Leitlinienprogramm Onkologie

Guideline Report

on the Guideline

"Diagnosis and Management of Carcinoma of the Oral Cavity"

AWMF Registry Number 007/100OL

Version 2.0 November 2012

Guideline Report

DKG Krebsgesellschaft · Deutsche Krebshilfe Helfen. Forschen. Informieren. · AWMF

Contents

List of figures

List of tables

1. About this guideline report

1.1. Authors of the Guideline Report

Prof. Dr. Dr. Wolff K.-D., GL Coordinator, DGMKG

PD Dr. Nast A., Rosumeck S, Dr. Sammain A. (Division of Evidence Based Medicine, Dermatology Clinic of Charité University Medical Hospital Berlin)

Dr. Follmann M., MPH, MSc (German Cancer Society (DKG), German Guideline Program in Oncology)

1.2. Publisher

German Guideline Program in Oncology
of the Association of the Scientific Medical Societies in Germany, the German Cancer Society and German Cancer Aid

Office: c/o German Cancer Society
Kuno-Fischer-Strasse 8
14057 Berlin

leitlinienprogramm@krebsgesellschaft.de
www.leitlinienprogramm-onkologie.de

1.3. Coordinating Association

German Society for Oral and Maxillofacial Surgery

1.4. Guideline Funding

This guideline has been funded by German Cancer Aid under the auspices of the German Guideline Program in Oncology.

1.5. Contact

Univ.-Prof. Dr. med. Dr. med. dent. Klaus-Dietrich Wolff
Clinic and Polyclinic for Oral and Maxillofacial Surgery
Rechts der Isar Hospital, Munich Technical University
Ismaninger Str. 22, 81675 Munich
Tel.: 0049 89 4140-2921
Fax: 0049 89 4140-4993
wolff@mkg.med.tum.de
www.med.tum.de

1.6. Abbreviations

Abbreviation	Definition
>/<	superior/inferior
>>/<<	significantly superior/inferior
+	positive
-	negative
5-FU	5-fluorouracil
AAT	arm abduction test
AEK	German Society for Cancer Research
AJCC	American Joint Committee on Cancer
ANOVA	Analysis of Variance
AWMF	Association of the Scientific Medical Societies in Germany
BLD	baseline differences
BMI	body mass index
C	control
CBCT	cone-beam CT
CE	clinical examination
CECT	contrast-enhanced CT
CI	confidence interval
CK20-RT-PCR	cytokeratin-20 reverse transcription polymerase chain reaction
CND	comprehensive neck dissection
cN (pN)	clinical N-stage
CT/MRI	computed tomography/magnetic resonance imaging
cT (pT)	clinical T-stage
CUP	cancer of unknown primary
CXR	chest X-ray
DFS	disease free survival
(DW)-MRI	diffusion-weighted magnetic resonance imaging
DGMKG	German Society for Oral and Maxillofacial Surgery
DKG	German Cancer Society
DÖSAK	German/Austrian/Swiss Working Group on Maxillofacial Tumors
DVSG	German Association for Social Work in Healthcare
ECS	extracapsular spread

Abbreviation	Definition
EGF	endothelial growth factor
END	elective neck dissection
FDG	fluorodeoxyglucose
FDG-PET	fluorodesoxyglucose-positron emission tomography
FET-PET	fluoroethyltyrosine positron emission tomography
FN	false negative
FNB	fine-needle biopsy
FNR	false negative rate
FP	false positive
GL	guideline
GTV	gross tumor volume
HE	histological staging
HGIN	high-grade intraepithelial neoplasia
HN malig.	head and neck malignancy
ENT	ear, nose and throat medicine
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
HR-QOL	health-related quality of life
IHC	immunohistochemistry
IMRT	intensity-modulated radiation therapy
IQWiG	Institute for Quality and Efficiency in Healthcare
k	Kappa
KOK	Society for Oncology Nursing and Pediatric Oncology Nursing
KQ	key question
LLC	lower lip carcinoma
LN	lymph node
LNM	lymph node metastasis
LS	lymphoscintigraphy
LCR	locoregional recurrence
MIBI	methoxyisobutylisonitrile
MFS	maxillofacial surgery
MM	marginal mandibulectomy

Abbreviation	Definition
MRND	modified radical neck dissection
MRT	magnetic resonance tomography
MSCT	multislice computed tomography
NA	not applicable
NBI	narrow band imaging
NCR	neck control rate
ND	neck dissection
NHS	National Health Service
NPQ	negative probability quotient
NPV	negative predictive value
ns	not significant
OBS	observation
OCLNM	occult cervical lymph node metastasis
GGPO	German Guideline Program in Oncology
OM	occult metastasis
OOSCC	oral and oropharyngeal squamous cell carcinoma
OPG	orthopantomogram
OR	odds ratio
OS	overall survival
OSCC	oral squamous cell carcinoma
p	p-value
PET	positron emission tomography
PNI	peripheral nerve invasion
PPQ	positive probability quotient
PPV	positive predictive value
PR	panoramic radiography
PT	primary tumor
pt	patient
pts	patients
QOL	quality of life
RCT	randomized controlled trial
RND	radical neck dissection

Abbreviation	Definition
ROC	receiver operating characteristics
RT	radiotherapy
SAN	spinal accessory nerve
SCC	squamous cell carcinoma
SCM	sternocleidomastoideus
SIGN	Scottish Intercollegiate Guidelines Network
SLN	sentinel lymph node
SLNB	sentinel lymph node biopsy
SM	segmental mandibulectomy
SND	selective neck dissection
SOHND/SOND	selective supraomohyoid neck dissection
SPECT	single photon emission computed tomography
SPIR	spectral presaturation with inversion recovery
ss	statistically significant/statistically significant difference
SS-IHC	serial sections with immunohistochemistry
STIR	short-term inversion recovery
SUV	standardized uptake value
tn	true negative
TND	therapeutic neck dissection (RND, MRND, SND)
TNM	tumor node metastasis
tp	true positive
TV	tumor volume
TYR-PET	tyrosin positron emission tomography
UADT	upper aerodigestive tract (excludes parotid, skin; includes tonsils)
UICC	Union for International Cancer Control
US	ultrasound
US+CAD	ultrasound + computer-aided diagnosis
USgFNAC	ultrasound-guided fine needle aspiration cytology
UW-QOL	University of Washington Quality of Life Questionnaire
v	volume
WHO	World Health Organization
WW	watch and wait

2. About this Guideline

2.1. Project plan

In order to achieve the best therapeutic outcome in the management of carcinoma of the oral cavity, namely to improve long-term prognosis and enhance quality of life, the interdisciplinary treatment concept should be based – in conjunction with the introduction of head and neck modules at certified oncology centers – upon the framework of an evidence-based guideline (S3). To this end, a major application for support from the German Guideline Program in Oncology (GGPO) was filed in March 2010 and approved by the steering committee on July 16, 2010. All Section B working groups of the German Cancer Society (DKG), as well as all cancer working groups of the professional associations, were invited to contribute. Only a few declined, resulting in a Guideline Development Group composed of 21 specialist disciplines, working groups, associations and self-help groups. The kick-off meeting, attended by 37 participants, was held on November 22, 2010. A group of experts headed by Dr Nast of Charité Berlin was appointed to prepare the literature, a task which was completed in August 2011 following systematic database analysis and collation of evidence. The key questions agreed upon for the de novo review entailed imaging procedures, more in-depth examinations, as well as radical neck dissection and mandibular resection. Having screened the guidelines already in existence, the SIGN Guideline of the NHS (2006) proved most suitable as a basis for adaptation. Five key questions were defined and a further 43 questions covering 14 complex topics were agreed upon; these were assigned for the purposes of preparation to eight different task forces, namely TF 1: Epidemiology, triggering factors, early diagnosis; TF 2: Patient education; TF 3a: Diagnostics (clinical findings and imaging), follow-up; TF 3b: Diagnostics (pathology); TF 4a: Surgical treatment (primary tumor); TF 4b: Surgical treatment (lymph nodes); TF 5: Reconstruction, rehabilitation, logopedia; TF 6: Radiotherapy; TF 7: Pharmacotherapy; TF 8: Palliative care, psycho-oncology. The systematic literature review produced a total of approx. 3000 hits, with roughly 250 studies of interest, and ultimately 117 usable studies. By restricting the questions to squamous cell carcinoma of the oral cavity, often only a small number of cases were found with limited evidence. The first task-force meeting was held on July 8, 2011 in Munich, involving all eight task forces. With the exception of KQ 5 (mandibular resection), the overall quality of the data was good, permitting the other four key questions to be answered on the basis of the de novo review. It transpired that the remaining key questions could be answered by means of guideline adaptation (SIGN 2006) [1] and expert consensus. The body of text was written by the GL coordinator in agreement with the TF leaders, and was completed in good time prior to the subsequent consensus conference scheduled for December 1-2, 2011 in Berlin.

2.2. Additional guidance documents

This report is based on the full-length version of S3 Guideline "Diagnosis and Management of Carcinoma of the Oral Cavity", which can be found at the following addresses:

http://www.awmf.org/leitlinien/aktuelle-leitlinien.html

http://www.leitlinienprogramm-onkologie.de/OL/leitlinien.html

http://www.krebsgesellschaft.de/wub_llevidenzbasiert,120884.html

http://www.krebshilfe.de/

http://www.mkg-chirurgie.de

The following documents accompany this Guideline Report:

- Full version
- Short version
- Patient guideline

All of these documents can likewise be found on the websites listed above.

Scope and Purpose

2.3. Target audience

This guideline applies specifically to squamous cell carcinoma of the oral cavity. The patient population to whom the guideline applies is clearly defined. It concerns any patient presenting with abnormalities of the mucous membranes of the oral cavity that require investigation, whether identified by the patient himself or by a medical examination (MFS, ENT, dentist, primary care physician or general practitioner, dermatologist). Patients of all ages and sexes are covered by this guideline. The guideline addresses all stages, including early forms (carcinoma in situ), of the disease. The existence of comorbidities does not preclude the application of this guideline.

Users of this guideline may be oral and maxillofacial surgeons, ENT specialists, radiotherapists, oncologists, primary care physicians/general practitioners, as well as dental practitioners and dentists specializing in oral surgery; carcinomas or metastatic carcinomas originating in tissues other than the oral mucosa are not covered by this guideline, nor are squamous cell carcinomas of the oral cavity associated with existing incurable tumors or severe diseases of different etiologies. Separate guidelines are available concerning the management of carcinomas in neighboring structures (larynx, pharynx, lips).

2.4. Objective

The guideline is designed to provide professionals with guidance and support when determining the necessary diagnostic and therapeutic measures for reliably achieving their therapeutic goals, namely to derive the best possible prognosis and quality of life from a specific combination of findings. The guideline aims to reflect the latest therapeutic standards based on scientifically validated data, and so contribute towards continuing professional development. It underlines the interdisciplinary nature of diagnostics, management and follow-up, and should precipitate the introduction of effective therapy. Based on the guideline, patients and their families should receive reliable, comprehensible information which helps them to understand and become actively involved in the proposed therapeutic concepts. Use of the guideline should reduce the frequency of avoidable complications and lay the foundation for improving the social and occupational welfare of patients.

Important basic goals:

- Circulation of evidence-based, formally agreed recommendations on health care practices across the board
- Proposal of solutions for interfaces both between the different disciplines (MFS/ENT/radiotherapy/oncology/pathology/anesthesia & intensive care, etc) and the different areas of care (primary prevention/secondary prevention/care/rehabilitation)

- Publication of GL-based quality indicators and patient guidelines, broadest possible implementation of the GL recommendations and quality indicators
- Consideration of GL recommendations in continuing professional medical development and training programs, and quality management systems.

3. Composition of the Guideline Development Group

3.1. Professional associations

The GL Development Group consists of the following members (Table 1):

Table 1 Composition of the GL Development Group

Organization	Authors
German Society for Oral and Maxillofacial Surgery (DGMKG)	Wolff K.-D., Grötz K., Reinert S., Pistner H.
German/Austrian/Swiss Working Group on Maxillofacial Tumors (DÖSAK)	Frerich, B.
Study Group on Maxillofacial Surgery	Reichert, T.
German Society of Dental, Oral & Craniomandibular Sciences	Schliephake, H.
German Society for Oto-Rhino-Laryngology	Bootz F., Westhofen M.
German Dental Association	Boehme, P.
Federal Association of Panel Dentists	Beck, J.
German Society of Pathology	Burkhardt A., Ihrler S.
German Society of Radiation Oncology	Fietkau R., Budach W., Wittlinger M.
German Society of Hematology and Oncology	Keilholz U., Gauler T., Eberhardt W.
German Society of Plastic and Reconstructive Surgery	Horch R., Germann G.
Working Group Head and Neck of the German Society of Radiology	Lell M.
KOK	Paradies K., Gittler-Hebestreit N.
AEK	Engers K.
Working Group on Orofacial Pain of the German Association for the Study of Pain	Schmitter M.
Working Group for Supportive Care in Cancer, Rehabilitation and Social Medicine within the German Cancer Society (ASORS)	Lübbe A.
Working Group on Tumor Pain of the German Pain Society	Wirz S.
Patient representative	Mantey W.
German Association for Social Work in Healthcare, National Cancer Center	Bikowski K.
German Logopedia Society	Nusser-Müller-Busch R.
Working Group for Psycho-Oncology of the German Cancer Society (PSO)	Singer S., Danker H.

Participants of (kick-off) meeting in Frankfurt on November 11, 2010

Ms K. Bikowski	German Association for Social Work in Healthcare, Cancer Center, Heidelberg
Prof. A. Burkhardt	German Society of Pathology, Reutlingen
Prof. K. Engers	Department of Cancer Research, Düsseldorf
Herr R. Erdmann	Division of Evidence Based Medicine, Charité Berlin (not eligible to vote)
Prof. B. Frerich	German Society for Oral and Maxillofacial Surgery, Rostock
Prof. T. Gauler	German Society for Oncology in Internal Medicine, Essen
Prof. R. Fietkau	German Society of Radiation Oncology, Erlangen
Prof. W. Budach	German Society of Radiation Oncology, Düsseldorf
Prof. K. Grötz	German Society for Oral and Maxillofacial Surgery, Wiesbaden
Prof. H. Horch	German Society of Plastic and Reconstructive Surgery, Erlangen
Prof. S. Ihrler	German Society of Pathology, Munich
PD M. Lell	Working Group Head and Neck of the German Society of Radiology, Erlangen
Ms W. Mantey	Patient representative, Berlin
Ms R. Nusser-Müller-Busch	German Logopedia Society, Frechen
Ms K. Paradies	Society for Oncology Nursing and Pediatric Oncology Nursing, Hamburg
Dr D. Pathirana	Division of Evidence Based Medicine, Charité Berlin (not eligible to vote)
Prof. H. Pistner	Guideline Officer of the German Society for Oral and Maxillofacial Surgery, Erfurt
Prof. T. Reichert	German Society for Oral and Maxillofacial Surgery, Regensburg
Ms S. Rosumeck	Division of Evidence Based Medicine, Charité Berlin (not eligible to vote)
Prof. M. Schmitter	Working Group on Orofacial Pain of the German Association for the Study of Pain

Prof. J. Werner	German Society for Oto-Rhino-Laryngology, Marburg
Prof. M. Westhofen	German Society for Oto-Rhino-Laryngology, Aachen
Dr S. Wirz	Working Group on Tumor Pain of the German Association for the Study of Pain, Essen
Dr M. Wittlinger	German Society of Radiation Oncology, Erlangen
Prof. K.-D. Wolff	German Society for Oral and Maxillofacial Surgery, Munich – guideline coordination

Moderation and guidance:

Prof. I. Kopp	Director of the Institute for Medical Information Management of the Association of the Scientific Medical Societies, Marburg
Dr M. Follmann, MPH, MSc	German Cancer Society, German Guideline Program in Oncology, Berlin
PD Dr A. Nast	Division of Evidence Based Medicine, Charité Berlin

Each participant at the kick-off meeting in November 2010 was issued with the standardized COI disclosure form of the AWMF for declaration of any potential conflicts of interest. The form was completed by all participants. The COI forms are appended to the report in chapter 8 Editoral Independence. The potential conflicts of interest were balanced, thus ruling out any substantial bias within the entire group. Furthermore, no areas were identified in which an abstention from voting on individual topics would have been necessary.

The **task forces were assigned** as follows (Table 2):

Table 2 Task force assignment

TF title	Coordinators (in alphabetical order)
1 Epidemiology, triggering factors, early diagnosis	Burkhardt A., Reichert T.
2 Patient education	Mantey W., Wolff K.D.
3a Diagnostics (clinical findings and imaging), follow-up	Frerich B., Lell M., Westhofen M.
3b Diagnostics (pathology)	Burkhardt A., Engers K., Ihrler S., Pistner H.,
4a Surgical treatment (primary tumor)	Ihrler S., Wolff K.D.
4b Surgical treatment (lymph nodes)	Frerich B., Ihrler S., Reichert T.
5 Reconstruction, rehab, logopedia	Bikowski K., Horch R., Nusser-Müller-Busch R., Westhofen M., Wolff K.D.
6 Radiotherapy	Budach W., Fietkau R., Gauler T., Grötz K., Wittlinger M.
7 Pharmacotherapy	Eberhardt W., Keilholz U.
8 Palliative care, psycho-oncology	Bikowski K., Grötz K., Schmitter M., Wirz S., Singer S.

4. Remit and Structure

Prior to elaboration of the guideline addressed herein, key questions were formulated at the kick-off meeting in November 2010, the structural content of which was to be used as a basis for the guideline. The formal structure of the guideline is based on the template of the German Guideline Program in Oncology (GGPO). The sequence of the main chapters was chosen to reflect existing, established oncology guidelines. In doing so the basic principle for formulating statements and recommendations was maintained, while adding explanatory passages of text with more detailed information on each.

The following key questions were initially agreed upon (Table 3):

Table 3 Initially agreed key questions

Question	Basis of evidence
1. Which diseases of the oral cavity pose an increased risk of oral cavity carcinoma?	Guideline adaptation
2. Which risk factors are associated with an increased incidence of oral cavity carcinoma?	Guideline adaptation
3. What are the prognostic factors in oral cavity carcinoma?	Guideline adaptation
4. Is there a suitable method for screening the general population?	Guideline adaptation
5. What issues should be addressed when providing patients with information?	Guideline adaptation
6. Which imaging method is best for diagnosing oral cavity carcinoma?	Guideline adaptation/de novo review (2003 onwards)
7 Which diagnostic imaging method is best for determining tumor infiltration of the mandible in oral cavity carcinoma?	Guideline adaptation/ de novo review (2003 onwards)
8. Which examinations are recommended for ruling out synchronous secondary tumors?	Guideline adaptation/de novo review (2003 onwards)
9. Which supplementary diagnostic methods should be performed on suspicion of metastasis?	Guideline adaptation/de novo review (2003 onwards)
10. Does the sentinel lymph node (SLN) play a part in PECA of the oral cavity?	Guideline adaptation/de novo review (2003 onwards)
11. Should deep invasion be considered in pT classification?	Guideline adaptation
12. What is the correlation between the histologic safety margin and prognosis in oral cavity carcinoma?	Guideline adaptation/ expert consensus
13. Which lymph nodes/regional lymph nodes should be removed by tumor surgery?	Guideline adaptation/de novo review (2003 onwards)
14. How wide a safety margin should be left from the macroscopically identifiable border of the tumor on resection?	Guideline adaptation/ expert consensus
15. Is intraoperative frozen-section analysis advisable in principle	Guideline adaptation/

Question	Basis of evidence
as a routine method for controlling the incision margins?	expert consensus
16. Is continuity resection of the mandible superior to wedge resection in oral cavity carcinoma?	Guideline adaptation/de novo review (2003 onwards)
17. If a tumor is localized to the tongue, floor of the mouth or mandible, should en bloc resection of the carcinoma with the conglomerate of lymph nodes be the aim?	Expert consensus
18. Do the radical nature and extent of neck dissection influence the prognosis?	Guideline adaptation/de novo review (2003 onwards)
19. In which situations is unilateral neck dissection sufficient?	Guideline adaptation/ de novo review (2003 onwards)
20. When resecting squamous cell carcinoma, is dissection of levels I-III equivalent to radical neck dissection if there is a clear suspicion of regional metastasis?	Guideline adaptation/ de novo review (2003 onwards)
21. Is coverage of the defect with microvascular anastomosis for squamous cell carcinoma the procedure of choice if primary wound closure is not possible due to the size of the defect?	Expert consensus
22. In prognostic terms, is primary reconstruction disadvantageous as opposed to secondary (including osseous) reconstruction?	Guideline adaptation/ de novo review (2003 onwards)
23. Which patients are indicated for primary radiotherapy?	Guideline adaptation/ expert consensus
24. How soon after surgery should radiotherapy be concluded?	Guideline adaptation/ expert consensus
25. Which radiation protocol should be used?	Guideline adaptation
26. When is adjuvant radiotherapy indicated?	Guideline adaptation
27. In cancer of the tongue, is radiotherapy/chemotherapy alone equivalent or superior to radical surgery in terms of survival?	Guideline adaptation/ expert consensus
28. Which patients should be given chemotherapy?	Guideline adaptation
29. Which protocols should be used?	Guideline adaptation
30. Is the outcome (mortality, morbidity, quality of life) improved by neoadjuvant therapy rather than surgery alone in the case of advanced (cT4, cN2+) carcinoma of the oral cavity?	Guideline adaptation/ expert consensus
31. Is neoadjuvant therapy equivalent or superior to postoperative radiochemotherapy (RCTx) in carcinoma of the oral cavity?	Expert consensus
32. Aside from surgery, are other (equivalent or superior) therapeutic options (in terms of outcome) available for pT1/2/3 pN0 cM0 squamous cell carcinoma?	Guideline adaptation/ de novo review (2003 onwards)
33. What are the therapeutic options in the case of pT4 pN0 M0 squamous cell carcinoma with osseous infiltration?	Guideline adaptation/ de novo review (2003 onwards)

Question	Basis of evidence
34. Is adjuvant radiochemotherapy indicated in pT1/2 pN1 squamous cell carcinoma?	Guideline adaptation
35. Do the results of surgery differ from primary RCTx in T3/4 N1 PECA?	Guideline adaptation/ expert consensus
36. Is surgery for pT1-4 pN2 squamous cell carcinoma or for capsule perforation in the lymph drainage vessels the primary therapeutic option?	Guideline adaptation/ expert consensus
37. What is the therapy of choice for tumors that are inoperable on functional or medical grounds?	Guideline adaptation/ expert consensus
38. Will a cautious approach to clinically negative (N0) neck worsen the prognosis?	Guideline adaptation/de novo review (2003 onwards)
39. Is bilateral neck dissection necessary for tumors crossing the midline or in a post-molar position?	Guideline adaptation/de novo review (2003 onwards)
40. Is curative, radical neck dissection with dissection of levels I-V superior to elective neck dissection if staging examinations (US, CT or MRI) reveal clear signs of cervical lymph node metastasis?	Guideline adaptation/ de novo review (2003 onwards)
41. Do selective and radical neck dissection for pN1 scenarios offer the same prognoses if followed by radiochemotherapy?	Guideline adaptation/ de novo review (2003 onwards)
42. Are there follow-up protocols that can influence mortality from carcinoma of the oral cavity? (Or do established follow-up protocols that have proved beneficial even exist?)	Guideline adaptation/ expert consensus

All key questions were agreed unanimously by the plenum.

Since not all the key questions listed here with a view to writing the guideline could be answered on the basis of the available evidence, five key questions (see 5 Methodology PICO strategy for key questions) were selected during the first consensus conference; evidence-based answers were to be formulated for incorporation in the guideline.

A systematic literature review with preparation of the evidence was undertaken by a group of experts headed by Dr Nast, commencing in spring 2011 and ending in June 2011. Out of a total of about 3000 relevant abstracts, roughly 250 articles were identified. Of these, 117 were ultimately deemed appropriate for closer analysis. As a result, the literature was summarized on the basis of the key questions and the results presented in evidence tables. A reprint of the tables is included as an annex. In a further step, the references used as the basis for SIGN Guideline No. 90 were compared against the results of our own de novo literature review, subjected to renewed analysis and taken into consideration when compiling the evidence tables. The system and methods used for review, text screening, study evaluation, compilation of the evidence tables, and formulation of recommendations and background texts, are presented below.

5. Methodology

5.1. Evidence base

At the first consensus conference on November 22, 2010, the following five key questions (see PICO strategy for key questions) were selected as answerable in the guideline on the basis of the available evidence:

1. Which imaging methods are to be recommended for diagnosis of a primary tumor?
2. Which examinations are recommended for ruling out synchronous secondary tumors?
3. Which supplementary diagnostic methods should be performed on suspicion of metastasis?
4. Which regional lymph nodes should be removed by tumor surgery?
5. Is continuity resection of the mandible superior to wedge resection in oral cavity carcinoma?

To ensure that the search was standardized, a PICO strategy was designed to begin with for the five key questions (see Table 4-8).

As the guideline is updated in the future, further key questions should be answered on an evidence-based level.

5.1.1. PICO strategy for key questions

Key question 1: Which imaging methods are to be recommended for diagnosis of a primary tumor? (Table 4):

Table 4 PICO strategy for key question 1

PICO factor	Description	Not relevant to search strategy
Patient/population	Human, adults	
Problem/disease 1 Illness	Head and neck neoplasms, mouth neoplasms Cancer, tumor, tumour, carcinoma, neoplasm, metastasis, metastases, squamous cell carcinoma + localization	
Problem/disease 2 Localization	Palate, tongue, mouth mucosa, mouth floor, uvula, gingival, lips	
Intervention/comparator intervention	CT, MRT, OPG, DVT, isotopes, PET, sonography, echography, ultrasound	
Outcomes		x
Study design	SIGN filter: RCT, observational studies	

PICO factor	Description	Not relevant to search strategy
Health economics		x
Health system/ geographical reference		x
Relevant period	2003 onwards	
Language	German, English	

Key question 2: Which examinations are recommended for ruling out synchronous secondary tumors? (Table 5):

Table 5 PICO strategy for key question 2

PICO factor	Description	Not relevant to search strategy
Patient/population	Human, adults	
Problem/disease 1 Illness	Head and neck neoplasms, mouth neoplasms Cancer, tumor, tumour, carcinoma, neoplasm, metastasis, metastases, squamous cell carcinoma + localization	
Problem/disease 2 Localization	Palate, tongue, mouth mucosa, mouth floor, uvula, gingival, lips	
Intervention/comparator intervention	Endoscopy, panendoscopy, bronchoscopy, EGD, chest X-ray, PET, staging, secondary primary	
Outcomes		x
Study design	SIGN filter: RCT, observational studies, diagnostic studies	
Health economics		x
Health system/ geographical reference		x
Relevant period	2003 onwards	
Language	German, English	

Key question 3: Which supplementary diagnostic methods should be performed on suspicion of metastasis? (Table 6):

Table 6 PICO strategy for key question 3

PICO factor	Description	Not relevant to search strategy
Patient/population	Human, adults	

PICO factor	Description	Not relevant to search strategy
Problem/disease 1 Illness	Head and neck neoplasms, mouth neoplasms Cancer, tumor, tumour, carcinoma, neoplasm, metastasis, metastases, squamous cell carcinoma + localization	
Problem/disease 2 Localization	Palate, tongue, mouth mucosa, mouth floor, uvula, gingival, lips	
Intervention/comparator intervention	Chest X-ray, scintigraphy, PET/CT, sonography, echography, ultrasound, fine-needle biopsy, fine-needle aspiration biopsy, staging, secondary primary	
Outcomes		x
Study design	SIGN filter: RCT, observational studies, diagnostic studies	
Health economics		x
Health system/ geographical reference		x
Relevant period	2003 onwards	
Language	German, English	

Key question 4: Which regional lymph nodes should be removed by tumor surgery? (Table 7):

Table 7 PICO strategy for key question 4

PICO factor	Description	Not relevant to search strategy
Patient/population	Human, adults	
Problem/disease 1 Illness	Head and neck neoplasms, mouth neoplasms Cancer, tumor, tumour, carcinoma, neoplasm, metastasis, metastases, squamous cell carcinoma + localization	
Problem/disease 2 Localization	Palate, tongue, mouth mucosa, mouth floor, uvula, gingival, lips	
Intervention/comparator intervention	Selective lymph node dissection, lymph node dissection, neck dissection, modified neck dissection, radical neck dissection, lymph node excision	
Outcomes		x
Study design	SIGN filter: RCT, observational studies	

PICO factor	Description	Not relevant to search strategy
Health economics		x
Health system/ geographical reference		x
Relevant period	2003 onwards	
Language	German, English	

Key question 5: Is continuity resection of the mandible superior to wedge resection in oral cavity carcinoma? (Table 8):

Table 8 PICO strategy for key question 5

PICO factor	Description	Not relevant to search strategy
Patient/population	Human, adults	
Problem/disease 1 Illness	Head and neck neoplasms, mouth neoplasms Cancer, tumor, tumour, carcinoma, neoplasm, metastasis, metastases, squamous cell carcinoma + localization	
Problem/disease 2 Localization	Palate, tongue, mouth mucosa, mouth floor, uvula, gingival, lips	
Intervention/comparator intervention	Mandibular surgery, segmental resection, rim resection, block resection	
Outcomes		x
Study design	SIGN filter: RCT, observational studies	
Health economics		x
Health system/ geographical reference		x
Relevant period	2003 onwards	
Language	German, English	

5.1.2. Guideline adaptation

5.1.2.1. Search

An explorative search into existing, published guidelines was last undertaken in March 2011 by searching the web libraries of the Guidelines International Network (GIN, www.g-i-n.net), the Association of the Scientific Medical Societies in Germany (AWMF e.V., www.awmf.org), the Scottish Intercollegiate

Guidelines Network (SIGN, www.sign.ac.uk) and the Trip database (www.tripdatabase.com).

The following search terms were used: ((guideline* or recommendation* or review*) AND ((“head and neck”) OR “oral cavity” OR mouth OR tongue) AND ((“squamous cell carcinoma”) OR carcinoma* OR cancer*))).

This resulted in a total of 28 hits.

5.1.2.2. Guideline selection

The identified articles were reviewed for their topical relevance (inclusion criterion), resulting in the inclusion of SIGN Guideline 90, “Diagnosis and management of head and neck cancer” [1].

The exclusion criteria were language (if not English, French or German) and content (if not addressing diagnosis, management or follow-up of oral cavity carcinoma). Furthermore, only guidelines published since the year 2000 were considered.

Other guidelines which were not reviewed in more detail focused on specific questions or anatomic localizations that were not related to the oral cavity, and so were not considered as an overall basis for development of this guideline. Further guidelines were found that had long been obsolete. Based on its extensive coverage of head and neck carcinomas, including all aspects of diagnosis, management and follow-up, as well as a systematic literature review with well-documented evidence testing and a transparent consensus process, the decision was made to adapt the SIGN Guideline (GIN 170) published in October 2008.

5.1.2.3. Guideline assessment

At the first consensus conference on November 22, 2010, it was agreed that the SIGN Guideline would be used as the basis for evidence, by applying the AGREE II assessment approach. The guideline has already been assessed by the Canadian Partnership Against Cancer [2] using the AGREE II concept (Figure 1):

AGREE II – Quality of Reporting Assessment

Number of Reviewers: 2

Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6
Scope and Purpose:	Stakeholder Involvement:	Rigor:	Clarity Presentation:	Applicability:	Editorial Independence:
72.2%	72.2%	85.4%	91.7%	68.8%	91.7%

Figure 1 AGREE II assessment of the SIGN Guideline

Two independent reviewers performed the assessment on behalf of the Canadian Partnership Against Cancer. High scores were attained in all six domains,

and in particular domain 3 (rigor of development). This demonstrated that the guideline was not only up-to-date, but could be used as the basis for the German guideline, "Diagnosis and Management of Carcinoma of the Oral Cavity".

5.1.2.4. Guideline summaries/extracts

Topically relevant recommendations and statements from the SIGN Guideline were translated and adopted directly by referring to the relevant sources. The evidence grading structure of SIGN was likewise incorporated in this guideline (see 5.2.1 Levels of evidence).

5.1.2.5. Adaptation process

The recommendations derived from guideline adaptation are based on the corresponding recommendations in the following chapters of the SIGN Guideline: 3: Referral and diagnosis, 4: Histopathology reporting, 5: Overview of treatment of the primary tumor, 7: Treatment: surgery as the major treatment modality, and 14: Oral cavity cancer.

5.1.2.6. Further reference guidelines

No other guidelines were adapted. In case of specific, in-depth questions, reference was made to corresponding, pre-existing guidelines.

5.1.3. Systematic reviews and meta-analyses

A systematic search for existing meta-analyses, and systematic reviews of the Medline and Embase databases (via OvidSP), were last undertaken on June 9, 2011. The topical relevance of the findings, based on the titles and abstracts of the 72 hits, was examined by two different reviewers (DP and AS, see Figure 2). Ultimately, two reviews were relevant to the key questions and the full text was obtained for further evaluation [3, 4]. Both articles were screened for literature overlapping chronologically with the search in the SIGN Guideline, "Diagnosis and Management of Head and Neck Cancer": firstly until February 2005 [3] and secondly from 1970 to 2007 [4]. The references for the identified articles were therefore reviewed manually for relevant studies published in or after 2003. This resulted in the inclusion of four further studies [5-8].

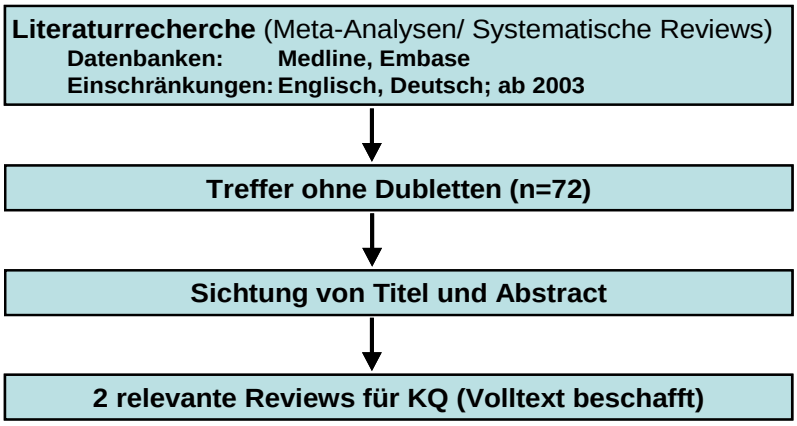

Figure 2 Screening process meta-analyses/systematic reviews

IQWiG report

At the meeting of the task forces it was decided that the relevance of the studies cited in the IQWiG report should be checked. As a result, the studies by Hafidh et al. 2006 and Wax et al. 2003 [9, 10] were selected for further evaluation.

5.1.4. De novo

5.1.4.1. Review

Based on the literature cited in the SIGN Guideline, "Diagnosis and Management of Head and Neck Cancer", an adapted screening strategy was developed for the period after 2003. There was an overlap of one year with the strategy of the SIGN Guideline, since the SIGN review covered the period of 1998 to about 2004.

The initial systematic de novo review was performed on January 26, 2011 in Medline and Embase via the OvidSP platform. An example of the search strategy is provided below (Table 9):

Table 9 Search strategy in Medline

	Medline search strategy dated 01/26/2011
SIGN filter randomized controlled trials	
1.	Randomized Controlled Trials as Topic/
2.	randomized controlled trial/
3.	Random Allocation/
4.	Double-Blind Method/
5.	Single-Blind Method/
6.	clinical trial/
7.	clinical trial, phase I.pt.
8.	clinical trial, phase II.pt.
9.	clinical trial, phase III.pt.
10.	clinical trial, phase IV.pt.
11.	controlled clinical trial.pt.
12.	randomized controlled trial.pt.
13.	multicenter study.pt.
14.	clinical trial.pt.
15.	exp Clinical Trials as topic/
16.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17.	(clinical adj trial$).tw.
18.	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
19.	Placebos/
20.	placebo$.tw.
21.	randomly allocated.tw.
22.	(allocated adj2 random$).tw.
23.	17 or 18 or 19 or 20 or 21 or 22
24.	16 or 23
25.	case report.tw.
26.	letter/
27.	historical article/
28.	25 or 26 or 27
29.	24 not 28
SIGN filter observational studies	
30.	Epidemiologic studies/
31.	exp case control studies/
32.	exp cohort studies/
33.	Case control.tw.
34.	(cohort adj (study or studies)).tw.
35.	Cohort analy$.tw.
36.	(follow up adj (study or studies)).tw.
37.	(observational adj (study or studies)).tw.
38.	Longitudinal.tw.
39.	Retrospective.tw.
40.	Cross sectional.tw.

41.	Cross-sectional studies/
42.	30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
SIGN filter diagnostic studies	
43.	exp "Sensitivity and Specificity"/
44.	sensitivity.tw.
45.	specificity.tw.
46.	((pre-test or pretest) adj probability).tw.
47.	post-test probability.tw.
48.	predictive value$.tw.
49.	likelihood ratio$.tw.
50.	43 or 44 or 45 or 46 or 47 or 48 or 49
51.	29 or 42
52.	29 or 42 or 50
Oral cavity carcinoma basic search terms	
53.	"Head and Neck Neoplasms"/
54.	exp Mouth Neoplasms/
55.	53 or 54
56.	(cancer* or tumo?r* or carcinoma* or neoplasm* or metastas?s or squamous cell carcinoma).tw.
57.	squamous cell carcinoma/
58.	neoplasms, squamous cell/
59.	56 or 57 or 58
60.	(palate or palatal).tw.
61.	palate/
62.	tongue*.tw.
63.	tongue/
64.	((oral or buccal or mouth or cheek$) adj (mucous or (mucosa adj membrane$))).tw.
65.	mouth mucosa/
66.	(mouth adj3 (bottom or floor)).tw.
67.	mouth floor/
68.	uvula.tw.
69.	uvula/
70.	(gingival or gum$).tw.
71.	gingiva/
72.	(lip or lips).tw.
73.	lip/
74.	60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73
75.	59 and 74
76.	55 or 75
77.	51 and 76
Key question 1	
78.	Tomography, X-Ray Computed/
79.	"comput$ tomograph$".tw.
80.	(comput$ adj (axial or assisted) adj tomograph$).tw.
81.	((ct or cat) adj scan$).tw.

82.	exp isotopes/
83.	isotope$.tw.
84.	exp Magnetic Resonance Imaging/
85.	magnetic resonance imaging.tw.
86.	mri.tw.
87.	(mr adj (imaging or exam$)).tw.
88.	diagnostic imaging/
89.	Radiography, Panoramic/
90.	op$g.tw.
91.	exp Tomography, Emission-Computed/
92.	positron emission tomography.tw.
93.	pet.tw.
94.	exp Cone-Beam Computed Tomography/
95.	digital volume tomography.tw.
96.	ultrasonography/
97.	ultrasonics/
98.	(ultrasound$ or ultra sound$ or ultrason$).tw.
99.	echograph*.tw.
100.	78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99
101.	77 and 100
102.	limit 101 to (yr="2003 -Current" and "all adult (19 plus years)" and (english or german) and humans)
103.	52 and 76
Key question 2	
104.	bronchoscopy/
105.	bronchoscopy.tw.
106.	Endoscopy, Digestive System/
107.	endoscopy.tw.
108.	esophagoscopy.tw.
109.	laryngoscopy/
110.	laryngoscopy.tw.
111.	panendoscopy.tw.
112.	Tomography, X-Ray Computed/
113.	comput$ tomograph$.tw.
114.	(comput$ adj (axial or assisted) adj tomograph$).tw.
115.	((ct or cat) adj scan$).tw.
116.	positron emission tomography.tw.
117.	pet.tw.
118.	104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117
119.	119. 103 and 118
120.	limit 119 to (yr="2003 -Current" and "all adult (19 plus years)" and (english or german) and humans)
Key question 3	

121.	Tomography, X-Ray Computed/
122.	comput$ tomograph$.tw.
123.	(comput$ adj (axial or assisted) adj tomograph$).tw.
124.	((ct or cat) adj scan$).tw.
125.	positron emission tomography.tw.
126.	pet.tw.
127.	pet-ct.tw.
128.	Radionuclide Imaging/
129.	$scintigraphy.tw.
130.	ultrasonography/
131.	ultrasonics/
132.	(ultrasound$ or ultra sound$ or ultrason$).tw.
133.	echograph*.tw.
134.	Biopsy, Needle/
135.	fine needle aspiration.tw.
136.	fna.tw.
137.	((aspiration or puncture) adj biopsy).tw.
138.	neoplasm staging/
139.	staging.tw.
140.	secondary primary.tw.
141.	121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140
142.	103 and 141
143.	limit 142 to (yr="2003 -Current" and "all adult (19 plus years)" and (english or german) and humans)
Key question 4	
144.	exp Lymph Node Excision/
145.	exp lymph nodes/
146.	lymphadenectomy.tw.
147.	node negative.tw.
148.	node positive.tw.
149.	("lymph node" adj (excision or resection)).tw.
150.	((n0 or cn0 or n1 or n2 or n2a or n2b or n2c or n3) and neck).tw.
151.	supraomohyoid neck dissection.tw.
152.	radical neck dissection.tw.
153.	modified radical neck dissection.tw.
154.	selective neck dissection.tw.
155.	extended neck dissection.tw.
156.	144 or 145 or 146 or 147 or 148 or 149 or 150 or 151 or 152 or 153 or 154 or 155
157.	77 and 156
158.	limit 157 to (yr="2003-Current" and "all adult (19 plus years)" and (english or german) and humans)
Key question 5	
159.	Mandible/su [Surgery]

160.	rim resection.tw.
161.	bloc resection.tw.
162.	segmental resection.tw.
163.	marginal resection.tw.
164.	mandibular resection.tw.
165.	159 or 160 or 161 or 162 or 163 or 164
166.	77 and 165
167.	limit 166 to (yr="2003-Current" and "all adult (19 plus years)" and (english or german) and humans)
168.	102 or 120 or 143 or 158 or 167

In addition to the SIGN filters (see http://www.sign.ac.uk/methodology/filters.html, last accessed 01/31/2011) for "randomized controlled trials" and "observational studies", the filter "diagnostic studies" was also applied to key questions 2 and 3. Figure 3 Literature review lists the hits from the searches for each key question as well as the 3014 abstracts ultimately to be screened.

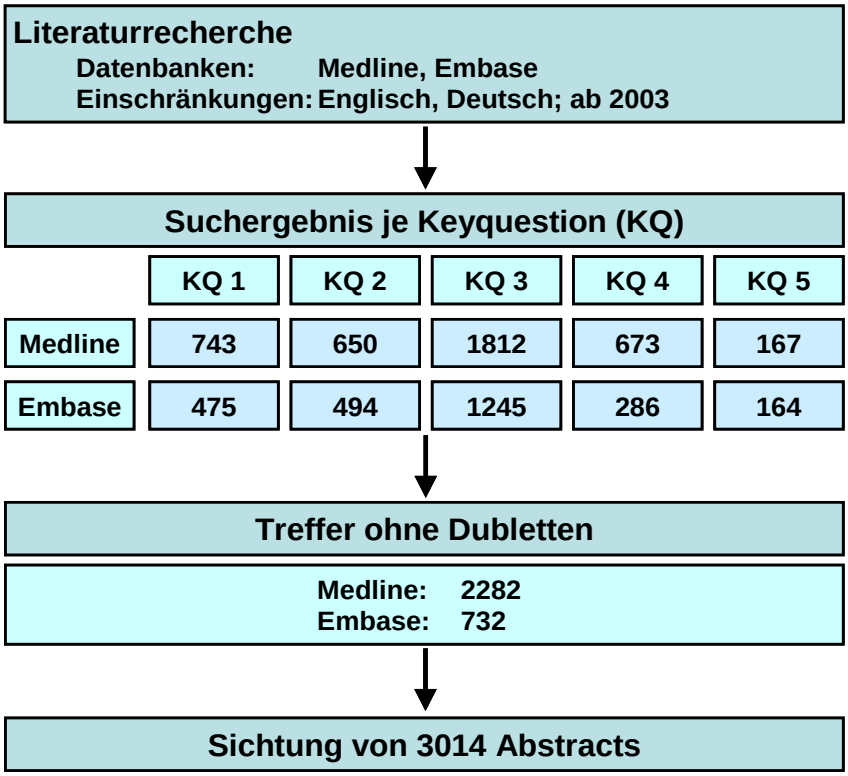

Figure 3 Literature review

Manual search

The study by Mucke et al. 2011 [11] was also included by the experts as a further source for evaluation.

5.1.4.2. Evidence selection

Screening by title and extract

The topical relevance (inclusion criterion, based on PICO concept) of the 3014 hits was examined by two different reviewers (DP and BS) based on their titles and abstracts. If there was any disagreement on the relevance of a particular abstract, further discussion ensued and/or a third independent reviewer was consulted (AN).

After screening the abstracts, a total of 246 appropriate references (see Figure 4) remained and were recorded in an EndNote database for the purpose of literature management. The full texts were procured and evaluated using a standardized GIN sheet (see 12.1 Literature evaluation sheet).

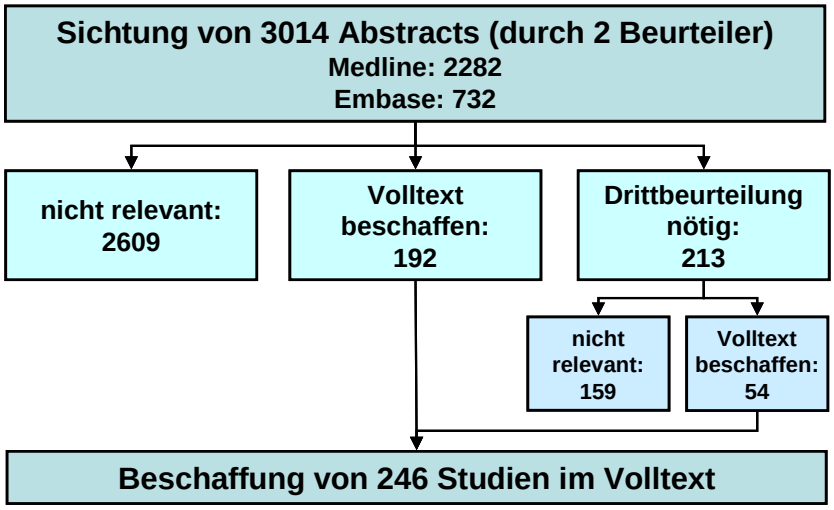

Figure 4 Screening of abstracts

Full-text screening

The 246 full-text articles were firstly reviewed for their suitability based on inclusion and exclusion criteria. This was undertaken by two independent reviewers (DP, BS), who compared the results, discussed the differences and if necessary consulted a third reviewer (AN). The applicable exclusion criteria were:

a) Language (if not English or German)

b) Inappropriate study design (case-control, cancer registry data)

c) Irrelevant topic/intervention

d) No original data

e) Surrogate parameters (by describing results not relevant to GL)

f) No (defined) oral cavity CA / (<50% oral cavity CA or no specification of localization in the head and neck region)

g) Baseline differences (groups not comparable)

h) < 10 patients per study group

i) No relevant efficacy data

j) Other (with statement of reason)

k) Full-text not retrievable

5.1.4.3. Review of evidence

Of the 246 full-text articles procured, a total of 117 studies were incorporated in the guideline as relevant to answering the five key questions (including manual search). At this stage, 129 studies were excluded from further evaluation.

The data were systematically extracted from the identified studies using the literature evaluation sheet of the Guidelines International Network (GIN, http://www.g-i-n.net). The template for either diagnostic studies or interventional studies was used for this purpose: two independent reviewers (AS, SS) each compared the results, discussed the differences and if necessary consulted a third reviewer (AN). The evaluation sheets can be viewed upon request at the Division of Evidence Based Medicine.

5.1.4.4. Evidence synthesis

Table 10 Key question 1

Which imaging methods are to be recommended for diagnosis of a primary tumor?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
Abler 2005 [12]	Retrospective	152	CT Scintigraphy	1) Sensitivity 2) Specificity for bone invasion	1) 59 2) 83 1) 80 2) 81	At stages T1 and T2 in particular, the number of false-positive findings on preoperative staging was unexpectedly large; here, new examination methods such as PET or PET/CT should enable more exact diagnosis.	OSCC cT1-4 cN0/+ cM?	Scintigraphy > CT	3	KQ 5
Babin 2008 [13]	Prospective	17	CT PET/CT	1) Sensitivity 2) Specificity 3) PPV 4) NPV for bone invasion	1) 33 2) 100 3) 100 4) 87 1) 100 2) 85 3) 60 4) 100	PET/CT fusion shows sensitivity of 100% with specificity of 85%. This result encourages the use of PET/CT when assessing mandibular invasion.	18F-FDG PET RS poorly described OOSCC (10 OSCC) cT1-4 cN? cM0	PET/CT > CT	3	
Baek 2008 [14]	Retrospective	64	CT MRI (n=27) PET/CT	1) Estimated PT volume (cm^3) 2) Pathologic volume (cm^3) 3) Difference 1 vs 2 (p-value) 4) PT detection rate	1) 3.6 2) 10.7 3) 0.0063 4) 75.0 * *** 1) 5.1 2) 12.5 3) 0.049 4) 85.2 ** *** 1) 10.8 2) 9.2 3) 0.60 **** 4) 95.3* **	For pts with OCC with dental artifacts on the conventional imaging, PET/CT could provide useful clinical information about the PT, particularly in cases with advanced tumors.	18F-FDG PET *p=0.0016; **p=0.54; ***p=1; ****SUV=3.5 OSCC (with dental artifacts) cT1-4 cN? cM?	PET/CT >> CT * PET/CT > MRI ** CT = MRI ***	3	

Which imaging methods are to be recommended for diagnosis of a primary tumor?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
Bolzoni 2004 [15]	Prospective	43	MRI	1) Sensitivity 2) Specificity 3) Accuracy 4) NPV 5) PPV for mandibular invasion	1) 93 2) 93 3) 93 4) 96 5) 87.5	MRI is commonly considered the technique of choice for treatment planning in advanced OOSCC because of its accuracy in depicting soft-tissue involvement. This study demonstrates the additional diagnostic value of MRI in detecting bone invasion.	OOSCC (29 OSCC) CT1-4 cN? cM? (DN / RD)	NA	2^-	
Brockenbrough 2003 [16]	Retrospective	36	DentaScan Software CT	1) Sensitivity2) Specificity3) PPV4) NPVfor bone invasion	1) 952) 793) 874) 92	DentaScan is an accurate method of preoperative evaluation for mandibular invasion in pts with OSCC.	In-/exclusion poorly addressed; no data for comparatorOSCC (fixed to mandible)cT1-T4 cN? cM? (DN/RD)	NA	3	
Dammann 2005 [17]	Prospective	64	CT	1) Sensitivity 2) Specificity 3) Accuracy for PT detection	1) 61 * ** 2) 100 3) 66	MRI is recommended as the method of choice in the preoperative evaluation of OSCC and oropharyngeal SCC. PET can provide relevant diagnostic information in case of equivocal findings by MRI or CT. Routine use of PET, however, does not appear to be necessary if optimized MRI is available.	18F-FDG PET * p < 0.0001; ** p < 0.0007 OOSCC (55 OSCC) cT1-4 cN0/+ cM0-1 (DN)	MRI >> CT* PET >> CT** MRI = PET	2^+	KQ 3
			MRI		1) 92 * 2) 63 3) 88					
			PET		1) 87 ** 2) 63 3) 84					

Which imaging methods are to be recommended for diagnosis of a primary tumor?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
Ekberg 2007 [18]	Retrospective	80	PET	1) Sensitivity 2) Specificity 3) PPV 4) NPV for PT staging / occult PT detection / recurrent PT detection / recurrency detection during follow-up (no suspicion) / overall 5) Mean SUV in TN vs TP	1) 95/78/90/100/91 2) 100/89/75/77/80 3) 100/88/86/25/90 4) 33/80/82/100/82 5) 3.98 vs 7.17*	The results suggest an important role for PET in staging, on suspicion of RD, and for detecting occult PT. For reasons of economy PET for follow-up might have to be reserved for pts with a high risk of RD. A prospective study might further clarify how best to select pts for PET.	18F-FDG PET * $p < 0.05$ no RS, BLD (ie tumor, stage) HNSCC (40 OSCC) cT1-4c N0/+ cM0-1 (DN / RD)	NA	3	
Goerres 2003 [19]	Retrospective	34	PET	1) Sensitivity for PT detection 2) Treatment change by adding PET to CT + X-ray	1) 97 2) 15	Whole body PET provides relevant additional information to a standard CS procedure in patients with OSCC. The detection of distant metastases and 2nd PT can have a great impact on patient management.	18F-FDG PET RS inhomogeneous OSCC CT1-4 cN0-3 cM0 (DN)	NA	3	
Goerres 2005 [20]	Prospective	34	PET/CT SPECT/CT	1) Sensitivity 2) Specificity 3) Accuracy 4) PPV 5) NPV for bone invasion	1) 100 2) 91 3) 94 4) 86 5) 100 1) 92 2) 86 3) 88 4) 79 5) 95	The assessment of cortical erosion with CECT and the CT information from PET/CT are the most reliable methods for detecting bone invasion in pts with oral cavity carcinoma. ^{18}F-FDG uptake seen on PET/CT images does not improve identification of bone infiltration.	18F-FDG PET No p-values; bone resection only in pts with suspect imaging or intraoperative suspicion OCC (31 OSCC) cT1-4 cN? CM? (DN / RD)	CECT = PET/CT > SPECT/CT	2	

Which imaging methods are to be recommended for diagnosis of a primary tumor?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
			CECT		1) 92 2) 100 3) 97 4) 100 5) 96					
Gu 2010 [21]	Retrospective	46	CT	1) Sensitivity2) Specificity3) PPV4) NPV5) Accuracyfor mandibular invasion	1) 41.72) 1003) 1004) 82.95) 84.8	In conclusion, sensitivities and specificities of CT, MRI, and PET/CT appeared to be similar in the detection of mandibular invasion by SCC of the oral cavity. The combined analysis of CT, MR, US, and PET/CT yielded improved sensitivity compared with the single use of these techniques, but without a ss difference.	18F-FDG PETRS (histology) poorly describedOSCCCT? cN? CM? (DN / RD)	CT + MRI +PET/CT>CT=MRI= PET/CT	3	
			MRI		1) 58.3 2) 97.1 3) 87.5 4) 86.8 5) 87.0					
			PET/CT		1) 58.3 2) 97.1 3) 87.5 4) 86.8 5) 87.0					
			CT + MRI		1) 66.7 2) 100 3) 100 4) 89.5 5) 91.3					
			CT + PET/CT		1) 66.7 2) 100 3) 100 4) 89.5 5) 91.3					
			MRI + PET/CT		1) 75.0 2) 100 3) 100 4) 91.9 5) 93.5					
			CT + MRI + PET/CT		1) 83.3 2) 100 3) 100 4) 94.4 5) 95.7					

Which imaging methods are to be recommended for diagnosis of a primary tumor?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
Hendrikx 2010 [22]	Retrospective	23	OPT MRI CBCT	1) Sensitivity2) Specificity3) PPV4) NPVfor mandibular invasion5) Test efficiency	1) 54.5*2) 91.7*3) 85.74) 68.85) 73.9 1) 81.8 2) 66.7 3) 69.2 4) 80 5) 73.9 1) 90.9* 2) 100* 3) 100 4) 92.3 5) 95.7	CBCT has the potential to become a new diagnostic tool in the OSCC screening procedure to predict mandibular invasion or erosion, but its value may be limited by its relatively low sensitivity. A prospective study will start on 64 pts (alpha=0.05; power 0.8; effect size 0.5) to improve these results statistically.	*ssBLD?; in-/exclusion criteria poorly addressedOSCCcT? cN? cM?	CBCT>>OPT*CBCT >MRI	3	
Imaizumi 2006 [23]	Retrospective	51	CT MRI	1) Sensitivity 2) Specificity 3) PPV 4) NPV 5) Accuracy for involvement of mandibular cortex / bone marrow / inferior alveolar canal	1) 100 / 100 / 100 2) 88* / 88 / 96** 3) 89 / 89 / 71 4) 100 / 100 / 100 5) 94 / 94 / 96 1) 96 / 96 / 100 2) 54* / 81 / 70** 3) 67 / 83 / 26 4) 93 / 95 / 100 5) 74 / 88 / 73	In assessing the presence and extent of mandibular invasion by squamous cell carcinoma, the specificity of MRI imaging was significantly lower than that of CT.	* p= 0.004, **p= 0.002 OSCC cT? cN? cM?	CT >> MRI* **	3	
Jones 2005 [24]	Retrospective	88	PET	1) Sensitivity 2) Specificity for PT detection (DN / RD)	1) 96.3 / 85.7 2) NA / 50.0	Overall PET has a useful role in the diagnosis of HN malig., and in the demonstration of occult/hidden PT, distant & metastatic disease. It should always be used as an adjunct to other clinical information and results must be interpreted in the light of clinical findings.	18F-FDG PET In-/exclusion criteria poorly addressed OOSCC (79 OSCC) cT? cN0/+ cM0-1 DN (n=54) / RD (n=34)	NA	3	KQ 2 und 3
Krabbe 2008 [25]	Not cited	38	PET	1) Sensitivity for PT detection	1) 95	Although PET performed better than conventional imaging modalities, sensitivity was lower than	18F-FDG PET RS NA in 8 pts; no data for comparator	NA	3	KQ 3

Which imaging methods are to be recommended for diagnosis of a primary tumor?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
						desired. As a consequence, clinical application of PET in the patient staged as cN0 is limited.	OOSCC (35 OSCC) cT1-4 cN0 cM?			
Nakamoto 2009 [26]	Retrospective	46	MRI+PET MRI	1) Sensitivity for PT detection	1) 100 1) 98	Image fusion from MRI + PET might be useful in evaluating HNCA, especially in suspected RD rather than in DN.	18F-FDG PETOO-CAcT? cN? cM? (DN / RD)	MRI + PET=MRI	3	KQ 2 and 3
Ng 2005 [27]	Prospective	124	CT + MRI PET CT + MRI + PET	1) Accuracy for PT detection	1) 87.1 1) 98.4 1) 99.2	PET is superior to CT+MRI in the detection of cervical status of OSCC. The sensitivity of PET for the detection of LNM on a level-by-level basis was ss higher than that of CT+MRI, whereas specificities appeared to be similar. Visual correlation of PET+CT+MRI showed a trend of increased diagnostic accuracy over PET alone but without a ss difference, and its sensitivity was still not high enough to replace pathologic LN staging based on ND.	18F-FDG PET OSCC cT1-4 cN? CM? (DN)	CT + MRI + PET > PET > CT + MRI	2^{++}	KQ 3
Nishiyama 2005 [28]	Prospective	53	PET	1) PT detection rate	1) 96.2	The results of this study show a high rate of simultaneous primary tumors in patients with primary HN malig. PET appears to be a promising imaging modality for the detection of simultaneous tumors in head and neck cancer pts.	18F-FDG PET RS inhomogeneous; in-/exclusion unclear HNSCC (22 OSCC) cT? cN? cM?	NA	3	KQ 2

Which imaging methods are to be recommended for diagnosis of a primary tumor?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
Pauleit 2006 [29]	Prospective	21	FET PET FDG PET CT	1) Sensitivity 2) Specificity 3) Accuracy for PT detection	1) 75 2) 95 3) 90* 1) 93 2) 79 3) 83** 1) 64 2) 86 3) 80* **	FET may not replace FDG in the PET diagnostics of head and neck cancer but may be a helpful additional tool in selected patients, because FET might better differentiate tumor tissue from inflammatory tissue. The sensitivity of FET in SCC, however, was inferior to that of FDG because of lower SUVs.	* ss, ** ss 18F-FDG PET 18F-FDG PET HNSCC (14 OSCC) cT? cN? cM?	FET PET = FDG PET >> CT* **	2-	
Pentenero 2008 [30]	Prospective	19	PET/CT	1) Sensitivity 2) Accuracy 3) PPV for PT detection	1) 84.2 2) 84.2 3) 100	In conclusion, PET/CT showed high accuracy in determining the extension and/or the depth of invasion of the PT; Nevertheless, PET/CT was not accurate in ruling out LNM.	$_{18}$F-FDG PET OCC (18 OSCC) cT? cN0/+ cM?	NA	3	KQ 3
Rajesh 2008 [31]	Retrospective	23	MRI SPECT CT (n=?)	1) Sensitivity2) Specificity3) FP (n)4) FN (n)for bone invasion	1) 1002) 753) 14) 0 1) 100 2) 50 3) 2 4) 0 1) NA 2) NA 3) 0 4) 1	The addition of SPECT and CT to routine MRI staging protocols may no longer be indicated. CT may be useful in some selected cases to assess maxillary involvement because of the thinner cortex of the maxilla.	99mTc-MDP SPECT OSCCcT? cN? CM?	MRI>SPECT+CT	3	
Rao 2004 [31]	Prospective	51	CE OPT CE + OPT	1) Sensitivity 2) Specifity 3) PPV 4) NPV for mandibular invasion	1) 96 2) 65 3) 72 4) 100 1) 92 2) 88 3) 88 4) 100 1) 100 2) 58 3) 70 4) 100	The high FP rates associated with these basic investigative modalities advocate the use of more sophisticated diagnostic tools like bone scans, CT scan, etc, and careful correlation of the observations.	In-/exclusion criteria poorly addressed, different data in abstract vs tables 1-3 OSCC cT? cN? CM?	CE + OPT > OPT > CE	2-	

Which imaging methods are to be recommended for diagnosis of a primary tumor?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
Roh 2007 [32]	Not cited	167	PET/CT (n=63)	1) Sensitivity 2) Accuracy for PT detection	1) 97 2) NA*	Compared with PET alone, preoperative PET/CT may not yield ss improved diagnostic accuracy in pts with HNSCC. Moreover, despite their high accuracy, PET and PET/CT may not abrogate the need for conventional imaging and pathologic staging based on primary resection and ND.	18F-FDG PET * ss HNSCC (54 OSCC) cT1-4 cN0/+ CM?	PET = PET/CT >> MRI + CT*	3	KQ 3
			PET (n=104)		1) 98 2) NA*					
			CT + MRI (n=156)		1) 87 2) NA*					
Seitz 2009 [33]	Retrospective	66	MRI PET/CT	1) Sensitivity 2) Specificity for PT detection 3) GTV (ml)	1) 100 2) 80 3) 17.6* 1) 96.72 2) 60 3) 18.8*	The diagnostic performance of PET/CT in the local staging of oral cancer is not superior to MRI.	18F-FDG PET SUV-influence by 5 ACCA?; * p ≤0.007 between RS, PET/CT, MRI 50 OSCC cT1-4cN0/+cM? (DN/RD)	MRI = PET/CT	3	KQ 3
Van Cann 2008 [34]	Retrospective	67	CE	1) Sensitivity2) Specificityfor bone invasion	1) 59.12) 73.9	This study suggests that a considerable reduction in mandibular resections can be achieved in SCC, adjacent or fixed to the mandible, by following the principle of first performing CT or MRI followed by bone SPECT. The latter is only necessary when CT/MRI does not show signs of mandibular invasion. When the bone SPECT scan does not show mandibular invasion, periosteal stripping can be considered.	OSCCcT1-4 cN? M?	Algorithm:1. CT/MRI 2. SPECT	3	
			X-ray		1) 61.4 2) 60.9					
			SPECT (n=66)		1) 100 2) 56.5					
			CT (n=66)		1) 58.1 2) 95.7					
			MRI (n=66)		1) 62.8 2) 100					
Vidiri 2007 [35]	Retrospective	60	CE	1) Sensitivity 2) Specificity 3) Accuracy 4) NPV 5) PPV	1) NA/100 2) NA/30 3) 62/74.1 4) NA/100 5) NA/70.8	In the present study, MRI was seen to be an adequate technique for the assessment of oral cavity malignancies, in the evaluation of depth invasion, presence and	50 (51?) OSCC cT1-4 cN? M?	MRI > CE	3	

Which imaging methods are to be recommended for diagnosis of a primary tumor?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
			MRI	for T stage / mandibular invasion	1) NA/94.1 2) NA/60 3) 82/81.5 4) NA/85.7 5) NA/80	extension of mandibular involvement.				
Vidiri 2010 [21]	Retrospective	36	MRI	1) Sensitivity 2) Specificity 3) Accuracy 4) PPV 5) NPV for mandibular invasion	1) 93 2) 82 3) 86* 4) 76 5) 95	MRI was found to have a higher sensitivity compared to MDCT in the assessment of mandibular involvement from SCC arising in the oral cavity although no statistically significant differences were noted.	RS (histology) poorly described; * ns OSCC cT1-4 cN? M?	MRI > MDCT*	3	
			MDCT		1) 79 2) 82 3) 81* 4) 73 5) 86					
Wallowy 2009 [36]	Retrospective	84	PET (n=80)	1) PT detection rate	1) 92.5	PET may play an important role in initial staging and the detection of distant metastases and synchronous PT. Setting an SUV threshold for determining malignancies can support interpretation. In borderline cases interdisciplinary evaluation by means of other diagnostic modalities remains crucial.	18F-FDG PET OOSCC (82 OSCC) cT1-4 cN0/+ cM0-1	NA	3	KQ 2
Wiener 2006 [37]	Retrospective	52	MSCT	1) Sensitivity2) Specificity3) Accuracy4) PPV5) NPVfor bone invasion/muscle infiltration6) PT detection rate	1) 71.4*/72.2 2) 95.5*/61 3) 92.3/63.5 4) 71.2/NA 5) 95.5/NA 6) 69.2	Preoperative MRI is recommended as the basic imaging modality of choice for treatment planning of OSCC. MSCT is a valid alternative imaging method especially in cases with low patient compliance.	*nsT stage: MRI > MSCT (ns)OSCCcT1-4 cN? cM?	MRI>MSCT*	3	KQ 3
			MRI		1) 100*/81.8 2) 93.3*/63.4 3) 94.2/67.3 4) 69.9/NA 5) 100/NA 6) 84.6					

Table 11 Key question 2

Which examinations are recommended for ruling out synchronous secondary tumors?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
Bisase 2008 [38]	Retrospective	52	Chest CT	1) Suspect imaging 2) Treatment change 3) Detection of DM or 2nd malig.	1) 3.8 2) 0 3) 0	There is a low rate of simultaneous thoracic abnormalities in pts with early TSCC. This may justify further rationalization of the routine use of CT of the chest.	No RS described TSCC cT1-T2 cN? cM0-1 (DN)	NA	3	
Chow 2009 [39]	Retrospective	118	OGD (n=118) + Chromo-endoscopy (n=65)	1) Univariate analyses 2) Multivariate analyses for RF (p-value) for simultaneous esophageal NPL	1) OSCC << other (0.002) 2) OSCC << other (0.009)	Clinically important esophageal lesions rarely coexist with OSCC, for which the benefit of routine OGD is questionable. Chromoendoscopy enhances the identification of early but clinically important esophageal abnormalities if OGD is performed for SCC in the larynx, hypopharynx, and oropharynx.	No RS described; in-/exclusion criteria poorly addressed HNSCC (69 OSCC) cT? cN? cM0-1 (DN)	NA	3	
Fielding 2010 [40]	Prospective	66 9	WLPE WLPE + autofluorescence	1) Treatment Change (n) PBA	1) 5/66* 1) 9/66*	Adding autofluorescence to panendoscopy in pts with HN malig. changed management in a clinically significant number of pts.	* p = 0.02 HNSCC (34 OSCC) CT? cN? CM0-1	WLPE + autofluorescence >> WLPE*	2+	
Ghosh 2009 [41]	Retrospective	1882	Chest X-ray (n=1480)	1) Sensitivity 2) specificity 3) PPV 4) NPV for detection of pulmonary lesions in general / primary bronchial CA / pulmonary metastases	1) 55.2/65.3/46.9 2) 97.2/98.8/98.5 3) 45.1/50/40.5 4) 98.2/99.4/98.8 5) RD >> DN (<0.0001) > 60y >> ≤ 60y (0.0072) T1-2 << T3-4 (0.0143) 6) RD >> DN (<0.001)	Our data confirms that chest X-ray is not an adequate substitute for thoracic CT in screening for sporadic synchronous bronchogenic tumors in groups not undergoing thoracic CT. Therefore, on the basis of our findings, we propose that thoracic CT should remain as the investigation of choice for the screening of synchronous pulmonary tumors in all pts presenting with HNSCC,	NNS reported; 3.6% synchronous pulmonary tumors (40/1882 pulmonary metastases; 27/1882 primary bronchial tumors) HNSCC (761 OSCC) CT1-4 cN0/+ cM0-1 (DN / RD)	CT > X-ray	3	

Which examinations are recommended for ruling out synchronous secondary tumors?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
		1144	Chest CT (n=1144)	5) ss RF (p-value for pulmonary metastases 6) ss RF (p-value) for primary bronchial CA	1) 89.7/96.6/85.4 2) 94.2/99.1/95.3 3) 53.1/72.5/44.5 4) 99.2/99.9/99.3	irrespective of the locoregional extent of the presenting disease.				
Jones 2005 [24]	Retrospective	88	PET	1) Sensitivity2) Specificity for detection of distant metasta-sis(DN/RD)	1) NA/1002) NA/100	Overall PET has a useful role in the diagnosis of HN malig., and in the demonstration of occult or hidden tumors, distant and metastatic disease. It should always be used as an adjunct to other clinical information and results must be interpreted in the light of clinical findings.	18F-FDG PET in-/ exclusion criteria poorly addressed OOSCC (79 OSCC)cT? cN0/+ cM0-1(54 DN/34 RD)	NA	3	KQ 1 and 3
Keith 2006 [42]	Prospective	116*	Chest X-ray	1) Treatment change (n) 2) Detection of pulmonary malignancy (n) 3) ss RF for pulmonary malignancy	1) 2/116 2) 2/116	This series of DN OOSCC had a lower incidence of coincident thoracic malignancy than had previously been shown. We suggest that, until larger series are accrued, there is a role for staging all DN OSCC with thorac-ic spiral CT. Where resources are scarce, pts at particular risk (and to be targeted) may be those with advanced stage disease (stage III+IV), previous HNSCC, and pharyngeal disease.	*116 DN + 11 RD (no data on 1 + 2) OOSCC (81 OSCC) cT? cN? cM0-1 (DN/RD)	CT > Chest X-ray	2+	
			CT		1) 4/116 (3.5%) 2) 4/116 (3.5%) 3) All ns (stage I+II vs III+IV; RD vs DN; OSCC vs oropharyngeal SCC)					
Kesting 2009 [43, 44]	Retrospective	570	OGD	1) Simultaneous esophag. malig. 2) ss RF(p-value) for Barret eso. 3) Simultaneous pulmonary	1) 0 2) Stage I+II << III+IV (0.006)	NBI seems to be useful and reliable for screening for esoph-ageal SCC in pts with HN malig.	OSCC cT? cN? CM0-1 (DN)	NA	2-	

Which examinations are recommended for ruling out synchronous secondary tumors?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
			Bronchos-copy	malignancy 4) ss RF(p-value) for lung cancer	3) 2 4) Stage I+II >> III+IV (0.038); (ns = sex, age, site, grade)					
Krabbe 2009 [45]	Retrospective	149	CXR (n=106)	1) Sensitivity2) Specificity for detection ofdistant metastasis / sec-ondary PT / overall	1) 20/58/41** ***2) NA/NA/93	PET is able to detect DM and 2nd PT in HNSCC with high specificity & sensitivity. With regard to detection of intrapulmonary malignancy, PET and CT per-formed similarly in terms of sensitivity, but the specificity of PET was ss higher. CXR fell ss behind in sensitivity compared with PET and CT, rendering this technique as ss less valid for the detection of distant disease in HNSCC.	18F-FDG PET*, **,*** = ssDifferent data in abstract vs table 3HNSCC (84 OSCC)cT? cN? CM0-1 (DN)	PET >> CT*PET >> X-ray** CT >> X-ray***	2^{++}	
			Chest CT (n=82)		1) 55/92/74*** 2) NA/NA/63*					
			PET		1) 85/100/92** 2) NA/NA/93*					
Lee 2010 [46]	Not cited	69	WLPE	1) Sensitivity 2) Specificity 3) PPV 4) NPV 5) Accuracy for detection of simultaneous esophageal NPL 6) ss 7) ns	1) 62.9* 2) 70 3) 88 4) 35 5) 64.4** 6) Reflux, esophageal symptoms, weight loss, esophagitis 7) Age, sex, social behavior, H. pylori, Barrett	Compared with current ap-proaches, NBI followed by high magnification significantly in-creases the accuracy of detec-tion of esophageal neoplasia in pts with HN malig. The result warrants conduction of a pro-spective randomized controlled study to confirm its efficacy.	* ** p < 0.01, *** p = 0.13 HN malig. cT? cN? cM0-1 (DN/RD)	NBI + Magnification > NBI*** >> WLPE* **	3	
			NBI	RF for esophageal NPL	1) 100* 2) 40 3) 85.4 4) 100 5) 86.7** ***					

Which examinations are recommended for ruling out synchronous secondary tumors?

First author	Study type	Patient number	Groups	Outcome	Result (in %)	Author's conclusion	Comments	Summary	Evidence level	Cross-reference
			NBI + Magnifica-tion		1) 100 2) 80 3) 94.6 4) 100 5) 95.6 ***					
Loh 2005 [47]	Prospective	102	Chest CT	1) Suspect lesion2) TP (n)3) FP (n)4) Positive X-ray findings in TP 5) ss RF(p-value) for pulmonary malig-nancy6) ns RF(p-value) for pulmo-nary malignancy	1) 19.32) 11/20 3) 9/204) 36.4 (4/11)5) Unknown / oral / glottis << supra-glottis / orophar. / hypopharynx (0.02) N0-1 << N2-3 (0.02)6) T1-3 < T4 (0.08)	The detection rate of lung metas-tasis or a synchronous lung PT by CT scan is 10.8%. We recom-mend the use of CT scans of the thorax in screening the lungs of newly diagnosed pts with T4 and/or N2 or N3 oropharyngeal, hypopharyngeal, and supraglottic SCC.	RS inhomogene-ousHNSCC (46 OSCC)cT1-4 cN0-3 CM0-1	Chest CT>Chest X-ray	2^{-}	
Nakamoto 2009 [26]	Retrospective	15	MRI + PET MRI	1) Sensitivity for 2nd PT in PBA (LBA*)	1) 100 ** (95*) 1) 50 ** (55*)	Image fusion from MRI + PET might be useful in evaluating HN malig., especially in suspected RD rather than in DN.	18F-FDG PET *p=0.013, ** ns OO-CA cT? cN? cM0-1 (RD)	MRI + PET >> MRI*	3	KQ 1 and 3
Nishiyama 2005 [28]	Prospective	53	PET	1) Detection of simultaneous malignancy 2) FN for simultaneous malignancy	1) 11 2) 16.7 (1/6)	The results of this study show a high rate of simultaneous primary tumors in patients with primary HN malig. FDG PET appears to be a promising imaging modality for the detection of simultaneous tumors in HN malig. pts.	18F-FDG PET RS inhomogeneous; in-/excl. poorly addressed HNSCC (22 OSCC) cT? cN? cM0-1	PET > CT + US	3	KQ 1
			CT + US		1) NA 2) 66.6 (4/6)					
Takenaka 2009 [48]	Prospective	142	NBI	1) Sensitivity 2) Specificity 3) PPV 4) NPV 5) Accuracy	1) 90.9 2) 95.4* 3) 62.5 4) 99.2 5) 95.1**	NBI seems to be useful and reliable for screening for esoph-ageal SCC in pts with HN malig.	* p <0.001, ** p =0.01 HNSCC (84 OSCC) cT? cN? CM0-1	NBI >> Lugol chromoendoscopy * **	2^{++}	

Which examinations are recommended for ruling out synchronous secondary tumors?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
			Lugol chromoendoscopy	for detection of esophageal HGIN and SCC	1) 100 2) 84.7* 3) 35.5 4) 100 5) 85.9**					
Wallowy 2009 [36]	Retrospective	84	PET (n=80)	1) TP/mean SUV2) FP/mean SUV3) p-value 1 vs 24) SUV threshold above findings were malignant for distant lesions	1) 31/3.962) 69/2.653) 0.0064) 6.5	PET may play an important role in initial staging and the detection of DM and synchronous PT. Setting an SUV threshold for determining malignancies can support interpretation. In borderline cases, however, interdisciplinary evaluation by means of other diagnostic modalities remains crucial.	18F-FDG PETOOSCC (82 OSCC)cT1-4 cN0/+ cM0-1	NA	3	KQ 1
Brouwer 2006 [49]	Prospective	34*	Whole-body PET + Chest CT	1) Added value of PET to chest CT for detection of DM and 2nd PT	1) 6	Our findings suggest that whole-body PET may have additional value in screening for DM and 2nd PT, if applied to the subset of pts who are at substantial risk.	18F-FDG PET * All had RF for DM: ≥ 3 LNM (1), bilat. LNM (11), LNM >6cm (10), level IV LNM (1), LCR (6), 2nd PT(5) HNSCC cT? cN? cM?	PET + chest CT > chest CT	2	

Table 12 Key question 3

Which supplementary diagnostic methods should be performed on suspicion of metastasis?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
Alvarez Amezaga 2007 [3]	Prospective	25	SLNB (n=24)	1) Sensitivity 2) Specificity 3) Accuracy 4) NPQ 5) PPQ 6) OR for LNM detection in cT1-T4 (n=24) / cT1-T2 (n=14) 7) Detection of SLN 8) Mean n° SLN	1) 66.6/100 2) 100/NA 3) 96/100 4) 0.37/NA 5) 24.43/NA 6) 66.6/161 7) 96 8) 3.2	Our data* provide a certain degree of evidence that, due to its high sensitivity, the SLNB procedure can be applied to the initial stages of OSCC. Thus it is a valid alternative to elective stage dissection. It reduces both time spent in surgery and postoperative morbidity. The technique should be carried out using LSG vital dye and an intraoperative gamma probe.	* = additional meta-analyses method: LSG + probe + dye OOSCC(21 (22?) OSCC) cT1-T4 cN0 cM? (DN)	SLNB in cT1-T2 cN0 = ND	2^{+}	
Balogova 2008 [50]	Prospective	27	FDG PET/CT FET PET/CT	1) Sensitivity 2) Specificity 3) Accuracy for overall diagnostic performance (PBA/SBA)	1) 100/95* 2) 71/63** 3) 93/83 1) 70/64* 2) 100/100** 3) 78/78	Although its good specificity was confirmed, FET did not appear to be suited as a first-line PET tracer in HNSCC imaging and cannot replace FDG for staging due to insufficient sensitivity. However, it was useful in a few selected cases to favor a WW approach when FDG and FET was discovered in pts referred for systematic FDG PET during follow-up. In contrast, 2nd PT should not be ruled out if FDG is clearly positive in the lungs or the digestive tract.	* p < 0.02 ** p < 0.01 18F-FDG PET 18F-FET PET measured variable (LN/PT) poorly described HNSCC (? OSCC) cT? cN0/+ cM0-1 (DN/RD)	FDG PET/CT > FET PET/CT	3	
Barzan 2004 [51]	Prospective	59 41	SLNBcN0* SLNB cN+**	1) SLN0 and non-SLN0 2) SLN+ 3) SLN0 but LNM at same level (=FN) 4) SLN0 and other level LNM (=FN) 5) SLN not found	1) 34 pts2) 14 pts3) 2 pts4) 1***pts5) 8 pts 1) 21 pts 2) 4 pts 3) 0 pts 4) 0 pts 5) 16 pts	The strategy of the SLN is reliable; of course, to be confirmed as a standard approach, it requires prospective and, possibly, multicenter trials with a larger number of pts, homogeneously staged, treated and followed. Moreover, the SLN would be used also in tumors of the oropharynx, hypopharynx and larynx, and it may also prove useful in the choice of surgical treatment of the contralateral neck in N+ pts with tumors close to the midline. The technique may be usefully employed within the framework of a multidisciplinary team.	*cN0 = ipsilateral cN0**cN+ = ipsilateral cN+ and contralateral cN0; contralateral cN0 was evaluated;***salivary glandmethod: LSG + probeHNSCC (51 OSCC)cT1-4 cN0/+ cM?	NA	2^{++}	

Which supplementary diagnostic methods should be performed on suspicion of metastasis?

First author	Study type	Patient number	Groups	Outcome	Result (in %)	Author's conclusion	Comments	Summary	Evidence level	Cross-reference
Bilde 2006 [52]	Prospective	34	SPECT/CT + SLNB (n=33) LSG + SLNB	1) SLN detection 2) No. of SLN 3) Mean No. of SLN/pts 4) No. FN SLN 5) Increase of SLN identified by SPECT/CT compared to LSG	1) 94 2) 107 3) 3 4) 0 5) 47 1) NA 2) 88 3) 2 4) NA	SPECT/CT may improve the localization of SLNs in pts with OSCC. Compared with planar LSG, SPECT/CT detected more SLNs and provided additional anatomical and spatial information about their localization. New generation SPECT with higher resolution CT scanners are expected to provide more accurate information about the localization of SLNs.	Method: planar LSG + probe and SPECT/CT OSCC cT1-T2 cN0 cM0	SPECT/CT > LSG	2-	
Borgermeester 2008 [53]	Prospective	126 37	FNAC + END*** FNAC + WW****	1) Sensitivity 2) Specificity for LNM detection 3) Sensitivity for levels (I/II/III/IV/V) 4) 1-y OS/3-y OS/5-y OS	1) 39 2) 100 3) 12/20/20/25/20 4) 89**/81**/75* ** 1) 18 2) 100 3) NA 4) 100/90/79*	Although the sensitivity of USgFNAC in this study is low, especially in small OSCC, the prognosis in the WW group is not affected. However, a WW strategy is only advantageous to a minority of the pts. Elective neck treatment is a safer policy for most pts.	USgFNAC; BLD * ns; ** data for T2 HNSCC only HNSCC (112 OSCC) cT1-4 cN0 cM0 *** only pts with T2-4 **** only pts with T1 and/or minor depth infiltration (less than 5 mm) or contraindication for major surgery.	END > WW	2+	
Brouwer 2004 [54]	Not cited	15	CT(n=7) MRI (n=7) USgFNAC (n=11) PET	1) TP/FN/FP/TN (n)2) Sensitivity3) Specificityfor LNM detection	1) 0/3/0/4 1) 2/0/0/5 1) 2/0/0/9 1) 2/1/1/11 2) 67 3) 92	It is unlikely that PET is superior in the detection of occult LNM in HN-CA pts with a palpable cN0. The applied histopath. method seems to be the most important factor for the differences in sensitivity in reported PET studies. New approaches such as the use of monoclonal antibodies labeled with a positron emitter may improve the results of PET.	18F-FDG PETOOSCC (9 OSCC)cT1-4 cN0 cM0	PET=ohers	3	
Burcia 2010 [55]	Prospective	50	Intraoperative imprint cytology HE IHC	1) Sensitivity 2) NPV for SLN+ detection (IHC = RS) 3) LNM size 4) 5-y DSS	1) 20.8 2) 86 3) 4.25 mm 4) 85* 1) 37.5 2) 89 3) 2.5 mm 1) 100 2) 100 3) 350 µm	The SLNB technique appeared to be the best staging method in cN0 pts and provided evidence that routinely undiagnosed LNM may have clinical significance.	Method: LSG + probe * ns for pSLN+ vs pSLN0 (p=0.15) **based on SLNB (n=148) using SS-IHC ***based on routine HE and intraoperative imprint cytology of both the 1075 non-SLN collected with ND and the 148 previously excised SLN	pSLN staging** > pN staging***	3	

Which supplementary diagnostic methods should be performed on suspicion of metastasis?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
			pSLN staging** pN staging***	5) Sensitivity 6) NPV for N staging (pN stage = RS/pSLN = RS)	5) 100/100 6) 100/100 5) 100/50 6) 100/78		OOSCC cT1-2 cN0			
Burns 2009 [56]	Prospective	13	SLNB	1) SLN found (No.) 2) SLN TN (No.) 3) SLN FN (No.)	1) 13/13 2) 8/13 3) 1/13	In view of these findings, we would recommend the use of SLNB in cases of OOSCC in order to aid the differentiation of those pts whose necks are harboring occult disease and who require further treatment. SNLB alone can be used to stage the cN0 neck for the majority of early OOSCC	Method: LSG + probe + dye OOSCC (10 OSCC, tab.1) cT1-3 cN0 cM?	SLNB > no SLNB	3	
Cammilleri 2004 [57]	Prospective	14	SLNB + LSG	1) SLN detected by LSG 2) SLN+ and other LN+(No.) 3) SLN+ and other LN-(No.) 4) SLN- and other LN+(No.) 5) SLN- and other LN-(No.)	1) 100 2) 3 3) 2 4) 0 5) 9	The results of this preliminary study are encouraging. They showed that SLN in squamous cell carcinoma of the head and neck N0 is accurately feasible and could predict the presence of OM. Nevertheless, more data are needed to validate these results.	Method: LSG + probe HNSCC (13 OSCC) cT1-2 cN0 cM?	NA	3	
Chone 2008 [58]	Prospective	35	SLNB	1) Sensitivity 2) Specificity 3) NPV 4) Accuracy for LNM detection	1) 82 2) 100 3) 95 4) 96	Based on the data from this study, with an NPV of 95%, it is acceptable for the clinician just to follow up this neck without submitting it to END when SLN is histopathologically negative, with an FN rate of 5%. Even supposing that this 5% of necks with OM after negative SNB will recur, this rate of recurrence would be the same as that observed after SOHND or even after RND.	Method: LSG + probe HNSCC (24 OSCC) cT1-3c cN0 cM?	NA	2-	
Civantos 2003 [59]	Not cited	18	SLNB	1) FN (No.) 2) FP (No.) 3) SLN detected by LSG (No.) 4) SLN+ (No.)	1) 1 2) 1 3) 18/18 4) 10 5) 1	Gross tumor replacement of lymph node architecture may obstruct and redirect lymphatic flow. The LSG/SNLB tech-nique correctly identified the presence of cancer in the most radioactive cervical nodes in 10 of 18 pts. PET scan was not	Method: LSG + probe OSCC cT1-3c cN0 cM?	NA	3	

Which supplementary diagnostic methods should be performed on suspicion of metastasis?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
			CT PET	5) SLN0 and non-SLN+ (No.)	1) 7 2) 0 1) 7 2) 0	helpful in detecting subclinical cervical metastases. Equivocal findings on CT might indicate a group of pts for whom selective neck dissection would remain the preferred approach. We believe the LS/SNB technique was promising for oral cancer.				
Civantos 2010 [60]	Prospective	140	SLNB +HE SLNB + IHC	1) NPV2) NPV for cT1/ cT2	1) 942) NA 1) 96 2) 100/94	For T1 or T2 N0 OSCC, SLNB with step sectioning and IHC, by surgeons of mixed experience levels, correctly predicted a pathologically negative neck in 96% of pts. We conclude that it is reasonable to initiate clinical trials involving SLNB, with completion ND only for pts with positive sentinel nodes, as a lower morbidity approach for selected pts with T1 and T2 oral cancers.	Method: LSG + probeOSCCcT1-2c cN0 cM?	IHC>HE	2^{++}	
Dammann 2005 [17]	Prospective	64	CT MRI PET	1) Sensitivity 2) Specificity 3) Accuracy for LNM detection (regions) 4) AUC	1) 80 2) 93 3) 92 4) 0.909 ± 0.032 1) 93 2) 95 3) 94 4) 0.938 ± 0.027 1) 85 2) 98 3) 96 4) 0.926 ± 0.029	MRI is recommended as the method of choice in the preoperative evaluation of SCC of the oral cavity and the oropharynx. Diagnostic performance in lymph nodes is similar for MRI, CT, and PET. PET can provide relevant diagnostic information in case of equivocal findings from MRI or CT. Routine use of PET, however, does not appear to be necessary if optimized MRI is available.	18F-FDG PET DN 55 OSCC cT1-4 cN0/+ cM0-1	MRI = CT = PET	2^{+}	KQ 1
De Zinis 2006 [61]	Retrospective	89	CS *	1) Sensitivity 2) Accuracy for PT detection	1) 76 2) 74	The high prevalence of clinical and OM in this setting suggests that ND should be performed on a nearly routine basis, even for lesions with a low-T category and a cN0 neck. ND should always encompass level IV due to the possibility of skip metastases, particularly in TSCC. In pts with a cN+ neck, levels from I to V should be addressed, particularly in the presence of metastases at levels III and IV.	Bilateral metastases only if PT is midline (p=0.009) * CS not defined OSCC cT1/+ cN0/+ cM?	NA	3	KQ 4

Which supplementary diagnostic methods should be performed on suspicion of metastasis?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
Dirix 2010 [62]	Prospective	22	CT + MRI* DW-MRI*	1) Sensitivity2) Specificity3) Accuracy4) NPV5) PPV for LNM detection (lesion/level/side)	1) 42.2/46.9/62.5 2) 93.5/95.8/82.4 3) 81.8/83.6/72.7 4) 84.6/84.4/70 5) 65.5/78.9/76.9 1) 88.9/93.8/100 2) 97.4*/96.9/82.4 3) 95.5/96.1/90.9 4) 96.8/97.9/100 5) 90.9/90.9/84.2	These results suggest that DW-MRI is superior to anatomical imaging with CT + MRI for pre-RT cervical nodal staging, with a potential impact on organ sparing and tumor control. A larger trial prospectively comparing DW-MRI and FDG-PET will be designed to confirm these findings.	* Nodal staging agreement between imaging and pathology ss stronger for DW-MRI vs CT + MRI HNSCC (11 OSCC)cT? cN? CM?	DW-MRI>>CT + MRI*	2-	
Freire 2003 [63]	Prospective	48	CE CT	1) Sensitivity 2) Specificity 3) PPV 4) NPV 5) Efficiency for LNM detection (SBA; homolateral / contralateral)	1) 77/66 2) 71/100 3) 77/100 4) 71/83 5) 0.52/0.50 1) 55(16*)/16(0*) 2) 76(73*)/90(90*) 3) 75(20*)/50(0*) 4) 57(68*)/64(81*) 5) 0.50(0.47*)/ 0.50(0.50*)	CE was more efficient than CT in identifying LNM. Lymphatic drainage of the HN regions is complex, and LSG can be useful in OOSCC in clinical stages I and II, but further studies are necessary to standardize the methodology.	*Data for 21 pts considered as cN0 in CE OOSCC (40 OSCC) cT1-4 cN0-3 cM?	CE > CT	2+	
Gencoglu 2003 [64]	Prospective	26	FNAC	1) Sensitivity 2) Specificity 3) Accuracy for LNM detection	1) 71.4 2) 100 3) 88.8	FNAC is recommended as a first-line investigation in palpable head and neck masses. FNAC was performed for palpable cN+ of LLC pts. A literature review failed to reveal any other reports which evaluated the correlation of the results of FNAC with the histopathological reports in pts with palpable neck masses and LLC.	RS limited LLC cT1-4 cN+ cM?	NA	2-	
Haerle 2009 [65]	Prospective	58	LSG + SLNB	1) No. of hot spots detected 2) NPV of SLNB	1) 125 2) 98	SPECT/CT has the potential to detect more SLNs, which might harbor occult disease, than LSG alone. With regard to	Method: planar LSG + probe and SPECT/CT	LSG + SPECT/CT	2-	

Which supplementary diagnostic methods should be performed on suspicion of metastasis?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
			LSG + SPECT/CT + SLNB		1) 137 2) 98	the excellent results achieved with LSG and the intraoperative use of the gamma probe, SPECT/CT is not indispensable for successful SNB. Both imaging modalities have difficulties in detecting level I SN close to the injection site.	OOSCC (48 OSCC) cT1-2 cN0 cM?	> LSG		
Hafidh 2006 [65]	Prospective	48	CT MRI PET	1) Sensitivity 2) PPV 3) Accuracyfor LNM detection	1) 422) 883) 40 1) 55 2) 100 3) 55 1) 73 2) 93 3) 70	Although PET has higher sensitivity in detecting nodal disease, it has only slightly improved the classification of N+ necks. The findings of this study cast doubt on the merit of routine addition of PET to the current investigative protocols for HNSCC pts.	18F-FDG PETHNSCC (17 OSCC)cT0-4 cN0-3 cM? (DN)	CT=MRI=PET	3	
Hart 2005 [65]	Prospective	20	SLNB	1) SLN detection 2) Rate of SLN+ 3) FN 4) NPV of SLN	1) 100 2) 20 3) 0 4) 100	In this study, the SLN had a NPV of 100%. SLNB is feasible and appears to accurately predict the presence of OM disease. Although further study is warranted, SLNB could potentially guide HN oncologists to the patient with N0 disease who would benefit most from SND and prevent the morbidity of unnecessary ND.	Method: LSG + probe OOSCC (19 OSCC) cT1-4 cN0 cM?	NA	3	
Hoft 2004 [5]	Not cited	50	SLNB	1) FN 2) SLN detection	1) 0 2) 92	Based on the limited number of pts in this study, SLNB seems to have a high diagnostic value in HNSCC.	Method: LSG + probe HNSCC (22 OSCC) cT1-4 cN0 cM? (DN)	NA	3	
Hohlweg-Majert 2009 [66]	Not cited	45	US** CT	1) Sensitivity 2) Specificity 3) NPV 4) PPV for LNM detection	1) 74.1* 2) 91.5 3) 93.7 4) 66.7 1) 67.9* 2) 90.0 3) 92 4) 74.4	Cervical LN staging can be performed safely by US. It is an inexpensive, easy-to-handle, and cost-effective diagnostic method. However, only the uppermost regions of the neck are accessible with a linear transducer. Despite this restriction, US is a reliable and valuable tool for screening LN in the case of HN malignancy.	* ss ** B-scan HN malig. 37 OSCC cT1-4 cN0-3 cM?	US >> CT*	3	

Which supplementary diagnostic methods should be performed on suspicion of metastasis?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
Hyde 2003 [6]	Not cited	19	SLNB PET (n=18)	1) FN 2) FP for LNM detection	1) 1/4 2) NA 1) 4/4 2) 2/18	SLNB and imaging with probe and Patent Blue Dye guided harvest is feasible in pts with OSCC and can predict cervical LN status. PET may be less useful.	18F-FDG PET method: LSG+probe+dye OSCC cT1-4 cN0 cM? (DN)	SLNB > PET	3	
Jeong 2007 [67]	Prospective	47	PET	1) Sensitivity2) Specificity3) PPV4) NPV5) Accuracyfor LNM detection (level)6) Max. SUV pN+/pN0	1) 80.3*2) 92.8*3) 79*4) 93.35) 89.7*6) 11.9/3.7***	Integrated PET/CT is more accurate than conventional PET and CECT alone for evaluating the cervical nodes in pts with HNSCC.	* ** p < 0.05, *** p <0.001HNSCC (21 OSCC)ct? cN0-3 cM? (DN)	PET/CT>>CECT* **>PET	2-	
			CECT		1) 90.2 2) 93.9** 3) 83.3** 4) 96.6 5) 93**					
			PET/CT		1) 91.8* 2) 98.9* ** 3) 96.6* ** 4) 97.3 5) 97.1* **					
Joeng 2006 [68]	Prospective	20	LSG + SLNB Gamma probe + SLNB	1) NPV 2) FN 3) Accuracy for LNM detection by SLNB 4) SLN detection	1) 100 2) 100 3) 0 4) 95 4) 100	Our radiolocalization technique of SLN using 99mTc filtered tin colloid in N0 OSCC is technically feasible and appears to accurately predict the presence of the LNM.	OSCC cT1-2 cN0 cM?	LSG = gamma probe	2-	
Jones 2005 [24]	Retrospective	88	PET	1) Sensitivity 2) Specificity for LNM detection	1) NA/100 2) NA/100	PET has a useful role in the diagnosis of HN malig., and in the demonstration of occult or hidden tumors, distant and metastatic disease. It should always be used as an adjunct to other clinical information and results must be interpreted in the light of clinical findings.	18F-FDG PET In-/exclusion unclear OOSCC (79 OSCC) cT? cN0/+ cM0-1 (54 DN/34 RD)	NA	3	KQ 1 and 2
Keski-Santti 2008 [69]	Prospective	13	SLNB	1) SLN detection 2) Rate of SLN+ 3) FN	1) 100 2) 15 3) 0	Although SLNB is not yet validated for clinical use as a replacement for END in pts with OSCC, it can be recommended for pts who do not fulfill the criteria for END according to current treatment protocols.	Method: LSG + probe + dye OSCC cT1 cN0 cM?	SLNB > END	3	

Which supplementary diagnostic methods should be performed on suspicion of metastasis?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
Keski-Santti 2008 [70]	Prospective	46	SLNB	1) Sensitivity2) Accuracyfor LNM detection	1) 672) 94	Sensitivity of SLNB for detection of subclinical metastasis seems to be poor in cases where only one SLN can be identified. The results of this study do not entitle us to entirely replace END by SLNB in pts with OSCC.	Method: LSG + probe + dyeOOSCC (45 OSCC)cT1-3 cN0 cM0	END>SLNB	2-	
Khafif 2006 [71]	Prospective	20	SLNB	1) Sensitivity 2) Accuracy for LNM detection 3) Rate SLN+ 4) Improvement in SLN detection by SPECT/CT	1) 87.5 2) 95 3) 40 4) 30	Fused SPECT/CT images improved pre-OP identification + localization of SLN before SNLB in OSCC pts. The value of the additional use of blue dye injection for SLNB in these pts is yet to be deter-mined.	Method: LSG + SPECT/CT + probe + dye OSCC cT1-T4 cN0 cM? (DN)	NA	3	
Kim 2008 [72]	Retrospective	82	CT + MRI	1) Sensitivity 2) Specificity 3) Accuracy 4) NPV 5) PPV for LNM detection (SBA/level) 6) 3y-DFS 7) 3y-LCR 8) ss predictors for 3y-LCR (p<0.03) *** 9) ss predictors for 3y-DFS (p<0.05)***	1) 65*/65** 2) 81/94 3) 75/89 4) 76/94 5) 72/65 6) 72 7) 74 8) T1-2/T3-4 pN0/pN+ SUV ≤5.0/>5.0 9) Age ≤55y/>55y PT ≤8mm/ >8mm T1-2/T3-4 pN0/pN+ TNM I-II/III-IV SUV ≤5.0/>5.0	PET may have potential roles in initial staging, survival prediction, and the detection of recurrences and secondary cancers.	* p = 0.031, ** p = 0.002 *** univariate analyses 18F-FDG PET OSCC cT1-4 cN0-2 cM0 (DN)	PET >> CT + MRI* **	3	
			PET		1) 84*/88** 2) 77/93 3) 80/92 4) 87/98 5) 72/69					

Which supplementary diagnostic methods should be performed on suspicion of metastasis?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
Kontio 2004 [7]	Not cited	15	SLNB	1) FN necks (No.) 2) SLN detection by LSG (No.) 3) SLN detection by LSG+probe +dye (No.)	1) 1/42) 14/153) 15/15	Our results show that SLNB is a promising tool for use in pts with OSCC. However, further studies are necessary.	Method: LSG + probe + dyeOSCCcT1-2 cN0 cM0	NA	3	
Kovacs 2004 [73]	Prospective	62	CT	1) Sensitivity 2) Specificity 3) Accuracy 4) PPV 5) NPV for LNM detection* 6) SLNB+ in PET-cN0 (n°)	1) 89 2) 77 3) 80.5 4) 61.5 5) 94.5	Diagnostics using PET in combination with LSG/ SLNB considerably reduced the number of extensive ND in OOSCC as compared to CT without locoregional hazard.	18F-FDG PET *all ns RS limited (WW) OOSCC (54 OSCC) cT1-3 cN0/+ cM?	PET = CT*	2-	
			PET		1) 72 2) 82 3) 79 4) 62 5) 88 6) 3/38					
Krabbe 2008 [25]	Not cited	38	CT/ MRI/ FNAC	1) Sensitivity 2) Specificity 3) Accuracy 4) PPV** 5) NPV** for LNM detection	1) 50 2) 70 3) 66 4) 31 5) 84	Although PET performed better than conventional imaging modalities, sensitivity was lower than desired. As a consequence, clinical application of PET in the patient staged as cN0 is limited.	18F-FDG PET USgFNAC RS NA in 8 pts OOSCC (35 OSCC) cT1-4 cN0 cM?	PET > CT/ MRI/ FNAC	3	KQ 1
			PET		1) 50 2) 97 3) 87 4) 80 5) 88					
Krabbe 2010 [74]	Prospective	27	FDG PET	1) Sensitivity 2) Specificity 3) Accuracy for LNM detection	1) 67 2) 97 3) 89	Because of bilateral accumulation of ^{11}C-TYR in salivary glands, ^{11}C-TYR PET is not suitable as a replacement for ^{18}FDG PET in staging SCC of OOSCC (detection of LNM, especially in levels IB and II, is impaired).	18F-FDG PET 11C-TYR PET OOSCC (24 OSCC) cT? cN? cM?	FDG PET > TYR PET	2-	
			TYR PET		1) 33 2) 100 3) 31					
Lee 2005 [75]	Retrospective	31	SPECT	1) Sensitivity2) Specificity 3) Predictabilityfor LNM	1) 59.1* 2) 87.5* 3) 83.7	CT was more accurate than SPECT in detecting cervical LNM, but the most accurate detection was possible when	99mTc-MIBI SPECT*nsHNSCC (17 OSCC)cT? cN? cM?	SPECT + CT > CT > SPECT	3	

Which supplementary diagnostic methods should be performed on suspicion of metastasis?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
			CT SPECT + CT	detection	1) 68.2* 2) 93.1* 3) 89.8 1) 40.9 2) 99.3 3) 91.6	the two methods were employed together. The combined use of SPECT+ CT may be helpful for the prediction of cervical LNM.				
Nahmias 2007 [76]	Not cited	70	PET/CT cN0 (n= 51*)	1) Sensitivity 2) Specificity	1) 79/26 2) 82/99 3) 33.33	In the final analysis, the HN oncologic surgeon should not depend on the results of the PET/CT scan to determine which pts will benefit from ND. Rather, time-honored principles of neck surgery should be followed, particularly with regard to the liberal execution of prophylactic ND in pts with cN0 necks.	18F-FDG PET * n= neck sides; no study duration/time span; no design; in-/exclusion unclear HN-CA (58 OSCC) cT? cN0/+ cM? (DN)	NA	3	
			PET/CT cN+ (n= 23*)	for LNM detection (neck/nodes)	1) 95/62 2) 25/99					
			PET/CT	3) OM	1) 88/48 2) 76/99					
Nakamoto 2009 [26]	Retrospective	46	MRI + PET MRI	1) Sensitivity 2) Specificity 3) Accuracy for LNM detection	1) 85 2) 92 3) 89 1) 85 2) 92 3) 89	Image fusion from MR + PET might be useful in evaluating HN-CA, especially in suspected RD rather than in DN.	18F-FDG PET OO-CA cT? cN? cM? (DN/RD)	MRI + PET = MRI	3	KQ 1 and 2
Ng 2005 [27]	Prospective	124	CT + MRI	1) Sensitivity2) Specificity3) Accuracy4) PPV5) NPVfor LNM detection (LBA)6) AUC (ROC)	1) 52.6* 2) 94.5 3) 86.4 4) 69.4 5) 89.3 6) 0.801**	PET is superior to CT+MRI in the detection of cervical status of OSCC. The sensitivity of PET for the detection of LNM on a level-by-level basis was significantly higher than that of CT+MRI, whereas their specificities appeared to be similar. Visual correlation of PET+CT+MRI showed a trend towards increased diagnostic accuracy over PET alone but without a significant difference, and its sensitivity was still not high enough to replace pathologic LN staging based on ND.	18F-FDG PET* p < 0.001 no major limitations** p = 0.002 for nodal detectionOSCCcT1-4 cN? CM? (DN)	PET>>CT + MRI* **	2^{++}	KQ 1
			PET		1) 74.7* 2) 93 3) 89.5 4) 71.7 5) 93.9 6) 0.896**					
			CT + MRI + PET		1) 77.9 2) 94.5 3) 91.3 4) 77.1 5) 94.7 6) 0.913					

Which supplementary diagnostic methods should be performed on suspicion of metastasis?

First author	Study type	Patient number	Groups	Outcome	Result (in %)	Author's conclusion	Comments	Summary	Evidence level	Cross-reference
Ng 2006 [77]	Prospective	134	CT/MRI (n=25/109) PET PET + CT/MRI	1) Sensitivity 2) Specificity 3) Accuracy 4) PPV 5) NPV for LNM detection (LBA/PBA)	1) 21.6*/31.4 2) 97.5/91.9 3) 89.1/76.1 4) 52.4/57.9 5) 90.8/79.1 1) 41.2* **/51.4 2) 96.8***/91.9 3) 90.6/81.3 4) 61.8/69.2 5) 92.9/84.3 1) 47.1**/57.1 2) 98***/96 3) 92.3/85.5 4) 75/83.3 5) 93.6/86.4	PET was superior to CT or MRI for detecting palpably occult neck metastasis of OSCC. Because PET could reduce the probability of occult neck metastasis to less than 15% in T1-T3 tumors, it should be indicated for evaluation of these subpopulations.	18F-FDG PET * p = 0.021, ** p= 0.25, *** p= 0.125 OSCC cT1-4 cN0 cM? (DN)	PET + CT/MRI > PET** *** >> CT/MRI*	2^{++}	
Nieuwenhuis 2005 [78]	Not cited	22	SLNB	1) Sensitivity2) Accuracy 3) FN (n)for LNM detection4) SLN detection by LSG	1) 892) 953) 1/224) 78	Our study seems to validate the SN hypothesis for OOSCC. The role of SLNB in the management of the N0 neck in such pts has yet to be established through prospective trials. SN identification (and thus biopsy) does not seem to be reliable in pts with tumors located in or close to the midline.	Method: LSG + probe OOSCC (18 OSCC)cT2-4 cN0 cM?	SLNB>WW	3	
Payoux 2005 [79]	Prospective	30	SLNB	1) Sensitivity 2) SLN detection (n) 3) FN SLN (n)	1) 86 2) 29/30 3) 1/29	This prospective study shows that SLN is useful for the staging of N0 necks. The SLN technique has the potential to decrease the need for ND, which is usually performed in cN0, thus reducing both associated morbidity for pts and cost.	Method: LSG + probe OOSCC (26 OSCC) cT1-4 cN0c M?	SLNB > ND	2^{-}	
Pentenero 2008 [30]	Prospective	19	PET/CT CT + MRI	1) Specificity 2) Accuracy 3) NPV for LNM detection (level/SBA)	1) 95.9/83.3 2) 89.9/68.2 3) 93.4/78.9 1) 97.4/89.5 2) 93.7/77.3 3) 96.1/85	In conclusion, PET/CT showed high accuracy in determining the extension and/or the depth of invasion of the PT; nonetheless, further studies are needed to clarify its role in N staging as our results do not support the planning of nodal therapy based on PET/CT data alone.	OCC 18 OSCC cT? cN0/+ cM?	CT + MRI > PET/CT	3	KQ 1

Which supplementary diagnostic methods should be performed on suspicion of metastasis?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
Piao 2009 [80]	Not cited	56	PET/CT	1) Sensitivity 2) Specificity 3) Accuracy for LNM detection (level/LBA)	1) 83.5/62.8 2) 90.8/98.4 3) 89.0/96.3	Combined PET/CT enabled the early detection of LNM of OOSCC, but the diagnosis of metastasis was not accurate if the metastases had a maximum diameter of <10 mm. Combined PET/CT can accurately detect LNM levels, delivering reliable information to surgeons for early treatment of pts.	18F-FDG PET OOSCC (51 OSCC) cT? cN? CM?	NA	3	
Roh 2007 [32]	Not cited	167	PET/CT (n=63)	1) Sensitivity2) Specificity3) Accuracy4) PPV5) NPVfor LNM detection (SBA/level)	1) 91**/90*2) 87**/943) 89/934) 88/775) 90/98	Compared with PET alone, preoperative PET/CT may not yield ss improved diagnostic accuracy in pts with HNSCC. Moreover, despite their high accuracy, PET and PET/CT may not abrogate the need for conventional imaging and pathologic staging based on primary resection and ND.	18F-FDG PET* p <0.001, ** p <0.05 *** = CT/MRI vs PET/CT or PET alone)HNSCC (54 OSCC) cT? cN? CM?	PET/CT>PET >> MRI + CT* **	3	KQ 1
			PET (n=104)		1) 60**/87* 2) 88**/93 3) 89/92 4) 92/77 5) 86/96					
			CT + MRI*** (n=63)		1) 76**/60* 2) 83**/92 3) 79/86 4) 83/63 5) 76/91					
			CT + MRI*** (n=104)		1) 77**/67* 2) 81**/90 3) 79/85 4) 86/64 5) 71/91					
Ross 2004 [8]	Prospective	61	SLNB	1) Sensitivity for LNM detection 2) ss predictors for LNM 3) ns predictors (p-value) for LNM	1) 93 2) cT1 vs cT2 PNI Bone invasion Cohesive tumor front 3) PT ≤2 cm vs >2 cm (p=0.063) Vascular invasion (p=0.214)	Both clinical staging and routine pathologic staging underestimate the presence of LNM. Staging with either SLNB alone or SLNB-assisted END shows promise in the management of the cN0 neck by identifying pts with micrometastases (pN1mi).	Method: LSG + probe OOSCC cT1-2 cN0 cM?	NA	2-	

Which supplementary diagnostic methods should be performed on suspicion of metastasis?

First author	Study type	Patient number	Groups	Outcome	Result (in %)	Author's conclusion	Comments	Summary	Evidence level	Cross-reference
Santaolalla 2009 [81]	I) Prospective II) Retrospective	22	I) SLNB	1) Sensitivity2) Specificity 3) NPV 4) PPVfor LNM detection in SLNB5) ss differences (p-value) of the behavior of group I) and II)	1) 732) 1003) 804) 100	SLNB is a technique that facilitates the study of metastasis in OO-CA and reduces morbidity in pts affected by this pathology.	Method: LSG + probeOSCCCT1-3 cN0 cM0	SLNB>>no SLNB*	3	
		22	II) No SLNB		5) Extension of ND (0.003) Hospital stay (0.01) Complications (0.034*) Bed occupation (0.002)					
Schoder 2006 [82]	Prospective	31	PET/CT	1) Sensitivity 2) Specificity 3) PPV 4) NPV 5) Accuracy for LNM detection (level/SBA) 6) OM	1) 67/67 2) 95/85 3) 50/60 4) 98/88 5) 94/80 6) 25	Despite a reasonably high overall accuracy, the clinical application of PET/CT in the cN0 neck may be limited by the suboptimal sensitivity for small metastases and the relatively high number of FP findings. Therefore, the clinical management of pts with OSCC and N0 neck should not be based on PET/CT findings alone.	18F-FDG PET OSCC cT1-4 cN0 cM?	NA	2-	
Schroeder 2008 [83]	Prospective	13	CT	1) Sensitivity 2) Specificity 3) Accuracy 4) PPV 5) NPV for LNM detection	1) 100 2) 50 3) 69.2 4) 55.6 5) 100	The detectability threshold of OM appears to be below the spatial and contrast resolution of CT, MRI and PET. The decision for END in pts with cT1-T2 cN0 cM0 OSCC cannot be based upon cross-sectional imaging at the resolutions currently available.	18F-FDG PET ss difference RS vs imaging RS: END small sample size OOSCC (10/17 OSCC (13 evaluated)) cT1-2 cN0 cM0 (DN)	CT = MRI = PET	3	
			MRI		1) 80 2) 12.5 3) 38.5 4) 36.4 5) 50					
			PET		1) 0 2) 87 3) 53.8 4) 0 5) 59					
Schwartz 2005 [84]	Prospective	20	CT	1) Sensitivity2) Specificity3) NPV4) PPV for LNM detection(level)*	1) 782) 98.53) 924) 95	These early findings suggest that PET/CT is superior to CT alone for geographic localization of diseased LN levels. Confirmatory trials to substantiate	18F-FDG PET* p-value for agreement between imaging results of PET/CT vs CT alone and RS by two- and	PET/CT >> CT*	3	

Which supplementary diagnostic methods should be performed on suspicion of metastasis?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
			PET/CT		1) 96 2) 98.5 3) 98.5 4) 96	the accuracy of PET/CT neck staging should be prioritized	one-sided McNemar's testing: =0.06/0.03;OOSCC (8 OSCC)cT1-4 cN? cM?			
Seitz 2009 [33]	Retrospective	66	MRI PET/CT	1) Sensitivity 2) Specificity for LNM detection	1) 88.46 2) 75 1) 83.81 2) 73.91	The diagnostic performance of PET/CT in the local staging of oral cancer is not superior to MRI.	18F-FDG PET * p ≤ 0.007 between RS, PET/CT and MRI OCC (50 OSCC) cT1-4 cN0/+ cM? (DN/RD)	MRI = PET/CT	3	KQ 1
Stoeckli 2007 [85]	Prospective	79	SLNB* (n=28) SNLB concept** (n=51)	1) Sensitivity 2) NPV for LNM detection	1) 100 2) 100 1) NA 2) 94	SLNB is technically feasible and reproducible with a high SLN detection rate. Validation against END revealed an NPV of 100%. Application of the SLNB concept in clinical practice was very successful. The recurrence rate within the neck was very low and the morbidity and cost of END could be spared to 60% of the pts.	Method: LSG + probe (+dye only few pts) *END in all **END only if pSLN+ OSCC cT1-2 cN? cM?	SLNB concept > END	2+	
Sumi 2007 [86]	Retrospective	38	CT MRI	1) Sensitivity 2) Specificity 3) NPV 4) PPV 5) Accuracy 6) AUC for ability to differentiate RLNs from LNMs (nodes <1 cm** / ≥1 cm)	1) 68/98 2) 79/89 3) 72/96 4) 79/95 5) 73/95 6) 0.797*/NA 1) 83/100 2) 89/98 3) 84/100 4) 89/99 5) 86/99 6) 0.925*/NA	MRI is superior to CT in the diagnosis of LNM from HNSCC.	* p = 0.0148, ** p < 0.05 overall diagnostic ability for differentiation of RLN vs LNM (for LNs <1 cm) HNSCC (22 OSCC) cT? cN? cM?	MRI >> CT* **	3	
Thomsen 2005 [87, 88]	Not cited	40	SLNB	1) % upstaged by SLNB 2) Ability to differentiate TN vs TP by SLNB	1) 28 2) 0.001	#1521SLNB upstaged 28% of the pts. SLN close to the PT were difficult to find. Added oblique planar images and/or tomographic images revealed extra clinical relevant hotspots in 38% of pts. Reproducibility proved excellent.#1566SLNB improved the staging of	Method: planar LSG or oblique planar LSG + tomographic images + probe + dye OSCC cT1-T2 cN0 cM0	Oblique planar LSG and/or tomographic images>planar LSG	3	

Which supplementary diagnostic methods should be performed on suspicion of metastasis?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
			US MRI SLNB Histopathology/ follow-up	1) Sensitivity 2) Specificity 3) Accuracy 4) PPV 5) NPV for LNM detection	1) 87 2) 85 3) 85 4) 57 5) 96 1) 36 2) 93 3) 81 4) 56 5) 85 1) 80 2) 100 3) 96 4) 100 5) 96 1-5) 100	pts with small N0 oral cancers. Combined SLNB and Doppler US may further improve staging. MRI and simple palpation did not prove useful for staging these pts with the applied criteria for malignancy.		SLNB + US > MRI (+ CE)		
To 2003 [89]	Retrospective	30	US	1) Sensitivity 2) Specificity 3) Accuracy for LNM detection	1) 47 2) 93 3) 70	It is concluded that US alone is inadequate for making decisions regarding neck management of pts with T1-2 N0 TSCC and cannot replace a policy of selective neck dissection.	Small sample size TSCC cT1-2 cN0 cM? (DN)	NA	3	
Tuli 2008 [90]	Prospective	20	CT MRI SPECT	1) Sensitivity 2) Specificity 3) PPV for LNM detection	1) 11 2) 98.38 3) 33 1) 33 2) 98.38 3) 60 1) 55.5 2) 100 3) 71	In this preliminary prospective study, we observed that 40% (8/20) of the cN0 TSCC harbored LNM. 99m-MIBI-SPECT is a more effective imaging modality in the staging of cN0 LNM in TSCC as compared with CT or MRI.	99m-MIBI-SPECT TSCC CT1-2 cN0 cM0	SPECT > MR > CT	3	
Wensing 2006 [91]	Prospective	28	PET	1) Sensitivity2) Specificity3) Accuracy for LNM detection	1) 332) 763) 63	In pts with cN0 OSCC, PET does not contribute to the pre-OP workup. PET does not replace SOHND as a staging procedure.	18F-FDG PET OSCC cT1-4 cN0 cM0	SOHND>PET	2˙	

Which supplementary diagnostic methods should be performed on suspicion of metastasis?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
Wiener 2006 [37]	Retrospective	52	MSCT MRI	1) Sensitivity 2) Specificity 3) Accuracy 4) PPV 5) NPV for LNM detection	1) 78.9 2) 75.7 3) 76.9 4) 65.1 5) 86.2 1) 84.2 2) 63.6 3) 71.1 4) 57.1 5) 87.5	Pre-OP MRI is recommended as the basic imaging modality of choice for treatment planning of OSCC. MSCT is a valid alternative imaging method especially in cases with low patient compliance. In the N-staging both imaging modalities were not accurate or suitable for diagnosing small metastatic nodules. Therefore, additional contrast media such as super paramagnetic iron oxides may improve the diagnostic performance.	OSCC cT1-4 cN? cM?	MRI > MSCT*	3	KQ 1
Yamane 2007 [92]	Not cited	109	Intraoral US + CAD	1) Sensitivity 2) Specificity 3) Accuracy for prediction of OM 4) ss predictors for LNM (p-value)	1) 87.2 2) 84.3 3) 85.3 4) Irregularity of invasive front (p=0.02) Entropy (p=0.047) Tumor thickness (p=0.027)	Intraoral US in conjunction with the proposed CAD system allows tissue characterization and prediction of subclinical LNM.	TSCC cT1-2 cN0 cM0	NA	2-	
Yamazaki 2008 [93]	Retrospective	26	PET CT	1) Sensitivity 2) Specificity 3) Accuracy 4) PPV 5) NPV for LNM detection	1) 74 2) 92 3) 80 4) 94 5) 65 1) 78 2) 58 3) 71 4) 78 5) 58	PET is a useful tool for preoperative evaluation of the neck because it accurately detects LNM ≥1 cm and has fewer FP results than CT. The high specificity of PET for LNM may play an important role in avoiding unnecessary ND.	18F-FDG PET OSCC cT1-3 cN? cM?	PET > CT	3	
Yen 2005 [94]	Prospective	102	MRI + CT (n=51) MRI + CT +	1) Sensitivity 2) Specificity 3) Accuracy for LNM detection*/total lesions 4) 2-y LCR	1) 63/84 2) 96/96 3) 91/92 4) 87** 1) 85/93 2) 97/97 3) 96/96 4) 86**	The role of PET for BSCC with cM0 is limited. Although PET is superior to CT/MRI in identifying LNM, it does not improve LCR.	18F-FDG PET * p=0.026 in assessing the regional nodes, ** ns BSCC cT? cN? cM0 (DN) AJCC c-stage I-IV	MRI + CT + PET >> MRI + CT*	2++	

Which supplementary diagnostic methods should be performed on suspicion of metastasis?										
First author	Study type	Patient number	Groups	Outcome	Result (in %)	Author's conclusion	Comments	Summary	Evidence level	Cross-reference
			PET (n=51)							

Table 13 Key question 4

Which regional lymph nodes should be removed by tumor surgery?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
Akhtar 2007 [95]	Not cited	94	RND	1) OM rate 2) RD (neck/ PT site) 3) DFS/survival with disease/ death of disease at last follow-up (mean 4y) 4) LNM involvement of levels	1) 32 (30/94) 2) 6/4 3) 89/6/4 4) 73 = I-III 6 = III 13 = I-IV 6 = I+II+V	The overall micrometastases rate in our pts (32%) warrants END in early cases also. The incidence of metastases to level IV and V from T1-T2 TSCC is low so these LN should not be removed routinely. SOHND is sufficient most of the time. Only when there is intraoperative suspicion of extensive metastases in levels I, II, or III should one consider addressing levels IV and V.	MRND TSCC cT1-2 cN0 cM?	SOHND > RND	3	
Batstone 2009 [96]	Observational	66	ND involving level I	1) Marginal mandibular nerve injury (neck/pts)	1) 18 / 23	The rate of smile asymmetry following ND is relatively high; however, severe injuries to the marginal mandibular nerve are uncommon.	OOSCC (61 OSCC) cT? cN? cM?	NA	2+	
Corlette 2005 [97]	Prospective	48 8	END TND	1) LNM involvement of level IIb	1) 4 1) 25	Level IIb nodes can be left in situ for END of UADT PT in nontonsillar cN0 necks without ss compromising regional clearance of micrometastases. For TNDs, level IIb should be dissected.	OSCC cT1-2 cN0/+ cM?	NA	2+	
D'Cruz 2009 [98]	Retrospective	359	WW (n = 200) END (n = 159)	1) 3y-/5y-DFS* 2) 3y-/5y-OS** 3) Nodal RD 4) ss predictors for nodal RD 5) OM	1) 71/68 2) 62/60 3) 47 1) 76/74 2) 69/60 3) 5.7 4) PT-grade (p= 0.03) PNI (p= 0.01) 5) 20.1	END did not impact DSF or OS. Current literature still remains divided on this issue, emphasizing the need for a RCT.	BLD * p = 0.53, ** p = 0.24 TSCC cT1-2 cN0 cM?	END > WW	3	

Which regional lymph nodes should be removed by tumor surgery?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
Elsheikh 2005 [99]	Prospective	48	SND	1) LNM involvement of level IIb 2) LNM involvement of level IIb in TSCC 3) Predicting factors for level IIb involvement	1) 10 2) 22 3) All level IIb + had TSCC All level IIb + had level IIa +	Level IIb LNM was only found in association with TSCC. Although this region may be preserved by elective SOHND in pts with OSCC, it should be included whenever the tongue is the primary site.	SOHND OSCC cT1-4 cN0 cM?	NA	2˙	
De Zinis 2006 [61]	Retrospective	89	NDpN0 (n = 43) ND pN+ (n = 46)	1) 5y-OS2) OM3) LNM involvement of levels	1) 74.5*2) NA3) NA 1) 38.3* 2) 25 3) 56 = I 59 = II 26 = III 15 = IV 4 = V	The high prevalence of clinical and OM in this setting suggests that ND should be performed on a nearly routine basis, even for lesions with a low T category and a cN0 neck. ND should always encompass level IV due to the possibility of skip metastases, particularly in TSCC. In pts with a cN+ neck, levels from I to V should be addressed, particularly in the presence of LNM at levels III and IV.	SND or RNDBilateral metastases only if PT is midline (p=0.009)* ssOSCCcT1/+ cN0/+ cM?	NA	3	KQ 3
Huang 2008 [100]	Retrospective	380	WW (n = 56) SND (n = 287) RND (n = 37)	1) 5y OS* 2) 5y DFS* 3) 5y NCR* 4) OM in cT1/ cT2/cT1+cT2 5) LNM involvement of levels (all ND)	1) 75.1 2) 55.6 3) 69*** 1) 87.2 2) 78.5 3) 86*** 1) 79.6 2) 83.3 3) 92*** 4) 14.6**/5.2**/10.1 5) 39.4 = I 51.5 = II 9.1 = III 6.1 = IV 0 = V	END should be performed routinely in pts with early-stage TSCC, even in the presence of cN0 from CT scans and MRI.	SOHND and MRND * ss between END and WW, ** p = 0.005 *** data out of graph; BLD TSCC T1-2 cN0 cM?	END >> WW*	3	

Which regional lymph nodes should be removed by tumor surgery?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
Inoue 2006 [101]	Cross-sectional	33	I) Control group	1) ss better score in QOL: a=stiffness b=constriction c=appearance d=pain e=numbness f=shoulder drop g=reach hand above2) ss better score in AAT	1) I > III-Vx for a,b,c I > IV-Vx for d,e I > III for g 2) I > III-Vx	Modifications to RND contribute to improvements in the postoperative QOL after ND. A multicenter study using the arm abduction test and questionnaire used in this study is currently in progress (#0242 Nibu, 2010) to further evaluate the impact of modifications to RND on QOL after surgery.	Pts of this study served as control group for #1304 Koo 2006* 115 ND in 74 pts. ** n = NDBLDHNSCC (24 OSCC)cT? cN? cM?	NA	3	
		74*	III) ND level I-III (n = 9**)		1) III > IV-Vx for d,e III > Vx for f					
			IV) ND level II-IV (n = 32**)		1) IV > Vx for f					
			V) ND level I-V or II-V (SAN preserved (n = 24**)		1) V > Vx for g 2) V > Vx					
			Vx) ND level I-V or II-V (SAN sacrificed (n = 50**)		1) NA 2) NA					
Iype 2008 [102]	Retrospective	219	SND	1) 3y-/5y-DFS 2) RD in pN0/ pN+/all 3) PT T1-2/T3-4 4) pN0 (n) 5) LNM involvement levels	1) 80/67 2) 12.4/15.5/13.2 3) 84/16 4) 73.5 (161) 5) 27.5 = I 20.6 = II 17.2 = I+II 17.2 = II+III 8.6= I-III 6.8= III	SOHND is a sound and effective procedure in the management of cN0 in OSCC. cN0 but pN+ neck requires adjuvant RT. It probably has a therapeutic role in the selected cases of OSCC with pN1 neck, and in these cases an extension of dissection to levels IV and V is beneficial.	SOHND OSCC cT1-4 cN0 cM?	NA	2-	
Jin 2008 [103]	Retrospective	100	ND (n = 72) orWW (n = 28)	1) OCLNM rate 2) ss RF for OCLNM 3) LNM involvement levels	1) 22 2) Pathological grade Degree of differentation Depth of invasion Mode of tumor growth T stage 3) 4.5 = I 4.5 = I+II	The most common regions with OCLNM in cN0 pts with TSCC were levels I-III in the ipsilateral neck. SOHND should be the elective treatment to the neck in pts with cN0-TSCC by consideration of the clinical and pathological factors for the depth of invasion, forms of growth, pathological grade, and degree of differentiation. The treatment of WW without consideration of the above-mentioned factors is not acceptable.	*ND n= 72 , WW n = 28TSCCT1-4 cN0 cM?	NA	3	

Which regional lymph nodes should be removed by tumor surgery?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
					4.5 = I-III 40.0 = II 22.7 = II+III 4.5 = III 4.5 = III+IV					
Kohler 2010 [104]	Retrospective	481	RND (n = 336/336*) MRND (preserving NA) (n = 106/91*) MRND (preserving NA + IJV) (n = 79/54*)	1) Impact on DFS (p-value) 2) Impact on RD of the neck (p-value)	1) ns (0.185) 2) ns (0.878)	The use of MRND has no ss impact on the pathological staging, DFS or DSS.	No staging reported (→ BLD?) *n = ND/pts OOSCC (429 OSCC) cT1-4 cNx? cM? (DN)	RND = MRND	3	
Koo 2006 [105]	Retrospective	66	Contralateral pN+** (n = 7) Contralateral pN0** (n = 59)	1) 5y-DSS 2) Contralateral pN+ by T stage (1/2/3/4) 3) ss RF for contralateral pN+	1) 43* 2) 0/8/25/18 3) Ipsilateral pN+ PT crosses midline T1-2 << T3-4 1) 79* 2) NA 3) NA	The risk of contralateral OCLNM in OSCC > T3 classification or those crossing the midline with unilateral LNM was high, and pts who presented with a contralateral LNM had a worse prognosis than those whose disease was staged as N0. Therefore, we advocate contralateral END or RT in pts with OSCC with ipsilateral LNM or tumors, or both, whose disease is >T3 or crossing the midline.	*ss **contralateral cN0 ipsilateral cN0-2 OSCC cT1-4 cN0-2 cM? (DN)	NA	3	
Laverick 2004 [106]	Prospective	266	WW (n=58) Unilateral ND level III-IV (n=153) Unilateral ND level V (n=22)	1) 3y survival 2) Difference in UW-QOL shoulder disability score at > 18 month compared to baseline (0-100 with 100 being best)	1) 812) -5* 1) 71 2) -13* 1) 64 2) -21*	There is little subjective morbidity associated with shoulder dysfunction after a unilateral level III or IV ND compared with pts undergoing PT surgery without ND. More extensive surgery in the neck, whether bilaterally removing levels I to III or IV, or extend-	* ssHNSCC (238 OSCC)cT? cN? cM? (DN)	WW>unilateral ND level III-IV>bilateral ND level III-IV>unilateral ND level V	2^{++}	

Which regional lymph nodes should be removed by tumor surgery?

First author	Study type	Patient number	Groups	Outcome	Result (in %)	Author's conclusion	Comments	Summary	Evidence level	Cross-reference
			Bilateral ND level III-IV (n=33)		1) 57 2) -17*	ing posteriorly to include level V, is associated with ss worse shoulder dysfunction.				
Liaw 2006 [107]	Retrospective	257	SND pN0 (n=202) SND pN1 (n=23) SND pN2 (n=32)	1) 3y-/5y-neck DFS 2) DFS (p-values: pN0 vs pN1/ pN0 vs pN2/ pN1 vs pN2)	1) 86.7/84.2 2) 0.064/<0.0001/ NA 1) 56.9/56.9 2) NA/NA/0.008 1) 27.5/27.5	This study showed that SOHND is effective for pN0 OSCC, relatively effective for pN1, and less effective for pN2a. These findings also suggest that when SOHND is used to treat N2a OSCC, postoperative RT or RND may be needed to improve the neck DFS rate.	SOHND OSCC cT? cN? cM?	NA	2-	
Lim 2004 [108]	Prospective	74	SND	1) LNM involvement of level IIb 2) Isolated LNM involvement of level IIb 3) RD level IIa + IIb 4) pN+ 5) LNM involvement of levels	1) 5 (4/74) 2) 0 3) 3 4) 32 (24/74) 5) 7 = I 19 = IIa 5 = IIb 1 = III	Level IIb LNM was rare in this study, and nodal RD in this area after SOHND in OSCC was infrequent. Therefore, this region may be preserved in elective SOHND in pts with OSCC.	SOHND OSCC cT1-4 cN0 cM?	NA	3	
Mourouzis 2010 [109]	Retrospective	17	WW in cN0 (n=13) ND in cN+ (n=4)	1) 5y-DFS 2) RD (local/ neck/distant)	1) 2/13 2) 0/2/1 1) 0/4 2) 2/4/0	SCC of the maxillary gingiva, alveolus and hard palate should be treated aggressively and END should be considered because of the high risk of OM.	ns OSCC cT1-4 cN0/+ cM?	END > WW	3	
Nibu 2010 [110]	Longitudinal multicenter	140 224*	Control group SOHND (n=64**) SND II-IV (n=124**) CND (I-V or II-V) + SAN preserved (n=75**) CND (I-V or II-V) + SAN resected (n=45**)	1) Improvement of 1y vs post-OP QOL: a=stiffness b=constriction c=appearance d=pain e=numbness f=shoulder drop g=reach above h=neck appearance 2) Improvement of 1y vs post-OP AAT	1) ns2) ns 1) ss: a, b, d, f, g,h 2) ss 1) ss: a, b, f, g, h 2) ns 1) ss: g 2) ss 1) ns 2) ss	The study demonstrated that rehabilitation, in addition to modifications to RND, contributed to the improvement.	* 308 ND in 224 pts** n = ND HNSCC (89 OSCC)cT? cN? cM?	NA	2-	

Which regional lymph nodes should be removed by tumor surgery?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
Patel 2008 [111]	Retrospective	205	SND (n=54) RND (n=151)	1) 5y-DSS 2) 5y distant control rate 3) 5y-LCR 4) ss RF for distant failure***	1) 59** 2) 91* 3) 96** 4) ECS pN classification PT site 1) 43** 2) 75* 3) 86**	Pts undergoing CND had more extensive disease. SLND can be used to effectively treat cN0+ in selected pts.	ss BLD: pN 2/3 (p=0.001), ECS (p=0.001), PT site (p=0.03) * p=0.02; ** p=0.06; *** p<0.001 CND I-V , SND I-IV HNSCC (67 OSCC) cT? cN+ cM?	SND > RND	3	
Pathak 2006 [112]	Retrospective	398	SND in pN+ (n=52) SND in pN0 (n=346)	1) RR during follow-up (38 months)	1) 5.5 2) 6	SOHND is an oncologically sound procedure for pN0-OSCC and for selected groups of low-volume pN+-OSCC in general and gingivo-buccal cancer in particular. It meets the combined goal of optimal treatment with minimal morbidity.	SOHND OSCC cT1-4 cN0-2 cM?	pN+ = pN0	2-	
Rapoport 2007 [113]	Retrospective	460	RND (n=445**) SND (n=128**)	1) RR (pN0/pN+)2) pN+ (cN0/cN+)3) LNM involvement of levels	1) 3.9 (3.1/4.3)* 2) 38.6/61.3 3) 4.7 = Ia' 16.8 = Ib 35.2 = IIa 4.9 = IIb 16.8 = III 8.3 = VI 5.4=V 1) 5.1 (4.1/10.0)* 2) 17.1/82.9	The choice of SND in levels I to IV in cases of SCC in the lower region of the mouth associated with palpable metastases at level I is feasible without loss of oncological results.	* ns** n = NDSND I - IVOSCCcT1-4 cN0-3 cM?	RND=SND I - IV	2-	
Santoro 2008 [114]	Prospective	114*	ND in cN0 (n=92**) ND in cN+ (n=56**)	1) Level IIb involvement 2) pN+ at level IIa + IIb	1) 2 2) 100*** 1) 5	The incidence of metastases at level IIb is low, also in N+ necks, therefore dissection of this level could be unnecessary in N0 necks. Furthermore, an interesting statistical association between the presence of metastases at level IIb and at level IIa was recorded.	HNSCC (47 OSCC) cT1-4 cN0/+ cM?	NA	2-	

Which regional lymph nodes should be removed by tumor surgery?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
Shepard 2010 [115]	Retrospective	156	SND (n=69) RND (n=87)	1) 5y-OS 2) 3y-LCR (ipsilateral)	1) 46* 2) 95.9** 1) 33* 2) 86**	These results demonstrate high rates of regional disease control (96%) following SND and RT in pts with LNM. In this population, performing SND with adjuvant RT in the majority of pts is supported as an effective treatment approach.	BLD (pN1-2 and ECS ss more often in CND) * p = 0.14; ** p = 0.053 SND I-IV; CND I-V HNSCC (70 OSCC) cT? cN+ cM? (DN) (stage III or IV)	SND > CND	2+	
Yu 2006 [116]	Retrospective	455	SND (n=193) RND (n=262)	1) RD 2) Median time to RD (month) 3) 5y-OS 4) 5y-DFS 5) OM by group 6) OM by T-stage (2/3/4)	1) 15.1 2) 18 3) 72.4 4) 68.4 5) 34.7 6) 25.6/40.4/43* 1) 16.4 2) 12 3) 67.1 4) 65.2 5) 32.8	SOHND compares favorably with RND for the staging and treatment of pts with OSCC and cN0	* p = 0.0001 SOHND OSCC cT? cN0 cM0 (DN)	SND > RND	2-	
Yuen 2009 [117]	Prospective	71	SND (n=36) WW (n = 35)	1) RD (nodal)2) 5y-DSS	1) 6*2) 89 1) 37* 2) 87	Observation may be an acceptable alternative to END if strictly adhering to a cancer surveillance protocol.	SOHNDsample size calc.; rand.* ssTSCCT1-2 cN0 cM? (DN)	SND>>WW*	1-	

Table 14 Key question 5

Is continuity resection of the mandible superior to wedge resection in oral cavity carcinoma?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
Abler 2005 [12]	Retrospective	152	Continuity resection (n=112) Wedge resection (n=40)	1) Relapse rate 2) Impaired wound healing	1) 24 2) 40 1) 12.5 2) 33	-pT1-pT3 >5 mm margin to mandible + bone staging negative = no bone resection - pT1-pT3 <5 mm margin to mandible + bone staging negative intraoperative periost frozen section analysis: → If negative: no bone resection. → If positive: wedge and/or ... resection - pT1-pT3: if preoperative staging for osseous infiltration is positive: continuity resection.	BLD (in procedures preserving continuity the baseline finding is generally lower, sometimes RT post op.) OSCC cT1-4 cN0/+ cM?	NA	3	KQ 1
Muscatello 2010 [118]	Retrospective	56	MM	1) RR (nodal/local) 2) 5y-DFS 3) 5y-OS	1) 10.7/8.9 2) 77.3 3) 60.7	MM allows resection in a safe tissue or to excise tumors of the FOM with a limited involvement of the alveolar periosteum. Whenever the PT is close to the mandible or when it adheres to the alveolar periosteum, MM offers the possibility to perform an oncologically sound procedure.	OSCC cT1-4 cN0-2 cM? (DN)	NA	3	
Namaki 2004 [119]	Retrospective	18	Glossectomy (n=6) MM (n=6) SM (n=6)	1) Masticatory efficiency pre-treatment vs post-treatment (12m)** 2) Eating ability pre-treatment vs post-treatment (12m)***	1) 0.58 → 1.04* 2) 4.50 → 6 1) 1.21 → 0.85 2) 6 → 4* 1) 1.19 → 0.56 2) 5 → 3*	Results of the present study suggest that the QOL of pts undergoing marginal mandibulectomy is better than those undergoing segmental mandibulectomy.	** Absorbance unit of ATP granules ***Grade measured using the questionnaire devised by Shinohara * ss (intragroup) OSCC T1-4 cN0/+ cM?	MM > SM	3	
Rogers 2004 [120]	Not cited	73	RM (n=32) SM (n=41)	1) QOL pre- → post-surgery; (mean 18m)	1) 83 → 76* (-7) 1) 78→ 62* (-16)	After SM and reconstruction using composite free tissue transfer, the UW-QOL scores were relatively good. The only difference between RM and SM was noted in the small resections without radiotherapy, and some of this was reflected in differences at baseline.	BLD * ss (intragroup) OSCC cT1-4 cN? cM? (DN)	NA	2^{++}	

Is continuity resection of the mandible superior to wedge resection in oral cavity carcinoma?										
First author	**Study type**	**Patient number**	**Groups**	**Outcome**	**Result (in %)**	**Author's conclusion**	**Comments**	**Summary**	**Evidence level**	**Cross-reference**
Mucke 2011 [11]	Retrospective	334	MM (n=116) RM (n=68) SM (n=150)	1) Bone invasion 2) Mean survival w/o bone invasion (all pts) 3) ss factors influencing OS in univariate analysis (all pts) 4) ss factors influencing OS in multivariate analysis (all pts)	1) 15.5 2) 71.6/72.9* 3) Age, extent of mandibulectomy, tumor & nodal & UICC stage, reconstruction 4) Age, tumor & nodal stage, reconstruction, recurrence 1) 50.0 1) 84.7	If bone invasion is identified histologically in a resected specimen, the prognosis is not worsened and additional surgery need not be undertaken in adequately resected margins. Although the mandible should be preserved if feasible, the choice of treatment should always provide a safe resection margin. The high rates of unsuspected bone invasion found in this study should be kept in mind in pts with OSCC close to the mandible.	* ns OSCC cT1-4 cN1-4 cM0	NA	2-	

5.2. Formulation of recommendations and formal consensus

5.2.1. Levels of evidence

The evidence-based assessments relate to the five defined key questions, by referring to the results of the 117 listed studies used to answer the said questions, as well as the studies incorporated in the SIGN guideline entitled "Diagnosis and Management of Head and Neck Cancer" [1].

Each of the studies included has been awarded an evidence level (EL) with regard to methodical quality. The evidence has been graded in the same way as in the SIGN Guideline, using the following system (Table 15):

Table 15 Levels of evidence

Grade	Description
1++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies, or good-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

http://www.sign.ac.uk/Guidelines/fulltext/50/annexb.html

The studies were largely graded as 2++ to 3. Only one study achieved an evidence level of 1-. Detailed explanations of how the individual evidence levels were awarded are provided below:

2^{++}	Prospective with n ≥ 100 and no methodical limitations (RS, OSCC ≥ 50%, etc)
2^{+}	Prospective with n ≥ 100, but methodical limitations (RS, BLD, OSCC ≤ 50%, etc)
2^{-}	Prospective with n = 21 to 99 or no information on OSCC, *or* retrospective or not cited with n ≥ 100 and no methodical limitations (RS, OSCC ≥ 50%, etc)
3	Prospective study with n ≤ 20, *or* retrospective with n ≥ 100 but methodical limitations (RS, BLD, OSCC ≤ 50%, etc), *or* retrospective with n < 100

5.2.2. Grades of recommendation

The grade of recommendation relates to the clinical assessment of the strength and applicability of the systematically recovered evidence, and is based on considered judgment. The grades of recommendation have been awarded within the scope of a structured process of consensus Aside from the underlying evidence, they also take the following aspects into account:

- Consistency of study results
- Clinical relevance of endpoints and effect sizes
- Benefit-risk ratio
- Ethical and legal obligations
- Patient preferences
- Applicability to target patient group and the German health system
- Feasibility in everyday clinical practice, particularly in the different areas of care

In short, the grades of recommendation are an expression of the certainty with which the anticipated benefit of the intervention outweighs the potential risk (net benefit) and the degree to which the expected positive outcome can be attained in the patients in question. A negative recommendation ("must not") is an expression of the certainty concerning the lack of benefit or the presence of a potential risk, respectively.

Statements/recommendations agreed by the Guideline Development Group on the basis of expert consensus (not from a systematic search or guideline adaptation) are identified as such and graded "**GCP**". No symbols have been used for the grading; the strength of the recommendation is derived implicitly from syntax (must/should/may).

Table 16 Grades of recommendation

Grade of recommendation	Description	Syntax
A	Strongly recommended	must
B	Recommended	should
0	Open recommendation	may

5.2.3. Formal process of consensus

The passages requiring consensus were discussed and within the framework of the conference.

The formal consensus-reaching process was moderated by a certified AWMF guideline advisor. The consensus conference was organized as a nominal group process, commencing with a presentation of the balance of evidence from the perspective of the experts, with subsequent discussion. Based on a handout, each group member commented on the draft recommendations, and noted any alternative suggestions. The process then entailed consecutive discussion, preliminary voting, debate/discussion, and final vote. In principle, a strong consensus (> 95%) was the goal. If consensus was lacking and agreement could not be reached even after in-depth discussion and renewed presentation of the evidence, the difference in opinion was noted against the corresponding recommendation. All consensus passages were graphically highlighted. Table 17 lists the relevant consensus scores.

Table 17 Strength of consensus

Strong consensus	> 95% of participants
Consensus	> 75% - 95%
Majority in agreement	> 50% - 75%
No consensus	< 50% of participants

5.2.4. Consensus conference

The consensus conference was held in Berlin on December 1st and 2nd, 2011, and was attended by the following participants:

Eligible to vote:

Dr J. Beck	Federal Association of Panel Dentists
Ms K. Bikowski	German Association for Social Work in Healthcare, Cancer Center
Prof. A. Burkhardt	German Society of Pathology
Prof. K. Engers	Department of Cancer Research
Prof. B. Frerich	German Society for Oral and Maxillofacial Surgery
Prof. T. Gauler	German Society for Oncology in Internal Medicine
Prof. W. Budach	German Society of Radiation Oncology
Prof. S. Ihrler	German Society of Pathology
Prof. M. Lell	Working Group Head and Neck of the German Society of Radiology
Ms W. Mantey	Patient representative
Ms R. Nusser-Müller-Busch	German Logopedia Society
Dr N. Gittler-Hebestreit	Society for Oncology Nursing and Pediatric Oncology Nursing
Prof. H. Pistner	Guideline Officer of the German Society for Oral and Maxillofacial Surgery
Prof. T. Reichert	German Society for Oral and Maxillofacial Surgery
Prof. H. Schliephake	German Society of Dental, Oral & Craniomandibular Sciences
Prof. M. Westhofen	German Society for Oto-Rhino-Laryngology
Dr S. Wirz	Working Group on Tumor Pain of the German Association for the Study of Pain
Dr M. Wittlinger	German Society of Radiation Oncology
Dr P. Boehme	German Dental Association
Prof. F. Bootz	German Society for Oto-Rhino-Laryngology
Mr H. Danker	Working Group for Psycho-Oncology of the German Cancer Society
Prof. A. Lübbe	Working Group for Supportive Care in Cancer, Rehabilitation and Social Medicine
Prof. K.-D. Wolff	German Society for Oral and Maxillofacial Surgery – guideline coordination

Moderation and guidance (not eligible to vote):

Prof. I. Kopp	Director of the Institute for Medical Information Management of the Association of the Scientific Medical Societies, Marburg (AWMF)
Dr M. Follmann, MPH, MSc	German Cancer Society (DKG) German Guideline Program in Oncology
Dr A. Sammain	Division of Evidence Based Medicine, Charité - University Medical Hospital Berlin
J. Weitz	Assistant at the Clinic for Oral & Maxillofacial Surgery, TU Munich
M. Keul	Secretary to the Clinic for Oral & Maxillofacial Surgery, TU Munich

The minutes of the voting procedure can be provided upon request by the guideline's coordinator, Prof. Wolff, Munich.

6. Quality Indicators

Quality indicators are parameters which are documented with a view to assessing the quality of underlying structures, processes and results, respectively [Ärztliches Zentrum für Qualität in der Medizin (ÄZQ), Gramsch E, Hoppe JD, Jonitz G, Köhler A, Ollenschläger G, Thomeczek C, (eds.). Kompendium Q-M-A. Qualitätsmanagement in der ambulanten Versorgung. 3rd ed. Köln: Dt. Ärzte-Verl.; 2008]. The overriding objective of their use is to continually improve health care. Quality indicators, as quality-related parameters, are therefore an important aspect of quality management. It should be remembered that individual indicators illustrate only one aspect of the complex scenario of health care provision. The selection of suitable indicators is therefore very important.

The selection of the quality indicators herein is based on the methods of the National Disease Management Guidelines (German Agency for Quality in Medicine (ÄZQ)). Quality Indicators. Manual for Authors. Berlin: ÄZQ; 2009. (äzq publications; 36). Available from: http://www.aezq.de/edocs/pdf/schriftenreihe/schriftenreihe36.pdf). All strong recommendations (recommendation grade A) served as the basis for the quality indicators, along with statements of high-level evidence (LoE 1). These recommendations and statements were translated by a methodologist into potential indicators and reviewed by the experts of the Quality Indicators Task Force in writing, on the basis of the following criteria:

1. Relevance of the indicator to the health care system: Is the procedure measured by the indicator of major importance based on a large number of cases, wide diversity of care, recognized inadequate or excessive levels of care? Can morbidity or even mortality, and quality of life respectively, be improved as a result?

2. Clarity of the definition: Is the potential indicator clearly and unambiguously defined with respect to denominator and numerator, or can the requisite definitions be clearly derived from the guideline, respectively?

3. Ability to influence the strength of the indicator: Can the parameter be influenced by the service provider?

4. Evidence and consensus base for the indicator: This criterion has not been assessed due to the fact that pre-selection took place and only strong recommendations (recommendation grade A/must) or statements of evidence level 1 were included; the evidence base for the indicator was presented for assessment.

5. Risk of disincentive: The question of whether the indicator gives rise to a risk of disincentive, which cannot be counterbalanced by an alternative indicator or other information, can be assessed here.

Indicators with at least 75% agreement under each criterion were deemed accepted. Following written assessment, methodically moderated telephone conferences were held to discuss both the accepted indicators and those indicators not accepted due to a particular criterion.

The indicators were then ultimately accepted or rejected.

The indicators are to be understood as preliminary proposals. A final assessment can only be made once data are available from the necessary pilot study.

Further information on general methodology can be found on the website of the German Guideline Program in Oncology: www.leitlinienprogramm-onkologie.de.

The indicators themselves can be found in the full and short versions of the guideline.

7. External Appraisal and Adoption

No external peer review was carried out.

The consensus-based draft guideline was presented to the boards of the professional associations for approval and was subsequently adopted.

8. Editorial Independence

Any potential conflicts of interest are disclosed in tabulated format (see COI sheets). Funding for the guideline was provided solely by the German Guideline Program in Oncology. The standardized sheets were discussed by the group, and no participant had to be excluded from the GL development process due to potential conflicts of interest. Furthermore, no areas were identified in which an abstention from voting on individual topics would have been necessary.

The literature review, assessment of the evidence and compilation of the evidence tables ensued independently at the dEBM (Division of Evidence Based Medicine, working group headed by Dr Nast, Dermatology Clinic, Charité University Medical Hospital Berlin). The clinical experts were not involved in the assessment of the evidence or compilation of the evidence tables.

All members of the Guideline Development Group disclosed in writing that there were no financial or other commercial conflicts of interest vis-a-vis third parties that could exert an influence on the content of the guideline. The guideline has been funded exclusively by the GGPO. The funds were used predominantly for the external procurement of literature and organization of the guideline development meetings (kick-off meeting, task force meetings, consensus conference). Neither the German Association of Oral & Maxillofacial Surgeons (DGMKG) nor the other actively involved professional associations, task forces or institutions received any financial reward or other means of support from commercial stakeholders for developing this S3 guideline.

Table 18 Summary of conflicts of interest

	Question	Wolff	Böhme	Erdmann	Nusser
1	Advisor, expert or paid member of the scientific board of a health care company (eg pharmaceutical industry, medical device industry), commercial contract research organization or insurance company	No	No	No	No
2	Fees for talks and training activities, or paid authorships or co-authorships on behalf of a health care company, commercial contract research organization or insurance company	Yes: Sanofi	No	No	No
3	Financial support (third-party funds) for research projects or direct financing for institute staff from a health care company, commercial contract research organization or insurance company	No	No	No	No
4	Proprietary interest in medicinal products/ medical devices (eg patent, copyright, sales license)	No	No	No	No
5	Ownership of shares, stocks, equity funds in a health care company	No	No	No	No
6	Personal relationship with any authorized representative of a health care company	No	No	No	No
7	Membership of a society/professional association involved in the development of the guideline, holder of a mandate within the scope of guideline development	DGMKG, Working Group on Maxillofacial Surgery, VHZMK, EACMFS, DÖSAK, AHMO, DGZMK, DKG, ISKH	BZÄK ZZQS	No	Not specified
8	Political, academic (eg affiliation to certain "schools"), scientific or personal interests that could give rise to potential conflicts	No	No	No	No

	Question	Pistner	Lell	Bikowski	Mantey
1	Advisor, expert or paid member of the scientific board of a health care company (eg pharmaceutical industry, medical device industry), commercial contract research organization or insurance company	Yes: Synthes	Yes: Bracco, Siemens, Bayer-Schering	No	No
2	Fees for talks and training activities, or paid authorships or co-authorships on behalf of a health care company, commercial contract research organization or insurance company	Yes: M+K Dental-implantate, Novartis	Yes: speaker Siemens, Bracco Schering	No	No
3	Financial support (third-party funds) for research projects or direct financing for institute staff from a health care company, commercial contract research organization or insurance company	Äsculap	Yes: Siemens, Bayer Schering	No	No
4	Proprietary interest in medicinal products/ medical devices (eg patent, copyright, sales license)	No	No	No	No
5	Ownership of shares, stocks, equity funds in a health care company	Fresenius Rhön-Kl., Sana- Kl.	No	No	No
6	Personal relationship with any authorized representative of a health care company	No	No	No	No
7	Membership of a society/professional association involved in the development of the guideline, holder of a mandate within the scope of guideline development	DGMKG, AGKi, DGZMK, DÖSAK	DRG	DVSG e.V.	No
8	Political, academic (eg affiliation to certain "schools"), scientific or personal interests that could give rise to potential conflicts	No	No	No	No

	Question	Burkhardt	Bootz	Nast	Schliephake
1	Advisor, expert or paid member of the scientific board of a health care company (eg pharmaceutical industry, medical device industry), commercial contract research organization or insurance company	No	No	No	No
2	Fees for talks and training activities, or paid authorships or co-authorships on behalf of a health care company, commercial contract research organization or insurance company	No	No	Yes: Janssen, Abbott, Wyeth, Pfizer	No
3	Financial support (third-party funds) for research projects or direct financing for institute staff from a health care company, commercial contract research organization or insurance company	No	No	Yes: Wyeth	No
4	Proprietary interest in medicinal products/ medical devices (eg patent, copyright, sales license)	Yes (see annex)	No	No	No
5	Ownership of shares, stocks, equity funds in a health care company	No	No	No	No
6	Personal relationship with any authorized representative of a health care company	No	No	No	No
7	Membership of a society/professional association involved in the development of the guideline, holder of a mandate within the scope of guideline development	ESoP,DGP, IAP, IAOP, AAOMFP, Working Group on Oral Pathology, IAC	General Secretary of DGHNO	DDG	DGMKG, DGZMK, VHZMK, GGI
8	Political, academic (eg affiliation to certain "schools"), scientific or personal interests that could give rise to potential conflicts	Yes: abstention from voting on "brush biopsy"	No	No	No

	Question	Westhofen	Reichert	Budach	Danker
1	Advisor, expert or paid member of the scientific board of a health care company (eg pharmaceutical industry, medical device industry), commercial contract research organization or insurance company	No	No	Merck	No
2	Fees for talks and training activities, or paid authorships or co-authorships on behalf of a health care company, commercial contract research organization or insurance company	Merck	No	Merck	Pfizer
3	Financial support (third-party funds) for research projects or direct financing for institute staff from a health care company, commercial contract research organization or insurance company	No	No	Merck	No
4	Proprietary interest in medicinal products/ medical devices (eg patent, copyright, sales license)	No	No	No	No
5	Ownership of shares, stocks, equity funds in a health care company	No	No	No	No
6	Personal relationship with any authorized representative of a health care company	No	No	No	No
7	Membership of a society/professional association involved in the development of the guideline, holder of a mandate within the scope of guideline development	DGHNO, BVHNO	No	DEGRO, German Society for Radiotherapy, ESTRO, ASTRO, ASCO, ARO	DKG, AGPSO
8	Political, academic (eg affiliation to certain "schools"), scientific or personal interests that could give rise to potential conflicts	No	No	No	No

	Question	Weis	Sammain	Rosumeck	Engers
1	Advisor, expert or paid member of the scientific board of a health care company (eg pharmaceutical industry, medical device industry), commercial contract research organization or insurance company	Not specified	No	No	No
2	Fees for talks and training activities, or paid authorships or co-authorships on behalf of a health care company, commercial contract research organization or insurance company	Not specified	No	No	No
3	Financial support (third-party funds) for research projects or direct financing for institute staff from a health care company, commercial contract research organization or insurance company	Not specified	No	No	No
4	Proprietary interest in medicinal products/ medical devices (eg patent, copyright, sales license)	Not specified	No	No	No
5	Ownership of shares, stocks, equity funds in a health care company	Not specified	No	No	No
6	Personal relationship with any authorized representative of a health care company	Not specified	No	No	No
7	Membership of a society/professional association involved in the development of the guideline, holder of a mandate within the scope of guideline development	Not specified	No	No	German Pathology Society, DKG
8	Political, academic (eg affiliation to certain "schools"), scientific or personal interests that could give rise to potential conflicts	Not specified	No	No	No

	Question	Frerich	Gauler	Lübbe	Beck
1	Advisor, expert or paid member of the scientific board of a health care company (eg pharmaceutical industry, medical device industry), commercial contract research organization or insurance company	Yes: Sanofi (2010)	Yes: Amgen, Merck, Boehringer, Lilly, Genmab, Roche, Novartis	No	No
2	Fees for talks and training activities, or paid authorships or co-authorships on behalf of a health care company, commercial contract research organization or insurance company	No	Yes: Amgen, Merck, Boehringer, Novartis, GSH, Bayer, Sanofi, Pfizer, Wyeth, Roche, Astra	No	No
3	Financial support (third-party funds) for research projects or direct financing for institute staff from a health care company, commercial contract research organization or insurance company	Yes (Astratech)	No	No	No
4	Proprietary interest in medicinal products/ medical devices (eg patent, copyright, sales license)	Yes (bioreactors)	No	No	No
5	Ownership of shares, stocks, equity funds in a health care company	Yes (Novatissue GmbH)	Yes: Bayer	No	No
6	Personal relationship with any authorized representative of a health care company	No	No	No	No
7	Membership of a society/professional association involved in the development of the guideline, holder of a mandate within the scope of guideline development	DGMKG DÖSAK	ESMO, DKG, AIO, IASLC	ASORS, DKG	KZBV
8	Political, academic (eg affiliation to certain "schools"), scientific or personal interests that could give rise to potential conflicts	No	No	No	No

	Question	Werner	Pathirana	Wittlinger	Gauler
1	Advisor, expert or paid member of the scientific board of a health care company (eg pharmaceutical industry, medical device industry), commercial contract research organization or insurance company	Yes: Sanofi, Morita, Merck	No	No	Not specified
2	Fees for talks and training activities, or paid authorships or co-authorships on behalf of a health care company, commercial contract research organization or insurance company	Yes: Morita, Merck, Storz	Yes: Pfizer	No	Not specified
3	Financial support (third-party funds) for research projects or direct financing for institute staff from a health care company, commercial contract research organization or insurance company	Morita, Cochlear, Storz	No	No	Not specified
4	Proprietary interest in medicinal products/ medical devices (eg patent, copyright, sales license)	Patent: ozone/oxygene mixture	No	No	Not specified
5	Ownership of shares, stocks, equity funds in a health care company	No	No	No	Not specified
6	Personal relationship with any authorized representative of a health care company	No	No	No	Not specified
7	Membership of a society/professional association involved in the development of the guideline, holder of a mandate within the scope of guideline development	DGHNO	DDG	Not specified	Not specified
8	Political, academic (eg affiliation to certain "schools"), scientific or personal interests that could give rise to potential conflicts	No	No	Not specified	Not specified

	Question	Gittler-Hebe-steit	Grötz	Horch	Ihrler
1	Advisor, expert or paid member of the scientific board of a health care company (eg pharmaceutical industry, medical device industry), commercial contract research organization or insurance company	No	No	Yes: KCI	No
2	Fees for talks and training activities, or paid authorships or co-authorships on behalf of a health care company, commercial contract research organization or insurance company	No	Yes: Amgen, Artoss, Astra, Camlog, Geistlich, Mectron, Medupdate, MIP, Novartis, Nobel, Riemser, Roche, Straumann, Zepf	Yes: KCI	No
3	Financial support (third-party funds) for research projects or direct financing for institute staff from a health care company, commercial contract research organization or insurance company	No	No	Yes: Baxter AG, KCI	No
4	Proprietary interest in medicinal products/ medical devices (eg patent, copyright, sales license)	No	No	No	No
5	Ownership of shares, stocks, equity funds in a health care company	No	No	No	No
6	Personal relationship with any authorized representative of a health care company	No	No	No	No
7	Membership of a society/professional association involved in the development of the guideline, holder of a mandate within the scope of guideline development	No	ASORS, DEGRO, DKG, DGZMK, DGMKG	Not specified	Not specified
8	Political, academic (eg affiliation to certain "schools"), scientific or personal interests that could give rise to potential conflicts	No	No	Not specified	Not specified

	Question	Paradies	Schmitter	Wirz
1	Advisor, expert or paid member of the scientific board of a health care company (eg pharmaceutical industry, medical device industry), commercial contract research organization or insurance company	No	No	No
2	Fees for talks and training activities, or paid authorships or co-authorships on behalf of a health care company, commercial contract research organization or insurance company	No	No	Yes: Mundipharma, Cephalean, Grünenthal, Silly, Dr. Kode, Pfizer
3	Financial support (third-party funds) for research projects or direct financing for institute staff from a health care company, commercial contract research organization or insurance company	No	Yes: 3M Sirona	No
4	Proprietary interest in medicinal products/ medical devices (eg patent, copyright, sales license)	No	No	No
5	Ownership of shares, stocks, equity funds in a health care company	No	No	No
6	Personal relationship with any authorized representative of a health care company	No	No	No
7	Membership of a society/professional association involved in the development of the guideline, holder of a mandate within the scope of guideline development	Not specified	Not specified	Not specified
8	Political, academic (eg affiliation to certain "schools"), scientific or personal interests that could give rise to potential conflicts	Not specified	Not specified	Not specified

9. Distribution and Implementation

The distribution and implementation strategy comprises the following activities:

- Publication as a "set of guidelines" (full version + short version + patient version + guideline report)
- Publication of the short version in the German Medical Journal [*Deutsches Ärzteblatt*] http://www.aerzteblatt.de/int/archive/article/132920
- Distribution via publishing bodies and congresses of collaborative professional associations and organizations; press conferences
- Circulation of information to joint self-governing bodies and professional organizations
- Development of quality indicators and establishment of such in the documentation sheets/key performance sheets of certified centers

Implementation of the GL will be facilitated and ensured not only by publication in medical journals or on the Internet, but also by systematically targeting the relevant users. This will be achieved by circulating the content at trade congresses, training events for physicians and patient information events, as well as by incorporating the GL in the Intranet systems of the relevant clinics and hospitals. To guarantee that the GL is immediately on hand when consulting with a patient, particular importance shall be placed on providing all potential users with advanced and continuing professional training. The advanced dental training workshops which are held regularly on a regional and national level provide the perfect basis for such a purpose; certified medical training with the award of training credits would also be possible to this end. The following strategies have been instigated and shall be supported by the Guideline Development Group for launching the guideline:

- Dissemination by means of free Internet access at the addresses listed under 1.2
- Printing and publishing in dentistry journals and the German *Zahnärztliche Mitteilungen* dental journal
- Publication as a brochure for dental practitioners and leaflet for patients
- Public relations: press releases
- Trials using quality circles (with systematic support and evaluation by the ZZQ (Agency for Quality in Dentistry); the project is currently in the planning stage and will be conducted in the fall of 2006 by quality circles in Hamburg)

- Continuing education, especially via the training programs of the Dental Association, lectures by authors of the guideline, and personal interactive teaching

10. Period of Validity

This S3 Guideline, "Diagnosis and Management of Carcinoma of the Oral Cavity", is valid until December 21, 2015.

Any emerging data that could necessitate revision of individual sections or recommendations shall be monitored by the Guideline Development Group. Readers are invited to forward any appropriate information to the persons listed below.

The date of publication, announcement of scheduled revisions, and any interim updates (amendments), will be disclosed in the publicly accessible registry of guidelines of the AWMF (http://www.awmf-leitlinien.de). Only the very latest version as stated in the AWMF Registry is valid.

The Chairman of the DGMKG should be contacted with regard to updating the Guideline.

11. References

1. Scottish Intercollegiate Guidelines Network, *Diagnosis and management of head and neck cancer. A national clinical guideline.* . 2006.
2. Canadian Partnership Against Cancer. *Search SAGE (Standards and Guidelines Evidence). Detailed Result - Diagnosis and management of head and neck cancer. A national clinical guideline.* 2011 15.05.2012]; Available from: http://www.cancerview.ca/.
3. Alvarez Amezaga, J., et al., *Diagnostic efficacy of sentinel node biopsy in oral squamous cell carcinoma. Cohort study and meta-analysis.* Medicina Oral, Patologia Oral y Cirugia Bucal, 2007. **12**(3): p. E235-43.
4. O'Neill, J.P., et al., *Controversies in the management of tongue base cancer.* Irish Journal of Medical Science, 2009. **178**(1): p. 1-5.
5. Hoft, S., et al., *Sentinel lymph-node biopsy in head and neck cancer.* Br J Cancer, 2004. **91**(1): p. 124-8.
6. Hyde, N.C., et al., *A new approach to pre-treatment assessment of the N0 neck in oral squamous cell carcinoma: the role of sentinel node biopsy and positron emission tomography.* Oral Oncol, 2003. **39**(4): p. 350-60.
7. Kontio, R., et al., *Sentinel lymph node biopsy in oral cavity squamous cell carcinoma without clinically evident metastasis.* Head Neck, 2004. **26**(1): p. 16-21.
8. Ross, G.L., et al., *Improved staging of cervical metastases in clinically node-negative patients with head and neck squamous cell carcinoma.* Ann Surg Oncol, 2004. **11**(2): p. 213-8.
9. Hafidh, M.A., et al., *Evaluation of the impact of addition of PET to CT and MR scanning in the staging of patients with head and neck carcinomas.* Eur Arch Otorhinolaryngol, 2006. **263**(9): p. 853-9.
10. Wax, M.K., et al., *The role of positron emission tomography in the evaluation of the N-positive neck.* Otolaryngol Head Neck Surg, 2003. **129**(3): p. 163-7.
11. Mucke, T., et al., *The role of tumor invasion into the mandible of oral squamous cell carcinoma.* J Cancer Res Clin Oncol, 2011. **137**(1): p. 165-71.
12. Abler, A., M. Roser, and D. Weingart, *[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.
13. Babin, E., et al., *PET/CT for assessing mandibular invasion by intraoral squamous cell carcinomas.* Clinical Otolaryngology, 2008. **33**(1): p. 47-51.
14. Baek, C.-H., 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.
15. Bolzoni, A., 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.
16. Brockenbrough, J.M., G.J. Petruzzelli, and L. Lomasney, *DentaScan as an accurate method of predicting mandibular invasion in patients with squamous cell carcinoma of the oral cavity.* Archives of Otolaryngology -- Head & Neck Surgery, 2003. **129**(1): p. 113-7.
17. Dammann, F., 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.
18. Ekberg, T., et al., *Clinical impact of positron emission tomography (PET) with (18F)fluorodeoxyglucose (FDG) in head and neck tumours.* Acta Oto-Laryngologica, 2007. **127**(2): p. 186-93.
19. Goerres, G.W., et al., *Impact of whole body positron emission tomography on initial staging and therapy in patients with squamous cell carcinoma of the oral cavity.* Oral Oncology, 2003. **39**(6): p. 547-51.
20. Goerres, G.W., et al., *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.
21. Vidiri, A., 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.
22. Hendrikx, A.W.F., et al., *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.
23. Imaizumi, A., 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.
24. Jones, J., et al., *Positron emission tomography (PET) in the management of oro-pharyngeal cancer.* European Journal of Surgical Oncology, 2005. **31**(2): p. 170-6.
25. Krabbe, C.A., 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.
26. Nakamoto, Y., 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.
27. Ng, S.-H., 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.
28. Nishiyama, Y., et al., *FDG PET as a procedure for detecting simultaneous tumours in head and neck cancer patients.* Nuclear Medicine Communications, 2005. **26**(3): p. 239-44.
29. Pauleit, D., 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.
30. Pentenero, M., et al., *Accuracy of 18F-FDG-PET/CT for staging of oral squamous cell carcinoma.* Head & Neck, 2008. **30**(11): p. 1488-96.
31. Rajesh, A., et al., *Can magnetic resonance imaging replace single photon computed tomography and computed tomography in detecting bony invasion in patients with oral squamous cell carcinoma?* British Journal of Oral & Maxillofacial Surgery, 2008. **46**(1): p. 11-4.
32. Roh, J.-L., 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.
33. Seitz, O., 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.
34. Van Cann, E.M., 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.
35. Vidiri, A., 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.
36. Wallowy, P., et al., *18F-FDG PET for detecting metastases and synchronous primary malignancies in patients with oral and oropharyngeal cancer.* Nuclear-Medizin, 2009. **48**(5): p. 192-9; quiz N42.
37. Wiener, E., et al., *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.
38. Bisase, B., C. Kerawala, and J. Lee, *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.
39. Chow, T.-L., et al., *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.
40. Fielding, D., et al., *Autofluorescence improves pretreatment mucosal assessment in head and neck cancer patients.* Otolaryngology - Head & Neck Surgery, 2010. **142**(3 Suppl 1): p. S20-6.
41. Ghosh, S.K., 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.

42. Keith, D.J.W., T.K. Ong, and I.C. Martin, *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.
43. Kesting, M.R., 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.
44. Kesting, M.R., 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.
45. Krabbe, C.A., et al., *FDG-PET and detection of distant metastases and simultaneous tumors in head and neck squamous cell carcinoma: a comparison with chest radiography and chest CT.* Oral Oncology, 2009. **45**(3): p. 234-40.
46. Lee, C.T., 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.
47. Loh, K.S., et al., *A rational approach to pulmonary screening in newly diagnosed head and neck cancer.* Head & Neck, 2005. **27**(11): p. 990-4.
48. Takenaka, R., 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.
49. Brouwer, J., et al., *Screening for distant metastases in patients with head and neck cancer: is there a role for (18)FDG-PET?* Oral Oncology, 2006. **42**(3): p. 275-80.
50. Balogova, S., 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.
51. Barzan, L., et al., *An extended use of the sentinel node in head and neck squamous cell carcinoma: results of a prospective study of 100 patients.* Acta Otorhinolaryngologica Italica, 2004. **24**(3): p. 145-9.
52. Bilde, A., et al., *The role of SPECT-CT in the lymphoscintigraphic identification of sentinel nodes in patients with oral cancer.* Acta Oto-Laryngologica, 2006. **126**(10): p. 1096-103.
53. Borgemeester, M.C., 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.
54. Brouwer, J., et al., *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.
55. Burcia, V., et al., *Neck restaging with sentinel node biopsy in T1-T2N0 oral and oropharyngeal cancer: Why and how?* Otolaryngology - Head & Neck Surgery, 2010. **142**(4): p. 592-7.e1.
56. Burns, P., et al., *Sentinel lymph node biopsy in node-negative squamous cell carcinoma of the oral cavity and oropharynx.* Journal of Laryngology & Otology, 2009. **123**(4): p. 439-43.
57. Cammilleri, S., et al., *Ability of lymphoscintigraphy to direct sentinel node biopsy in the clinically NO check for patients with head and neck squamous cell carcinoma; a prospective study (preliminary results).* Bulletin du Cancer, 2004. **91**(4): p. E1-4.
58. Chone, C.T., et al., *Predictive value of sentinel node biopsy in head and neck cancer.* Acta Oto-Laryngologica, 2008. **128**(8): p. 920-4.
59. Civantos, F.J., et al., *Sentinel node biopsy in oral cavity cancer: correlation with PET scan and immunohistochemistry.* Head & Neck, 2003. **25**(1): p. 1-9.
60. Civantos, F.J., et al., *Sentinel lymph node biopsy accurately stages the regional lymph nodes for T1-T2 oral squamous cell carcinomas: results of a prospective multi-institutional trial.* Journal of Clinical Oncology, 2010. **28**(8): p. 1395-400.
61. De Zinis, L.O.R., et al., *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.
62. Dirix, P., et al., *Diffusion-weighted MRI for nodal staging of head and neck squamous cell carcinoma: impact on radiotherapy planning.* International Journal of Radiation Oncology, Biology, Physics, 2010. **76**(3): p. 761-6.

63. Freire, A.R.S., et al., *Computed tomography and lymphoscintigraphy to identify lymph node metastases and lymphatic drainage pathways in oral and oropharyngeal squamous cell carcinomas.* European Archives of Oto-Rhino-Laryngology, 2003. **260**(3): p. 148-52.
64. Gencoglu, U., et al., *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.
65. Haerle, S.K., et al., *Is there an additional value of SPECT/CT over planar lymphoscintigraphy for sentinel node mapping in oral/oropharyngeal squamous cell carcinoma?* Annals of Surgical Oncology, 2009. **16**(11): p. 3118-24.
66. Hohlweg-Majert, B., et al., *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.
67. Jeong, H.-S., 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.
68. Jeong, H.S., 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.
69. Keski-Santti, H., et al., *Sentinel lymph node biopsy as an alternative to wait and see policy in patients with small T1 oral cavity squamous cell carcinoma.* Acta Oto-Laryngologica, 2008. **128**(1): p. 98-102.
70. Keski-Santti, H., et al., *Sentinel lymph node biopsy or elective neck dissection for patients with oral squamous cell carcinoma?* European Archives of Oto-Rhino-Laryngology, 2008. **265 (SUPPL. 1)**: p. S13-S17.
71. Khafif, A., et al., *Lymphoscintigraphy for sentinel node mapping using a hybrid single photon emission CT (SPECT)/CT system in oral cavity squamous cell carcinoma.* Head & Neck, 2006. **28**(10): p. 874-9.
72. Kim, S.Y., 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.
73. Kovacs, A.F., et al., *Positron emission tomography in combination with sentinel node biopsy reduces the rate of elective neck dissections in the treatment of oral and oropharyngeal cancer.* Journal of Clinical Oncology, 2004. **22**(19): p. 3973-80.
74. Krabbe, C.A., et al., *Detection of cervical metastases with (11)C-tyrosine PET in patients with squamous cell carcinoma of the oral cavity or oropharynx: A comparison with (18)F-FDG PET.* Head & Neck, 2010. **32**(3): p. 368-74.
75. Lee, B.-J., et al., *Usefulness of technetium-99m methoxyisobutylisonitrile single-photon emission computed tomography and computed tomography in the evaluation of cervical lymph node metastasis.* Journal of Laryngology & Otology, 2005. **119**(11): p. 882-7.
76. Nahmias, C., 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.
77. Ng, S.-H., 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.
78. Nieuwenhuis, E.J.C., et al., *Histopathologic validation of the sentinel node concept in oral and oropharyngeal squamous cell carcinoma.* Head & Neck, 2005. **27**(2): p. 150-8.
79. Payoux, P., et al., *Effectiveness of lymphoscintigraphic sentinel node detection for cervical staging of patients with squamous cell carcinoma of the head and neck.* Journal of Oral & Maxillofacial Surgery, 2005. **63**(8): p. 1091-5.
80. Piao, Y., 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.
81. Santaolalla, F., et al., *Comparative study of patients with and without sentinel lymph node biopsy (SLNB) in oral and oropharyngeal cancer: is SLNB an accurate and useful procedure?* Acta Oto-Laryngologica, 2009. **129**(2): p. 199-204.

82. Schoder, H., et al., *18F-FDG PET/CT for detecting nodal metastases in patients with oral cancer staged N0 by clinical examination and CT/MRI.* Journal of Nuclear Medicine, 2006. **47**(5): p. 755-62.
83. Schroeder, U., 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.
84. Schwartz, D.L., 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.
85. Stoeckli, S.J., *Sentinel node biopsy for oral and oropharyngeal squamous cell carcinoma of the head and neck.* Laryngoscope, 2007. **117**(9): p. 1539-51.
86. Sumi, M., et al., *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.
87. Thomsen, J.B., et al., *Staging N0 oral cancer: lymphoscintigraphy and conventional imaging.* Acta Radiologica, 2005. **46**(5): p. 492-6.
88. Thomsen, J.B., et al., *Sentinel lymph node biopsy in oral cancer: validation of technique and clinical implications of added oblique planar lymphoscintigraphy and/or tomography.* Acta Radiologica, 2005. **46**(6): p. 569-75.
89. To, E.W.H., 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.
90. Tuli, H.S., et al., *Diagnostic accuracy of 99mTc-MIBI-SPECT in the detection of lymph node metastases in patients with carcinoma of the tongue: comparison with computed tomography and MRI.* Nuclear Medicine Communications, 2008. **29**(9): p. 803-8.
91. Wensing, B.M., 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.
92. Yamane, M., et al., *Noninvasive quantitative assessment of oral tongue cancer by intraoral ultrasonography.* Head & Neck, 2007. **29**(4): p. 307-14.
93. Yamazaki, Y., 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.
94. Yen, T.-C., 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.
95. Akhtar, S., M. Ikram, and S. Ghaffar, *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.
96. Batstone, M.D., et al., *Marginal mandibular nerve injury during neck dissection and its impact on patient perception of appearance.* Head & Neck, 2009. **31**(5): p. 673-8.
97. Corlette, T.H., et al., *Neck dissection of level IIb: is it really necessary?* Laryngoscope, 2005. **115**(9): p. 1624-6.
98. D'Cruz, A.K., 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.
99. Elsheikh, M.N., M.E. Mahfouz, and E. Elsheikh, *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.
100. Huang, S.-F., 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.
101. Inoue, H., et al., *Quality of life after neck dissection.* Archives of Otolaryngology -- Head & Neck Surgery, 2006. **132**(6): p. 662-6.
102. Iype, E.M., et al., *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.
103. Jin, W.L., et al., *Occult cervical lymph node metastases in 100 consecutive patients with cN0 tongue cancer.* Chinese Medical Journal, 2008. **121 (19)**: p. 1871-1874.

104. Kohler, H.F., I.W.d. Cunha, and L.P. Kowalski, *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.
105. Koo, B.S., et al., *Management of contralateral N0 neck in oral cavity squamous cell carcinoma.* Head & Neck, 2006. **28**(10): p. 896-901.
106. Laverick, S., et al., *The Impact of Neck Dissection on Health-Related Quality of Life.* Archives of Otolaryngology - Head and Neck Surgery, 2004. **130 (2)**: p. 149-154.
107. Liaw, G.-A., 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.
108. Lim, Y.C., et al., *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.
109. Mourouzis, C., C. Pratt, and P.A. Brennan, *Squamous cell carcinoma of the maxillary gingiva, alveolus, and hard palate: is there a need for elective neck dissection?* British Journal of Oral & Maxillofacial Surgery, 2010. **48**(5): p. 345-8.
110. Nibu, K.-i., et al., *Quality of life after neck dissection: a multicenter longitudinal study by the Japanese Clinical Study Group on Standardization of Treatment for Lymph Node Metastasis of Head and Neck Cancer.* International Journal of Clinical Oncology, 2010. **15**(1): p. 33-8.
111. Patel, R.S., et al., *Effectiveness of selective neck dissection in the treatment of the clinically positive neck.* Head & Neck, 2008. **30**(9): p. 1231-6.
112. Pathak, K.A., et al., *Selective neck dissection (I-III) for node negative and node positive necks.* Oral Oncology, 2006. **42 (8)**: p. 837-841.
113. Rapoport, A., 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.
114. Santoro, R., et al., *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.
115. Shepard, P.M., et al., *Therapeutic selective neck dissection outcomes.* Otolaryngology - Head & Neck Surgery, 2010. **142**(5): p. 741-6.
116. Yu, S., et al., *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.
117. Yuen, A.P.-W., 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.
118. Muscatello, L., et al., *Marginal mandibulectomy in oral cancer surgery: A 13-year experience.* European Archives of Oto-Rhino-Laryngology, 2010. **267 (5)**: p. 759-764.
119. Namaki, S., et al., *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.
120. Rogers, S.N., et al., *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.

12. Annexes

12.1. Literature evaluation sheet

Diagnostic studies

HEADINGS	DESCRIPTION
Bibliographic citation	Use Vancouver style (Authors. Title. Journal name. Publication date; volume (issue):page numbers) Insert the link to the publication.
Sources of funding and competing interest	Report: ➢ The source of funding cited in the paper: give name(s) of organisation or corporation. Specify if possible the source type (public research funds, NGO, government, academic/university healthcare industry or other) ➢ Competing interests: Write “Stated” or “Not stated” and specify if any
Setting	Multicenter, country(ies), healthcare setting
Objective(s) of the study	Report, as cited by author(s), the objective(s) of the study including both primary and secondary aims, if applicable.
Questions addressed	Mention the questions really addressed (eg include all questions even if only one is relevant for you at the moment, do not report questions planned to be addressed but on which no results are included) in the study including the following elements: ➢ Accuracy (comparison with a reference standard test) ➢ Reproducibility ➢ Cut-off determination ➢ Comparison of two or more tests
METHODS	
Study design (cited by author or actual)	Specify the study design: prospective study, randomized study, cross-sectional study, retrospective study, cohort study, case control study, other. Precise if it’s the design cited by author(s).
Reference standard test	Describe the reference standard test: ➢ What (including the provider’s name if applicable), by whom and how, when ➢ Cut-offs, categories of results ➢ Blinding (investigator) to clinical information and/or to index test results,

	if applicable
Diagnostic test(s) evaluated	Describe the evaluated test(s): ➢ What (including the provider's name if applicable), by whom and how, when ➢ Cut-offs, categories of results ➢ Blinding (investigator) to clinical information and/or to index test results, if applicable
Time interval and treatment(s) administered between the test	Specify if any
Investigator(s) and assessor(s) training	Report the number, training and expertise of the people executing (investigators) and reading the evaluated test(s) and the reference standard test(s) (assessors)
Study population expected	Describe the: ➢ Aimed eligibility criteria (i.e. inclusion-exclusion criteria, stage/characteristics of the disease) ➢ Prevalence estimation of the disease in the general population ➢ Previous test(s) and/or treatment(s) undertaken
RESULTS	
Numbers	Report: ➢ Number of patients needed, involved and analysed ➢ Number of patients excluded and reasons (i.e. non-interpretable test(s) results, incomplete or missing data)
Patients and disease characteristics	Describe the actual population involved in the study: ➢ Patients: gender, age, risk factors,… ➢ Disease characteristics ➢ Include the prevalence estimation of the disease in the study population
Accuracy	Give all available figures (including sub-group figures) with 95% confidence intervals when available: ➢ Sensitivity (Se) ➢ Specificity (Sp) ➢ Positive Predictive Value (PPV) ➢ Negative Predictive Value (NPV) ➢ Likelihood ratios (LR+, LR-)

	➢ Area under the ROC curve
Reproducibility	Give all available figures with 95% confidence intervals when available: ➢ Quantitative test: o Number of repetitions of the evaluated test o Extent of values tested o Bland & Altman agreement method o Intraclass correlation coefficient ➢ Qualitative test: o Inter-rater reliability o Test-retest reliability o Correlation coefficient
Cut-off determination	Threshold tested, if any. Precise Se and Sp values corresponding to the cut-off selected
Comparison of two or more tests	➢ Quantitative test: report the area under the ROC curve ➢ Qualitative test: report percentage comparison: IC, p values
Adverse effects	Describe adverse effects as reported in the paper, if any: from performing tests, related to participants to the tests or related to the results of the tests
CRITICAL APPRAISAL OF THE STUDY QUALITY	
Authors conclusion	Report the authors' conclusion
Results validity	Discuss the validity of the results and potential bias present: ➢ Internal validity: study design, sample size, blinding, appropriateness of the reference standard test as a gold standard, limitations of the reference standard test (i.e. incomplete reference standard test), interpretation of the results (taking into account the study hypotheses), comment on patients lost to follow-up (if applicable), use of inappropriate statistical analysis, etc. ➢ External validity: setting, population involved, test used, etc. General comments, including own conclusion of the reviewer, if possible.
Other & addendum	Further calculations made by the reviewer

Intervention studies

HEADINGS	DESCRIPTION
Bibliographic citation	Use Vancouver style (Authors. Title. Journal name. Publication date; volume (issue):page numbers) Insert the link to the publication.
Sources of funding and competing interest	Report: ➢ The source of funding cited in the paper: give name(s) of organisation or corporation. Specify if possible the source type (public research funds, NGO, government, academic/university healthcare industry or other) ➢ Competing interests: Write "Stated" or "Not stated" and specify if any
Setting	Number of centres, countries involved, healthcare setting, urban/rural/mixed
METHODS	
Study design (cited by author or actual)	Specify the study design: prospective study, randomized study, cross-sectional study, retrospective study, cohort study, case control study, other. Precise if it's the design cited by author(s).
Eligibility criteria	State the inclusion and exclusion criteria cited in the paper.
Interventions	Precise details of the interventions for each group (including dose, length, regimen and timing when relevant)
Primary outcome measure	State primary outcome measure identified by author(s), usually the one used for sample size calculation
Secondary outcome measure(s)	State secondary outcome measures identified by the author(s)
Sample size	Give the number of patients needed (= the calculated before protocol) as cited (described) by the author(s) (should clearly report if it is numbers by group or not)
Randomisation method	Describe the randomisation method and the blinding method, if relevant (as cited by authors)
RESULTS	
Numbers	Give the number of patients involved in each group as described by the author(s) Give the number of patients analysed by group as described by the author(s), in particular in the intention to treat analysis in comparative studies

Study duration	Start and end dates of the study (precise if includes follow-up or not), precise inclusion and follow-up periods (length rather than dates)
Patient characteristics and group comparability	Describe baseline characteristics cited in the paper (precise if it is on involved and/or analysed numbers) Highlight discrepancies between groups (.i.e involved and analysed)
Effect size – primary outcome	Summary of the primary outcome in each and between groups: effect size and its precision (mean or percentage, p -value, CI: if one or another not reported precise that it is not cited)
Effect size – secondary outcome(s)	Summary of the secondary outcome(s) in each and between groups: effect size and its precision (mean or percentage, p value, CI: if one or another not reported precise that it is not cited)
Harms (adverse events)	Define and describe observed harms per group as reported in the paper. Specify mean(s) or percentage(s) and p value(s), if available.
CRITICAL APPRAISAL OF THE STUDY QUALITY	
Authors conclusion	Report the authors' conclusion
Results validity	Detailed comments on: ➢ External validity: setting, inclusion/exclusion criteria, interventions, etc. ➢ Internal validity: sample size (alpha and beta used for calculation), randomisation and blinding, use of inappropriate statistical analysis, group comparability at baseline, etc. General comments (including own conclusion of the reviewer if possible)
Other & addendum	Further calculations made by the reviewer (NNT, RR, OR, CI, ..)