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German Guideline Program in Oncology (GGPO)

Evidence-based Guideline Oral Cavity Cancer

Version 3.0 - January 2021
AWMF-Registernummer: 007/100OL

Guideline (Long Version)

DKG KREBSGESELLSCHAFT
Deutsche Krebshilfe HELFEN. FORSCHEN. INFORMIEREN.
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Important Updates

Major changes in the update of the guideline (version 3.0)

Within the framework of the update, all recommendations were checked for topicality. For this purpose, a systematic search for prioritised topics and survey of the experts involved were conducted. Prioritised topics were sentinel lymph node biopsy, new findings on the differential indication of neck dissection, neoadjuvant therapy in advanced tumour stages and adjuvant radiotherapy in pT1/2 pN1 findings. In addition, further questions on the indication of PET/CT, CAD/CAM technology for bony reconstruction, the differential indication for panendoscopy and immunotherapy were examined in working groups. The new TNM classification and classification of tumour stages were incorporated.

As a result of the update process, 74 statements or recommendations were reviewed and confirmed and 24 were modified or added entirely.

An overview of the changes can be found in section Chapter 12.1.

1. Information about this Guideline

1.1. Editors

German Guideline Program in Oncology (GGPO) of the Association of the Scientific Medical Societies (AWMF), the German Cancer Society (DKG) and the German Cancer Aid (DKH).

1.2. Leading Scientific Societies

Deutsche Gesellschaft für Mund-, Kiefer- und Gesichtschirurgie (DGMKG)

1.3. Funding of the Guideline

This guideline was supported by the German Cancer Aid within the framework of the guideline program oncology.

1.4. Contact

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1.5. How to cite

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1.6. Special Comment

Medicine is subject to a continuous process of development, so that all information, in particular on diagnostic and therapeutic procedures, can only ever correspond to the state of knowledge at the time of printing of the guideline. The greatest possible care has been taken wither gard to the recommendations given for therapy and the selection and dosage of medications. Nevertheless, users are urged to consult the manufacturers' package inserts and expert information and, in case of doubt, to consult a specialist. In the general interest, any discrepancies should be reported to the OL editorial office.

The user himself remains responsible for any diagnostic and therapeutic application, medication and dosage.

In this guideline, registered trademarks (protected trade names) are not specially marked. Therefore, it cannot be concluded from the absence of a corresponding reference that it is a free trade name.

1.7. Objectives of the Guideline Program for Oncology

The Association of the Scientific Medical Societies in Germany (AWMF), the German Cancer Society (DKG) and the German Cancer Aid (Deutsche Krebshilfe) have set the goal of jointly promoting and supporting the development, updating and use of scientifically based and practicable guidelines in oncology with the German Guideline Program in Oncology (GGPO). The basis of this program is based on the medical-scientific findings of the professional societies and the DKG, the consensus of medical experts, users and patients, as well as the set of rules for the development of guidelines by the AWMF and the professional support and funding by the German Cancer Aid. In order to reflect the current state of medical knowledge and to take medical progress into account, guidelines must be regularly reviewed and updated. The application of the AWMF regulations should be the basis for the development of high-quality oncological guidelines. As guidelines are an important instrument of quality assurance and quality management in oncology, they should be introduced into the daily care routine in a targeted and sustainable manner. Thus, active implementation measures and also evaluation programmes are an important part of the promotion of the Oncology Guidelines Programme. The aim of the programme is to create professional and medium-term financially secure conditions for the development and provision of high-quality guidelines in Germany. This is because these high-quality guidelines not only serve the structured transfer of knowledge, but can also find their place in the design of the structures of the health care system. Mention should be made here of evidence-based guidelines as a basis for creating and updating disease management programmes or the use of quality indicators extracted from guidelines in the context of the certification of organ tumour centres.

1.8. Additional Documents relating to this Guideline

This document is the consultation version of the long version of the updated S3 guideline Diagnostics and therapy of oral cavity carcinoma. In addition to the long version, there are the following supplementary documents to this guideline, which have also been or will be updated.

- Short version of the guideline
- Lay version (patient guideline)
- Guideline report on the guideline development process

This guideline and all supplementary documents can be accessed via the following pages.

- Oncology Guideline Program(https://www.leitlinienprogramm-onkologie.de/leitlinien/mundhoehlenkarzinom/)
- AWMF(https://www.awmf.org/leitlinien/detail/ll/007-100OL.html)
- Guidelines International Network(www.g-i-n.net)

1.9. Composition of the Guideline Group

1.9.1. Guideline Coordination

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1.9.2. Participating professional associations and organizations

Table 1: Participating professional associations and organizations

Participating professional associations and organizations	Elected Representative(s)
Abteilung Experimentelle Krebsforschung der Deutschen Krebsgesellschaft (AEK)	Prof. Fr. Roland Moll (1) Prof. Dr. Rainer Engers (2)
Arbeitsgemeinschaft für Kieferchirurgie (AG Kiefer)	Prof. Dr. Dr Jürgen Hoffmann (3) Prof. Dr. Dr. Hendrik Terheyden (1) Prof. Dr. Dr. Torsten E. Reichert (2)
Arbeitsgemeinschaft Kopf-Hals der Deutschen Röntgengesellschaft (AG Kopf Hals der DRG)	Prof. Dr. Michael Lell (1)
Arbeitsgemeinschaft Mund- und Gesichtsschmerz der Deutschen Gesellschaft zum Studium des Schmerzes (DGSS)	Prof. Dr. Marc Schmitter (2) PD Dr. Nikolaos Giannakopoulos (3)
Arbeitsgemeinschaft Psychoonkologie der Deutschen Krebsgesellschaft (PSO)	Prof. Dr. Susanne Singer (1) Dr. Helge Danker (1)
Arbeitsgemeinschaft Radioonkologie in der DKG (ARO)	Prof. Dr. Rainer Fietkau (1) Prof. Dr. Dr. Esther Troost (3)
Arbeitsgemeinschaft Supportive Maßnahmen in der Onkologie, Rehabilitation und Sozialmedizin (ASORS)	Prof. Dr. Dr. Bilal Al-Nawas (3) PD Dr. med. Andreas S. Lübbe (2)
Bundesverband Deutscher Pathologen e.V. (BDP)	Prof. Dr. Stephan Ihrler (3) Prof. Dr. Arne Burkhardt (3)
Bundeszahnärztekammer (BZÄK)	Prof. Dr. Katrin Hertrampf (3) Dr. Peter Böhme (2)
Charite Comprehensive Cancer Center (CCCC)	Prof. Dr. Ulrich Keilholz (2)
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Participating professional associations and organizations	Elected Representative(s)
Deutsche Dermatologische Gesellschaft e.V. (DDG)	Prof. Dr. Roland Kaufmann (3)
Deutsche Gesellschaft für Hals-, Nasen- und Ohrenheilkunde e.V. (DGHNO)	Prof. Dr. Martin Westhofen (3) Prof. Dr. Friedrich Bootz (1)
Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie e.V. (DGHO)	Prof. Dr. Ulrich Keilholz (2) PD Dr. med. Wilfried Eberhardt (2) Dr. Thomas Gauler (1)
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Deutsche Gesellschaft für Pathologie e.V. (DGP)	Prof. Dr. Stephan Ihrler (1) Prof. Dr. Arne Burkhardt (1)
Deutsche Gesellschaft für Plastische- und Wiederherstellungschirurgie (DGPW)	Prof. Dr. Dr. Raymund Horch (1) Dr. Andreas Kehrer (3) Prof. Dr. Günter Germann (2)
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Deutsche Gesellschaft für Ultraschall in der Medizin e.V. (DEGUM)	Prof. Dr. Martin Westhofen (2) Prof. Dr. Alessandro Bozzato (3)

Participating professional associations and organizations	Elected Representative(s)
Deutsche Gesellschaft für Zahn-, Mund- und Kieferheilkunde (DGZMK)	Prof. Dr. Dr. Henning Schliephake (1)
Deutsche Schmerzgesellschaft e.V. (DGSS)	PD Dr. med. Stefan Wirz (1)
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Deutscher Bundesverband für Logopädie e.V. (DBL)	Frau Ricki Nusser-Müller-Busch (2) PD Dr. Bastian Schilling (3)
Kassenzahnärztliche Bundesvereinigung (KZBV)	Dr. Jörg Beck (1) Prof. Dr. Katrin Hertrampf (3)
Konferenz onkologischer Kranken- und Kindererkrankenpflege, eine Arbeitsgemeinschaft in der Deutschen Krebsgesellschaft e.V. (KOK)	Kerstin Paradies (2) Dr. Norbert Gittler-Hebestreit (2)
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1: 2010-2019

2: 2010-2012

3: 2017-2019

Table 2: Composition of Guideline Workgroups

Workgroup	Composition of Workgroup
1 Epidemiology, risk factors, screening	Prof. Dr. Arne Burkhardt Prof. Dr. Dr. Torsten E. Reichert
2 Patient information	W. Mantey Univ.-Prof. Dr. med. Dr. med. Klaus-Dietrich Wolff
3a Diagnosis (clinical and imaging), follow-up	Prof. Dr. Dr. Bernhard Frerich Prof. Dr. Michael Lell Prof. Dr. Martin Westhofen

Workgroup	Composition of Workgroup
3b Diagnosis (pathology)	Prof. Dr. Arne Burkhardt K. Engers Prof. Dr. Stephan Ihrler Prof. Dr. Dr. Hans Pistner
4a Surgical therapy (primary tumour)	Prof. Dr. Stephan Ihrler Univ.-Prof. Dr. med. Dr. med. Klaus-Dietrich Wolff
4b Surgical zherapy (lymph nodes)	Prof. Dr. Dr. Bernhard Frerich Prof. Dr. Stephan Ihrler Prof. Dr. Dr. Torsten E. Reichert
5 Reconstruction, rehabilitation, logopedics	Kirsten Bikowski Prof. Dr. Dr. Raymund Horch Frau Ricki Nusser-Müller-Busch Prof. Dr. Martin Westhofen Univ.-Prof. Dr. med. Dr. med. Klaus-Dietrich Wolff
6 Radiation therapy	Prof. Dr. Wilfried Budach Prof. Dr. Rainer Fietkau Dr. Thomas Gauler Prof. Dr. Dr. Knut Grötz Dr. Michael Wittlinger
7 Drug therapy	Wilfried Eberhardt Prof. Dr. Ulrich Keilholz
8 Supportive therapy, psychooncology	Kirsten Bikowski Prof. Dr. Dr. Knut Grötz PD Dr. med. Andreas S. Lübbe Prof. Dr. Marc Schmitter Susanne Singer PD Dr. med. Stefan Wirz

1.9.3. Patient Involvement

The guideline was developed with the direct involvement of patient representatives (see listing in chapter 1.9.2.).

1.9.4. Methodological Support

Via German Guideline Program in Oncology (GGPO):

- Dr. M. Follmann MPH MSc (OL-Office), Berlin
- Dipl.-Soz.Wiss. T. Langer (OL-Office), Berlin
- Dr. S. Blödt, MScPH (AWMF) · Prof. I. Kopp (AWMF)

Via external contractors:

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- Dr. C. Dressler (Division of Evidence Based Medicine), Berlin
- Dr. med. Simone Wesselmann, MBA (Certification section of the German Cancer Society) - Compilation of quality indicators

Via the representative of the leading professional society:

- Prof. H. Pistner, Erfurt

1.10. Abbreviations Used

Table 3: Abbreviations Used

Abbreviation	Explanation
Abbreviation	**Explanation**
5-FU	5-fluorouracil
AEK	Working Group for Experimental Cancer Research
AWMF	consortium of scientific medical societies
BMI	Body Mass Index
CT	Computed tomography
CUP	Cancer of unknown primary
DGMKG	German Society for Oral and Maxillofacial Surgery
DKG	German Cancer Society
DÖSAK	German-Austrian-Swiss Working Group for Tumours in the Maxillofacial Region
DVSG	German Association for Social Work in Health Care
FDG-PET-CT	Fluorodeoxyglucose positron emission tomography- Computed tomography
FNB	Fine needle biopsy

Abbreviation	Explanation
HPV	human papilloma virus
HR	hazard ratio
IMRT	Intensity modulated radiotherapy
IQWiG	Institute for Quality and Efficiency in Health Care
LK	Lymph nodes
LL	Guideline
MRI	Magnetic resonance imaging
ND	neck dissection
NHS	National Health Service
OL	DKG guideline programme on oncology
PDL	Programs death ligand
PET	Positron Emission Tomography
r/mSCCHN	Recurrent or metastatic head and neck squamous cell carcinoma
RCT	Radiotherapy/ Radiochemotherapy
SIGN	Scottish Intercollegiate Guidelines Network
SLN	Sentinel Lymph Node (Engl.: sentinel lymph node)
TNM (eng)	Tumor Nodes Metastases
UICC	Union international contre le cancer
WHO	World Health Organization

2. Introduction

2.1. Scope and Purpose

2.1.1. Objective and Key Questions

The aim of this updated guideline is to optimize the patient's perspective by implementing the advances in diagnostics and therapy that have become possible in recent years, for example in imaging, molecular diagnostics or reconstructive procedures. An adequate interdisciplinary approach is crucial in order to achieve an improved prognosis and also an improved post-therapeutic quality of life. The present guideline is an instrument that provides the basis for clear, treatment-relevant decision-making processes. It is intended to help ensure that the therapy of patients with oral cavity carcinoma is implemented at a scientifically proven, high level and across the board in the general population.

The present guideline was developed according to the current state of the scientific literature and the results of international studies. In addition to the systematic search and appraisal of primary studies, the initial version on which this update is based identified an evidence-based source guideline, the SIGN 90 guideline of the National Health Service (NHS) Scotland, whose recommendations have been incorporated [5]. Specific questions to be answered by a de novo search using the latest current literature were related to the following topics:

1. does the sentinel lymph node (SLN) play a role in oral squamous cell carcinoma?
2. Is modified radical neck dissection plus adjuvant radiotherapy superior to selective neck dissection with adjuvant radiotherapy for proven LK involvement in level IIb or III?
    i. Comparison of level I-III neck dissection with level I-V neck dissection with N1 subgroup analysis or >50% N1 in the patient population.
    ii. Is additional level IV and V neck dissection for LK involvement in level III or IIb preferable to dissection only to level III?
3. is there an indication for neck dissection in cT1/cT2 carcinoma of the maxilla, even if there is a concomitant cN0 neck on imaging? (Neck Dissection versus „wait and see“ under imaging).
4. What are the indications for neoadjuvant therapy in the treatment of oral cavity carcinoma stage T3/4 Nx M0?
    i. Is neoadjuvant radiochemotherapy superior to adjuvant radiochemotherapy?
5. Is there an indication for adjuvant radiochemotherapy in pT1/2 pN1 squamous cell carcinoma?

In addition, other key questions were formulated that were found to be significant based on experience with the guideline initial version. After preparation in working groups, these questions were answered by expert consensus and corresponding statements or recommendations were formulated. With the help of explanations added in background texts, it is also made possible for colleagues outside the field to inform patients about the procedure of the specialists and to advise them about concomitant symptoms or risks of the therapy. Thus, this guideline provides a scientifically validated treatment recommendation for oral cavity carcinoma which, in

the opinion of the authors, will lead to an improvement in the prognosis of the affected patients if applied consistently.

2.1.2. Target Audience

The recommendations of this guideline are primarily addressed to all those who are active in the prevention, diagnosis, therapy and aftercare of oral cavity carcinoma in the outpatient and inpatient sector. The addressees are thus mainly physicians for oral and maxillofacial surgery, otorhinolaryngology, radiotherapy, oncology, but also especially dentists and specialists for oral surgery as well as dermatologists. According to the general definition, the guideline is intended to provide decision-making aids, but not to be a guideline. The treating physician or dentist is still obligated to find a course of action appropriate to the individual situation, taking into account the patient's overall situation and together with the patient. It is nevertheless recommended that deviations from the guideline be justified and recorded.

The guideline should also be made available to general practitioners and higher-level organizations (e.g.). health insurance funds or institutions of medical self-administration) as well as the interested professional public for information purposes.

2.1.3. Validity and Update Process

The S3 guideline is to be updated continuously. The validity period is estimated to be 5 years. A revision will take place in 2024 at the latest. If there is an urgent need for changes in the meantime, updates will be published as new versions.

Comments and hints for the update process from the practice are explicitly desired and can be sent to the following address: mundhoehlenkarzinom@leitlinienprogramm-onkologie.de

2.2. Methodology

The methodological approach used in the preparation of the guideline is described in the guideline report.

2.2.1. Levels of Evidence (LoE)

Scheme of evidence grading according to SIGN

Grade	Description
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with very low risk of systematic error (bias).
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with low risk of systematic error (bias)
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with high risk of systematic error (bias)

Grade	Description
1- -	All-or-none
2++	High quality systematic reviews of case-control or cohort studies or High-quality case-control or cohort studies with very low risk of systematic bias (confounding, bias, „chance“) and high probability of causal relationship
2+	Well-conducted case-control or cohort studies with low risk of systematic bias (confounding, bias, „chance“) and moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of systematic bias (confounding, bias, „chance“) and a significant risk that the relationship is not causal.
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

2.2.2. Grades of Recommendation (GoR)

The methodology of the Guideline Program in Oncology provides for the assignment of grades of recommendation (see the following Table Scheme of recommendation grading) by the guideline authors within the framework of a formal consensus process. Accordingly, AWMF-certified guideline consultants conducted moderated, nominal group processes or structured consensus conferences [6]. During these processes, recommendations were formally voted on by the voting mandate holders (see above). The results of the respective votes (consensus strength) are assigned to the recommendations according to the categories in Table Consensus strength assigned to the recommendations.

Table Scheme of recommendation grading

Recommendation grade	Description	Expression
A	Strong recommendation	shall/shall not
B	Recommendation	should/should not
0	Recommendation open	can

Table consensus strength

Consensus Strength	Percentage consensus
Strong consensus	> 95 % of those voting
Consensus	> 75 – 95 % of those voting
Majority Consent	> 50 – 75 % of those eligible to vote
Dissent	< 50 % of those entitled to vote

The decision criteria for determining the grades of recommendation are explained in the guideline report for this guideline.

2.2.3. Statements

Statements are statements or explanations of specific facts or questions without an immediate call for action. They are adopted in accordance with the procedure for recommendations within the framework of a formal consensus process and can be based either on study results or on expert opinions.

2.2.4. Expert Consensus (EK)

Statements/recommendations that were decided by the guideline group on the basis of expert consensus (not on the basis of a systematic search or guideline adaptation) are identified as such with the grading „EK“. No symbols or letters were used for the graduation of the expert consensus; the strength of the expert consensus results from the wording used (should/should/could) according to the gradation in the table for the gradation of recommendations.

2.2.5. Independence and Disclosure of Possible Conflicts of Interest

The German Cancer Aid (Deutsche Krebshilfe) provided the financial means for the preparation and updating of the present guideline via the Guideline Programme in Oncology (OL). The development of the guideline was editorially independent of the funding agencies; there were no additional sponsors.

The financial resources were used exclusively for personnel costs, commissioning of the external evidence review, office supplies, literature procurement, and for the WG meetings and consensus conferences (rent, technology, catering, moderator fees, travel and hotel costs).

A standardized declaration (AWMF form, version 2.2 as of 06/2016) on facts and relationships that may indicate conflicts of interest was obtained from all members of the guideline group. The information on conflicts of interest was assessed by a working group with regard to its relevance for the guideline process and management of conflicts of interest was defined. Full details of conflict of interest management can be found in the guideline report.

3. Methodologies

4. Risk factors

4.1. Nicotine and alcohol abuse

3.1	Evidence-based Statement	checked 2021
ST	Tobacco use is a major risk factor for the development of oral cavity carcinoma.	
LoE **2+**	[15]; [16]; [17]; [18]; [19]; [20]; [21]; [22]; [23]; [24]	
	Strong Consensus	

3.2	Evidence-based Statement	checked 2021
ST	Alcohol consumption is a major risk factor for the development of oral cavity carcinoma.	
LoE **2++**	[25]; [26]	
	Consensus	

Background

The main risk factors for the occurrence of oral cavity carcinoma are chronic tobacco or alcohol abuse, and much less frequently other factors. Chronic tobacco or alcohol abuse increases the risk of disease up to 6-fold, and a combination of both risk factors increases the risk up to 30-fold [40], [15], [29]. For lip carcinoma, lip contact with cigarettes is also considered a major risk factor, regardless of the total amount of tobacco use [27]. Furthermore, the use of chewing tobacco is a predisposing factor for the development of oral cavity carcinoma [28]. In addition to the use of tobacco or alcohol, an unbalanced diet, such as excessive consumption of meat or fried food, may also increase the risk of developing carcinoma in the oral cavity [30], [31], [32], [33]. Conversely, a balanced Mediterranean diet has been shown to more than halve the risk of developing carcinoma in the oral cavity when adjusted for nicotine consumption and BMI [34].

The key protective elements of the Mediterranean diet are citrus fruits, vegetables - especially fresh tomatoes - olive oil and fish oils [35], [36], [37], [38]. Increasing the intake of polyunsaturated fatty acids to 1 g/week also reduces the risk of oral cavity carcinoma [39].

3.3	**Consensus-based Recommendation**	**checked 2021**
EC	The addressees of this guideline should advise their patients to give up tobacco consumption and to reduce alcohol consumption to a large extent.	
	Strong Consensus	

4.2. Other risk factors

3.4	**Evidence-based Statement**	**modified 2021**
ST	HPV diagnosis has no valid utility as a prognostic factor in oral squamous cell carcinoma.	
LoE **2+**	[41]; [42]; [43]	
	Consensus	

Background

If a predominantly white lesion of the oral mucosa is found that cannot be assigned to another precisely identifiable lesion, it is a leukoplakia, some of which will transfer to carcinoma [54], [57]. In the WHO classification of head and neck tumors (2005), the concept of squamous intraepithelial neoplasia (SIN) is applied to precursor lesions of squamous cell carcinoma. The term intraepithelial neoplasia is equivalent to the old term epithelial dysplasia and is to be preferred, as the potentially neoplastic character of the lesions is thus also reflected in the nomenclature. To improve readability, the term precursor lesion is used uniformly in the following text instead of the otherwise very different terms (precancerous lesion, precancerous lesion, potentially malignant lesion, precursor lesion, etc.).

A distinction is made between low-grade, moderate-grade and high-grade intraepithelial neoplasia in analogy to the grades of dysplasia [59], [62], [64] In this nomenclature, high-grade intraepithelial neoplasia [64] corresponds to the old term carcinoma in situ (carcinoma risk of 90%). Leukoplakia must be closely monitored for dignity, if necessary by repeated histological or cytological examinations. Complete removal is recommended for dysplastic lesions. As a general rule, any mucosal change that persists for longer than 2 weeks is suspicious of tumor and must be clarified.

The diagnosis and management of precursor lesions is dealt with in a separate guideline (AWMF 007-092).

In addition to the factors mentioned above, there is evidence to suggest that genetic predisposing factors may also favour the development of carcinomas in the head and neck region; for the identification of these risk factors there are currently no screening methods available [65], [66], [67], [68], [70]. Multiple prospective and retrospective studies have addressed HPV association in head and neck carcinomas to investigate the etiological significance and prognostic significance in the respective localizations [80], [53], [71], [70] .

Detection of high-risk HPV DNA in the oral cavity varies from 4 to 43% in different studies ([75], [50], [79], [73], [72]), with HPV16 being the most commonly detected

high-risk HPV type. HPV18 as well as other high-risk types were rarely detected in oral cavity carcinomas ([77], [51], [69]). The high discrepancy between p16 immunohistochemistry or HPV RNA and HPV DNA detection indicates that HPV DNA is frequently detectable in this location but is probably not biologically active in the majority of cases [74]. Data with combined HPV detection methods from retrospective studies are often lacking. Simultaneous DNA, RNA, and/or p16 testing have significantly lower detection rates [44]. In the largest systematic study to date with 3680 patients with head and neck carcinomas, in which 1264 oral cavity carcinomas were investigated, HPV DNA could be detected in 7.4% (n = 93) of cases. However, the simultaneous detection rate of HPV DNA and HPV RNA was only 3.9% (n = 49) and decreased to 3.0% (n = 38) with simultaneous detection of HPV DNA and HPV RNA and p16 [44].

Also, several retrospective and prospective serologic studies for various HPV16 antibodies show only a small increased risk of disease for oral cavity carcinoma, in contrast to oropharyngeal carcinoma. The prevalence of HPV16 E6 or E7 antibodies in oral cavity carcinomas ranged from 0 to 13.9% in patients, and from 0.5 to 11.1% in matched controls ([56], [49], [55]). In several case-control studies embedded in prospective cohort studies, the relative risk of developing oral cavity carcinoma was not significantly increased in the presence of E6 or E7 antibodies ([56], [55]). The same was true for L1 antibodies, which were not significantly associated with the development of oral cavity carcinoma, with relative risks ranging from 1.0 to 1.2 ([56], [55]). The risk of developing oral cavity carcinomas is thus significantly lower than that for oropharyngeal carcinomas, where the risk is significantly increased 2.4 to 274-fold in the presence of E6 or E7 antibodies ([56], [55], [60]).

The prevalence of HPV-driven tumors in the oral cavity is estimated to be less than 5% based on current studies; higher estimates in older literature are predominantly based on HPV DNA detection alone, which in most cases is attributed to transient infection in the oral cavity or a false positive test result. The use of combined HPV detection methods (e.g., DNA detection combined with RNA detection or p16 immunohistochemistry) is strongly recommended ([78]). Furthermore, in advanced tumor stage, clinical differentiation between oral cavity carcinoma and oropharyngeal carcinoma may be difficult, thus falsifying the actual proportion of HPV-associated oral cavity carcinomas. A valid statement on the prognostic significance of HPV association in patients with oral cavity carcinoma does not exist. Rather, the different studies show contrasting results (good prognosis: [76], [47], [45], [63]; poor prognosis: [52], [46], [61]; no influence: [51], [74], [58], [48], [81]). In 3 RTOG studies as well as in the DAHANCA consortium (Denmark), no improved survival rates regarding HPV status in non-oropharyngeal carcinomas in contrast to patients with HPV-associated oropharyngeal carcinomas could be found either ([58], [45]). Clinical studies on de-intensified therapy concepts in HPV-associated oral cavity carcinomas do not seem useful due to the lack of prognostic significance of HPV status, and thus no adaptation of therapy compared to noxious-associated carcinomas.

Thus, HPV status does not play a role as a prognostic factor in oral cavity carcinoma according to current studies. In summary, there is no evidence that justifies routine HPV diagnostics in patients with oral cavity carcinoma.

5. Screening and prevention

5.1. Screening

4.1	Consensus-based Recommendation	checked 2021
EC	Dental and medical examinations shall include an inspection of the entire oral mucosa in every patient.	
	Strong Consensus	

Background

Since the growth of tumors is often painless in the beginning, it is not uncommon for patients to present for clarification of the findings only after a delay of several weeks. This behavior of the patients causes a delayed diagnosis and is the main reason for a delay in the start of treatment [82], [83], [84]. Another reason for a delayed start of treatment is the misinterpretation of the findings, e.g. as a pressure sore or bite injury. Therefore, it cannot be assumed that changes in the oral mucosa are perceived by the patient himself or interpreted as threatening. Regular examination of the oral mucosa, not only in the dental practice but also by maxillofacial surgeons and ENT or general practitioners as well as dermatologists (especially in the context of skin cancer screening, which includes the oral cavity), is therefore of major importance in terms of tumor screening and early detection. This is especially true for patients with already known typical risk factors or predisposing diseases of the oral mucosa.

In order to detect tumor growth at the earliest possible stage, the use of toluidine blue as a screening method has been tested; however, this measure has not been found to be effective for initial diagnosis at the dentist's office [85]. On the value of brush biopsy, which is available as an easy-to-use technique in dental practice, the S2k guideline on the diagnosis and treatment of precursor lesions is discussed. Currently, there is no evidence for an effective screening program for the detection or early detection of head and neck cancer [86].

5.2. Prevention

4.2	Evidence-based Recommendation	checked 2021
GoR A	Education about signs, symptoms, and risk factors of oral cavity carcinoma shall be improved.	
LoE 1+	[87]	
	Strong Consensus	

Background

Public awareness of oral cavity carcinoma is low [80], [93], [88], [89], [90]. It has been shown that the availability of information about oral cavity carcinoma in written form

(educational brochures) significantly improves the level of knowledge of patients and leads to an increased willingness to undergo preventive examinations in the dental practice [91], [92]. A randomized controlled trial showed that patients who had read an information leaflet about carcinomas in the head and neck region avoided the typical risk factors more than those who had not been provided with such a leaflet. A questionnaire about symptoms and risks of oral cavity carcinoma could be answered with significantly better results by those who had read an information leaflet than by a non-educated control group [87]. Thus, it should be demanded that educational brochures about symptoms and risk factors of oral cavity carcinoma should be available at medical and dental facilities.

6. Primary diagnostics

6.1. Clinical examination

5.1	Consensus-based Recommendation	checked 2021
EC	All patients with an unclear mucosal change lasting more than two weeks shall be referred immediately to a specialist for clarification.	
	Consensus	

5.2	Consensus-based Statement	checked 2021
ST	In order to exclude synchronous secondary tumors, an examination of the ear, nose and throat - and possibly endoscopy - shall be performed as part of the primary diagnosis of oral cavity carcinoma.	
	Consensus	

Background

Any change of the oral mucosa with excess tissue and/or tissue defect as well as a change in color or hardening of the mucosa are suspicious for squamous cell carcinoma. Typically, there is a central ulcer with a peripheral rim and whitish (leukoplakic) deposits due to keratinization, which may also be completely absent. All areas, especially the tongue and the floor of the mouth, may be affected. Early findings present e.g. as nodular epithelial thickening or a flat surface defect. Later, there is a two-dimensional spread or even a deep cone-shaped growth. A loosening of the teeth or a swelling of the lymph nodes in the neck may be present initially already, which can be confused with inflammatory diseases, such as periodontitis or lymphadenitis. Progressive tumour growth leads to functional impairments such as difficulties in mouth opening, swallowing, chewing or speaking, as well as to nutritional disorders; in some cases, the tumour may break into the jawbone with fracture or break through to the outer skin. Severe pain develops, also radiating into the entire head and neck region. In up to 40% of patients, despite clinically unremarkable findings, the neck lymph nodes have already been affected at the time of initial diagnosis; systemic tumour spread, especially to the lungs, is also possible. If simultaneous involvement of several regions of the oral cavity or pharynx is present, the term multilocular tumor growth is used. For this reason, and because of a possible presence of synchronous

second carcinomas in the region of the pharynx or larynx [97], [99], [98], mirror examination or an endoscopy [101], [102], [103], [104], [105], [107] belongs to the primary clinical diagnosis in oral cavity carcinoma.

Detection rates of second cancers by panendoscopy in the primary diagnosis of oral cavity carcinoma are reported to be in the single digits according to recent studies: 1.1% ([96]), 5.56% ([106]), for populations with no history of risk again significantly lower down to 0% ([100]). Disadvantages of panendoscopy include anesthesiologic complications and surgical complications such as esophageal perforation, bleeding, and dental fractures. Critically discussed is a delay in the start of tumor therapy due to a preceding panendoscopy ([94], [109]). Panendoscopy should therefore only be performed as part of the primary diagnosis of oral cavity carcinoma in order to exclude synchronous secondary tumours if there are conspicuous findings in terms of specular or radiological findings.

The guideline group sees a great need for research to clarify the value of panendoscopy for the detection of secondary tumors.

Other symptoms of oral cavity carcinoma may include foetor, bleeding, obstruction of denture fit, numbness, or loss of adjacent teeth. Common symptoms include fatigue, loss of performance, loss of appetite, and weight loss. Immediate referral to a specialist should be made for the following findings if they persist for more than two weeks [108]:

- white or red patches on the oral mucosa at any location
- presence of a mucosal defect or ulceration
- swelling of the oral cavity
- unexplained loosening of teeth not associated with periodontal disease
- persistent, especially unilateral foreign body sensation
- pain
- dysphagia or pain when swallowing
- difficulty in speaking
- decreased tongue mobility
- numbness of the tongue, teeth or lip
- unexplained bleeding
- swelling of the throat
- foetor
- change in occlusion

Early detection and early treatment improve the prognosis of oral cavity carcinoma [95]. More intensive public education and accelerated referral of patients with unclear findings to specialists is desirable to shorten the time interval from the first symptom to the initiation of tumor-specific treatment [82], [83], [84].

7. Imaging techniques and further diagnostics

The diagnosis of oral cavity carcinoma includes not only clinical examination but also imaging measures such as ultrasound diagnostics, CT or MRI, X-ray thorax or CT thorax; furthermore, PET/CT can be used for special indications. As basic dental diagnostics, a panoramic slice image should be available for the assessment of the dental status, also with regard to a possible radiation therapy.

7.1. Imaging methods for the diagnosis of the primary tumor

6.1	Evidence-based Recommendation	checked 2021
GoR **B**	CT or MRI should be performed to determine the local extent of oral cavity carcinoma.	
LoE **3**	[110]; [111]; [112]	
	Strong Consensus	

6.2	Consensus-based Recommendation	checked 2021
EC	In order to avoid distortions of the contrast medium behaviour at the primary tumour, tumour biopsy should only be performed after the imaging of the slice.	
	Consensus	

6.3	Consensus-based Recommendation	checked 2021
EC	The panoramic slice image is part of the basic dental diagnostics and should be available before the start of specific tumor therapy.	
	Consensus	

6.4	Consensus-based Recommendation	checked 2021
EC	If metal artifacts are expected in the oral cavity, MRI should be preferred to CT for evaluation of the primary tumor.	
	Strong Consensus	

6.5	Evidence-based Statement	checked 2021
ST	There is conflicting and no robust evidence for the superiority of CT or MRI for the assessment of bone invasion by carcinoma of the oral mucosa.	
LoE **3**	[113]; [114]	
	Consensus	

6.6	**Evidence-based Statement**	**checked 2021**
ST	There is conflicting and no robust evidence for the superiority of CT or MRI to assess the extent of the primary tumor.	
LoE **3**	[110]; [111]; [113]; [115]	
	Strong Consensus	

6.7	**Evidence-based Statement**	**checked 2021**
ST	There is no established evidence for the superior test performance or additional benefit of cone beam CT (dental CT) over panoramic slice imaging for the assessment of mandibular bone invasion.	
LoE **3**	[116]	
	Strong Consensus	

6.8	**Evidence-based Statement**	**checked 2021**
ST	PET-CT has no value in the primary diagnosis of the local extension of a known oral cavity carcinoma.	
LoE **2+**	[117]; [118]; [119]; [120]; [121]; [122]; [123]	
	Strong Consensus	

6.9	**Consensus-based Statement**	**new 2021**
ST	In locoregionally advanced tumors, FDG-PET/CT can be performed to exclude distant metastases prior to function-restricting therapeutic measures.	
	Consensus	

Background

Although panoramic slice imaging for the evaluation of the dental system as a simple, quickly available and clear overall view is still part of basic dental diagnostics, it is not considered sufficient for the evaluation of bone invasion on the maxilla or mandible [138]. CT or MRI should be performed to diagnose squamous cell carcinoma of the oral cavity and determine the T category [125], [126], [127], [139], [140]. Although PET-CT can occasionally be helpful for the diagnosis of an unknown primary tumor or for the determination of the glucose metabolism of a tumor that has already been pretreated by radiotherapy, as well as in cases of CT artifacts, it has no role in defining the tumor

margins of known, nonpretreated oral cavity carcinomas [141], [142], [143]. PET-CT, despite its high sensitivity, has no improved significance for the diagnosis of primary tumors of the oral cavity and therefore cannot replace the established procedures CT or MRI [131], [132], [134], [144], [133], [135], [136].

The role of FDG-PET/CT in the diagnosis of recurrence is discussed in Chapter 9.7.

The literature is inconsistent regarding the superiority of CT or MRI for the diagnosis of the primary tumor in the oral cavity. A number of authors consider MRI to be the method of choice because of its higher sensitivity; other publications consider CT to be better or at least equivalent [129], [128]. The CT examination is generally better tolerated by patients than the MRI examination because of the short examination time [125], [145]. Factors in favour of MRI are: better soft tissue contrast with higher detail recognition of soft tissues and superficial structures and, above all, the lower artefacts caused by metallic dental fillings or implants [126]. This is reflected in an improvement in the detection of perineural, intramuscular [145] or perivascular tumor extension, as well as the assessment of involvement of the skull base, orbit or cervical spine [110]. CT is considered advantageous for cortical erosion [129], and MRI for the assessment of bone marrow infiltration [130]. While CT is occasionally considered advantageous for the assessment of cortical erosion [113], MRI provides better visualization of perineural, intramuscular [145], [125] or perivascular tumor extension as well as more accurate diagnosis of any involvement of the skull base, orbit or cervical spine. It has been shown that CT is perceived as more comfortable than MRI due to the faster examination technique [145].

There is no evidence for a better assessability of tumor invasion into the bone by the 18F-FDG-uptake at PET-CT [131], [137]. A combination of the examination modalities CT, MRI and PET-CT does not lead to a significant improvement [146].

The meta-analysis by Kyzas et al. [124] published in 2008 included 32 studies on the diagnostic value of FDG-PET/CT in patients with a head and neck tumor. For cN0 patients, the sensitivity of FDG-PET alone was 50% (95% CI = 37-63%), and the specificity was 87% (95% CI = 76-93%). In studies with FDG-PET and anatomic imaging, the respective sensitivities and specificities were 80%/86% and 75%/79%, but not specified for cN0 patients.

7.2. Diagnostic imaging techniques for the detection of metastasis

6.10	Evidence-based Recommendation	checked 2021
GoR **A**	To determine the N category, the entire region from the skull base to the upper thoracic aperture shall be examined with CT or MRI.	
LoE **2+**	[110]; [147]; [148]; [149]; [150]; [151]; [152]	
	Strong Consensus	

6.11	Evidence-based Statement	checked 2021
ST	The diagnostic specificity of lymph node staging in the neck can be improved by ultrasound-guided fine-needle biopsy.	
LoE **2++**	[153]; [154]; [155]	
	Strong Consensus	

6.12	Evidence-based Statement	checked 2021
ST	The diagnostic specificity and sensitivity of lymph node staging in the neck can be improved by FDG-PET-CT.	
LoE **2+**	[156]; [157]; [158]; [118]; [159]; [150]; [151]; [160]; [161]	
	Strong Consensus	

Background

CT and MRI are of similar accuracy for the diagnosis of cervical lymph node metastases; they are clearly superior to clinical examination [149]. Here, CT appears to be slightly more reliable than MRI for visualizing infrahyoid lymph node metastases, while the latter appears to better visualize nodes along the vascular nerve sheath [125], [176]. MRI is therefore recommended for routine diagnosis to determine soft tissue infiltration and lymph node status [177]. In a direct comparison study, MRI performed better than CT in terms of sensitivity, specificity and accuracy for the determination of cervical lymph node metastases [152]. In combination with FDG-PET, the diagnostic accuracy of MRI can be increased [151], without, however, allowing a reliable statement on the dignity of the detected lymph nodes [178], [164], [165]. In principle, however, PET is much less informative as a stand-alone method than in combination with CT or MRI [144], [178], [162], [166] and should therefore always be performed as a hybrid procedure (PET-CT or PET-MRI).

The accuracy of CT, MRI and ultrasound in the assessment of lymph node metastases is comparable, although the data on this is sparse. In borderline large lymph nodes (short diameter > 5mm) on CT or MRI without signs of central necrosis, targeted ultrasound-guided fine-needle biopsy or FDG-PET may increase diagnostic accuracy [180], [181]. However, the value of PET-CT for the diagnosis of cervical lymph nodes is controversial because of the high number of false positive findings [132], [136], [137], [124], [164], [167], [168], [169], [170]. Especially for lymph nodes less than 10 mm this method is considered unsuitable [169], [170].

A standard method for the assessment of cervical lymph nodes is ultrasound examination, for which individual studies have reported higher sensitivity and specificity than for CT [171] or MRI [172]. It is an inexpensive method that is frequently repeatable in follow-up, but its accuracy and significance are highly dependent on the experience of the examiner. However, other studies indicate that the reliability of ultrasound staging of the neck is limited because of low specificity [173].

Few studies addressed the sensitivity of ultrasound-guided fine-needle biopsy (FNB) for determining LK dignity. While the sensitivity of this method is low in small tumors with clinical N0 neck [174], [175], it can be helpful in palpable LK for preoperative confirmation of dignity [179], [180], [181], [163]. In palpable lymph nodes, ultrasound-guided fine-needle aspiration has a higher specificity than CT [158], but overall no higher diagnostic reliability [153].

7.3. Imaging and diagnostics to exclude synchronous second tumors, distant metastases, unknown primary tumors (CUP) and recurrences

6.13	Evidence-based Recommendation	checked 2021
GoR **A**	In patients with advanced oral cavity carcinoma (stage III, IV), a chest CT shall be performed to exclude pulmonary tumor involvement (filia, second carcinoma).	
LoE **3**	[182]; [183]; [184]; [185]	
	Strong Consensus	

6.14	Consensus-based Recommendation	checked 2021
EC	An abdominal ultrasound examination can be performed as part of the primary diagnostic workup.	
	Strong Consensus	

6.15	Evidence-based Recommendation	checked 2021
GoR **0**	In patients with suspected recurrence in the head and neck region, PET-CT can be performed if this could not be confirmed or eliminated with CT and/or MRI.	
LoE **3**	[186]; [187]; [188]	
	Strong Consensus	

6.16	Consensus-based Recommendation	checked 2021
EC	In patients with suspected recurrence in the head and neck region, sonography of the head and neck region can be indicated to substantiate the indication for further measures.	
	Strong Consensus	

Background

The incidence of synchronous second tumors or distant metastases in carcinomas of the oral cavity ranges from 4% to 33%, depending on the size of the primary tumor, with a particularly high incidence in stages T3/T4 and patients with lymph node involvement in level IV [194], [195], [196]. However, in other retrospective studies, pulmonary secondary carcinoma was detected in only 3.5% and 3.8% of newly diagnosed carcinomas of the oral cavity, leading the authors to question regular use of chest CT as part of primary staging [197], [198]. As the T category increases, a higher probability of the presence of a second tumor of the lung has been demonstrated [112]; therefore, in advanced tumors (T3/T4), a chest CT is already recommended as part of the diagnosis of the primary tumor [183]. Both LK metastases and a pulmonary second carcinoma can be detected by CT with high sensitivity and specificity [182]. In patients with suspected recurrence in the head and neck region, sonography of the head and neck region may also be indicated to justify the need for further measures [171]. In comparison with bone scintigraphy and abdominal ultrasound, CT proved to be the safest screening method for the detection of distant metastases [183]. This also applies with high significance to the comparison of thoracic CT with conventional radiography of the lung [182], where CT detected either metastasis or synchronous second carcinoma in approximately 11% of cases and was recommended as a screening method for patients with advanced primary tumor [185]. Due to its high sensitivity and the preferential localization of second tumors in the lung, chest CT is even recommended for all patients with head and neck tumors to exclude synchronous second carcinomas [125], [202], [190], [191].

In a study by the Institute for Quality and Efficiency in Health Care, a benefit assessment of positron emission tomography (PET and PET/CT) for head and neck tumors was performed. The primary objective was to assess the benefit of the method in metastatic cervical lymphadenopathy for the detection of the unknown primary tumor (CUP syndrome). In addition, the extent to which PET or PET/CT is superior to standard diagnostic procedures without PET was reviewed. For this purpose, a systematic database analysis was performed, whereby only one usable comparative study could be identified with regard to recurrence-free 2-year survival, with which a patient-relevant benefit of PET was neither proven nor refuted [118]. For the question of staging of the primary tumor, CT and SPECT showed a higher specificity compared to PET, especially for the detection of bone invasion [117]. PET also did not perform better than CT or MRI for the diagnosis of cervical lymph node metastases, while for the detection of distant metastases PET tended to have a higher sensitivity than CT [189].

For recurrence detection, the few usable studies identified by IQWiG in the technology comparison PET vs. combination of CT and/or MRI showed that PET had a significantly higher pooled sensitivity than the combination of CT and/or MRI. Here, specificity is reduced by false positive findings due to enhancement in inflammatory lesions. However, FDG-PET had a higher reliability with a sensitivity of 100% and a specificity of 61-71% than CT and/or MRI [165], [192], [193]. Also for the detection of an unknown primary tumor, a good pooled sensitivity was shown with 84% for PET/CT, which is why the assumption was made that both the combination with CT as well as PET alone is able to diagnose additional primary tumors after expired primary diagnosis with CT and/or MRI. This is also confirmed by other studies, according to which FDG-PET not only diagnoses distant metastases more reliably, but also detects 24-26% more primary tumors than CT or MRI [199], [200], [201].

8. Biopsy and histopathology

7.1	Consensus-based Recommendation	checked 2021
EC	The sample shall be taken from the periphery of the tumor and be representative. Clinically relevant information shall be provided to the pathologist. If the findings are unclear, the biopsy shall be repeated . The pathologist should be consulted prior to re-biopsy.	
	Consensus	

Background

Tumor detection by obtaining a histological sample is a prerequisite for initiating tumor-specific therapy. Since the biopsy leads to a local tissue reaction, which may distort the contrast agent behavior during imaging, in case of clinically obvious tumor findings, sampling is recommended only after contrast agent-assisted imaging has been performed. The tissue sample should be taken from the progression zone of the tumor, i.e., from its marginal area, and under no circumstances from the necrotic center. The usual form of biopsy collection is incisional biopsy with a scalpel. In case of a brush biopsy, care must be taken to ensure that it is performed sufficiently deep with removal of coherent tissue particles and provocation of bleeding to avoid false negative findings. Photo documentation of the tumor prior to sampling is desirable. If the histology results are unexpectedly negative, the biopsy should be repeated at least once. A reference pathology should be consulted if the histological picture is unclear. The histopathologic findings should include all parameters that have been shown to be useful for staging and prognosis of oral cavity carcinoma. These include tumor location, macroscopic tumor size, histologic tumor type according to WHO, histologic tumor grade, depth of invasion, lymphatic vessel invasion, blood vessel invasion, and perineural invasion, locally infiltrated structures, classification pT, details of affected districts and infiltrated structures, and R status [203], [204], [205], [206], [207], [208], [209], [210], [220], [211], [212], [213], [214], [215], [216], [217], [218], [219].

8.1. Staging

The staging of oral cavity carcinoma is performed according to the classification of the UICC TNM classification of malignant tumors, which describes the anatomical extent of the disease in relation to the primary tumor, the presence of regional lymph node metastases and distant metastasis with organ involvement (see Appendix Chapter 12.2). The possibility of occult metastasis also has a direct impact on treatment planning [221], [222].

8.2. Primary tumor

7.2	**Consensus-based Recommendation**	**checked 2021**
EC	To avoid a positive resection margin associated with a worse prognosis, the technique of intraoperative rapid section histology may be helpful.	
	Consensus	

7.3	**Consensus-based Recommendation**	**checked 2021**
EC	Histologically, the distance from the resected margin to the primary tumor on the formalin-fixed specimen should be at least 3-5 mm. The orienting value for resection is 10 mm from the palpable tumor margin.	
	Consensus	

7.4	**Evidence-based Recommendation**	**checked 2021**
GoR **A**	In correspondence with the clinician, the histopathological report shall describe the exact location of any R+ situation that may be present. The tumour specimen shall be sent to the pathologist with clear designation of the anatomical topography. Suture or color marking may be done for this purpose. The histopathologic findings shall include: Tumor location, macroscopic tumor size, histologic tumor type according to WHO, histologic tumor grade, depth of invasion, lymphatic vessel invasion, blood vessel invasion and perineural invasion, locally infiltrated structures, classification pT, details of affected districts and infiltrated structures, R status.	
LoE **2++**	[203]; [223]; [224]; [225]; [226]; [227]; [228]; [229]; [230]; [231]; [232]; [233]; [234]; [235]; [236]; [237]; [238]; [220]	
	Consensus	

There is clear evidence of the influence of tumor grading on prognosis, with higher grading being associated with poorer prognosis [204], [205], [206], [207]. The T category describes the maximum extent of the primary tumor and the presence or absence of invasion of the tumor into adjacent structures. Higher categories in the TNM classification correlate with poorer prognosis [205],[208], [209], [210]. Tumor thickness greater than 4 mm is associated with poorer prognosis [205],[208], [209], [210]. Perineural infiltration is a meaningful parameter for a higher risk of recurrence and a worse prognosis [235]. Certain histologically differentiable tumor types behave differently from conventional squamous cell carcinoma. Papillary and verrucous carcinomas generally have a better prognosis, whereas basaloid and spindle cell variants behave more aggressively [220]. Discontinuous infiltrative tumor growth, as opposed to continuous growth with a clearly definable growth front, results in a poorer prognosis, especially on the tongue and floor of the mouth [211], [212], [213]. The nature of the resection margins of the

primary tumor or the presence of dysplasia in the margins of the tumor influence local recurrence. A distance of less than one millimeter between the histologically detectable tumor margin and the resection margin is considered a positive resection margin (classification according to RCP, Royal College of Pathologists) [214], [215], [216], [217]. A resection with a histologically confirmed margin of safety of 1-3 mm is termed a close resection margin, and one with at least 5 mm is termed a safe resection margin [217], [218], [219], [221], [222], [239] . The histopathological findings should describe the exact location of any R+ situation that may be present, in communication with the clinician. The tumor specimen should be sent to the pathologist with clear designation of the anatomic topography to avoid ambiguity in reporting the findings. Thread or color marking can be done for this purpose. Although an improvement in prognosis through the use of frozen section histology for intraoperative assessment of tumor margins has not been demonstrated [218], [219], this method is helpful in avoiding uncontrolled or unnecessarily radical resections. It can thus be assumed that intraoperative frozen section histology makes a significant contribution to safeguarding an R0 resection and to preserving structure and function.

8.3. Cervical lymph node metastases

7.5	Evidence-based Recommendation	checked 2021
GoR **A**	The histopathological findings of the neck dissection specimen shall include the side of the neck, the type of neck dissection, the cleared levels, the total number of lymph nodes with number of affected lymph nodes, the levels of the affected lymph nodes, the diameter of the largest affected lymph node, additional structures removed, and if present, a growth that crosses the capsule.	
LoE **2++**	[223]; [240]; [241]; [242]; [243]; [244]; [245]; [246]; [111]	
	Strong Consensus	

Background

Local metastasis of the primary tumor to the cervical lymph nodes is a reliable parameter for prognosis, with the course of the disease being less favorable the more nodes are involved. Furthermore, involvement of the caudal levels (IV and V) and cross-capsular growth negatively influence the prognosis [204], [239], [247],[248], [249], [250], [251], [252], [253] . An exclusively immunohistological assessment of the tumor is currently of uncertain significance [254].

The methods and procedure for the detection of distant metastasis are described in chapter Chapter 7.3.Chapter 7.3The classification of lymph node levels is shown in the Chapter 12.3.

8.4. Other prognostic factors

A number of studies deal with the role of HPV (human papilloma virus) infection in head and neck cancer. Five studies showed that HPV infection in oropharyngeal tumors was associated with younger age of patients, absence of risk factors, high proliferation

indices, higher grading, basaloid subtype, better response to radiotherapy and better prognosis [53],[255], [256], [257], [258].

Results of studies looking at the validity of proliferation indices and molecular markers are still considered inconstant for predicting individual disease progression. However, high expression of Ki-67 could be correlated with the risk of rapid tumor progression [218], [259], [260] .

9. Therapy of oral cavity carcinoma

9.1. General treatment recommendations

8.1	Consensus-based Recommendation	checked 2021
EC	The treatment of oral cavity carcinoma shall be carried out in an interdisciplinary manner after coordination of each individual case within tumour boards involving the specialist disciplines of oral and maxillofacial surgery, otorhinolaryngology, radiotherapy, oncology, pathology and radiology.	
	Strong Consensus	

8.2	Consensus-based Recommendation	checked 2021
EC	The patient shall be informed in detail and repeatedly about his disease, treatment options and secondary disorders.	
	Strong Consensus	

8.3	Evidence-based Recommendation	checked 2021
GoR **B**	Patients with oral cavity carcinoma should be examined by an experienced dentist to determine their dental status before treatment begins.	
LoE **3**	[261]; [262]	
	Strong Consensus	

8.4	Evidence-based Recommendation	checked 2021
GoR **B**	If the patient's general condition permits, surgery should be performed for curatively resectable oral cavity carcinomas, if necessary in combination with immediate reconstruction. In the case of advanced carcinomas, postoperative therapy should also be performed.	
LoE **3**	[263]; [264]; [265]; [266]	
	Strong Consensus	

Background 8.1-8.4

- The options for curative treatment are
- surgical therapy alone
- radiotherapy alone
- radiotherapy in combination with chemotherapy, and
- combinations of surgical therapy, radiotherapy and chemotherapy.

The treatment of oral cavity carcinoma generally depends on the location and size of the primary tumor, the general condition of the patient, the anticipated treatment-related morbidity with its functional and aesthetic consequences, and the anticipated success of the treatment.

The aim of the treatment is to achieve permanent or as long as possible locoregional tumor control with as little functional or aesthetic impairment as possible. During the treatment of oral cavity carcinoma, the most important functions to be maintained or restored are articulation, phonation, and chewing and swallowing. Therapy, which is basically interdisciplinary, should be planned and carried out in accordance with the present guideline and after consultation within a tumor board established at the center. Members of the tumor board are, in addition to the oral and maxillofacial surgeon, a physician for ear, nose and throat medicine, radiotherapy, oncology, pathology, radiology and, if necessary, plastic surgery or neurosurgery. This composition corresponds to the specifications of the German Cancer Society for the "Head and Neck Module". The definition of oncological organ centres can be found at www.onkozert.de.

Prospective randomized controlled multicenter studies that allow a statement on the superiority of surgical therapy or radiotherapy could be found neither for early (stage I and II) nor for advanced oral cavity carcinoma (stage III and IV) [269],[270], [271],[272], [273],[274], [275], [276], [277], [278], [279], [280], [281], [282], [283], [284], [285], [286], [287], [288].

Before treatment, the patient should be informed in detail and several times about his disease, treatment options and secondary disorders [290], [91], [289]. Likewise, for prophylactic reasons, early dental care of the patient is essential in order to counteract the otherwise frequent occurrence of radiation caries, tooth loss and possible infected osteoradionecrosis in the case of planned or previous radiation therapy [267], [268]. Furthermore, professional nutritional counselling is important to determine the necessary calorie and nutrient intake and to implement the necessary measures (see chapter on Chapter 10.4).

9.2. Surgical treatment of the primary tumor

8.5	Evidence-based Recommendation	checked 2021
GoR **A**	The therapy of oral cavity carcinoma shall take into account the individual situation of the patient. A decision on surgical therapy should be made taking into account the achievability of tumor-free resection margins and the postoperative quality of life.	
LoE **3**	[235]; [291]; [292]; [293]; [294]; [295]; [296]; [297]	
	Strong Consensus	

8.6	Consensus-based Recommendation	new 2021
EC	HPV-positive and/or p16-positive oral cavity carcinomas shall not be treated differently from alcohol- and nicotine-associated carcinomas.	
	Consensus	

8.7	Evidence-based Recommendation	checked 2021
GoR **B**	In case of a microscopically remaining tumor (missed R0 resection), a targeted resection should be performed to improve the patient's prognosis.	
LoE **3**	[234]	
	Strong Consensus	

8.8	Evidence-based Recommendation	checked 2021
GoR **B**	The continuity of the mandible should be maintained during tumor resection if there is no evidence of tumor invasion into the bone on imaging or intraoperatively.	
LoE **3**	[298]; [299]; [300]; [301]; [302]; [303]	
	Strong Consensus	

Background

No suitable studies could be found to identify the best therapy for oral cavity carcinoma. The only published prospective randomized study comparing survival rates after surgical therapy in combination with adjuvant radiotherapy with

radiochemotherapy alone was statistically inconclusive due to insufficient case numbers [315]. A large number of non-randomized, retrospective or monocentric studies describe survival rates or quality of life after both surgical therapy and radiotherapy. However, due to flaws in study design or conduct, no recommendation regarding the best modality of therapy can be derived from them [269], [270], [271], [272], [273], [274], [275], [276], [277], [278], [279], [280], [281], [282], [283], [284], [285], [286], [287], [288].

However, it has been shown overall that small and superficial carcinomas of the oral cavity (T1, T2) can be cured by both surgery and radiotherapy [304], [306], [316], [317], [318]. For tumors with bone invasion, no evidence was found for better local tumor control with surgical therapy compared to radiation. However, the risk of osteoradionecrosis with subsequent loss of the jaw is significantly increased after radiotherapy in these carcinomas [319], [320]. Furthermore, advanced carcinomas of the oral cavity (T3, T4) have been shown to have a higher recurrence rate after radiotherapy alone than other head and neck carcinomas [266]. Patients with advanced carcinomas of the oral cavity (T3, T4) should therefore be treated with combined surgery and radiotherapy [265].

- Due to the lack of evidence on the question of definitive local therapy, the following criteria must be considered when deciding on surgery:
- likelihood of functional impairment
- resectability of the tumour
- general health of the patient and
- wishes of the patient.

In operable patients with resectable oral cavity carcinomas, tumor resection should be performed in combination with reconstruction.

No controlled randomized comparative studies are available for the selection of the resection technique of the primary tumor or for the technique of reconstruction. Therefore, the decision on the approach to resection as well as reconstruction depends primarily on the experience of the surgeon as well as the patient's wishes.

When assessing the resectability of a tumor, it must be taken into account that a failed R0 resection significantly worsens the prognosis [305], [306], [307], [308], [309], [310]. If a targeted resection with tumor-free margins is successful in these cases, this improves local tumor control [234]. Postoperative radiotherapy with an effective tumor dose of at least 60 Gy is also likely to improve local tumor control in patients with scarce or histologically affected resection margins [321].

If achieving tumor-free resection margins requires removal of the mandibular bone, continuity of the mandible should be preserved by box-shaped resection or resection of the internal brace in appropriate cases [311], [312], [313], [314]. Continuity-preserving resections are generally indicated when the macroscopic tumor distance to the mandible is more than 5 mm or when, in the case of clinically directly adjacent tumors, intraoperative frozen section examination of the periosteum shows no tumor involvement [302]. Even with periosteal involvement, mandibular continuity can be preserved in appropriate cases if there is no evidence of cortical erosion on imaging or intraoperative findings [301]. In these cases, box or internal brace resection results in a significantly improved quality of life compared to segmental resection [303]. A continuity resection is recommended if a clear bone infiltration was recognizable in the preoperative imaging (see chapter Chapter 7.1) [302]. If segmental resection cannot be avoided, an adequate reconstruction of the mandible with a bone graft can achieve a quality of life comparable to continuity-preserving techniques [322].

As described in detail in the background text on diagnostics, HPV status does not play a role as a prognostic factor in oral cavity carcinoma – in contrast to oropharyngeal carcinoma- according to current studies. Therefore, HPV-positive oral cavity carcinomas should not be treated differently from alcohol- and nicotine-associated carcinomas.

9.3. Cervical lymph node excision

8.9	Evidence-based Statement	checked 2021
ST	In oral cavity carcinoma, occult metastasis to the cervical lymph nodes occurs in 20-40%. Levels I-III are almost always affected, and only very rarely level V.	
LoE **3**	[223]; [323]; [324]; [325]; [326]; [327]; [328]; [329]; [330]; [331]; [332]; [333]; [334]; [335]; [336]; [337]	
	Strong Consensus	

8.10	Evidence-based Statement	checked 2021
ST	If a clinically unremarkable lymph node status is present (cN0), the results of selective neck dissection (levels I-III) do not differ from those of modified radical or radical neck dissection.	
LoE **3**	[325]; [336]; [338]; [339]; [340]; [341]; [342]; [343]; [344]; [345]; [346]	
	Strong Consensus	

8.11	Evidence-based Recommendation	checked 2021
GoR **A**	Patients with clinically unremarkable lymph node status (cN0) shall undergo elective neck dissection regardless of T category.	
LoE **3**	[336]; [347]; [348]; [349]; [350]; [351]; [352]; [353]; [354]; [355]; [356]	
	Strong Consensus	

8.12	**Evidence-based Statement**	**new 2021**
ST	For maxillary carcinoma, the evidence is insufficient to derive a general recommendation against neck dissection level I-III (SOHND) and for a „wait and see“.	
LoE **3**		
	Strong Consensus	

8.13	**Consensus-based Recommendation**	**new 2021**
EC	In the case of cT1cN0-carcinoma of the maxilla, neck dissection level I-III may be forgeone if the localization is limited to the alveolar process and hard palate, the depth of invasion is less than 3 mm, permanent close follow-up is ensured, and the T category has been confirmed after histological workup.	
	Consensus	

Background 8.9 - 8.13.

An integral part of the therapy of oral cavity carcinoma is the treatment of the cervical lymph nodes, which - depending on the preoperative diagnosis - can be classified as clinically inconspicuous, suspicious or highly suspicious of tumor involvement. However, when deciding on therapy, it must be taken into account that even with clinically and in imaging inconspicuous findings (cN0), occult metastases are still found histologically in 20-40% [204], [253], [319], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367], [372]. A depth invasion of the primary tumor of more than 4mm on MRI is frequently associated with the presence of ipsilateral cervical lymph node metastases [323]. Furthermore, it has been shown that in the histological workup of specimens of elective neck lymph node excisions in a high percentage even an extracapsular growth of the lymph nodes inconspicuous according to clinical criteria has been present [204], [253], [319], [357], [358], [359], [360], [361], [362], [363], [364], [365], [366], [367]. If prophylactic neck dissection is not performed, the prognosis is significantly reduced, even if a radical neck lymph node excision is subsequently performed if metastasis has occurred [366], [368], [176], [369], [370], [371].

According to the current classification according to Robbins, the following six lymph node levels are distinguished, which can be cleared out during neck dissection (see figure in the appendix) [373]:

Table 4: Classification of the cervical lymph nodes according to Robbins

Level	Designation	anatomical limitation
IA and IB	submental nodes and submandibular nodes	ventral and dorsal of the anterior digastric belly

Level	Designation	anatomical limitation
II A and II B	upper jugular lymph node group	ventral and dorsal to the jugular vein
III	middle jugular lymph node group	between level of hyoid bone and cricothyroid membrane
IV	lower jugular lymph node group	between level of membrana cricothyroidea and clavicle
V A and VB	posterior cervical triangle	between SCM and trapezius above and below the omohyoideus
VI	anterior pretracheal lymph node group	between level of hyoid and jugulum

Depending on the intention, one speaks of an elective (prophylactic) neck dissection if a cN0 finding is present and a curative neck dissection if the presence of one or more lymph node metastases is suspected on the basis of the clinical and radiological preliminary examinations. Regarding the extent of neck dissection, the following modifications are distinguished [203],[394]:

Radical neck dissection

Dissection of level I-V together with sacrifice of the accessorius nerve, jugular vein and sternocleidomastoid muscle.

Modified radical neck dissection

Removal of level I-V with preservation of one or more non-lymphatic structures

Selective Neck Dissection

Removal of fewer levels than I-V; in the case of oral cavity carcinoma, usually removal of levels I-III

Extended Neck Dissection

Evacuation or removal of additional lymph node groups or non-lymphatic structures.

The risk of occult metastasis with clinically unremarkable neck findings (cN0) necessitates a recommendation for indication of elective (prophylactic) neck lymph node evacuation. However, no prospective randomized studies are available that specify a risk threshold above which an elective neck dissection must be performed. Thus, conversely, no recommendation can be made to omit elective neck dissection for oral cavity carcinoma [395],[396]. However, a computer-assisted risk analysis using retrospective data showed that the probability of occult metastasis of more than 20% for oral cavity carcinoma clearly justifies an elective neck dissection [397]. Randomized

clinical studies comparing the results of elective neck dissection with those of follow-up alone in the case of clinically inconspicuous neck findings lead to the conclusion that in the case of metastasis occurring later, a worse prognosis can generally be expected despite subsequent therapeutic neck lymph node excision ("salvage neck dissection") [366],[368], [176],[369], [370], [387], [371] . Due to the up to six-fold increased incidence of later lymph node metastases in the "wait and see" concept, there was a significantly shorter disease-free survival time in the observation groups [391],[392]. Thus, even in cases of inital squamous cell carcinoma of the oral cavity and clinically unremarkable neck, elective neck dissection is recommended [366],[368], [176],[369], [370], [387], [371], [388],[389], [391],[392], [398]. In another prospective randomized study with very strict, close follow-up of patients who did not undergo neck dissection, regular selective neck lymph node dissection (level I-III) was recommended - also taking into account the patient compliance required for this purpose [399].

The professional literature search to answer the question of whether neck dissection can be omitted for cT1 cN0 squamous cell carcinoma of the maxilla was only able to identify 4 corresponding studies, even after expansion to the cT2 category. All of these were case series (LoE 3) with a high risk of bias. In the „wait and see“ – group lymph node involvement was found in 2/15 [393] and in the group of patients treated with neck dissection occult metastases were detected in 2/8 [400] and 2/5 cases [376] for cT1 and in 4/19 [400] and 3/18 patients [376] for cT2. While Berger et al. [412] found metastases in 6% in the category pT1 and in 41% in pT2 in a total collective of 171 patients, Poeschl et al. [411][374], [375] did not describe occult metastases or lymph node recurrences in any of the mentioned categories (T1: 8 patients, T2: 9 patients). Oral cavity carcinomas with an invasion depth of less than 3 mm have only a very low probability of metastasis, which is why a wait-and-see approach may be justified in these cases. However, the problem of exact preoperative determination of the depth of invasion precludes a general recommendation to forego neck dissection in superficially growing, invasive oral cavity carcinoma.

In some studies, the ventro-dorsal location of the tumor is described as significant for the risk of neck lymph node metastasis. Thus, these are found less frequently in precanine location [390] or anterior location [393].

The question of which levels of the neck should be removed in the case of clinically unremarkable lymph node findings during an elective neck dissection has been answered in studies. For oral cavity carcinoma, it was shown early on that metastasis essentially occurs to levels I-III, while level V is affected in only about 1% [377], [378], [401] . In tongue carcinomas, a more frequent metastasis was also observed in level IV, so that its clearance can be additionally considered in tongue carcinomas [402]. Depending on the localization of the primary tumor in the oral cavity, level IIB is rarely affected in the case of a clinically inconspicuous neck, and in fact in up to 5%, whereby it is here almost without exception tongue carcinomas [403], [404], [405]. Level IIB clearance must therefore be required for tongue carcinomas, whereas a waiver of level IIB clearance may be considered for oral floor carcinomas if there is otherwise no evidence of lymph node filiarization [406].

The likelihood of contra- or bilateral metastasis is increased in carcinomas of the floor of the mouth and in midline-near carcinomas in general [407], [408]. Numerous therapeutic studies have failed to demonstrate statistically significant differences between selective neck dissection (level I-III) and modified radical neck dissection [357], [366], [379], [380], [381], [382], [383], [384], [385] or radical neck dissection [386], [409] with regard to locoregional tumor control and overall survival in cN0 neck. If the histopathological workup of the specimen of a selective neck

dissection (level I-III) shows lymph node involvement, the extension of the excision to level IV and V as well as adjuvant radiotherapy is recommended in some cases [398], [410]. There is no evidence to support a general recommendation to forego adjuvant radiotherapy even in the case of non-capsular pN1 findings.

8.14	Evidence-based Statement	new 2021
ST	There is no robust evidence from clinically controlled trials for the suitability of SLN biopsy as a method to avoid elective neck lymph node excision.	
LoE	[413]; [414]; [415]; [416]; [417]; [418]; [419]	
	Strong Consensus	

Background 8.14

Several systematic reviews, of which at least 50% of the included sources were designed as studies, have addressed the issue of SLN biopsy in oral cavity carcinoma. Studies over the past 20 years were summarized and detection rates consistently above 95% were found. In the most comprehensive and recent one by Liu et al. [416], which is also rated with only a low risk of bias, 66 studies involving 3566 patients were compiled and the sensitivity of SLN biopsy in terms of detecting lymph node metastasis is reported to be 0.87 [0.85-0.89] (when including all studies including validation studies with immediately following neck dissection). Considering only the studies in which patients with negative SLN were followed up and the false negatives were detected over the course, the sensitivity is 0.85 [0.82-0.88].

Although there has been no randomized comparison of the two approaches to date, all available data suggest that SLN biopsy is noninferior to elective neck dissection in terms of reliability in predicting lymph node status [374].

Since the accuracy of SLN biopsy is highly dependent on how carefully it is performed, this method requires special expertise. This is particularly true for the floor of the mouth, because here, due to the proximity of the tumor to the first lymph node stations, the „uptake“ of the SLN and the peritumoral injection area can overlap („shine-through“ effect), making the detection of the SLN more prone to error. Therefore, it is not always recommended for the floor of the mouth [420] or, if detection is uncertain, level Ia/Ib clearance should be performed. If a transcervical approach by resection or reconstruction is necessary, selective neck dissection should also be preferred.

However, in previous results, SLN biopsy is equivalent to conventional excision for small squamous cell carcinoma (T1/T2) in terms of survival [421], [422]. In terms of postoperative quality of life and functionality, there are advantages for SLN biopsy [423], as well as in terms of lower complication rates [422].

8.15	Consensus-based Recommendation	new 2021
EC	SLN biopsy can be offered for early, transorally resectable oral cavity carcinomas that do not require a transcervical approach in the same procedure.	
	Consensus	

8.16	**Consensus-based Recommendation**	**new 2021**
EC	In case of a positive sentinel lymph node and in case of an uncertain detection, a complete neck dissection shall be performed.	
	Strong Consensus	

8.17	**Evidence-based Statement**	**checked 2021**
ST	The preservation of the accessorius nerve during neck dissection leads to an improvement in the quality of life.	
LoE **3**	[424]; [425]	
	Strong Consensus	

8.18	**Evidence-based Statement**	**checked 2021**
ST	The results of a modified radical neck dissection may be equivalent to those of a radical neck dissection in selected cases where metastasis has already occurred.	
LoE **3**	[343]; [426]; [427]; [428]; [429]; [430]; [431]; [432]; [433]; [434]	
	Strong Consensus	

8.19	**Evidence-based Statement**	**checked 2021**
ST	The results of a selective neck dissection (level I-III) in combination with postoperative radiochemotherapy may be equivalent to those of a modified radical neck dissection with postoperative radiotherapy in selected cases where lymph node metastasis has already occurred.	
LoE **3**	[435]; [436]; [437]	
	Strong Consensus	

8.20	**Evidence-based Statement**	**new 2021**
ST	The evidence is insufficient at this time to derive a clear formulation for a recommendation for neck dissection level I-III (SOHND) rather than neck dissection level I-V for invasive oral cavity carcinoma with cN1.	
LoE **3**	[374]; [376]; [362]; [438]; [439]; [440]; [441]; [442]	
	Strong Consensus	

8.21	**Consensus-based Recommendation**	**new 2021**
EC	In the presence of a cN1 or N1 subgroup, selective neck dissection can only be performed up to level III as an alternative to MRND up to level V, provided there is no extranodal growth and the neck dissection extends at least one level more caudally than the level of LK metastasis.	
	Strong Consensus	

8.22	**Evidence-based Statement**	**new 2021**
ST	For invasive oral cavity carcinoma with LK metastasis in level IIb-III, neither MRND (level I-V) nor SOHND (I-III) has been sufficiently proven to be superior in terms of LK recurrence or survival rates.	
LoE **3**	[374]; [376]; [362]; [438]; [439]; [440]; [441]; [442]	
	Strong Consensus	

8.23	**Evidence-based Recommendation**	**checked 2021**
GoR **A**	If lymph node involvement is clinically suspected (cN+), appropriate neck lymph node excision, usually a modified radical neck dissection, shall be performed.	
LoE **3**	[328]; [343]; [345]; [426]; [427]; [428]; [429]; [430]; [431]; [432]; [433]; [434]	
	Strong Consensus	

Background

In the literature, uniform consensus exists that surgical treatment is usually required for clinically and radiologically abnormal neck findings. If the affected lymph nodes are fixed or unresectable, radiochemotherapy may be the only therapeutic option. In the histopathological workup of neck dissection specimens of stages N2 and N3, residual tumor cells were found in more than 30% despite previous radiochemotherapy,

although a complete remission was clinically evident post radiationem [459], [460], [461].

Since the risk of additional occult metastases in clinically inconspicuous levels is high in clinically conspicuous lymph node findings (cN+), local clearance of the affected lymph node region alone may not be sufficient. Therefore, at least a selective neck dissection of levels I-IV or a modified radical or radical neck dissection must be performed [359], [386]. In general, for oral cavity carcinoma involving levels I-III, the probability of level IV involvement is reported to be 7-17% and level V 0-6% [377], [365]. Nevertheless, the risk of "skip metastases" is pointed out, which can lead to involvement of level V, although there was no metastasis in levels II -IV [445]. In the case of clinically conspicuous neck findings (cN+), an infestation of level IIB is to be expected in 5% [406], which should therefore be cleared in any case [444]. With increasing T category, involvement of several ipsilateral lymph nodes and higher grading, the risk of contralateral metastasis increases [463],[465], especially in carcinomas near the midline and in carcinomas of the floor of the mouth [407],[465]. In these cases, therefore, elective excision of levels I-III on the contralateral side of the neck should be considered [466].

Numerous retrospective and prospective studies have been performed to decide on the extent of radicality of neck dissection in cases of positive lymph node status. In comparable tumor and lymph node stages, modified radical neck dissection yields equally reliable local tumor control as radical neck dissection [384], [446], [447], [448], [449], [450], [451], [452], [453], [454]. Preservation of non-lymphatic structures, especially the accessorius nerve, results in improved quality of life [424]. Level V evacuation is associated with an increased risk of damage to the accessorius nerve and a negative impact on quality of life [425]. It has also been shown that in selected patients without locally advanced lymph node involvement, selective neck dissection combined with postoperative radiochemotherapy provides tumor control as reliable as more radical neck lymph node excision alone. In selected patients without locally advanced lymph node involvement, selective neck-dissection in combination with postoperative radiochemotherapy provides reliable regional tumor control [455],[456], [457]. A study of selective neck dissection with clearance of levels I-III showed no differences in local tumor control between pN0 and pN+ findings over a period of 38 months when only singular and small lymph nodes were involved in the pN+ group [469]. However, there is currently insufficient evidence to generally recommend the concept of selective neck dissection for a cN+ finding. Retrospective data suggest that the risk of local lymph node recurrence increases with histologically confirmed size of the affected lymph node greater than 3 cm (N2) and with two or more affected lymph nodes [471]. Postoperative radio- or radiochemotherapy significantly reduces the risk of recurrence in the neck in these cases [108], [357], [362], [366], [473], [474].

With regard to the question of whether neck dissection level I-III (SOHND) is preferable to neck dissection level I-V (MRND) in patients with invasive oral cavity carcinoma with N1 subgroup or N1 in more than 50% of patients, five relevant publications were included [376], [441], [442], [440], [440]. The results of the studies showed slight advantages of MRND over SOHND with regard to the occurrence of LK metastases, occurrence of locoregional recurrence, 3-year survival and overall survival. In the paper by Feng et al, 2/11 patients in the N1 SND subgroups showed regional recurrence, both of whom died. In the CND group („comprehensive ND"), the N1 subgroup showed regional or locoregional recurrence in 3/29, of whom 2 died. In Schiff et al, the N1 SND group with radiotherapy showed ipsilateral lymph node metastases in 0/23 patients and in N1 SND without radiotherapy in 2/24 patients. In the N1 RND group with

radiatio, ipsilateral lymph node metastases occurred in 0/2 patients and in N1 RND without radiatio in 0/1 patients. In Shin et al, N1 subgroup analysis was available for regional recurrence rate only. Here, 2/11 patients in the N1 SND subgroups showed regional recurrence, both of whom died. In the CND group, the N1 subgroup showed regional or locoregional recurrence in 3/29, of whom 2 died. In the paper by Liao et al, results in the N1 subgroup for 123 with SND and for 28 with CND could be extracted from the data collected. A 5-year overall survival rate of 51% and disease-related survival of 70% was reported for the N1 SND group. For the N1 CND group, 5-year overall survival rates were 68% and disease-related 81%. Disease-free survival at 5 years was 64% for the N1 SND group and 77% for the N1 CND group.

However, it is important to note that these are all retrospective case series with a high risk of bias (LoE 3). This contrasts with other studies according to which modified radical neck dissection should not be considered standard therapy [462] and level I to III dissection is usually considered sufficient [464], [467], especially when followed by adjuvant radio/radiochemotherapy. The decision on the extent of neck dissection depends not only on the lymph node metastasis N1 a/b but also on the location and category of the primary tumor and the histopathological feature such as lymphangiosis [468], perineural invasion or vascular invasion [470]. The included studies also suggest further differentiation between level IV and V. In any case, neck dissection should not only refer to the level of the manifest lymph node metastasis, but should also include a level further caudal to it.In the case of level IIB and III involvement, extension of neck dissection to level IV, but not to level V, is indicated [472].

If both categories N2 or N3 underwent radiation that did not result in complete remission of the neck lymph node findings, a follow-up neck dissection may improve both locoregional tumor control and overall survival compared with follow-up alone [475], [476]. In principle, it has also been shown that modified radical neck-dissection following radiochemotherapy, in the sense of a neoadjuvant treatment concept, increases disease-free survival as well as overall survival in N2 and N3 stages but not in N1 stages, irrespective of the response rate to radiochemotherapy [458]. However, the likelihood of successful salvage neck-dissection if lymph node recurrence has already occurred after radiochemotherapy is low [477]. If the primary tumor is small but the lymph nodes in the neck are advanced, it is possible to perform only an adequate neck dissection and then irradiate the primary tumor and the neck without having to accept a loss of local tumor control [478], [479].

The question of whether adjuvant radio(chemo)therapy is recommended in cases of small primary tumor (pT1,pT2) with a lymph node metastasis (pN1) and absence of other risk factors has not been considered in prospective studies to date. The results of a prospective multicenter study (DOESAK-pN1) are not yet available. A systematic review summarizing data from older retrospective studies concludes that adjuvant radiotherapy does not confer a survival benefit [491]. Only one case-control study was found, which described advantages for adjuvant radiotherapy with regard to locoregional control, but no difference in overall survival. [490]. Another retrospective study describes a survival advantage for adjuvant RT in the subgroup analysis of patients younger than 70 years, as well as in pT2, but not in pT1. [443]. In another retrospective analysis, the effect of adjuvant RT in pN1 is rather questioned [492].

A benefit of prophylactic lymph node dissections in lip carcinoma is currently not proven [480] and none of the lymph node treatment concepts have been randomized prospectively studied so far. A separate S2k guideline on lip carcinoma is in preparation (https://www.awmf.org/leitlinien/detail/anmeldung/1/ll/007-103.html).

However, some studies indicate that from tumor size T2 the risk of lymph node metastases increases significantly and the prognosis deteriorates significantly [481], [482], [483][484], so that from T3 at the latest an elective neck dissection of level I-III should be recommended.

Likewise for high-risk tumors

- from a tumour thickness (Td) of 5 mm
- from differentiation grade G3
- in the presence of desmoplasia
- in case of perineural growth
- in case of lymphatic or blood vessel invasion
- bone infiltration
- immunosuppression

are defined [485], [486], [487], [488], [489].

In case of clinical suspicion of involvement of regional lymph nodes (cN+), therapeutic lymphadenectomy of the respective regions is indicated, provided that the primary tumor is treated surgically. In cases of manifest lymph node metastases, regional dissection of levels I-V is indicated, usually in the form of a function-preserving modified radical neck dissection (MRND).

In the case of recurrence in the lymphatic region, reoperation is reasonable if it is technically feasible without vital threat to the patient. If this is not the case or if only an R1 resection is successful, radiation treatment should be considered.

The results of a selective neck dissection (level I-III) in combination with postoperative radiochemotherapy may be equivalent to those of a modified radical neck dissection with postoperative radiotherapy in selected cases where lymph node metastasis has already occurred.

9.4. Reconstruction

8.24	Evidence-based Recommendation	checked 2021
GoR **A**	Reconstructive measures shall always be part of a surgical concept. The planning of the reconstruction shall take into account the overall oncological situation. The cost of the reconstruction shall be justified by the expected functional or aesthetic improvement.	
LoE **3**	[493]; [494]; [495]	
	Strong Consensus	

8.25	Evidence-based Statement	checked 2021
ST	Reconstruction in the oral cavity with microsurgically anastomosed grafts is a proven method. In many cases, the technique of microvascular tissue transfer is already indicated during tumor resection in order to achieve reliable defect coverage.	
LoE 3	[493]; [494]; [495]; [496]; [497]; [498]; [499]; [500]; [501]; [502]; [503]	
	Strong Consensus	

8.26	Consensus-based Recommendation	new 2021
EC	The planned bony reconstruction of the maxilla and mandible can be carried out with CAD/CAM support. This is especially true for complex (multi-segment) defects.	
	Consensus	

Background

As a consequence of the removal of the primary tumor with a sufficient safety margin, defects often develop that require reconstructive measures. The aim of these measures is to preserve - or, in the case of secondary reconstruction, to restore - chewing, speaking and swallowing function as well as facial aesthetics. Reconstructive procedures include local flap plasty, free skin, mucosa, or bone grafting, muscle-targeted grafts, and microvascular tissue transfer. Particularly for defects of the maxilla and the orbital region, defect prosthodontics and epithetics continue to be suitable.

While the indication for immediate soft tissue reconstruction is often based on the need for safe defect coverage, the question of primary bone reconstruction is still controversial. In contrast to soft tissue, histological evidence of tumor-free resection margins cannot be provided intraoperatively for bone, so that if residual tumor is detected later, a bone graft that has already been inserted must be removed again. Although it has been shown that immediate osseous reconstruction can preserve patients' quality of life after mandibular continuity resection [322], the bridging plate for mandibular replacement therefore remains a viable reconstructive option, in part because of its ease of use. The reconstructive techniques vary depending on the anatomical localization as well as the patient's resilience and desire. For example, it has been shown that the muscle-targeted myocutaneous pectoralis major flap is particularly suitable for older patients with low weight-bearing capacity [495]. However, no randomized controlled multicenter study could be identified in which the results of different reconstruction techniques were prospectively compared. However, evidence exists from numerous retrospective case series that microvascular tissue transfer is a safe and reliable technique that has been particularly successful for intraoral reconstruction [504], [505], [506], [507], [508], [509], [510], [511]. In a retrospective case series of 400 consecutive microsurgically anastomosed grafts, complete graft loss was reported in less than 1%, partial necrosis rate in 3%, and perioperative mortality of 1.3% [494].

Extensive defects of the maxilla and/or mandible may occur as part of tumor resection for oral cavity carcinoma with bone involvement. Bony reconstruction is usually performed using alloplastic material or autologous bone. CAD/CAM techniques can be used for this purpose. In recent years, virtual planning has been established, especially for the microvascular fibula graft [512], [513], [514]. In this process, resection and reconstruction of the maxilla and/or mandible are planned virtually in advance and osteotomy templates are fabricated.

Furthermore, a patient-specific implant can also be fabricated. These procedures often allow the practitioner to achieve a higher accuracy of reconstruction with better function and esthetic outcome [515], [516], [517], [518], [519], [520] . Whether this ultimately leads to a higher quality of life for patients has not yet been scientifically proven.

9.5. Radiotherapy

8.27	Evidence-based Recommendation	checked 2021
GoR **A**	Interruption of radiotherapy leads to deterioration of tumor control and shall be avoided.	
LoE **2+**	[521]; [522]; [523]	
	Strong Consensus	

8.28	Consensus-based Statement	checked 2021
ST	In the case of primary percutaneous irradiation alone, an alternative fractionation (hyperfractionation/acceleration) should be chosen.	
	Strong Consensus	

Background

Conservative, curative intent treatment of oral cavity carcinoma consists of radiotherapy or a combination of radiotherapy and chemotherapy. Chemotherapy alone is used for oral cavity carcinoma with palliative intention.

Radiotherapy makes use of ionizing radiation to treat malignant tumors. Ionizing radiation can be directed at the tumor from the outside (percutaneous radiation therapy) or directly into the tumor after implantation of special catheters in an afterloading procedure (afterloading: remotely controlled introduction of a radioactive radiation source from the outside). The total dose of radiotherapy is usually administered in several single doses either conventionally fractionated (1.8-2.0 Gy daily, 5x/week), accelerated (>10 Gy/week) or hyperfractionated (1.1-1.2 Gy, 2x daily). The total dose of radiation treatment acting on the tumor is limited by the radiation tolerance of the surrounding healthy tissues, which must be included in the radiation field despite maximum tissue protection. Various classifications are in use for graduating the radiation-related side effects (radiation toxicities) on the healthy

surrounding tissue [527], [528], [529], with grade 1 usually representing the mildest and grade 4 the most severe toxicity.

Radiation therapy can be used with curative intent (primary radical radiation therapy), to improve local tumor control after or before surgical therapy (adjuvant or neoadjuvant radiation therapy), and to relieve tumor-related symptoms (palliative radiation therapy).

The effect of radiation therapy on the tumor and surrounding healthy tissues depends on the total dose, the single dose, and the total duration of treatment.

In conventional fractionation, the total dose of approximately 70 Gy is divided into daily single doses of 1.8 - 2 Gy, five times per week. Modifications are hypo-fractionation, hyperfractionation and accelerated fractionation. In hypofractionation, much higher individual doses than the usual 1.8 - 2 Gy are administered in preferably palliative situations. In hyperfractionation, smaller but more numerous individual doses are administered; in this case, the total dose can be increased. While the total weekly dose of approximately 10 Gy is maintained with hyperfractionation, all forms of accelerated irradiation aim for a higher total weekly dose and thus a shortening of the total treatment time. Studies show that both modifications in the treatment of head and neck cancer can lead to improved locoregional tumor control compared with conventional fractionation, but temporarily to increased radiation toxicity [530], [531], [532], [533], [534], [535], [536], [537].

Recent meta-analyses based on randomized clinical trials and based on individual patient data on alternative fractionation to definitive radiotherapy performed alone (hyperfractionation/acceleration) [524], [538] show, in addition to improved locoregional control, a significant improvement in overall survival compared with conventional fractionation. Subgroup analysis shows that especially young patients (< 50 years) benefit significantly from alternative fractionation with regard to survival.

It has been clearly demonstrated that prolongation of treatment time, for example by interruption of radiation due to complications in the course of the disease, leads to a deterioration of local tumor control [525], [526].

In order to reduce the toxicity of radiotherapy, while at the same time not worsening local tumor control or overall survival, intensity-modulated radiotherapy (IMRT) has been introduced for patients with head and neck cancer. The goal of avoiding radiation-induced xerostomia by dose reduction to the parotid glands was achieved in initial case series [539]. IMRT may also be indicated in secondary radiation therapy, for example to treat a recurrent tumor [540].

There is no established evidence that direct application of radiation by an implantable radiation source (brachytherapy) leads to an improvement in local tumor control or overall survival compared with percutaneous irradiation or surgery for head and neck cancer. However, case series are available showing local tumor control at 5 years of 65-97% for tongue and oral floor carcinoma at initial tumor stages (T1, T2) [316], [541], [542], [543], [544], [545], [546], [547], [548] and in advanced carcinomas 49-70% describe [316], [543], [547], [549]. The optimal tumor dose is reported to be 65 Gy [544], which should not be exceeded to avoid necrosis or bone complications [549], [550], [551]. A combination of brachytherapy with percutaneous radiotherapy is possible [552], [553]. Compared to percutaneous radiotherapy alone, however, no reliable improvement in quality of life could be achieved with this combination [554].

9.6. Radiotherapy in combination with chemotherapy

8.29	**Evidence-based Statement**	**checked 2021**
ST	Neoadjuvant or adjuvant chemotherapy has no beneficial effect in oral squamous cell carcinoma in conjunction with surgery.	
LoE **1++**	[524]; [555]; [556]	
	Consensus	

8.30	**Consensus-based Recommendation**	**checked 2021**
EC	In the case of simultaneous primary radiochemotherapy, chemotherapy should be given with cisplatin or a cisplatin-containing combination.	
	Strong Consensus	

8.31	**Evidence-based Recommendation**	**checked 2021**
GoR **A**	In patients with advanced, inoperable and non-metastatic oral cavity carcinoma, primary radiochemotherapy shall be preferred to radiotherapy alone, especially in the age groups up to 70 years.	
LoE **1++**	[555]; [557]	

8.32	**Consensus-based Recommendation**	**checked 2021**
EC	Radiochemotherapy shall only take place at facilities where radiation- or chemotherapy-related acute toxicities can be identified and adequately treated.	
	Strong Consensus	

8.33	**Consensus-based Recommendation**	**checked 2021**
EC	As an alternative to radiochemotherapy, a combination of radiotherapy with cetuximab can be performed.	
	Strong Consensus	

Background 8.29 to 8.33

While no curative effect has been found for chemotherapy alone in the treatment of squamous cell carcinoma of the head and neck region, a survival benefit has been

clearly demonstrated for the combination of radiotherapy with chemotherapy [558], [524]. This amounts to 17% in comparison with radiotherapy alone for oral cavity carcinoma [524]. It could be shown that the effect of chemotherapy accompanying radiotherapy is particularly given in patients under 60 years of age and amounts to 22-24% in this group as well as 12% in the 60-70 year olds [558], [524].

In principle, chemotherapy can be neoadjuvant, adjuvant or concomitant with other therapeutic modalities, usually radiotherapy. While in neoadjuvant therapy chemotherapy is given in the weeks before radiotherapy or surgery, in adjuvant therapy it is given after radiotherapy or surgery has been performed. Chemotherapy is often given concomitantly with radiotherapy, namely after surgical treatment has been performed (adjuvant radiochemotherapy). Chemotherapy alone leads to a statistically non-significant survival benefit of 2% at 5 years when applied neoadjuvantly and to no effect when applied adjuvantly [558], [524], [560], [561]. Thus, there is no evidence supporting a benefit of neoadjuvant or adjuvant chemotherapy in combination with surgery [558], [524], [559], [560], [561]. In contrast, neoadjuvant chemotherapy with cisplatin and 5-FU improves 5-year survival by a statistically significant 5% compared with locoregional therapy (surgery) alone in patients with nonmetastatic head and neck cancer [558], [524].

However, at the time of the guideline update, no new data could be elicited to recommend neoadjuvant radiotherapy or chemotherapy.

When chemotherapy is given concomitantly with radiotherapy, there is an 8% improvement in 5-year overall survival for both resectable and non-resectable tumors compared with radiotherapy alone, as well as improved local tumor control, also 8% [524]. Prognostic improvement with chemotherapy accompanying radiotherapy has been described predominantly with conventional radiotherapy, but also with modified radiotherapy [558], [524], [562].

Compared to other chemotherapeutic agents, cisplatin is of greatest importance in this regard, as it is as effective as its sole administration when compared to polychemotherapy containing cisplatin , but polychemotherapy without cisplatin leads to significantly worse outcomes [558], [524], [562].

However, the survival benefits achieved by combination with chemotherapy are accompanied by a significant increase in acute radiation toxicity. Thus, in addition to increased adverse effects on hematology, there is an increase in mucositis [268], [271], [563], [564],[565], [566],[567], [568],[570], [571],[572], [573], as well as increased long-term sequelae, especially dental damage [268], [574]. These increased side effects have been found more frequently in combination with conventional radiotherapy [268], [570], [575], [576], [577]. It is therefore recommended that radiochemotherapy should only be given at institutions where radiation- or chemotherapy-related acute toxicities can be identified and adequately treated.

For patients with unresectable, locally advanced squamous cell carcinoma of the head and neck region, initial results of a phase III trial showed a significant survival benefit with neoadjuvant cisplatin/5-FU and doxetacel pretreatment compared with cisplatin/5-FU combination therapy prior to radical radiotherapy [569][578]. A similar study also showed a significant improvement in overall survival with the addition of doxetacel to cisplatin/5-FU induction chemotherapy compared with cisplatin and 5-FU induction alone followed by carboplatin radiochemotherapy [578].

A randomized multicenter trial evaluated the benefit of the EGF receptor-targeted monoclonal antibody cetuximab in combination with radical radiotherapy for advanced

head and neck cancer, but without inclusion of oral cavity carcinoma. This showed an improvement in local tumor control and overall survival of 11 and 10%, respectively, compared with radiotherapy alone, with no increase in radiation toxicity [579]. However, cetuximab administration resulted in third-degree acneiform skin lesions in 17% of patients and other infusion-related toxicities in 3%.

8.34	Consensus-based Recommendation	new 2021
EC	In the presence of a pN1 category of pT1 or pT2 squamous cell carcinoma, the indication for adjuvant radio(chemo)therapy can be offered.	
	Strong Consensus	

8.35	Evidence-based Recommendation	checked 2021
GoR A	Postoperative radio- or radiochemotherapy shall be given in cases of advanced T category (T3/T4), scarce or positive resection margins, perineural invasion, vascular invasion, and/or lymph node involvement.	
LoE 1++	[341]; [471]; [580]; [581]; [582]; [583]; [584]; [585]	
	Consensus	

8.36	Evidence-based Recommendation	checked 2021
GoR A	Postoperative radiotherapy shall be conventionally fractionated and delivered at 54-60 Gy in 27-30 fractions over 5.5-6 weeks for average risk tumors and 66 Gy in 33 fractions over 6.5 weeks for tumors at increased risk of recurrence.	
LoE 1++	[580]; [581]; [585]; [586]	
	Consensus	

8.37	Evidence-based Recommendation	checked 2021
GoR B	Postoperative radiotherapy should be started as early as possible and completed within a maximum period of 11 weeks after surgery.	
LoE 2++	[587]; [588]	
	Strong Consensus	

8.38	Evidence-based Recommendation	checked 2021
GoR **B**	If radiotherapy is indicated, patients with increased histopathological risk criteria for tumor recurrence (resection margin <5mm and/or extracapsular tumor growth) should receive adjuvant treatment in the form of radiochemotherapy with cisplatin after tumor resection.	
LoE **2++**	[580]; [581]; [585]; [589]; [590]; [591]	
	Strong Consensus	

8.39	Evidence-based Recommendation	checked 2021
GoR **0**	Patients with small and accessible tumors (T1 / T2) of the oral cavity can be treated by interstitial brachytherapy in selected cases.	
LoE **3**	[592]; [593]; [594]; [595]	
	Consensus	

Background 8.34-8.39

Numerous studies have been conducted on the indication and effectiveness of radiotherapy or radiochemotherapy for the treatment of oral cavity carcinoma, but no randomized clinical trials could be found that compared radiotherapy or radiochemotherapy with the results of surgery alone. However, monocentric case series show that small and superficial carcinomas of the oral cavity can be cured by radiotherapy as well as surgery [304], [306], [316], [317], [318]. Similarly, in the treatment of clinically inconspicuous neck (cN0), the results of elective neck dissection are not significantly different from those of prophylactic radiotherapy in terms of local tumour control at 5 years [607]. The risk of osteoradionecrosis is increased when tumors arrode the jawbone [319], [320].

While there is no indication for radiochemotherapy in initial stages or smaller oral cavity carcinomas, advanced operable carcinomas of the oral cavity should be treated with a combination of surgery and radiochemotherapy [304],[596]. According to the results of two multicenter phase III trials on adjuvant therapy of advanced head and neck carcinomas, subgroup analysis of risk profiles recommends radiochemotherapy with cisplatin in the presence of resection margins less than 5 mm and extracapsular tumor growth, provided that an indication for radiotherapy has been made, taking into account the overall situation [608].

On the question of whether adjuvant radio/radiochemotherapy is indicated for pT1/2 pN1 squamous cell carcinoma of the oral cavity with complete tumor resection (R0) and without extracapsular spread, a systematic de novo search could not include any randomized controlled trials from 1994 onward. A prospective study on this issue launched by the DGMKG was still awaiting its final analysis at the time of the LL-update.

Non-randomized studies suggest that patients with positive resection margins and/or lymph node involvement benefit from adjuvant radiochemotherapy in terms of local

tumor freedom and overall survival at three years [609] and that this reduces the risk of lymph node recurrence, especially in patients with poorly differentiated tumors [382], [597], [599], [600], [601].

Postoperative adjuvant radiotherapy performs significantly better than neoadjuvant treatment with respect to local tumor control in patients with surgically removed T2-T4 carcinomas without lymph node involvement [620], [610].

Taking into account the histopathological tumor characteristics associated with an increased risk of recurrence, the indications for radio- or radiochemotherapy were more precisely defined. Extracapsular growth of lymph node metastases was shown to be the most important risk factor for local recurrence after neck dissection [239],[248], [611], [612], [613], [614], [615]. Also elevated local recurrence rates are found with close or positive resection margins, advanced tumor stage, any lymph node involvement greater than 3cm in diameter, multiple lymph node involvement, and vascular or nerve infiltration [216],[248], [604],[611], [614],[615], [616],[617]. Locoregional tumor control is particularly worsened in all cases with two or more of the above risk factors [305],[611], [612]. While a dose of 54-60 Gy in 27-30 fractions distributed over 5 days/week is considered sufficient in average risk cases, in the described cases of a strongly increased risk of tumor recurrence, adjuvant radiotherapy should be applied with a conventional fractionation and with not less than 57.6 Gy [585]. Thus, in the case of a close R0 or an R1 resection, local tumor control of up to 92% can be achieved with doses of at least 60 Gy [321]. Especially in cases of extracapsular lymph node growth, a dose increase to at least 63 Gy in fractions of 1.8 Gy or a boost to 66 Gy in 33 fractions is indicated [473], [474], [602]. Postoperative accelerated radiotherapy offers no advantage over conventional radiotherapy in terms of overall survival [603], [604]. The time from surgery to cessation of radiotherapy significantly affects locoregional control and overall survival and should be 11 weeks or less [604], [605].

In patients with histopathological criteria for increased recurrence, adjuvant radiochemotherapy should be given after resection of oral cavity carcinoma instead of adjuvant radiotherapy, because the combination with chemotherapy (cisplatin) leads to an improvement in local tumor control, disease-free survival, and overall survival [473], [474], [606], [618]. This effect is particularly pronounced after R1 resections and in affected lymph nodes with extracapsular growth [591].

There are no randomized controlled trials comparing the outcome of brachytherapy with percutaneous radiation in patients with head and neck cancer. Evidence for an indication for brachytherapy comes from large case series of experienced centers.

With interstitial brachytherapy , local tumor control rates at 5 years of 79-97% for T1 and 65-8% for T2 tumors have been achieved in patients with early stages of tongue or oral floor carcinoma [316],[541], [542],[543], [544], [545], [546], [547], [548]. The 5-year local tumor control was comparable to surgical resection alone at the same centers [592]. The 5-year local tumor control in patients with T3 - oral cavity carcinomas was 49-70% [316], [543], [547], [549].

While a dose of 65 Gy resulted in optimal local control [598], an increase in dose only increased the risk of complications such as necrosis and osteonecrosis [549], [550], [551]. A dose rate greater than 0.55 Gy/hour and a source distance greater than 15 mm significantly increased the risk for soft tissue and bone necrosis [546], [552], [553], [619].

9.7. Prevention and treatment of radiation-related side effects

8.40	**Evidence-based Statement**	**checked 2021**
ST	There is evidence that intensity-modulated radiotherapy (IMRT) can reduce the frequency and severity of radiation-induced xerostomia.	
LoE **3**	[539]	
	Strong Consensus	

8.41	**Consensus-based Recommendation**	**checked 2021**
EC	Patients undergoing radiation treatment for carcinoma of the oral cavity shall receive optimal dental and oral care.	
	Strong Consensus	

8.42	**Consensus-based Recommendation**	**checked 2021**
EC	Patients shall receive a dental examination and, if necessary, conservative and/or surgical dental rehabilitation before undergoing radio/radiochemotherapy in the oral cavity to prevent osteoradionecrosis.	
	Strong Consensus	

8.43	**Consensus-based Recommendation**	**checked 2021**
EC	At the beginning of radiation therapy in the oral cavity, a fluoridation splint and, if necessary, a spacer splint shall be made.	
	Consensus	

8.44	**Evidence-based Recommendation**	**checked 2021**
GoR **B**	Patients who have been irradiated for carcinoma of the oral cavity should be offered pilocarpine orally three times daily if residual salivary gland function is preserved, provided there are no contraindications.	
LoE **1+**	[621]; [622]	
	Consensus	

Background

The side effects of radiotherapy are caused by the unavoidable co-irradiation of healthy neighbouring tissues surrounding the tumour. A distinction is made between acute side effects that occur during or immediately after radiotherapy and late side effects that become apparent only after months or years.

The most important acute side effect of radiation and/or cytostatic treatment in the head and neck region is mucositis, an inflammatory, painful damage of the mucosal epithelium and the submucosa of the irradiated aerodigestive tract. Various classifications are in use for grading radiation-related side effects (radiation toxicities) on healthy surrounding tissues [527], [528], [529], with grade 1 usually representing the mildest and grade 4 the most severe toxicity. As the dose of radiation increases, the severity of mucositis also increases, so that food intake may be significantly limited when grade 3 or grade 4 is reached. If severe pain is present, it is often necessary to insert a PEG tube and - also because of the increased risk of local and systemic infections - to keep the patient in hospital. Similar to the mucous membrane, the outer skin of the head, face and neck can also be affected by acute radiation damage.

Late damage includes damage to the dental structure and periodontium. In the treatment of oral cavity carcinoma, early dental care is therefore essential for prophylactic reasons in order to counteract the otherwise frequent loss of teeth or radiation caries in the case of planned or previous radiation therapy; this also includes the preparation of a fluoridation and, if necessary, a spacer splint before the start of radiation therapy [267], [268]. Furthermore, pronounced and permanent dry mouth (xerostomia) often occurs when the salivary glands, especially the parotid gland, are located in the radiation field. This side effect can be mitigated by the technique of IMRT. As a consequence of xerostomia, speech, swallowing and taste disorders result, as well as further damage to the hard tooth substance due to the missing cleaning effect of the saliva. A feared long-term complication is infected osteoradionecrosis, which occurs in approximately 5% of irradiated patients and can lead to partial loss of the mandible. The risk of osteoradionecrosis is increased if tumor erosion has occurred on the mandible and it is therefore in the direct radiation field [319], [320], [624]. Surgical treatment of infected osteoradionecrosis of the mandible is technically demanding and can usually only be solved in the long term by microvascular bone transfer. Finally, fibrosis occurs as a late consequence of radiotherapy in the region of the masticatory and pharyngeal muscles, which can lead to a restriction of swallowing function and mouth opening (trismus).

Currently, there are no studies available that provide a detailed description of the quality of life after radio- or radiochemotherapy.

Prophylaxis and treatment of radiation-induced mucositis initially involves basic oral care, which should be performed by the patient but also by nursing staff according to established oral care protocols. Symptomatic treatment mainly includes sufficient pain therapy according to WHO guidelines, starting with topical analgesics and ending with opioid therapy. The use of benzidamine - mouth rinses reduces the number and severity of oral mucosal lesions and reduces the pain of mucositis [626], [627], [628] . In the largest of the present studies, a treatment regimen of 4-8 times daily applications of a 15 ml rinse solution was used. Irrigation occurred before the start of radiation treatment, extended continuously throughout the radiation period, and was not completed until 2-3 weeks after the end of therapy [625]. Most patients in this study had been treated with conventional fractionated radiotherapy, so the benefit of benzidamine in the case of radiochemotherapy or modified fractionated radiotherapy cannot be proven with certainty. However, no evidence is found for the benefit of other interventions or agents for the treatment of radiation-induced

mucositis [629], [630], [648], [631], [632], [633], [634], [635], [636], [637], [638], [639], [640], [641], [642].

Acute and late-onset xerostomia caused by radio- or radiochemotherapy can be significantly reduced by administration of amifostine concurrent with radiation [630]. There is no evidence that this affects the response rate to radiotherapy, the recurrence rate at 18 months or overall survival at 24 months [629], [648]. Vomiting was observed significantly more often with amifostine administration than in a control group, but not hypotension or nausea [648]. The administration of amifostine for the prevention of radiation-induced xerostomia cannot be recommended outside of clinical trials.

In order to reduce xerostomia while not worsening local tumor control or overall survival, intensity-modulated radiotherapy (IMRT) has been introduced for patients with head and neck cancer. The goal of avoiding radiation-induced xerostomia by dose reduction to the parotid glands was achieved in initial case series [539].

Oral application of pilocarpine to the oral mucosa occupied by salivary glands during radiotherapy resulted in a significantly improved salivary flow rate after three months compared to a placebo group [621]. However, this effect did not affect the patients' quality of life. With completed conventional fractionated radiotherapy and pre-existing xerostomia but residual function of individual salivary glands, oral administration of pilocarpine (5-10 mg three times daily) resulted in significant subjective improvement in dry mouth and reduced need for artificial saliva compared to a placebo group [623]. An optimal duration of pilocarpine application could not be determined.

No specific data could be found on the prophylaxis and treatment of radiation damage to the external skin of the head and neck region, as most studies included radiation to the chest region. No evidence was found to suggest that washing during radiotherapy increases acute radiation-induced skin toxicity [643]. Prophylactic application of aloe vera gel or aqueous or sucralfate-containing creams does not reduce the frequency or severity of acute skin toxicity [645],[646], [647] . In a small randomized clinical trial, CAVILON® No-sting Barrier Film (3M®) reduced the duration of moist skin desquamation compared with a 10% glycerin cream [644]. However, the evidence from this study is insufficient to recommend a specific intervention for the prevention or treatment of radiation-induced skin damage.

9.8. Treatment of locoregional recurrence

The most frequent reason for unsuccessful primary tumor treatment and subsequent tumor-related death is locoregional tumor recurrence; it occurs in approximately one fifth of patients with oral cavity carcinoma. The curative therapeutic options available in these cases are repeat surgery (salvage surgery) and/or radio- or radiochemotherapy.

The decision on the appropriate procedure for local tumor recurrence should be made on the basis of the patient's individual situation, taking into account the stage of the tumor recurrence and its potential resectability, the previous treatment, the probable effectiveness of the therapy in weighing its risks and its impact on the quality of life, the general physical condition and, last but not least, the patient's wishes. The therapy decision should be made by the interdisciplinary team of the tumor board after histological recurrence confirmation and re-staging. Patients and their relatives should be informed in detail about the treatment risks and the prospects of success of renewed surgical or conservative therapy, also with regard to a permanent cure, especially taking into account the expected quality of life. In the decision-making process, the possibility of palliative therapy should also be considered.

8.45	**Evidence-based Recommendation**	**checked 2021**
GoR **B**	Salvage surgery should be considered in all patients with a resectable locoregional recurrence after previous radiotherapy or surgery. The procedure should only be performed by an experienced surgical team with extensive reconstruction capabilities and in a facility with an appropriate intensive care facility.	
LoE **3**	[649]; [650]	
	Strong Consensus	

8.46	**Consensus-based Recommendation**	**new 2021**
EC	Salvage lymph node dissection may be foregone if FDG-PET findings are negative and non-necrotic lymph nodes are present on anatomic imaging after primary RCTx. Salvage lymph node dissection may be foregone if FDG-PET findings are negative and non-necrotic lymph nodes are present on anatomic imaging after primary RCTx.	
	Consensus	

8.47	**Evidence-based Recommendation**	**checked 2021**
GoR **B**	In already irradiated patients with a non-resectable locoregional recurrence, a second irradiation with curative intention should be considered. Irradiation should only be performed in an institution with adequate expertise and ideally within a clinical therapy study.	
LoE **3**	[651]; [652]; [653]; [654]; [655]; [656]	
	Strong Consensus	

Background

In a meta-analysis of large retrospective case series, a 5-year survival rate of 39% was determined for the surgical treatment of tumor recurrence after previous irradiation of laryngeal, pharyngeal or oral cavity carcinomas , and of 43.4% specifically for oral cavity carcinoma [649]. The disease-free survival decreases with increasing stage of tumor recurrence [180], [657], whereby a correlation of the treatment success to the original tumor stage could not be found. Likewise, there was no correlation between disease-free survival after salvage therapy and the original, primarily applied treatment modality [649]. In salvage surgery for tumor recurrence, reported complication rates varied from 39-53%, of which 18.5-27% were classified as significant complications and had a lethal outcome in 3.2-5.2% [657], [658]. An increased number of complications was noted with increasing tumor stages [650]. There is insufficient evidence to suggest that complication rates of salvage surgery are higher in previously irradiated patients than in the non-irradiated collective [657], [658]. Depending on the tumor stage, but

not the localization of the recurrence, half of the patients regained their preoperative quality of life [649].

An important therapeutic option is radio- or radiochemotherapy, which can be performed with a high tumor dose if previously treated only surgically. An indication for this procedure is particularly given if the recurrence does not appear resectable or surgery would lead to an unacceptable impairment of quality of life. Even if the recurrence region has already been pre-irradiated, there may be a possibility of re-irradiation. No randomized trials were found that compared overall survival or quality of life after re-irradiation, salvage surgery, or palliative chemotherapy for advanced tumor recurrence in the head and neck region.

Loo et al. [668] studied a cohort of 34 patients with head and neck tumor and cN2 status who had received FDG PET/CT scanning before and 3 months after (sequential) radiochemotherapy (N=27 concurrent cisplatin chemotherapy, N=19 IMRT). Lymph node dissection was performed only in patients with increased FDG-PET avidity. The median follow-up time was 39.1 months. Only one patient had FDG-PET-positive lymph node findings, which turned out to be false positive. The negative predictive value was 100%.

A prospective randomized trial compared FDG-PET/CT-guided follow-up with planned lymph node dissection in radiochemotherapy-treated patients with nodally advanced (cN2/N3) head and neck tumor [669]. After a median follow-up of 36 months, the 2-year overall superiority of the total 564 included patients was 84.9% in the image-guided follow-up group (N=54 lymph node dissections) and 81.5% in the lymph node dissection group (N=221).

In patients with small, early recurrences (T1N0 and T2N0) or second cancers in a previously irradiated region, brachytherapy alone with 60 Gy results in local tumor control of 69-80% and overall survival of 30% at 5 years [659],[660]. Repeat radio- or radiochemotherapy is often offered when there is a non-resectable recurrence and thus no other option for curative intended treatment. Numerous smaller studies with a selected patient population have described 5-year survival rates between 9 and 20% and local tumor control rates of 11-48% [661], [662], [663], [664]. Here, tumor control was significantly better if the second irradiation could be performed with more than 50 Gy [661], [662], [664]. Local side effects on healthy tissue are associated with serious late radiation damage in 9-18% [663],[665], [667] . In large case series, fibrosis of the neck muscles was described in 41%, oral mucosal necrosis in also 41%, trismus in 30% and lethal complications in 11% after secondary radiation [653]. Serious acute radiation toxicity is more likely in patients over 80 years of age, especially in second radiation treatments to the neck [666]. There is evidence that IMRT may help to improve the therapeutic index of second radiation [540].

9.9. Palliative and palliative medical treatment

8.48	Consensus-based Recommendation	checked 2021
EC	Patients with incurable tumor disease but a good general and performance status shall receive palliative platinum-based chemotherapy in combination with cetuximab. Monotherapy should be considered for patients with reduced general condition. Excessive toxicity from combination chemotherapy should be avoided.	
	Consensus	

8.49	Evidence-based Recommendation	checked 2021
GoR **0**	Palliative radiotherapy can be considered in patients with incurable oral cavity carcinoma.	
LoE **3**	[670]	
	Strong Consensus	

8.50	Evidence-based Recommendation	checked 2021
GoR **0**	In patients with incurable oral cavity carcinoma, palliative surgical and/or radiological interventional measures can be considered to ameliorate tumor-associated complications.	
LoE **3**	[671]; [672]; [673]; [674]; [675]; [676]	
	Strong Consensus	

Background 8.48 - 8.50

Oral cavity carcinoma must be considered incurable when

- the locoregional tumor growth has progressed so far that resection is no longer possible for anatomical and/or functional reasons and no curative effect can be expected from radiotherapy either,
- the patient's general condition is so severely reduced that surgical therapy is impossible and the performance of radiotherapy is also ruled out,
- the patient has suffered a locoregional recurrence after radical surgical or conservative therapy has already been performed and salvage therapy (rescue surgery, second radiation treatment) is no longer possible for surgical or radiobiological reasons,
- distant metastases are present.

Patients with a tumour that can no longer be cured have a wide range of physical and psychological concomitant problems that represent an additional challenge for treatment. For this reason, these patients should be given professionally conducted supportive therapy at an early stage.

8.51	**Evidence-based Recommendation**	**new 2021**
GoR **A**	The antibody pembrolizumab, which targets the PD-1 receptor, shall be used in patients with PD-L1-expressing tumor and immune cells (CPS ≥1) as first line monotherapy or in combination with platinum and 5-fluorouracil.	
LoE **1+**		
	Consensus	

8.52	**Evidence-based Recommendation**	**new 2021**
GoR	In patients pathologically lacking PD-L1 expressing tumor or immune cells (CPS<1), the EGRF receptor targeting antibody cetuximab should be used as first line therapy in combination with platinum (preferably cisplatin) and 5-fluorouracil (EXTREME regimen) in the palliative setting in patients in good general condition who no longer qualify for local therapy.	
LoE		
	Strong Consensus	

8.53	**Consensus-based Recommendation**	**new 2021**
EC	After 4-6 cycles of this combination, PD-L1 positive patients shall receive maintenance therapy until progression with pembrolizumab or PD-L1 negative patients with cetuximab.	
	Strong Consensus	

8.54	**Consensus-based Recommendation**	**new 2021**
EC	After failure of platinum-containing first-line therapy with cetuximab, second-line therapy shall be given with a checkpoint inhibitor according to the approval status.	
	Strong Consensus	

8.55	**Consensus-based Recommendation**	**new 2021**
EC	After failure of a platinum-containing first-line therapy with pembrolizumab, a second-line therapy with a taxane, possibly in combination with cetuximab, can be carried out.	
	Consensus	

8.56	**Consensus-based Recommendation**	**new 2021**
EC	After failure of first-line therapy with pembrolizumab as monotherapy, second-line therapy with platinum/5-FU and cetuximab can be given.	
	Strong Consensus	

8.57	**Consensus-based Recommendation**	**new 2021**
EC	A combination of several immunotherapies cannot be recommended in clinical practice and should be further tested in clinical trials.	
	Strong Consensus	

8.58	**Consensus-based Recommendation**	**new 2021**
EC	Cross-sectional imaging (e.g. CT) should be performed every 6 to 12 weeks during ongoing palliative systemic therapy, depending on the line of therapy and the dynamics of the disease.	
	Strong Consensus	

Background

Although palliative chemotherapy is an important treatment option, there are no randomized prospective multicenter trials demonstrating evidence of improved quality of life with this intervention compared with supportive therapy alone. Furthermore, no evidence-based trial exists to demonstrate the benefit of a specific palliative chemotherapy regimen.

In patients with advanced, recurrent, or metastatic head and neck cancer, palliative intent chemotherapy can achieve response rates of 10-35% [689], [691], [692], [693], [695]. Patients with incurable tumor disease but good general and performance status should be assigned to palliative platinum-based chemotherapy in combination with cetuximab. Monotherapy should be considered for patients with reduced general condition. Excessive toxicity from combination chemotherapy should generally be avoided [682]. In a study with high-dose cytarabine in combination with cisplatin/5-FU, a response rate of 57% was reported [696]. It has been clearly demonstrated that especially patients with a better general and performance status benefit from palliative chemotherapy [694].

Chemotherapy with cisplatin alone has been shown to result in longer survival compared to treatment with methotrexate, but has higher toxicity [690]. Although the response rate of palliative chemotherapy can be improved by a combination of different cytostatic drugs there is no evidence for prolonged survival [689], [691], [692], [693], [680]. The improvement in response rate with combination chemotherapy is accompanied by increased hematologic and also general toxicity [691], [692], [693]. While the combination of cisplatin and paclitaxel at three-hour paxlitaxel infusion does not differ from the combination of cisplatin and 5-FU in toxicity, response rate, or achieved survival [697], 24-hour paxlitaxel infusion is associated with excessively increased hematologic toxicity [698].

The combination of the EGFR monoclonal antibody cetuximab with platinum derivatives and 5-fluorouracil has been considered standard therapy in this setting for the past 10 years based on data from the randomized phase III EXTREME trial [701]. This triple combination was the first ever to show a significantly increased response rate, progression-free and overall survival (10.1 vs 7.4 months with a HR of 0.8) compared to platinum in combination with 5-FU and was thus positive in all efficacy parameters. In the overall survival subgroup analysis of this study, the 88 patients with oral cavity carcinoma showed the greatest benefit compared to the other tumor sites oropharynx/hypopharynx and larynx with a HR of 0.42, making the EXTREME protocol particularly recommended for oral cavity carcinomas [701] . The overall survival benefit was also confirmed in the long-term follow-up of this study with a follow-up time of more than 5 years [703]. In addition, quality of life improved during the course of therapy with at most an insignificant increase in toxicity and a reduction in tumor-related symptoms [701], [700]. Maintenance therapy with cetuximab was well tolerated in this phase III study [702]. To date, a predictive biomarker for selecting patients for this therapy has not been identified [702], [699].

Other EGFR antibodies such as panitumumab and zalutumumab or the VEGF antibody bevacizumab failed to match or exceed the data of the EXTREME trial or were too toxic, making cetuximab the only approved EGFR antibody in combination with platinum-containing chemotherapy in first-line palliative therapy of recurrent or metastatic squamous cell carcinoma of the head and neck (r/mSCCHN).

Tyrosine kinase inhibitors such as gefitinib, erlotinib, and afatinib have also failed to demonstrate significant benefit in the palliative systemic treatment of r/mSCCHN, either as monotherapy or in combination with chemotherapy.

Therefore, there has long been no standard of care after progression on or after first-line platinum-containing therapy, particularly after progression on the EXTREME protocol. In this palliative second-line setting, taxanes, methotrexate, or cetuximab have been used in the past based on phase II/III data. If there was a gap of more than 6 months from the previous platinum-containing first-line combination, renewed platinum therapy (possibly also as a combination) was also considered.

It is in this setting that data on the effect of immunotherapies are now available. Here, almost all data in palliative systemic therapy were generated from studies in which oral cavity carcinoma was only a part of the included patients. Check-Mate-141 is a randomized phase III trial of nivolumab, a monoclonal antibody against PD1, in patients with r/mSCCHN and progression under/after platinum-containing chemotherapy within 6 months. In a 2:1 ratio, a total of 361 patients, 48% of whom had oral cavity carcinoma, were randomized to the control arm consisting of either docetaxel, methotrexate, or cetuximab at the discretion of the study site. Regarding the primary endpoint overall survival, immunotherapy (nivolumab) was shown to be superior to the control arm with a median survival of 7.5 vs 5.1 months (HR 0.70 p=0.01, HR 0.73 for oral cavity carcinoma) with a doubling of overall survival at 1 year (36.0 vs 16.6%) [678]. This was also confirmed at 2 years follow-up with 16.9 vs 6.0 % . [679]. The remission rate with nivolumab was higher (13.3 vs 5.8%), but progression-free survival did not improve (median 2.0 vs 2.3 months, HR 0.89 p=0.32). In the 78 patients with progression at or within 6 months of a curative platinum-containing therapy approach, this benefit of nivolumab over the control arm was shown to be [681]. Since this thus palliative first-line setting was not compared against a platinum-containing combination and certainly not against the EXTREME regimen, the value of nivolumab in this setting remains unclear. The 2-year follow-up data showed that both HPV+ and HPV- benefited from immunotherapy with nivolumab, as did PD-L1+ (tumor proportion score TPS >1%) and negative with trend towards PD-L1+. [679]. This benefit in overall survival is greatest

(HR 0.32) for TPS > 50% (approximately 20% of patients). In addition, the significantly lower rate of serious adverse events (13.1 vs 35.1%), the only marginally increased rate of immune-mediated adverse events, and the improved quality of life and symptom control during ongoing therapy and thereafter argue for the use of nivolumab as second-line therapy under or after failure of platinum-containing chemotherapy [678].

A large phase III trial of 882 patients [677]evaluated the administration of pembrolizumab alone or in combination with chemotherapy against cetuximab with chemotherapy for recurrent or metastatic head and neck squamous cell carcinoma. Here, the subgroup of patients with oral cavity carcinoma was approximately 30 %. Pembrolizumab alone showed improved overall survival of 14.9 versus 10.7 months compared with cetuximab in combination with chemotherapy in a population with a CPS score of 20. With a CPS of 1, the survival benefit was 2 months. In combination with chemotherapy, pembrolizumab improved survival by 2.3 months (13.0 versus 10.7 months) over cetuximab with chemotherapy in the overall population, with a benefit of 3.7 months in patients with a CPS score of 20 and 3.2 months in those with a CPS score of 1. Neither pembrolizumab alone nor in combination with chemotherapy improved progression-free survival. Grade 3 or worse adverse events occurred in 55% of patients treated with pembrolizumab alone (164 of 300) and were 85% when combined with chemotherapy (235 of 276 patients). This was consistent with the frequency of adverse events in the group of patients treated with cetuximab in combination with chemotherapy (83%). Lethal adverse events with pembrolizumab occurred in 8% (alone) or 12% (in combination with chemotherapy) and in 10% when cetuximab was given in combination with chemotherapy (see the evidence profile in the guideline report for further details).

Regular cross-sectional imaging should be performed every 12 weeks in patients with r/mSCCHN on ongoing therapy, and every 6 weeks if there are signs of clinical progression, in order to make a timely change in therapy to an effective 2nd line therapy.

As with chemotherapy, there are no evidence-based studies for palliative radiotherapy that can demonstrate the effectiveness of this treatment modality for incurable head and neck cancer. Clinical trials have failed to identify recommendations for optimal dosing or timing of palliative radiotherapy.

In a clinical trial of 505 patients with incurable head and neck carcinoma, short-term palliative radiotherapy of 20 Gy in 5 fractions over 5 days resulted in sustained symptom improvement in 55% of patients [670].

Palliative intent surgical intervention may be warranted if a reduction in tumor mass can be expected to improve symptoms, especially pain reduction, bleeding reduction, or respiratory improvement. However, even for palliative surgical interventions, no studies were identified that showed their evidence in terms of prolongation of life or improvement in quality of life.

Small retrospective studies and clinical experience suggest that palliative surgical and interventional radiological measures such as tracheostomy placement, tumor reduction by laser, embolization, percutaneous endoscopic gastrostomy (PEG placement) and nerve blocks have a firm role in the management of specific tumor-associated problems. Their indication may be for upper airway obstruction, for debridement of necrotically disintegrated, bacterially colonized tumor masses, for bleeding, dysphagia, and pain [683],[684], [685],[686], [687], [688].

10. Aftercare and rehabilitation

10.1. Aftercare

9.1	Consensus-based Recommendation	checked 2021
EC	The maximum follow-up intervals should be 3 months for the 1st and 2nd year and 6 months for the 3rd to 5th year, even if the patient is symptom-free. A structured individual follow-up plan should be established for each patient. The patient's quality of life should be surveyed at regular intervals. After the 5th year, the usual screening measures should be applied.	
	Strong Consensus	

Background

An essential part of the entire therapy is a regular tumor follow-up, which should be carried out, if necessary, interdisciplinary with the attending radiation oncologist and ear, nose and throat specialist as well as in communication with the attending specialist colleague in private practice. The importance of tumor follow-up is evident from the fact that about one fifth of patients with oral cavity carcinoma develop a local tumor recurrence, which occurs in 76% within the first two years; even in the third year after completion of primary treatment, 11% of recurrences still develop [704]. The main goal of tumor follow-up is thus the careful examination of the oral cavity and neck to exclude regrowing tumors, which, according to the results of a retrospective study, lead to symptoms in only 61%, i.e. are not noticed by 39% of patients [704]. Another benefit of tumor follow-up is the detection of metachronous second tumors in the upper aerodigestive tract and lung, which are associated with a similar risk profile as oral cavity carcinoma and occur in 4-33% of patients with carcinomas of the oral cavity and pharynx [194], [195], [196] .

Furthermore, the assessment of the functional follow-up (chewing, speaking and swallowing function), the pain status and the necessity of rehabilitative (speech therapy, swallowing training) or supportive measures (pain therapy, nutrition therapy, physiotherapy, lymphatic drainage) is the task of tumor follow-up. Particularly in patients with incurable tumor disease, but also in cases of functional or aesthetic impairments , it should be examined whether there is a need for psychosocial care. If primary reconstructive measures were not performed during tumor resection and there are disabilities of speech, swallowing and masticatory function, the possibility of secondary reconstruction can be discussed during the follow-up consultation, provided there is no evidence of active tumor activity. The same applies to the question of masticatory rehabilitation by means of prosthetic or implantological measures.

During the tumor follow-up, the health-related quality of life should be regularly observed and should be regularly observed and questioned in a standardized manner. Under certain circumstances, the need for psycho-oncology can be recognized in time and therapy can be initiated in this regard. [716].

The general quality of life of the patients and their psychosocial condition should also be observed and questioned during the entire follow-up. It can be considered certain that a severe depressive mood occurs 2-3 months after diagnosis and, provided there is no recurrence, the quality of life subsequently improves slowly and continuously [705], [706]. Due to these psychological burdens and also the fact that

functions such as eating, drinking, speaking, salivation, taste, smell as well as sexual life no longer have the quality as before the disease, the patients often need social and psychological support [707].

The maximum follow-up intervals are 3 months for the 1st and 2nd year and 6 months for the 3rd to 5th year, even if the patient is free of symptoms. After the 5th year, the usual screening measures should be applied. In the case of special risk constellations or acute complaints, more frequent examinations may be necessary in cooperation with the specialist colleagues in charge. Further information on the procedure for known precursor lesions of the oral mucosa can be found in the corresponding guideline (AWMF 007-092).

The examinations required at each follow-up appointment are the careful and systematic inspection and palpation of the entire oral cavity, oropharynx and neck. Easily obtained and useful clues to the possible presence of tumor recurrence can also be elicited by asking about pain and weight loss [708], [709]. An inexpensive and directly feasible measure for checking the cervical lymph nodes is ultrasound examination. To check the local findings and detect possible secondary tumors, a CT or MRI should be performed at 6-month intervals for the first two years and then every 12 months until the fifth year. If there is a suspicion of locoregional recurrence, distant metastasis, or a second tumor that requires further clarification based on these examinations, PET may be considered [193], [710]. To avoid imaging bias, sampling from the suspicious region should be done only after imaging. There is no evidence that regular chest radiographs or determination of tumor markers in serum have any benefit in tumor follow-up [463], [711], [712], [713], [714] . Prophylactic administration of β-carotene has also not been shown to be justified [715].

The HPV status of the tumor and the patient should not affect tumor follow-up intervals [717]. If the risk of recurrence is high, intensification of tumor follow-up to a 6- to 8-week interval is recommended for the first two years. For the following three years, check-ups can be performed at 3-month intervals [718]. Furthermore, if the risk of recurrence is high, follow-up can be extended beyond the usual 5-year interval or the subsequent screening measures. Factors for a particularly high risk of recurrence include:

- first two years after tumor or lymph node recurrence [718], [719]
- patient age less than 45 years at initial diagnosis
- continued exposure to risk factors such as tobacco or alcohol [720]
- tumor thickness ≥5 mm [721],[722]
- perineural invasion [722], [723], [724], [725], [726]
- high T stage (T3 + T4) [724], [727], [728], [729]
- high pN stage (from N2) [724], [726], [728]
- extracapsular spread [730]
- degree of keratinization of the primary tumor [730]
- high LNR (Lymph node ratio: ratio of positive to negative lymph nodes) [726], [727], [731], [732]

10.2. Kaufunktionelle rehabilitation

9.2	Evidence-based Recommendation	checked 2021
GoR **B**	Patients who have undergone surgery and/or radiation treatment for oral cavity carcinoma should have their chewing ability restored by masticatory rehabilitation with implants or conventional prosthetic treatment. Furthermore, regular dental monitoring should be performed in these patients. Dental-surgical measures should be performed in these patients by specialists experienced in this clinical picture.	
LoE **3**	[261]; [262]; [733]; [734]; [735]; [736]	
	Consensus	

Background 9.2

It is well documented that about 90% of patients with carcinoma in the oral cavity also suffer from caries, periodontal disease or infection of the oral mucosa [739], but are often unaware of the need for dental treatment [740]. Furthermore, it is known that, especially after radiotherapy, there is sometimes considerable damage to the tooth structure and periodontium, and complications after tooth extractions (wound healing disorders, infected osteoradionecrosis of the jaws) can be a considerable problem [267], [268]. It is therefore imperative to give these patients professional dental control and to have any interventions on the irradiated jaw performed exclusively by appropriately trained specialists with surgical expertise [261]. Even under the optimal conditions of continuous dental care, the manageability of patients can be problematic, with 51% of them dropping out of follow-up over time [261].

Since patients are masticatorily disabled after tumor-related tooth and/or jaw section removal and have a significantly lower quality of life than prosthetically restored patients [733], the organization of dental rehabilitation is an important task of tumor aftercare. In this context, prosthetic restoration can be problematic due to the postoperatively altered anatomy and not infrequently requires special commitment on the part of the practitioner. Although the placement of dental implants in the remaining jawbone or in microvascular anastomosed bone grafts has led to a considerable expansion of prosthetic possibilities, an increased implant loss rate in irradiated bone - especially in smokers - must be expected [737], [738]. There is insufficient evidence for a most appropriate prosthetic approach in patients who have undergone surgery and/or radiation for oral cavity carcinoma [736].

On the issue of implant restoration after irradiation of the head and neck region, reference is made to the S3 guideline "Implant restoration for oral rehabilitation associated with head and neck irradiation" (AWMF 007-089).

Background 9.3

The most serious complication for patients who have received radio- or radiochemotherapy for carcinoma of the oral cavity or oropharynx is infected osteoradionecrosis of the jawbone. Its average incidence is reported to be 5% [741]. The risk of osteoradionecrosis increases even further when radiation has been given for tumor invasion of the jawbone [319], [320]. The molar region of the mandible is most commonly affected, and often infected osteoradionecrosis is preceded by tooth

extraction [741]. Radiotherapy of tumour recurrence with total doses above 60 Gy, often in conjunction with chemotherapy, is responsible for infected osteoradionecrosis in 20% of cases [743],[748], [750], [751] . Treatment of this complication ranges from systemic antibiotic therapy to ablation of the infected bone and sequestrotomy to continuity resection of the affected portion of the jaw, with subsequent reconstruction being technically challenging due to previous surgery and radiation [742][749][752]. There is insufficient evidence to support the benefit of hyperbaric oxygen therapy for the prevention or treatment of osteoradionecrosis. A multicenter case-control study showed no benefit of hyperbaric oxygen therapy in patients with osteoradionecrosis when performed without further surgical intervention [744]. A systematic review found only weak evidence for an effect of hyperbaric oxygen therapy in preventing osteoradionecrosis after tooth extractions [746]. Evidence exists for the benefit of hyperbaric oxygen therapy when used additionally as part of a surgical or reconstructive procedure [743] , [745]. Despite clinical observations that hyperbaric oxygen therapy can reduce the loss rate of dental implants [735], a systematic review found no evidence for or against the benefit of such an intervention [747].

9.3	Evidence-based Statement	checked 2021
ST	Infected osteoradionecrosis of the jaws is a serious complication of treatment. There is no evidence of an effect of hyperbaric oxygen therapy alone for the prophylaxis or treatment of this complication. Hyperbaric oxygen therapy may be useful in conjunction with surgical procedures for the prophylaxis or treatment of osteoradionecrosis.	
LoE **3**	[324]; [753]; [741]; [742]; [744]; [746]; [747]	
	Consensus	

10.3. Speech and swallowing rehabilitation

9.4	Evidence-based Recommendation	checked 2021
GoR **B**	Patients with chewing, speaking and swallowing disorders should receive adequate functional therapy. The patients should already be presented to appropriately qualified therapists before the start of treatment if chewing, swallowing and/or speech disorders are to be expected as a consequence of the planned surgical or conservative measures.	
LoE **2+**	[754]; [755]; [756]; [757]; [758]; [759]	
	Strong Consensus	

9.5	Evidence-based Recommendation	checked 2021
GoR **B**	Patients with dysphagia should be submitted to adequate diagnostics, e.g. high-frequency fluroscopy with contrast medium or fiberoptic endoscopy.	
LoE **2+**	[757]; [758]	
	Strong Consensus	

9.6	Evidence-based Recommendation	checked 2021
GoR **B**	Patients who have problems with food intake and speech because of oral cavity carcinoma and/or receive radio/radiochemotherapy should have access to a speech therapist experienced with this condition before, during and after treatment.	
LoE **2+**	[760]	
	Strong Consensus	

Background

Speech, language and swallowing impairments due to tumour or treatment should be assessed by speech therapists, phoniatrists and/or physiotherapists [754].

Any patient who is unable to feed themselves adequately with solid or liquid food or maintain an adequate amount of drink (dysphagia) due to a chewing, transport or swallowing disorder is at significant nutritional risk. Untreated or poorly controlled dysphagia reduces quality of life, interferes with targeted treatment of the tumor, and can lead to life-threatening complications, such as aspiration pneumonia [755]. The risk of aspiration has been reported to be 14% for patients with oral cavity carcinoma [756]. After completion of head and neck radiation, 17 – 36% of patients remain tube dependent, and 10-15% die in 3-5 years from aspiration [764]. Patients who have received radio-chemotherapy for advanced carcinoma of the head and neck suffer aspiration pneumonia in approximately one third [760]. Prophylaxis of this complication is among the most important tasks of dysphagia treatment [761]. Modification of head and body posture during swallowing, for example, can significantly reduce the risk of aspiration [755]. Swallowing therapy should therefore be carried out by adequately trained speech therapists [762], [763].

Diagnostically, high-frequency fluoroscopy or endoscopy can be performed to clarify the risk of aspiration before starting treatment [757].

Fluoroscopy has also been useful in assessing the risk of aspiration pneumonia in patients who have received radio-chemotherapy [760]. At the same time, this method can be used to diagnose recurrence [756]. Likewise, fiberoptic endoscopic evaluation of the swallowing process is a suitable tool for the diagnosis of dysphagia. Secretions and mucus in the larynx/pharynx can be visualized and evaluated. Fiberoptic

endoscopic evaluation can be used for targeted treatment planning. This method is inexpensive and is a reliable alternative to fluorscopy [758].

The aim of speech and swallowing rehabilitation is to bring the mobility of the remaining mucosal structures and the structures of the oral cavity, e.g. tongue, to the achievable optimum and to carry out a structured tracheal cannula management in wearers of a tracheal cannula. This is intended to create the conditions for the best possible communication and food intake. Specially after glossectomy or other major resections, speech therapy has proven to be helpful [759].

Various authors recommend keeping the phases of oral food abstinence as short as possible, since even a 2-week interruption of oral food intake can have negative consequences [765]. For this reason, therapy should be started about 14 days before the start of radio/radiochemotherapy [766]. Patients who are able to resume oral feeding prior to radiotherapy/radiochemotherapy keep the structures elastic during radiation by regular oral movements.

Lymphatic drainage may be useful after completion of radio/radiochemotherapy to treat facial or cervical lymphedema. This treatment should be carried out at a sufficient time interval from the tumour therapy and only by practitioners experienced in this field.

10.4. Nutritional Therapy

9.7	Evidence-based Recommendation	checked 2021
GoR **B**	Patients who are at risk of malnutrition due to tumor or treatment should receive professional nutritional counseling and nutritional therapy at an early stage.	
LoE **2+**	[767]; [768]; [769]; [770]; [771]; [772]	
	Strong Consensus	

Background

Early measures to ensure adequate nutrition, either by placement of a PEG tube or a nasogastric feeding tube, as well as further continuous nutritional counseling and diet modification in case of dysphagia contribute significantly to treatment success and quality of life in patients with head and neck cancer. A retrospective review identified factors according to which patients require professional nutritional counseling and nutritional support [768]. These are:

- alcohol abuse
- involvement of the root of the tongue
- pharyngectomy
- reconstruction with pectoralis major flap
- radiation therapy
- advanced tumor growth
- poorly differentiated tumors

Feeding via a PEG tube has been shown to be safe and effective, but there is no evidence for the appropriate timing of PEG placement [773], [774]. Prophylactic PEG placement

is recommended when intensive radio(chemo)therapy is planned [771]. Compared to the nasogastric feeding tube, which is a foreign body impairing swallowing and speech, the PEG tube is considered more comfortable due to its higher wearing comfort, although it is more often associated with persistent dysphagia and an increased need for pharyngoesophageal dilatations [772]. Further information on nutrition therapy can be found in the S3 guideline "Parenteral nutrition" (AWMF 073-018).

10.5. Psychosocial counselling and care

9.8	Consensus-based Recommendation	checked 2021
EC	Patients with oral cavity carcinoma shall be offered psychosocial care by social workers.	
	Strong Consensus	

9.9	Consensus-based Recommendation	checked 2021
EC	To ensure continuity of psycho-oncological care after inpatient treatment, patients with oral cavity carcinoma shall be informed about further outpatient and aftercare services (cancer counselling centres, established psychotherapists, self-help groups, social counselling).	
	Strong Consensus	

Background

It has been demonstrated that a quarter of all patients with oral cavity carcinoma suffer from anxiety and depression and have difficulty maintaining their quality of life [775], [776]. The complex needs of patients with oral cavity carcinoma necessitate active psychosocial support, which should continue for at least three months after completion of therapy [775], [777]. There are no studies that have examined the clinical benefits of psychosocial therapy, specifically in patients with oral cavity carcinoma, evidence-based. However, the effectiveness of psycho-oncological interventions in cancer patients in general is well established (see S3 guideline Psychooncological diagnosis, counselling and treatment of cancer patients, AWMF 032-052OL). It has not yet been clarified when therapy should be provided by social workers and when by psychologists. However, it is known that 59% of patients want support from a social worker and 22% from a psychologist [778]. There is no evidence based on scientific evidence as to which range of psychosocial support benefits patients with oral cavity carcinoma the most. A systematic review has identified factors that indicate a particular need for psychosocial support before treatment begins [779]. These factors are:

- low level of education
- childlessness
- male gender
- alcohol abuse
- unemployment

Another predictor of increased psychological distress is lack of social support [778]. Common problems expressed by patients relate to social interaction, communication

and fear of lack of economic security. Times of worst psychosocial situation of the patient are diagnosis and start of therapy [780]. Patients with oral cavity carcinoma may experience a renewed loss of quality of life after initial improvement during the first phase of treatment. As part of their inpatient stay, patients should be offered a rehabilitation programme via the social services department.

There are S3 guidelines for supportive therapy and pyschooncological care that are also valid for the treatment of patients with oral cavity carcinoma (see https://www.awmf.org/uploads/tx_szleitlinien/032-054OLl_S3_Supportiv_2017-05.pdf and https://www.leitlinienprogramm-onkologie.de/leitlinien/psychoonkologie/).

11. Quality indicators

Quality indicators are measured variables whose collection serves to assess the quality of the underlying structures, processes or results. Quality indicators are an important instrument of quality management [592]. The aim of their use is the continuous improvement of care by presenting the results of care, critically reflecting on them and, if necessary, improving them. The present selection of quality indicators was prepared according to the methodology of the guideline programme on oncology [593]. For the derivation process, a „Quality Indicators Working Group“ (AG QI) was constituted. This group created the final set of quality indicators based on the existing quality indicators of the 2012 guideline, the strong recommendations (recommendation strength A, „should“) of the updated guideline, the results of the existing quality indicators from the certified head and neck tumor centers of the German Cancer Society[1] and the results of the search for existing national and international quality indicators. The exact procedure and composition of the WG QI are presented in the guideline report.

After a face-to-face meeting and a telephone conference of this WG, a new indicator was adopted (QI 1: R0 situation after curative surgery). Of ten quality indicators existing since 2012 (version 1.0), one indicator was deleted (patients with ear, nose and throat examination to exclude synchronous second tumours). The guidelines thus continue to contain ten quality indicators.

The numerator is always a subset of the denominator.

QIs 1 and 6 can be documented with the basic oncology dataset.

[1] See https://www.krebsgesellschaft.de/jahresberichte.html

Table 5: Quality Indicators

Quality Indicator	Reference Recommendation	Evidence Basis / Additional Information
QI 1: R0 situation after curative surgery		
Enumerator Number of patients with R0 as a result of surgical therapy **Denominator**	In order to exclude synchronous secondary tumors, an examination of the ear, nose and throat - and possibly endoscopy - shall be performed as part of the	Not a recommendation, but derived from a specific guideline objective.

Quality Indicator	Reference Recommendation	Evidence Basis / Additional Information
All patients with first diagnosis of oral cavity carcinoma and resection with curative intention Quality Objective: As often as possible R0 status after completion of curative intended surgical therapy.	primary diagnosis of oral cavity carcinoma.	
QI 2: Imaging techniques and further diagnostics/ Imaging techniques and diagnostics for the detection of metastasis		
Enumerator Number of patients with examination of the region from the skull base to the upper thoracic aperture with CT or MRI to determine the N category **Denominator** All patients with oral cavity carcinoma	**6.10** To determine the N category, the entire region from the skull base to the upper thoracic aperture shall be examined with CT or MRI.	All patients with oral cavity carcinomaRecommended LoE 2+, strong consensus.
QI 3: Imaging and further diagnostics/ Imaging and diagnostics to exclude synchronous second tumours, distant metastases, unknown primary tumours (CUP) and recurrences		
Enumerator Number of patients with chest CT to exclude pulmonary tumor involvement (filia, second carcinoma) **Denominator** All patients with oral cavity carcinoma stage III + IV	**6.13** In patients with advanced oral cavity carcinoma (stage III, IV), a chest CT shall be performed to exclude pulmonary tumor involvement (filia, second carcinoma).	Recommendation LoE 3, strong consensus
QI 4: Biopsy and histopathology		
Enumerator Number of patients for whom the histopathological findings are documented as	**7.4** In correspondence with the clinician, the histopathological report shall describe the exact	Recommendation LoE 2++, strong consensus

Quality Indicator	Reference Recommendation	Evidence Basis / Additional Information
follows: tumour location, macroscopic tumour size, histological tumour type according to WHO, histological tumour grade, depth of invasion, lymph vessel invasion, blood vessel invasion and perineural invasion, locally infiltrated structures, classification pT, details of affected areas and infiltrated structures, R-status. **Denominator** All patients with oral cavity carcinoma and surgery	location of any R+ situation that may be present. The tumour specimen shall be sent to the pathologist with clear designation of the anatomical topography. Suture or color marking may be done for this purpose. The histopathologic findings shall include: Tumor location, macroscopic tumor size, histologic tumor type according to WHO, histologic tumor grade, depth of invasion, lymphatic vessel invasion, blood vessel invasion and perineural invasion, locally infiltrated structures, classification pT, details of affected districts and infiltrated structures, R status.	
QI 5: Treatment recommendations		
Enumerator Number of patients with interdisciplinary treatment after coordination in tumour boards involving the specialist disciplines of oral and maxillofacial surgery, otorhinolaryngology, radiotherapy, oncology, pathology and radiology **Denominator** All patients with oral cavity carcinoma Interdisciplinary treatment was considered very important. The highest possible indicator expression is aimed for	**8.1** The treatment of oral cavity carcinoma shall be carried out in an interdisciplinary manner after coordination of each individual case within tumour boards involving the specialist disciplines of oral and maxillofacial surgery, otorhinolaryngology, radiotherapy, oncology, pathology and radiology.	EK, strong consensus

Quality Indicator	Reference Recommendation	Evidence Basis / Additional Information
QI 6: Treatment recommendations/ cervical lymph node evacuation		
Enumerator Number of patients with elective neck dissection **Denominator** All patients with oral cavity carcinoma and cNO of any T category.	**8.11** Patients with clinically unremarkable lymph node status (cN0) shall undergo elective neck dissection regardless of T category.	Recommendation LoE 3, strong consensus
QI 7: Treatment recommendations/ radiotherapy		
Enumerator Number of patients without interruption of radiotherapy **Denominator** All patients with oral cavity carcinoma and radiotherapy Definition „Interruption“: An interruption occurs if it delays the recommended time to completion of 11 weeks.	**8.27** Interruption of radiotherapy leads to deterioration of tumor control and shall be avoided.	Recommendation LoE 2+, strong consensus
QI 8: Treatment recommendations/ radiotherapy in combination with chemotherapy		
Enumerator Number of patients with postoperative radio- or radiochemotherapy **Denominator** All patients with T3/T4 category, scarce or positive resection margins, perineural or vascular invasion or LK+. Definition „close“ Safety distance: 1-3 mm	**8.35** Postoperative radio- or radiochemotherapy shall be given in cases of advanced T category (T3/T4), scarce or positive resection margins, perineural invasion, vascular invasion, and/or lymph node involvement.	Recommendation LoE 1++, consensus
QI 9: Treatment recommendations/ prevention and treatment of radiation-related side effects		

Quality Indicator	Reference Recommendation	Evidence Basis / Additional Information
Enumerator Number of patients with dental examination before the start of radio- or radiochemotherapy **Denominator** All patients with oral cavity carcinoma and radio- or radiochemotherapy	**8.42** Patients shall receive a dental examination and, if necessary, conservative and/or surgical dental rehabilitation before undergoing radio/radiochemotherapy in the oral cavity to prevent osteoradionecrosis.	EK, strong consensus
QI 10: Aftercare and rehabilitation/ Psychosocial counselling and care		
Enumerator Number of patients with documented offer of psychosocial care by a social worker **Denominator** All patients with oral cavity carcinoma The social worker should communicate the availability of the service to the patient.	**9.8** Patients with oral cavity carcinoma shall be offered psychosocial care by social workers.	EK, strong consensus

12. Appendix

12.1. Overview of changes in version 3.0

Table 6: modified and new recommendations and statements in version 3.0

Version 2.0	Version 3.0
To exclude synchronous second tumours, an ear, nose and throat examination should be performed as part of the primary diagnosis of oral cavity carcinoma, with endoscopy if necessary.	Retained after deletion of the amendment as part of the consultation: An ear, nose and throat examination, endoscopy if necessary, should be performed as part of the primary diagnosis of oral cavity carcinoma to exclude synchronous second tumours.
PET-CT has no value in the primary diagnosis of local	Modified:

Version 2.0	Version 3.0
extension of a known oral cavity carcinoma	In locoregionally advanced tumors, FDG-PET/CT may be performed to exclude distant metastases prior to function-restricting therapeutic measures.
	New: HPV-positive and/or p16-positive oral cavity carcinomas should be treated no differently than alcohol- and nicotine-associated carcinomas.
	New: For maxillary carcinoma, the evidence is insufficient to derive a general recommendation against neck dissection level I-III (SOHND) and for a ,,wait and see" approach.
	New: For cT1cN0 carcinoma of the maxilla, neck dissection level I-III can be waived if localization is limited to alveolar process and hard palate, depth of invasion is less than 3mm, permanent angmaschic follow-up is ensured, and T category is confirmed after histological workup.
	New: There is no robust evidence from clinically controlled trials for the appropriateness of SLN biopsy as a method to avoid elective neck lymph node evacuation.
	New: SLN biopsy can be offered for early, transorally resectable oral cavity carcinomas that do not require a transcervical approach in the same procedure.
	New: If the sentinel lymph node is positive and detection is uncertain, a completion neck dissection should be performed.
	New: Evidence is insufficient at this time to derive a clear formulation for a recommendation for neck dissection level I-III (SOHND) rather than neck dissection level I-V for invasive oral cavity carcinoma with cN1.
	New: In the presence of a cN1 or N1 subgroup, selective neck dissection may be performed only to level III as an alternative to MRND to level V, provided there is no extranodal growth and the neck dissection extends at least one level more caudally than the level of LK metastasis.
	New: For invasive oral cavity carcinoma with LK metastasis in level IIb-III, in terms of incidence of LK recurrence or survival rates,

Version 2.0	Version 3.0
	neither MRND (level I-V) nor SOHND (I-III) has adequate trial evidence of superiority.
	New: Planned bony reconstruction of the maxilla and mandible can be CAD/CAM-assisted. This is especially true for complex(multi-segmental) defects.
	New: In the presence of a pN1 category of pT1 or pT2 squamous cell carcinoma, the indication for adjuvant radio(chemo)therapy can be offered.
	New: Salvage lymph node dissection may be omitted in the presence of negative FDG-PET findings and non-necrotic lymph nodes on anatomic imaging after primary RCTx.
Patients with incurable tumor disease but good general and performance status should receive palliative platinum-based chemotherapy in combination with cetuximab. Monotherapy should be considered for patients with reduced general condition. Excessive toxicity from combination chemotherapy should be avoided.	Modified: Pembrolizumab, an antibody directed against the PD-1 receptor, should be used as first-line monotherapy or in combination with platinum and 5-fluorouracil in patients with PD-L1-expressing tumor and immune cells (CPS ≥1).
	New: In patients pathologically lacking PD-L1-expressing tumor or immune cells (CPS<1), the EGRF receptor-targeting antibody cetuximab should be used as first line therapy in combination with platinum (preferably cisplatin) and 5-fluorouracil (EXTREME regimen) in the palliative setting in patients in good general health who no longer qualify for local therapy.
	New: After 4-6 cycles of this combination, maintenance therapy until progression should be given with pembrolizumab in PD-L1 positive patients or cetuximab in PD-L1 negative patients if the disease is not progressive.
	New:

Version 2.0	Version 3.0
	After failure of first-line platinum-containing therapy with cetuximab, second-line therapy with a checkpoint inhibitor should be given according to approval status.
	New: After failure of first-line platinum-containing therapy with pembrolizumab, second-line therapy with a taxane, in combination with cetuximab if appropriate.
	New: After failure of first-line therapy with pembrolizumab as monotherapy, second-line therapy with platinum/5-FU and cetuximab may be given.
	A combination of multiple immunotherapies cannot be recommended in clinical practice and should be further evaluated in clinical trials.
	Cross-sectional imaging (e.g. CT) should be performed every 6 to 12 weeks during ongoing palliative systemic therapy, depending on the line of therapy and the dynamics of the disease.

12.2. TNM classification

Table 7: T-classification (primary tumor)

T-Classification	Definition
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Largest tumour extension ≤2 cm, depth of invasion (DOI) ≤5 mm
T2	Largest tumour extension ≤2 cm, DOI >5 mm and ≤10 mm OR Tumour >2 cm but ≤4 cm, and DOI ≤10 mm
T3	Largest tumor extension >4cm OR any tumor >10 mm DOI
T4	Infiltration into adjacent structures

Table 8: N classification (regional lymph node metastases)

N classification	Definition
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in solitary ipsilateral lymph node up to 3cm and ENE(-)
N2a	Metastasis in solitary ipsilateral lymph node up to 3 cm and ENE(+); or metastasis in solitary ipsilateral lymph node 3 to 6 cm and ENE(-)
N2b	Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm and ENE(-)
N2c	Metastases in bilateral or contralateral lymph nodes, none greater than 6 cm and ENE(-)
N3a	Metastasis in solitary lymph node greater than 6 cm and ENE(-)
N3b	Metastasis in solitary ipsilateral lymph node greater than 3 cm and ENE(+); OR metastasis in multiple ipsilateral, contralateral OR bilateral lymph nodes, at least one of which is ENE(+); OR metastasis in a solitary contralateral lymph node, 3 cm or smaller and ENE(+)
ENE=extranodal extension: extranodal growth	

Table 9: M-Classification

M-Classification	Definition
MX	Distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastasis(s)

Table 10: R status

R-Status	Definition
RX	Presence of residual tumor cannot be assessed
R0	No residual tumor

R-Status	Definition
R1	Microscopic residual tumor
R2	Macroscopic residual tumor

Table 11: Grading

Grading	Definition
GX	Degree of differentiation cannot be determined
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Table 12: L (lymphatic vessel invasion)

L(lymphatic vessel invasion)	Definition
L0	No lymphatic vessel invasion
L1	Lymphatic vessel invasion

Table 13: V (vein invasion)

V (Vein Invasion)	Definition
V0	Vein invasion not detectable
V1	Vein invasion microscopically detectable
V2	Vein invasion macroscopically detectable

Table 14: Tumor stages according to UICC criteria

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0

Stage	T	N	M
III	T1, T2	N1	M0
	T3	N0, N1	M0
IVA	T1, T2, T3	N2	M0
	T4a	N0, N1, N2	M0
IVB	T4b	any N	M0
	each T	N3	M0
IVC	each T	any N	M1

12.3. Classification of the cervical lymph nodes

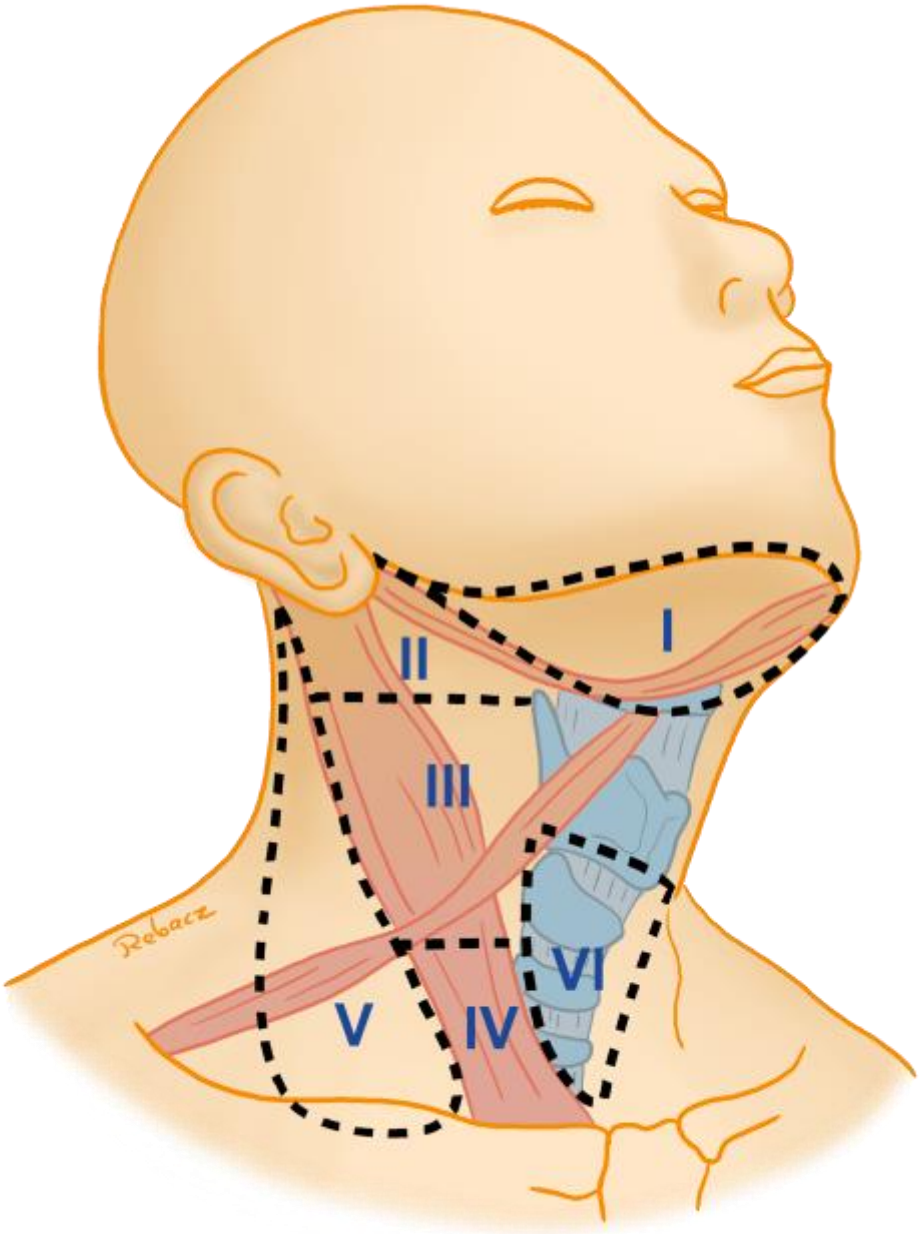

Figure 1: Classification of the cervical lymph nodes according to Robbins

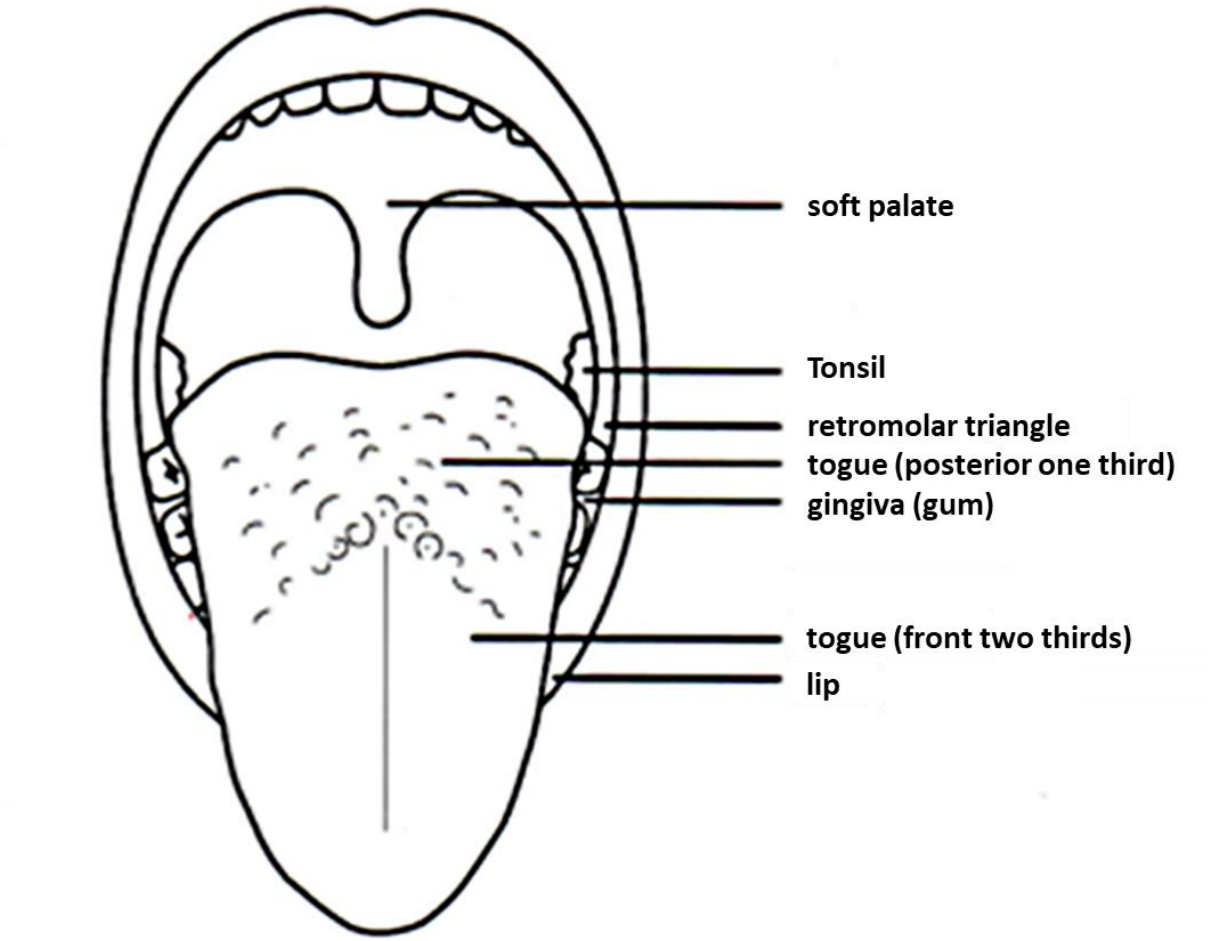

Figure 2: Structure of the oral cavity (a)

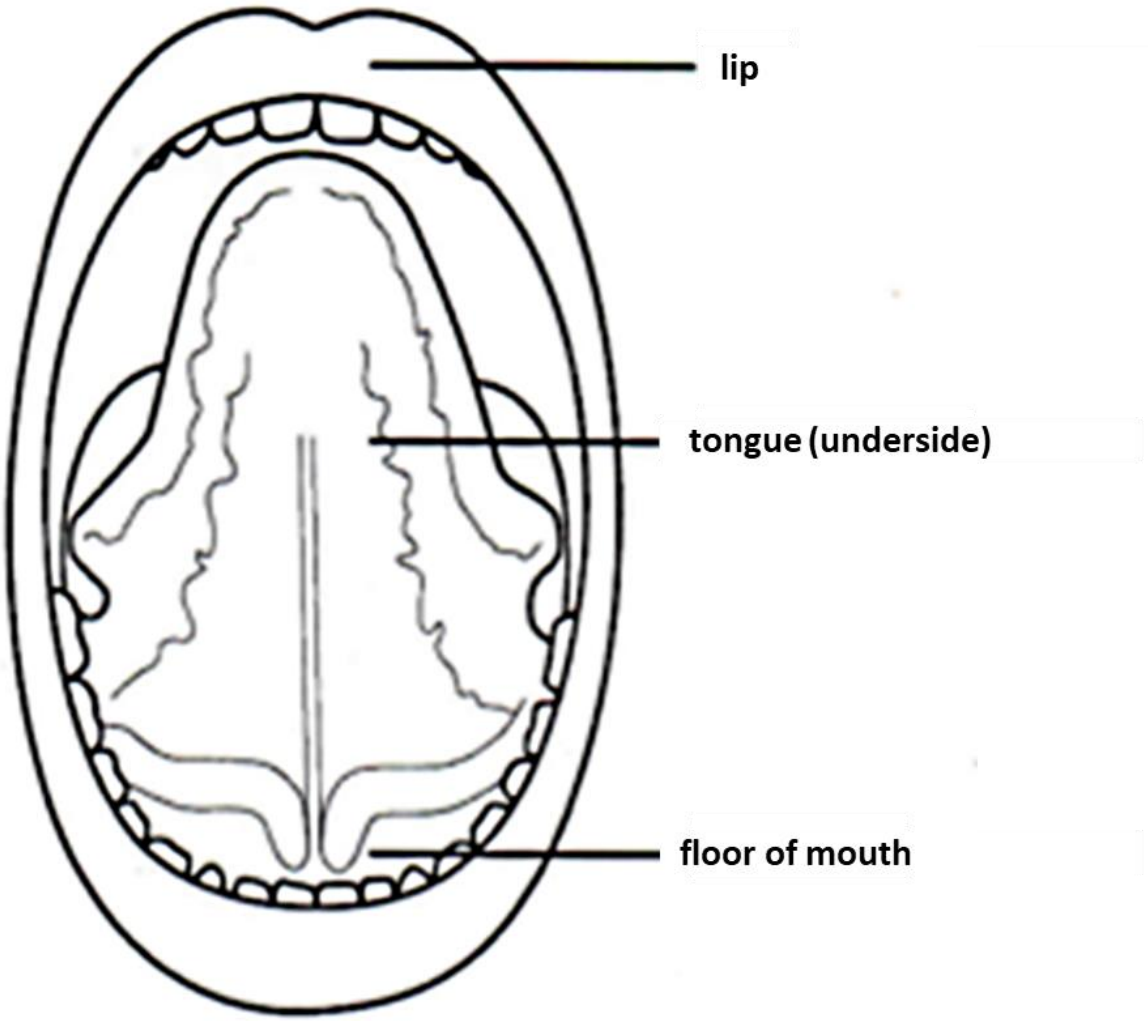

Figure 3: Structure of the oral cavity (b)

13. Evidence tables

14. List of Figures

15. List of Tables

16. Bibliography

1. Lippman, S. M., Spitz, M., Trizna, Z., Benner, S. E., Hong, W. K., Epidemiology, biology, and chemoprevention of aerodigestive cancer. Cancer, 1994. 74(9 Suppl): p. 2719-25.
2. Horowitz, A. M., Canto, M. T., Child, W. L., Maryland adults' perspectives on oral cancer prevention and early detection. J Am Dent Assoc, 2002. 133(8): p. 1058-63.
3. Warnakulasuriya, K. A., Harris, C. K., Scarrott, D. M., Watt, R., Gelbier, S., Peters, T. J., et.al. An alarming lack of public awareness towards oral cancer. Br Dent J, 1999. 187(6): p. 319-22.
4. Vora, A. R., Yeoman, C. M., Hayter, J. P., Alcohol, tobacco and paan use and understanding of oral cancer risk among Asian males in Leicester. Br Dent J, 2000. 188(8): p. 444-51.
5. Scottish Intercollegiate Guidelines Network, SIGN 90: Diagnosis and management of head and neck cancer, 2006.
6. Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften - Ständige Kommission Leitlinien, AWMF-Regelwerk „Leitlinien", 1. Auflage 2012. 2013:, http://www.awmf.org/leitlinien/awmf-regelwerk/awmf-regelwerk.html
7. Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. (GEKID) in Zusammenarbeit mit dem Robert Koch Institut: 5. überarbeitete, aktualisierte Ausgabe, Saarbrücken 2006.
8. Lo, W. L., Kao, S. Y., Chi, L. Y., Wong, Y. K., Chang, R. C., Outcomes of oral squamous cell carcinoma in Taiwan after surgical therapy: factors affecting survival. J Oral Maxillofac Surg, 2003. 61(7): p. 751-8.
9. Howaldt, H. P., Vorast, H., Blecher, J. C., Reicherts, M., Kainz, M., Ergebnisse aus dem DÖSAK Tumorregister. Mund-, Kiefer- und Gesichtschirurgie, 2000. 4 Suppl 1: p. S216-25.
10. Talamini, R., Bosetti, C., La Vecchia, C., Dal Maso, L., Levi, F., Bidoli, E., et.al. Combined effect of tobacco and alcohol on laryngeal cancer risk: a case-control study. Cancer Causes Control, 2002. 13(10): p. 957-64.
11. La Vecchia, C., Tavani, A., Franceschi, S., Levi, F., Corrao, G., Negri, E., Epidemiology and prevention of oral cancer. Oral Oncol, 1997. 33(5): p. 302-12.
12. Figuero Ruiz, E., Carretero Pelaez, M. A., Cerero Lapiedra, R., Esparza Gomez, G., Moreno Lopez, L. A., Effects of the consumption of alcohol in the oral cavity: relationship with oral cancer. Med Oral, 2004. 9(1): p. 14-23.
13. Cruz, G. D., Le Geros, R. Z., Ostroff, J. S., Hay, J. L., Kenigsberg, H., Franklin, D. M., Oral cancer knowledge, risk factors and characteristics of subjects in a large oral cancer screening program. J Am Dent Assoc, 2002. 133(8): p. 1064-71; quiz 1094.
14. Hay, J. L., Ostroff, J. S., Cruz, G. D., LeGeros, R. Z., Kenigsberg, H., Franklin, D. M., Oral cancer risk perception among participants in an oral cancer screening program. Cancer Epidemiol Biomarkers Prev, 2002. 11(2): p. 155-8.
15. Altieri, A., Bosetti, C., Talamini, R., Gallus, S., Franceschi, S., Levi, F., et.al. Cessation of smoking and drinking and the risk of laryngeal cancer. Br J Cancer, 2002. 87(11): p. 1227-9.
16. Balaram, P., Sridhar, H., Rajkumar, T., Vaccarella, S., Herrero, R., Nandakumar, A., et.al. Oral cancer in southern India: the influence of smoking, drinking, paan-chewing and oral hygiene. Int J Cancer, 2002. 98(3): p. 440-5.
17. Cheng, Y. J., Hildesheim, A., Hsu, M. M., Chen, I. H., Brinton, L. A., Levine, P. H., et.al. Cigarette smoking, alcohol consumption and risk of nasopharyngeal carcinoma in Taiwan. Cancer Causes Control, 1999. 10(3): p. 201-7.
18. De Boer, M. F., Van den Borne, B., Pruyn, J. F., Ryckman, R. M., Volovics, L., Knegt, P. P., et.al. Psychosocial and physical correlates of survival and recurrence in patients with head and neck carcinoma: results of a 6-year longitudinal study. Cancer, 1998. 83(12): p. 2567-79.
19. de Graeff, A., de Leeuw, J. R., Ros, W. J., Hordijk, G. J., Blijham, G. H., Winnubst, J. A., Sociodemographic factors and quality of life as prognostic indicators in head and neck cancer. Eur J Cancer, 2001. 37(3): p. 332-9.

20. De Stefani, E., Boffetta, P., Oreggia, F., Mendilaharsu, M., Deneo-Pellegrini, H., Smoking patterns and cancer of the oral cavity and pharynx: a case-control study in Uruguay. Oral Oncol, 1998. 34(5): p. 340-6.
21. Franceschi, S., Levi, F., La Vecchia, C., Conti, E., Dal Maso, L., Barzan, L., et.al. Comparison of the effect of smoking and alcohol drinking between oral and pharyngeal cancer. Int J Cancer, 1999. 83(1): p. 1-4.
22. Lissowska, J., Pilarska, A., Pilarski, P., Samolczyk-Wanyura, D., Piekarczyk, J., Bardin-Mikollajczak, A., et.al. Smoking, alcohol, diet, dentition and sexual practices in the epidemiology of oral cancer in Poland. Eur J Cancer Prev, 2003. 12(1): p. 25-33.
23. Perea-Milla Lopez, E., Minarro-Del Moral, R. M., Martinez-Garcia, C., Zanetti, R., Rosso, S., Serrano, S., et.al. Lifestyles, environmental and phenotypic factors associated with lip cancer: a case-control study in southern Spain. Br J Cancer, 2003. 88(11): p. 1702-7.
24. Critchley, J. A., Unal, B., Health effects associated with smokeless tobacco: a systematic review. Thorax, 2003. 58(5): p. 435-43.
25. Bagnardi, V., Blangiardo, M., La Vecchia, C., Corrao, G., Alcohol consumption and the risk of cancer: a meta-analysis. Alcohol Res Health, 2001. 25(4): p. 263-70.
26. Corrao, G., Bagnardi, V., Zambon, A., Arico, S., Exploring the dose-response relationship between alcohol consumption and the risk of several alcohol-related conditions: a meta-analysis. Addiction, 1999. 94(10): p. 1551-73.
27. Perea-Milla Lopez, E., Minarro-Del Moral, R. M., Martinez-Garcia, C., Zanetti, R., Rosso, S., Serrano, S., et.al. Lifestyles, environmental and phenotypic factors associated with lip cancer: a case-control study in southern Spain. Br J Cancer, 2003. 88(11): p. 1702-7.
28. Critchley, J. A., Unal, B., Health effects associated with smokeless tobacco: a systematic review. Thorax, 2003. 58(5): p. 435-43.
29. Corrao, G., Bagnardi, V., Zambon, A., Arico, S., Exploring the dose-response relationship between alcohol consumption and the risk of several alcohol-related conditions: a meta-analysis. Addiction, 1999. 94(10): p. 1551-73.
30. Bosetti, C., Gallus, S., Trichopoulou, A., Talamini, R., Franceschi, S., Negri, E., et.al. Influence of the Mediterranean diet on the risk of cancers of the upper aerodigestive tract. Cancer Epidemiol Biomarkers Prev, 2003. 12(10): p. 1091-4.
31. Bosetti, C., Talamini, R., Levi, F., Negri, E., Franceschi, S., Airoldi, L., et.al. Fried foods: a risk factor for laryngeal cancer?. Br J Cancer, 2002. 87(11): p. 1230-3.
32. Levi, F., Pasche, C., Lucchini, F., Chatenoud, L., Jacobs, D. R., Jr., La Vecchia, C., Refined and whole grain cereals and the risk of oral, oesophageal and laryngeal cancer. Eur J Clin Nutr, 2000. 54(6): p. 487-9.
33. Oreggia, F., De Stefani, E., Boffetta, P., Brennan, P., Deneo-Pellegrini, H., Ronco, A. L., Meat, fat and risk of laryngeal cancer: a case-control study in Uruguay. Oral Oncol, 2001. 37(2): p. 141-5.
34. Bosetti, C., La Vecchia, C., Talamini, R., Negri, E., Levi, F., Fryzek, J., et.al. Energy, macronutrients and laryngeal cancer risk. Ann Oncol, 2003. 14(6): p. 907-12.
35. Uzcudun, A. E., Retolaza, I. R., Fernandez, P. B., Sanchez Hernandez, J. J., Grande, A. G., Garcia, A. G., et.al. Nutrition and pharyngeal cancer: results from a case-control study in Spain. Head Neck, 2002. 24(9): p. 830-40.
36. Franceschi, S., Favero, A., Conti, E., Talamini, R., Volpe, R., Negri, E., et.al. Food groups, oils and butter, and cancer of the oral cavity and pharynx. Br J Cancer, 1999. 80(3-4): p. 614-20.
37. De Stefani, E., Oreggia, F., Boffetta, P., Deneo-Pellegrini, H., Ronco, A., Mendilaharsu, M., Tomatoes, tomato-rich foods, lycopene and cancer of the upper aerodigestive tract: a case-control in Uruguay. Oral Oncol, 2000. 36(1): p. 47-53.
38. Bosetti, C., La Vecchia, C., Talamini, R., Negri, E., Levi, F., Dal Maso, L., et.al. Food groups and laryngeal cancer risk: a case-control study from Italy and Switzerland. Int J Cancer, 2002. 100(3): p. 355-60.

39. Tavani, A., Pelucchi, C., Parpinel, M., Negri, E., Franceschi, S., Levi, F., et.al. n-3 polyunsaturated fatty acid intake and cancer risk in Italy and Switzerland. Int J Cancer, 2003. 105(1): p. 113-6.
40. Talamini, R., Bosetti, C., La Vecchia, C., Dal Maso, L., Levi, F., Bidoli, E., et.al. Combined effect of tobacco and alcohol on laryngeal cancer risk: a case-control study. Cancer Causes Control, 2002. 13(10): p. 957-64.
41. Dahlstrom, K. R., Adler-Storthz, K., Etzel, C. J., Liu, Z., Dillon, L., El-Naggar, A. K., et.al. Human papillomavirus type 16 infection and squamous cell carcinoma of the head and neck in never-smokers: a matched pair analysis. Clin Cancer Res, 2003. 9(7): p. 2620-6.
42. Herrero, R., Castellsague, X., Pawlita, M., Lissowska, J., Kee, F., Balaram, P., et.al. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. J Natl Cancer Inst, 2003. 95(23): p. 1772-83.
43. Cruz, G. D., Le Geros, R. Z., Ostroff, J. S., Hay, J. L., Kenigsberg, H., Franklin, D. M., Oral cancer knowledge, risk factors and characteristics of subjects in a large oral cancer screening program. J Am Dent Assoc, 2002. 133(8): p. 1064-71; quiz 1094.
44. Castellsague, X., Alemany, L., Quer, M., Halec, G., Quiros, B., Tous, S., et.al. HPV Involvement in Head and Neck Cancers: Comprehensive Assessment of Biomarkers in 3680 Patients. J Natl Cancer Inst, 2016. 108(6): p. djv403., https://www.ncbi.nlm.nih.gov/pubmed/26823521
45. Chung, C. H., Zhang, Q., Kong, C. S., Harris, J., Fertig, E. J., Harari, P. M., et.al. p16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. J Clin Oncol, 2014. 32(35): p. 3930-8., https://www.ncbi.nlm.nih.gov/pubmed/25267748
46. Duray, A., Descamps, G., Decaestecker, C., Remmelink, M., Sirtaine, N., Lechien, J., et.al. Human papillomavirus DNA strongly correlates with a poorer prognosis in oral cavity carcinoma. Laryngoscope, 2012. 122(7): p. 1558-65., https://www.ncbi.nlm.nih.gov/pubmed/22532307
47. Elango, K. J., Suresh, A., Erode, E. M., Subhadradevi, L., Ravindran, H. K., Iyer, S. K., et.al. Role of human papilloma virus in oral tongue squamous cell carcinoma. Asian Pac J Cancer Prev, 2011. 12(4): p. 889-96., https://www.ncbi.nlm.nih.gov/pubmed/21790221
48. Fakhry, C., Westra, W. H., Wang, S. J., van Zante, A., Zhang, Y., Rettig, E., et.al. The prognostic role of sex, race, and human papillomavirus in oropharyngeal and nonoropharyngeal head and neck squamous cell cancer. Cancer, 2017. 123(9): p. 1566-1575., https://www.ncbi.nlm.nih.gov/pubmed/28241096
49. Anantharaman, D., Gheit, T., Waterboer, T., Abedi-Ardekani, B., Carreira, C., McKay-Chopin, S., et.al. Human papillomavirus infections and upper aero-digestive tract cancers: the ARCAGE study. J Natl Cancer Inst, 2013. 105(8): p. 536-45., https://www.ncbi.nlm.nih.gov/pubmed/23503618
50. Hubbers, C. U., Akgul, B., HPV and cancer of the oral cavity. Virulence, 2015. 6(3): p. 244-8., https://www.ncbi.nlm.nih.gov/pubmed/25654476
51. Isayeva, T., Li, Y., Maswahu, D., Brandwein-Gensler, M., Human papillomavirus in non-oropharyngeal head and neck cancers: a systematic literature review. Head Neck Pathol, 2012. 6 Suppl 1: p. S104-20., https://www.ncbi.nlm.nih.gov/pubmed/22782230
52. Kozomara, R., Jovic, N., Magic, Z., Brankovic-Magic, M., Minic, V., p53 mutations and human papillomavirus infection in oral squamous cell carcinomas: correlation with overall survival. J Craniomaxillofac Surg, 2005. 33(5): p. 342-8., https://www.ncbi.nlm.nih.gov/pubmed/16129609
53. Dahlstrom, K. R., Adler-Storthz, K., Etzel, C. J., Liu, Z., Dillon, L., El-Naggar, A. K., et.al. Human papillomavirus type 16 infection and squamous cell carcinoma of the head and neck in never-smokers: a matched pair analysis. Clin Cancer Res, 2003. 9(7): p. 2620-6.
54. van der Waal, I., Scully, C., Oral cancer: comprehending the condition, causes, controversies, control and consequences. 6. Co-morbidities. Dent Update, 2011. 38(4): p. 283-4.

55. Kreimer, A. R., Johansson, M., Waterboer, T., Kaaks, R., Chang-Claude, J., Drogen, D., et.al. Evaluation of human papillomavirus antibodies and risk of subsequent head and neck cancer. J Clin Oncol, 2013. 31(21): p. 2708-15., https://www.ncbi.nlm.nih.gov/pubmed/23775966
56. Kreimer, A. R., Johansson, M., Yanik, E. L., Katki, H. A., Check, D. P., Lang Kuhs, K. A., et.al. Kinetics of the Human Papillomavirus Type 16 E6 Antibody Response Prior to Oropharyngeal Cancer. J Natl Cancer Inst, 2017. 109(8):, https://www.ncbi.nlm.nih.gov/pubmed/28376197
57. Axell, T., Hypersensitivity of the oral mucosa: clinics and pathology. Acta Odontol Scand, 2001. 59(5): p. 315-9.
58. Lassen, P., Primdahl, H., Johansen, J., Kristensen, C. A., Andersen, E., Andersen, L. J., et.al. Impact of HPV-associated p16-expression on radiotherapy outcome in advanced oropharynx and non-oropharynx cancer. Radiother Oncol, 2014. 113(3): p. 310-6., https://www.ncbi.nlm.nih.gov/pubmed/25544647
59. Macfarlane, G. J., Boyle, P., Scully, C., Oral cancer in Scotland: changing incidence and mortality. BMJ, 1992. 305(6862): p. 1121-3.
60. Anderson, K. S., Wallstrom, G., Langseth, H., Posner, M., Cheng, J. N., Alam, R., et.al. Pre-diagnostic dynamic HPV16 IgG seropositivity and risk of oropharyngeal cancer. Oral Oncol, 2017. 73: p. 132-137., https://www.ncbi.nlm.nih.gov/pubmed/28939065
61. Lee, L. A., Huang, C. G., Liao, C. T., Lee, L. Y., Hsueh, C., Chen, T. C., et.al. Human papillomavirus-16 infection in advanced oral cavity cancer patients is related to an increased risk of distant metastases and poor survival. PLoS One, 2012. 7(7): p. e40767., https://www.ncbi.nlm.nih.gov/pubmed/22808258
62. Department of Dental Services. Screening for oral cancer., London: Royal College of Surgeons of England. 1994.
63. Li, H., Torabi, S. J., Yarbrough, W. G., Mehra, S., Osborn, H. A., Judson, B., Association of Human Papillomavirus Status at Head and Neck Carcinoma Subsites With Overall Survival. JAMA Otolaryngol Head Neck Surg, 2018. 144(6): p. 519-525., https://www.ncbi.nlm.nih.gov/pubmed/29801040
64. British Dental Association, Opportunistic oral cancer screening. BDA occasional paper, 2000. 6:
65. Elahi, A., Zheng, Z., Park, J., Eyring, K., McCaffrey, T., Lazarus, P., The human OGG1 DNA repair enzyme and its association with orolaryngeal cancer risk. Carcinogenesis, 2002. 23(7): p. 1229-34.
66. Elahi, A., Bendaly, J., Zheng, Z., Muscat, J. E., Richie, J. P., Jr., Schantz, S. P., et.al. Detection of UGT1A10 polymorphisms and their association with orolaryngeal carcinoma risk. Cancer, 2003. 98(4): p. 872-80.
67. Cheng, L., Sturgis, E. M., Eicher, S. A., Spitz, M. R., Wei, Q., Expression of nucleotide excision repair genes and the risk for squamous cell carcinoma of the head and neck. Cancer, 2002. 94(2): p. 393-7.
68. Zheng, Y., Shen, H., Sturgis, E. M., Wang, L. E., Eicher, S. A., Strom, S. S., et.al. Cyclin D1 polymorphism and risk for squamous cell carcinoma of the head and neck: a case-control study. Carcinogenesis, 2001. 22(8): p. 1195-9.
69. Lingen, M. W., Xiao, W., Schmitt, A., Jiang, B., Pickard, R., Kreinbrink, P., et.al. Low etiologic fraction for high-risk human papillomavirus in oral cavity squamous cell carcinomas. Oral Oncol, 2013. 49(1): p. 1-8., https://www.ncbi.nlm.nih.gov/pubmed/22841678
70. Zheng, Z., Park, J. Y., Guillemette, C., Schantz, S. P., Lazarus, P., Tobacco carcinogen-detoxifying enzyme UGT1A7 and its association with orolaryngeal cancer risk. J Natl Cancer Inst, 2001. 93(18): p. 1411-8.
71. Herrero, R., Castellsague, X., Pawlita, M., Lissowska, J., Kee, F., Balaram, P., et.al. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. J Natl Cancer Inst, 2003. 95(23): p. 1772-83.
72. Miller, C. S., Johnstone, B. M., Human papillomavirus as a risk factor for oral squamous cell carcinoma: a meta-analysis, 1982-1997. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2001. 91(6): p. 622-35., https://www.ncbi.nlm.nih.gov/pubmed/11402272

73. Ndiaye, C., Mena, M., Alemany, L., Arbyn, M., Castellsague, X., Laporte, L., et.al. HPV DNA, E6/E7 mRNA, and p16INK4a detection in head and neck cancers: a systematic review and meta-analysis. Lancet Oncol, 2014. 15(12): p. 1319-31., https://www.ncbi.nlm.nih.gov/pubmed/25439690
74. Reuschenbach, M., Kansy, K., Garbe, K., Vinokurova, S., Flechtenmacher, C., Toth, C., et.al. Lack of evidence of human papillomavirus-induced squamous cell carcinomas of the oral cavity in southern Germany. Oral Oncol, 2013. 49(9): p. 937-942., https://www.ncbi.nlm.nih.gov/pubmed/23608471
75. Saraiya, M., Unger, E. R., Thompson, T. D., Lynch, C. F., Hernandez, B. Y., Lyu, C. W., et.al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. J Natl Cancer Inst, 2015. 107(6): p. djv086., https://www.ncbi.nlm.nih.gov/pubmed/25925419
76. Schwartz, S. R., Yueh, B., McDougall, J. K., Daling, J. R., Schwartz, S. M., Human papillomavirus infection and survival in oral squamous cell cancer: a population-based study. Otolaryngol Head Neck Surg, 2001. 125(1): p. 1-9., https://www.ncbi.nlm.nih.gov/pubmed/11458206
77. Syrjanen, S., Lodi, G., von Bultzingslowen, I., Aliko, A., Arduino, P., Campisi, G., et.al. Human papillomaviruses in oral carcinoma and oral potentially malignant disorders: a systematic review. Oral Dis, 2011. 17 Suppl 1: p. 58-72., https://www.ncbi.nlm.nih.gov/pubmed/21382139
78. von Knebel Doeberitz, M., The causal role of human papillomavirus infections in non-anogenital cancers. It's time to ask for the functional evidence. Int J Cancer, 2016. 139(1): p. 9-11., https://www.ncbi.nlm.nih.gov/pubmed/26999772
79. Yete, S., D'Souza, W., Saranath, D., High-Risk Human Papillomavirus in Oral Cancer: Clinical Implications. Oncology, 2018. 94(3): p. 133-141., https://www.ncbi.nlm.nih.gov/pubmed/29241220
80. Cruz, G. D., Le Geros, R. Z., Ostroff, J. S., Hay, J. L., Kenigsberg, H., Franklin, D. M., Oral cancer knowledge, risk factors and characteristics of subjects in a large oral cancer screening program. J Am Dent Assoc, 2002. 133(8): p. 1064-71; quiz 1094.
81. Zafereo, M. E., Xu, L., Dahlstrom, K. R., Viamonte, C. A., El-Naggar, A. K., Wei, Q., et.al. Squamous cell carcinoma of the oral cavity often overexpresses p16 but is rarely driven by human papillomavirus. Oral Oncol, 2016. 56: p. 47-53., https://www.ncbi.nlm.nih.gov/pubmed/27086486
82. Pitiphat, W., Diehl, S. R., Laskaris, G., Cartsos, V., Douglass, C. W., Zavras, A. I., Factors associated with delay in the diagnosis of oral cancer. J Dent Res, 2002. 81(3): p. 192-7.
83. Jones, T. M., Hargrove, O., Lancaster, J., Fenton, J., Shenoy, A., Roland, N. J., Waiting times during the management of head and neck tumours. J Laryngol Otol, 2002. 116(4): p. 275-9.
84. Hollows, P., McAndrew, P. G., Perini, M. G., Delays in the referral and treatment of oral squamous cell carcinoma. Br Dent J, 2000. 188(5): p. 262-5.
85. West Midlands Health Technology Assessment Collaboration (WMHTAC). The effectiveness of Toludine Blue Dye as an adjunct to oral cancer screening in general dental practice: Report 24. University of Birmingham: Department of Public Health & Epidemiology; 2000.
86. Kujan, O., Glenny, A. M., Duxbury, A. J., Thakker, N., Sloan, P., Screening programmes for the early detection and prevention of oral cancer. Cochrane Database Syst Rev, 2003. p. CD004150.
87. Humphris, G. M., Freeman, R., Clarke, H. M., Risk perception of oral cancer in smokers attending primary care: a randomised controlled trial. Oral Oncol, 2004. 40(9): p. 916-24.
88. Horowitz, A. M., Canto, M. T., Child, W. L., Maryland adults' perspectives on oral cancer prevention and early detection. J Am Dent Assoc, 2002. 133(8): p. 1058-63.
89. Warnakulasuriya, K. A., Harris, C. K., Scarrott, D. M., Watt, R., Gelbier, S., Peters, T. J., et.al. An alarming lack of public awareness towards oral cancer. Br Dent J, 1999. 187(6): p. 319-22.
90. Vora, A. R., Yeoman, C. M., Hayter, J. P., Alcohol, tobacco and paan use and understanding of oral cancer risk among Asian males in Leicester. Br Dent J, 2000. 188(8): p. 444-51.

91. Humphris, G. M., Ireland, R. S., Field, E. A., Randomised trial of the psychological effect of information about oral cancer in primary care settings. Oral Oncol, 2001. 37(7): p. 548-52.
92. Humphris, G. M., Ireland, R. S., Field, E. A., Immediate knowledge increase from an oral cancer information leaflet in patients attending a primary health care facility: a randomised controlled trial. Oral Oncol, 2001. 37(1): p. 99-102.
93. Hay, J. L., Ostroff, J. S., Cruz, G. D., LeGeros, R. Z., Kenigsberg, H., Franklin, D. M., Oral cancer risk perception among participants in an oral cancer screening program. Cancer Epidemiol Biomarkers Prev, 2002. 11(2): p. 155-8.
94. Kerawala, C. J., Bisase, B., Lee, J., The use of examination under anaesthesia and panendoscopy in patients presenting with oral cavity and oropharyngeal squamous cell carcinoma. Ann R Coll Surg Engl, 2009. 91(7): p. 609-12., https://www.ncbi.nlm.nih.gov/pubmed/19686610
95. Pitiphat, W., Diehl, S. R., Laskaris, G., Cartsos, V., Douglass, C. W., Zavras, A. I., Factors associated with delay in the diagnosis of oral cancer. J Dent Res, 2002. 81(3): p. 192-7.
96. Noor, A., Stepan, L., Kao, S. S., Dharmawardana, N., Ooi, E. H., Hodge, J. C., et.al. Reviewing indications for panendoscopy in the investigation of head and neck squamous cell carcinoma. J Laryngol Otol, 2018. 132(10): p. 901-905., https://www.ncbi.nlm.nih.gov/pubmed/30289089
97. Day, G. L., Blot, W. J., Second primary tumors in patients with oral cancer. Cancer, 1992. 70(1): p. 14-9.
98. Day, T. A., Davis, B. K., Gillespie, M. B., Joe, J. K., Kibbey, M., Martin-Harris, B., et.al. Oral cancer treatment. Curr Treat Options Oncol, 2003. 4(1): p. 27-41.
99. de Vries, N., Van der Waal, I., Snow, G. B., Multiple primary tumours in oral cancer. Int J Oral Maxillofac Surg, 1986. 15(1): p. 85-7.
100. Rodriguez-Bruno, K., Ali, M. J., Wang, S. J., Role of panendoscopy to identify synchronous second primary malignancies in patients with oral cavity and oropharyngeal squamous cell carcinoma. Head Neck, 2011. 33(7): p. 949-53., https://www.ncbi.nlm.nih.gov/pubmed/21674670
101. Chow, Tam-Lin, Lee, Daniel Tai-Yam, Choi, Chi-Yee, Chan, Tony Tung-Fei, Lam, Siu-Ho, Prediction of simultaneous esophageal lesions in head and neck squamous cell carcinoma: a multivariate analysis. Archives of Otolaryngology—Head & Neck Surgery, 2009. 135(9): p. 882-5.
102. Fielding, David, Agnew, Julienne, Wright, David, Hodge, Robert, Autofluorescence improves pretreatment mucosal assessment in head and neck cancer patients. Otolaryngology - Head & Neck Surgery, 2010. 142(3 Suppl 1): p. S20-6.
103. Kesting, Marco Rainer, Schurr, Christian, Robitzky, Luisa, Steinstraesser, Lars, Nieberler, Markus, Baurecht, Hansjorg, et.al. Results of esophagogastroduodenoscopy in patients with oral squamous cell carcinoma—value of endoscopic screening: 10-year experience. Journal of Oral & Maxillofacial Surgery, 2009. 67(8): p. 1649-55.
104. Kesting, Marco Rainer, Robitzky, Luisa, Al-Benna, Sammy, Steinstraesser, Lars, Baurecht, Hansjorg, Wolff, Klaus-Dietrich, et.al. Bronchoscopy screening in primary oral squamous cell carcinoma: a 10-year experience. British Journal of Oral & Maxillofacial Surgery, 2009. 47(4): p. 279-83.
105. Lee, C. T., Chang, C. Y., Lee, Y. C., Tai, C. M., Wang, W. L., Tseng, P. H., et.al. Narrow-band imaging with magnifying endoscopy for the screening of esophageal cancer in patients with primary head and neck cancers. Endoscopy, 2010. 42(8): p. 613-9.
106. Sharma, S. J., Linke, J. J., Kroll, T., Wuerdemann, N., Klussmann, J. P., Guntinas-Lichius, O., et.al. Rigid Triple Endoscopy Improves Clinical Staging of Primary Head and Neck Cancer. Oncol Res Treat, 2018. 41(1-2): p. 35-38., https://www.ncbi.nlm.nih.gov/pubmed/29402786
107. Takenaka, Ryuta, Kawahara, Yoshiro, Okada, Hiroyuki, Hori, Keisuke, Inoue, Masafumi, Kawano, Seiji, et.al. Narrow-band imaging provides reliable screening for esophageal malignancy in patients with head and neck cancers. American Journal of Gastroenterology, 2009. 104(12): p. 2942-8.

108. Scottish Executive Health Department, Scottish Referral Guidelines for Suspected CancerScottish Executive Health Department, 2002.
109. Vergez, S., Moriniere, S., Dubrulle, F., Salaun, P. Y., De Mones, E., Bertolus, C., et.al. Initial staging of squamous cell carcinoma of the oral cavity, larynx and pharynx (excluding nasopharynx). Part I: Locoregional extension assessment: 2012 SFORL guidelines. Eur Ann Otorhinolaryngol Head Neck Dis, 2013. 130(1): p. 39-45., https://www.ncbi.nlm.nih.gov/pubmed/23347771
110. Wolmark, N., Mamounas, E. P., Baehner, F. L., Butler, S. M., Tang, G., Jamshidian, F., et.al. Prognostic Impact of the Combination of Recurrence Score and Quantitative Estrogen Receptor Expression (ESR1) on Predicting Late Distant Recurrence Risk in Estrogen Receptor-Positive Breast Cancer After 5 Years of Tamoxifen: Results From NRG Oncology/National Surgical Adjuvant Breast and Bowel Project B-28 and B-14. J Clin Oncol, 2016. 34(20): p. 2350-8., https://www.ncbi.nlm.nih.gov/pubmed/27217450
111. Leslie, A., Fyfe, E., Guest, P., Goddard, P., Kabala, J. E., Staging of squamous cell carcinoma of the oral cavity and oropharynx: a comparison of MRI and CT in T- and N-staging. J Comput Assist Tomogr, 1999. 23(1): p. 43-9.
112. Kaanders, J. H., Hordijk, G. J., Carcinoma of the larynx: the Dutch national guideline for diagnostics, treatment, supportive care and rehabilitation. Radiother Oncol, 2002. 63(3): p. 299-307.
113. Imaizumi, A., Yoshino, N., Yamada, I., Nagumo, K., Amagasa, T., Omura, K., et.al. A potential pitfall of MR imaging for assessing mandibular invasion of squamous cell carcinoma in the oral cavity. Ajnr: American Journal of Neuroradiology, 2006. 27(1): p. 114-22.
114. Bolzoni, Andrea, Cappiello, Johnny, Piazza, Cesare, Peretti, Giorgio, Maroldi, Roberto, Farina, Davide, et.al. Diagnostic accuracy of magnetic resonance imaging in the assessment of mandibular involvement in oral-oropharyngeal squamous cell carcinoma: a prospective study. Archives of Otolaryngology—Head & Neck Surgery, 2004. 130(7): p. 837-43.
115. Van Cann, E. M., Koole, R., Oyen, W. J. G., de Rooy, J. W. J., de Wilde, P. C., Slootweg, P. J., et.al. Assessment of mandibular invasion of squamous cell carcinoma by various modes of imaging: constructing a diagnostic algorithm. International Journal of Oral & Maxillofacial Surgery, 2008. 37(6): p. 535-41.
116. Hendrikx, A. W. F., Maal, T., Dieleman, F., Van Cann, E. M., Merkx, M. A. W., Cone-beam CT in the assessment of mandibular invasion by oral squamous cell carcinoma: results of the preliminary study. International Journal of Oral and Maxillofacial Surgery, 2010. 39 (5): p. 436-439.
117. Goerres, Gerhard W., Schmid, Daniel T., Schuknecht, Bernhard, Eyrich, Gerold K., Bone invasion in patients with oral cavity cancer: comparison of conventional CT with PET/CT and SPECT/CT.[Erratum appears in Radiology. 2006 Apr;239(1):303]. Radiology, 2005. 237(1): p. 281-7.
118. Yen, Tzu-Chen, Chang, Joseph Tung-Chieh, Ng, Shu-Hang, Chang, Yu-Chen, Chan, Sheng-Chieh, Wang, Hung-Ming, et.al. Staging of untreated squamous cell carcinoma of buccal mucosa with 18F-FDG PET: comparison with head and neck CT/MRI and histopathology. Journal of Nuclear Medicine, 2005. 46(5): p. 775-81.
119. Hafidh, M. A., Lacy, P. D., Hughes, J. P., Duffy, G., Timon, C. V., Evaluation of the impact of addition of PET to CT and MR scanning in the staging of patients with head and neck carcinomas. European Archives of Oto-Rhino-Laryngology, 2006. 263(9): p. 853-9.
120. Wax, M. K., Myers, L. L., Gona, J. M., Husain, S. S., Nabi, H. A., The role of positron emission tomography in the evaluation of the N-positive neck. Otolaryngol Head Neck Surg, 2003. 129(3): p. 163-7.
121. Krabbe, Christiaan A., Dijkstra, Pieter U., Pruim, Jan, van der Laan, Bernard F. M., van der Wal, Jacqueline E., Gravendeel, Joost P., et.al. FDG PET in oral and oropharyngeal cancer. Value for confirmation of N0 neck and detection of occult metastases. Oral Oncology, 2008. 44(1): p. 31-6.

122. Nahmias, Claude, Carlson, Eric R., Duncan, Lisa D., Blodgett, Todd M., Kennedy, Jason, Long, Misty J., et.al. Positron emission tomography/computerized tomography (PET/CT) scanning for preoperative staging of patients with oral/head and neck cancer. Journal of Oral & Maxillofacial Surgery, 2007. 65(12): p. 2524-35.
123. Seitz, Oliver, Chambron-Pinho, Nicole, Middendorp, Markus, Sader, Rober, Mack, Martin, Vogl, Thomas J., et.al. 18F-Fluorodeoxyglucose-PET/CT to evaluate tumor, nodal disease, and gross tumor volume of oropharyngeal and oral cavity cancer: comparison with MR imaging and validation with surgical specimen. Neuroradiology, 2009. 51(10): p. 677-86.
124. Kyzas, P. A., Evangelou, E., Denaxa-Kyza, D., Ioannidis, J. P., 18F-fluorodeoxyglucose positron emission tomography to evaluate cervical node metastases in patients with head and neck squamous cell carcinoma: a meta-analysis. J Natl Cancer Inst, 2008. 100(10): p. 712-20.
125. Wilson JA, editor, Effective head and neck cancer management: consensus documentBritish Association of Otorhinolaryngologists, Head and Neck Surgeons, 1998.
126. Leslie, A., Fyfe, E., Guest, P., Goddard, P., Kabala, J. E., Staging of squamous cell carcinoma of the oral cavity and oropharynx: a comparison of MRI and CT in T- and N-staging. J Comput Assist Tomogr, 1999. 23(1): p. 43-9.
127. Kaanders, J. H., Hordijk, G. J., Carcinoma of the larynx: the Dutch national guideline for diagnostics, treatment, supportive care and rehabilitation. Radiother Oncol, 2002. 63(3): p. 299-307.
128. Van Cann, E. M., Koole, R., Oyen, W. J., de Rooy, J. W., de Wilde, P. C., Slootweg, P. J., et.al. Assessment of mandibular invasion of squamous cell carcinoma by various modes of imaging: constructing a diagnostic algorithm. Int J Oral Maxillofac Surg, 2008. 37(6): p. 535-41., https://www.ncbi.nlm.nih.gov/pubmed/18406107
129. Imaizumi, A., Yoshino, N., Yamada, I., Nagumo, K., Amagasa, T., Omura, K., et.al. A potential pitfall of MR imaging for assessing mandibular invasion of squamous cell carcinoma in the oral cavity. Ajnr: American Journal of Neuroradiology, 2006. 27(1): p. 114-22.
130. Bolzoni, Andrea, Cappiello, Johnny, Piazza, Cesare, Peretti, Giorgio, Maroldi, Roberto, Farina, Davide, et.al. Diagnostic accuracy of magnetic resonance imaging in the assessment of mandibular involvement in oral-oropharyngeal squamous cell carcinoma: a prospective study. Archives of Otolaryngology—Head & Neck Surgery, 2004. 130(7): p. 837-43.
131. Goerres, Gerhard W., Schmid, Daniel T., Schuknecht, Bernhard, Eyrich, Gerold K., Bone invasion in patients with oral cavity cancer: comparison of conventional CT with PET/CT and SPECT/CT.[Erratum appears in Radiology. 2006 Apr;239(1):303]. Radiology, 2005. 237(1): p. 281-7.
132. Yen, Tzu-Chen, Chang, Joseph Tung-Chieh, Ng, Shu-Hang, Chang, Yu-Chen, Chan, Sheng-Chieh, Wang, Hung-Ming, et.al. Staging of untreated squamous cell carcinoma of buccal mucosa with 18F-FDG PET: comparison with head and neck CT/MRI and histopathology. Journal of Nuclear Medicine, 2005. 46(5): p. 775-81.
133. Hafidh, M. A., Lacy, P. D., Hughes, J. P., Duffy, G., Timon, C. V., Evaluation of the impact of addition of PET to CT and MR scanning in the staging of patients with head and neck carcinomas. European Archives of Oto-Rhino-Laryngology, 2006. 263(9): p. 853-9.
134. Wax, M. K., Myers, L. L., Gona, J. M., Husain, S. S., Nabi, H. A., The role of positron emission tomography in the evaluation of the N-positive neck. Otolaryngol Head Neck Surg, 2003. 129(3): p. 163-7.
135. Krabbe, Christiaan A., Dijkstra, Pieter U., Pruim, Jan, van der Laan, Bernard F. M., van der Wal, Jacqueline E., Gravendeel, Joost P., et.al. FDG PET in oral and oropharyngeal cancer. Value for confirmation of N0 neck and detection of occult metastases. Oral Oncology, 2008. 44(1): p. 31-6.
136. Nahmias, Claude, Carlson, Eric R., Duncan, Lisa D., Blodgett, Todd M., Kennedy, Jason, Long, Misty J., et.al. Positron emission tomography/computerized tomography (PET/CT) scanning for preoperative staging of patients with oral/head and neck cancer. Journal of Oral & Maxillofacial Surgery, 2007. 65(12): p. 2524-35.

137. Seitz, Oliver, Chambron-Pinho, Nicole, Middendorp, Markus, Sader, Rober, Mack, Martin, Vogl, Thomas J., et.al. 18F-Fluorodeoxyglucose-PET/CT to evaluate tumor, nodal disease, and gross tumor volume of oropharyngeal and oral cavity cancer: comparison with MR imaging and validation with surgical specimen. Neuroradiology, 2009. 51(10): p. 677-86.
138. Rao, L. P., Das, S. R., Mathews, A., Naik, B. R., Chacko, E., Pandey, M., Mandibular invasion in oral squamous cell carcinoma: investigation by clinical examination and orthopantomogram. International Journal of Oral & Maxillofacial Surgery, 2004. 33(5): p. 454-7.
139. Vidiri, A., Ruscito, P., Pichi, B., Pellini, R., Covello, R., Sperduti, I., et.al. Oral cavity and base of the tongue tumors. Correlation between clinical, MRI and pathological staging of primary tumor. Journal of Experimental and Clinical Cancer Research, 2007. 26 (4): p. 575-582.
140. Vidiri, Antonello, Guerrisi, Antonino, Pellini, Raul, Manciocco, Valentina, Covello, Renato, Mattioni, Oreste, et.al. Multi-detector row computed tomography (MDCT) and magnetic resonance imaging (MRI) in the evaluation of the mandibular invasion by squamous cell carcinomas (SCC) of the oral cavity. Correlation with pathological data. Journal of Experimental & Clinical Cancer Research, 2010. 29: p. 73.
141. Babin, E., Desmonts, C., Hamon, M., Benateau, H., Hitier, M., PET/CT for assessing mandibular invasion by intraoral squamous cell carcinomas. Clinical Otolaryngology, 2008. 33(1): p. 47-51.
142. Baek, Chung-Hwan, Chung, Man Ki, Son, Young-Ik, Choi, Joon Young, Kim, Hyung-Jin, Yim, Yoo Jeong, et.al. Tumor volume assessment by 18F-FDG PET/CT in patients with oral cavity cancer with dental artifacts on CT or MR images. Journal of Nuclear Medicine, 2008. 49(9): p. 1422-8.
143. Pauleit, Dirk, Zimmermann, Andre, Stoffels, Gabriele, Bauer, Dagmar, Risse, Jorn, Fluss, Michael O., et.al. 18F-FET PET compared with 18F-FDG PET and CT in patients with head and neck cancer. Journal of Nuclear Medicine, 2006. 47(2): p. 256-61.
144. Roh, Jong-Lyel, Yeo, Nam-Kyung, Kim, Jae Seung, Lee, Jeong Hyun, Cho, Kyung-Ja, Choi, Seung-Ho, et.al. Utility of 2-[18F] fluoro-2-deoxy-D-glucose positron emission tomography and positron emission tomography/computed tomography imaging in the preoperative staging of head and neck squamous cell carcinoma. Oral Oncology, 2007. 43(9): p. 887-93.
145. Wiener, Edzard, Pautke, Christoph, Link, Thomas M., Neff, Andreas, Kolk, Andreas, Comparison of 16-slice MSCT and MRI in the assessment of squamous cell carcinoma of the oral cavity. European Journal of Radiology, 2006. 58(1): p. 113-8.
146. Gu, Dong Hyeon, Yoon, Dae Young, Park, Chan Hee, Chang, Suk Ki, Lim, Kyoung Ja, Seo, Young Lan, et.al. CT, MR, (18)F-FDG PET/CT, and their combined use for the assessment of mandibular invasion by squamous cell carcinomas of the oral cavity. Acta Radiologica, 2010. 51(10): p. 1111-9.
147. Dammann, Florian, Horger, Marius, Mueller-Berg, Marcus, Schlemmer, Heinz, Claussen, Claus D., Hoffman, Juergen, et.al. Rational diagnosis of squamous cell carcinoma of the head and neck region: comparative evaluation of CT, MRI, and 18FDG PET.[Erratum appears in AJR Am J Roentgenol. 2005 Jun;184(6):1968]. AJR, 2005. 184(4): p. 1326-31.
148. Wiener, Edzard, Pautke, Christoph, Link, Thomas M., Neff, Andreas, Kolk, Andreas, Comparison of 16-slice MSCT and MRI in the assessment of squamous cell carcinoma of the oral cavity. European Journal of Radiology, 2006. 58(1): p. 113-8.
149. van den Brekel, M. W., Castelijns, J. A., Stel, H. V., Golding, R. P., Meyer, C. J., Snow, G. B., Modern imaging techniques and ultrasound-guided aspiration cytology for the assessment of neck node metastases: a prospective comparative study. Eur Arch Otorhinolaryngol, 1993. 250(1): p. 11-7.
150. Ng, Shu-Hang, Yen, Tzu-Chen, Liao, Chun-Ta, Chang, Joseph Tung-Chieh, Chan, Sheng-Chieh, Ko, Sheung-Fat, et.al. 18F-FDG PET and CT/MRI in oral cavity squamous cell carcinoma: a prospective study of 124 patients with histologic correlation. Journal of Nuclear Medicine, 2005. 46(7): p. 1136-43.

151. Ng, Shu-Hang, Yen, Tzu-Chen, Chang, Joseph Tung-Chieh, Chan, Sheng-Chieh, Ko, Sheung-Fat, Wang, Hung-Ming, et.al. Prospective study of [18F]fluorodeoxyglucose positron emission tomography and computed tomography and magnetic resonance imaging in oral cavity squamous cell carcinoma with palpably negative neck. Journal of Clinical Oncology, 2006. 24(27): p. 4371-6.
152. Sumi, Misa, Kimura, Yasuo, Sumi, Tadateru, Nakamura, Takashi, Diagnostic performance of MRI relative to CT for metastatic nodes of head and neck squamous cell carcinomas. Journal of Magnetic Resonance Imaging, 2007. 26(6): p. 1626-33.
153. Takes, R. P., Righi, P., Meeuwis, C. A., Manni, J. J., Knegt, P., Marres, H. A., et.al. The value of ultrasound with ultrasound-guided fine-needle aspiration biopsy compared to computed tomography in the detection of regional metastases in the clinically negative neck. Int J Radiat Oncol Biol Phys, 1998. 40(5): p. 1027-32.
154. Stokkel, M. P., ten Broek, F. W., Hordijk, G. J., Koole, R., van Rijk, P. P., Preoperative evaluation of patients with primary head and neck cancer using dual-head 18fluorodeoxyglucose positron emission tomography. Ann Surg, 2000. 231(2): p. 229-34.
155. Adams, S., Baum, R. P., Stuckensen, T., Bitter, K., Hor, G., Prospective comparison of 18F-FDG PET with conventional imaging modalities (CT, MRI, US) in lymph node staging of head and neck cancer. Eur J Nucl Med, 1998. 25(9): p. 1255-60.
156. Kim, S. Y., Roh, J. L., Kim, J. S., Ryu, C. H., Lee, J. H., Cho, K. J., et.al. Utility of FDG PET in patients with squamous cell carcinomas of the oral cavity. European Journal of Surgical Oncology, 2008. 34(2): p. 208-15.
157. Schwartz, David L., Ford, Eric, Rajendran, Joseph, Yueh, Bevan, Coltrera, Marc D., Virgin, Jeffery, et.al. FDG-PET/CT imaging for preradiotherapy staging of head-and-neck squamous cell carcinoma. International Journal of Radiation Oncology, Biology, Physics, 2005. 61(1): p. 129-36.
158. Gencoglu, U., Guneren, E., Gozu, A., Ozsoy, Z., Vural, G., The coherence between fine needle aspiration cytology and histopathology of palpable neck nodes in lower lip carcinoma patients. European Journal of Plastic Surgery, 2003. 26 (2): p. 82-84.
159. Roh, Jong-Lyel, Yeo, Nam-Kyung, Kim, Jae Seung, Lee, Jeong Hyun, Cho, Kyung-Ja, Choi, Seung-Ho, et.al. Utility of 2-[18F] fluoro-2-deoxy-D-glucose positron emission tomography and positron emission tomography/computed tomography imaging in the preoperative staging of head and neck squamous cell carcinoma. Oral Oncology, 2007. 43(9): p. 887-93.
160. Balogova, S., Perie, S., Kerrou, K., Grahek, D., Montravers, F., Angelard, B., et.al. Prospective comparison of FDG and FET PET/CT in patients with head and neck squamous cell carcinoma. Molecular Imaging & Biology, 2008. 10(6): p. 364-73.
161. Jeong, Han-Sin, Baek, Chung-Hwan, Son, Young-Ik, Ki Chung, Man, Kyung Lee, Dong, Young Choi, Joon, et.al. Use of integrated 18F-FDG PET/CT to improve the accuracy of initial cervical nodal evaluation in patients with head and neck squamous cell carcinoma. Head & Neck, 2007. 29(3): p. 203-10.
162. Schwartz, David L., Ford, Eric, Rajendran, Joseph, Yueh, Bevan, Coltrera, Marc D., Virgin, Jeffery, et.al. FDG-PET/CT imaging for preradiotherapy staging of head-and-neck squamous cell carcinoma. International Journal of Radiation Oncology, Biology, Physics, 2005. 61(1): p. 129-36.
163. Gencoglu, U., Guneren, E., Gozu, A., Ozsoy, Z., Vural, G., The coherence between fine needle aspiration cytology and histopathology of palpable neck nodes in lower lip carcinoma patients. European Journal of Plastic Surgery, 2003. 26 (2): p. 82-84.
164. Schroeder, Ursula, Dietlein, Markus, Wittekindt, Claus, Ortmann, Monika, Stuetzer, Hartmut, Vent, Julia, et.al. Is there a need for positron emission tomography imaging to stage the N0 neck in T1-T2 squamous cell carcinoma of the oral cavity or oropharynx?. Annals of Otology, Rhinology & Laryngology, 2008. 117(11): p. 854-63.

165. Nakamoto, Yuji, Tamai, Ken, Saga, Tsuneo, Higashi, Tatsuya, Hara, Tadashi, Suga, Tsuyoshi, et.al. Clinical value of image fusion from MR and PET in patients with head and neck cancer. Molecular Imaging & Biology, 2009. 11(1): p. 46-53.
166. Jeong, H. S., Baek, C. H., Son, Y. I., Cho, D. Y., Man, K. C., Min, J. Y., et.al. Sentinel lymph node radiolocalization with 99mTc filtered tin colloid in clinically node-negative squamous cell carcinomas of the oral cavity. Journal of Korean Medical Science, 2006. 21 (5): p. 865-870.
167. Pentenero, Monica, Cistaro, Angela, Brusa, Mario, Ferraris, Maria Maddalena, Pezzuto, Carla, Carnino, Riccardo, et.al. Accuracy of 18F-FDG-PET/CT for staging of oral squamous cell carcinoma. Head & Neck, 2008. 30(11): p. 1488-96.
168. Wensing, Bart M., Vogel, Wouter V., Marres, Henri A. M., Merkx, Matthias A. W., Postema, Ernst J., Oyen, Wim J. G., et.al. FDG-PET in the clinically negative neck in oral squamous cell carcinoma.[Erratum appears in Laryngoscope. 2006 Jul;116(7 Pt 1):1302]. Laryngoscope, 2006. 116(5): p. 809-13.
169. Yamazaki, Yutaka, Saitoh, Masaaki, Notani, Ken-ichi, Tei, Kanchu, Totsuka, Yasunori, Takinami, Shu-ichi, et.al. Assessment of cervical lymph node metastases using FDG-PET in patients with head and neck cancer. Annals of Nuclear Medicine, 2008. 22(3): p. 177-84.
170. Piao, Yongnan, Bold, Bayarkhuu, Tayier, Abulajiang, Ishida, Ryuji, Omura, Ken, Okada, Norihiko, et.al. Evaluation of 18F-FDG PET/CT for diagnosing cervical nodal metastases in patients with oral cavity or oropharynx carcinoma. Oral Surgery Oral Medicine Oral Pathology Oral Radiology & Endodontics, 2009. 108(6): p. 933-8.
171. Hohlweg-Majert, Bettina, Metzger, Marc C., Voss, Pit J., Holzle, Frank, Wolff, Klaus-Dietrich, Schulze, Dirk, Preoperative cervical lymph node size evaluation in patients with malignant head/neck tumors: comparison between ultrasound and computer tomography. Journal of Cancer Research & Clinical Oncology, 2009. 135(6): p. 753-9.
172. Thomsen, J. B., Sorensen, J. A., Grupe, P., Karstoft, J., Krogdahl, A., Staging N0 oral cancer: lymphoscintigraphy and conventional imaging. Acta Radiologica, 2005. 46(5): p. 492-6.
173. To, E. W. H., Tsang, W. M., Cheng, J., Lai, E., Pang, P., Ahuja, A. T., et.al. Is neck ultrasound necessary for early stage oral tongue carcinoma with clinically N0 neck?. Dento-Maxillo-Facial Radiology, 2003. 32(3): p. 156-9.
174. Borgemeester, Maarten C., van den Brekel, Michiel W. M., van Tinteren, Harm, Smeele, Ludi E., Pameijer, Frank A., van Velthuysen, Marie-Louise F., et.al. Ultrasound-guided aspiration cytology for the assessment of the clinically N0 neck: factors influencing its accuracy. Head & Neck, 2008. 30(11): p. 1505-13.
175. Brouwer, Jolijn, de Bree, Remco, Comans, Emile F. I., Castelijns, Jonas A., Hoekstra, Otto S., Leemans, C. Rene, Positron emission tomography using [18F]fluorodeoxyglucose (FDG-PET) in the clinically negative neck: is it likely to be superior?. European Archives of Oto-Rhino-Laryngology, 2004. 261(9): p. 479-83.
176. van den Brekel, M. W., Castelijns, J. A., Snow, G. B., Diagnostic evaluation of the neck. Otolaryngol Clin North Am, 1998. 31(4): p. 601-20.
177. Dammann, Florian, Horger, Marius, Mueller-Berg, Marcus, Schlemmer, Heinz, Claussen, Claus D., Hoffman, Juergen, et.al. Rational diagnosis of squamous cell carcinoma of the head and neck region: comparative evaluation of CT, MRI, and 18FDG PET.[Erratum appears in AJR Am J Roentgenol. 2005 Jun;184(6):1968]. AJR, 2005. 184(4): p. 1326-31.
178. Ng, Shu-Hang, Yen, Tzu-Chen, Chang, Joseph Tung-Chieh, Chan, Sheng-Chieh, Ko, Sheung-Fat, Wang, Hung-Ming, et.al. Prospective study of [18F]fluorodeoxyglucose positron emission tomography and computed tomography and magnetic resonance imaging in oral cavity squamous cell carcinoma with palpably negative neck. Journal of Clinical Oncology, 2006. 24(27): p. 4371-6.
179. Takes, R. P., Righi, P., Meeuwis, C. A., Manni, J. J., Knegt, P., Marres, H. A., et.al. The value of ultrasound with ultrasound-guided fine-needle aspiration biopsy compared to

computed tomography in the detection of regional metastases in the clinically negative neck. Int J Radiat Oncol Biol Phys, 1998. 40(5): p. 1027-32.
180. Stokkel, M. P., ten Broek, F. W., Hordijk, G. J., Koole, R., van Rijk, P. P., Preoperative evaluation of patients with primary head and neck cancer using dual-head 18fluorodeoxyglucose positron emission tomography. Ann Surg, 2000. 231(2): p. 229-34.
181. Adams, S., Baum, R. P., Stuckensen, T., Bitter, K., Hor, G., Prospective comparison of 18F-FDG PET with conventional imaging modalities (CT, MRI, US) in lymph node staging of head and neck cancer. Eur J Nucl Med, 1998. 25(9): p. 1255-60.
182. Arunachalam, P. S., Putnam, G., Jennings, P., Messersmith, R., Robson, A. K., Role of computerized tomography (CT) scan of the chest in patients with newly diagnosed head and neck cancers. Clin Otolaryngol Allied Sci, 2002. 27(12383307): p. 409-411.
183. Andrle, J., Schartinger, V. H., Schwentner, I., Deibl, M., Sprinzl, G. M., Initial staging examinations for head and neck squamous cell carcinoma: are they appropriate?. J Laryngol Otol, 2009. 123(8): p. 885-8.
184. Ghosh, Samit K., Roland, Nicholas J., Kumar, Aman, Tandon, Sankalap, Lancaster, Jeffrey L., Jackson, Shaun R., et.al. Detection of synchronous lung tumors in patients presenting with squamous cell carcinoma of the head and neck. Head & Neck, 2009. 31(12): p. 1563-70.
185. Loh, Kwok Seng, Brown, Dale H., Baker, James T., Gilbert, Ralph W., Gullane, Patrick J., Irish, Jonathan C., A rational approach to pulmonary screening in newly diagnosed head and neck cancer. Head & Neck, 2005. 27(11): p. 990-4.
186. Nakamoto, Yuji, Tamai, Ken, Saga, Tsuneo, Higashi, Tatsuya, Hara, Tadashi, Suga, Tsuyoshi, et.al. Clinical value of image fusion from MR and PET in patients with head and neck cancer. Molecular Imaging & Biology, 2009. 11(1): p. 46-53.
187. Bongers, Vivian, Hobbelink, Monique G., van Rijk, Peter P., Hordijk, Gert-Jan, Cost-effectiveness of dual-head 18F-fluorodeoxyglucose PET for the detection of recurrent laryngeal cancer. Cancer Biother Radiopharm, 2002. 17(12136522): p. 303-306.
188. Lonneux, M., Lawson, G., Ide, C., Bausart, R., Remacle, M., Pauwels, S., Positron emission tomography with fluorodeoxyglucose for suspected head and neck tumor recurrence in the symptomatic patient. Laryngoscope, 2000. 110(10983949): p. 1493-1497.
189. Kyzas, P. A., Evangelou, E., Denaxa-Kyza, D., Ioannidis, J. P., 18F-fluorodeoxyglucose positron emission tomography to evaluate cervical node metastases in patients with head and neck squamous cell carcinoma: a meta-analysis. J Natl Cancer Inst, 2008. 100(10): p. 712-20.
190. Arunachalam, P. S., Putnam, G., Jennings, P., Messersmith, R., Robson, A. K., Role of computerized tomography (CT) scan of the chest in patients with newly diagnosed head and neck cancers. Clin Otolaryngol Allied Sci, 2002. 27(12383307): p. 409-411.
191. Ghosh, Samit K., Roland, Nicholas J., Kumar, Aman, Tandon, Sankalap, Lancaster, Jeffrey L., Jackson, Shaun R., et.al. Detection of synchronous lung tumors in patients presenting with squamous cell carcinoma of the head and neck. Head & Neck, 2009. 31(12): p. 1563-70.
192. Bongers, Vivian, Hobbelink, Monique G., van Rijk, Peter P., Hordijk, Gert-Jan, Cost-effectiveness of dual-head 18F-fluorodeoxyglucose PET for the detection of recurrent laryngeal cancer. Cancer Biother Radiopharm, 2002. 17(12136522): p. 303-306.
193. Lonneux, M., Lawson, G., Ide, C., Bausart, R., Remacle, M., Pauwels, S., Positron emission tomography with fluorodeoxyglucose for suspected head and neck tumor recurrence in the symptomatic patient. Laryngoscope, 2000. 110(10983949): p. 1493-1497.
194. Haughey, B. H., Gates, G. A., Arfken, C. L., Harvey, J., Meta-analysis of second malignant tumors in head and neck cancer: the case for an endoscopic screening protocol. Ann Otol Rhinol Laryngol, 1992. 101(2 Pt 1): p. 105-12.
195. de Bree, R., Deurloo, E. E., Snow, G. B., Leemans, C. R., Screening for distant metastases in patients with head and neck cancer. Laryngoscope, 2000. 110(3 Pt 1): p. 397-401.

196. Warner, Giles C., Cox, Graham J., Evaluation of chest radiography versus chest computed tomography in screening for pulmonary malignancy in advanced head and neck cancer. J Otolaryngol, 2003. 32(12866595): p. 107-109.
197. Keith, D. J. W., Ong, T. K., Martin, I. C., The role of thoracic computed tomography in staging newly-diagnosed oral squamous cell carcinoma. British Journal of Oral & Maxillofacial Surgery, 2006. 44(3): p. 198-202.
198. Bisase, Brian, Kerawala, Cyrus, Lee, Jonathan, The role of computed tomography of the chest in the staging of early squamous cell carcinoma of the tongue. British Journal of Oral & Maxillofacial Surgery, 2008. 46(5): p. 367-9.
199. Jungehulsing, M., Scheidhauer, K., Damm, M., Pietrzyk, U., Eckel, H., Schicha, H., et.al. 2[F]-fluoro-2-deoxy-D-glucose positron emission tomography is a sensitive tool for the detection of occult primary cancer (carcinoma of unknown primary syndrome) with head and neck lymph node manifestation. Otolaryngol Head Neck Surg, 2000. 123(3): p. 294-301.
200. Johansen, Jorgen, Eigtved, Annika, Buchwald, Christian, Theilgaard, Sune A., Hansen, Hanne S., Implication of 18F-fluoro-2-deoxy-D-glucose positron emission tomography on management of carcinoma of unknown primary in the head and neck: a Danish cohort study. Laryngoscope, 2002. 112(12439171): p. 2009-2014.
201. Regelink, G., Brouwer, J., de Bree, R., Pruim, J., van der Laan, B. F., Vaalburg, W., et.al. Detection of unknown primary tumours and distant metastases in patients with cervical metastases: value of FDG-PET versus conventional modalities. Eur J Nucl Med Mol Imaging, 2002. 29(8): p. 1024-30.
202. van den Brekel, M. W., Castelijns, J. A., Stel, H. V., Golding, R. P., Meyer, C. J., Snow, G. B., Modern imaging techniques and ultrasound-guided aspiration cytology for the assessment of neck node metastases: a prospective comparative study. Eur Arch Otorhinolaryngol, 1993. 250(1): p. 11-7.
203. Reviews., EBM, Multi-agent chemotherapy for early breast cancer. Cochrane Database of Systematic Review., 2003.
204. Coatesworth, Andrew P., MacLennan, Ken, Squamous cell carcinoma of the upper aerodigestive tract: the prevalence of microscopic extracapsular spread and soft tissue deposits in the clinically N0 neck. Head Neck, 2002. 24(11891957): p. 258-261.
205. Carinci, F., Pelucchi, S., Farina, A., De Franciscis, G., Calearo, C., Extension as a prognostic factor in oropharyngeal cancer: largest mucosal dimension compared with number of (sub)sites involved. Br J Oral Maxillofac Surg, 1998. 36(6): p. 440-445.
206. Hirvikoski, P., Kumpulainen, E., Virtaniemi, J., Pirinen, R., Salmi, L., Halonen, P., et.al. Enhanced apoptosis correlates with poor survival in patients with laryngeal cancer but not with cell proliferation, bcl-2 or p53 expression. Eur J Cancer, 1999. 35(10448265): p. 231-237.
207. Fortin, A., Couture, C., Doucet, R., Albert, M., Allard, J., Tetu, B., Does histologic grade have a role in the management of head and neck cancers?. J Clin Oncol, 2001. 19(11689578): p. 4107-4116.
208. Yamazaki, H., Inoue, T., Teshima, T., Tanaka, E., Koizumi, M., Kagawa, K., et.al. Tongue cancer treated with brachytherapy: is thickness of tongue cancer a prognostic factor for regional control?. Anticancer Res, 1998. 18(2B): p. 1261-5.
209. O'Brien, C. J., Lauer, C. S., Fredricks, S., Clifford, A. R., McNeil, E. B., Bagia, J. S., et.al. Tumor thickness influences prognosis of T1 and T2 oral cavity cancer—but what thickness?. Head Neck, 2003. 25(11): p. 937-45.
210. Nishimaki, Tadashi, Kanda, Tatsuo, Nakagawa, Satoru, Kosugi, Shin-ichi, Tanabe, Tadashi, Hatakeyama, Katsuyoshi, Outcomes and prognostic factors after surgical resection of hypopharyngeal and cervical esophageal carcinomas. Int Surg, 2002. 87(1): p. 38-44.
211. Ang, K. Kian, Berkey, Brian A., Tu, Xiaoyu, Zhang, Hua-Zhong, Katz, Ruth, Hammond, Elizabeth H., et.al. Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. Cancer Res, 2002. 62(12499279): p. 7350-7356.

212. Spiro, R. H., Guillamondegui, O., Paulino, A. F., Huvos, A. G., Pattern of invasion and margin assessment in patients with oral tongue cancer. Head Neck, 1999. 21(5): p. 408-413.
213. Wong, R. J., Keel, S. B., Glynn, R. J., Varvares, M. A., Histological pattern of mandibular invasion by oral squamous cell carcinoma. Laryngoscope, 2000. 110(1): p. 65-72.
214. Weijers, M., Snow, G. B., Bezemer, P. D., van der Wal, J. E., van der Waal, I., The clinical relevance of epithelial dysplasia in the surgical margins of tongue and floor of mouth squamous cell carcinoma: an analysis of 37 patients. J Oral Pathol Med, 2002. 31(11896817): p. 11-15.
215. Bailey, J. S., Blanchaert, R. H., Ord, R. A., Management of oral squamous cell carcinoma treated with inadequate excisional biopsy. J Oral Maxillofac Surg, 2001. 59(11526566): p. 1007-1010.
216. McMahon, J., O'Brien, C. J., Pathak, I., Hamill, R., McNeil, E., Hammersley, N., et.al. Influence of condition of surgical margins on local recurrence and disease-specific survival in oral and oropharyngeal cancer. Br J Oral Maxillofac Surg, 2003. 41(4): p. 224-31.
217. Slootweg, Pieter J., Hordijk, Gert Jan, Schade, Yolanda, van Es, Robert J. J., Koole, Ronald, Treatment failure and margin status in head and neck cancer. A critical view on the potential value of molecular pathology. Oral Oncol, 2002. 38(12110346): p. 500-503.
218. Ribeiro, N. F. F., Godden, D. R. P., Wilson, G. E., Butterworth, D. M., Woodwards, R. T. M., Do frozen sections help achieve adequate surgical margins in the resection of oral carcinoma?. Int J Oral Maxillofac Surg, 2003. 32(12729775): p. 152-158.
219. DiNardo, L. J., Lin, J., Karageorge, L. S., Powers, C. N., Accuracy, utility, and cost of frozen section margins in head and neck cancer surgery. Laryngoscope, 2000. 110(10 Pt 1): p. 1773-6.
220. Recht, A., Edge, S. B., Solin, L. J., Robinson, D. S., Estabrook, A., Fine, R. E., et.al. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol, 2001. 19(5): p. 1539-69., https://www.ncbi.nlm.nih.gov/pubmed/11230499
221. Spector, J. G., Sessions, D. G., Haughey, B. H., Chao, K. S., Simpson, J., El Mofty, S., et.al. Delayed regional metastases, distant metastases, and second primary malignancies in squamous cell carcinomas of the larynx and hypopharynx. Laryngoscope, 2001. 111(11404625): p. 1079-1087.
222. Ozdek, A., Sarac, S., Akyol, M. U., Unal, O. F., Sungur, A., Histopathological predictors of occult lymph node metastases in supraglottic squamous cell carcinomas. Eur Arch Otorhinolaryngol, 2000. 257(11052252): p. 389-392.
223. Coatesworth, Andrew P., MacLennan, Ken, Squamous cell carcinoma of the upper aerodigestive tract: the prevalence of microscopic extracapsular spread and soft tissue deposits in the clinically N0 neck. Head Neck, 2002. 24(11891957): p. 258-261.
224. Carinci, F., Pelucchi, S., Farina, A., De Franciscis, G., Calearo, C., Extension as a prognostic factor in oropharyngeal cancer: largest mucosal dimension compared with number of (sub)sites involved. Br J Oral Maxillofac Surg, 1998. 36(6): p. 440-445.
225. Hirvikoski, P., Kumpulainen, E., Virtaniemi, J., Pirinen, R., Salmi, L., Halonen, P., et.al. Enhanced apoptosis correlates with poor survival in patients with laryngeal cancer but not with cell proliferation, bcl-2 or p53 expression. Eur J Cancer, 1999. 35(10448265): p. 231-237.
226. Fortin, A., Couture, C., Doucet, R., Albert, M., Allard, J., Tetu, B., Does histologic grade have a role in the management of head and neck cancers?. J Clin Oncol, 2001. 19(11689578): p. 4107-4116.
227. Yamazaki, H., Inoue, T., Teshima, T., Tanaka, E., Koizumi, M., Kagawa, K., et.al. Tongue cancer treated with brachytherapy: is thickness of tongue cancer a prognostic factor for regional control?. Anticancer Res, 1998. 18(2B): p. 1261-5.
228. O'Brien, C. J., Lauer, C. S., Fredricks, S., Clifford, A. R., McNeil, E. B., Bagia, J. S., et.al. Tumor thickness influences prognosis of T1 and T2 oral cavity cancer—but what thickness?. Head Neck, 2003. 25(11): p. 937-45.

229. Nishimaki, Tadashi, Kanda, Tatsuo, Nakagawa, Satoru, Kosugi, Shin-ichi, Tanabe, Tadashi, Hatakeyama, Katsuyoshi, Outcomes and prognostic factors after surgical resection of hypopharyngeal and cervical esophageal carcinomas. Int Surg, 2002. 87(1): p. 38-44.
230. Ang, K. Kian, Berkey, Brian A., Tu, Xiaoyu, Zhang, Hua-Zhong, Katz, Ruth, Hammond, Elizabeth H., et.al. Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. Cancer Res, 2002. 62(12499279): p. 7350-7356.
231. Spiro, R. H., Guillamondegui, O., Paulino, A. F., Huvos, A. G., Pattern of invasion and margin assessment in patients with oral tongue cancer. Head Neck, 1999. 21(5): p. 408-413.
232. Wong, R. J., Keel, S. B., Glynn, R. J., Varvares, M. A., Histological pattern of mandibular invasion by oral squamous cell carcinoma. Laryngoscope, 2000. 110(1): p. 65-72.
233. Weijers, M., Snow, G. B., Bezemer, P. D., van der Wal, J. E., van der Waal, I., The clinical relevance of epithelial dysplasia in the surgical margins of tongue and floor of mouth squamous cell carcinoma: an analysis of 37 patients. J Oral Pathol Med, 2002. 31(11896817): p. 11-15.
234. Bailey, J. S., Blanchaert, R. H., Ord, R. A., Management of oral squamous cell carcinoma treated with inadequate excisional biopsy. J Oral Maxillofac Surg, 2001. 59(11526566): p. 1007-1010.
235. McMahon, J., O'Brien, C. J., Pathak, I., Hamill, R., McNeil, E., Hammersley, N., et.al. Influence of condition of surgical margins on local recurrence and disease-specific survival in oral and oropharyngeal cancer. Br J Oral Maxillofac Surg, 2003. 41(4): p. 224-31.
236. Slootweg, Pieter J., Hordijk, Gert Jan, Schade, Yolanda, van Es, Robert J. J., Koole, Ronald, Treatment failure and margin status in head and neck cancer. A critical view on the potential value of molecular pathology. Oral Oncol, 2002. 38(12110346): p. 500-503.
237. Ribeiro, N. F. F., Godden, D. R. P., Wilson, G. E., Butterworth, D. M., Woodwards, R. T. M., Do frozen sections help achieve adequate surgical margins in the resection of oral carcinoma?. Int J Oral Maxillofac Surg, 2003. 32(12729775): p. 152-158.
238. DiNardo, L. J., Lin, J., Karageorge, L. S., Powers, C. N., Accuracy, utility, and cost of frozen section margins in head and neck cancer surgery. Laryngoscope, 2000. 110(10 Pt 1): p. 1773-6.
239. Brasilino de Carvalho, M., Quantitative analysis of the extent of extracapsular invasion and its prognostic significance: a prospective study of 170 cases of carcinoma of the larynx and hypopharynx. Head Neck, 1998. 20(1): p. 16-21.
240. Brasilino de Carvalho, M., Quantitative analysis of the extent of extracapsular invasion and its prognostic significance: a prospective study of 170 cases of carcinoma of the larynx and hypopharynx. Head Neck, 1998. 20(1): p. 16-21.
241. Tankere, F., Camproux, A., Barry, B., Guedon, C., Depondt, J., Gehanno, P., Prognostic value of lymph node involvement in oral cancers: a study of 137 cases. Laryngoscope, 2000. 110(11129021): p. 2061-2065.
242. Woolgar, J. A., Rogers, S. N., Lowe, D., Brown, J. S., Vaughan, E. D., Cervical lymph node metastasis in oral cancer: the importance of even microscopic extracapsular spread. Oral Oncol, 2003. 39(12509965): p. 130-137.
243. Suoglu, Y., Erdamar, B., Katircioglu, O. S., Karatay, M. C., Sunay, T., Extracapsular spread in ipsilateral neck and contralateral neck metastases in laryngeal cancer. Ann Otol Rhinol Laryngol, 2002. 111(5 Pt 1): p. 447-54.
244. Greenberg, Jayson S., Fowler, Robert, Gomez, Jose, Mo, Vivian, Roberts, Dianna, El Naggar, Adel K., et.al. Extent of extracapsular spread: a critical prognosticator in oral tongue cancer. Cancer, 2003. 97(12627511): p. 1464-1470.
245. Esposito, E. D., Motta, S., Cassiano, B., Motta, G., Occult lymph node metastases in supraglottic cancers of the larynx. Otolaryngol Head Neck Surg, 2001. 124(3): p. 253-7.

246. Enepekides, D. J., Sultanem, K., Nguyen, C., Shenouda, G., Black, M. J., Rochon, L., Occult cervical metastases: immunoperoxidase analysis of the pathologically negative neck. Otolaryngol Head Neck Surg, 1999. 120(5): p. 713-717.
247. Tankere, F., Camproux, A., Barry, B., Guedon, C., Depondt, J., Gehanno, P., Prognostic value of lymph node involvement in oral cancers: a study of 137 cases. Laryngoscope, 2000. 110(11129021): p. 2061-2065.
248. Woolgar, J. A., Rogers, S. N., Lowe, D., Brown, J. S., Vaughan, E. D., Cervical lymph node metastasis in oral cancer: the importance of even microscopic extracapsular spread. Oral Oncol, 2003. 39(12509965): p. 130-137.
249. Suoglu, Y., Erdamar, B., Katircioglu, O. S., Karatay, M. C., Sunay, T., Extracapsular spread in ipsilateral neck and contralateral neck metastases in laryngeal cancer. Ann Otol Rhinol Laryngol, 2002. 111(5 Pt 1): p. 447-54.
250. Greenberg, Jayson S., Fowler, Robert, Gomez, Jose, Mo, Vivian, Roberts, Dianna, El Naggar, Adel K., et.al. Extent of extracapsular spread: a critical prognosticator in oral tongue cancer. Cancer, 2003. 97(12627511): p. 1464-1470.
251. Esposito, E. D., Motta, S., Cassiano, B., Motta, G., Occult lymph node metastases in supraglottic cancers of the larynx. Otolaryngol Head Neck Surg, 2001. 124(3): p. 253-7.
252. Enepekides, D. J., Sultanem, K., Nguyen, C., Shenouda, G., Black, M. J., Rochon, L., Occult cervical metastases: immunoperoxidase analysis of the pathologically negative neck. Otolaryngol Head Neck Surg, 1999. 120(5): p. 713-717.
253. Byers, R. M., El-Naggar, A. K., Lee, Y. Y., Rao, B., Fornage, B., Terry, N. H., et.al. Can we detect or predict the presence of occult nodal metastases in patients with squamous carcinoma of the oral tongue?. Head Neck, 1998. 20(2): p. 138-44.
254. Ferlito, A., Partridge, M., Brennan, J., Hamakawa, H., Lymph node micrometastases in head and neck cancer: a review. Acta Otolaryngol, 2001. 121(6): p. 660-5.
255. Lindel, K., Beer, K. T., Laissue, J., Greiner, R. H., Aebersold, D. M., Human papillomavirus positive squamous cell carcinoma of the oropharynx: a radiosensitive subgroup of head and neck carcinoma. Cancer, 2001. 92(4): p. 805-13.
256. Buchwald, C., Lindeberg, H., Pedersen, B. L., Franzmann, M. B., Human papilloma virus and p53 expression in carcinomas associated with sinonasal papillomas: a Danish Epidemiological study 1980-1998. Laryngoscope, 2001. 111(6): p. 1104-10.
257. Friesland, S., Mellin, H., Munck-Wikland, E., Nilsson, A., Lindholm, J., Dalianis, T., et.al. Human papilloma virus (HPV) and p53 immunostaining in advanced tonsillar carcinoma—relation to radiotherapy response and survival. Anticancer Res, 2001. 21(1B): p. 529-34.
258. Gillison, M. L., Koch, W. M., Capone, R. B., Spafford, M., Westra, W. H., Wu, L., et.al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. J Natl Cancer Inst, 2000. 92(9): p. 709-20.
259. Takes, R. P., Baatenburg De Jong, R. J., Alles, M. J., Meeuwis, C. A., Marres, H. A., Knegt, P. P., et.al. Markers for nodal metastasis in head and neck squamous cell cancer. Arch Otolaryngol Head Neck Surg, 2002. 128(5): p. 512-8.
260. Helliwell, T. R., Molecular markers of metastasis in squamous carcinomas. J Pathol, 2001. 194(3): p. 289-93.
261. Epstein, J. B., Lunn, R., Le, N., Stevenson-Moore, P., Periodontal attachment loss in patients after head and neck radiation therapy. Oral Surgery Oral Medicine Oral Pathology Oral Radiology & Endodontics, 1998. 86(6): p. 673-7.
262. Denis, F., Garaud, P., Bardet, E., Alfonsi, M., Sire, C., Germain, T., et.al. Late toxicity results of the GORTEC 94-01 randomized trial comparing radiotherapy with concomitant radiochemotherapy for advanced-stage oropharynx carcinoma: comparison of LENT/SOMA, RTOG/EORTC, and NCI-CTC scoring systems. Int J Radiat Oncol Biol Phys, 2003. 55(1): p. 93-8.
263. dos Santos, C. R., Goncalves Filho, J., Magrin, J., Johnson, L. F., Ferlito, A., Kowalski, L. P., Involvement of level I neck lymph nodes in advanced squamous carcinoma of the larynx. Ann Otol Rhinol Laryngol, 2001. 110(10): p. 982-4.

264. Johansen, L. V., Grau, C., Overgaard, J., Hypopharyngeal squamous cell carcinoma—treatment results in 138 consecutively admitted patients. Acta Oncol, 2000. 39(4): p. 529-36.
265. Rodgers, L. W., Jr., Stringer, S. P., Mendenhall, W. M., Parsons, J. T., Cassisi, N. J., Million, R. R., Management of squamous cell carcinoma of the floor of mouth. Head Neck, 1993. 15(1): p. 16-9.
266. Levendag, P. C., Nowak, P. J., van der Sangen, M. J., Jansen, P. P., Eijkenboom, W. M., Planting, A. S., et.al. Local tumor control in radiation therapy of cancers in the head and neck. Am J Clin Oncol, 1996. 19(5): p. 469-477.
267. Epstein, J. B., Lunn, R., Le, N., Stevenson-Moore, P., Periodontal attachment loss in patients after head and neck radiation therapy. Oral Surgery Oral Medicine Oral Pathology Oral Radiology & Endodontics, 1998. 86(6): p. 673-7.
268. Denis, F., Garaud, P., Bardet, E., Alfonsi, M., Sire, C., Germain, T., et.al. Late toxicity results of the GORTEC 94-01 randomized trial comparing radiotherapy with concomitant radiochemotherapy for advanced-stage oropharynx carcinoma: comparison of LENT/SOMA, RTOG/EORTC, and NCI-CTC scoring systems. Int J Radiat Oncol Biol Phys, 2003. 55(1): p. 93-8.
269. Crampette, L., Garrel, R., Gardiner, Q., Maurice, N., Mondain, M., Makeieff, M., et.al. Modified subtotal laryngectomy with cricohyoidoepiglottopexy—long term results in 81 patients. Head Neck, 1999. 21(2): p. 95-103.
270. Giovanni, A., Guelfucci, B., Gras, R., Yu, P., Zanaret, M., Partial frontolateral laryngectomy with epiglottic reconstruction for management of early-stage glottic carcinoma. Laryngoscope, 2001. 111(4 Pt 1): p. 663-8.
271. Luukkaa, M., Aitasalo, K., Pulkkinen, J., Lindholm, P., Valavaara, R., Grenman, R., Neodymium YAG contact laser in the treatment of cancer of the mobile tongue. Acta Otolaryngol, 2002. 122(3): p. 318-22.
272. Edwards, D. M., Johnson, N. W., Treatment of upper aerodigestive tract cancers in England and its effect on survival. Br J Cancer, 1999. 81(2): p. 323-9.
273. Bahadur, S., Thakar, A., Mohanti, B. K., Lal, P., Results of radiotherapy with, or without, salvage surgery versus combined surgery and radiotherapy in advanced carcinoma of the hypopharynx. J Laryngol Otol, 2002. 116(1): p. 29-32.
274. Leon, X., Quer, M., Orus, C., Moran, J., Recher, K., Results of an organ preservation protocol with induction chemotherapy and radiotherapy in patients with locally advanced pyriform sinus carcinoma. Eur Arch Otorhinolaryngol, 2002. 259(1): p. 32-6.
275. Barzan, L., Talamini, R., Politi, D., Minatel, E., Gobitti, C., Franchin, G., Squamous cell carcinoma of the hypopharynx treated with surgery and radiotherapy. J Laryngol Otol, 2002. 116(1): p. 24-8.
276. MacKenzie, R. G., Franssen, E., Balogh, J. M., Gilbert, R. W., Birt, D., Davidson, J., Comparing treatment outcomes of radiotherapy and surgery in locally advanced carcinoma of the larynx: a comparison limited to patients eligible for surgery. Int J Radiat Oncol Biol Phys, 2000. 47(1): p. 65-71.
277. Porter, M. J., McIvor, N. P., Morton, R. P., Hindley, A. C., Audit in the management of T3 fixed-cord laryngeal cancer. Am J Otolaryngol, 1998. 19(6): p. 360-4.
278. Staton, J., Robbins, K. T., Newman, L., Samant, S., Sebelik, M., Vieira, F., Factors predictive of poor functional outcome after chemoradiation for advanced laryngeal cancer. Otolaryngol Head Neck Surg, 2002. 127(1): p. 43-7.
279. Terrell, J. E., Fisher, S. G., Wolf, G. T., Long-term quality of life after treatment of laryngeal cancer. The Veterans Affairs Laryngeal Cancer Study Group. Arch Otolaryngol Head Neck Surg, 1998. 124(9): p. 964-71.
280. Bergqvist, M., Brodin, O., Pouzon, A., Linder, A., Hesselius, P., Blomquist, E., Radiation treatment of T1-T4 squamous cell carcinoma of the larynx: a retrospective analysis and long-term follow-up of 135 patients. Anticancer Res, 2002. 22(2B): p. 1239-42.

281. Paisley, S., Warde, P. R., O'Sullivan, B., Waldron, J., Gullane, P. J., Payne, D., et.al. Results of radiotherapy for primary subglottic squamous cell carcinoma. Int J Radiat Oncol Biol Phys, 2002. 52(5): p. 1245-50.
282. Orus, C., Leon, X., Vega, M., Quer, M., Initial treatment of the early stages (I, II) of supraglottic squamous cell carcinoma: partial laryngectomy versus radiotherapy. Eur Arch Otorhinolaryngol, 2000. 257(9): p. 512-6.
283. Medini, E., Medini, I., Lee, C. K., Gapany, M., Levitt, S. H., Curative radiotherapy for stage II-III squamous cell carcinoma of the glottic larynx. Am J Clin Oncol, 1998. 21(3): p. 302-5.
284. Lavertu, P., Bonafede, J. P., Adelstein, D. J., Saxton, J. P., Strome, M., Wanamaker, J. R., et.al. Comparison of surgical complications after organ-preservation therapy in patients with stage III or IV squamous cell head and neck cancer. Arch Otolaryngol Head Neck Surg, 1998. 124(4): p. 401-6.
285. Mendenhall, W. M., Amdur, R. J., Stringer, S. P., Villaret, D. B., Cassisi, N. J., Radiation therapy for squamous cell carcinoma of the tonsillar region: a preferred alternative to surgery?. J Clin Oncol, 2000. 18(11): p. 2219-25.
286. Mendenhall, W. M., Stringer, S. P., Amdur, R. J., Hinerman, R. W., Moore-Higgs, G. J., Cassisi, N. J., Is radiation therapy a preferred alternative to surgery for squamous cell carcinoma of the base of tongue?. J Clin Oncol, 2000. 18(1): p. 35-42.
287. Tschudi, D., Stoeckli, S., Schmid, S., Quality of life after different treatment modalities for carcinoma of the oropharynx. Laryngoscope, 2003. 113(11): p. 1949-54.
288. Pfreundner, L., Hoppe, F., Willner, J., Preisler, V., Bratengeier, K., Hagen, R., et.al. Induction chemotherapy with paclitaxel and cisplatin and CT-based 3D radiotherapy in patients with advanced laryngeal and hypopharyngeal carcinomas—a possibility for organ preservation. Radiother Oncol, 2003. 68(2): p. 163-70.
289. Newell, R., Ziegler, L., Stafford, N., Lewin, R. J., The information needs of head and neck cancer patients prior to surgery. Ann R Coll Surg Engl, 2004. 86(6): p. 407-10.
290. Humphris, G. M., Freeman, R., Clarke, H. M., Risk perception of oral cancer in smokers attending primary care: a randomised controlled trial. Oral Oncol, 2004. 40(9): p. 916-24.
291. Parsons, J. T., Mendenhall, W. M., Stringer, S. P., Cassisi, N. J., Million, R. R., An analysis of factors influencing the outcome of postoperative irradiation for squamous cell carcinoma of the oral cavity. Int J Radiat Oncol Biol Phys, 1997. 39(1): p. 137-48.
292. Sessions, D. G., Spector, G. J., Lenox, J., Parriott, S., Haughey, B., Chao, C., et.al. Analysis of treatment results for floor-of-mouth cancer. Laryngoscope, 2000. 110(10): p. 1764-1772.
293. Kovacs, A. F., Relevance of positive margins in case of adjuvant therapy of oral cancer. Int J Oral Maxillofac Surg, 2004. 33(5): p. 447-453.
294. O'Brien, C. J., Adams, J. R., McNeil, E. B., Taylor, P., Laniewski, P., Clifford, A., et.al. Influence of bone invasion and extent of mandibular resection on local control of cancers of the oral cavity and oropharynx. Int J Oral Maxillofac Surg, 2003. 32(5): p. 492-497.
295. Hicks, W. L., Loree, T. R., Garcia, R. I., Maamoun, S., Marshall, D., Orner, J. B., et.al. Squamous cell carcinoma of the floor of mouth: a 20-year review. Head Neck, 1997. 19(5): p. 400-405.
296. Loree, T. R., Strong, E. W., Significance of positive margins in oral cavity squamous carcinoma. Am J Surg, 1990. 160(4): p. 410-414.
297. Sutton, D. N., Brown, J. S., Rogers, S. N., Vaughan, E. D., Woolgar, J. A., The prognostic implications of the surgical margin in oral squamous cell carcinoma. Int J Oral Maxillofac Surg, 2003. 32(1): p. 30-34.
298. Brown, J. S., Kalavrezos, N., D'Souza, J., Lowe, D., Magennis, P., Woolgar, J. A., Factors that influence the method of mandibular resection in the management of oral squamous cell carcinoma. Br J Oral Maxillofac Surg, 2002. 40(4): p. 275-284.

299. Wolff, Diana, Hassfeld, Stefan, Hofele, Christof, Influence of marginal and segmental mandibular resection on the survival rate in patients with squamous cell carcinoma of the inferior parts of the oral cavity. J Craniomaxillofac Surg, 2004. 32(5): p. 318-323.
300. Munoz Guerra, Mario Fernando, Naval Gias, Luis, Campo, Francisco Rodriguez, Perez, Jesus Sastre, Marginal and segmental mandibulectomy in patients with oral cancer: a statistical analysis of 106 cases. J Oral Maxillofac Surg, 2003. 61(11): p. 1289-1296.
301. Muscatello, L., Lenzi, R., Pellini, R., Giudice, M., Spriano, G., Marginal mandibulectomy in oral cancer surgery: A 13-year experience. European Archives of Oto-Rhino-Laryngology, 2010. 267 (5): p. 759-764.
302. Abler, A., Roser, M., Weingart, D., [On the indications for and morbidity of segmental resection of the mandible for squamous cell carcinoma in the lower oral cavity]. Mund-, Kiefer- und Gesichtschirurgie, 2005. 9(3): p. 137-42.
303. Namaki, Shunsuke, Matsumoto, Mitsuhiko, Ohba, Hiroiku, Tanaka, Hiroshi, Koshikawa, Noriaki, Shinohara, Mitsuyo, Masticatory efficiency before and after surgery in oral cancer patients: comparative study of glossectomy, marginal mandibulectomy and segmental mandibulectomy. Journal of Oral Science, 2004. 46(2): p. 113-7.
304. Rodgers, L. W., Jr., Stringer, S. P., Mendenhall, W. M., Parsons, J. T., Cassisi, N. J., Million, R. R., Management of squamous cell carcinoma of the floor of mouth. Head Neck, 1993. 15(1): p. 16-9.
305. Parsons, J. T., Mendenhall, W. M., Stringer, S. P., Cassisi, N. J., Million, R. R., An analysis of factors influencing the outcome of postoperative irradiation for squamous cell carcinoma of the oral cavity. Int J Radiat Oncol Biol Phys, 1997. 39(1): p. 137-48.
306. Sessions, D. G., Spector, G. J., Lenox, J., Parriott, S., Haughey, B., Chao, C., et.al. Analysis of treatment results for floor-of-mouth cancer. Laryngoscope, 2000. 110(10): p. 1764-1772.
307. Kovacs, A. F., Relevance of positive margins in case of adjuvant therapy of oral cancer. Int J Oral Maxillofac Surg, 2004. 33(5): p. 447-453.
308. O'Brien, C. J., Adams, J. R., McNeil, E. B., Taylor, P., Laniewski, P., Clifford, A., et.al. Influence of bone invasion and extent of mandibular resection on local control of cancers of the oral cavity and oropharynx. Int J Oral Maxillofac Surg, 2003. 32(5): p. 492-497.
309. Hicks, W. L., Loree, T. R., Garcia, R. I., Maamoun, S., Marshall, D., Orner, J. B., et.al. Squamous cell carcinoma of the floor of mouth: a 20-year review. Head Neck, 1997. 19(5): p. 400-405.
310. Loree, T. R., Strong, E. W., Significance of positive margins in oral cavity squamous carcinoma. Am J Surg, 1990. 160(4): p. 410-414.
311. Brown, J. S., Kalavrezos, N., D'Souza, J., Lowe, D., Magennis, P., Woolgar, J. A., Factors that influence the method of mandibular resection in the management of oral squamous cell carcinoma. Br J Oral Maxillofac Surg, 2002. 40(4): p. 275-284.
312. Wolff, Diana, Hassfeld, Stefan, Hofele, Christof, Influence of marginal and segmental mandibular resection on the survival rate in patients with squamous cell carcinoma of the inferior parts of the oral cavity. J Craniomaxillofac Surg, 2004. 32(5): p. 318-323.
313. Munoz Guerra, Mario Fernando, Naval Gias, Luis, Campo, Francisco Rodriguez, Perez, Jesus Sastre, Marginal and segmental mandibulectomy in patients with oral cancer: a statistical analysis of 106 cases. J Oral Maxillofac Surg, 2003. 61(11): p. 1289-1296.
314. Namaki, Shunsuke, Matsumoto, Mitsuhiko, Ohba, Hiroiku, Tanaka, Hiroshi, Koshikawa, Noriaki, Shinohara, Mitsuyo, Masticatory efficiency before and after surgery in oral cancer patients: comparative study of glossectomy, marginal mandibulectomy and segmental mandibulectomy. Journal of Oral Science, 2004. 46(2): p. 113-7.
315. Soo, K. C., Tan, E. H., Wee, J., Lim, D., Tai, B. C., Khoo, M. L., et.al. Surgery and adjuvant radiotherapy vs concurrent chemoradiotherapy in stage III/IV nonmetastatic squamous cell head and neck cancer: a randomised comparison. Br J Cancer, 2005. 93(3): p. 279-86.

316. Lefebvre, J. L., Coche-Dequeant, B., Buisset, E., Mirabel, X., Van, J. T., Prevost, B., Management of early oral cavity cancer. Experience of Centre Oscar Lambret. Eur J Cancer B Oral Oncol, 1994. 30(3): p. 216-20.
317. Panje, W. R., Smith, B., McCabe, B. F., Epidermoid carcinoma of the floor of the mouth: surgical therapy vs combined therapy vs radiation therapy. Otolaryngol Head Neck Surg, 1980. 88(6): p. 714-720.
318. Iyer, Shridhar Ganpathi, Pradhan, S. A., Pai, P. S., Patil, S., Surgical treatment outcomes of localized squamous carcinoma of buccal mucosa. Head Neck, 2004. 26(10): p. 897-902.
319. Turner, S. L., Slevin, N. J., Gupta, N. K., Swindell, R., Radical external beam radiotherapy for 333 squamous carcinomas of the oral cavity—evaluation of late morbidity and a watch policy for the clinically negative neck. Radiother Oncol, 1996. 41(1): p. 21-9.
320. Glanzmann, C., Gratz, K. W., Radionecrosis of the mandibula: a retrospective analysis of the incidence and risk factors. Radiother Oncol, 1995. 36(2): p. 94-9100.
321. Zelefsky, M. J., Harrison, L. B., Fass, D. E., Armstrong, J. G., Shah, J. P., Strong, E. W., Postoperative radiation therapy for squamous cell carcinomas of the oral cavity and oropharynx: impact of therapy on patients with positive surgical margins. Int J Radiat Oncol Biol Phys, 1993. 25(1): p. 17-21.
322. Rogers, Simon N., Devine, John, Lowe, Derek, Shokar, Parminder, Brown, James S., Vaugman, E. David, Longitudinal health-related quality of life after mandibular resection for oral cancer: a comparison between rim and segment. Head & Neck, 2004. 26(1): p. 54-62.
323. Byers, R. M., El-Naggar, A. K., Lee, Y. Y., Rao, B., Fornage, B., Terry, N. H., et.al. Can we detect or predict the presence of occult nodal metastases in patients with squamous carcinoma of the oral tongue?. Head Neck, 1998. 20(2): p. 138-44.
324. Turner, S. L., Slevin, N. J., Gupta, N. K., Swindell, R., Radical external beam radiotherapy for 333 squamous carcinomas of the oral cavity—evaluation of late morbidity and a watch policy for the clinically negative neck. Radiother Oncol, 1996. 41(1): p. 21-9.
325. Spiro, R. H., Morgan, G. J., Strong, E. W., Shah, J. P., Supraomohyoid neck dissection. Am J Surg, 1996. 172(8988669): p. 650-653.
326. Nieuwenhuis, Eline J. C., Castelijns, Jonas A., Pijpers, Rik, van den Brekel, Michiel W. M., Brakenhoff, Ruud H., van der Waal, Isaac, et.al. Wait-and-see policy for the N0 neck in early-stage oral and oropharyngeal squamous cell carcinoma using ultrasonography-guided cytology: is there a role for identification of the sentinel node?. Head Neck, 2002. 24(11891961): p. 282-289.
327. Shah, J. P., Candela, F. C., Poddar, A. K., The patterns of cervical lymph node metastases from squamous carcinoma of the oral cavity. Cancer, 1990. 66(1): p. 109-113.
328. Spiro, J. D., Spiro, R. H., Shah, J. P., Sessions, R. B., Strong, E. W., Critical assessment of supraomohyoid neck dissection. Am J Surg, 1988. 156(4): p. 286-289.
329. Byers, R. M., Wolf, P. F., Ballantyne, A. J., Rationale for elective modified neck dissection. Head Neck Surg, 1988. 10(3): p. 160-167.
330. Smith, G. I., O'Brien, C. J., Clark, J., Shannon, K. F., Clifford, A. R., McNeil, E. B., et.al. Management of the neck in patients with T1 and T2 cancer in the mouth. Br J Oral Maxillofac Surg, 2004. 42(6): p. 494-500.
331. Crean, St-John, Hoffman, A., Potts, John, Fardy, M. J., Reduction of occult metastatic disease by extension of the supraomohyoid neck dissection to include level IV. Head Neck, 2003. 25(12953312): p. 758-762.
332. Hao, Sheng-Po, Tsang, Ngan Ming, The role of supraomohyoid neck dissection in patients of oral cavity carcinoma(small star, filled). Oral Oncol, 2002. 38(11978555): p. 309-312.
333. O'Brien, C. J., Traynor, S. J., McNeil, E., McMahon, J. D., Chaplin, J. M., The use of clinical criteria alone in the management of the clinically negative neck among patients with squamous cell carcinoma of the oral cavity and oropharynx. Arch Otolaryngol Head Neck Surg, 2000. 126(3): p. 360-5.

334. Henick, D. H., Silver, C. E., Heller, K. S., Shaha, A. R., El, G. H., Wolk, D. P., Supraomohyoid neck dissection as a staging procedure for squamous cell carcinomas of the oral cavity and oropharynx. Head Neck, 1995. 17(2): p. 119-123.
335. Cole, I., Hughes, L., The relationship of cervical lymph node metastases to primary sites of carcinoma of the upper aerodigestive tract: a pathological study. Aust N Z J Surg, 1997. 67(12): p. 860-865.
336. McGuirt, W. F., Johnson, J. T., Myers, E. N., Rothfield, R., Wagner, R., Floor of mouth carcinoma. The management of the clinically negative neck. Arch Otolaryngol Head Neck Surg, 1995. 121(7873143): p. 278-282.
337. Kligerman, J., Lima, R. A., Soares, J. R., Prado, L., Dias, F. L., Freitas, E. Q., et.al. Supraomohyoid neck dissection in the treatment of T1/T2 squamous cell carcinoma of oral cavity. Am J Surg, 1994. 168(7977957): p. 391-394.
338. Johnson, J. T., Carcinoma of the larynx: selective approach to the management of cervical lymphatics. Ear Nose Throat J, 1994. 73(5): p. 303-5.
339. Manni, J. J., van den Hoogen, F. J., Supraomohyoid neck dissection with frozen section biopsy as a staging procedure in the clinically node-negative neck in carcinoma of the oral cavity. Am J Surg, 1991. 162(4): p. 373-376.
340. Leon, X., Quer, M., Orus, C., Sancho, F. J., Bague, S., Burgues, J., Selective dissection of levels II-III with intraoperative control of the upper and middle jugular nodes: a therapeutic option for the N0 neck. Head Neck, 2001. 23(6): p. 441-446.
341. Byers, R. M., Modified neck dissection. A study of 967 cases from 1970 to 1980. Am J Surg, 1985. 150(4): p. 414-21.
342. Bocca, E., Pignataro, O., Oldini, C., Cappa, C., Functional neck dissection: an evaluation and review of 843 cases. Laryngoscope, 1984. 94(7): p. 942-945.
343. Molinari, R., Cantu, G., Chiesa, F., Grandi, C., Retrospective comparison of conservative and radical neck dissection in laryngeal cancer. Ann Otol Rhinol Laryngol, 1980. 89(6 Pt 1): p. 578-81.
344. Spiro, R. H., Gallo, O., Shah, J. P., Selective jugular node dissection in patients with squamous carcinoma of the larynx or pharynx. Am J Surg, 1993. 166(4): p. 399-402.
345. Bier, J., Radical neck dissection versus conservative neck dissection for squamous cell carcinoma of the oral cavity. Recent Results Cancer Res, 1994. 134: p. 57-62.
346. Results of a prospective trial on elective modified radical classical versus supraomohyoid neck dissection in the management of oral squamous carcinoma. Brazilian Head and Neck Cancer Study Group. Am J Surg, 1998. 176(5): p. 422-7.
347. Fakih, A. R., Rao, R. S., Borges, A. M., Patel, A. R., Elective versus therapeutic neck dissection in early carcinoma of the oral tongue. Am J Surg, 1989. 158(4): p. 309-313.
348. van den Brekel, M. W., Castelijns, J. A., Snow, G. B., Diagnostic evaluation of the neck. Otolaryngol Clin North Am, 1998. 31(4): p. 601-20.
349. Ho, C. M., Lam, K. H., Wei, W. I., Lau, W. F., Treatment of neck nodes in oral cancer. Surg Oncol, 1992. 1(1341238): p. 73-78.
350. Lydiatt, D. D., Robbins, K. T., Byers, R. M., Wolf, P. F., Treatment of stage I and II oral tongue cancer. Head Neck, 1993. 15(4): p. 308-312.
351. Grandi, C., Mingardo, M., Guzzo, M., Licitra, L., Podrecca, S., Molinari, R., Salvage surgery of cervical recurrences after neck dissection or radiotherapy. Head Neck, 1993. 15(4): p. 292-295.
352. Vandenbrouck, C., Sancho-Garnier, H., Chassagne, D., Saravane, D., Cachin, Y., Micheau, C., Elective versus therapeutic radical neck dissection in epidermoid carcinoma of the oral cavity: results of a randomized clinical trial. Cancer, 1980. 46(2): p. 386-390.
353. Dias, F. L., Kligerman, J., Matos de Sa, G., Arcuri, R. A., Freitas, E. Q., Farias, T., et.al. Elective neck dissection versus observation in stage I squamous cell carcinomas of the tongue and floor of the mouth. Otolaryngol Head Neck Surg, 2001. 125(1): p. 23-29.

354. Wolfensberger, M., Zbaeren, P., Dulguerov, P., Muller, W., Arnoux, A., Schmid, S., Surgical treatment of early oral carcinoma-results of a prospective controlled multicenter study. Head Neck, 2001. 23(7): p. 525-530.
355. D'Cruz, Anil K., Siddachari, Ravichand C., Walvekar, Rohan R., Pantvaidya, Gouri H., Chaukar, Devendra A., Deshpande, Mandar S., et.al. Elective neck dissection for the management of the N0 neck in early cancer of the oral tongue: need for a randomized controlled trial. Head & Neck, 2009. 31(5): p. 618-24.
356. Huang, Shiang-Fu, Kang, Chung-Jan, Lin, Chen-Yu, Fan, Kang-Hsing, Yen, Tzu-Chen, Wang, Hung-Ming, et.al. Neck treatment of patients with early stage oral tongue cancer: comparison between observation, supraomohyoid dissection, and extended dissection. Cancer, 2008. 112(5): p. 1066-75.
357. Spiro, R. H., Morgan, G. J., Strong, E. W., Shah, J. P., Supraomohyoid neck dissection. Am J Surg, 1996. 172(8988669): p. 650-653.
358. Nieuwenhuis, Eline J. C., Castelijns, Jonas A., Pijpers, Rik, van den Brekel, Michiel W. M., Brakenhoff, Ruud H., van der Waal, Isaac, et.al. Wait-and-see policy for the N0 neck in early-stage oral and oropharyngeal squamous cell carcinoma using ultrasonography-guided cytology: is there a role for identification of the sentinel node?. Head Neck, 2002. 24(11891961): p. 282-289.
359. Spiro, J. D., Spiro, R. H., Shah, J. P., Sessions, R. B., Strong, E. W., Critical assessment of supraomohyoid neck dissection. Am J Surg, 1988. 156(4): p. 286-289.
360. Smith, G. I., O'Brien, C. J., Clark, J., Shannon, K. F., Clifford, A. R., McNeil, E. B., et.al. Management of the neck in patients with T1 and T2 cancer in the mouth. Br J Oral Maxillofac Surg, 2004. 42(6): p. 494-500.
361. Crean, St-John, Hoffman, A., Potts, John, Fardy, M. J., Reduction of occult metastatic disease by extension of the supraomohyoid neck dissection to include level IV. Head Neck, 2003. 25(12953312): p. 758-762.
362. Hao, Sheng-Po, Tsang, Ngan Ming, The role of supraomohyoid neck dissection in patients of oral cavity carcinoma(small star, filled). Oral Oncol, 2002. 38(11978555): p. 309-312.
363. O'Brien, C. J., Traynor, S. J., McNeil, E., McMahon, J. D., Chaplin, J. M., The use of clinical criteria alone in the management of the clinically negative neck among patients with squamous cell carcinoma of the oral cavity and oropharynx. Arch Otolaryngol Head Neck Surg, 2000. 126(3): p. 360-5.
364. Henick, D. H., Silver, C. E., Heller, K. S., Shaha, A. R., El, G. H., Wolk, D. P., Supraomohyoid neck dissection as a staging procedure for squamous cell carcinomas of the oral cavity and oropharynx. Head Neck, 1995. 17(2): p. 119-123.
365. Cole, I., Hughes, L., The relationship of cervical lymph node metastases to primary sites of carcinoma of the upper aerodigestive tract: a pathological study. Aust N Z J Surg, 1997. 67(12): p. 860-865.
366. McGuirt, W. F., Johnson, J. T., Myers, E. N., Rothfield, R., Wagner, R., Floor of mouth carcinoma. The management of the clinically negative neck. Arch Otolaryngol Head Neck Surg, 1995. 121(7873143): p. 278-282.
367. Kligerman, J., Lima, R. A., Soares, J. R., Prado, L., Dias, F. L., Freitas, E. Q., et.al. Supraomohyoid neck dissection in the treatment of T1/T2 squamous cell carcinoma of oral cavity. Am J Surg, 1994. 168(7977957): p. 391-394.
368. Fakih, A. R., Rao, R. S., Borges, A. M., Patel, A. R., Elective versus therapeutic neck dissection in early carcinoma of the oral tongue. Am J Surg, 1989. 158(4): p. 309-313.
369. Ho, C. M., Lam, K. H., Wei, W. I., Lau, W. F., Treatment of neck nodes in oral cancer. Surg Oncol, 1992. 1(1341238): p. 73-78.
370. Lydiatt, D. D., Robbins, K. T., Byers, R. M., Wolf, P. F., Treatment of stage I and II oral tongue cancer. Head Neck, 1993. 15(4): p. 308-312.

371. Vandenbrouck, C., Sancho-Garnier, H., Chassagne, D., Saravane, D., Cachin, Y., Micheau, C., Elective versus therapeutic radical neck dissection in epidermoid carcinoma of the oral cavity: results of a randomized clinical trial. Cancer, 1980. 46(2): p. 386-390.
372. Akhtar, Shabbir, Ikram, Mubasher, Ghaffar, Shehzad, Neck involvement in early carcinoma of tongue. Is elective neck dissection warranted?. JPMA - Journal of the Pakistan Medical Association, 2007. 57(6): p. 305-7.
373. Robbins, K. Thomas, Clayman, Garry, Levine, Paul A., Medina, Jesus, Sessions, Roy, Shaha, Ashok, et.al. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. Arch Otolaryngol Head Neck Surg, 2002. 128(12117328): p. 751-758.
374. D'Cruz, A. K., Vaish, R., Kapre, N., Dandekar, M., Gupta, S., Hawaldar, R., et.al. Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer. N Engl J Med, 2015. 373(6): p. 521-9., https://www.ncbi.nlm.nih.gov/pubmed/26027881
375. De Silva, R. K., Siriwardena, Bsms, Samaranayaka, A., Abeyasinghe, Wamul, Tilakaratne, W. M., A model to predict nodal metastasis in patients with oral squamous cell carcinoma. PLoS One, 2018. 13(8): p. e0201755., https://www.ncbi.nlm.nih.gov/pubmed/30091996
376. Feng, Z., Li, J. N., Li, C. Z., Guo, C. B., Elective neck dissection versus observation for cN0 neck of squamous cell carcinoma primarily located in the maxillary gingiva and alveolar ridge: a retrospective study of 129 cases. Oral Surg Oral Med Oral Pathol Oral Radiol, 2013. 116(5): p. 556-61., https://www.ncbi.nlm.nih.gov/pubmed/24119520
377. Shah, J. P., Candela, F. C., Poddar, A. K., The patterns of cervical lymph node metastases from squamous carcinoma of the oral cavity. Cancer, 1990. 66(1): p. 109-113.
378. Byers, R. M., Wolf, P. F., Ballantyne, A. J., Rationale for elective modified neck dissection. Head Neck Surg, 1988. 10(3): p. 160-167.
379. Johnson, J. T., Carcinoma of the larynx: selective approach to the management of cervical lymphatics. Ear Nose Throat J, 1994. 73(5): p. 303-5.
380. Manni, J. J., van den Hoogen, F. J., Supraomohyoid neck dissection with frozen section biopsy as a staging procedure in the clinically node-negative neck in carcinoma of the oral cavity. Am J Surg, 1991. 162(4): p. 373-376.
381. Leon, X., Quer, M., Orus, C., Sancho, F. J., Bague, S., Burgues, J., Selective dissection of levels II-III with intraoperative control of the upper and middle jugular nodes: a therapeutic option for the N0 neck. Head Neck, 2001. 23(6): p. 441-446.
382. Byers, R. M., Modified neck dissection. A study of 967 cases from 1970 to 1980. Am J Surg, 1985. 150(4): p. 414-21.
383. Bocca, E., Pignataro, O., Oldini, C., Cappa, C., Functional neck dissection: an evaluation and review of 843 cases. Laryngoscope, 1984. 94(7): p. 942-945.
384. Molinari, R., Cantu, G., Chiesa, F., Grandi, C., Retrospective comparison of conservative and radical neck dissection in laryngeal cancer. Ann Otol Rhinol Laryngol, 1980. 89(6 Pt 1): p. 578-81.
385. Spiro, R. H., Gallo, O., Shah, J. P., Selective jugular node dissection in patients with squamous carcinoma of the larynx or pharynx. Am J Surg, 1993. 166(4): p. 399-402.
386. Bier, J., Radical neck dissection versus conservative neck dissection for squamous cell carcinoma of the oral cavity. Recent Results Cancer Res, 1994. 134: p. 57-62.
387. Grandi, C., Mingardo, M., Guzzo, M., Licitra, L., Podrecca, S., Molinari, R., Salvage surgery of cervical recurrences after neck dissection or radiotherapy. Head Neck, 1993. 15(4): p. 292-295.
388. Dias, F. L., Kligerman, J., Matos de Sa, G., Arcuri, R. A., Freitas, E. Q., Farias, T., et.al. Elective neck dissection versus observation in stage I squamous cell carcinomas of the tongue and floor of the mouth. Otolaryngol Head Neck Surg, 2001. 125(1): p. 23-29.
389. Wolfensberger, M., Zbaeren, P., Dulguerov, P., Muller, W., Arnoux, A., Schmid, S., Surgical treatment of early oral carcinoma-results of a prospective controlled multicenter study. Head Neck, 2001. 23(7): p. 525-530.

390. Sagheb, K., Sagheb, K., Taylor, K. J., Al-Nawas, B., Walter, C., Cervical metastases of squamous cell carcinoma of the maxilla: a retrospective study of 25 years. Clin Oral Investig, 2014. 18(4): p. 1221-7., http://www.ncbi.nlm.nih.gov/pubmed/23934238
391. D'Cruz, Anil K., Siddachari, Ravichand C., Walvekar, Rohan R., Pantvaidya, Gouri H., Chaukar, Devendra A., Deshpande, Mandar S., et.al. Elective neck dissection for the management of the N0 neck in early cancer of the oral tongue: need for a randomized controlled trial. Head & Neck, 2009. 31(5): p. 618-24.
392. Huang, Shiang-Fu, Kang, Chung-Jan, Lin, Chen-Yu, Fan, Kang-Hsing, Yen, Tzu-Chen, Wang, Hung-Ming, et.al. Neck treatment of patients with early stage oral tongue cancer: comparison between observation, supraomohyoid dissection, and extended dissection. Cancer, 2008. 112(5): p. 1066-75.
393. Beltramini, G. A., Massarelli, O., Demarchi, M., Copelli, C., Cassoni, A., Valentini, V., et.al. Is neck dissection needed in squamous-cell carcinoma of the maxillary gingiva, alveolus, and hard palate? A multicentre Italian study of 65 cases and literature review. Oral Oncol, 2012. 48(2): p. 97-101., https://www.ncbi.nlm.nih.gov/pubmed/21993155
394. Robbins, K. Thomas, Clayman, Garry, Levine, Paul A., Medina, Jesus, Sessions, Roy, Shaha, Ashok, et.al. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery. Arch Otolaryngol Head Neck Surg, 2002. 128(12117328): p. 751-758.
395. Piedbois, P., Mazeron, J. J., Haddad, E., Coste, A., Martin, M., Levy, C., et.al. Stage I-II squamous cell carcinoma of the oral cavity treated by iridium-192: is elective neck dissection indicated?. Radiother Oncol, 1991. 21(2): p. 100-106.
396. Yuen, A. P., Wei, W. I., Lam, L. K., Ho, W. K., Kwong, D., Results of surgical salvage of locoregional recurrence of carcinoma of the tongue after radiotherapy failure. Ann Otol Rhinol Laryngol, 1997. 106(9): p. 779-782.
397. Weiss, M. H., Harrison, L. B., Isaacs, R. S., Use of decision analysis in planning a management strategy for the stage N0 neck. Arch Otolaryngol Head Neck Surg, 1994. 120(8018319): p. 699-702.
398. Iype, Elizabeth Mathew, Sebastian, Paul, Mathew, Aleyamma, Balagopal, P. G., Varghese, Bipin T., Thomas, Shaji, The role of selective neck dissection (I-III) in the treatment of node negative (N0) neck in oral cancer. Oral Oncology, 2008. 44(12): p. 1134-8.
399. Yuen, Anthony Po-Wing, Ho, Chiu Ming, Chow, Tam Lin, Tang, Lap Chiu, Cheung, Wing Yung, Ng, Raymond Wai-Man, et.al. Prospective randomized study of selective neck dissection versus observation for N0 neck of early tongue carcinoma. Head & Neck, 2009. 31(6): p. 765-72.
400. Givi, B., Eskander, A., Awad, M. I., Kong, Q., Montero, P. H., Palmer, F. L., et.al. Impact of elective neck dissection on the outcome of oral squamous cell carcinomas arising in the maxillary alveolus and hard palate. Head Neck, 2016. 38 Suppl 1: p. E1688-94., https://www.ncbi.nlm.nih.gov/pubmed/26614119
401. Jin, W. L., Ye, W. M., Zheng, J. W., Zhou, L., Zhu, H. G., Zhang, Z. Y., et.al. Occult cervical lymph node metastases in 100 consecutive patients with cN0 tongue cancer. Chinese Medical Journal, 2008. 121 (19): p. 1871-1874.
402. Byers, R. M., Weber, R. S., Andrews, T., McGill, D., Kare, R., Wolf, P., Frequency and therapeutic implications of „skip metastases" in the neck from squamous carcinoma of the oral tongue. Head Neck, 1997. 19(1): p. 14-9.
403. Corlette, Toby H., Cole, Ian E., Albsoul, Nader, Ayyash, Mohammad, Neck dissection of level IIb: is it really necessary?. Laryngoscope, 2005. 115(9): p. 1624-6.
404. Elsheikh, Mohamed Nasser, Mahfouz, Magdy Elsayed, Elsheikh, Ehab, Level IIb lymph nodes metastasis in elective supraomohyoid neck dissection for oral cavity squamous cell carcinoma: a molecular-based study. Laryngoscope, 2005. 115(9): p. 1636-40.
405. Lim, Young Chang, Song, Mee Hyun, Kim, Sang Cheol, Kim, Kwang Moon, Choi, Eun Chang, Preserving level IIb lymph nodes in elective supraomohyoid neck dissection for oral

cavity squamous cell carcinoma. Archives of Otolaryngology—Head & Neck Surgery, 2004. 130(9): p. 1088-91.
406. Santoro, Roberto, Franchi, Alessandro, Gallo, Oreste, Burali, Giulia, de' Campora, Enrico, Nodal metastases at level IIb during neck dissection for head and neck cancer: clinical and pathologic evaluation. Head & Neck, 2008. 30(11): p. 1483-7.
407. Kowalski, L. P., Bagietto, R., Lara, J. R., Santos, R. L., Tagawa, E. K., Santos, I. R., Factors influencing contralateral lymph node metastasis from oral carcinoma. Head Neck, 1999. 21(2): p. 104-110.
408. De Zinis, Luca Oscar Redaelli, Bolzoni, Andrea, Piazza, Cesare, Nicolai, Piero, Prevalence and localization of nodal metastases in squamous cell carcinoma of the oral cavity: role and extension of neck dissection. European Archives of Oto-Rhino-Laryngology, 2006. 263(12): p. 1131-5.
409. Yu, Shibin, Li, Jinrong, Li, Zubing, Zhang, Wenfeng, Zhao, Jihong, Efficacy of supraomohyoid neck dissection in patients with oral squamous cell carcinoma and negative neck. American Journal of Surgery, 2006. 191(1): p. 94-9.
410. Liaw, Gwo-An, Yen, Ching-Yu, Chiang, Wei-Fan, Lee, Chin-Hai, Yang, Cheng, Chiou, Chang-Ta, et.al. Outcome of treatment with total main tumor resection and supraomohyoid neck dissection in oral squamous cell carcinoma. Journal of the Formosan Medical Association, 2006. 105(12): p. 971-7.
411. Poeschl, P. W., Seemann, R., Czembirek, C., Russmueller, G., Sulzbacher, I., Selzer, E., et.al. Impact of elective neck dissection on regional recurrence and survival in cN0 staged oral maxillary squamous cell carcinoma. Oral Oncol, 2012. 48(2): p. 173-8., https://www.ncbi.nlm.nih.gov/pubmed/21974917
412. Berger, M., Grau, E., Saure, D., Ristow, O., Thiele, O., Hofele, C., et.al. Occurrence of cervical lymph node metastasis of maxillary squamous cell carcinoma - A monocentric study of 171 patients. J Craniomaxillofac Surg, 2015. 43(10): p. 2195-9., https://www.ncbi.nlm.nih.gov/pubmed/26515265
413. Alvarez Amezaga, J., Barbier Herrero, L., Pijoan del Barrio, J. I., Martin Rodriguez, J. C., Romo Simon, L., Genolla Subirats, J., et.al. Diagnostic efficacy of sentinel node biopsy in oral squamous cell carcinoma. Cohort study and meta-analysis. Med Oral Patol Oral Cir Bucal, 2007. 12(3): p. E235-43.
414. Govers, T. M., Hannink, G., Merkx, M. A., Takes, R. P., Rovers, M. M., Sentinel node biopsy for squamous cell carcinoma of the oral cavity and oropharynx: a diagnostic meta-analysis. Oral Oncol, 2013. 49(8): p. 726-32., https://www.ncbi.nlm.nih.gov/pubmed/23680537
415. Lin, R., Yan, J., Liu, W., Fan, T., Tang, L., The predictive value of cervical lymph node metastasis through sentinel lymph node biopsy in patients with oral cancer: A meta-analysis. J Cancer Res Ther, 2016. 12(Supplement): p. C256-C259., https://www.ncbi.nlm.nih.gov/pubmed/28230030
416. Liu, M., Wang, S. J., Yang, X., Peng, H., Diagnostic Efficacy of Sentinel Lymph Node Biopsy in Early Oral Squamous Cell Carcinoma: A Meta-Analysis of 66 Studies. PLoS One, 2017. 12(1): p. e0170322., https://www.ncbi.nlm.nih.gov/pubmed/28107500
417. Paleri, V., Rees, G., Arullendran, P., Shoaib, T., Krishman, S., Sentinel node biopsy in squamous cell cancer of the oral cavity and oral pharynx: a diagnostic meta-analysis. Head Neck, 2005. 27(9): p. 739-47., https://www.ncbi.nlm.nih.gov/pubmed/16047368
418. Thompson, C. F., St John, M. A., Lawson, G., Grogan, T., Elashoff, D., Mendelsohn, A. H., Diagnostic value of sentinel lymph node biopsy in head and neck cancer: a meta-analysis. Eur Arch Otorhinolaryngol, 2013. 270(7): p. 2115-22., https://www.ncbi.nlm.nih.gov/pubmed/23263205
419. Yamauchi, K., Kogashiwa, Y., Nakamura, T., Moro, Y., Nagafuji, H., Kohno, N., Diagnostic evaluation of sentinel lymph node biopsy in early head and neck squamous cell

carcinoma: a meta-analysis. Head Neck, 2015. 37(1): p. 127-33., https://www.ncbi.nlm.nih.gov/pubmed/24478151

420. Alkureishi, L. W., Ross, G. L., Shoaib, T., Soutar, D. S., Robertson, A. G., Thompson, R., et.al. Sentinel node biopsy in head and neck squamous cell cancer: 5-year follow-up of a European multicenter trial. Ann Surg Oncol, 2010. 17(9): p. 2459-64., https://www.ncbi.nlm.nih.gov/pubmed/20552410
421. Fan, S. F., Zeng, Z. Y., Peng, H. W., Guo, Z. M., Wang, S. L., Zhang, Q., Sentinel lymph node biopsy versus elective neck dissection in patients with cT1-2N0 oral tongue squamous cell carcinoma. Oral Surg Oral Med Oral Pathol Oral Radiol, 2014. 117(2): p. 186-90., https://www.ncbi.nlm.nih.gov/pubmed/24332157
422. Moya-Plana, A., Auperin, A., Guerlain, J., Gorphe, P., Casiraghi, O., Mamelle, G., et.al. Sentinel node biopsy in early oral squamous cell carcinomas: Long-term follow-up and nodal failure analysis. Oral Oncol, 2018. 82: p. 187-194., https://www.ncbi.nlm.nih.gov/pubmed/29909896
423. Schiefke, F., Akdemir, M., Weber, A., Akdemir, D., Singer, S., Frerich, B., Function, postoperative morbidity, and quality of life after cervical sentinel node biopsy and after selective neck dissection. Head Neck, 2009. 31(4): p. 503-12., https://www.ncbi.nlm.nih.gov/pubmed/19156833
424. Inoue, Hiroyuki, Nibu, Ken-Ichi, Saito, Miki, Otsuki, Naoki, Ishida, Haruhiko, Onitsuka, Tetsuro, et.al. Quality of life after neck dissection. Archives of Otolaryngology—Head & Neck Surgery, 2006. 132(6): p. 662-6.
425. Laverick, S., Lowe, D., Brown, J. S., Vaughan, E. D., Rogers, S. N., The Impact of Neck Dissection on Health-Related Quality of Life. Archives of Otolaryngology - Head and Neck Surgery, 2004. 130 (2): p. 149-154.
426. Jesse, R. H., Ballantyne, A. J., Larson, D., Radical or modified neck dissection: a therapeutic dilemma. Am J Surg, 1978. 136(707734): p. 516-519.
427. Lingeman, R. E., Helmus, C., Stephens, R., Ulm, J., Neck dissection: radical or conservative. Ann Otol Rhinol Laryngol, 1977. 86(6 Pt 1): p. 737-44.
428. Brandenburg, J. H., Lee, C. Y., The eleventh nerve in radical neck surgery. Laryngoscope, 1981. 91(11): p. 1851-1859.
429. Andersen, P. E., Shah, J. P., Cambronero, E., Spiro, R. H., The role of comprehensive neck dissection with preservation of the spinal accessory nerve in the clinically positive neck. Am J Surg, 1994. 168(7977984): p. 499-502.
430. Bocca, E., Pignataro, O., A conservation technique in radical neck dissection. Ann Otol Rhinol Laryngol, 1967. 76(5): p. 975-987.
431. Chu, W., Strawitz, J. G., Results in suprahyoid, modified radical, and standard radical neck dissections for metastatic squamous cell carcinoma: recurrence and survival. Am J Surg, 1978. 136(707733): p. 512-515.
432. Kohler, Hugo Fontan, Cunha, Isabella Werneck da, Kowalski, Luiz Paulo, Impact of modified radical neck dissections on the number of retrieved nodes, recurrence and survival. Revista Brasileira de Otorrinolaringologia, 2010. 76(3): p. 374-7.
433. Patel, Rajan S., Clark, Jonathan R., Gao, Kan, O'Brien, Christopher J., Effectiveness of selective neck dissection in the treatment of the clinically positive neck. Head & Neck, 2008. 30(9): p. 1231-6.
434. Rapoport, Abrao, Ortellado, Daniel Kanabben, Amar, Ali, Lehn, Carlos Neutzling, Dedivitis, Rogerio Aparecido, Perez, Ricardo Salinas, et.al. Radical versus supraomohyoid neck dissection in the treatment of squamous cell carcinoma of the inferior level of the mouth. Revista Brasileira de Otorrinolaringologia, 2007. 73(5): p. 641-6.
435. Chepeha, Douglas B., Hoff, Paul T., Taylor, Rodney J., Bradford, Carol R., Teknos, Theodoros N., Esclamado, Ramon M., Selective neck dissection for the treatment of neck metastasis from squamous cell carcinoma of the head and neck. Laryngoscope, 2002. 112(12148849): p. 434-438.

436. Andersen, Peter E., Warren, Frank, Spiro, Jeffrey, Burningham, Alan, Wong, Richard, Wax, Mark K., et.al. Results of selective neck dissection in management of the node-positive neck. Arch Otolaryngol Head Neck Surg, 2002. 128(12365890): p. 1180-1184.
437. Shepard, Peter M., Olson, Jordan, Harari, Paul M., Leverson, Glen, Hartig, Gregory K., Therapeutic selective neck dissection outcomes. Otolaryngology - Head & Neck Surgery, 2010. 142(5): p. 741-6.
438. Koerdt, S., Rockl, J., Rommel, N., Mucke, T., Wolff, K. D., Kesting, M. R., Lymph node management in the treatment of oral cancer: Analysis of a standardized approach. J Craniomaxillofac Surg, 2016. 44(10): p. 1737-1742., https://www.ncbi.nlm.nih.gov/pubmed/27580851
439. Liang, L. Z., Liu, X. Q., Kong, Q. Y., Liao, G. Q., Selective Versus Comprehensive Neck Dissection in Patients With T1 and T2 Oral Squamous Cell Carcinoma and cN0pN(+) Neck. J Oral Maxillofac Surg, 2016. 74(6): p. 1271-6., https://www.ncbi.nlm.nih.gov/pubmed/26850871
440. Liao, C. T., Hsueh, C., Lee, L. Y., Lin, C. Y., Fan, K. H., Wang, H. M., et.al. Neck dissection field and lymph node density predict prognosis in patients with oral cavity cancer and pathological node metastases treated with adjuvant therapy. Oral Oncol, 2012. 48(4): p. 329-36., https://www.ncbi.nlm.nih.gov/pubmed/22104249
441. Schiff, B. A., Roberts, D. B., El-Naggar, A., Garden, A. S., Myers, J. N., Selective vs modified radical neck dissection and postoperative radiotherapy vs observation in the treatment of squamous cell carcinoma of the oral tongue. Arch Otolaryngol Head Neck Surg, 2005. 131(10): p. 874-8., https://www.ncbi.nlm.nih.gov/pubmed/16230589
442. Shin, Y. S., Koh, Y. W., Kim, S. H., Choi, E. C., Selective neck dissection for clinically node-positive oral cavity squamous cell carcinoma. Yonsei Med J, 2013. 54(1): p. 139-44., https://www.ncbi.nlm.nih.gov/pubmed/23225810
443. Chen, M. M., Harris, J. P., Hara, W., Sirjani, D., Divi, V., Association of Postoperative Radiotherapy With Survival in Patients With N1 Oral Cavity and Oropharyngeal Squamous Cell Carcinoma. JAMA Otolaryngol Head Neck Surg, 2016. 142(12): p. 1224-1230., https://www.ncbi.nlm.nih.gov/pubmed/27832255
444. Lim, Young Chang, Song, Mee Hyun, Kim, Sang Cheol, Kim, Kwang Moon, Choi, Eun Chang, Preserving level IIb lymph nodes in elective supraomohyoid neck dissection for oral cavity squamous cell carcinoma. Archives of Otolaryngology—Head & Neck Surgery, 2004. 130(9): p. 1088-91.
445. De Zinis, Luca Oscar Redaelli, Bolzoni, Andrea, Piazza, Cesare, Nicolai, Piero, Prevalence and localization of nodal metastases in squamous cell carcinoma of the oral cavity: role and extension of neck dissection. European Archives of Oto-Rhino-Laryngology, 2006. 263(12): p. 1131-5.
446. Jesse, R. H., Ballantyne, A. J., Larson, D., Radical or modified neck dissection: a therapeutic dilemma. Am J Surg, 1978. 136(707734): p. 516-519.
447. Lingeman, R. E., Helmus, C., Stephens, R., Ulm, J., Neck dissection: radical or conservative. Ann Otol Rhinol Laryngol, 1977. 86(6 Pt 1): p. 737-44.
448. Brandenburg, J. H., Lee, C. Y., The eleventh nerve in radical neck surgery. Laryngoscope, 1981. 91(11): p. 1851-1859.
449. Andersen, P. E., Shah, J. P., Cambronero, E., Spiro, R. H., The role of comprehensive neck dissection with preservation of the spinal accessory nerve in the clinically positive neck. Am J Surg, 1994. 168(7977984): p. 499-502.
450. Bocca, E., Pignataro, O., A conservation technique in radical neck dissection. Ann Otol Rhinol Laryngol, 1967. 76(5): p. 975-987.
451. Chu, W., Strawitz, J. G., Results in suprahyoid, modified radical, and standard radical neck dissections for metastatic squamous cell carcinoma: recurrence and survival. Am J Surg, 1978. 136(707733): p. 512-515.

452. Kohler, Hugo Fontan, Cunha, Isabella Werneck da, Kowalski, Luiz Paulo, Impact of modified radical neck dissections on the number of retrieved nodes, recurrence and survival. Revista Brasileira de Otorrinolaringologia, 2010. 76(3): p. 374-7.
453. Patel, Rajan S., Clark, Jonathan R., Gao, Kan, O'Brien, Christopher J., Effectiveness of selective neck dissection in the treatment of the clinically positive neck. Head & Neck, 2008. 30(9): p. 1231-6.
454. Rapoport, Abrao, Ortellado, Daniel Kanabben, Amar, Ali, Lehn, Carlos Neutzling, Dedivitis, Rogerio Aparecido, Perez, Ricardo Salinas, et.al. Radical versus supraomohyoid neck dissection in the treatment of squamous cell carcinoma of the inferior level of the mouth. Revista Brasileira de Otorrinolaringologia, 2007. 73(5): p. 641-6.
455. Chepeha, Douglas B., Hoff, Paul T., Taylor, Rodney J., Bradford, Carol R., Teknos, Theodoros N., Esclamado, Ramon M., Selective neck dissection for the treatment of neck metastasis from squamous cell carcinoma of the head and neck. Laryngoscope, 2002. 112(12148849): p. 434-438.
456. Andersen, Peter E., Warren, Frank, Spiro, Jeffrey, Burningham, Alan, Wong, Richard, Wax, Mark K., et.al. Results of selective neck dissection in management of the node-positive neck. Arch Otolaryngol Head Neck Surg, 2002. 128(12365890): p. 1180-1184.
457. Shepard, Peter M., Olson, Jordan, Harari, Paul M., Leverson, Glen, Hartig, Gregory K., Therapeutic selective neck dissection outcomes. Otolaryngology - Head & Neck Surgery, 2010. 142(5): p. 741-6.
458. Brizel, David M., Prosnitz, Robert G., Hunter, Shannon, Fisher, Samuel R., Clough, Robert L., Downey, Mary Ann, et.al. Necessity for adjuvant neck dissection in setting of concurrent chemoradiation for advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys, 2004. 58(15050318): p. 1418-1423.
459. Brizel, David M., Prosnitz, Robert G., Hunter, Shannon, Fisher, Samuel R., Clough, Robert L., Downey, Mary Ann, et.al. Necessity for adjuvant neck dissection in setting of concurrent chemoradiation for advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys, 2004. 58(15050318): p. 1418-1423.
460. Frank, Douglas K., Hu, Kenneth S., Culliney, Bruce E., Persky, Mark S., Nussbaum, Moses, Schantz, Stimson P., et.al. Planned neck dissection after concomitant radiochemotherapy for advanced head and neck cancer. Laryngoscope, 2005. 115(15933512): p. 1015-1020.
461. Wang, S. J., Wang, M. B., Yip, H., Calcaterra, T. C., Combined radiotherapy with planned neck dissection for small head and neck cancers with advanced cervical metastases. Laryngoscope, 2000. 110(11081586): p. 1794-1797.
462. Pagedar, N. A., Gilbert, R. W., Selective neck dissection: a review of the evidence. Oral Oncol, 2009. 45(4-5): p. 416-20., https://www.ncbi.nlm.nih.gov/pubmed/19091624
463. Ritoe, S. C., Krabbe, P. F., Jansen, M. M., Festen, J., Joosten, F. B., Kaanders, J. H., et.al. Screening for second primary lung cancer after treatment of laryngeal cancer. Laryngoscope, 2002. 112(11): p. 2002-8.
464. Agarwal, S. K., Akali, N. R., Sarin, D., Prospective analysis of 231 elective neck dissections in oral squamous cell carcinoma with node negative neck-To decide the extent of neck dissection. Auris Nasus Larynx, 2018. 45(1): p. 156-161., https://www.ncbi.nlm.nih.gov/pubmed/28662778
465. Koo, Bon Seok, Lim, Young Chang, Lee, Jin Seok, Choi, Eun Chang, Management of contralateral N0 neck in oral cavity squamous cell carcinoma. Head & Neck, 2006. 28(10): p. 896-901.
466. Koo, Bon Seok, Lim, Young Chang, Lee, Jin Seok, Choi, Eun Chang, Management of contralateral N0 neck in oral cavity squamous cell carcinoma. Head & Neck, 2006. 28(10): p. 896-901.
467. Bajwa, M. S., McMillan, R., Khattak, O., Thomas, M., Krishnan, O. P., Webster, K., Neck recurrence after level I-IV or I-III selective neck dissection in the management of the clinically

N0 neck in patients with oral squamous cell carcinoma. Head Neck, 2011. 33(3): p. 403-6., https://www.ncbi.nlm.nih.gov/pubmed/20629073

468. Jones, H. B., Sykes, A., Bayman, N., Sloan, P., Swindell, R., Patel, M., et.al. The impact of lymphovascular invasion on survival in oral carcinoma. Oral Oncol, 2009. 45(1): p. 10-5., https://www.ncbi.nlm.nih.gov/pubmed/18620889
469. Pathak, K. A., Das, A. K., Agarwal, R., Talole, S., Deshpande, M. S., Chaturvedi, P., et.al. Selective neck dissection (I-III) for node negative and node positive necks. Oral Oncology, 2006. 42 (8): p. 837-841.
470. Matsushita, Y., Yanamoto, S., Takahashi, H., Yamada, S., Naruse, T., Sakamoto, Y., et.al. A clinicopathological study of perineural invasion and vascular invasion in oral tongue squamous cell carcinoma. Int J Oral Maxillofac Surg, 2015. 44(5): p. 543-8., https://www.ncbi.nlm.nih.gov/pubmed/25697063
471. Vikram, B., Strong, E. W., Shah, J. P., Spiro, R., Failure in the neck following multimodality treatment for advanced head and neck cancer. Head Neck Surg, 1984. 6(3): p. 724-9.
472. Cariati, P., Cabello Serrano, A., Fernandez Solis, J., Martinez Lara, I., Distribution of cervical metastasis in tongue cancer: Are occult metastases predictable? A retrospective study of 117 oral tongue carcinomas. J Craniomaxillofac Surg, 2018. 46(1): p. 155-161., https://www.ncbi.nlm.nih.gov/pubmed/29174473
473. Bernier, J., Domenge, C., Ozsahin, M., Matuszewska, K., Lefebvre, J. L., Greiner, R. H., et.al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med, 2004. 350(19): p. 1945-52.
474. Cooper, J. S., Pajak, T. F., Forastiere, A. A., Jacobs, J., Campbell, B. H., Saxman, S. B., et.al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med, 2004. 350(19): p. 1937-44.
475. Argiris, Athanassios, Stenson, Kerstin M., Brockstein, Bruce E., Mittal, Bharat B., Pelzer, Harold, Kies, Merrill S., et.al. Neck dissection in the combined-modality therapy of patients with locoregionally advanced head and neck cancer. Head Neck, 2004. 26(15122662): p. 447-455.
476. Clayman, G. L., Johnson, C. J., Morrison, W., Ginsberg, L., Lippman, S. M., The role of neck dissection after chemoradiotherapy for oropharyngeal cancer with advanced nodal disease. Arch Otolaryngol Head Neck Surg, 2001. 127(11177029): p. 135-139.
477. Mabanta, S. R., Mendenhall, W. M., Stringer, S. P., Cassisi, N. J., Salvage treatment for neck recurrence after irradiation alone for head and neck squamous cell carcinoma with clinically positive neck nodes. Head Neck, 1999. 21(7): p. 591-594.
478. Byers, R. M., Clayman, G. L., Guillamondequi, O. M., Peters, L. J., Goepfert, H., Resection of advanced cervical metastasis prior to definitive radiotherapy for primary squamous carcinomas of the upper aerodigestive tract. Head Neck, 1992. 14(2): p. 133-138.
479. Reddy, A. N., Eisele, D. W., Forastiere, A. A., Lee, D. J., Westra, W. H., Califano, J. A., Neck dissection followed by radiotherapy or chemoradiotherapy for small primary oropharynx carcinoma with cervical metastasis. Laryngoscope, 2005. 115(7): p. 1196-200.
480. Bhandari, K., Wang, D. C., Li, S. C., Jiang, B. H., Guo, Y. X., Koirala, U., et.al. Primary cN0 lip squamous cell carcinoma and elective neck dissection: Systematic review and meta-analysis. Head Neck, 2015. 37(9): p. 1392-400., https://www.ncbi.nlm.nih.gov/pubmed/24839013
481. Eskiizmir, G., Ozgur, E., Karaca, G., Temiz, P., Yanar, N. H., Ozyurt, B. C., Stage is a prognostic factor for surgically treated patients with early-stage lip cancer for whom a ‚wait and see' policy in terms of neck status has been implemented. J Laryngol Otol, 2017. 131(10): p. 889-894., https://www.ncbi.nlm.nih.gov/pubmed/28807064
482. Altinyollar, H., Bulut, H., Berberoglu, U., Is suprahyoid dissection a diagnostic operation in lower lip carcinoma?. J Exp Clin Cancer Res, 2002. 21(1): p. 29-30., https://www.ncbi.nlm.nih.gov/pubmed/12071525

483. Agostini, T., Spinelli, G., Arcuri, F., Perello, R., Metastatic Squamous Cell Carcinoma of the Lower Lip: Analysis of the 5-Year Survival Rate. Arch Craniofac Surg, 2017. 18(2): p. 105-111., https://www.ncbi.nlm.nih.gov/pubmed/28913316
484. Vanderlei, J. P., Pereira-Filho, F. J., da Cruz, F. A., de Mello, F. L., Kruschewsky Lde, S., de Freitas, L. C., et.al. Management of neck metastases in T2N0 lip squamous cell carcinoma. Am J Otolaryngol, 2013. 34(2): p. 103-6., https://www.ncbi.nlm.nih.gov/pubmed/23164629
485. Khalil, H. H., Elaffandi, A. H., Afifi, A., Alsayed, Y., Mahboub, T., El-Refaie, K. M., Sentinel lymph node biopsy (SLNB) in management of N0 stage T1-T2 lip cancer as a „same day" procedure. Oral Oncol, 2008. 44(6): p. 608-12., https://www.ncbi.nlm.nih.gov/pubmed/17936674
486. Wermker, K., Belok, F., Schipmann, S., Klein, M., Schulze, H. J., Hallermann, C., Prediction model for lymph node metastasis and recommendations for elective neck dissection in lip cancer. J Craniomaxillofac Surg, 2015. 43(4): p. 545-52., https://www.ncbi.nlm.nih.gov/pubmed/25753473
487. Vartanian, J. G., Carvalho, A. L., de Araujo Filho, M. J., Junior, M. H., Magrin, J., Kowalski, L. P., Predictive factors and distribution of lymph node metastasis in lip cancer patients and their implications on the treatment of the neck. Oral Oncol, 2004. 40(2): p. 223-7., https://www.ncbi.nlm.nih.gov/pubmed/14693248
488. Ozkul, Y., Songu, M., Imre, A., Tunc, E., Ozkul, Z., Arslanoglu, S., et.al. Early stage squamous cell carcinoma of the lower lip: predictive factors for recurrence. J Laryngol Otol, 2016. 130(4): p. 369-72., https://www.ncbi.nlm.nih.gov/pubmed/26860988
489. Szewczyk, M., Pazdrowski, J., Golusinski, P., Danczak-Pazdrowska, A., Marszalek, S., Golusinski, W., Analysis of selected risk factors for nodal metastases in head and neck cutaneous squamous cell carcinoma. Eur Arch Otorhinolaryngol, 2015. 272(10): p. 3007-12., https://www.ncbi.nlm.nih.gov/pubmed/25217080
490. Barry, C. P., Wong, D., Clark, J. R., Shaw, R. J., Gupta, R., Magennis, P., et.al. Postoperative radiotherapy for patients with oral squamous cell carcinoma with intermediate risk of recurrence: A case match study. Head Neck, 2017. 39(7): p. 1399-1404., https://www.ncbi.nlm.nih.gov/pubmed/28452199
491. Moergel, M., Meurer, P., Ingel, K., Wendt, T. G., Al-Nawas, B., Effectiveness of postoperative radiotherapy in patients with small oral and oropharyngeal squamous cell carcinoma and concomitant ipsilateral singular cervical lymph node metastasis (pN1) : A meta-analysis. Strahlenther Onkol, 2011. 187(6): p. 337-43., https://www.ncbi.nlm.nih.gov/pubmed/21603991
492. Unterhuber, T., Duma, M. N., Rau, A., Nieberler, M., Wolff, K. D., Kesting, M. R., Oral squamous cell carcinoma: the impact of stage-dependent therapy regimes on postoperative disease recurrence. Oral Surg Oral Med Oral Pathol Oral Radiol, 2016. 121(2): p. 133-8., https://www.ncbi.nlm.nih.gov/pubmed/26711710
493. Villaret, D. B., Futran, N. A., The indications and outcomes in the use of osteocutaneous radial forearm free flap. Head Neck, 2003. 25(6): p. 475-81.
494. Suh, J. D., Sercarz, J. A., Abemayor, E., Calcaterra, T. C., Rawnsley, J. D., Alam, D., et.al. Analysis of outcome and complications in 400 cases of microvascular head and neck reconstruction. Arch Otolaryngol Head Neck Surg, 2004. 130(8): p. 962-6.
495. Castelli, M. L., Pecorari, G., Succo, G., Bena, A., Andreis, M., Sartoris, A., Pectoralis major myocutaneous flap: analysis of complications in difficult patients. Eur Arch Otorhinolaryngol, 2001. 258(10): p. 542-5.
496. Chiarini, L., De Santis, G., Bedogni, A., Nocini, P. F., Lining the mouth floor with prelaminated fascio-mucosal free flaps: clinical experience. Microsurgery, 2002. 22(5): p. 177-86.
497. Azizzadeh, B., Yafai, S., Rawnsley, J. D., Abemayor, E., Sercarz, J. A., Calcaterra, T. C., et.al. Radial forearm free flap pharyngoesophageal reconstruction. Laryngoscope, 2001. 111(5): p. 807-10.

498. Jol, J. K., Quak, J. J., de Bree, R., Leemans, C. R., Larynx preservation surgery for advanced posterior pharyngeal wall carcinoma with free flap reconstruction: a critical appraisal. Oral Oncol, 2003. 39(6): p. 552-8.
499. Disa, J. J., Pusic, A. L., Hidalgo, D. A., Cordeiro, P. G., Microvascular reconstruction of the hypopharynx: defect classification, treatment algorithm, and functional outcome based on 165 consecutive cases. Plast Reconstr Surg, 2003. 111(2): p. 652-60; discussion 661-3.
500. Genden, E. M., Kaufman, M. R., Katz, B., Vine, A., Urken, M. L., Tubed gastro-omental free flap for pharyngoesophageal reconstruction. Arch Otolaryngol Head Neck Surg, 2001. 127(7): p. 847-53.
501. Hayden, R. E., Deschler, D. G., Lateral thigh free flap for head and neck reconstruction. Laryngoscope, 1999. 109(9): p. 1490-4.
502. Makitie, A. A., Beasley, N. J., Neligan, P. C., Lipa, J., Gullane, P. J., Gilbert, R. W., Head and neck reconstruction with anterolateral thigh flap. Otolaryngol Head Neck Surg, 2003. 129(5): p. 547-55.
503. Julieron, M., Germain, M. A., Schwaab, G., Marandas, P., Bourgain, J. L., Wibault, P., et.al. Reconstruction with free jejunal autograft after circumferential pharyngolaryngectomy: eighty-three cases. Ann Otol Rhinol Laryngol, 1998. 107(7): p. 581-7.
504. Villaret, D. B., Futran, N. A., The indications and outcomes in the use of osteocutaneous radial forearm free flap. Head Neck, 2003. 25(6): p. 475-81.
505. Chiarini, L., De Santis, G., Bedogni, A., Nocini, P. F., Lining the mouth floor with prelaminated fascio-mucosal free flaps: clinical experience. Microsurgery, 2002. 22(5): p. 177-86.
506. Azizzadeh, B., Yafai, S., Rawnsley, J. D., Abemayor, E., Sercarz, J. A., Calcaterra, T. C., et.al. Radial forearm free flap pharyngoesophageal reconstruction. Laryngoscope, 2001. 111(5): p. 807-10.
507. Jol, J. K., Quak, J. J., de Bree, R., Leemans, C. R., Larynx preservation surgery for advanced posterior pharyngeal wall carcinoma with free flap reconstruction: a critical appraisal. Oral Oncol, 2003. 39(6): p. 552-8.
508. Disa, J. J., Pusic, A. L., Hidalgo, D. A., Cordeiro, P. G., Microvascular reconstruction of the hypopharynx: defect classification, treatment algorithm, and functional outcome based on 165 consecutive cases. Plast Reconstr Surg, 2003. 111(2): p. 652-60; discussion 661-3.
509. Genden, E. M., Kaufman, M. R., Katz, B., Vine, A., Urken, M. L., Tubed gastro-omental free flap for pharyngoesophageal reconstruction. Arch Otolaryngol Head Neck Surg, 2001. 127(7): p. 847-53.
510. Hayden, R. E., Deschler, D. G., Lateral thigh free flap for head and neck reconstruction. Laryngoscope, 1999. 109(9): p. 1490-4.
511. Makitie, A. A., Beasley, N. J., Neligan, P. C., Lipa, J., Gullane, P. J., Gilbert, R. W., Head and neck reconstruction with anterolateral thigh flap. Otolaryngol Head Neck Surg, 2003. 129(5): p. 547-55.
512. Zheng, G. S., Su, Y. X., Liao, G. Q., Chen, Z. F., Wang, L., Jiao, P. F., et.al. Mandible reconstruction assisted by preoperative virtual surgical simulation. Oral Surg Oral Med Oral Pathol Oral Radiol, 2012. 113(5): p. 604-11., http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22676986
513. Zweifel, D. F., Simon, C., Hoarau, R., Pasche, P., Broome, M., Are virtual planning and guided surgery for head and neck reconstruction economically viable?. J Oral Maxillofac Surg, 2015. 73(1): p. 170-5., http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=25443385
514. Okay, D., Al Shetawi, A. H., Moubayed, S. P., Mourad, M., Buchbinder, D., Urken, M. L., Worldwide 10-Year Systematic Review of Treatment Trends in Fibula Free Flap for Mandibular

Reconstruction. J Oral Maxillofac Surg, 2016. 74(12): p. 2526-2531., https://www.ncbi.nlm.nih.gov/pubmed/27400143

515. Roser, S. M., Ramachandra, S., Blair, H., Grist, W., Carlson, G. W., Christensen, A. M., et.al. The accuracy of virtual surgical planning in free fibula mandibular reconstruction: comparison of planned and final results. J Oral Maxillofac Surg, 2010. 68(11): p. 2824-32., http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20828910
516. Weitz, J., Bauer, F. J., Hapfelmeier, A., Rohleder, N. H., Wolff, K. D., Kesting, M. R., Accuracy of mandibular reconstruction by three-dimensional guided vascularised fibular free flap after segmental mandibulectomy. Br J Oral Maxillofac Surg, 2016. 54(5): p. 506-10., https://www.ncbi.nlm.nih.gov/pubmed/26898519
517. Antony, A. K., Chen, W. F., Kolokythas, A., Weimer, K. A., Cohen, M. N., Use of virtual surgery and stereolithography-guided osteotomy for mandibular reconstruction with the free fibula. Plast Reconstr Surg, 2011. 128(5): p. 1080-4., http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22030490
518. Ritschl, L. M., Mucke, T., Fichter, A., Gull, F. D., Schmid, C., Duc, J. M. P., et.al. Functional Outcome of CAD/CAM-Assisted versus Conventional Microvascular, Fibular Free Flap Reconstruction of the Mandible: A Retrospective Study of 30 Cases. J Reconstr Microsurg, 2017. 33(4): p. 281-291., https://www.ncbi.nlm.nih.gov/pubmed/28099975
519. Schepers, R. H., Raghoebar, G. M., Vissink, A., Stenekes, M. W., Kraeima, J., Roodenburg, J. L., et.al. Accuracy of fibula reconstruction using patient-specific CAD/CAM reconstruction plates and dental implants: A new modality for functional reconstruction of mandibular defects. J Craniomaxillofac Surg, 2015. 43(5): p. 649-57., https://www.ncbi.nlm.nih.gov/pubmed/25911122
520. Wilde, F., Hanken, H., Probst, F., Schramm, A., Heiland, M., Cornelius, C. P., Multicenter study on the use of patient-specific CAD/CAM reconstruction plates for mandibular reconstruction. Int J Comput Assist Radiol Surg, 2015. 10(12): p. 2035-51., https://www.ncbi.nlm.nih.gov/pubmed/25843949
521. Duncan, W., MacDougall, R. H., Kerr, G. R., Downing, D., Adverse effect of treatment gaps in the outcome of radiotherapy for laryngeal cancer. Radiother Oncol, 1996. 41(3): p. 203-7.
522. Robertson, C., Robertson, A. G., Hendry, J. H., Roberts, S. A., Slevin, N. J., Duncan, W. B., et.al. Similar decreases in local tumor control are calculated for treatment protraction and for interruptions in the radiotherapy of carcinoma of the larynx in four centers. Int J Radiat Oncol Biol Phys, 1998. 40(2): p. 319-29.
523. Jacobsen, P. B., Donovan, K. A., Vadaparampil, S. T., Small, B. J., Systematic review and meta-analysis of psychological and activity-based interventions for cancer-related fatigue. Health Psychol, 2007. 26(6): p. 660-7.
524. Bourhis, J., Overgaard, J., Audry, H., Ang, K. K., Saunders, M., Bernier, J., et.al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet, 2006. 368(9538): p. 843-54., https://www.ncbi.nlm.nih.gov/pubmed/16950362
525. Duncan, W., MacDougall, R. H., Kerr, G. R., Downing, D., Adverse effect of treatment gaps in the outcome of radiotherapy for laryngeal cancer. Radiother Oncol, 1996. 41(3): p. 203-7.
526. Robertson, C., Robertson, A. G., Hendry, J. H., Roberts, S. A., Slevin, N. J., Duncan, W. B., et.al. Similar decreases in local tumor control are calculated for treatment protraction and for interruptions in the radiotherapy of carcinoma of the larynx in four centers. Int J Radiat Oncol Biol Phys, 1998. 40(2): p. 319-29.
527. Cox, J. D., Stetz, J., Pajak, T. F., Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys, 1995. 31(5): p. 1341-6.

528. Rubin, P., Constine, L. S., Fajardo, L. F., Phillips, T. L., Wasserman, T. H., RTOG Late Effects Working Group. Overview. Late Effects of Normal Tissues (LENT) scoring system. Int J Radiat Oncol Biol Phys, 1995. 31(5): p. 1041-2.
529. The National Cancer Institute, Cancer Therapy Evaluation Programme., 2006.
530. Wiernik, G., Bates, T. D., Bleehen, N. M., Brindle, J. M., Bullimore, J., Fowler, J. F., et.al. Final report of the general clinical results of the British Institute of Radiology fractionation study of 3F/wk versus 5F/wk in radiotherapy of carcinoma of the laryngo-pharynx. Br J Radiol, 1990. 63(747): p. 169-80.
531. Rezvani, M., Alcock, C. J., Fowler, J. F., Haybittle, J. L., Hopewell, J. W., Wiernik, G., Normal tissue reactions in the British Institute of Radiology Study of 3 fractions per week versus 5 fractions per week in the treatment of carcinoma of the laryngo-pharynx by radiotherapy. Br J Radiol, 1991. 64(768): p. 1122-33.
532. Gowda, R. V., Henk, J. M., Mais, K. L., Sykes, A. J., Swindell, R., Slevin, N. J., Three weeks radiotherapy for T1 glottic cancer: the Christie and Royal Marsden Hospital Experience. Radiother Oncol, 2003. 68(2): p. 105-11.
533. Stuschke, M., Thames, H. D., Hyperfractionated radiotherapy of human tumors: overview of the randomized clinical trials. Int J Radiat Oncol Biol Phys, 1997. 37(2): p. 259-67.
534. Cancer Care Ontario Practice Guidelines Initiative, Accelerated radiotherapy for locally advanced squamous cell carcinoma of the head and neck, revised 2002, 2002.
535. Overgaard, J., Hansen, H. S., Specht, L., Overgaard, M., Grau, C., Andersen, E., et.al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. Lancet, 2003. 362(9388): p. 933-40.
536. Hliniak, A., Gwiazdowska, B., Szutkowski, Z., Kraszewska, E., Kukolowicz, P., Jarzabski, A., et.al. A multicentre randomized/controlled trial of a conventional versus modestly accelerated radiotherapy in the laryngeal cancer: influence of a 1 week shortening overall time. Radiother Oncol, 2002. 62(1): p. 1-10.
537. Horiot, J. C., Bontemps, P., van den Bogaert, W., Le Fur, R., van den Weijngaert, D., Bolla, M., et.al. Accelerated fractionation (AF) compared to conventional fractionation (CF) improves loco-regional control in the radiotherapy of advanced head and neck cancers: results of the EORTC 22851 randomized trial. Radiother Oncol, 1997. 44(2): p. 111-21.
538. Glenny, A. M., Furness, S., Worthington, H. V., Conway, D. I., Oliver, R., Clarkson, J. E., et.al. Interventions for the treatment of oral cavity and oropharyngeal cancer: radiotherapy. Cochrane Database Syst Rev, 2010. p. CD006387.
539. Chao, K. S., Deasy, J. O., Markman, J., Haynie, J., Perez, C. A., Purdy, J. A., et.al. A prospective study of salivary function sparing in patients with head-and-neck cancers receiving intensity-modulated or three-dimensional radiation therapy: initial results. Int J Radiat Oncol Biol Phys, 2001. 49(4): p. 907-16.
540. Chen, Y. J., Kuo, J. V., Ramsinghani, N. S., Al-Ghazi, M. S., Intensity-modulated radiotherapy for previously irradiated, recurrent head-and-neck cancer. Med Dosim, 2002. 27(2): p. 171-6.
541. Podd, T. J., Carton, A. T., Barrie, R., Dawes, P. K., Roberts, J. T., Stassen, L. F., et.al. Treatment of oral cancers using iridium-192 interstitial irradiation. Br J Oral Maxillofac Surg, 1994. 32(7947563): p. 207-213.
542. Shibuya, H., Hoshina, M., Takeda, M., Matsumoto, S., Suzuki, S., Okada, N., Brachytherapy for stage I & II oral tongue cancer: an analysis of past cases focusing on control and complications. Int J Radiat Oncol Biol Phys, 1993. 26(1): p. 51-58.
543. Pernot, M., Hoffstetter, S., Peiffert, D., Luporsi, E., Marchal, C., Kozminski, P., et.al. Epidermoid carcinomas of the floor of mouth treated by exclusive irradiation: statistical study of a series of 207 cases. Radiother Oncol, 1995. 35(7480819): p. 177-185.

544. Mazeron, J. J., Crook, J. M., Benck, V., Marinello, G., Martin, M., Raynal, M., et.al. Iridium 192 implantation of T1 and T2 carcinomas of the mobile tongue. Int J Radiat Oncol Biol Phys, 1990. 19(6): p. 1369-1376.
545. Matsumoto, S., Takeda, M., Shibuya, H., Suzuki, S., T1 and T2 squamous cell carcinomas of the floor of the mouth: results of brachytherapy mainly using 198Au grains. Int J Radiat Oncol Biol Phys, 1996. 34(8598360): p. 833-841.
546. Leung, T. W., Wong, V. Y., Kwan, K. H., Ng, T. Y., Wong, C. M., Tung, S. Y., et.al. High dose rate brachytherapy for early stage oral tongue cancer. Head Neck, 2002. 24(3): p. 274-81.
547. Hareyama, M., Nishio, M., Saito, A., Kagami, Y., Asano, K., Oouchi, A., et.al. Results of cesium needle interstitial implantation for carcinoma of the oral tongue. Int J Radiat Oncol Biol Phys, 1993. 25(1): p. 29-34.
548. Bachaud, J. M., Delannes, M., Allouache, N., Benchalal, M., Alzieu, C., David, J. M., et.al. Radiotherapy of stage I and II carcinomas of the mobile tongue and/or floor of the mouth. Radiother Oncol, 1994. 31(3): p. 199-206.
549. Pernot, M., Malissard, L., Hoffstetter, S., Luporsi, E., Peiffert, D., Aletti, P., et.al. The study of tumoral, radiobiological, and general health factors that influence results and complications in a series of 448 oral tongue carcinomas treated exclusively by irradiation. Int J Radiat Oncol Biol Phys, 1994. 29(4): p. 673-9.
550. Pernot, M., Luporsi, E., Hoffstetter, S., Peiffert, D., Aletti, P., Marchal, C., et.al. Complications following definitive irradiation for cancers of the oral cavity and the oropharynx (in a series of 1134 patients). Int J Radiat Oncol Biol Phys, 1997. 37(3): p. 577-85.
551. Fujita, M., Hirokawa, Y., Kashiwado, K., Akagi, Y., Kashimoto, K., Kiriu, H., et.al. An analysis of mandibular bone complications in radiotherapy for T1 and T2 carcinoma of the oral tongue. Int J Radiat Oncol Biol Phys, 1996. 34(2): p. 333-9.
552. Mazeron, J. J., Crook, J., Martin, M., Peynegre, R., Pierquin, B., Iridium 192 implantation of squamous cell carcinomas of the oropharynx. Am J Otolaryngol, 1989. 10(5): p. 317-21.
553. Pernot, M., Malissard, L., Taghian, A., Hoffstetter, S., Luporsi, E., Forcard, J. J., et.al. Velotonsillar squamous cell carcinoma: 277 cases treated by combined external irradiation and brachytherapy—results according to extension, localization, and dose rate. Int J Radiat Oncol Biol Phys, 1992. 23(4): p. 715-23.
554. Hammerlid, E., Mercke, C., Sullivan, M., Westin, T., A prospective quality of life study of patients with oral or pharyngeal carcinoma treated with external beam irradiation with or without brachytherapy. Oral Oncol, 1997. 33(3): p. 189-96.
555. Pignon, J. P., Bourhis, J., Domenge, C., Designe, L., Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet, 2000. 355(9208): p. 949-55.
556. Licitra, L., Locati, L. D., Cavina, R., Garassino, I., Mattavelli, F., Pizzi, N., et.al. Primary chemotherapy followed by anterior craniofacial resection and radiotherapy for paranasal cancer. Ann Oncol, 2003. 14(3): p. 367-72.
557. Bourhis J, Amand C, Pignon JP. Update of MACH-NC (Meta-Analysis of Chemotherapy in Head and Neck Cancer) database focused on concomitant chemoradiotherapy: 5505. J Clin Oncol 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition) 2004;22(14S (July 15 Supplement)).
558. Pignon, J. P., Bourhis, J., Domenge, C., Designe, L., Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet, 2000. 355(9208): p. 949-55.
559. Licitra, L., Locati, L. D., Cavina, R., Garassino, I., Mattavelli, F., Pizzi, N., et.al. Primary chemotherapy followed by anterior craniofacial resection and radiotherapy for paranasal cancer. Ann Oncol, 2003. 14(3): p. 367-72.

560. Pignon, J. P., le Maitre, A., Maillard, E., Bourhis, J., Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol, 2009. 92(1): p. 4-14.
561. Blanchard, P., Baujat, B., Holostenco, V., Bourredjem, A., Baey, C., Bourhis, J., et.al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. Radiother Oncol, 2011. 100(1): p. 33-40.
562. Budach, W., Hehr, T., Budach, V., Belka, C., Dietz, K., A meta-analysis of hyperfractionated and accelerated radiotherapy and combined chemotherapy and radiotherapy regimens in unresected locally advanced squamous cell carcinoma of the head and neck. BMC Cancer, 2006. 6: p. 28.
563. Cancer Care Ontario Practice Guidelines Initiative, Concomitant chemotherapy and radiotherapy in squamous cell head and neck cancer (excluding nasopharynx), 2000.
564. Henk, J. M., Bishop, K., Shepherd, S. F., Treatment of head and neck cancer with CHART and nimorazole: phase II study. Radiother Oncol, 2003. 66(1): p. 65-70.
565. Olmi, P., Crispino, S., Fallai, C., Torri, V., Rossi, F., Bolner, A., et.al. Locoregionally advanced carcinoma of the oropharynx: conventional radiotherapy vs. accelerated hyperfractionated radiotherapy vs. concomitant radiotherapy and chemotherapy—a multicenter randomized trial. Int J Radiat Oncol Biol Phys, 2003. 55(1): p. 78-92.
566. Wendt, T. G., Grabenbauer, G. G., Rodel, C. M., Thiel, H. J., Aydin, H., Rohloff, R., et.al. Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: a randomized multicenter study. J Clin Oncol, 1998. 16(4): p. 1318-24.
567. Jeremic, B., Shibamoto, Y., Milicic, B., Nikolic, N., Dagovic, A., Aleksandrovic, J., et.al. Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial. J Clin Oncol, 2000. 18(7): p. 1458-64.
568. Grau, C., Prakash Agarwal, J., Jabeen, K., Rab Khan, A., Abeyakoon, S., Hadjieva, T., et.al. Radiotherapy with or without mitomycin c in the treatment of locally advanced head and neck cancer: results of the IAEA multicentre randomised trial. Radiother Oncol, 2003. 67(1): p. 17-26.
569. Calais, G., Alfonsi, M., Bardet, E., Sire, C., Germain, T., Bergerot, P., et.al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. J Natl Cancer Inst, 1999. 91(24): p. 2081-6.
570. Calais, G., Alfonsi, M., Bardet, E., Sire, C., Germain, T., Bergerot, P., et.al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. J Natl Cancer Inst, 1999. 91(24): p. 2081-6.
571. Zakotnik, B., Smid, L., Budihna, M., Lesnicar, H., Soba, E., Furlan, L., et.al. Concomitant radiotherapy with mitomycin C and bleomycin compared with radiotherapy alone in inoperable head and neck cancer: final report. Int J Radiat Oncol Biol Phys, 1998. 41(5): p. 1121-7.
572. Fountzilas, G., Ciuleanu, E., Dafni, U., Plataniotis, G., Kalogera-Fountzila, A., Samantas, E., et.al. Concomitant radiochemotherapy vs radiotherapy alone in patients with head and neck cancer: a Hellenic Cooperative Oncology Group Phase III Study. Med Oncol, 2004. 21(2): p. 95-107.
573. El-Sayed, S., Nelson, N., Adjuvant and adjunctive chemotherapy in the management of squamous cell carcinoma of the head and neck region. A meta-analysis of prospective and randomized trials. J Clin Oncol, 1996. 14(3): p. 838-47.
574. Yu, E., Shenouda, G., Beaudet, M. P., Black, M. J., Impact of radiation therapy fraction size on local control of early glottic carcinoma. Int J Radiat Oncol Biol Phys, 1997. 37(3): p. 587-91.
575. Adelstein, D. J., Li, Y., Adams, G. L., Wagner, H., Jr., Kish, J. A., Ensley, J. F., et.al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol, 2003. 21(1): p. 92-8.

576. Forastiere, A. A., Goepfert, H., Maor, M., Pajak, T. F., Weber, R., Morrison, W., et.al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med, 2003. 349(22): p. 2091-8.
577. Gupta, N. K., Swindell, R., Concomitant methotrexate and radiotherapy in advanced head and neck cancer: 15-year follow-up of a randomized clinical trial. Clin Oncol (R Coll Radiol), 2001. 13(5): p. 339-44.
578. Vermorken JB, Remenar E, Van Herpen C, J GL, Stewart S, Gorlia T, et al. Standard cisplatin/infusional 5-fluorouracil (PF) vs docetaxel (T) plus PF (TPF) as neoadjuvant chemotherapy for nonresectable locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN): A phase III trial of the EORTC Head and Neck Cancer Group (EORTC #24971). Abstract No: 5508. Journal of Clinical Oncology, 2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition) 2004;22(14S July 15 Supplement).
579. Bonner, J. A., Harari, P. M., Giralt, J., Azarnia, N., Shin, D. M., Cohen, R. B., et.al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med, 2006. 354(6): p. 567-78.
580. Bernier, J., Domenge, C., Ozsahin, M., Matuszewska, K., Lefebvre, J. L., Greiner, R. H., et.al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med, 2004. 350(19): p. 1945-52.
581. Cooper, J. S., Pajak, T. F., Forastiere, A. A., Jacobs, J., Campbell, B. H., Saxman, S. B., et.al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med, 2004. 350(19): p. 1937-44.
582. Bartelink, H., Breur, K., Hart, G., Annyas, B., van Slooten, E., Snow, G., The value of postoperative radiotherapy as an adjuvant to radical neck dissection. Cancer, 1983. 52(6): p. 1008-1013.
583. Jesse, R. H., Fletcher, G. H., Treatment of the neck in patients with squamous cell carcinoma of the head and neck. Cancer, 1977. 39(Suppl 2): p. 868-872.
584. Lundahl, R. E., Foote, R. L., Bonner, J. A., Suman, V. J., Lewis, J. E., Kasperbauer, J. L., et.al. Combined neck dissection and postoperative radiation therapy in the management of the high-risk neck: a matched-pair analysis. Int J Radiat Oncol Biol Phys, 1998. 40(9486600): p. 529-534.
585. Peters, L. J., Goepfert, H., Ang, K. K., Byers, R. M., Maor, M. H., Guillamondegui, O., et.al. Evaluation of the dose for postoperative radiation therapy of head and neck cancer: first report of a prospective randomized trial. Int J Radiat Oncol Biol Phys, 1993. 26(1): p. 3-11.
586. Sanguineti, G., Richetti, A., Bignardi, M., Corvo, R., Gabriele, P., Sormani, M. P., et.al. Accelerated versus conventional fractionated postoperative radiotherapy for advanced head and neck cancer: results of a multicenter Phase III study. Int J Radiat Oncol Biol Phys, 2005. 61(3): p. 762-71.
587. Ang, K. K., Trotti, A., Brown, B. W., Garden, A. S., Foote, R. L., Morrison, W. H., et.al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys, 2001. 51(3): p. 571-8.
588. Awwad, H. K., Lotayef, M., Shouman, T., Begg, A. C., Wilson, G., Bentzen, S. M., et.al. Accelerated hyperfractionation (AHF) compared to conventional fractionation (CF) in the postoperative radiotherapy of locally advanced head and neck cancer: influence of proliferation. Br J Cancer, 2002. 86(4): p. 517-23.
589. Bataini, J. P., Bernier, J., Asselain, B., Lave, C., Jaulerry, C., Brunin, F., et.al. Primary radiotherapy of squamous cell carcinoma of the oropharynx and pharyngolarynx: tentative multivariate modelling system to predict the radiocurability of neck nodes. Int J Radiat Oncol Biol Phys, 1988. 14(3350718): p. 635-642.
590. Bachaud, J. M., Cohen-Jonathan, E., Alzieu, C., David, J. M., Serrano, E., Daly-Schveitzer, N., Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial. Int J Radiat Oncol Biol Phys, 1996. 36(5): p. 999-1004.

591. Bernier, J., Cooper, J. S., Pajak, T. F., van Glabbeke, M., Bourhis, J., Forastiere, A., et.al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck, 2005. 27(10): p. 843-50.
592. Lefebvre, J. L., Coche-Dequeant, B., Buisset, E., Mirabel, X., Van, J. T., Prevost, B., Management of early oral cavity cancer. Experience of Centre Oscar Lambret. Eur J Cancer B Oral Oncol, 1994. 30(3): p. 216-20.
593. Pernot, M., Hoffstetter, S., Peiffert, D., Luporsi, E., Marchal, C., Kozminski, P., et.al. Epidermoid carcinomas of the floor of mouth treated by exclusive irradiation: statistical study of a series of 207 cases. Radiother Oncol, 1995. 35(7480819): p. 177-185.
594. Hareyama, M., Nishio, M., Saito, A., Kagami, Y., Asano, K., Oouchi, A., et.al. Results of cesium needle interstitial implantation for carcinoma of the oral tongue. Int J Radiat Oncol Biol Phys, 1993. 25(1): p. 29-34.
595. Pernot, M., Malissard, L., Hoffstetter, S., Luporsi, E., Peiffert, D., Aletti, P., et.al. The study of tumoral, radiobiological, and general health factors that influence results and complications in a series of 448 oral tongue carcinomas treated exclusively by irradiation. Int J Radiat Oncol Biol Phys, 1994. 29(4): p. 673-9.
596. Levendag, P. C., Nowak, P. J., van der Sangen, M. J., Jansen, P. P., Eijkenboom, W. M., Planting, A. S., et.al. Local tumor control in radiation therapy of cancers in the head and neck. Am J Clin Oncol, 1996. 19(5): p. 469-477.
597. Vikram, B., Strong, E. W., Shah, J. P., Spiro, R., Failure in the neck following multimodality treatment for advanced head and neck cancer. Head Neck Surg, 1984. 6(3): p. 724-9.
598. Mazeron, J. J., Crook, J. M., Benck, V., Marinello, G., Martin, M., Raynal, M., et.al. Iridium 192 implantation of T1 and T2 carcinomas of the mobile tongue. Int J Radiat Oncol Biol Phys, 1990. 19(6): p. 1369-1376.
599. Bartelink, H., Breur, K., Hart, G., Annyas, B., van Slooten, E., Snow, G., The value of postoperative radiotherapy as an adjuvant to radical neck dissection. Cancer, 1983. 52(6): p. 1008-1013.
600. Jesse, R. H., Fletcher, G. H., Treatment of the neck in patients with squamous cell carcinoma of the head and neck. Cancer, 1977. 39(Suppl 2): p. 868-872.
601. Lundahl, R. E., Foote, R. L., Bonner, J. A., Suman, V. J., Lewis, J. E., Kasperbauer, J. L., et.al. Combined neck dissection and postoperative radiation therapy in the management of the high-risk neck: a matched-pair analysis. Int J Radiat Oncol Biol Phys, 1998. 40(9486600): p. 529-534.
602. Peters, L. J., Goepfert, H., Ang, K. K., Byers, R. M., Maor, M. H., Guillamondegui, O., et.al. Evaluation of the dose for postoperative radiation therapy of head and neck cancer: first report of a prospective randomized trial. Int J Radiat Oncol Biol Phys, 1993. 26(1): p. 3-11.
603. Sanguineti, G., Richetti, A., Bignardi, M., Corvo, R., Gabriele, P., Sormani, M. P., et.al. Accelerated versus conventional fractionated postoperative radiotherapy for advanced head and neck cancer: results of a multicenter Phase III study. Int J Radiat Oncol Biol Phys, 2005. 61(3): p. 762-71.
604. Ang, K. K., Trotti, A., Brown, B. W., Garden, A. S., Foote, R. L., Morrison, W. H., et.al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys, 2001. 51(3): p. 571-8.
605. Awwad, H. K., Lotayef, M., Shouman, T., Begg, A. C., Wilson, G., Bentzen, S. M., et.al. Accelerated hyperfractionation (AHF) compared to conventional fractionation (CF) in the postoperative radiotherapy of locally advanced head and neck cancer: influence of proliferation. Br J Cancer, 2002. 86(4): p. 517-23.
606. Bachaud, J. M., Cohen-Jonathan, E., Alzieu, C., David, J. M., Serrano, E., Daly-Schveitzer, N., Combined postoperative radiotherapy and weekly cisplatin infusion for locally advanced

head and neck carcinoma: final report of a randomized trial. Int J Radiat Oncol Biol Phys, 1996. 36(5): p. 999-1004.
607. Chow, J. M., Levin, B. C., Krivit, J. S., Applebaum, E. L., Radiotherapy or surgery for subclinical cervical node metastases. Arch Otolaryngol Head Neck Surg, 1989. 115(8): p. 981-4.
608. Bernier, J., [Adjuvant treatment of head and neck cancers: advances and challenges]. Bulletin du Cancer, 2007. 94(9): p. 823-7.
609. Huang, D. T., Johnson, C. R., Schmidt-Ullrich, R., Grimes, M., Postoperative radiotherapy in head and neck carcinoma with extracapsular lymph node extension and/or positive resection margins: a comparative study. Int J Radiat Oncol Biol Phys, 1992. 23(4): p. 737-742.
610. Tupchong, L., Scott, C. B., Blitzer, P. H., Marcial, V. A., Lowry, L. D., Jacobs, J. R., et.al. Randomized study of preoperative versus postoperative radiation therapy in advanced head and neck carcinoma: long-term follow-up of RTOG study 73-03. Int J Radiat Oncol Biol Phys, 1991. 20(1): p. 21-8.
611. Peters, L. J., Weber, R. S., Morrison, W. H., Byers, R. M., Garden, A. S., Goepfert, H., Neck surgery in patients with primary oropharyngeal cancer treated by radiotherapy. Head Neck, 1996. 18(6): p. 552-9.
612. Snow, G. B., Annyas, A. A., van Slooten, E. A., Bartelink, H., Hart, A. A., Prognostic factors of neck node metastasis. Clin Otolaryngol Allied Sci, 1982. 7(3): p. 185-92.
613. Goffinet, D. R., Fee, W. E., Jr., Goode, R. L., Combined surgery and postoperative irradiation in the treatment of cervical lymph nodes. Arch Otolaryngol, 1984. 110(11): p. 736-8.
614. Barzan, L., Talamini, R., Analysis of prognostic factors for recurrence after neck dissection. Arch Otolaryngol Head Neck Surg, 1996. 122(12): p. 1299-302.
615. Hinerman, R. W., Mendenhall, W. M., Morris, C. G., Amdur, R. J., Werning, J. W., Villaret, D. B., Postoperative irradiation for squamous cell carcinoma of the oral cavity: 35-year experience. Head Neck, 2004. 26(11): p. 984-94.
616. Close, L. G., Brown, P. M., Vuitch, M. F., Reisch, J., Schaefer, S. D., Microvascular invasion and survival in cancer of the oral cavity and oropharynx. Arch Otolaryngol Head Neck Surg, 1989. 115(11): p. 1304-9.
617. Foote, R. L., Buskirk, S. J., Stanley, R. J., Grambsch, P. M., Olsen, K. D., DeSanto, L. W., et.al. Patterns of failure after total laryngectomy for glottic carcinoma. Cancer, 1989. 64(1): p. 143-9.
618. Fietkau, R., Lautenschläger, C., Sauer, R., Dunst, J., Becker, A., MBaumann, M., et.al. Postoperative concurrent radiochemotherapy versus radiotherapy in high-risk SCCA of the head and neck: Results of the German phase III trial ARO 96-3. J Clin Oncol, 2006 ASCO Annual Meeting Proceedings Part I. Vol 24, No. 18S (June 20 Supplement), 2006: 5507
619. Mazeron, J. J., Crook, J. M., Marinello, G., Walop, W., Pierquin, B., Prognostic factors of local outcome for T1, T2 carcinomas of oral tongue treated by iridium 192 implantation. Int J Radiat Oncol Biol Phys, 1990. 19(2): p. 281-5.
620. Kramer, F. J., Janssen, M., Eckardt, A., Second primary tumours in oropharyngeal squamous cell carcinoma. Clin Oral Investig, 2004. 8(2): p. 56-62.
621. Fisher, J., Scott, C., Scarantino, C. W., Leveque, F. G., White, R. L., Rotman, M., et.al. Phase III quality-of-life study results: impact on patients' quality of life to reducing xerostomia after radiotherapy for head-and-neck cancer—RTOG 97-09. Int J Radiat Oncol Biol Phys, 2003. 56(3): p. 832-6.
622. Cancer Care Ontario Practice Guidelines Initiative. Symptomatic treatment of radiation-induced xerostomia in head and neck cancer patients (revised). 2002. [cited 11 August 2006]. Available from url: http://www.cancercare.on.ca/pdf/pebc5-8s.pdf
623. Cancer Care Ontario Practice Guidelines Initiative, Symptomatic treatment of radiation-induced xerostomia in head and neck cancer patients (revised), 2002.

624. Tong, A. C., Leung, A. C., Cheng, J. C., Sham, J., Incidence of complicated healing and osteoradionecrosis following tooth extraction in patients receiving radiotherapy for treatment of nasopharyngeal carcinoma. Aust Dent J, 1999. 44(3): p. 187-94.
625. Epstein, J. B., Silverman, S., Jr., Paggiarino, D. A., Crockett, S., Schubert, M. M., Senzer, N. N., et.al. Benzydamine HCl for prophylaxis of radiation-induced oral mucositis: results from a multicenter, randomized, double-blind, placebo-controlled clinical trial. Cancer, 2001. 92(4): p. 875-85.
626. Epstein, J. B., Silverman, S., Jr., Paggiarino, D. A., Crockett, S., Schubert, M. M., Senzer, N. N., et.al. Benzydamine HCl for prophylaxis of radiation-induced oral mucositis: results from a multicenter, randomized, double-blind, placebo-controlled clinical trial. Cancer, 2001. 92(4): p. 875-85.
627. Prada, A., Chiesa, F., Effects of benzydamine on the oral mucositis during antineoplastic radiotherapy and/or intra-arterial chemotherapy. Int J Tissue React, 1987. 9(2): p. 115-9.
628. Kim, J. H., Chu, F. C., Lakshmi, V., Houde, R., Benzydamine HCl, a new agent for the treatment of radiation mucositis of the oropharynx. Am J Clin Oncol, 1986. 9(2): p. 132-4.
629. Sutherland, S. E., Browman, G. P., Prophylaxis of oral mucositis in irradiated head-and-neck cancer patients: a proposed classification scheme of interventions and meta-analysis of randomized controlled trials. Int J Radiat Oncol Biol Phys, 2001. 49(4): p. 917-30.
630. Cancer Care Ontario Practice Guidelines Initiative, The role of amifostine as a radioprotectant in the management of patients with squamous cell head and neck cancer. Practice Guideline Report #5-8 - 2004 Update. 2004. [cited 11 August 2006]. Available from url: http://www.cancercare.on.ca/pdf/pebc5-8f.pdf, 2004.
631. Sprinzl, G. M., Galvan, O., de Vries, A., Ulmer, H., Gunkel, A. R., Lukas, P., et.al. Local application of granulocyte-macrophage colony stimulating factor (GM-CSF) for the treatment of oral mucositis. Eur J Cancer, 2001. 37(16): p. 2003-9.
632. Makkonen, T. A., Minn, H., Jekunen, A., Vilja, P., Tuominen, J., Joensuu, H., Granulocyte macrophage-colony stimulating factor (GM-CSF) and sucralfate in prevention of radiation-induced mucositis: a prospective randomized study. Int J Radiat Oncol Biol Phys, 2000. 46(3): p. 525-34.
633. Grotz, K. A., Wustenberg, P., Kohnen, R., Al-Nawas, B., Henneicke-von Zepelin, H. H., Bockisch, A., et.al. Prophylaxis of radiogenic sialadenitis and mucositis by coumarin/troxerutine in patients with head and neck cancer—a prospective,randomized, placebo-controlled, double-blind study. Br J Oral Maxillofac Surg, 2001. 39(1): p. 34-9.
634. Kaushal, V., Verma, K., Manocha, S., Hooda, H. S., Das, B. P., Clinical evaluation of human placental extract (placentrex) in radiation-induced oral mucositis. Int J Tissue React, 2001. 23(3): p. 105-10.
635. Kostrica, R., Rottenberg, J., Kvech, J., Betka, J., Jablonicky, P., Randomised, double-blind comparison of efficacy and tolerability of diclofenac mouthwash versus placebo in mucositis of oral cavity by radiotherapy. J Clin Res, 2002. 5(1-15): p. 1-15.
636. Saarilahti, K., Kajanti, M., Joensuu, T., Kouri, M., Joensuu, H., Comparison of granulocyte-macrophage colony-stimulating factor and sucralfate mouthwashes in the prevention of radiation-induced mucositis: a double-blind prospective randomized phase III study. Int J Radiat Oncol Biol Phys, 2002. 54(2): p. 479-85.
637. Stokman, M. A., Spijkervet, F. K., Burlage, F. R., Dijkstra, P. U., Manson, W. L., de Vries, E. G., et.al. Oral mucositis and selective elimination of oral flora in head and neck cancer patients receiving radiotherapy: a double-blind randomised clinical trial. Br J Cancer, 2003. 88(7): p. 1012-6.
638. Dodd, M. J., Miaskowski, C., Greenspan, D., MacPhail, L., Shih, A. S., Shiba, G., et.al. Radiation-induced mucositis: a randomized clinical trial of micronized sucralfate versus salt & soda mouthwashes. Cancer Invest, 2003. 21(1): p. 21-33.

639. El-Sayed, S., Nabid, A., Shelley, W., Hay, J., Balogh, J., Gelinas, M., et.al. Prophylaxis of radiation-associated mucositis in conventionally treated patients with head and neck cancer: a double-blind, phase III, randomized, controlled trial evaluating the clinical efficacy of an antimicrobial lozenge using a validated mucositis scoring system. J Clin Oncol, 2002. 20(19): p. 3956-63.
640. Ertekin, M. V., Koc, M., Karslioglu, I., Sezen, O., Zinc sulfate in the prevention of radiation-induced oropharyngeal mucositis: a prospective, placebo-controlled, randomized study. Int J Radiat Oncol Biol Phys, 2004. 58(1): p. 167-74.
641. Trotti, A., Garden, A., Warde, P., Symonds, P., Langer, C., Redman, R., et.al. A multinational, randomized phase III trial of iseganan HCl oral solution for reducing the severity of oral mucositis in patients receiving radiotherapy for head-and-neck malignancy. Int J Radiat Oncol Biol Phys, 2004. 58(3): p. 674-81.
642. Worthington, H. V., Clarkson, J. E., Eden, O. B., Interventions for preventing oral candidiasis for patients with cancer receiving treatment. Cochrane Database Syst Rev, 2002. p. CD003807.
643. Roy, I., Fortin, A., Larochelle, M., The impact of skin washing with water and soap during breast irradiation: a randomized study. Radiother Oncol, 2001. 58(3): p. 333-9.
644. Graham, P., Browne, L., Capp, A., Fox, C., Graham, J., Hollis, J., et.al. Randomized, paired comparison of No-Sting Barrier Film versus sorbolene cream (10% glycerine) skin care during postmastectomy irradiation. Int J Radiat Oncol Biol Phys, 2004. 58(1): p. 241-6.
645. Graham, P., Browne, L., Capp, A., Fox, C., Graham, J., Hollis, J., et.al. Randomized, paired comparison of No-Sting Barrier Film versus sorbolene cream (10% glycerine) skin care during postmastectomy irradiation. Int J Radiat Oncol Biol Phys, 2004. 58(1): p. 241-6.
646. Williams, M. S., Burk, M., Loprinzi, C. L., Hill, M., Schomberg, P. J., Nearhood, K., et.al. Phase III double-blind evaluation of an aloe vera gel as a prophylactic agent for radiation-induced skin toxicity. Int J Radiat Oncol Biol Phys, 1996. 36(2): p. 345-9.
647. Wells, M., Macmillan, M., Raab, G., MacBride, S., Bell, N., MacKinnon, K., et.al. Does aqueous or sucralfate cream affect the severity of erythematous radiation skin reactions? A randomised controlled trial. Radiother Oncol, 2004. 73(2): p. 153-62.
648. Clarkson, J. E., Worthington, H. V., Eden, O. B., Eden, T. O. B., Interventions for preventing oral mucositis for patients with cancer receiving treatment. Cochrane Database of Systematic Reviews, 2003., https://doi.org//10.1002/14651858.CD000978
649. Goodwin, W. J., Jr., Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means?. Laryngoscope, 2000. 110(3 Pt 2 Suppl 93): p. 1-18.
650. Agra, I. M., Carvalho, A. L., Pontes, E., Campos, O. D., Ulbrich, F. S., Magrin, J., et.al. Postoperative complications after en bloc salvage surgery for head and neck cancer. Arch Otolaryngol Head Neck Surg, 2003. 129(12): p. 1317-21.
651. Peiffert, D., Pernot, M., Malissard, L., Aletti, P., Hoffstetter, S., Kozminski, P., et.al. Salvage irradiation by brachytherapy of velotonsillar squamous cell carcinoma in a previously irradiated field: results in 73 cases. Int J Radiat Oncol Biol Phys, 1994. 29(4): p. 681-6.
652. Mazeron, J. J., Langlois, D., Glaubiger, D., Huart, J., Martin, M., Raynal, M., et.al. Salvage irradiation of oropharyngeal cancers using iridium 192 wire implants: 5-year results of 70 cases. Int J Radiat Oncol Biol Phys, 1987. 13(7): p. 957-62.
653. Haraf, D. J., Weichselbaum, R. R., Vokes, E. E., Re-irradiation with concomitant chemotherapy of unresectable recurrent head and neck cancer: a potentially curable disease. Ann Oncol, 1996. 7(9): p. 913-8.
654. Pomp, J., Levendag, P. C., van Putten, W. L., Reirradiation of recurrent tumors in the head and neck. Am J Clin Oncol, 1988. 11(5): p. 543-9.
655. Stevens, K. R., Jr., Britsch, A., Moss, W. T., High-dose reirradiation of head and neck cancer with curative intent. Int J Radiat Oncol Biol Phys, 1994. 29(4): p. 687-98.

656. Emami, B., Bignardi, M., Spector, G. J., Devineni, V. R., Hederman, M. A., Reirradiation of recurrent head and neck cancers. Laryngoscope, 1987. 97(1): p. 85-8.
657. Goodwin, W. J., Jr., Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means?. Laryngoscope, 2000. 110(3 Pt 2 Suppl 93): p. 1-18.
658. Agra, I. M., Carvalho, A. L., Pontes, E., Campos, O. D., Ulbrich, F. S., Magrin, J., et.al. Postoperative complications after en bloc salvage surgery for head and neck cancer. Arch Otolaryngol Head Neck Surg, 2003. 129(12): p. 1317-21.
659. Peiffert, D., Pernot, M., Malissard, L., Aletti, P., Hoffstetter, S., Kozminski, P., et.al. Salvage irradiation by brachytherapy of velotonsillar squamous cell carcinoma in a previously irradiated field: results in 73 cases. Int J Radiat Oncol Biol Phys, 1994. 29(4): p. 681-6.
660. Mazeron, J. J., Langlois, D., Glaubiger, D., Huart, J., Martin, M., Raynal, M., et.al. Salvage irradiation of oropharyngeal cancers using iridium 192 wire implants: 5-year results of 70 cases. Int J Radiat Oncol Biol Phys, 1987. 13(7): p. 957-62.
661. Haraf, D. J., Weichselbaum, R. R., Vokes, E. E., Re-irradiation with concomitant chemotherapy of unresectable recurrent head and neck cancer: a potentially curable disease. Ann Oncol, 1996. 7(9): p. 913-8.
662. Pomp, J., Levendag, P. C., van Putten, W. L., Reirradiation of recurrent tumors in the head and neck. Am J Clin Oncol, 1988. 11(5): p. 543-9.
663. Stevens, K. R., Jr., Britsch, A., Moss, W. T., High-dose reirradiation of head and neck cancer with curative intent. Int J Radiat Oncol Biol Phys, 1994. 29(4): p. 687-98.
664. Emami, B., Bignardi, M., Spector, G. J., Devineni, V. R., Hederman, M. A., Reirradiation of recurrent head and neck cancers. Laryngoscope, 1987. 97(1): p. 85-8.
665. Dawson, L. A., Myers, L. L., Bradford, C. R., Chepeha, D. B., Hogikyan, N. D., Teknos, T. N., et.al. Conformal re-irradiation of recurrent and new primary head-and-neck cancer. Int J Radiat Oncol Biol Phys, 2001. 50(2): p. 377-85.
666. Ohizumi, Y., Tamai, Y., Imamiya, S., Akiba, T., Complications following re-irradiation for head and neck cancer. Am J Otolaryngol, 2002. 23(4): p. 215-21.
667. Ohizumi, Y., Tamai, Y., Imamiya, S., Akiba, T., Complications following re-irradiation for head and neck cancer. Am J Otolaryngol, 2002. 23(4): p. 215-21.
668. Loo, S. W., Geropantas, K., Beadsmoore, C., Montgomery, P. Q., Martin, W. M., Roques, T. W., Neck dissection can be avoided after sequential chemoradiotherapy and negative post-treatment positron emission tomography-computed tomography in N2 head and neck squamous cell carcinoma. Clin Oncol (R Coll Radiol), 2011. 23(8): p. 512-7., https://www.ncbi.nlm.nih.gov/pubmed/21501953
669. Mehanna, H., Wong, W. L., McConkey, C. C., Rahman, J. K., Robinson, M., Hartley, A. G., et.al. PET-CT Surveillance versus Neck Dissection in Advanced Head and Neck Cancer. N Engl J Med, 2016. 374(15): p. 1444-54., https://www.ncbi.nlm.nih.gov/pubmed/27007578
670. Mohanti, B. K., Umapathy, H., Bahadur, S., Thakar, A., Pathy, S., Short course palliative radiotherapy of 20 Gy in 5 fractions for advanced and incurable head and neck cancer: AIIMS study. Radiother Oncol, 2004. 71(3): p. 275-80.
671. Laccourreye, O., Lawson, G., Muscatello, L., Biacabe, B., Laccourreye, L., Brasnu, D., Carbon dioxide laser debulking for obstructing endolaryngeal carcinoma: a 10-year experience. Ann Otol Rhinol Laryngol, 1999. 108(5): p. 490-4.
672. Wilner, H. I., Lazo, A., Metes, J. J., Beil, K. A., Nowack, P., Jacobs, J., Embolization in cataclysmal hemorrhage caused by squamous cell carcinomas of the head and neck. Radiology, 1987. 163(3): p. 759-62.
673. Citardi, M. J., Chaloupka, J. C., Son, Y. H., Ariyan, S., Sasaki, C. T., Management of carotid artery rupture by monitored endovascular therapeutic occlusion (1988-1994). Laryngoscope, 1995. 105(10): p. 1086-92.

674. Morrissey, D. D., Andersen, P. E., Nesbit, G. M., Barnwell, S. L., Everts, E. C., Cohen, J. I., Endovascular management of hemorrhage in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg, 1997. 123(1): p. 15-9.
675. Paiva, M. B., Blackwell, K. E., Saxton, R. E., Calcaterra, T. C., Ward, P. H., Soudant, J., et.al. Palliative laser therapy for recurrent head and neck cancer: a Phase II clinical study. Laryngoscope, 1998. 108(9): p. 1277-83.
676. Paleri, V., Stafford, F. W., Sammut, M. S., Laser debulking in malignant upper airway obstruction. Head Neck, 2005. 27(4): p. 296-301.
677. Burtness, B, Harrington, KJ, Greil, R, Soulières, D, Tahara, M, de Castro, G, et.al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study., 2019. 394 (10212)(10212): p. 1915-1928., https://pubmed.ncbi.nlm.nih.gov/31679945
678. Ferris, R. L., Blumenschein, G., Jr., Fayette, J., Guigay, J., Colevas, A. D., Licitra, L., et.al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. N Engl J Med, 2016. 375(19): p. 1856-1867., https://www.ncbi.nlm.nih.gov/pubmed/27718784
679. Ferris, R. L., Blumenschein, G., Jr., Fayette, J., Guigay, J., Colevas, A. D., Licitra, L., et.al. Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumor PD-L1 expression. Oral Oncol, 2018. 81: p. 45-51., https://www.ncbi.nlm.nih.gov/pubmed/29884413
680. Gibson, M. K., Li, Y., Murphy, B., Hussain, M. H., DeConti, R. C., Ensley, J., et.al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. J Clin Oncol, 2005. 23(15): p. 3562-7., https://www.ncbi.nlm.nih.gov/pubmed/15908667
681. Gillison, M. L., Blumenschein, G., Jr., Fayette, J., Guigay, J., Colevas, A. D., Licitra, L., et.al. CheckMate 141: 1-Year Update and Subgroup Analysis of Nivolumab as First-Line Therapy in Patients with Recurrent/Metastatic Head and Neck Cancer. Oncologist, 2018. 23(9): p. 1079-1082., https://www.ncbi.nlm.nih.gov/pubmed/29866947
682. Bonner, J. A., Harari, P. M., Giralt, J., Azarnia, N., Shin, D. M., Cohen, R. B., et.al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med, 2006. 354(6): p. 567-78.
683. Laccourreye, O., Lawson, G., Muscatello, L., Biacabe, B., Laccourreye, L., Brasnu, D., Carbon dioxide laser debulking for obstructing endolaryngeal carcinoma: a 10-year experience. Ann Otol Rhinol Laryngol, 1999. 108(5): p. 490-4.
684. Wilner, H. I., Lazo, A., Metes, J. J., Beil, K. A., Nowack, P., Jacobs, J., Embolization in cataclysmal hemorrhage caused by squamous cell carcinomas of the head and neck. Radiology, 1987. 163(3): p. 759-62.
685. Citardi, M. J., Chaloupka, J. C., Son, Y. H., Ariyan, S., Sasaki, C. T., Management of carotid artery rupture by monitored endovascular therapeutic occlusion (1988-1994). Laryngoscope, 1995. 105(10): p. 1086-92.
686. Morrissey, D. D., Andersen, P. E., Nesbit, G. M., Barnwell, S. L., Everts, E. C., Cohen, J. I., Endovascular management of hemorrhage in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg, 1997. 123(1): p. 15-9.
687. Paiva, M. B., Blackwell, K. E., Saxton, R. E., Calcaterra, T. C., Ward, P. H., Soudant, J., et.al. Palliative laser therapy for recurrent head and neck cancer: a Phase II clinical study. Laryngoscope, 1998. 108(9): p. 1277-83.
688. Paleri, V., Stafford, F. W., Sammut, M. S., Laser debulking in malignant upper airway obstruction. Head Neck, 2005. 27(4): p. 296-301.

689. A phase III randomised trial of cisplatinum, methotrextate, cisplatinum + methotrexate and cisplatinum + 5-FU in end stage squamous carcinoma of the head and neck. Liverpool Head and Neck Oncology Group. Br J Cancer, 1990. 61(2): p. 311-5.
690. A phase III randomised trial of cisplatinum, methotrextate, cisplatinum + methotrexate and cisplatinum + 5-FU in end stage squamous carcinoma of the head and neck. Liverpool Head and Neck Oncology Group. Br J Cancer, 1990. 61(2): p. 311-5.
691. Clavel, M., Vermorken, J. B., Cognetti, F., Cappelaere, P., de Mulder, P. H., Schornagel, J. H., et.al. Randomized comparison of cisplatin, methotrexate, bleomycin and vincristine (CABO) versus cisplatin and 5-fluorouracil (CF) versus cisplatin © in recurrent or metastatic squamous cell carcinoma of the head and neck. A phase III study of the EORTC Head and Neck Cancer Cooperative Group. Ann Oncol, 1994. 5(6): p. 521-6.
692. Forastiere, A. A., Metch, B., Schuller, D. E., Ensley, J. F., Hutchins, L. F., Triozzi, P., et.al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. J Clin Oncol, 1992. 10(8): p. 1245-51.
693. Jacobs, C., Lyman, G., Velez-Garcia, E., Sridhar, K. S., Knight, W., Hochster, H., et.al. A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. J Clin Oncol, 1992. 10(2): p. 257-63.
694. Jacobs, C., Lyman, G., Velez-Garcia, E., Sridhar, K. S., Knight, W., Hochster, H., et.al. A phase III randomized study comparing cisplatin and fluorouracil as single agents and in combination for advanced squamous cell carcinoma of the head and neck. J Clin Oncol, 1992. 10(2): p. 257-63.
695. Schornagel, J. H., Verweij, J., de Mulder, P. H., Cognetti, F., Vermorken, J. B., Cappelaere, P., et.al. Randomized phase III trial of edatrexate versus methotrexate in patients with metastatic and/or recurrent squamous cell carcinoma of the head and neck: a European Organization for Research and Treatment of Cancer Head and Neck Cancer Cooperative Group study. J Clin Oncol, 1995. 13(7): p. 1649-55.
696. Jelic, S., Stamatovic, Lj, Vucicevic, S., Petrovic, Z., Kreacic, M., Babovic, N., et.al. Use of high-dose cytarabine to enhance cisplatin cytotoxicity-effects on the response and overall survival rates of advanced head and neck cancer patients. Eur J Cancer, 2002. 38(11): p. 1478-89.
697. Gibson, M. K., Li, Y., Murphy, B., Hussain, M. H., DeConti, R. C., Ensley, J., et.al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. J Clin Oncol, 2005. 23(15): p. 3562-7.
698. Forastiere, A. A., Leong, T., Rowinsky, E., Murphy, B. A., Vlock, D. R., DeConti, R. C., et.al. Phase III comparison of high-dose paclitaxel + cisplatin + granulocyte colony-stimulating factor versus low-dose paclitaxel + cisplatin in advanced head and neck cancer: Eastern Cooperative Oncology Group Study E1393. J Clin Oncol, 2001. 19(4): p. 1088-95.
699. Licitra, L., Mesia, R., Rivera, F., Remenar, E., Hitt, R., Erfan, J., et.al. Evaluation of EGFR gene copy number as a predictive biomarker for the efficacy of cetuximab in combination with chemotherapy in the first-line treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck: EXTREME study. Ann Oncol, 2011. 22(5): p. 1078-87., https://www.ncbi.nlm.nih.gov/pubmed/21048039
700. Mesia, R., Rivera, F., Kawecki, A., Rottey, S., Hitt, R., Kienzer, H., et.al. Quality of life of patients receiving platinum-based chemotherapy plus cetuximab first line for recurrent and/or metastatic squamous cell carcinoma of the head and neck. Ann Oncol, 2010. 21(10): p. 1967-73., https://www.ncbi.nlm.nih.gov/pubmed/20335368
701. Vermorken, J. B., Mesia, R., Rivera, F., Remenar, E., Kawecki, A., Rottey, S., et.al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med, 2008. 359(11): p. 1116-27., https://www.ncbi.nlm.nih.gov/pubmed/18784101

702. Vermorken, J. B., Psyrri, A., Mesia, R., Peyrade, F., Beier, F., de Blas, B., et.al. Impact of tumor HPV status on outcome in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck receiving chemotherapy with or without cetuximab: retrospective analysis of the phase III EXTREME trial. Ann Oncol, 2014. 25(4): p. 801-7., https://www.ncbi.nlm.nih.gov/pubmed/24577117
703. Vermorken, Jan Baptist, Remenar, Eva, Hitt, Ricardo, Kawecki, Andrzej, Rottey, Sylvie, Knierim, Luise, et.al. Platinum-based chemotherapy (CT) plus cetuximab in recurrent or metastatic squamous cell carcinoma of the head and neck cancer (R/M-SCCHN): 5-year follow-up data for the extreme trial. Journal of Clinical Oncology, 2014. 32(15_suppl): p. 6021-6021., https://doi.org/10.1200/jco.2014.32.15_suppl.6021
704. Boysen, M., Lovdal, O., Tausjo, J., Winther, F., The value of follow-up in patients treated for squamous cell carcinoma of the head and neck. Eur J Cancer, 1992. 28(2-3): p. 426-30.
705. Hammerlid, E., Persson, L. O., Sullivan, M., Westin, T., Quality-of-life effects of psychosocial intervention in patients with head and neck cancer. Otolaryngol Head Neck Surg, 1999. 120(4): p. 507-16.
706. Hammerlid, E., Silander, E., Hornestam, L., Sullivan, M., Health-related quality of life three years after diagnosis of head and neck cancer—a longitudinal study. Head Neck, 2001. 23(2): p. 113-25.
707. Bjordal, K., Ahlner-Elmqvist, M., Hammerlid, E., Boysen, M., Evensen, J. F., Biorklund, A., et.al. A prospective study of quality of life in head and neck cancer patients. Part II: Longitudinal data. Laryngoscope, 2001. 111(8): p. 1440-52.
708. Smit, M., Balm, A. J., Hilgers, F. J., Tan, I. B., Pain as sign of recurrent disease in head and neck squamous cell carcinoma. Head Neck, 2001. 23(5): p. 372-5.
709. Nguyen, N. P., Sallah, S., Karlsson, U., Antoine, J. E., Combined chemotherapy and radiation therapy for head and neck malignancies: quality of life issues. Cancer, 2002. 94(4): p. 1131-41.
710. Stokkel, M. P., Terhaard, C. H., Hordijk, G. J., van Rijk, P. P., The detection of local recurrent head and neck cancer with fluorine-18 fluorodeoxyglucose dual-head positron emission tomography. Eur J Nucl Med, 1999. 26(7): p. 767-73.
711. Shah, S. I., Applebaum, E. L., Lung cancer after head and neck cancer: role of chest radiography. Laryngoscope, 2000. 110(12): p. 2033-6.
712. Merkx, M. A., Boustahji, A. H., Kaanders, J. H., Joosten, F., Marres, H. A., Bruaset, I., et.al. A half-yearly chest radiograph for early detection of lung cancer following oral cancer. Int J Oral Maxillofac Surg, 2002. 31(4): p. 378-82.
713. Gottschlich, S., Maune, S., Maass, J. D., Gorogh, T., Hoffmann, M., Hoffmann-Fazel, A., et.al. Serum p53 autoantibodies in the follow-up of head and neck cancer patients. Oncology, 2000. 59(1): p. 31-5.
714. Krimmel, M., Hoffmann, J., Krimmel, C., Cornelius, C. P., Schwenzer, N., Relevance of SCC-Ag, CEA, CA 19.9 and CA 125 for diagnosis and follow-up in oral cancer. J Craniomaxillofac Surg, 1998. 26(4): p. 243-8.
715. Mayne, S. T., Cartmel, B., Baum, M., Shor-Posner, G., Fallon, B. G., Briskin, K., et.al. Randomized trial of supplemental beta-carotene to prevent second head and neck cancer. Cancer Res, 2001. 61(4): p. 1457-63.
716. Bissinger, O., Rau, A., Koerdt, S., Wolff, K. D., Kesting, M. R., Gotz, C., Evaluating tumour after care in oral squamous cell carcinoma: Insights into patients‘ health related quality of life. J Craniomaxillofac Surg, 2017. 45(2): p. 262-266., http://www.ncbi.nlm.nih.gov/pubmed/28049604
717. Gotz, C., Drecoll, E., Straub, M., Bissinger, O., Wolff, K. D., Kolk, A., Impact of HPV infection on oral squamous cell carcinoma. Oncotarget, 2016. 7(47): p. 76704-76712., http://www.ncbi.nlm.nih.gov/pubmed/27732948
718. Brands, M. T., Brennan, P. A., Verbeek, A. L. M., Merkx, M. A. W., Geurts, S. M. E., Follow-up after curative treatment for oral squamous cell carcinoma. A critical appraisal of the

guidelines and a review of the literature. Eur J Surg Oncol, 2018. 44(5): p. 559-565., http://www.ncbi.nlm.nih.gov/pubmed/29433990

719. Wensing, B. M., Merkx, M. A., Krabbe, P. F., Marres, H. A., Van den Hoogen, F. J., Oral squamous cell carcinoma and a clinically negative neck: the value of follow-up. Head Neck, 2011. 33(10): p. 1400-5., http://www.ncbi.nlm.nih.gov/pubmed/21928412
720. Digonnet, A., Hamoir, M., Andry, G., Haigentz, M., Jr., Takes, R. P., Silver, C. E., et.al. Post-therapeutic surveillance strategies in head and neck squamous cell carcinoma. Eur Arch Otorhinolaryngol, 2013. 270(5): p. 1569-80., http://www.ncbi.nlm.nih.gov/pubmed/22972497
721. Heiduschka, G., Virk, S. A., Palme, C. E., Ch'ng, S., Elliot, M., Gupta, R., et.al. Margin to tumor thickness ratio - A predictor of local recurrence and survival in oral squamous cell carcinoma. Oral Oncol, 2016. 55: p. 49-54., http://www.ncbi.nlm.nih.gov/pubmed/26861256
722. Low, T. H., Gao, K., Gupta, R., Clifford, A., Elliott, M., Ch'ng, S., et.al. Factors predicting poor outcomes in T1N0 oral squamous cell carcinoma: indicators for treatment intensification. ANZ J Surg, 2016. 86(5): p. 366-71., http://www.ncbi.nlm.nih.gov/pubmed/26991038
723. Flynn, C. J., Khaouam, N., Gardner, S., Higgins, K., Enepekides, D., Balogh, J., et.al. The value of periodic follow-up in the detection of recurrences after radical treatment in locally advanced head and neck cancer. Clin Oncol (R Coll Radiol), 2010. 22(10): p. 868-73., http://www.ncbi.nlm.nih.gov/pubmed/20650620
724. Lee, C. C., Huang, C. Y., Lin, Y. S., Chang, K. P., Chi, C. C., Lin, M. Y., et.al. Prognostic Performance of a New Staging Category to Improve Discrimination of Disease-Specific Survival in Nonmetastatic Oral Cancer. JAMA Otolaryngol Head Neck Surg, 2017. 143(4): p. 395-402., http://www.ncbi.nlm.nih.gov/pubmed/28125757
725. Lin, C. S., de Oliveira Santos, A. B., Silva, E. L., de Matos, L. L., Moyses, R. A., Kulcsar, M. A., et.al. Tumor volume as an independent predictive factor of worse survival in patients with oral cavity squamous cell carcinoma. Head Neck, 2017. 39(5): p. 960-964., http://www.ncbi.nlm.nih.gov/pubmed/28276113
726. Safi, A. F., Grandoch, A., Nickenig, H. J., Zoller, J. E., Kreppel, M., The importance of lymph node ratio for locoregional recurrence of squamous cell carcinoma of the tongue. J Craniomaxillofac Surg, 2017. 45(7): p. 1058-1061., http://www.ncbi.nlm.nih.gov/pubmed/28529103
727. Dirven, R., Ebrahimi, A., Moeckelmann, N., Palme, C. E., Gupta, R., Clark, J., Tumor thickness versus depth of invasion - Analysis of the 8th edition American Joint Committee on Cancer Staging for oral cancer. Oral Oncol, 2017. 74: p. 30-33., http://www.ncbi.nlm.nih.gov/pubmed/29103748
728. Ermer, M. A., Kirsch, K., Bittermann, G., Fretwurst, T., Vach, K., Metzger, M. C., Recurrence rate and shift in histopathological differentiation of oral squamous cell carcinoma - A long-term retrospective study over a period of 13.5 years. J Craniomaxillofac Surg, 2015. 43(7): p. 1309-13., http://www.ncbi.nlm.nih.gov/pubmed/26116970
729. Kanatas, A., Bala, N., Lowe, D., Rogers, S. N., Outpatient follow-up appointments for patients having curative treatment for cancer of the head and neck: are the current arrangements in need of change?. Br J Oral Maxillofac Surg, 2014. 52(8): p. 681-7., http://www.ncbi.nlm.nih.gov/pubmed/25037165
730. Wolfer, S., Elstner, S., Schultze-Mosgau, S., Degree of Keratinization Is an Independent Prognostic Factor in Oral Squamous Cell Carcinoma. J Oral Maxillofac Surg, 2018. 76(2): p. 444-454., http://www.ncbi.nlm.nih.gov/pubmed/28738193
731. Hosni, A., McMullen, C., Huang, S. H., Xu, W., Su, J., Bayley, A., et.al. Lymph node ratio relationship to regional failure and distant metastases in oral cavity cancer. Radiother Oncol, 2017. 124(2): p. 225-231., http://www.ncbi.nlm.nih.gov/pubmed/28838425
732. Son, H. J., Roh, J. L., Cho, K. J., Choi, S. H., Nam, S. Y., Kim, S. Y., Nodal factors predictive of recurrence and survival in patients with oral cavity squamous cell carcinoma. Clin Otolaryngol, 2018. 43(2): p. 470-476., http://www.ncbi.nlm.nih.gov/pubmed/28981214

733. Allison, P. J., Locker, D., Feine, J. S., The relationship between dental status and health-related quality of life in upper aerodigestive tract cancer patients. Oral Oncol, 1999. 35(2): p. 138-43.
734. Granstrom, G., Radiotherapy, osseointegration and hyperbaric oxygen therapy. Periodontol 2000, 2003. 33: p. 145-62.
735. Mericske-Stern, R., Perren, R., Raveh, J., Life table analysis and clinical evaluation of oral implants supporting prostheses after resection of malignant tumors. Int J Oral Maxillofac Implants, 1999. 14(5): p. 673-80.
736. McCord, J. F., Michelinakis, G., Systematic review of the evidence supporting intra-oral maxillofacial prosthodontic care. Eur J Prosthodont Restor Dent, 2004. 12(3): p. 129-35.
737. Granstrom, G., Radiotherapy, osseointegration and hyperbaric oxygen therapy. Periodontol 2000, 2003. 33: p. 145-62.
738. Mericske-Stern, R., Perren, R., Raveh, J., Life table analysis and clinical evaluation of oral implants supporting prostheses after resection of malignant tumors. Int J Oral Maxillofac Implants, 1999. 14(5): p. 673-80.
739. Rosenberg, S. W., Oral complications of cancer therapies. Chronic dental complications. NCI Monogr, 1990. p. 173-8.
740. Toljanic, J. A., Heshmati, R. H., Bedard, J. F., Dental follow-up compliance in a population of irradiated head and neck cancer patients. Oral Surgery Oral Medicine Oral Pathology Oral Radiology & Endodontics, 2002. 93(1): p. 35-8.
741. Tong, A. C., Leung, A. C., Cheng, J. C., Sham, J., Incidence of complicated healing and osteoradionecrosis following tooth extraction in patients receiving radiotherapy for treatment of nasopharyngeal carcinoma. Aust Dent J, 1999. 44(3): p. 187-94.
742. Ang, E., Black, C., Irish, J., Brown, D. H., Gullane, P., O'Sullivan, B., et.al. Reconstructive options in the treatment of osteoradionecrosis of the craniomaxillofacial skeleton. Br J Plast Surg, 2003. 56(2): p. 92-9.
743. Ang, E., Black, C., Irish, J., Brown, D. H., Gullane, P., O'Sullivan, B., et.al. Reconstructive options in the treatment of osteoradionecrosis of the craniomaxillofacial skeleton. Br J Plast Surg, 2003. 56(2): p. 92-9.
744. Annane, D., Depondt, J., Aubert, P., Villart, M., Gehanno, P., Gajdos, P., et.al. Hyperbaric oxygen therapy for radionecrosis of the jaw: a randomized, placebo-controlled, double-blind trial from the ORN96 study group. J Clin Oncol, 2004. 22(24): p. 4893-900.
745. Bennett, M. H., Feldmeier, J., Hampson, N., Smee, R., Milross, C., Hyperbaric oxygen therapy for late radiation tissue injury. Cochrane Database Syst Rev, 2005. p. CD005005.
746. Bennett, M. H., Feldmeier, J., Hampson, N., Smee, R., Milross, C., Hyperbaric oxygen therapy for late radiation tissue injury. Cochrane Database Syst Rev, 2005. p. CD005005.
747. Coulthard, P., Esposito, M., Worthington, H. V., Jokstad, A., Therapeutic use of hyperbaric oxygen for irradiated dental implant patients: a systematic review. J Dent Educ, 2003. 67(1): p. 64-8.
748. Jereczek-Fossa, B. A., Orecchia, R., Radiotherapy-induced mandibular bone complications. Cancer Treat Rev, 2002. 28(1): p. 65-74.
749. Reuther, T., Schuster, T., Mende, U., Kubler, A., Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumour patients—a report of a thirty year retrospective review. Int J Oral Maxillofac Surg, 2003. 32(3): p. 289-95.
750. Reuther, T., Schuster, T., Mende, U., Kubler, A., Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumour patients—a report of a thirty year retrospective review. Int J Oral Maxillofac Surg, 2003. 32(3): p. 289-95.
751. Pasquier, D., Hoelscher, T., Schmutz, J., Dische, S., Mathieu, D., Baumann, M., et.al. Hyperbaric oxygen therapy in the treatment of radio-induced lesions in normal tissues: a literature review. Radiother Oncol, 2004. 72(1): p. 1-13.

752. Pasquier, D., Hoelscher, T., Schmutz, J., Dische, S., Mathieu, D., Baumann, M., et.al. Hyperbaric oxygen therapy in the treatment of radio-induced lesions in normal tissues: a literature review. Radiother Oncol, 2004. 72(1): p. 1-13.
753. Glanzmann, C., Gratz, K. W., Radionecrosis of the mandibula: a retrospective analysis of the incidence and risk factors. Radiother Oncol, 1995. 36(2): p. 94-9100.
754. Royal College of Speech and Language Therapists (RCSLT), Clinical Guidelines., 2004.
755. Sullivan, P., Guildford, A., Swallowing intervention in oncologySingular Publishing Group INC, 1999.
756. Kreuzer, S. H., Schima, W., Schober, E., Pokieser, P., Kofler, G., Lechner, G., et.al. Complications after laryngeal surgery: videofluoroscopic evaluation of 120 patients. Clin Radiol, 2000. 55(10): p. 775-81.
757. Stenson, K. M., MacCracken, E., List, M., Haraf, D. J., Brockstein, B., Weichselbaum, R., et.al. Swallowing function in patients with head and neck cancer prior to treatment. Arch Otolaryngol Head Neck Surg, 2000. 126(3): p. 371-7.
758. Aviv, J. E., Prospective, randomized outcome study of endoscopy versus modified barium swallow in patients with dysphagia. Laryngoscope, 2000. 110(4): p. 563-74.
759. Furia, C. L., Kowalski, L. P., Latorre, M. R., Angelis, E. C., Martins, N. M., Barros, A. P., et.al. Speech intelligibility after glossectomy and speech rehabilitation. Arch Otolaryngol Head Neck Surg, 2001. 127(7): p. 877-83.
760. Eisbruch, A., Lyden, T., Bradford, C. R., Dawson, L. A., Haxer, M. J., Miller, A. E., et.al. Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys, 2002. 53(1): p. 23-8.
761. Sullivan P, Guildford A. Swallowing intervention in oncology. San Diego: Singular Publishing Group INC; 1999.
762. Kreuzer, S. H., Schima, W., Schober, E., Pokieser, P., Kofler, G., Lechner, G., et.al. Complications after laryngeal surgery: videofluoroscopic evaluation of 120 patients. Clin Radiol, 2000. 55(10): p. 775-81.
763. Stenson, K. M., MacCracken, E., List, M., Haraf, D. J., Brockstein, B., Weichselbaum, R., et.al. Swallowing function in patients with head and neck cancer prior to treatment. Arch Otolaryngol Head Neck Surg, 2000. 126(3): p. 371-7.
764. Nguyen, N. P., Moltz, C. C., Frank, C., Vos, P., Smith, H. J., Karlsson, U., et.al. Dysphagia following chemoradiation for locally advanced head and neck cancer. Ann Oncol, 2004. 15(3): p. 383-8.
765. Gillespie, M. B., Brodsky, M. B., Day, T. A., Lee, F. S., Martin-Harris, B., Swallowing-related quality of life after head and neck cancer treatment. Laryngoscope, 2004. 114(8): p. 1362-7.
766. Kulbersh, B. D., Rosenthal, E. L., McGrew, B. M., Duncan, R. D., McColloch, N. L., Carroll, W. R., et.al. Pretreatment, preoperative swallowing exercises may improve dysphagia quality of life. Laryngoscope, 2006. 116(6): p. 883-6.
767. NHS Quality Improvement Scotland, Clinical Standards: food, fluid and nutritional care in hospitals, 2003.
768. Schweinfurth, J. M., Boger, G. N., Feustel, P. J., Preoperative risk assessment for gastrostomy tube placement in head and neck cancer patients. Head Neck, 2001. 23(5): p. 376-82.
769. Deurloo, E. E., Schultze Kool, L. J., Kroger, R., van Coevorden, F., Balm, A. J., Percutaneous radiological gastrostomy in patients with head and neck cancer. European Journal of Surgical Oncology, 2001. 27(1): p. 94-7.
770. Beaver, M. E., Myers, J. N., Griffenberg, L., Waugh, K., Percutaneous fluoroscopic gastrostomy tube placement in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg, 1998. 124(10): p. 1141-4.

771. Lee, J. H., Machtay, M., Unger, L. D., Weinstein, G. S., Weber, R. S., Chalian, A. A., et.al. Prophylactic gastrostomy tubes in patients undergoing intensive irradiation for cancer of the head and neck. Arch Otolaryngol Head Neck Surg, 1998. 124(8): p. 871-5.
772. Mekhail, T. M., Adelstein, D. J., Rybicki, L. A., Larto, M. A., Saxton, J. P., Lavertu, P., Enteral nutrition during the treatment of head and neck carcinoma: is a percutaneous endoscopic gastrostomy tube preferable to a nasogastric tube?. Cancer, 2001. 91(9): p. 1785-90.
773. Deurloo, E. E., Schultze Kool, L. J., Kroger, R., van Coevorden, F., Balm, A. J., Percutaneous radiological gastrostomy in patients with head and neck cancer. European Journal of Surgical Oncology, 2001. 27(1): p. 94-7.
774. Beaver, M. E., Myers, J. N., Griffenberg, L., Waugh, K., Percutaneous fluoroscopic gastrostomy tube placement in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg, 1998. 124(10): p. 1141-4.
775. Chawla, S., Mohanti, B. K., Rakshak, M., Saxena, S., Rath, G. K., Bahadur, S., Temporal assessment of quality of life of head and neck cancer patients receiving radical radiotherapy. Qual Life Res, 1999. 8(1-2): p. 73-8.
776. Gritz, E. R., Carmack, C. L., de Moor, C., Coscarelli, A., Schacherer, C. W., Meyers, E. G., et.al. First year after head and neck cancer: quality of life. J Clin Oncol, 1999. 17(1): p. 352-60.
777. Zwahlen, R. A., Dannemann, C., Gratz, K. W., Studer, G., Zwahlen, D., Moergeli, H., et.al. Quality of life and psychiatric morbidity in patients successfully treated for oral cavity squamous cell cancer and their wives. J Oral Maxillofac Surg, 2008. 66(6): p. 1125-32.
778. Singer, S., Brown, A., Einenkel, J., Hauss, J., Hinz, A., Klein, A., et.al. Identifying tumor patients‘ depression. Support Care Cancer, 2011. 19(11): p. 1697-703.
779. Spelten, E. R., Sprangers, M. A., Verbeek, J. H., Factors reported to influence the return to work of cancer survivors: a literature review. Psychooncology, 2002. 11(2): p. 124-31.
780. Relic, A., Mazemda, P., Arens, C., Koller, M., Glanz, H., Investigating quality of life and coping resources after laryngectomy. Eur Arch Otorhinolaryngol, 2001. 258(10): p. 514-7.
781. Fielding, David, Agnew, Julienne, Wright, David, Hodge, Robert, Autofluorescence improves pretreatment mucosal assessment in head and neck cancer patients. Otolaryngology - Head & Neck Surgery, 2010. 142(3 Suppl 1): p. S20-6.
782. Royal College of Pathologists. Standards and Datasets for Reporting Cancers: Datasets for histopathology reports on head and neck carcinomas and salivary neoplasms. 2nd Edition. London: The Royal College of Pathologists; 2005. [cited 11 August 2006]. Available from url: http://www.rcpath.org/resources/pdf/HeadNeckDatasetJun05.pdf
783. Barnes L, Eveson JW, Reichart P, Sidransky D, editors. Pathology and Genetics of Head and Neck Tumours. Lyon: IARC Press; 2005. (WHO Classification of Tumours)
784. Board of the Faculty of Clinical Oncology. Guidelines for the Management of the Unscheduled Interruption or Prolongation of a Radical Course of Radiotherapy. 2nd Edition. London: The Royal College of Radiologists; 2002. [cited 11 August 2006]. Available from url: http://www.rcr.ac.uk/docs/oncology/pdf/gaps.pdf