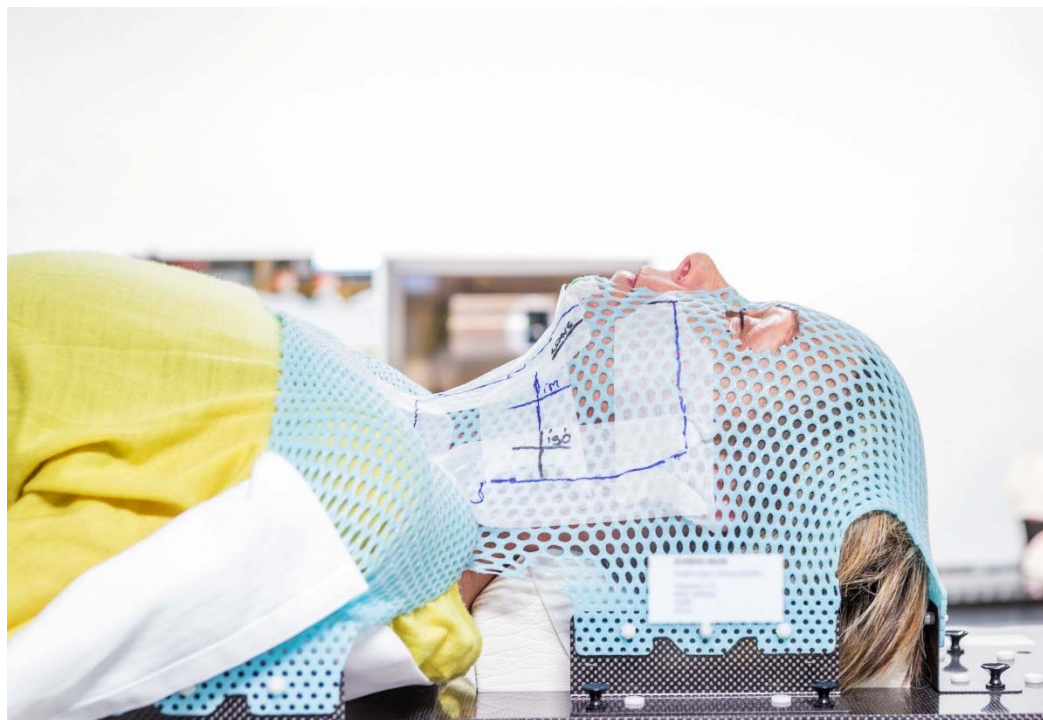


SUMMARY

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



SUMMARY

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

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■ FOREWORD

In July 2014, KCE published a clinical practice guideline about the diagnosis, treatment and follow-up of oral cavity cancer (KCE report 227). Today, a second guideline about head-and-neck cancer is lying in front of you, this time focused on the pharynx and larynx. Again, it concerns rather rare and complex problems, and what we highlighted in the foreword last year remains actual more than ever: "...always calling for a multidisciplinary approach. And what is at least as important as for the treatment itself is the fact that this multidisciplinary approach continues into the aftercare and rehabilitation phase ..."

But in the meantime, things kept moving. And we are not talking just about the diagnostic and therapeutic techniques – although these domains didn't stop progressing – but rather about the organization of care. Meanwhile, we published our conceptual framework for the reform of the hospital financing (KCE report 229) and in the spring of this year, the Minister launched her own action plan for the reform of the hospital financing. In this plan she focuses from the outset on a redesigned health care landscape in which networks become an essential element. This includes the concentration of expensive, complex and rare treatments and technology in specialized centres, where that necessary multidisciplinary approach can be realized. The message clearly arrived, because we see a flurry of activity to give concrete form to these networks.

If this also means that this concentration and further specialization gives an extra boost to the professionalization of the quality system, of which guidelines like these and quality indicators (currently in preparation) are key elements, then this should eventually lead to a demonstrable improvement of the management of the patient. And this is what it's all about at the end.

Christian LÉONARD
Deputy general director

Raf MERTENS
General director



■ SUMMARY

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1. INTRODUCTION

Head and neck cancer refers to a group of (1) rare cancers arising in the upper aerodigestive tract, including the oral cavity, larynx, oropharynx, hypopharynx, and (2) very rare tumours arising in the nasal cavity and paranasal sinus, nasopharynx, middle ear, salivary glands and skull base. The majority of these cancers are squamous cell carcinomas (SCC) and are associated with a history of excessive smoking and alcohol use.

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

2. OBJECTIVES AND SCOPE OF THIS GUIDELINE

In 2014, 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 was developed for that purpose (http://www.kcenet.be/files/KCE_219_proposal_cancer_head_and_neck.pdf).

The objective of the present clinical practice guideline (CPG) is to reduce the variability in clinical practice and to improve the communication between care providers and patients. During an initial scoping meeting it was decided to develop the CPG for head and neck cancer in two phases. The first part concerned the management of oral cavity cancer and was published in July 2014 (KCE report 227). This second part focuses on the management of patients with confirmed oropharyngeal, hypopharyngeal or laryngeal cancer. Aspects of screening and prevention are out of scope.

This guideline is intended to be used by all care providers involved in the management of patients with oropharyngeal, hypopharyngeal and laryngeal 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 to patients and their families, general practitioners, hospital managers and policy makers.



3. METHODS

3.1. Systematic review of the literature

First, a search in OVID Medline, the National Guideline Clearinghouse and the GIN database was done to identify recent (i.e. published after 2010) high-quality guidelines addressing the topic. Eighteen potentially relevant guidelines were appraised with the AGREE II instrument by two researchers independently. Seven guidelines were found to be of sufficient quality. The results of this guideline search were discussed during a scoping meeting with the guideline development group (GDG) and patient representatives on May 13, 2013. It was decided at that time to develop the guideline in two phases, with the first part focusing on oral cavity cancer, and this second part focusing on oropharyngeal, hypopharyngeal and laryngeal cancer. In contrast to the first part, the ADAPTE methodology was abandoned as no sufficiently good and recent guidelines were identified. Furthermore, several questions from the first part (on oral cavity cancer) were applicable to all head and neck squamous cell carcinomas (HNSCC) and could be used for this second part too:

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 PET or MRI in the detection of lymph node metastasis after chemoradiotherapy?
4. What is the clinical effectiveness of neck dissection after chemoradiotherapy in patients with HNSCC?
5. What is the clinical effectiveness of IMRT in patients with locally advanced HNSCC?
6. What is the clinical effectiveness of induction chemotherapy in patients with HNSCC?
7. What is the clinical effectiveness of primary chemoradiotherapy in patients with non-resectable M0 HNSCC?
8. What is the clinical effectiveness of treatment interventions in metastatic disease or recurrent disease not suitable for curative treatment?

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

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

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

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

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

Studies were searched in Medline, Embase and the Cochrane Library. 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 were searched. Only articles published in Dutch, English and French were included. The quality appraisal was performed using the AMSTAR checklist for systematic reviews, Cochrane Collaboration's tool for assessing risk of bias for RCTs and comparative observational studies, and the QUADAS-2 checklist for diagnostic accuracy studies.

3.2. 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, along with the evidence tables, was circulated to the GDG prior to the face-to-face meetings. Based on the discussions with the GDG, a second draft of the recommendations was prepared and once more circulated to the GDG for final approval.

To determine the level of evidence and strength of each recommendation, the GRADE methodology was followed (Tables 1 and 2). The strength of a recommendation depends on the balance between all desirable and all undesirable effects of an intervention (i.e., net clinical benefit), the quality of available evidence, values and preferences, and the estimated cost (resource utilization). For this guideline, no formal cost-effectiveness study was conducted. GRADE was not applied to prognostic questions.

As part of the standard KCE procedures, the current guideline was reviewed prior to its publication by three independent validators (cf. names in the colophon).

Finally, the recommendations prepared by the GDG were submitted to key representatives of the relevant stakeholders (see colophon), who acted as external reviewers of the draft guideline.

Declarations of interest of GDG members, validators and stakeholders were formally recorded and listed in the colophon.

Table 1 – Levels of evidence according to GRADE^{\$}

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 estimated is limited: the true effect may be substantially different from the estimate of the effect	RCTs with 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	

^{\$} Balshem H, Helfand M, Schunemann 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 2 – Strength of recommendations according to GRADE^{\$}

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).

^{\$} 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.



4. CLINICAL RECOMMENDATIONS

The details of the evidence used to formulate the recommendations below are available in the scientific report and its supplements. The tables follow the same sequence as the chapters of the scientific report.

Several recommendations from the first part (on oral cavity cancer) were considered to be applicable to all HNSCC, and were not again discussed by the GDG. They are not listed below, but are reported in the scientific report. These recommendations concern diagnosis and staging (in part), histopathology, follow-up, rehabilitation and supportive care.

4.1. Diagnosis and staging

Recommendations	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none">In patients with newly diagnosed oropharyngeal cancer, perform an MRI for primary T- and N-staging (i.e. before any treatment).	Strong	Very low
<ul style="list-style-type: none">In patients with newly diagnosed hypopharyngeal and laryngeal cancer, MRI is the preferred technique for primary T- and N-staging, but in these locations its quality is more dependent on patient and radiologist factors.	Weak	Very low
<ul style="list-style-type: none">In case (a good) MRI is technically impossible (e.g. pacemaker, cochlear implant, claustrophobia, etc.), likely to be distorted (e.g. anticipated motion artefacts, etc.), or not timely available, perform a contrast-enhanced CT for primary T- and N-staging in patients with oropharyngeal, hypopharyngeal and laryngeal cancer.	Weak	Very low
<ul style="list-style-type: none">In patients with stage I and II oropharyngeal, hypopharyngeal and laryngeal cancer and with low-risk features (e.g. no smoking), a whole-body FDG-PET/CT is not routinely recommended for the evaluation of metastatic spread and/or the detection of second primary tumours.	Weak	Low

4.2. HPV testing

Recommendations	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none">In patients with oropharyngeal cancer, p16 testing is recommended as it provides prognostic information. However, at present there is no evidence that it alters treatment decisions in these patients.	Weak	No GRADE
<ul style="list-style-type: none">Inclusion of p16-positive patients with oropharyngeal cancer in clinical trials should be encouraged.	Weak	No GRADE
<ul style="list-style-type: none">Due to insufficient evidence, routine p16 testing is not recommended in patients with hypopharyngeal and laryngeal cancer.	Weak	No GRADE



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

4.3.1. Surgical treatment

Recommendations	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none">The decision about treatment for early oropharyngeal, hypopharyngeal and laryngeal cancer should not only be based on efficacy, but also on the patient's general and functional status, age, morbidity and on the location of the tumour.	Weak	Very low
<ul style="list-style-type: none">In patients with early (stage I or II) oropharyngeal, hypopharyngeal or laryngeal cancer a single-modality function-sparing approach (e.g. surgery, external radiotherapy) should be preferred.	Weak	Very low
<ul style="list-style-type: none">In patients with advanced oropharyngeal, hypopharyngeal or laryngeal cancer, organ- and function-sparing procedures are recommended. However, in patients with T4a laryngeal cancer, total laryngectomy should be considered.	Weak	Very low

4.3.2. Radiotherapy

Recommendations	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none">In medically fit patients with locally-advanced (stage III and IV) non-metastatic oropharyngeal, hypopharyngeal or laryngeal cancer, primary concomitant platinum-based chemoradiotherapy is recommended (except in patients with T4a laryngeal cancer).	Weak	Very low
<ul style="list-style-type: none">IMRT is recommended in patients with advanced oropharyngeal, hypopharyngeal or laryngeal cancer.	Strong	Very low
<ul style="list-style-type: none">In patients with stage II oropharyngeal, hypopharyngeal or laryngeal cancer, primary radiotherapy with altered fractionation (hyperfractionation or accelerated fractionation without dose reduction) is recommended.	Strong	Low
<ul style="list-style-type: none">In patients with locally-advanced oropharyngeal, hypopharyngeal or laryngeal cancer in whom a non-surgical approach is chosen and in whom concomitant chemoradiotherapy is not an option, primary radiotherapy with hyperfractionation or accelerated fractionation without dose reduction can be considered.	Weak	Low
<ul style="list-style-type: none">Primary radiotherapy with accelerated fractionation with dose reduction is not recommended in patients with head and neck cancer.	Strong	Low



<ul style="list-style-type: none"> Postoperative radiotherapy should be performed for advanced pT categories (T3 and T4) and lymph node involvement (> pN1). It should be considered for peri-neural extension or lymphatic vessel infiltration. In high-risk patients (i.e. close or positive resection margins, extracapsular spread) postoperative chemoradiotherapy is recommended. 	Strong	Low
<ul style="list-style-type: none"> Postoperative radiotherapy should be fractionated conventionally (e.g. 60-66 Gy in 6 to 6.5 weeks, 2 Gy per day, 5 times a week). 	Weak	Low
<ul style="list-style-type: none"> Postoperative (chemo)radiotherapy should be commenced as early as possible, i.e. within 6 weeks after surgery, and should be completed within 11-13 weeks after surgery. 	Strong	Low
<ul style="list-style-type: none"> In concurrent postoperative chemoradiotherapy, radiotherapy should be fractionated conventionally (i.e. 2 Gy per fraction, 5 days per week, total dose 64-66 Gy) and chemotherapy should be platinum-based (100 mg/m² 3-weekly). 	Weak	Low

4.3.3. Induction chemotherapy

Recommendations	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none"> In patients with locally-advanced hypopharyngeal or laryngeal cancer, induction chemotherapy – followed by radiotherapy in responders and surgery in non-responders – is a valid option within the context of an organ-preserving treatment strategy. The preferred induction chemotherapy is TPF (<i>docetaxel, cisplatin and 5-fluoro-uracil</i>). 	Strong	Low
<ul style="list-style-type: none"> In patients with oropharyngeal cancer, the evidence is insufficient to recommend induction chemotherapy. 	Weak	Low
<ul style="list-style-type: none"> In strategies other than function-sparing, induction chemotherapy is not recommended as a standard treatment. 	Strong	Low



4.3.4. Management of the neck lymph nodes

Recommendations	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none">Management of the neck lymph nodes should follow the same treatment principles as those applied for the primary tumour (e.g. if the primary tumour is surgically treated, a neck dissection should be performed).	Weak	Very low
<ul style="list-style-type: none">In patients with oropharyngeal, hypopharyngeal and supraglottic cancer, bilateral selective neck treatment (<i>surgery or radiotherapy, cfr. supra</i>) is recommended. However, in small lateralised cancers, unilateral neck treatment can be considered.	Weak	Very low
<ul style="list-style-type: none">In patients with early (stage I or II) glottic cancer, neck treatment can be omitted, with the exception of supraglottic extension.	Weak	Very low
<ul style="list-style-type: none">In node-positive patients treated with primary (chemo)radiotherapy, a diagnostic evaluation of the neck with PET/CT or DW-MRI should be performed not earlier than three months after completion of the primary therapy.	Weak	Very low
<ul style="list-style-type: none">In patients with oropharyngeal, hypopharyngeal or laryngeal cancer (N1-3) and complete response to chemoradiotherapy (assessed by FDG-PET/CT or DW-MRI), there are no data to support an additional lymph node dissection.	Weak	Very low

4.4. Treatment of metastatic or recurrent disease not suitable for curative treatment

Recommendation	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none">In patients with metastatic HNSCC or recurrent disease that is not eligible for curative treatment, palliative chemotherapy or targeted therapies should be considered after discussion with the patient.	Strong	Very low

4.5. Salvage treatment

Recommendations	Strength of Recommendation	Level of Evidence
<ul style="list-style-type: none">In patients with a resectable locoregional recurrence after primary treatment with curative intent, salvage surgery should be considered. The procedure should only be performed by an experienced surgical team.	Weak	Very low
<ul style="list-style-type: none">In patients with a non-resectable locoregional recurrence after primary treatment with curative intent, re-irradiation, possibly with curative intent, should be considered. Irradiation should only take place in facilities with adequate expertise.	Weak	Very low



5. IMPLEMENTATION AND UPDATING OF THE GUIDELINE

5.1. Implementation

The implementation of this guideline will be facilitated by the College of Oncology and the professional associations involved in this guideline. An online implementation tool similar to the tools accompanying previous guidelines will be developed (www.collegeoncologie.be). To this end they can use various channels such as websites or continuing education, and, if desired, transform this material into attractive and user-friendly tools tailored to caregiver groups.

The following barriers for implementation were identified:

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

5.2. 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 scheduled after the publication of this guideline.

KCE previously recommended setting 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.

5.3. Guideline update

In view of the rapidly evolving evidence, this guideline should ideally be updated every 5 years.



■ RECOMMENDATION^a

To the attention of the Minister of Health and the Federal Public Service of Public Health:

- Insofar as all these cancers are rare, complex or both, the recommendations of KCE Report 219 - “Organisation of care for adults with rare cancers and cancers with complex diagnosis and/or treatment” fully apply.

^a The KCE has sole responsibility for the recommendations.



COLOPHON

Title:	Oropharyngeal, hypopharyngeal and laryngeal cancer: diagnosis, treatment and follow-up – Summary
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Disclaimer:

- **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.**
- **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.**
- **Finally, this report has been approved by common assent by the Executive Board (see <http://kce.fgov.be/content/the-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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