on conventional imaging techniques, the DKG guideline was used as a basis (Table 11).[1] Most of the DKG recommendations were merged after discussion with the GDG, and statements on technical issues were left out. Where the DKG guideline did not make a clear choice between CT or MRI for the T- and N-staging of oral cavity cancer, the GDG was clearly in favour of MRI as first-line imaging technique.

Table 11 – DKG recommendations on CT and MRI for staging of oral cavity cancer[1]

Original DKG recommendation	Original level of evidence	Decision
Computed tomography (CT) or magnetic resonance imaging (MRI) should be performed for the local staging of oral cavity cancer.	3 (Non-analytic studies, e.g. case reports, case series)	Merge with other recommendations
In order to avoid distortions of the contrast agent behaviour in the primary tumour, the tumour biopsy should only be performed after the imaging.	Expert opinion	Omitted: GDG not in agreement with recommendation, is based on expert opinion
In case of anticipated metal artefacts in the oral cavity, MRI should be preferred to CT for the assessment of the primary tumour.	Expert opinion	Merge with other recommendations
There is conflicting and no robust evidence for the superiority of CT or MRI to assess the extent of the primary tumour.	3 (Non-analytic studies, e.g. case reports, case series)	Merge with other recommendations Is rather a statement than a recommendation
To determine the N-category, the entire region from the skull base to the thorax should be examined with CT or MRI.	2+ (Well-performed case-control or cohort studies)	Merge with other recommendations
There is conflicting and no robust evidence for the superiority of CT or MRI for the evaluation of bone invasion by carcinoma of the oral mucosa.	3 (Non-analytic studies, e.g. case reports, case series)	See chapter on PET scan: chapter 3.1.4 Is rather a statement than a recommendation
Patients with advanced oral cavity cancer (stage III, IV) should undergo CT of the thorax to exclude pulmonary involvement (filia, metastasis).	3 (Non-analytic studies, e.g. case reports, case series)	See chapter on PET scan: chapter 3.1.4

Other considerations

Factor	Comment
Balance between clinical benefits and harms	The studies referenced in the DKG guideline do not support the superiority of CT over MRI or vice versa for the primary tumoural or nodal staging of oral cavity cancer: a well-performed CT is not necessarily inferior to MRI. However, because it renders less artefacts from dental amalgam, implants and fixed prostheses, and because of the reduced ionised radiation, MRI is the preferred imaging technique in tumours of the oral cavity. In case of contra-indications for MRI, CT remains valuable. Ideally, complete imaging information should be available before performing a biopsy.
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 CT or MRI on patient outcomes, such as survival.
Costs (resource allocation)	• The fee for a CT scan of the neck (nomenclature number 458813-458824) is € 131.50, while the fee for an MRI scan of the neck (459410-459421) is € 132.82. • The number of MRI units in Belgium is restricted by the government based on accreditation criteria. A hospital with an accredited MRI unit receives an annual lump sum payment from the government to operate its MRI unit. This lump sum is paid through part A3 and B3 of the hospital budget, representing about one third of the financing of MRI (KCE report 106). • For CT, these restrictions and annual payment are not in place, and financing only occurs through CT-specific fees.
Patients values and preferences	The patient representatives considered it necessary to receive adequate information about the imaging and other diagnostic/staging techniques that were planned for their work-up. Since patient information is a right that is also applicable to treatment and follow-up, a general recommendation was added to the beginning of this guideline (see chapter 3.1.1). No comments were received on the technical issues of and indications for these investigations.

Recommendations	Strength of Recommendation	Level of Evidence
• **Perform an MRI for primary T- and N-staging (i.e. before any treatment) in patients with newly diagnosed oral cavity cancer.**	Weak	Very low
• **In case MRI is technically impossible (e.g. pacemaker, cochlear implant, etc.), likely disturbed (e.g. anticipated motion artefacts, etc.) or not timely available, perform a contrast-enhanced CT for primary T- and N-staging in patients with oral cavity cancer.**	Weak	Very low

3.1.4 PET scan

Table 12 provides an overview of the recommendations on PET/CT available in the DKG guideline.[1] The detailed results of the literature update can be found in Appendix 2.2.1, Appendix 3.3.1, Appendix 4.1, Appendix 5.1 and Appendix 6.1 and are discussed below.

Table 12 – DKG recommendations on PET/CT for staging of oral cavity cancer[1]

Original DKG recommendation	Original level of evidence	Decision
The specificity and sensitivity of cervical lymph node staging can be improved with FDG-PET/CT.	2+ (Well-performed case-control or cohort studies)	Update with new evidence
Positron emission tomography (PET)-CT plays no part in the primary diagnosis of the local extension of a known oral cavity cancer.	2+ (Well-performed case-control or cohort studies)	Update with new evidence

3.1.4.1 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.[5, 6] From these reviews, 16 primary studies were selected that met our inclusion criteria.[7-22] In addition, 6 primary studies were identified that were published since the search date of the systematic reviews.[23-28] The 22 primary studies included a total of 1 534 patients, of which about two thirds had 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.[7-9,13,14,21,23,25,26] Four studies (513 patients) reported a patient-based analysis.[8,13,14,26] Pooled sensitivity was 78% (95%CI 71-84%) and pooled specificity 92% (95%CI 49-99%). Five studies reported a neck-side-based analysis.[7, 14, 21, 23, 25] Pooled sensitivity was 87% (95%CI 48-98%) and pooled specificity 88% (95%CI 68-96%). Finally, two studies reported a node-based analysis,[7,9] 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.[9-12,15-20,22-24, 27, 28] One study reported a patient-based analysis,[18] 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.[10,19, 23, 28] 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.[9, 10, 12, 15-19, 24, 27] 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.[11, 20, 23] 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,[20, 22] 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 13).[7, 9, 10, 15, 18, 20, 22-24, 27] Only in three studies PET[7] or PET/CT[10, 18] 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.[7] 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,[10] which was confirmed by Roh et al. (90% vs. 60%).[18] However, a third study (with a very low prevalence of 4%) found no difference in sensitivity between the two imaging modalities (0% vs. 0%) [15], and the statistical significance was also not confirmed using a patient-based (91% vs. 76%) [18] or neck-side-based analysis (83% vs. 71%).[10]

Four studies reporting a neck-side-based analysis were pooled.[7, 10, 20, 23] 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.[7, 9, 10, 15, 18, 20, 22, 24, 27] 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,[9, 10, 15, 18, 20, 22, 24, 27] 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,[9, 20, 22, 24] the difference in sensitivity was minimal (85% [70-94%] vs. 80% [71-87%]).

Table 13 – Comparison of PET or PET/CT with conventional imaging techniques for nodal staging: individual studies *

Comparison	Basis of analysis	N	Diagnostic accuracy (95%CI)			
			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%)

Comparison	Basis of analysis	N	Diagnostic accuracy (95%CI)			
			Sensitivity	Specificity	Sensitivity	Specificity
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.*

3.1.4.2 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.[29-31] From these reviews, 4 primary studies were selected that met our inclusion criteria.[32-35] In addition, 4 primary studies were identified that were published since the search date of the systematic reviews.[25, 36-38] The 8 primary studies included a total of 972 patients, of which about two thirds had oral cavity or oropharyngeal SCC.

3.1.4.2.1 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.[25, 32-35, 37, 38] 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 14).[33, 34, 37] In only one study, a significantly higher specificity was found for PET compared with CT (93% vs. 63%).[33] However, this was not confirmed in the two other studies. Sensitivities did not differ significantly.

Table 14 – Comparison of PET or PET/CT with conventional imaging techniques for the detection of distant metastases or second primary tumours*

Comparison	N	Diagnostic accuracy (95%CI)			
		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.[37] 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.[36] 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.[32, 37] 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.[37] 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.[32] 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.[37] 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.[37] 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.[37] 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.[37] 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	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. Screening all patients for distant metastases and/or second primary tumours is not necessary, but it is difficult to define the exact patient population that needs this screening. If, based on the patient profile and locoregional staging, the risk for metastasis (e.g. for stage III/IV) and/or second primary tumours (e.g. heavy smokers) is considered high, a whole-body FDG-PET/CT is indicated. Screening for distant metastases is of particular importance for patients with stage III or IV disease, while screening for second primary tumours is relevant for most stages in the presence of high-risk features, such as heavy smoking.
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 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.
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.[39] An American study reported that PET/CT is a more expensive test ($ 722 per patient versus $ 450 for traditional workup), but that it results an overall cost savings by reducing the number of futile radical treatments.[40] Another American study found an ICER of $ 8718 per life year saved or $ 2505 per quality-adjusted life-year.[41]
Patients values and preferences	The patient representatives considered it necessary to receive adequate information about the imaging and other diagnostic/staging techniques that were planned for their work-up. Since patient information is a right that is also applicable to treatment and follow-up, a general recommendation was added to the beginning of this guideline (see chapter 3.1.1). No comments were received on the technical issues of and indications for PET scan.

Recommendation	Strength of Recommendation	Level of Evidence
In patients with stage III and IV oral cavity cancer, and in patients with high-risk features irrespective of the locoregional staging (e.g. heavy smokers), perform a whole-body FDG-PET/CT for the evaluation of metastatic spread and/or the detection of second primary tumours.	Weak	Low

3.1.5 Other staging interventions

For the recommendations on other staging techniques, the DKG guideline was used as a basis (Table 15).[1]

Table 15 – DKG recommendations on other staging interventions for oral cavity cancer[1]

Original DKG recommendation	Original level of evidence	Decision
As part of primary diagnosis, an abdominal US should be performed.	Expert opinion	Omitted: GDG not in agreement with recommendation, is based on expert opinion.
The specificity of cervical lymph node staging can be improved with US-FNAC.	2++ (High-quality systematic reviews of case-control or cohort studies; high-quality case-control or cohort studies)	GDG agrees, but inter-rater variability is important. Therefore, recommendation was omitted after the stakeholder meeting.
To exclude synchronous secondary tumours, patients undergoing primary diagnosis of oral cavity cancer should also be examined by an ear, nose, and throat (ENT) specialist and endoscopy should be considered.	Expert opinion	GDG partly agrees and proposes some adjustments.
A panoramic section is one of the basic tools in dental diagnosis and should be obtained before the commencement of specific tumour therapy.	Expert opinion	GDG agrees, but with some exceptions Merged with the following recommendation: *Patients with carcinoma of the oral cavity should be examined by an experienced dental practitioner to ascertain their dental status prior to commencing treatment.*
There is no reliable evidence for higher test quality or additional benefits of cone beam CT (dental CT) versus the panoramic radiograph for assessment of bone invasion of the mandible.	3 (Non-analytic studies, e.g. case reports, case series)	Omitted, since MRI and PET/CT are already recommended for staging. Rather a statement than a recommendation.
There is no robust evidence for sentinel lymph node biopsy (SLNB) as a method to avoid elective cervical lymph node dissection.	Expert opinion	GDG agrees. However, this is a statement, not a recommendation.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	• No clinical benefits for abdominal US (expert opinion). • Diagnostic studies show a high specificity of US-FNAC for detecting cervical lymph nodes [Gencoglu 2003, Takes 1998]. The added value of US-guided FNAC is for those cases where it would alter the management of the patient, e.g. the need for a different neck node dissection procedure or a different radiation dose. Given the important inter-rater variability, it should only be done by an experienced physician. It is mainly its specificity that guides management. • The GDG agreed with the clinical benefits observed for an ENT evaluation and a dental evaluation with panoramic graph. Dental evaluation can also be performed by a maxillofacial surgeon. • In order to avoid the morbidity associated with LND of the neck, sentinel node procedure/biopsy has been suggested as an alternative, but available evidence is considered too limited to formulate a recommendation on it. Sentinel node biopsy is a diagnostic procedure that has been validated in a few prospective trials, and should only be performed in well-experienced centres.
Quality of evidence	• No sound evidence is available supporting the use of abdominal US; in view of the low clinical value, the recommendation was omitted. • According to the DKG guideline, high-quality cohort studies showed the high specificity of US-FNAC. • No evidence was referenced to support an ENT evaluation and dental evaluation.
Costs (resource allocation)	• No cost issues were identified.
Patients values and preferences	The patient representatives considered it necessary to receive adequate information about the imaging and other diagnostic/staging techniques that were planned for their work-up. Since patient information is a right that is also applicable to treatment and follow-up, a general recommendation was added to the beginning of this guideline (see chapter 3.1.1). No comments were received on the technical issues of and indications for these investigations. The period between the preventive (dental) measures and the treatment is often short, and therefore it is considered very important that these preventive measures are provided by a dedicated person.

Recommendations	Strength of Recommendation	Level of Evidence
• **To exclude synchronous secondary tumours in the head and neck area, all patients with oral cavity cancer 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 with carcinoma of the oral cavity 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

3.1.6 HPV testing

In the DKG guideline, a statement was included that "evidence of HPV 16 in the serum is associated with an increased risk of oral cavity carcinoma".[1] However, no recommendation was included on the actual use of HPV testing. Therefore, it was decided to perform a literature search on this topic. The detailed results of the literature update can be found in Appendix 2.2.2 and Appendix 3.3.2 and are discussed below.

One evidence-based guideline on the use of routine HPV testing in head and neck SCC was identified on the cancer care Ontario website.[42] A systematic review was performed to answer four research questions, of which the following three will be discussed in this guideline:

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.

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

The Cancer Care Ontario guideline[42] 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.[43] 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.[44] 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.[45] 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.[46] 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 overall survival had a higher HPV prevalence of 42% and 44% respectively.

Kreimer et al.[47] 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%).

3.1.6.2 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.[48] 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.[49] 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.[50] 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.[51] 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.[52] 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. 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.[53] 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.[54] used tumour specimens from 48 patients with head 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.[55] 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 overall survival 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.[56] 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.[57] 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 overall survival but sample sizes were small. Compared with HPV DNA status, calculated sensitivity and specificity were 73% and 77% respectively.

Pannone et al.[58] 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.[59] 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 overall survival ($p=0.005$) 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.

3.1.6.3 *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 overall survival (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.[60] 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.[61-63]

Ang et al.[62] 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.[61] 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 overall survival, 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 overall survival, 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.[63] 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. Overall survival 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.[64] 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.[65] 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%) (B-ENT 2014; 10(1): accepted for publication). Belgian data for oral cavity cancer are not available. The review of Kreimer et al.[47] 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

Factor	Comment
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
• **Due to insufficient evidence routine p16 testing is not recommended in patients with oral cavity cancer. In patients without any of the common risk factors (e.g. smoking, alcohol abuse) for oral cavity cancer, testing for p16 can be considered, although there is no evidence at present that it alters treatment decisions in these patients.**	Weak	No GRADE

3.2 Treatment of primary non-metastatic oral cavity cancer

3.2.1 Multidisciplinary treatment

The DKG guideline[1] included some general recommendations on the treatment of oral cavity cancer (Table 16). All were slightly adapted or accepted.

Table 16 – General DKG recommendations on treatment of oral cavity cancer[1]

Original DKG recommendation	Original level of evidence	Decision
Oral cavity carcinoma must be treated on an interdisciplinary basis after discussion of the case in question by a tumour board, comprising the specialist disciplines of oral and maxillofacial surgery, ENT, radiotherapy, oncology, pathology and radiology.	Expert opinion	GDG partly agrees and proposes some adjustments.
Patients with carcinoma of the oral cavity should be examined by an experienced dental practitioner to ascertain their dental status prior to commencing treatment.	3 (Non-analytic studies, e.g. case reports, case series)	Merged with the following recommendation: A panoramic section is one of the basic tools in dental diagnosis and should be obtained before the commencement of specific tumour therapy. See paragraph 3.1.5

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Interdisciplinary treatment is considered a standard approach for cancer patients. The GDG agrees with the recommendation, but added some disciplines. All relevant disciplines, including the general practitioner, are recommended to be present during the multidisciplinary discussions.
Quality of evidence	No evidence was referenced to support these recommendations.
Costs (resource allocation)	No cost issues were identified.
Patients values and preferences	The patient representatives underwrote the need of a multidisciplinary approach, and stressed the need of a good communication within the team.

Recommendations	Strength of Recommendation	Level of Evidence
• **Oral cavity 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 oral and maxillofacial surgery, 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

3.2.2 Surgical treatment

An overview of the recommendations on surgical treatment derived from the DKG guideline[1] can be found in Table 17.

Table 17 – DKG recommendations on surgical treatment of oral cavity cancer[1]

Original DKG recommendation	Original level of evidence	Decision
Provided the patient's general condition permits and the oral cavity carcinoma may be curatively resected, surgery should be performed and if possible combined with immediate reconstruction. Postoperative treatment should also be undertaken in advanced cancers.	3 (Non-analytic studies, e.g. case reports, case series)	GDG partly agrees and proposes some adjustments. The part on postoperative treatment is discussed in chapter 3.2.3.
The treatment for oral cavity carcinoma must take the patient's individual situation into account. The decision to perform surgery must be made on the basis of the ability to achieve tumour-free resection margins and postoperative quality of life.	3 (Non-analytic studies, e.g. case reports, case series)	Accepted
In case of a microscopic residual tumour (failed R0 resection), targeted follow-up resection should ensue with the aim of improving the patient's prognosis.	3 (Non-analytic studies, e.g. case reports, case series)	GDG partly agrees and proposes some adjustments.
Continuity of the mandible should be preserved on tumour resection, provided no radiological or intraoperative evidence has been found of tumour invasion of the bone.	3 (Non-analytic studies, e.g. case reports, case series)	Accepted

Other considerations

Factor	Comment
Balance between clinical benefits and harms	The aim of curative surgery is to completely remove the tumour and ensuring (if possible) that a margin of normal tissue surrounding the tumour is also removed. Evidence from case series suggests that the presence of positive margins leads to locoregional recurrence.[66] Most of these recommendations were accepted as formulated in the DKG guideline, or only slightly adapted. They reflect the balance between the aim of removing all tumour tissue but preserving as much functionality as possible. However, in case of upfront reconstruction with a free flap, targeted follow-up resection may be difficult to justify. Some tumours may be accessible through paramedian mandibulotomy, necessitating replating post-resection.
Quality of evidence	Only case series are referenced by the DKG guideline to support these recommendations.
Costs (resource allocation)	No cost issues were identified.
Patients values and preferences	No comments were received from the patient representatives.

Recommendations	Strength of Recommendation	Level of Evidence
• **Provided the patient's general condition permits it and the oral cavity carcinoma can be curatively resected, surgical resection of the tumour should be performed and followed by immediate reconstruction, when required.**	Strong	Very low
• **The treatment for oral cavity carcinoma must take the patient's individual situation into account. The decision to perform surgery must be made on the basis of the ability to achieve tumour-free resection margins and postoperative quality of life. For locally advanced tumours, the postoperative functional consequences need to be prospectively and carefully assessed. For instance, when a total glossectomy (+/- total laryngectomy) is the only oncologically suitable surgical option, non-surgical organ preservation protocols must be seriously considered.**	Strong	Very low
• **In case of a microscopically residual tumour (R1 resection), targeted follow-up resection should ensue with the aim of improving the patient's prognosis, whenever possible.**	Weak	Very low
• **Continuity of the mandible should be preserved on tumour resection or restored post-resection, provided no radiological or intraoperative evidence has been found of tumour invasion of the bone.**	Strong	Very low

3.2.3 Radiotherapy

3.2.3.1 Adapted recommendations

An overview of the recommendations on (chemo)radiotherapy derived from the German guideline[1] can be found in Table 18. In addition, the German guideline contained recommendations on the prevention and management of radiation-induced side effects (Table 19). Other recommendations on the prevention and treatment of radiation-induced side effects can be found in a previous KCE report [KCE 185].

Table 18 –DKG recommendations on (chemo)radiotherapy for oral cavity cancer[1]

Original DKG recommendation	Original level of evidence	Decision
Interruption to radiotherapy will be detrimental to tumour control and so must be avoided.	2+ (Well-performed case-control or cohort studies)	Accepted
If primary percutaneous irradiation is used alone, fractionation should be modified (hyperfractionation/acceleration).	Expert opinion	Omitted: no underlying evidence, and not applicable to all patients
In concurrent primary radiochemotherapy, chemotherapy should include cisplatin or a combination containing cisplatin.	Expert opinion	Accepted with small changes
Patients with advanced, inoperable and non-metastatic oral cavity carcinoma, especially those aged 70 or under, must preferably be administered primary radiochemotherapy rather than radiotherapy alone.	1++ (High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias)	Update with new evidence: see chapter 3.2.3.2
Radiochemotherapy must only be performed at facilities in which radiotherapy- or chemotherapy-induced acute toxicities can be diagnosed and adequately treated.	Expert opinion	Accepted with small changes
A combination of radiotherapy with cetuximab may be administered as an alternative to radiochemotherapy.	Expert opinion	Omitted: no evidence available, not reimbursed in Belgium
Postoperative radiotherapy or radiochemotherapy must be performed for advanced T categories (T3/T4), close or positive resection margins, perineural invasion, vascular invasion and/or lymph node involvement.	1++ (High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias)	GDG partly agrees and proposes some adjustments
Postoperative radiotherapy must be fractionated conventionally and constitute 54-60 Gy in 27-30 fractions over 5.5-6 weeks for an average risk, and 66 Gy in 33 fractions over 6.5 weeks for tumours with an increased risk of recurrence.	1++ (High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias)	GDG partly agrees and proposes some adjustments
Postoperative radiotherapy should be commenced as early as possible and be completed within a maximum of 11 weeks after surgery.	2++ (High-quality systematic reviews of case-control or cohort studies, or good-quality case-control or cohort studies with a very low risk of confounding or bias and a high	GDG partly agrees and proposes some adjustments

Original DKG recommendation	Original level of evidence	Decision
	probability that the relationship is causal)	
If radiotherapy is indicated, patients with increased histopathologic risk criteria for tumour recurrence (resection margin <5 mm and/or extracapsular tumour growth) after tumour resection should receive adjuvant treatment in the form of radiochemotherapy with cisplatin.	2++ (High-quality systematic reviews of case-control or cohort studies, or good-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal)	Merged with the following recommendation: 'Postoperative radiotherapy or radiochemotherapy must be performed for advanced T categories (T3/T4), close or positive resection margins, perineural invasion, vascular invasion and/or lymph node involvement.'
Patients with small but accessible tumours (T1/T2) in the oral cavity may be treated in selected cases with interstitial brachytherapy.	3 (Non-analytic studies, e.g. case reports, case series)	Accepted (with addition of example)

Table 19 –DKG recommendations on prevention and management of radiation-induced side effects[1]

Original DKG recommendation	Original level of evidence	Decision
There is evidence to suggest that the frequency and severity of radiation-induced xerostomia can be reduced by intensity-modulated radiotherapy (IMRT).	3 (Non-analytic studies, e.g. case reports, case series)	Is a statement and no recommendation. Will be part of the recommendation on IMRT, for which a new literature search was done.
Patients undergoing irradiation for carcinoma of the oral cavity must be provided with optimal dental and oral health care.	Expert opinion	Message is already included in a recommendation on dental assessment (see chapter 3.1.5).
Patients must undergo a dental examination and if necessary preservative and/or surgical restoration of the teeth prior to radio/radiochemotherapy of the oral cavity in order to avoid osteoradionecrosis.	Expert opinion	Message is already included in a recommendation on dental assessment (see chapter 3.1.5).
When starting radiotherapy of the oral cavity a fluoride gel tray, and spacer if necessary, must be prepared.	Expert opinion	Accepted with changes.
Patients having undergone irradiation for carcinoma of the oral cavity should be offered oral pilocarpine three times daily if there is evidence of residual salivary gland function, provided there are no contraindications.	1+ (Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias)	Omitted because too many side effects and contraindications in elderly.

3.2.3.2 *Primary chemoradiotherapy versus radiotherapy for non-resectable non-metastatic oral cavity cancer*

In the DKG guideline, the following recommendation was included: "Patients with advanced, inoperable and non-metastatic oral cavity carcinoma, especially those aged 70 or under, must preferably be administered primary radiochemotherapy rather than radiotherapy alone".[1] However, during the scoping phase for this guideline, the topic was considered to be sufficiently relevant for an update of the literature search. The detailed results of the literature update can be found in Appendix 2.2.10, Appendix 3.3.9, Appendix 4.9, Appendix 5.9 and Appendix 6.4, and are discussed below.

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.[67, 68] Another five RCTs which also involved patients with a stage lower than T4b were additionally included.[69-73]

The first RCT[67] 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 overall survival (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[69] 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 overall survival 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[70] 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. Overall survival, quality of life and recurrence rate were not assessed.

The fourth RCT[72] 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 overall survival, 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[68] 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 overall survival 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[73] 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 overall survival compared with patients treated with RT alone (25.6% vs. 15.8%, p=0.016). In patients with an oropharyngeal tumour overall survival 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 overall survival 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[71] 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 haematologic 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), dermatitis (pooled RR=1.20; 95% CI 0.90 to 1.62; Figure 88, Appendix 6.5), 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) and thrombocytopenia (pooled RR=8.63; 95% CI 1.11 to 67.05; Figure 91, Appendix 6.5).

Conclusions

Primary CRT vs. primary RT

- **Evidence of low to very low quality demonstrated that in adult patients with non-resectable (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.**
- **Evidence of moderate quality demonstrated that in adult patients with non-resectable (T4b) M0 HNSCC primary chemoradiotherapy results in better disease-free survival at 2 years compared to primary radiotherapy. Evidence of low quality demonstrated that chemoradiotherapy results in better disease-free survival compared to primary radiotherapy at 3, 5 and 10 years.**
- **Evidence of low to very low quality demonstrated that in adult patients with non-resectable (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 non-resectable (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, evidence of very low quality demonstrated that primary chemoradiotherapy leads to less erythema and moist desquamation compared to primary radiotherapy.**
- **Evidence of very low quality demonstrated that in adult patients with non-resectable (T4b) M0 HNSCC primary chemoradiotherapy results in more late toxicity of oesophagus and larynx compared to primary radiotherapy.**
- **Evidence of very low quality demonstrated that in adult patients with non-resectable (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 non-resectable (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 non-resectable (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.**

3.2.3.3 IMRT

In the DKG guideline, the following statement on IMRT was included: "There is evidence to suggest that the frequency and severity of radiation-induced xerostomia can be reduced by intensity-modulated radiotherapy".[1] However, during the scoping phase for this guideline, the topic was considered to be sufficiently relevant for an update of the literature search. The detailed results of the literature update can be found in Appendix 2.2.8, Appendix 3.3.7, Appendix 4.7 and Appendix 5.7, and are discussed below.

One systematic review was included that compared IMRT with two-dimensional external beam radiotherapy (2D-EBRT) in the treatment of head and neck cancer.[74] 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).[74] 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).[74]

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.[74] 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).[74] 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).[74] 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]).[74] 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.

The first observational study[75] 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[76] 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[77] 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, overall survival, (loco) regional control, recurrence rate, secondary tumours and adverse events were not assessed.

The fourth study[78] 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[79] 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[80] 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[81] 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[82] 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.

The first RCT[83] 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[84] 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 overall survival 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). Dysphagia occurred significantly less frequently after IMRT (pooled RR= 0.86; 95%CI 0.74 to 0.99) (Appendix 6.3, Figure 83).

In summary, no significant differences between IMRT and conventional radiotherapy were observed for DFS. There are indications that IMRT has better OS and local control. Overall, QoL (various measures) and adverse effects are in favour of IMRT (which confirms the conclusions of the included systematic review). The update included only 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-analysis.

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).**
- **Evidence of very low quality demonstrated 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.**
- **Evidence of very low quality demonstrated 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	Local control rates at five years of 79-97% (T1) and 65-87% (T2) were reported for interstitial brachytherapy in case series.[66] A dose of 65 Gy results in optimal local control. Doses in excess of 65 Gy result in an increased risk of necrosis and bone complications. 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. The role of adjuvant radiotherapy has not been clearly defined from RCTs. Pathological risk factors that predict local recurrence have been assessed in prospective studies and retrospective case series. Indications for adjuvant radiotherapy have been extrapolated from these risk factors.[66] Accelerated fractionation radiotherapy does not offer significant improvement in locoregional control or survival compared to conventional fractionation radiotherapy when delivered postoperatively to patients with high-risk adverse pathological factors.[66] The cumulative time of combined therapy (i.e. from surgery to completion of adjuvant radiotherapy) significantly affects locoregional control and survival in high-risk patients.[66] For both primary and postoperative chemoradiotherapy, chemotherapy should be platinum-based. However, in case of postoperative chemoradiotherapy, the evidence only supports the use of a dose of 100 mg/m² three times weekly. IMRT is potentially associated with a better (loco)regional control and quality of life and less adverse events compared with EBRT. However, the available evidence is mainly focused on tumour locations other than the oral cavity.

Factor	Comment
	Nevertheless, the GDG considered the beneficial effects to be extendable to oral cavity cancer. IMRT is a specific technique that should be performed in dedicated centres according to well-established procedures. Prolonging the overall time taken for the delivery of a radical course of radiotherapy due to an unscheduled interruption in treatment affects local control.[66] No clear benefit was found for the combination of radiotherapy with EGFR-inhibitors.
Quality of evidence	Evidence supporting the use of brachytherapy only comes from large case series.[66] RCTs were found comparing primary CRT with primary radiotherapy alone. The risk of bias was high in general. Only prognostic studies support the use of postoperative radiotherapy in patients with risk factors.[66] The DKG guideline referenced RCTs to support the use of conventionally fractionated postoperative radiotherapy.[1] RCTs support the use of platinum-based chemoradiotherapy.[1, 66] The evidence on IMRT is mainly limited to observational studies with a high risk of bias. The evidence on the combination of radiotherapy with EGFR-inhibitors is limited to one RCT with an unclear 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
• **Because of the increased caries risk induced by radiotherapy of the head and neck region, lifelong extra fluoride applications should be considered at least after the completion of radiotherapy.**	Weak	Very low
• **Patients with small but accessible tumours (T1/T2) in the oral cavity (e.g. lips) may be treated with interstitial brachytherapy in selected cases.**	Weak	Very low
• **Patients with advanced and non-metastatic oral cavity carcinoma who are not eligible for curative surgery (T4b, N3, unacceptable functional consequences, excessive comorbidity) should preferably be administered primary radiochemotherapy rather than radiotherapy alone.**	Weak	Very low
• **Postoperative radiotherapy should be performed for advanced T categories (T3/T4), close (< 4 mm) or positive resection margins, tumour thickness > 10 mm, lymph node involvement (> pN1) and extra capsular rupture/soft tissue infiltration. It should be considered for peri-neural**	Strong	High

Recommendations	Strength of Recommendation	Level of Evidence
extension or lymphatic vessels infiltration. For high-risk patients (e.g. close or positive resection margins, extracapsular spread) postoperative radiochemotherapy can be considered.		
• **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	High
• **Postoperative radiotherapy should be commenced as early as possible, i.e. within 6 weeks after surgery, and should be completed within 12-13 weeks after surgery.**	Strong	Low
• **In concurrent (primary or postoperative) radiochemotherapy, radiotherapy should be fractionated conventionally (i.e. 2 fractions per day, 5 days per week) and chemotherapy should be platinum-based (100 mg/m² three times weekly in case of postoperative radiochemotherapy).**	Strong	Very low
• **In view of the favourable benefit/risk balance, IMRT is recommended in patients with advanced oral cavity cancer.**	Strong	Very low
• **Interruption of radiotherapy will be detrimental to tumour control and should be avoided.**	Strong	Low
• **Radiochemotherapy should only be performed at facilities in which radiotherapy- or chemotherapy-induced acute toxicities can be adequately managed.**	Strong	Very low
• **Due to insufficient evidence the combination of radiotherapy with EGFR inhibitors is not recommended in patients with oral cavity cancer.**	Strong	Very low

3.2.4 Induction chemotherapy

In the DKG guideline, the following statement was included: "Neoadjuvant or adjuvant chemotherapy for squamous cell carcinoma of the oral cavity, combined with surgery, does not have a positive effect".[1] However, during the scoping phase for this guideline, the topic was considered to be sufficiently relevant for an update of the literature search. The detailed results of the literature update can be found in Appendix 2.2.9, Appendix 3.3.8, Appendix 4.8, Appendix 5.8 and Appendix 6.3, and are discussed below.

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.[85, 86]

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.[85] 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.[86] 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 overall survival (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 overall survival (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[85, 86] resulted in the inclusion of five additional relevant studies.

The first study[87] 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 followed by radiotherapy, 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 overall survival 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[88] 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 overall survival, 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[89] 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 overall survival (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[90] 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[91] 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 overall survival 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 ‘overall survival’ 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 'overall survival' and 'disease-free survival' were also performed (Figure 84, Appendix 6.4 and Figure 85, Appendix 6.4). The overall pooled result for 'overall survival' 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 'overall survival' (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[87, 89] was not significant: RR=2.11 (95%CI 0.75 to 5.92) (Figure 86, Appendix 6.4).

In summary, significant differences between induction chemotherapy followed by locoregional therapy vs. locoregional therapy were found for 'overall survival' 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

- **Evidence of moderate quality showed 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.**
- **Evidence of high quality showed 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 survival benefit of induction chemotherapy for patients with oral cavity cancer is only modest, and is not considered a proof of effectiveness for induction chemotherapy for oral cavity cancer specifically. Evidence on the safety of induction chemotherapy does not allow to draw firm conclusions.
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 oral cavity cancer, induction chemotherapy is not recommended.**	Strong	Very low

3.2.5 *Reconstructive surgery*

An overview of the recommendations on reconstructive surgery derived from the DKG guideline[1] can be found in Table 20.

Table 20 –DKG recommendations on surgical treatment of oral cavity cancer[1]

Original DKG recommendation	Original level of evidence	Decision
Reconstructive measures must basically form part of a surgical concept. When planning reconstruction, consideration must be given to the entire oncological scenario. The anticipated functional or aesthetic improvement must justify the efforts involved in reconstruction.	3 (Non-analytic studies, e.g. case reports, case series)	Accepted
Reconstruction of the oral cavity using microsurgical anastomosis is an established procedure. In many cases, microvascular tissue transfer is already indicated in association with tumour resection so as to safely cover the defect.	3 (Non-analytic studies, e.g. case reports, case series)	Omitted, because too detailed

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Surgical reconstruction aims to repair any physical deficit and restore or minimise functional deficit that would arise from the loss of resected tissue.
Quality of evidence	The evidence supporting reconstructive surgery comes from retrospective case series.[66]
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
• **Reconstructive measures must basically form part of a surgical concept. When planning reconstruction, consideration must be given to the entire oncological scenario. The anticipated functional or cosmetic improvement must justify the efforts involved in reconstruction.**	Strong	Very low

3.2.6 Management of the neck lymph nodes

Table 21 provides an overview of the recommendations on lymph node dissection available in the DKG guideline.[1] The entire chapter was submitted to an update of the literature because of disagreement with the original recommendations. The detailed results of the literature update can be found in Appendices 2.2.3 - 2.2.5, Appendices 3.3.3 - 3.3.4, Appendices 4.2 - 4.4 and Appendices 5.2 - 5.4, and are discussed below.

Table 21 – DKG recommendations on lymph node dissection for oral cavity cancer[1]

Original DKG recommendation	Original level of evidence	Decision
Occult metastases in the cervical lymph nodes are found in 20% - 40% of cases of oral cavity carcinoma, almost always affecting levels I-III, but very rarely level V.	3 (Non-analytic studies, e.g. case reports, case series)	Update with new evidence
If the lymph node status is clinically negative (cN0), then the results of selective neck dissection (level I-III) will not differ from those of modified radical or radical neck dissection.	3 (Non-analytic studies, e.g. case reports, case series)	Update with new evidence
In patients with a clinically negative lymph node status (cN0), elective neck dissection must be performed irrespective of T category.	3 (Non-analytic studies, e.g. case reports, case series)	Update with new evidence
Preservation of the accessory nerve on neck dissection results in improved quality of life.	3 (Non-analytic studies, e.g. case reports, case series)	Update with new evidence
The outcome of modified radical neck dissection may, in selected cases where metastasis has already occurred, be equivalent to radical neck dissection.	3 (Non-analytic studies, e.g. case reports, case series)	Update with new evidence
The outcome of selective neck dissection (level I-III) combined with postoperative radiochemotherapy may, in selected cases where lymph node metastasis has already occurred, be equivalent to modified radical neck dissection with postoperative radiotherapy.	3 (Non-analytic studies, e.g. case reports, case series)	Update with new evidence
If there is a clinical suspicion of lymph node involvement (cN+) the cervical lymph nodes must be appropriately removed, as a rule by means of modified radical neck dissection.	3 (Non-analytic studies, e.g. case reports, case series)	Update with new evidence

3.2.6.1 *Management of the clinically node negative neck*

One systematic review was included that compared the clinical effectiveness of elective lymph node dissection versus watchful waiting (WW) in patients with cN0 oral cavity cancer.[92] The review aimed to determine which surgical treatment modalities for oral cavity and oropharyngeal cancers result in increased overall survival, disease free survival, progression free survival and reduced recurrence. The search date was February 2011 and the overall risk of bias of this review was judged to be low. The review included seven studies (RCTs) (n=669 of whom 667 had cancer of the oral cavity). Four of the studies compared elective neck dissection (END) with various types of therapeutic (delayed) neck dissection in patients with oral cavity cancer and clinically negative neck nodes. Of these, two were considered to have an unclear risk of bias[93, 94] and two a high risk of bias.[95, 96] Three of these studies reported total mortality and disease-free survival (DFS). However, differences in type of surgery and duration of follow-up made meta-analysis inappropriate. One study showed a benefit for elective supraomohyoid neck dissection compared to therapeutic (delayed) neck dissection with respect to DFS (HR=0.32, 95%CI 0.12 to 0.84) and total mortality (RR=0.40, 95%CI 0.19 to 0.84). Two studies found no significant difference between elective radical neck dissection and therapeutic (delayed) radical neck dissection for DFS at one year (RR=1.20, 95%CI 0.82 to 1.75) and at three years (RR=0.79, 95%CI 0.51 to 1.23) and total mortality at one year (RR=0.74, 95%CI 0.39 to 1.43) and at three years (HR=1.35, 95%CI 0.59 to 3.07). All four studies found a reduced locoregional recurrence following END, but these differences were not statistically significant. None of these four studies reported on quality of life or adverse events. Bessell et al. concluded that there is weak evidence that elective neck dissection of clinically negative neck nodes at the time of removal of the primary tumour results in reduced locoregional recurrence, but that there is insufficient evidence to conclude that elective neck dissection reduces total mortality or disease free survival compared to therapeutic neck dissection.

The update of the search resulted in the inclusion of seven additional relevant observational studies [97-103] assessing the clinical effectiveness of elective lymph node dissection versus WW in patients with cN0 oral cavity cancer. Three of these studies addressed patients with tongue cancer only[97, 98, 101] and one study addressed both patients with tongue and buccal cancer[102] and presented the results separately. No recent randomized studies were identified that fulfilled the inclusion criteria.

The first study[99] performed a retrospective analysis comparing END with WW (observation) in 153 patients with T1 to T2 N0 oral squamous cell carcinoma (SCC) with a thickness of at least 4 mm. The risk of bias of this study was judged to be high. Compared to the WW group patients undergoing END were significantly more likely to have pT2 tumours, involved margins and to receive adjuvant radiotherapy. The END group also demonstrated non-significantly higher rates of perineural invasion and younger age. In a multivariable analysis (with T classification, tumour thickness, margin status, perineural invasion, provision of adjuvant radiotherapy and age included into the model), END was a significant predictor of improved overall survival (OS) (HR=0.3, 95%CI 0.1 to 0.6) and regional control (HR=0.1, 95%CI 0.0 to 0.3). The study did not report on DFS, quality of life or adverse events.

The second study [100] performed a retrospective analysis of 285 patients with T1–T2 oral cancer and a clinically negative neck (based on ultrasound-guided fine needle aspiration cytology) who were treated with transoral excision. Of these, 51 underwent END and 234 underwent WW. The risk of bias of this study was judged to be high. Patients in the END group were younger, had more pT2 tumours, more tumours of the floor of the mouth and less differentiated tumours (significant differences compared to the WW group). Five-year OS rates were not significantly different between the two groups (69.5% vs. 81.6%; p=0.082). After adjustment for pT-classification, tumour differentiation and age the difference in survival remained not significant (p=0.5). Regional recurrences were only presented for patients with metastases and the study did not report on quality of life or adverse events.

The third study[102] was a retrospective review of 265 patients with stage T1/T2 N0 squamous cell carcinoma of the oral tongue or buccal mucosa, who underwent curative surgery as first treatment. Of these, 184 underwent END and 81 WW (observation). The risk of bias of this study was judged to be high. Baseline characteristics were not reported per study group, which makes the interpretation of the validity of the results challenging. In addition, the results of the analyses were presented in a very confusing way which makes interpretation difficult. The 5-year DFS rates were 93.7% vs. 78.2% (p=0.001), respectively. The univariate HR for DFS was 0.55 (95%CI 0.31

to 0.97) and the multivariate HR (apparently with T-stage in the model) was 0.37 (95%CI 0.19 to 0.71). The 5-year OS rates were 94.7% vs. 78.7 (p=0.036), respectively. The univariate HR for OS was not presented; the multivariate HR (apparently with T-stage, age, gender, alcohol use, primary site and tumour differentiation in the model) was 0.34 (95%CI 0.17 to 0.68). Local, regional and locoregional recurrence were presented stratified for T-stage and tumour site (buccal or tongue). Quality of life or adverse events were not assessed.

The fourth study[103] evaluated the efficacy of selective submandibular neck dissection (SMND) in patients with oral SCC with or without nodal metastasis. Two hundred and twenty-nine patients with clinically negative necks were included. Among these, 110 underwent neck dissection and 119 patients underwent resection of the primary tumour only (WW). The risk of bias of this study was judged to be high. Both groups were very similar with respect to the distribution of the primary tumour site, clinical tumour stage and tumour differentiation. Other baseline prognostic factors were not reported. No significant differences in 5-year DFS (88.0% vs. 85.5%, p=0.78), regional recurrence (RR=0.82, 95%CI 0.45 to 1.50) and 5-year regional control rate 85.2% vs. 82.9%, p=0.68) were found between the two groups. Overall survival, quality of life or adverse events were not assessed.

Of the studies that included patients with tongue cancer, one study[97] performed a retrospective chart review of 63 patients with T1-T2N0 SCC of the oral tongue who underwent partial glossectomy with or without END. The risk of bias of this study was judged to be high. No baseline characteristics were reported, which makes the interpretation of the validity of the results challenging. The 5-year DFS of END was significantly higher than for non-END (100% and 68.7%, respectively, p=0.045) (T1N0M0). No significant differences in 5-year OS were found between the two groups (100% vs. 96%, p = 0.527) (stage I). The outcomes for regional recurrence were not specified per treatment group and the study did not report on quality of life or adverse events.

Another study[98] presented a large retrospective analysis of patients with T1-2 N0 SCC of the oral anterior tongue treated at a single institution. A total of 359 eligible patients with early tongue cancers were divided into 2 groups: END and WW. An analysis for survival outcomes and prognostic factors was conducted. The risk of bias of this study was judged to be high. There were more patients with T1 tumours and tumours with thickness <9 mm in the WW group compared with the elective neck dissection group. Three-year DFS was 76% for the END group versus 71% for the WW group. Five-year survival rates were 74% and 68%, respectively (p=0.53). The 3-year overall survival rate was 69% for the END group versus 62% for the WW group. Five-year OS rates were 60% in both groups (p=0.24). The study did not report on recurrences, quality of life or adverse events.

In the third study[101] 380 patients with cT1-2N0 oral tongue cancer were retrospectively reviewed. Patients were staged by means of computed tomography (CT) or magnetic resonance imaging (MRI). Of these, 324 patients received END of whom 287 received supraomohyoid neck dissection (SOND) and 37 modified radical neck dissection (MRND); 56 participants were in a WW (observation) group. The risk of bias of this study was judged to be high. There were statistically significantly more T1 tumours in the observation group compared to the END group. Statistically significant differences between the END group and the observation group were found for DFS (p=0.0001) and for 5-year OS (p=0.029) in favour of the END group. In a multivariate analysis with T-stage in the model the HR for 5-year DFS of SOND vs. the observation group was 0.32 (95%CI 0.19 to 0.52) and for MRND vs. the observation group 0.21 (95%CI 0.08 to 0.55). For 5-year OS HRs were 0.36 (95%CI 0.18 to 0.73) and 0.49 (95%CI 0.18 to 1.33), respectively. Patients who received END were associated with significantly better neck control (5-year neck control rate: 86.1%) compared with patients of the WW group (5-year neck control rate: 69.3%, p<0.001). In a multivariate analysis with T-stage in the model the HR for 5-year “neck control rate” of SOND vs. the observation group was 0.36 (95%CI 0.19 to 0.65) and for MRND vs. the observation group for 0.19 (95%CI 0.05 to 0.69). The study did not report on quality of life or adverse events.

The last study (already described in the previous section) presented their results also for tongue cancer separately.[102] For patients with T1 tongue cancer, the DFS rates were 77.8% for END and 91.8% for the WW (observation) group (p=0.483). For T2 tongue cancer patients rates were 90.2% and 71.4%, respectively (p=0.063). OS rates were 92.9% and 79.3% (p=0.075) for T1 tongue cancer and 94.8% and 65.0% (p=0.002) for T2 tongue cancer. Finally, in patients with T1 tongue cancer the difference in recurrence of END compared to observation was not statistically significant (RR=1.55; 95%CI 0.43 to 5.55), but for patients with T2 tongue cancer it was (RR=0.39; 95%CI 0.18 to 0.86).

This study also presented results for buccal cancer separately.[102] For patients with T1 buccal cancer, the DFS rates were 71.4% for END and 71.3% for the WW group (p=0.337). For T2 buccal cancer patients rates were 91.7% and 55.6%, respectively (p=0.034). OS rates were 100% and 95% (p=0.584) for T1 buccal cancer and 90.1% and 77.8% (p=0.494) for T2 buccal cancer. Finally, in patients with T1 buccal cancer the difference in recurrence of END compared to observation was not statistically significant (RR=0.75; 95%CI 0.20 to 2.88), but for patients with T2 buccal cancer it was (RR = 0.38; 95%CI 0.17 to 0.86).

These seven observational studies were not specifically designed to compare END with WW. Some were retrospective chart reviews or registries designed to assess prognostic factors for different patient groups. Therefore, in all studies baseline differences between the intervention groups with respect to important prognostic factors 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 should be interpreted cautiously.

Conclusions: oral cavity cancer cTanyN0M0 (general)

- **Evidence of very low quality demonstrated that in adult patients with oral cavity cancer cTanyN0M0 elective lymph node dissection results in better disease free survival compared to watchful waiting.**
- **The available evidence of very low quality does not allow to draw conclusions about the effect of elective lymph node dissection compared to watchful waiting on overall survival, locoregional, local or regional recurrence in adult patients with oral cavity cancer cTanyN0M0.**
- **Quality of life in adult patients with oral cavity cancer cTanyN0M0 after elective lymph node dissection compared to watchful waiting has not been studied by any of the included studies.**
- **Adverse events in adult patients with oral cavity cancer cTanyN0M0 after elective lymph node dissection compared to watchful waiting have not been studied by any of the included studies.**

Conclusions: tongue cancer

General

- **The available evidence of very low quality does not allow to draw conclusions about the effect of elective lymph node dissection compared to watchful waiting on overall survival and disease-free survival in adult patients with cancer of the tongue cT1-2N0M0.**
- **Evidence of very low quality demonstrated that in adult patients with cancer of the tongue cT1-2N0M0 elective lymph node dissection results in less (local, locoregional or regional) recurrence compared to watchful waiting.**

T1

- **The available evidence of very low quality does not allow to draw conclusions about the effect of elective lymph node dissection compared to watchful waiting on overall survival, disease-free survival, and (local, locoregional or regional) recurrence in adult patients with cancer of the tongue cT1N0M0.**

T2

- **The available evidence of very low quality does not allow to draw conclusions about the effect of elective lymph node dissection compared to watchful waiting on disease-free survival in adult patients with cancer of the tongue cT2N0M0.**
- **Evidence of very low quality demonstrated that in adult patients with cancer of the tongue cT2N0M0 elective lymph node dissection results in better overall survival compared to watchful waiting.**
- **Evidence of very low quality demonstrated that in adult patients with cancer of the tongue cT2N0M0 elective lymph node dissection results in less (local, locoregional or regional) recurrence compared to watchful waiting.**

Conclusions: buccal cancer

T1

- **The available evidence of very low quality does not allow to draw conclusions about the effect of elective lymph node dissection compared to watchful waiting on overall survival, disease-free survival, and (local, locoregional or regional) recurrence in adult patients with buccal cancer cT1N0M0.**

T2

- **Evidence of very low quality demonstrated that in adult patients with buccal cancer cT2N0M0 elective lymph node dissection results in better disease-free survival compared to watchful waiting.**
- **The available evidence of very low quality does not allow to draw conclusions about the effect of elective lymph node dissection compared to watchful waiting on overall survival in adult patients with buccal cancer cT2N0M0.**
- **Evidence of very low quality demonstrated that in adult patients with buccal cancer cT2N0M0 elective lymph node dissection results in less (local, locoregional or regional) recurrence compared to watchful waiting.**

3.2.6.2 Management of the clinically node positive neck

One systematic review was included that compared the clinical effectiveness of selective lymph node dissection in patients with oral cavity cancer.[92] The review aimed to determine which surgical treatment modalities for oral cavity and oropharyngeal cancers result in increased overall survival, disease free survival, progression free survival and reduced recurrence. The search date was February 2011 and the overall risk of bias of this review was judged to be low. The review included seven studies (RCTs) (n=669 of whom 667 had cancer of the oral cavity). Two of these studies were relevant and compared selective neck dissection with (modified) radical neck dissection in patients with oral cavity cancer and clinically negative or positive but movable neck nodes. The studies were judged as being of unclear and high risk of bias. As there were differences between the two studies with regard to patient characteristics at baseline and surgical procedures, meta-analysis was not undertaken. The study comparing supraomohyoid neck dissection with modified radical classical neck dissection found no significant differences for total mortality (HR=0.89; 95%CI 0.54 to 1.43). This study also compared resection alone to resection plus elective supraomohyoid dissection (at 5 years) and found no significant differences for disease recurrence (RR=0.82; 95%CI 0.43 to 1.59). The second included study compared selective neck dissection with radical neck dissection and found no significant differences between the groups for DFS (HR=1.75; 95% 0.90 to 3.45) and total mortality (HR=1.15; 95%CI 0.55 to 2.44).

The update of the search resulted in the inclusion of eight additional relevant observational studies.[101, 103-109] No recent randomized studies were identified that fulfilled the inclusion criteria. None of the included observational studies exactly fulfilled all elements of the research question. All studies also addressed N0 patients (instead of N+ patients) or radical neck dissection (instead of modified radical neck dissection) or both. In the absence of direct evidence, these studies were further processed. Therefore, for the GRADE assessments downgrading for indirectness was applied. One of the included studies assessed patients with oral tongue cancer only,[101] one assessed patients with cancer of the inferior level of the mouth (tongue, floor of the mouth, retromolar region and the lower gingiva) [107] and the remaining six studies assessed patients with mixed tumour locations.

In one study[101] a total of 324 patients with cT1-2N0 oral tongue cancer were retrospectively reviewed. Patients were staged by means of CT or MRI. Of these, 287 patients received supraomohyoid neck dissection (SOND) and 37 modified radical neck dissection (MRND). The risk of bias of this study was judged to be high. There were more T1 tumours in the SOND group compared to the MRND group. The distribution of other prognostic factors between these groups was not reported. DFS was 78.5% in the SOND group and 83.3% in the MRND group (p=0.645) and OS was 87.2% in the SOND group and 79.6% in the MRND group (p=0.174). No statistically significant difference between the groups was found for 5-year 'neck control rate" (p=0.81).The study did not report on quality of life or adverse events.

The second study[104] involved a retrospective chart review in which therapeutic selective neck dissection was compared to comprehensive neck dissection in primary HNSCC patients who underwent neck dissection

during primary treatment. Different types of neck dissections were performed for patients with N0 disease (elective selective neck dissection vs. elective comprehensive neck dissection (modified radical neck dissection)) and N+ disease (therapeutic selective neck dissection vs. therapeutic comprehensive neck dissection). Sixty-six patients were included (78 neck dissections) and the authors used neck dissections as unit of analysis instead of patients. Concurrent chemoradiotherapy was administrated when necessary (except for cN0 T1/early T2). The risk of bias of this study was judged to be high. Group comparability was unclear as patient characteristics were not specified per treatment group. No significant differences were found in recurrence rate between therapeutic selective neck dissection compared to comprehensive neck dissection in patients with N+ disease (RR=0.77; 95%CI 0.17 to 3.53) and regional control (92.0% vs. 87.8%, p=0.57). The results of overall survival were reported for both patients with N0 and N+ disease and did not show significant differences between selective neck dissection versus comprehensive neck dissection (64.0% vs. 46.8%, p=0.065). The study did not report on disease-free survival, quality of life or adverse events.

The third study[105] presented an observational cohort study of 44 patients with HNSCC and occult nodal metastasis. Selective neck dissection (SND) was compared with SND with a conversion to MRND when occult nodal metastases were found during the operation. For 29 patients SND was done and 15 patients had a conversion to MRND because of metastatic nodes found in the operative field. The risk of bias of this study was judged to be high. The authors stated that there were no statistically significant differences for primary tumour site or T and N distributions between the groups. Other patient characteristics were not specified per treatment group. No statistically significant differences were found for (loco)regional control between the two groups (logrank test: p=0.2719). As for the recurrence rate, only one patient of the SND group had a nodal recurrence (which occurred in the contralateral undissected neck) compared to two patients with nodal recurrences in the conversion MRND group (which occurred in a previously undissected neck) (RR=0.26; 95% 0.03 to 2.63). No statistically significant difference was found for overall survival between the two groups (logrank test: p=0.7596). The study did not report on quality of life or adverse events.

The fourth study[106] involved a retrospective review in which therapeutic selective neck dissection for HNSCC was compared with comprehensive procedures. Two hundred and five patients (232 neck dissections in total) were included. The risk of bias of this study was judged to be high. At baseline, the primary tumour site differed between groups and patients who underwent selective neck dissection had fewer adverse prognostic factors compared with patients undergoing comprehensive dissection. No statistically significant differences were found between the two groups for 5-year regional control (96% vs. 86%; p=0.06) and 5-year actuarial overall survival (43% vs. 33%; p=0.25). The risk ratio for ipsilateral neck recurrence for clinical neck stage N1-3 did not show a statistically significant difference between the two groups (RR=0.33; 95%CI 0.07 to 1.49). The study did not report on quality of life or adverse events.

The fifth study[107] was a chart review (460 patients) comparing selective neck dissection with radical neck dissection (RND) in patients with SSC of the inferior level of the mouth. The authors analysed neck dissections (n= 573) as unit of analysis instead of patients. The risk of bias of this study was judged to be high. The group comparability at baseline was unclear as patient characteristics were not specified per treatment group. No significant differences in the number of recurrences were found between the two groups (RR=1.31; 95%CI 0.53 to 3.28). When the number of recurrences was separated according to pN-stage, these results did not change (pN0: RR=1.29; 95%CI 0.36 to 4.70; pN+: RR=2.30; 95%CI 0.55 to 9.67). Disease-free survival, (loco) regional control, overall survival, quality of life or adverse events were not assessed.

The sixth study[108] involved a historical cohort study which evaluated the effectiveness of selective neck dissection in patients with nodal metastases from HNSCC. A chart review was performed on 156 patients with clinically positive regional nodal metastases managed initially with surgery, including neck dissection. Sixty-nine patients underwent selective neck dissection (less than 5 levels), 87 underwent comprehensive neck dissection. Postoperative radiotherapy was given to patients who had extracapsular spread or nodal staging of N2 or greater based on pathology. The risk of bias of this study was judged to be high. At baseline, there were significant differences between groups in primary tumour site, clinical and pathological nodal stage, extracapsular spread, and year of surgery. No significant differences in 3-year ipsilateral regional recurrence (96% vs. 86%; p=0.053) and 3-year regional recurrence (defined as regional recurrence without local recurrence) (HR=1/4.0 = 0.25; p=0.07) were found. The multivariate HR for

3-year regional recurrence (in which differences in nodal and primary tumour stage, primary tumour site, year of surgery, extracapsular spread, postoperative radiotherapy radiotherapy rates, and neck dissection type were considered) was 0.21 (p = 0.055). The 5-year OS rates were 46% vs. 33% (p=0.14). The univariate HR for survival was 1.41 (p=0.14) and the multivariate was HR for survival was 1.27 (p=0.41). Disease-free survival, quality of life or adverse events were not assessed.

The seventh study[103] included patients with both N0 and N+ oral SCC. In the N0 group selective submandibular neck dissection (SMND; 77 patients) was compared with modified radical neck dissection (MRND; 33 patients). In the N+ group 68 patients with N+ oral SCC were included of whom 32 received SMND and 36 RND. Because the comparator of the latter group does not exactly match the comparator of the research question, this group was not taken into account. For the N0 group the evidence was considered as indirect. The risk of bias of this study was judged to be high. Both groups were very similar with respect to the distribution of the primary tumour site, clinical primary tumour stage, tumour differentiation, mode of invasion, neoadjuvant and adjuvant chemoradiotherapy, pathological node stage and extracapsular spread. For the N0 group, regional recurrence occurred in 11/77 (14.3%) of the patients treated with SMND and in 5/33 (15.2%) in the MRND group (HR=0.94; 95%CI 0.34 to 2.62). The 5-year regional control rates were 85.2% and 83.3%, respectively (p=0.89). DFS, OS, quality of life, adverse events were not reported for this comparison.

In the last study[109] selective neck dissection was compared to comprehensive neck dissection (CND) in stage pN1 head and neck cancers. Sixty-one patients were included, of which 34 patients underwent SND and 27 CND. The risk of bias of this study was judged to be high. At baseline, no significant differences for age and gender and oncologic parameters existed, except for the side of the neck dissection. No significant differences in neck recurrence between the two groups were found (RR=1.59; 95%CI 0.15 to 16.60). Also the two- (67.6% vs. 81.5%; p>0.05) and five-year (58.0% vs. 66.0%; p>0.05) OS did not differ significantly between the two groups. DFS, (loco)regional control, quality of life or adverse events were not assessed.

Most of these observational studies were not specifically designed to compare selective lymph node dissection with modified radical lymph node dissection. Some were retrospective chart reviews or registries designed to assess prognostic factors for different patient groups. Therefore, in almost all studies baseline differences between the intervention groups with respect to important prognostic factors were present. Although some studies applied multivariate analyses to correct for these differences, there still appears to be a high risk of bias due to (rest) confounding by indication. Therefore, all studies must be considered high risk of bias and the results should be interpreted cautiously.

Conclusions

- **The available evidence of very low quality does not allow to draw conclusions about the effect of selective lymph node dissection compared to modified radical neck dissection on overall survival, disease-free survival, recurrence rate and (loco)regional control in adult patients with oral cavity cancer cTanyN+M0.**
- **Quality of life in adult patients with oral cavity cancer cTanyN+M0 after selective lymph node dissection compared to modified radical neck dissection has not been studied by any of the included studies.**
- **Adverse events in adult patients with oral cavity cancer cTanyN+M0 after selective lymph node dissection compared to modified radical neck dissection has not been studied by any of the included studies.**

3.2.6.3 Contralateral neck dissection

There is little evidence on the clinical effectiveness of contralateral elective lymph node dissection in patients with oral cavity squamous cell carcinoma (OCSCC). In the DKG guideline[1] this question was not covered. In addition, no systematic review on the topic was identified. Only observational studies were obtained.

Recurrence rate

Two comparative studies were included that evaluated the difference in contralateral neck recurrence.[110, 111] The retrospective study by Lim et al. included 54 patients with SCC of the tongue who received partial glossectomy and ipsilateral neck dissection; 25 of them received also contralateral neck dissection, while the other 29 had no surgical intervention at the contralateral side.[110] The study of Gonzalez-Garcia et al. included 315

patients with SCC of the oral cavity. Depending on the location (proximity of the midline) and TNM staging they were assigned to one of the six treatment groups (ipsilateral and/or contralateral dissection, radical vs. modified type III radical neck dissection).[111] In both studies, no statistically significant differences were observed between contralateral elective lymph node dissection and watchful waiting with regard to nodal recurrence rate in the contralateral neck (Lim: 0% vs. 0%; Gonzalez-Garcia: 7.3% (unilateral dissection) vs. 3.1% (bilateral dissection), p>0.05). However, these results should be interpreted with caution since selection bias is very plausible: one study[111] assigned the surgical intervention based on the TNM staging and location (midline or not) of the primary tumour, and in the other study [110] the treatment modality was dependent on the study period (the treatment protocol changed over time) and on the TNM staging. In addition, both studies had major methodological shortcomings.

Because of clinical heterogeneity (populations not comparable) and major methodological shortcomings no pooling of data was performed.

Five-year disease-free survival

In the Lim et al. study, there was no 5-year disease-free survival benefit for patients with squamous cell carcinoma of the tongue who had an elective lymph node dissection of the contralateral neck over patients who did not have any treatment of the contralateral neck (82% vs. 68%, p>0.05).[110] Again, the major methodological shortcomings, the small sample size and the fact that only patients with squamous cell carcinoma of the tongue were included, reduce the external and internal validity of the results.

Conclusions

- **At present there is no sound scientific evidence that contralateral elective neck dissection results in better survival or lower recurrence rate in patients with oral cavity squamous cell carcinoma.**

Other considerations

Factor	Comment
Balance between clinical benefits and harms	• Although evidence is limited, there are indications that elective lymph node dissection of the neck may result in improved disease-free survival. The GDG considers the data on the safety of watchful waiting as insufficient to recommend this treatment option. However, small tumours (e.g. T1 tumours of the oral tongue with a thickness of less than 4 mm) may be acceptable exceptions as the risk of occult lymph node metastases is very low for these tumours. In that case, good follow-up of the neck is needed. • The extent of the neck dissection depends on the risk of spread to the different levels of the neck, mainly determined by the thickness of the tumour, T-stage and localisation of the primary tumour. For all tumours of the oral cavity, at least unilateral dissection of level I, II and III should be performed. In some cases (e.g. anterior floor of mouth), inclusion of level IV may be beneficial. In general, it is advisable to avoid multimodality treatment in order to limit treatment-related toxicity as much as possible. If surgery is the preferred treatment for the primary tumour, also the neck should then be approached surgically. • Available data show no oncological benefit for (modified) radical lymphadenectomy compared to selective lymph node dissection, but (modified) radical lymphadenectomy is associated with adverse functional outcomes. Generally, it is recommended to perform LND of at least level I to IV but more extensive dissection may be needed depending on the number and location of involved lymph nodes. Resection of adjacent structures such as the

Factor	Comment
	jugular vein, accessory nerve or the sternocleidomastoid muscle should only be performed on indication, e.g. when invaded. • In case of clinically N0, dissection of lymph nodes of the contra-lateral neck is only indicated for those tumours that are located on or near the midline (i.e. not located at the lateral site of the neck). • If only one lymph node in level I or II contains metastatic disease and there is no capsular rupture, dissection of level IV can be omitted.
Quality of evidence	Only two comparative studies that suffered from severe methodological problems were identified.
Costs (resource allocation)	No cost issues were identified.
Patients values and preferences	No comments were received from the patient representatives.

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).**	Strong	Very low
• **Perform a selective neck dissection of at least level I, II and III in all patients with a cN_0M_0 oral cavity SCC that is treated surgically.**	Strong	Very low
• **A neck dissection can be omitted exceptionally in some patients with a $cT1N_0M_0$ oral cavity SCC, depending on the localisation and thickness of the tumour.**	Weak	Very low
• **Perform a selective ipsilateral neck dissection of at least level I, II, III and IV with – if oncologically feasible – preservation of the sternocleidomastoid muscle, jugular vein and spinal accessory nerve in all patients with a $cN+M_0$ oral cavity SCC that is treated surgically.**	Strong	Very low
• **Consider a contralateral neck dissection in patients with a non-metastatic oral cavity SCC that is at or crossing the midline or not clearly localized laterally.**	Weak	Very low

3.2.6.4 *Neck dissection after chemoradiotherapy*

Evaluation of neck disease after chemoradiotherapy

In the DKG guideline[1] the value of PET and MRI in the decision of neck dissection after (at least) chemoradiotherapy in patients with head and neck squamous cell carcinoma was not elaborated. Therefore, a literature search was performed (see Appendix 2.2.6, Appendix 3.3.5, Appendix 4.5, Appendix 5.5 and Appendix 6.2).

1. 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.[112, 113] From these reviews, 15 primary studies were selected that met our inclusion criteria.[114-128] In addition, 6 primary studies were identified that were published since the search date of the systematic reviews.[129-134] The 21 primary studies included a total of 963 patients, of which 43 (4%) had oral cavity SCC.

Table 22 – 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				

Study	N	N Oral cavity SCC	Diagnostic accuracy (95%CI) Sensitivity	Specificity
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.[115-117, 121, 123-125, 133, 134] Seven studies (339 patients, of whom 9 with oral cavity SCC) reported a patient-based analysis.[115-117, 123, 125, 133, 134] Six studies could be included in the meta-analysis, as Zundel 2011[134] 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 23).

Only two studies reported a hemi-neck-based analysis (Lyford-Pike 2009[121] and Ong 2008[124]). As a consequence, it was not possible to pool the accuracy estimates of the individual studies (which are reported in Table 22). The sensitivity ranged between 57-71% and the specificity between 74-89% (Table 23).

No studies reported a node-based analysis.

PET

Twelve studies evaluated FDG-PET.[114, 118-120, 122, 126-132] Seven studies (308 patients, of whom 31 with OCSCC) reported a patient-based analysis.[118, 120, 122, 126, 130-132] 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 23).

Four studies reported a hemi-neck-based analysis.[114, 119, 127, 128] The pooled sensitivity was 81% (95%CI 59-92%) and the pooled specificity 83% (95%CI 67-92%) (Table 23). One study (Kishino 2012[129]) evaluated the value of FDG-PET on a node-based analysis (Table 22); the sensitivity was 100% and the specificity 64% (Table 23).

PET/CT and PET combined

When the seven studies that reported a patient-based analysis with FDG-PET/CT[115-117, 121, 123-125, 133, 134] and the seven studies that reported a patient-based analysis with FDG-PET[118, 120, 122, 126, 130-132] 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[121, 124] and FDG-PET[114, 119, 127, 128] 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 23 – 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%	

	Sensitivity					Specificity				
		Range		Meta-analysis			Range		Meta-analysis	
	N studies	Low	High	Point estimate	95%CI	Low	High	Point estimate	95%CI	
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

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

2. 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.[135]

Lin et al.[135] 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

- **Evidence of very low quality shows that MRI has a high sensitivity to detect residual disease in lymph nodes after CRT in patients with HNSCC.**
- **Evidence of low quality shows 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
• **Consider performing a diagnostic evaluation of the neck with conventional imaging techniques (CT or MRI) or PET/CT three months after completion of primary (chemo)radiotherapy.**	Weak	Very low

Neck dissection after chemoradiotherapy

In the DKG guideline[1] the clinical effectiveness of neck dissection after chemoradiotherapy in patients with N2-3 head and neck squamous cell carcinoma was not elaborated. In addition, 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.

1. Disease-free survival

Brizel et al.[136] 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.

2. Progression-free survival

Goguen et al.[137] 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.

3. Overall survival

Cannady et al. demonstrated no benefit with regard to 3-year overall survival in 210 patients with HNSCC who had a lymph node dissection after CRT (86% vs. 85.2%, p>0.05).[138] 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 overall survival rate compared to those who did not have neck surgery (77% vs. 50%, p=0.04).[136] However, the results of both studies should be interpreted with caution.

Two studies reported the 5-year overall survival 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).[138, 139] Grabenbauer et al. also reported no statistically significant difference in 10-year overall survival between intervention and control groups (35% vs. 20%, p=0.9).[138, 139] However, both studies had serious methodological flaws, hence the results should be cautiously interpreted.

4. Regional recurrence rate

Five primary studies evaluated the difference in regional recurrence rate.[137, 139-142] Soltys et al.[140] treated 56 HNSCC patients with sequential CRT, Goguen et al.[137] offered 20 HNSCC patients induction chemotherapy followed by concurrent CRT and Forest[141] and McHam[142] treated 126 and 65 HNSCC patients respectively with concurrent CRT. They all come to comparable results[137, 140-142] 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.[139] 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.

5. 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).[139] Again, the serious methodological problems should be taken into account when interpreting these results.

6. 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).[138] 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.

7. 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).[143] Only the pain index of the SF-36[a] 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).**
- **Evidence of very low quality demonstrated 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.

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

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

3.3 Histopathology

For the recommendations on histopathology, the DKG guideline was used as a basis (Table 10).[1] However, for the present guideline a clear distinction was made between the biopsy (see chapter 3.1.2) and the resection specimen (this chapter).

Table 24 – DKG recommendations on biopsy for oral cavity cancer[1]

Original DKG recommendation	Original level of evidence	Decision
To avoid a positive resection margin (which is associated with a poorer prognosis), frozen sections taken intraoperatively may be useful.	Expert opinion	Accepted
For histology, the distance from the margin of the resected tissue to the primary tumour in the formalin-fixed specimen should be a minimum of 3-5 mm. **A distance of 10 mm from the palpable tumour margin should be taken as a guide for resection.**	Expert opinion	Is formulated in a confusing way, so will be reformulated. Also, a distance of 10 mm is not always technically and anatomically possible (e.g. tumours of the mobile tongue).
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.**	Expert opinion	GDG partly agrees and proposes some adjustments
The histopathological result must include: Tumor localization, macroscopic tumour size, histological tumour type as per WHO, histological tumor grade, depth of invasion, lymphatic, vascular and perineural invasion, locally infiltrated structures, pT classification, details of affected areas and infiltrated structures, R status.	2++ (High-quality systematic reviews of case-control or cohort studies, or good-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal)	

Original DKG recommendation	Original level of evidence	Decision
The histopathological findings from a neck dissection specimen must describe the side of the neck, type of neck dissection, eliminated levels, total number of lymph nodes plus number of lymph nodes affected, level of the affected lymph nodes, diameter of the largest affected lymph node, additionally removed structures and, if present, extracapsular spread.	2++ (High-quality systematic reviews of case-control or cohort studies, or good-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal)	GDG partly agrees and proposes some adjustments

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Several histopathological factors have an impact on patient prognosis and should be part of the pathology report.
Quality of evidence	The recommendations on the pathology report are supported by many prognostic studies that are referenced by the DKG guideline.[1]
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
• **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,**	Strong	Low

Recommendations	Strength of Recommendation	Level of Evidence
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).		
• **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

An overview of the recommendations on palliative treatment derived from the DKG guideline[1] can be found in Table 25. The entire chapter was submitted to an update of the literature because of disagreement with the original recommendations. The detailed results of the literature update can be found in Appendix 2.2.11, Appendix 3.3.10, Appendix 4.10 and Appendix 5.10, and are discussed below.

Table 25 – DKG recommendations on palliative treatment of oral cavity cancer[1]

Original DKG recommendation	Original level of evidence	Decision
Patients with incurable cancer but of good general health and fitness must be scheduled for palliative platinum-based chemotherapy combined with cetuximab. Consideration should be given to monotherapy in patients whose general health is diminished. Excessive toxicity from combined chemotherapy should be avoided.	Expert opinion	Update with new evidence
Palliative radiotherapy may be considered in patients with incurable carcinoma of the oral cavity.	3 (Non-analytic studies, e.g. case reports, case series)	Update with new evidence
With a view to improving tumour-associated complications, palliative surgery and/or radiological interventions may be considered in patients with incurable carcinoma of the oral cavity.	3 (Non-analytic studies, e.g. case reports, case series)	Update with new evidence

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,[144, 145] in which treatment was assigned based on the patient's profile (confounding by indication) and one RCT (Machiels 2011).

The included RCT[146] 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 overall survival (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[144] 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 overall survival 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 overall survival (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[145] 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 overall survival between palliative chemotherapy and supportive care were found (1-year overall survival 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 overall survival 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 overall survival 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

- **Evidence of very low quality demonstrated 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

- **Evidence of very low quality demonstrated 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

- **Evidence of very low quality demonstrated 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

- **Evidence of very low quality demonstrated 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.**
- **Evidence of low quality demonstrated 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 oral cavity cancer or recurrent disease that is not eligible for curative treatment, palliative chemotherapy or targeted treatment can be considered after discussion with the patient.**	Strong	Very low

3.5 Locoregional recurrence

An overview of the recommendations on locoregional recurrence derived from the DKG guideline[1] can be found in Table 26.

Table 26 – DKG recommendations on management of locoregional recurrence of oral cavity cancer[1]

Original DKG recommendation	Original level of evidence	Decision
PET/CT may be performed in patients with suspected recurrence in the head and neck if this could not be confirmed or ruled out by CT and/or MRI.	3 (Non-analytic studies, e.g. case reports, case series)	Accepted with small changes
An ultrasound of the head and neck may be indicated in patients with suspected recurrence in order to justify further action.	Expert opinion	Omitted, because no evidence available
Salvage surgery should be considered in any patient with a resectable locoregional recurrence having previously undergone radiotherapy or surgery. The procedure should only be performed by an experienced surgical team with adequate experience of reconstructive techniques at a facility that offers suitable intensive care support.	3 (Non-analytic studies, e.g. case reports, case series)	Accepted
Re-irradiation, possibly of a curative nature, should be considered in any patient with a non-resectable locoregional recurrence having already undergone irradiation. Irradiation should take place only at facilities with adequate expertise and ideally as part of a clinical therapeutic study.	3 (Non-analytic studies, e.g. case reports, case series)	Accepted

Other considerations

Factor	Comment
Balance between clinical benefits and harms	PET scan appears to have a better diagnostic accuracy than conventional imaging for the detection of recurrent disease.[1, 66] According to a meta-analysis of retrospective case series, the site-specific 5-year survival was 43.4% after salvage surgery for recurrent oral cavity cancer.[66] The reported 5-year survival after re-irradiation of a local recurrence ranges from 9-20%.[66] Several other treatment options are available for locoregional recurrence, e.g. photodynamic therapy, but the evidence was considered to be too poor to formulate a recommendation on it. These treatments can be considered if performed by a well-experienced team.
Quality of evidence	The evidence supporting these recommendations is limited to observational studies.
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 suspected recurrence in the head and neck that could not be confirmed or ruled out by CT and/or MRI, FDG-PET/CT may be performed.**	Weak	Very low
• **Salvage surgery should be considered in any patient with a resectable locoregional recurrence having previously undergone radiotherapy or surgery. The procedure should only be performed by an experienced surgical team with adequate experience of reconstructive techniques, and at a facility that offers suitable intensive care support.**	Weak	Very low
• **Re-irradiation, possibly with curative intent, should be considered in any patient with a non-resectable locoregional recurrence having already undergone irradiation. Irradiation should take place only at facilities with adequate expertise and ideally as part of a clinical therapeutic study.**	Weak	Very low

3.6 Follow-up

An overview of the recommendations on follow-up derived from the DKG guideline[1] can be found in Table 27.

Table 27 – DKG recommendations on follow-up of oral cavity cancer[1]

Original DKG recommendation	Original level of evidence	Decision
The maximum follow-up intervals, even if the patient is free of symptoms, should be 3 months in the first and second year, and 6 months in the third to fifth year. An individually structured follow-up schedule should be devised for each patient. The quality of life of the patients should be surveyed periodically. After five years, standard early screening measures should be undertaken.	Expert opinion	Accepted with changes

Other considerations

Factor	Comment
Balance between clinical benefits and harms	In patients with head and neck cancer, 76% of recurrences occur within the first two years post-treatment.[66] Several treatments can be associated with long-term adverse events. No evidence is available to support a specific frequency of follow-up.
Quality of evidence	No published evidence is available.
Costs (resource allocation)	No cost issues were considered.
Patients values and preferences	The patient representatives highlighted that the social situation of patients with head and neck cancer is often difficult, with many being addicted to smoking and/or alcohol. Special attention should be given to these aspects during follow-up, certainly because they interfere with the adherence of the patients to follow-up. Good communication between first and second-line care providers is considered important.

Recommendations	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

3.7.1 Dental rehabilitation

An overview of the recommendations on dental rehabilitation derived from the DKG guideline[1] can be found in Table 28.

Table 28 – DKG recommendations on dental rehabilitation of oral cavity cancer[1]

Original DKG recommendation	Original level of evidence	Decision
In patients having undergone surgery and/or irradiation for carcinoma of the oral cavity, the masticatory function should be restored with the help of functional masticatory rehabilitation, using implants or conventional prosthetics. The patients should also undergo routine dental check-ups. Dental surgery in such patients should be performed by colleagues with experience of such pathologies.	3 (Non-analytic studies, e.g. case reports, case series)	Accepted with small changes
Infected osteoradionecrosis of the jaw is a serious treatment complication. There is no evidence that hyperbaric oxygen therapy alone is effective as prophylaxis or treatment for such a complication. Hyperbaric oxygen therapy may be useful in combination with surgical interventions for prophylaxis or treatment of osteoradionecrosis.	3 (Non-analytic studies, e.g. case reports, case series)	Accepted with changes

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Many patients with head and neck cancer have dental disease at presentation.[66] Furthermore, treatments for oral cavity cancer (surgery and radiotherapy) have an important impact on the dental status. Infected osteoradionecrosis is a very serious complication after radiotherapy/chemotherapy, and requires specialist treatment. The evidence on hyperbaric oxygen therapy is too weak to justify a separate mentioning in the recommendation.
Quality of evidence	These recommendations are only supported by case series.[1]
Costs (resource allocation)	No cost issues were considered.
Patients values and preferences	The period between the preventive (dental) measures and the treatment is often short, and therefore it is considered very important that these preventive measures are provided by a dedicated person.

Recommendations	Strength of Recommendation	Level of Evidence
• **In patients having undergone surgery and/or irradiation for carcinoma of the oral cavity, 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

3.7.2 Speech and swallowing rehabilitation

An overview of the recommendations on speech and swallowing rehabilitation derived from the DKG guideline[1] can be found in Table 29.

Table 29 – DKG recommendations on speech and swallowing rehabilitation of oral cavity cancer[1]

Original DKG recommendation	Original level of evidence	Decision
Patients with difficulties chewing, speaking and swallowing should be 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 are likely to cause difficulties with chewing, swallowing and/or speech.	2+ (Well-performed case-control or cohort studies)	Accepted with small changes
Patients with dysphagia should undergo appropriate diagnostic procedures, e.g. high-frequency contrast-enhanced fluoroscopy or fiber-optic endoscopy.	2+ (Well-performed case-control or cohort studies)	Accepted with small changes
Patients having difficulty eating and speaking due to carcinoma of the oral cavity and/or undergoing radio/radiochemotherapy should have access to logopedists with experience of such pathologies before, during and after treatment.	2+ (Well-performed case-control or cohort studies)	Accepted with small changes

Other considerations

Factor	Comment
Balance between clinical benefits and harms	Patients with dysphagia and the inability to take adequate nutrition and hydration by mouth are considered at high nutritional risk and often have multiple risk factors for aspiration pneumonia. High-frequency contrast-enhanced fluoroscopy and fiber-optic endoscopy, in addition to clinical exam by a speech therapist, are valid methods for assessing dysphagia.[66]
Quality of evidence	Only observational studies are available to support these recommendations.
Costs (resource allocation)	No cost issues were considered.
Patients values and preferences	The period between the preventive measures and the treatment is often short, and therefore it is considered very important that these preventive measures are provided by a dedicated person.

Recommendations	Strength of Recommendation	Level of Evidence
• **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 carcinoma of the oral cavity 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

3.7.3 Nutritional therapy

An overview of the recommendations on nutritional therapy derived from the DKG guideline[1] can be found in Table 30.

Table 30 – DKG recommendations on nutritional therapy for oral cavity cancer[1]

Original DKG recommendation	Original level of evidence	Decision
Patients who due to the cancer or treatment are at risk of malnutrition should receive early professional dietary counselling and nutritional therapy.	2+ (Well-performed case-control or cohort studies)	Accepted with changes. The counselling should be for patients at risk, and should be throughout the clinical pathway.

Other considerations

Factor	Comment
Balance between clinical benefits and harms	All patients with head and neck cancer should be screened at diagnosis for nutritional status using a validated screening tool.[66] Early nutritional intervention and ongoing nutritional support in at-risk patients has an impact on treatment outcome and quality of life.[66]
Quality of evidence	Only observational studies are available to support these recommendations.
Costs (resource allocation)	No cost issues were considered.
Patients values and preferences	The period between the preventive measures and the treatment is often short, and therefore it is considered very important that these preventive measures are provided by a dedicated person.

Recommendations	Strength of Recommendation	Level of Evidence
• **Patients should be regularly screened for malnutrition due to oral cavity cancer or its treatment. Patients at risk for malnutrition should receive timely and ongoing professional dietary counselling and nutritional therapy.**	Strong	Low

3.7.4 Psychosocial counselling and support

An overview of the recommendations on psychosocial counselling and support derived from the DKG guideline[1] can be found in Table 30.

Table 31 – DKG recommendations on psychosocial counselling and support for oral cavity cancer[1]

Original DKG recommendation	Original level of evidence	Decision
Patients with carcinoma of the oral cavity must be offered psychosocial support from a social worker.	Expert opinion	To be merged with other recommendation
To guarantee the continuity of psycho-oncological support after hospitalized treatment, patients with oral cavity carcinoma must be informed about the continued outpatient follow-up care available (cancer advisory bodies, practicing psychotherapists, self-help groups, social counselling).	Expert opinion	To be merged with other recommendation

Other considerations

Factor	Comment
Balance between clinical benefits and harms	There is evidence that patients with head and neck cancer suffer from anxiety, depression, disturbance of body image and difficulty in maintaining quality of life.[66] No studies have addressed the clinical benefit of psychological support or who should provide the support.
Quality of evidence	Only observational studies are available to support these recommendations.
Costs (resource allocation)	No cost issues were considered.
Patients values and preferences	The period between the preventive measures and the treatment is often short, and therefore it is considered very important that these preventive measures are provided by a dedicated person. Information about the available patient support groups is considered essential, and these will be highlighted in a separate chapter.

Recommendations	Strength of Recommendation	Level of Evidence
• **Patients with oral cavity 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

Clinical guidelines provide a tool for care providers to consult at different stages of the patient management pathway: screening, diagnosis, treatment and follow-up. KCE formulates recommendations addressed to specific audiences (clinicians, decision-makers, sickness funds, RIZIV – INAMI, 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 19). 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.

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.
- In some centres treating patients with head and neck cancer, dedicated dentists, nutritional therapists, speech therapists, etc. may not be available.
- 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.

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 completion of the 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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