Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2018-B-208 Pembrolizumab

Stand: November 2018

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Pembrolizumab

als Monotherapie oder in Kombination mit Platin und 5-Fluorouracil zur Behandlung von erwachsenen Patienten mit rezidivierendem oder metastasierendem Plattenepithelkarzinom der Kopf-Hals-Region

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe „Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	*Operation (in Kombination mit Chemotherapie)* *Strahlentherapie (auch in Kombination mit Chemotherapie als Radiochemotherapie)*
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	*Es liegen keine Beschlüsse vor.*
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe „systematische Literaturrecherche“*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Pembrolizumab	Zugelassenes Anwendungsgebiet: KEYTRUDA ist **als Monotherapie** oder in Kombination mit Platin- und 5-Fluorouracil (5-FU)-Chemotherapie zur Erstlinienbehandlung des metastasierenden oder nicht resezierbaren rezidivierenden Plattenepithelkarzinoms der Kopf-Hals-Region (HNSCC) bei Erwachsenen mit PD-L1-exprimierenden Tumoren (Combined Positive Score [CPS] ≥ 1) angezeigt.
Cetuximab L01XC06 Erbitux®	Erbitux ist indiziert zur Behandlung von Patienten mit Plattenepithelkarzinom im Kopf-und Halsbereich • in Kombination mit einer Strahlentherapie für eine lokal fortgeschrittene Erkrankung, • in Kombination mit einer platin-basierten Chemotherapie für eine rezidivierende und/oder metastasierende Erkrankung. Abschnitt 4.2: Plattenepithelkarzinome des Kopf-Hals-Bereiches Bei Patienten mit rezidivierendem und/oder metastasierendem Plattenepithelkarzinom im Kopf- und Halsbereich wird Cetuximab in Kombination mit einer platin-basierten Chemotherapie angewendet, gefolgt von Cetuximab als Erhaltungstherapie bis zur Progression der Erkrankung.
Methotrexat L01BA01 z.B. Methotrexat medac	Karzinome im Kopf-Hals-Bereich zur palliativen Monotherapie im metastasierten Stadium oder bei Rezidiven
Cisplatin L01XA01 z.B. Cisplatin Teva®	Cisplatin Teva® wird angewendet zur Behandlung des: […] – fortgeschrittenen oder metastasierten Plattenepithelkarzinoms im Kopf- und Halsbereich […] Cisplatin kann als Mono- oder Kombinationstherapie angewendet werden.

Carboplatin L01XA02 Carboplatin onkovis	Carboplatin onkovis Infusionslösung ist allein oder in Kombination mit anderen anti-neoplastisch wirksamen Medikamenten bei der Behandlung folgender maligner Geschwülste angezeigt: […] – Plattenepithelkarzinome des Kopf-Hals-Bereiches.
Docetaxel L01CD02 z.B. Docetaxel Hospira	Docetaxel Hospira ist in Kombination mit Cisplatin und 5-Fluorouracil für die Induktionstherapie von Patienten mit lokal fortgeschrittenem Plattenepithelkarzinom im Kopf-Hals-Bereich angezeigt.
Bleomycin L01DC01 z.B. Bleomycin-Teva	Bleomycin wird fast immer in Kombination mit anderen Zytostatika und/oder einer Strahlentherapie verabreicht. Bleomycin ist indiziert für die Behandlung von: – Plattenepithelkarzinomen (SCC) von Kopf und Hals, […]
5-Fluorouracil L01BC02 z.B. Fluorouracil Accord	4.1. Anwendungsgebiete: […] – bei der Behandlung von lokal rezidivierendem oder metastasiertem Plattenepithelkarzinom des Kopfes und Halses. 4.2 Dosierung, Art und Dauer der Anwendung: […] – Karzinome des Kopfes und des Halses: Fluorouracil wird vorzugsweise in Kombination mit Cisplatin oder Carboplatin verwendet.
Mitomycin L01DC03 z.B. Mitomycin medac	Mitomycin wird in der palliativen Tumortherapie eingesetzt. Die intravenöse Anwendung von Mitomycin ist in der Monochemotherapie oder in kombinierter zytostatischer Chemotherapie bei Erwachsenen mit folgenden Erkrankungen angezeigt: […] • fortgeschrittene Kopf-Hals-Tumoren

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Inhaltsverzeichnis

Abkürzungsverzeichnis

5-FU	5-Fluorouracil
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Radiation Oncology
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BSC	Best supportive care
CCRT	Concurrent chemoradiotherapy
dCRT	definitive chemoradiotherapy
DFS	Disease Free Survival
dsg	Disease Site Group
EBS	evidence-based series
EGFR	Epidermal growth factor receptor
G-BA	Gemeinsamer Bundesausschuss
GE	gastroesophageal
GIN	Guidelines International Network
GoR	Grade of Recommendations
GURU	Guideline Resource Unit
HNSCC	squamous cell carcinoma of the head and neck
HR	Hazard Ratio
ICT	Induction chemotherapy
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KCE	Belgian Health Care Knowledge Centre
KI	Konfidenzintervall
lascchn	locally advanced nonmetastatic squamous cell carcinoma of the head and neck
LoE	Level of Evidence
LRR	Locoregional recurrence
mach-nc	Chemotherapy in Head and Neck Cancer
NCCN	National Comprehensive Cancer Network

NICE	National Institute for Health and Care Excellence
NOS	Newcastle-Ottawa scale
NPC	Nasopharyngeal cancer
OR	Odds Ratio
OS	Overall Survival
OSCC	squamous cell carcinomas of the oral cavity
pebc	Pharmacy Examining Board of Canada
PFS	Progression Free Survival
PS	Performance Status
QoL	Quality of Life
RMNPSCC	Recurrent and metastatic disease treatment
RR	Relatives Risiko
SCC	squamous cell carcinoma
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
TTCC	Treatment of Head and Neck Tumors
WHO	World Health Organization

1 Indikation

Indikation für die Synopse: Erstlinienbehandlung von erwachsenen Patienten mit rezidivierendem oder metastasierendem Plattenepithelkarzinom der Kopf-Hals-Region.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation *Plattenepithelkarzinom im Kopf-Hals-Bereich* durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 01.10.2018 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 1270 Quellen, die anschließend in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 11 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

Es konnten keine relevanten G-BA Beschlüsse/IQWiG Berichte in dem Anwendungsgebiet identifiziert werden.

3.2 Cochrane Reviews

Es wurden keine relevanten systematischen Reviews identifiziert.

3.3 Systematische Reviews

Garcia-Leon FJ et al., 2017 [3].

Treatment of Advanced Laryngeal Cancer and Quality of Life. Systematic Review

Fragestellung

to compare the quality of life of patients with advanced laryngeal cancer treated while preserving the organ (using chemotherapy and radiotherapy) in comparison with surgical treatment.

Methodik

Population:

- Primary advanced stage squamous cell carcinoma of the larynx (stages III and IV of the American Joint Committee on Cancer) with a diagnosis confirmed by biopsy and previously untreated.

Intervention/Komparator

- Patients were then treated by chemotherapy and radiotherapy while preserving the organ, and the results were compared with those of patients treated by surgery plus radiotherapy, analyzing their quality of life

Endpunkte:

- QoL

Recherche/Suchzeitraum:

- MedLine, EMBASE, and PubMed (1991---2014) and Web of Science (2012---2014)

Qualitätsbewertung der Studien:

- The criteria of the Cochrane Collaboration were used to assess the risk of bias and Scottish Intercollegiate Guidelines Network (SIGN) for the level of evidence

Ergebnisse

Anzahl eingeschlossener Studien:

- 3 studies with data corresponding to 211 patients were included (74 treated with preservation of the organ and 137 with surgery), of which 123 were in a retrospective cohort of a hospital15 while the others were in cancer registers: 46 patients in a randomised clinical trial and 42 in a transversal study.
- Induction chemotherapy was used in one study while it was used concomitantly in the other two.

Charakteristika der Population:

- All of the patients had stage III or IV tumours, distributed at 50% each in the only study for which this is known.

Table 2 Study Population Characteristics.

Study	Follow-up duration	Patients	Age	Stage	Location (%)	
	Time (range)	Number	Years (Range)	(%)	Glottis	Supraglottis
Bussu et al. (2013)[15, a]						
Preservation		34	M_e 64 (40–83)	III (41), IV (59)	27	73
Surgery		89	M_e 65 (31–79)	III (29), IV (71)	65	35
Total	M_e 26 months	123		III (33), IV (67)		
Terrel et al. (1998)[14]						
Preservation		21	$\bar{x}$ 61.2	III (57), IV (43)		
Surgery		25	$\bar{x}$ 55.7*	III (44), IV (56)		
Total	$\bar{x}$ 10.4 years (8.5–12.7)	46	$\bar{x}$ 58.3	III (50), IV (50)		
Hanna et al. (2004)[13]			$\bar{x}$±SD			
Preservation		19	60.8 (±8.6)			
Surgery		23	65.6 (±10.3)			
Total	$\bar{x}$ 15 months (3–53)	42		III, IV[b]		
Total						
Preservation		74				
Surgery		137				
Total		211				

SD: standard deviation; M_e: mean; $\bar{x}$: average.
[a] The duration of follow-up and age also include 43 patients treated with cricohyoidopexy.
[b] Without information on stage.
* $P<.005$.

Qualität der Studien:

- The quality of these studies was low.

Studienergebnisse:

- Keine metaanalytische Auswertung:
  - The results were contradictory, on occasion they favoured surgery, and on other occasions chemotherapy, but in general there were no statistical differences between the treatments.

Anmerkung/Fazit der Autoren

There are not enough studies of quality to establish differences in the quality of life in patients with advanced laryngeal cancer according to the treatment received.

Kommentare zum Review

- The studies were heterogeneous, with different methodology, undersized, limitations in quality with high risk of bias and use of different measurement scales.

3.4 Leitlinien

SIGN, 2014 [10].

Management of primary cutaneous squamous cell carcinoma. A national clinical guideline

Leitlinienorganisation/Fragestellung

Guideline for management of primary cutaneous SCC

Methodik

Grundlage der Leitlinie

- Peer reviewed and evidence based: Evidence for this guideline was synthesized in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2007-2012.

LoE/GoR

KEY TO EVIDENCE STATEMENTS AND RECOMMENDATIONS	
LEVELS OF EVIDENCE	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies High 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
RECOMMENDATIONS	
Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation). The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher quality evidence is more likely to be associated with strong recommendations than lower quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation. Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence, and the balance of benefits and harms of the options.	
R	For **'strong'** recommendations on interventions that 'should' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm.
R	For **'conditional'** recommendations on interventions that should be 'considered', the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.
GOOD PRACTICE POINTS	
✓	Recommended best practice based on the clinical experience of the guideline development group

Empfehlungen

Chemotherapy:

There is insufficient evidence on which to base any recommendation.

✓ Systemic chemotherapy for the management of patients with primary cutaneous SCC should not be used outside of a clinical trial.

Systemic chemotherapy may be appropriate for patients with metastatic SCC.

Referral to the multidisciplinary team

The guideline development group considers that referral is appropriate where any of the high-risk features identified in section 3 are present.

R **Where any of the following high-risk features are present, patients with primary SCC should be discussed at a skin cancer multidisciplinary team meeting:**

- **SCC arising on the ear**
- **tumour diameter >20 mm**
- **tumour thickness >4 mm**
- **tumour extension beyond dermis into or through subcutaneous fat**
- **perineural invasion**
- **poorly differentiated**
- **desmoplastic subtype**
- **immunosuppression.**

✓
- recurrent SCC
- established or suspected metastatic SCC
- nose, external lip, eyelid and scalp tumour site
- association with special clinical situations
- adenosquamous histological subtype
- spindle cell histological subtype
- pseudoangiosarcomatous histological subtype
- acantholytic histological subtype
- lymphovascular invasion
- tumour excision margins involved at deep or peripheral margins.

MDT discussion is desirable where:

- a tumour is at a surgically challenging site
- the referring clinician requests discussion due to specific clinical management issues, such as cognitive impairment or significant medical comorbidities.

All SCC including low risk SCC should be reported on a minimum dataset (*see Annex 5*) which allows all high-risk SCCs to be fast tracked to the MDT.

Data on all SCC should be subject to clinical audit and sent to the Cancer Registry.

Alberta Health Services (AHS), 2014 [2].

Oral cavity cancer

Leitlinienorganisation/Fragestellung

1. What diagnostic and baseline investigations are recommended for patients with suspected or confirmed oral cavity cancer?
2. What are the recommended treatment options for early-stage oral cavity cancer (T1–2, N0)?
3. What are the recommended treatment options for advanced-stage oral cavity cancer (T3, N0; T4a, Any N; T1–3, N1–3; T4b, any N or unresectable nodal disease or unfit for surgery)?

4. What is the recommended follow-up after treatment for oral cavity cancer?

Methodik

Grundlage der Leitlinie

This guideline was reviewed and endorsed by the Alberta Provincial Head and Neck Tumour Team. Members of the Alberta Provincial Head and Neck Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, head and neck reconstructive surgeons, nurses, pathologists, pharmacists, dentists, dietitians, and other allied health professionals. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Head and Neck Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

Recherche/Suchzeitraum:

- PubMED, MEDLINE and the Cochrane Database of Systematic Reviews were searched to May 6, 2013 for literature on the treatment of oral cavity cancer.

LoE/GoR

- Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations Guideline Resource Unit (GURU) does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating there recommendations including: Description of all known benefits and possible harms, Evidence summary quality/quantity/consistency of discussion, Discussion of the role of clinical experience, theory, values and opinions in developing the recommendation

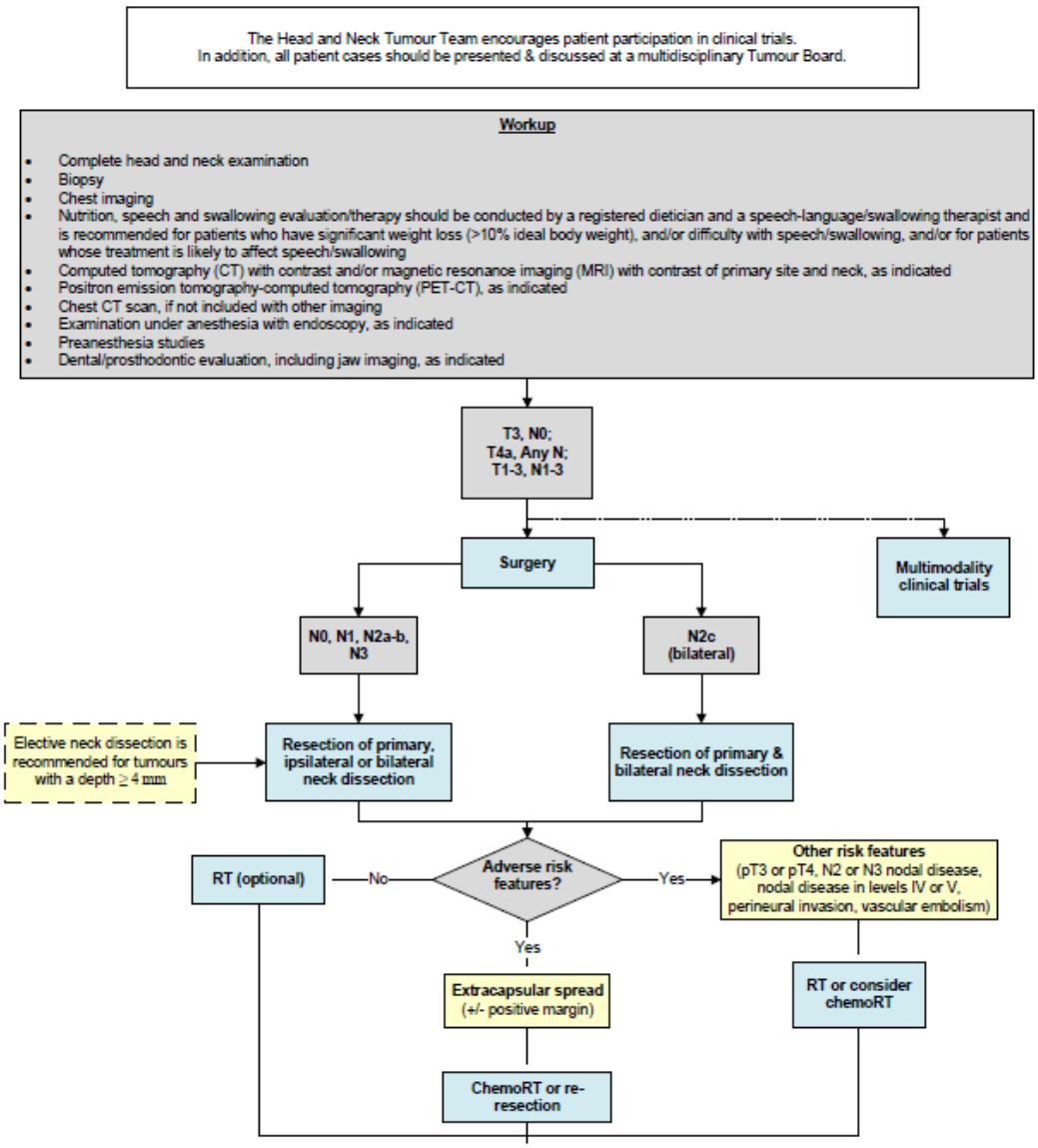
Recommendations

3a. Treatment options for advanced-stage oral cavity cancer (T3, N0; T1–3, N1–3; T4a, Any N).

- Inclusion of patients in multimodality clinical trials is recommended. In lieu of a clinical trial, patients should undergo surgery. Patients with N2c neck disease should undergo primary tumour resection and bilateral ND, while all other patients (N0, N1, N2a–b and N3) should undergo primary tumour resection. Ipsilateral or bilateral dissection may be indicated for some patients, especially if the depth of invasion is ≥ 4 mm; the decision should be based on clinical judgment and discussion at the multidisciplinary Tumour Board.
- If a patient has the following adverse risk features, treatment after resection includes:
  - Extracapsular spread +/- positive margin: chemoRT or re-resection
  - pT3 or pT4, and/or N2 or N3 nodal disease, and/or nodal disease in levels IV or V, and/or perineural invasion, and/or vascular embolism: RT alone; chemoRT may be considered, the decision should be based on clinical judgment and discussion at the multidisciplinary Tumour Board

If a patient has none of the above adverse risk features RT is considered optional before proceeding with follow–up and surveillance.

Advanced-Stage Oral Cavity Cancer (T3, N0; T4a, Any N; T1–3, N1–3)

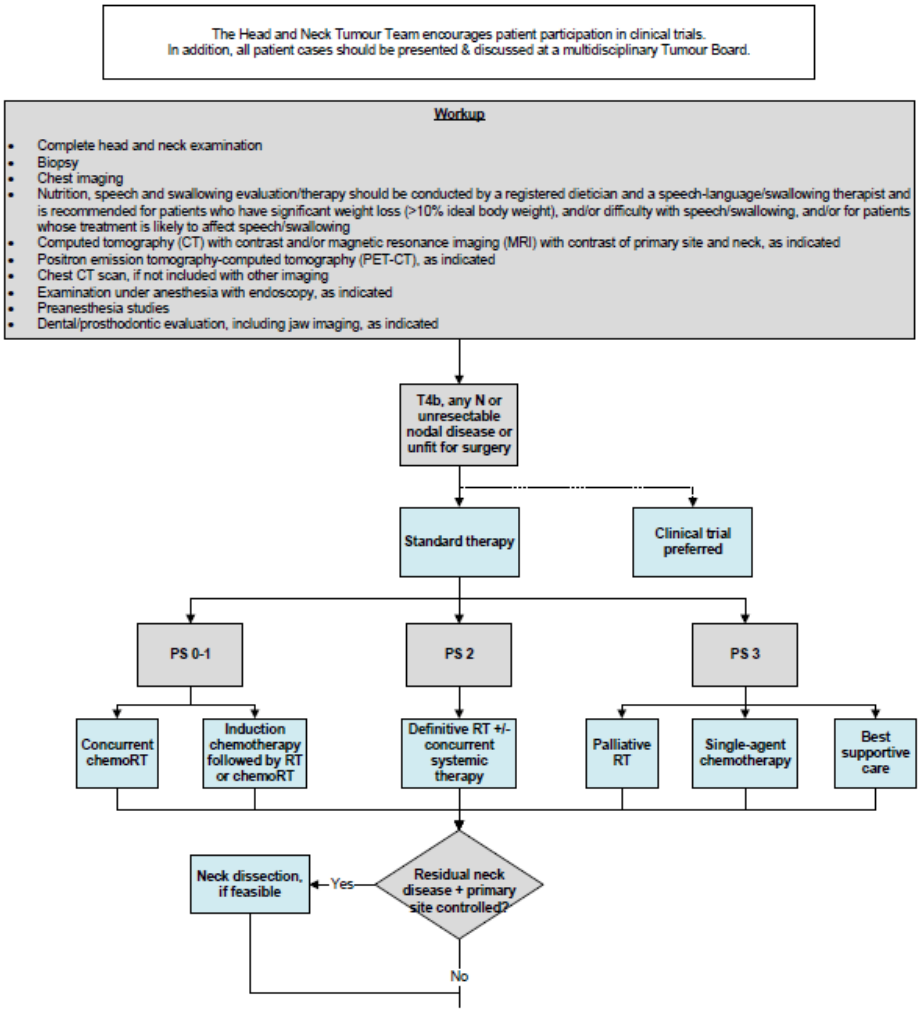


3b. Treatment options for very advanced-stage oral cavity cancer (T4b, Any N or unresectable nodal disease or unfit for surgery):

- Patient participation in clinical trials is recommended. In lieu of a clinical trial, patients should undergo therapy dependent on their Eastern Cooperative Oncology Group (ECOG) performance status (PS).
  - PS 0–1 patients should undergo both concurrent systemic therapy and RT or induction chemotherapy followed by RT or chemoRT. Induction chemotherapy should only be done in a tertiary setting due to toxicity concerns.
  - PS 2 patients should undergo RT with or without concurrent systemic therapy dependent on their treatment goals.
  - PS 3 patients have the option of undergoing palliative RT, single-agent chemotherapy or opt for best supportive care.

In the instance of residual neck disease and if feasible, conduct ND if the primary tumour site is controlled following the above treatments. For oral cavity cancers, the risk of regional metastases and the need for adjuvant elective ND increases as thickness of the lesion increases.

Very Advanced-Stage Oral Cavity Cancer (T4b, any N or unresectable nodal disease or unfit for surgery)



5. Follow-up and surveillance. The following schedule should be taken into account to manage complications related to treatment, to detect disease recurrence and/or the development of new disease:

- Head and neck examination (note that the ranges are based on risk of relapse, second primaries, treatment sequelae, and toxicities):
  - Year 1, every 1 to 3 months
  - Year 2, every 2 to 6 months
  - Year 3–5, every 4 to 8 months
  - After 5 years, annually, as clinically indicated

- Annual thyroid-stimulating hormone (TSH) screening up to 5 years only for those patients that receive post-operative RT to the neck
- Speech/swallowing assessment at 6 and 12 months post-RT; additional assessment and rehabilitation, as clinically indicated by a speech-language/swallowing therapist
- Hearing evaluation and rehabilitation, as clinically indicated
- Follow-up with a registered dietitian to evaluate nutritional status and until the patient achieves a nutritionally stable baseline
- Routine hospital-based dental follow-up/rehabilitation and evaluation up to 3 years, specifically:
  - Half-way through treatment
  - At the end of treatment
  - 6 weeks post treatment
  - 2–3 months post treatment
  - 6 months post treatment
  - 12 months post treatment
  - Yearly for the next 2 years
- Physiotherapy is indicated for all patients

Cancer Care Ontario (CCO), 2015 [11].

Epidermal Growth Factor Receptor (EGFR) Targeted Therapy in Stage III and IV Head and Neck Cancer

Leitlinienorganisation/Fragestellung

What are the benefits associated with the use of anti-epidermal growth factor receptor (anti-EGFR) therapies in squamous cell carcinoma of the head and neck (HNSCC)?

Methodik

Grundlage der Leitlinie

The evidence-based series (EBS) guidelines developed by the CCO PEBC use the methods of the Practice Guidelines Development Cycle (5). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by two members of the PEBC Head and Neck Cancer Disease Site Group (DSG) and two methodologists.

The systematic review is an update. The body of evidence in this review is primarily comprised of mature RCT data.

The PEBC is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ministry.

Recherche/Suchzeitraum:

- Bis 2011

LoE/GoR: Evidenzklassifizierung und Empfehlungsgraduierung mit verschiedenen Systemen (in Evidenztabellen dargestellt)

Sonstige methodische Hinweise

- These recommendations apply to adult patients with locally advanced non-metastatic (stage III or IV) or recurrent/metastatic HNSCC.

Recommendations

(…) 2. Untreated Recurrent and/or Metastatic HNSCC

- Cetuximab in combination with platinum-based combination chemotherapy is superior to chemotherapy alone in patients with recurrent and/or metastatic HNSCC, and is recommended to improve OS, PFS, and response rate in suitable patients.
  - Vermorken et al. reported that the addition of cetuximab to chemotherapy (cisplatin or carboplatin plus 5-FU) improved OS (10.1 months vs. 7.4 months; p=0.04), PFS (5.6 months vs. 3.3 months, p<0.001) and response rate (36% vs. 20%; p<0.001) compared to chemotherapy alone in patients with recurrent/metastatic HNSCC.
  - In a small randomized trial, Burtness et al. found that the addition of cetuximab to cisplatin improved the objective response rate (26% vs. 10%; p=0.03) but did not improve OS (9.2 months vs. 8.0 months; p=0.21) or PFS (4.2 months vs. 2.7 months; p=0.09), although the trial was inadequately powered to assess these outcomes.
  - In addition to the adverse effects mentioned above, hypomagnesemia was increased in patients receiving cetuximab in combination with cisplatin.

Pastor M et al., 2018 [8].

SEOM clinical guideline in nasopharynx cancer (2017)

Leitlinienorganisation/Fragestellung

Recommendations for the treatment of nasopharynx cancer

Methodik

Grundlage der Leitlinie

Methodology SEOM guidelines have been developed with the consensus of ten OC oncologists from the cooperative group Spanish Group for the Treatment of Head and Neck Tumors (TTCC) and SEOM. To assign a level and quality of evidence and a grade of recommendation to the different statements of this treatment guideline, the Infectious Diseases Society of America–US Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines was used. The final text has been reviewed and approved by all authors.

Recherche/Suchzeitraum:

- K.A.

LoE/GoR

Table 1 Strength of recommendation and quality of evidence score

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from ≥ 1 properly randomized, controlled trial
II	Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from > 1 center); from multiple time series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Recommendations

Treatment of locally advanced stage (III and IV A/B)

- Concurrent CT/RT is the standard treatment for loco regionally advanced nasopharyngeal carcinoma (with CDDP at 100 mg/m2 every 21 days) substantially improved loco regional control compared with exclusive RT, but distant metastasis is the main source of treatment failure [IA].
- Additional cycles of CT (with induction or adjuvant chemotherapy) could improve results and increases failure free survival, overall survival, and distant failure-free survival with acceptable toxicity profile but its role is uncertain [IB].
- A high rate of toxicity that usually leads to a low percentage of patients that are able to complete the adjuvant treatment and compliance is a significant problem with only about 50–75% of patients who were initially planned for adjuvant chemotherapy receiving the three planned cycles.
- Induction CT could avoid this problem [IIA].
- The use of one or another should be tailored according to the patient's clinical condition (ex, CT induction in highly symptomatic patients, adjuvant therapy to the rest).
- In patients with good general condition, TPF induction CT should be an option to be considered problem [IIB].
- When there is persistent cervical disease after standard CT/RT treatment, cervical rescue surgery should be performed. In cases with large cervical disease (N3), irrespective of the response to CT/RT, its systematic use could be considered. This could be especially relevant in cases with WHO type 1 histology WHO. However, the morbidity of this approach can be substantial and it has not been generally accepted. There are no studies to clarify this point definitively [IIIB].

Recurrent and metastatic disease treatment (RMNPSCC) (IV C)

- In the setting of local and/or regional relapse, the multidisciplinary team should assess the possibility of salvage local therapy, whether by surgery or re-irradiation, with or without CT. These approaches can rescue a small percentage of cases, albeit at the cost of high toxicity. The election of one or another approach has not been well established. The best results have

been achieved when the previous interval free of disease is longer. If loco-regional relapse of NPSCC occurs, local treatment with surgery and/or chemo-radiotherapy is recommended [IIB].

- When salvage treatment is not feasible or the patient develops a metastatic disease, the treatment of choice is palliative CT. A wide range of chemotherapy drugs has been tested mainly in retrospective and small phase II trials such as: platinum compounds (cisplatin, carboplatin), fluoropirimidines (5-fluorouracil, capecitabine), taxanes (paclitaxel, docetaxel), gemcitabine, anthracyclines, irinotecan and vinorelbine. Traditionally, the most used schedules included platinum-based combinations, mainly with 5-FU, with responses rates between 50 and 70% in retrospective uncontrolled studies.
- A recent phase III randomized trial comparing cisplatin-5-FU with cisplatin-gemcitabine in 362 patients, showed a significant advantage in terms of progression-free survival in the gemcitabine-based cohort. Owing to no other phase III trials in this setting, this schedule has become the new standard first line approach in RM-NPC. Cisplatin-gemcitabine is the first choice as first line palliative CT treatment in RM-NPSCC [IA].
- To date, there is not an established standard treatment after the failure of the first line. If the patient has a good performance status, any of the previously reported active drugs could be considered but the inclusion in clinical trials should be encouraged.

Quon H et al., 2017 [9].

American Society for Radiation Oncology (ASTRO)

Radiation Therapy for Oropharyngeal Squamous Cell Carcinoma: American Society of Clinical Oncology Endorsement of the American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline

Leitlinienorganisation/Fragestellung

What is the role of definitive or adjuvant radiation therapy in the treatment of oropharyngeal squamous cell carcinoma (OPSCC)?

→ Adults with any stage of OPSCC

Methodik

Grundlage der Leitlinie

An ASCO Expert Panel was convened to consider endorsing the ASTRO Radiotherapy for Oropharyngeal Squamous Cell Carcinoma Evidence-Based Guideline recommendations that were based on a systematic review of the medical literature. The ASCO Expert Panel considered the methodology used in the ASTRO guideline by considering the results from the AGREE II review instrument.

The ASTRO guideline was reviewed by ASCO content experts for clinical accuracy and by ASCO methodologists for developmental rigor. On favorable review, an ASCO Expert Panel was convened to review the guideline contents and recommendations. The ASCO guideline approval body, the Clinical Practice Guidelines Committee, approved the final endorsement.

Recherche/Suchzeitraum:

- search date of January 2014 to July 2016

LoE/GoR

- ASTRO recommendations are with qualifying statements or modifications added by the ASCO panel listed in bold italics

Recommendations

1. Recommendations for the addition of systemic therapy to definitive radiotherapy in the treatment of OPSCC.

- In the scenario of AJCC stage IVA-IVB disease:
  - Concurrent high-dose intermittent cisplatin should be delivered to patients with stage IVA-IVB OPSCC receiving definitive radiotherapy (Recommendation strength: strong; Quality of evidence: high).
  - Concurrent cetuximab or carboplatin-fluorouracil may be delivered to patients with stage IVA-IVB OPSCC receiving definitive radiotherapy who are not medically fit for high-dose cisplatin (Recommendation strength: conditional; Quality of evidence: high).
  - Concurrent weekly cisplatin may be delivered to patients with stage IVA-IVB OPSCC receiving definitive radiotherapy who are not medically fit for high-dose cisplatin, after a careful discussion of patient preferences and the limited prospective data supporting this regimen (Recommendation strength: conditional; Quality of evidence: low).
  - Concurrent cetuximab should not be delivered in combination with chemotherapy to patients with stage IVA-IVB OPSCC receiving definitive radiotherapy (Recommendation strength: strong; Quality of evidence: high).
  - Intra-arterial chemotherapy should not be delivered to patients with stage IVA-IVB OPSCC receiving definitive radiotherapy (Recommendation strength: strong, Quality of evidence: high).
- In the scenario of stage III disease:
  - Concurrent systemic therapy should be delivered to patients with T3 N0-1 OPSCC receiving definitive radiotherapy (Recommendation strength: strong, Quality of evidence: moderate).
  - Concurrent systemic therapy may be delivered to patients with T1-T2 N1 OPSCC receiving definitive radiotherapy who are considered at particularly significant risk for locoregional recurrence, after a careful discussion of patient preferences and the limited evidence supporting its use (Recommendation strength: conditional, Quality of evidence: low).

2. Recommendations for delivery of postoperative radiotherapy with and without systemic therapy following primary surgery of OPSCC.

- In the scenario of positive margins and/or extracapsular nodal extension:
  - Concurrent high-dose intermittent cisplatin should be delivered with postoperative radiotherapy to patients with positive surgical margins and/or extracapsular nodal extension; this high-risk population includes patients independent of HPV status or the extent of extranodal tumor (Recommendation strength: strong, Quality of evidence: moderate).
  - Concurrent weekly cisplatin may be delivered with postoperative radiotherapy to patients who are considered inappropriate for standard high-dose intermittent cisplatin after a

careful discussion of patient preferences and the limited evidence supporting this treatment schedule (Recommendation strength: conditional, Quality of evidence: low).

- For the high-risk postoperative patient unable to receive cisplatin-based concurrent chemoradiotherapy, radiotherapy alone should be routinely delivered without concurrent systemic therapy; given the limited evidence supporting alternative regimens, treatment with noncisplatin systemic therapy should be accompanied by a careful discussion of the risks and unknown benefits of the combination (Recommendation strength: strong, Quality of evidence: moderate).
- Patients treated with postoperative radiotherapy should not receive concurrent weekly carboplatin (Recommendation strength: strong, Quality of evidence: moderate).
- Patients treated with postoperative radiotherapy should not receive cetuximab, either alone or in combination with chemotherapy, although such regimens are currently under investigation (Recommendation strength: strong, Quality of evidence: low).
- Patients treated with postoperative radiotherapy should not routinely receive concurrent weekly docetaxel given the limited evidence supporting its use, although such regimens are currently under investigation (Recommendation strength: strong, Quality of evidence: low).
- Patients treated with postoperative radiotherapy should not receive concurrent mitomycin-C, alone or with bleomycin, given the limited evidence and experience supporting its use (Recommendation strength: strong, Quality of evidence: moderate).
- Postoperative chemotherapy should not be delivered alone or sequentially with postoperative radiotherapy (Recommendation strength: strong, Quality of evidence: high).

- In the scenario of intermediate-risk pathologic factors such as lymphovascular invasion (LVI), perineural invasion (PNI), T3-T4 disease, or positive lymph nodes:
  - Patients with intermediate-risk factors should not routinely receive concurrent systemic therapy with postoperative radiotherapy (Recommendation strength: strong, Quality of evidence: moderate).
  - Patients with intermediate-risk factors whose surgical procedure and/or pathologic findings imply a particularly significant risk of loco regional recurrence may receive concurrent cisplatin-based chemotherapy after a careful discussion of patient preferences and the limited evidence supporting its use in this scenario; alternative systemic treatment regimens should only be used in the context of a clinical trial (Recommendation strength: conditional, Quality of evidence: low).
  - Postoperative radiotherapy should be delivered to patients with pathologic T3 or T4 disease (Recommendation strength: strong, Quality of evidence: low).
  - Postoperative radiotherapy should be delivered to patients with pathologic N2 or N3 disease (Recommendation strength: strong, Quality of evidence: low).
  - Postoperative radiotherapy may be delivered to patients with pathologic N1 disease without extracapsular nodal extension after a careful discussion of patient preferences and the limited evidence of outcomes following surgery alone in this scenario (Recommendation strength: conditional, Quality of evidence: low).
  - Postoperative radiotherapy may be delivered to patients with LVI and/or PNI as the only risk factor(s) after a careful discussion of patient preferences and the limited evidence of outcomes following surgery alone in this scenario (Recommendation strength: conditional Quality of evidence: low).

- In the scenario of no pathologic risk factors: Postoperative radiotherapy may be delivered to patients without conventional adverse pathologic risk factors only if the clinical and surgical findings imply a particularly significant risk of loco regional recurrence, after a careful discussion of patient preferences and the potential harms and benefits of radiotherapy (Recommendation strength: conditional, Quality of evidence: low).

Iglesias Docampo LC et al., 2018 [6].

SEOM clinical guidelines for the treatment of head and neck cancer (2017)

Leitlinienorganisation/Fragestellung

Recommendations for the treatment of head and neck cancer

Methodik

Grundlage der Leitlinie

Methodology SEOM guidelines have been developed with the consensus of ten oncologists from the Spanish Group for the Treatment of Head and Neck Tumors (TTCC) and SEOM. To assign a level and quality of evidence and a grade of recommendation to the different statements of this treatment guideline, the Infectious Diseases Society of America-US Public Health Service Grading System for Ranking Recommendations in Clinical Guidelines was used. The final text has been reviewed and approved by all authors.

Recherche/Suchzeitraum:

- k.A.

LoE/GoR

Table 1 Strength of recommendation and quality of evidence score

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Quality of evidence	
I	Evidence from ≥ 1 properly randomized, controlled trial
II	Evidence from ≥ 1 well-designed clinical trial, without randomization; from cohort or case controlled analytic studies (preferably from > 1 centre); from multiple time series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

Recommendations

Recurrent and metastatic disease treatment

The multidisciplinary team will assess the possibility of salvage surgery (operable tumour) or re-irradiation with or without chemotherapy/cetuximab. In the presence of oligometastatic disease, treatment with curative intent should also be discussed.

Once this option is discarded the treatment of choice is palliative chemotherapy:

- First-line treatment

1. Chemotherapy-naive patients

- In the patient with a performance status of 0/1 the first choice is the combination of cisplatin, 5-fluorouracil, and cetuximab. If the patient is medically unfit to receive cisplatin the use of carboplatin may be an option. Cetuximab should be maintained until progression or unacceptable toxicity.
- If the patient cannot be treated with platinum (concomitant disease, previous treatment, etc.) or patients with PS 2, the treatment of choice is best supportive treatment of symptoms. In these patients, the combination ERBITAX (paclitaxel plus cetuximab) should be considered.
- The treatment of choice for patients with PS ¾ is best supportive care of symptoms.

2. Patients who have received chemotherapy for locoregional disease

- Patients with progressive disease more than 6 months after locoregional treatment can be treated like chemotherapy-naive patients.
- Patients with progressive disease within 6 months after last cisplatin dose should not receive cisplatin or carboplatin. ERBITAX combination or second-line therapy should be considered.

Grégoire V et al., 2015 [4].

Belgian Health Care Knowledge Centre (KCE)

Oropharyngeal, hypopharyngeal and laryngeal cancer: diagnosis, treatment and follow-up

Leitlinienorganisation/Fragestellung

This second part of the guideline provides recommendations based on current scientific evidence for the staging, treatment, follow-up and supportive care of patients with oropharyngeal, hypopharyngeal and laryngeal cancer.

Methodik

Grundlage der Leitlinie

The present guideline was developed using a standard methodology based on a systematic review of the evidence.

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

Recherche/Suchzeitraum:

- K.A. Suchzeitraum

LoE/GoR

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

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

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

Table 3 – Levels of evidence according to the GRADE system

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

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

Table 4 – Downgrading the quality rating of evidence using GRADE

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

Table 5 – Strength of recommendations according to the GRADE system

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

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

Table 6 – Factors that influence the strength of a recommendation

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

Recommendations

Treatment of metastatic or recurrent disease not suitable for curative treatment

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

Evidenzgrundlage:

Conclusions

Chemoradiotherapy versus best supportive care

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

Chemotherapy versus best supportive care

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

Radiotherapy versus best supportive care

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

Salvage surgery versus supportive care

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

EGFR inhibitors plus best supportive care versus best supportive care only

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

Salvage treatment

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

Grégoire V et al., 2014 [5].

Belgian Health Care Knowledge Centre (KCE)

Oral cavity cancer: diagnosis, treatment and follow-up

Leitlinienorganisation/Fragestellung

This first part of the guideline provides recommendations based on current scientific evidence for the staging, treatment, follow-up and supportive care of patients with oral cavity squamous cell cancer.

Methodik

Grundlage der Leitlinie

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

LoE/GoR

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Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
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Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention, i.e. the greater the resources consumed, the lower the likelihood that a strong recommendation is warranted

Recommendations

Treatment of metastatic or recurrent disease not suitable for curative treatment

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

- Evidenzgrundlage

Conclusions

Chemoradiotherapy versus best supportive care

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

Chemotherapy versus best supportive care

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Salvage surgery versus supportive care

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EGFR inhibitors plus best supportive care versus best supportive care only

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

Locoregional recurrence

Recommendations	Strength of Recommendation	Level of Evidence
• In patients with suspected recurrence in the head and neck that could not be confirmed or ruled out by CT and/or MRI, FDG-PET/CT may be performed.	Weak	Very low
• Salvage surgery should be considered in any patient with a resectable locoregional recurrence having previously undergone radiotherapy or surgery. The procedure should only be performed by an experienced surgical team with adequate experience of reconstructive techniques, and at a facility that offers suitable intensive care support.	Weak	Very low
• Re-irradiation, possibly with curative intent, should be considered in any patient with a non-resectable locoregional recurrence having already undergone irradiation. Irradiation should take place only at facilities with adequate expertise and ideally as part of a clinical therapeutic study.	Weak	Very low

Alberta Health Services (AHS), 2013 [1].

Nasopharyngeal cancer treatment

Leitlinienorganisation/Fragestellung

1. What diagnostic and baseline investigations are recommended for patients with suspected or confirmed NPC?
2. What are the recommended treatment options for NPC?
3. What is the recommended follow-up after treatment for NPC?

Methodik

Grundlage der Leitlinie

This guideline was reviewed and endorsed by the Alberta Provincial Head and Neck Tumour Team. Members of the Alberta Provincial Head and Neck Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, head and neck reconstructive surgeons, nurses, pathologists, pharmacists, dentists, dietitians, and other allied health professionals. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Head and Neck Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

Recherche/Suchzeitraum:

- PubMED, MEDLINE and Cochrane Database of Systematic Reviews were searched from 2000 to April 5, 2013 for literature on the treatment of NPC.
- The National Guidelines Clearinghouse and SAGE Directory of Cancer Guidelines were also searched from 2008 to April 5, 2013 for guidelines on nasopharyngeal cancer.

LoE/GoR

- Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations Guideline Resource Unit (GURU) does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating there recommendations including: Description of all known benefits and possible harms, Evidence summary quality/quantity/consistency of discussion, Discussion of the role of clinical experience, theory, values and opinions in developing the recommendation

Recommendations

- Advanced-stage (T1, N1–3; T2–4, Any N, M0): Concurrent chemoradiotherapy (chemoRT) with cisplatin is recommended. Adjuvant chemotherapy using platinum (cisplatin or carboplatin)/5-fluoruracil (5-FU) can be considered following primary treatment. The choice of chemotherapy should be individualized based on patient characteristics (performance status and goals of therapy). Where there is clinical evidence of residual disease in the neck, neck dissection is recommended, if feasible (see figure 1 below).
- Distant metastatic disease (Any T, Any N, M1): All treatment of patients with distant metastatic disease is palliative in nature. If available, patients should consider participating in a clinical trial. Palliative RT can be considered in select cases. In patients with good

performance status, palliative chemotherapy may be considered. Referral to palliative care services can be offered to patients (see figure 1 below).

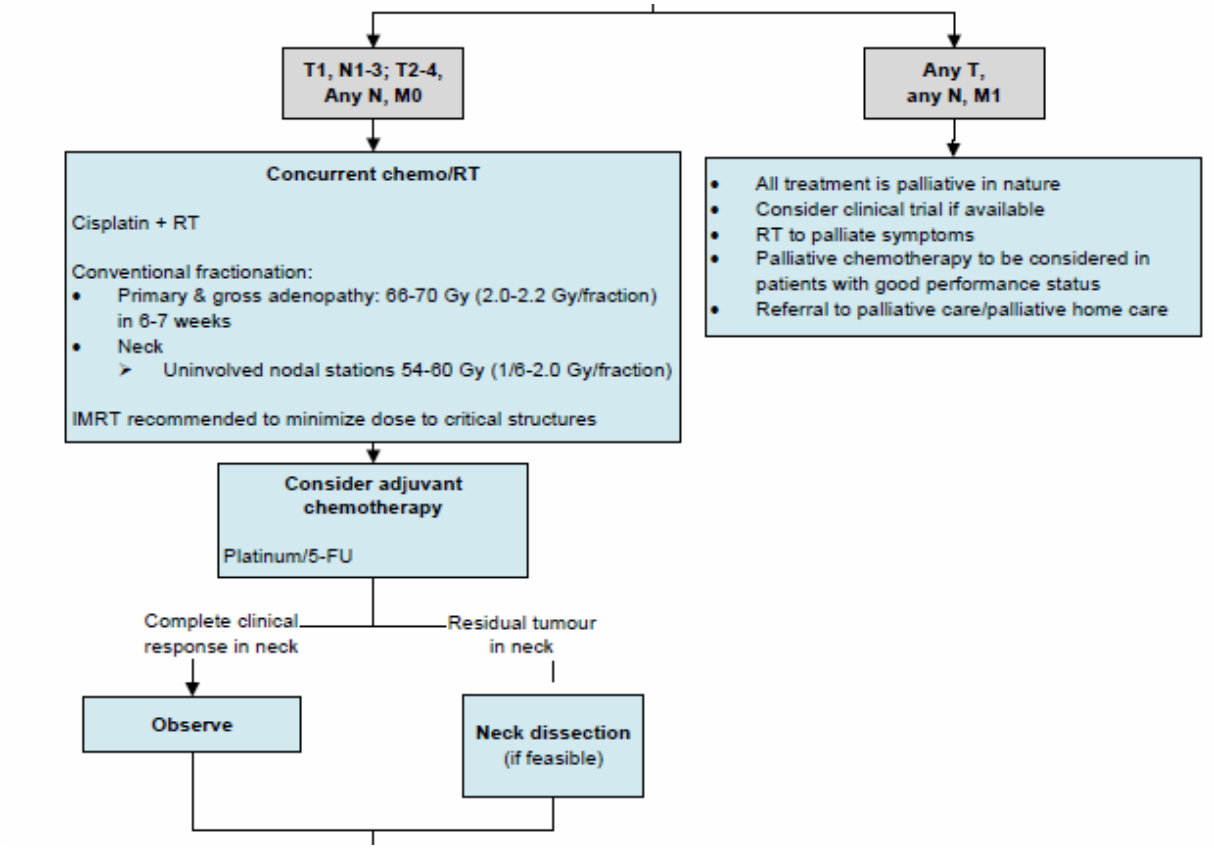

Figure 1: Therapy algorithm for advanced/metastatic disease

Recurrent or persistent disease:

- Restaging should be done to assess local, regional and distant disease. Biopsy of recurrent lesion(s) is recommended, as clinically indicated. Treatment should be individualized based on patient performance status and extent of disease (see figure 2 below).
- Treatment options include:
  - Salvage nasopharyngectomy, or
  - Re-irradiation with brachytherapy, and/or
  - Stereotactic guided treatments

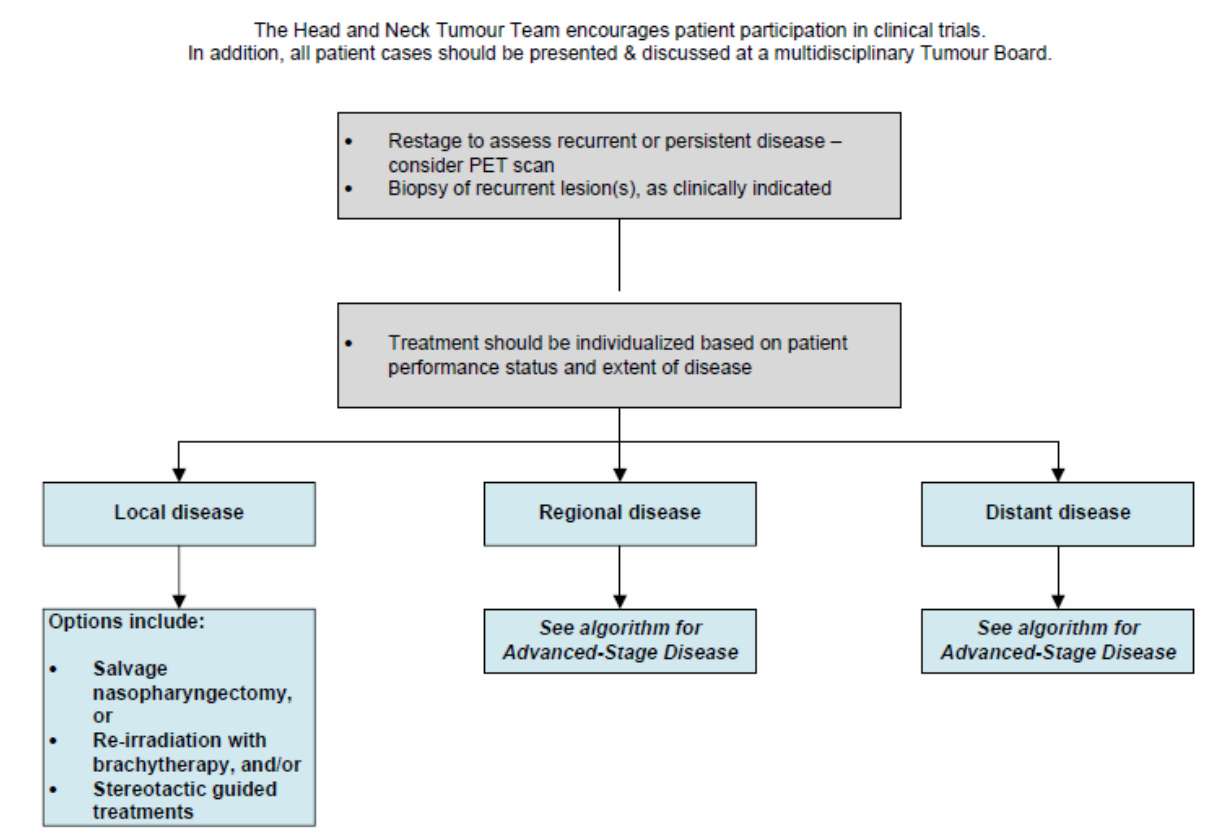

Figure 2: Treatment algorithm for recurrent/persistent disease

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NCCN, 2018 [7].

National Comprehensive Cancer Network (NCCN)

Head and neck cancers. Version 2.2018

Leitlinienorganisation/Fragestellung

Recommendations for the treatment of Head and neck cancers.

Methodik

Grundlage der Leitlinie

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Head and Neck Cancers, an electronic search of the PubMed database was performed to obtain key literature in the field of H&N cancers published between June 26, 2016 and May 30, 2017, using the following search terms: (head and neck cancer) OR (lip cancer) OR (oral cavity cancer) OR (oropharynx cancer) OR (hypopharynx cancer) OR (nasopharynx cancer) OR (larynx cancer) OR (paranasal tumor) OR (ethmoid sinus tumor) OR (maxillary sinus tumor) OR (salivary gland tumor) OR (mucosal melanoma head) OR (mucosal melanoma neck). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[4]

LoE/GoR

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

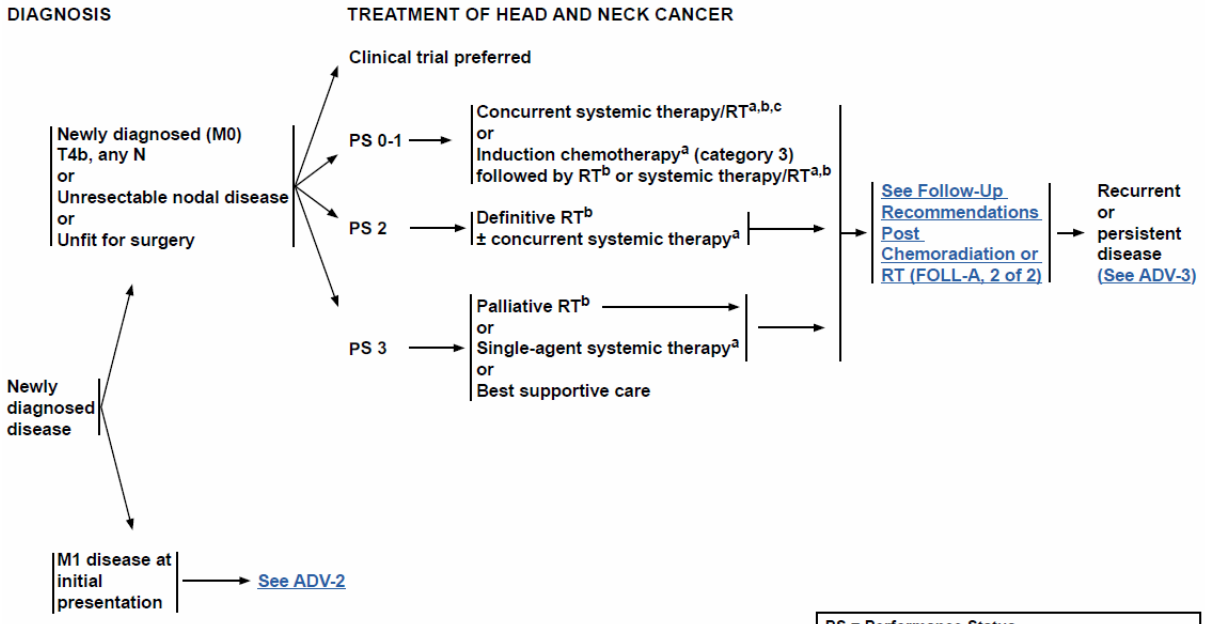
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

Sonstige methodische Hinweise

- Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz zur Fragestellung, wird die LL jedoch ergänzend dargestellt.

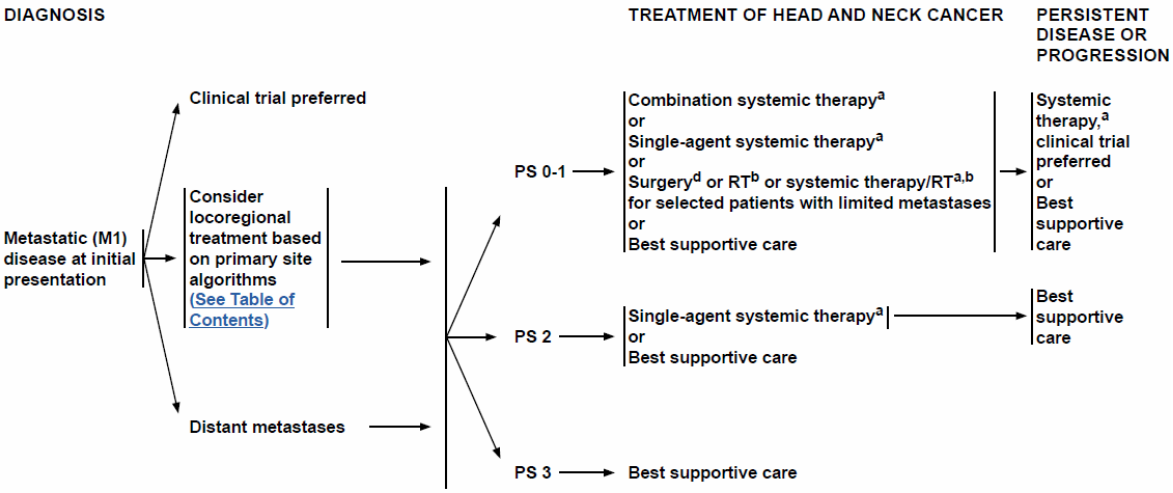
Recommendations



[a]See Principles of Systemic Therapy (CHEM-A).
[b]See Principles of Radiation Therapy (ADV-A).
[c]When using concurrent systemic therapy/RT, the preferred agent is cisplatin (category 1). See Principles of Systemic Therapy (CHEM-A).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

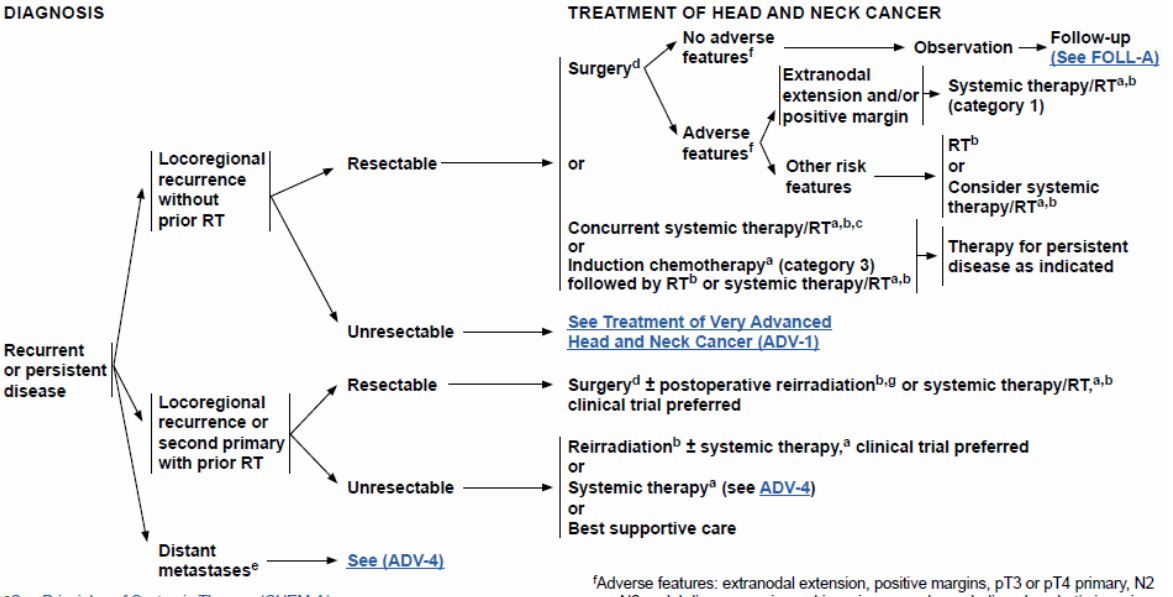
ADV-1



[a]See Principles of Systemic Therapy (CHEM-A).
[b]See Principles of Radiation Therapy (ADV-A).
[d]See Principles of Surgery (SURG-A).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

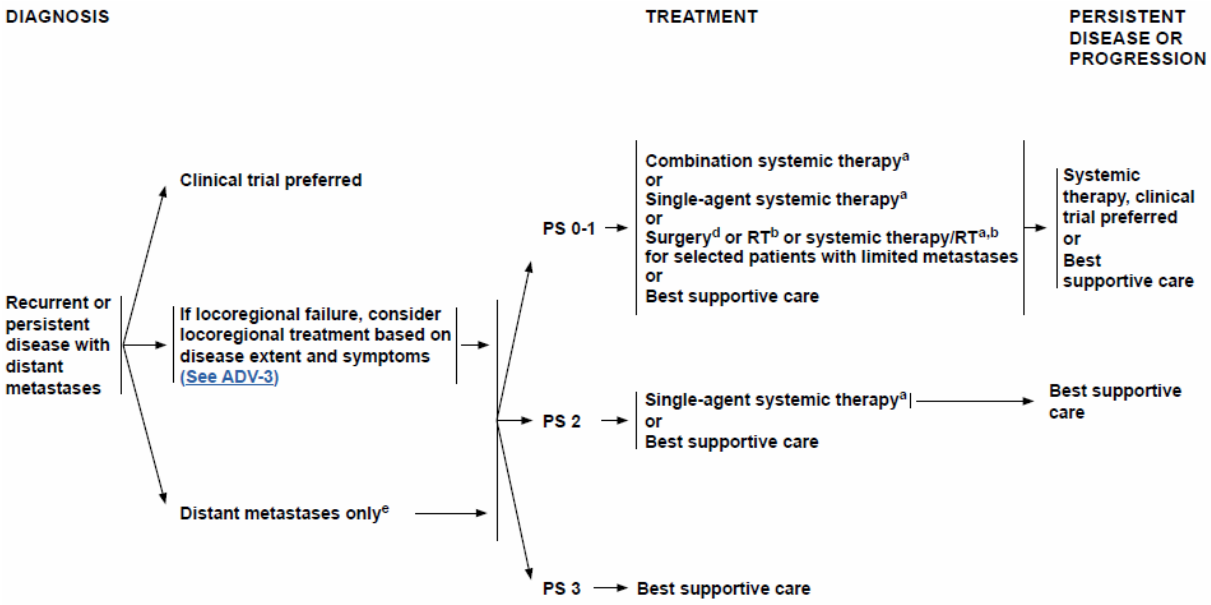
ADV-2



[a]See Principles of Systemic Therapy (CHEM-A).
[b]See Principles of Radiation Therapy (ADV-A).
[c]When using concurrent systemic therapy/RT, the preferred agent is cisplatin (category 1). See Principles of Systemic Therapy (CHEM-A).
[d]See Principles of Surgery (SURG-A).
[e]Consider palliative RT as clinically indicated (eg, bone metastases). (See RAD-A).
[f]Adverse features: extranodal extension, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism, lymphatic invasion (See Discussion).
[g]Reirradiation should be limited to a highly select subset of patients (Janot F, de Raucourt D, Benhamou E, et al. Randomized trial of postoperative reirradiation combined with chemotherapy after salvage surgery compared with salvage surgery alone in head and neck carcinoma. J Clin Oncol 2008;26:5518-5523).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ADV-3



[a]See Principles of Systemic Therapy (CHEM-A).
[b]See Principles of Radiation Therapy (ADV-A).
[d]See Principles of Surgery (SURG-A).
[e]Consider palliative RT as clinically indicated (eg, bone metastases). (See RAD-A).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

ADV-4

PRINCIPLES OF SYSTEMIC THERAPY

The choice of systemic therapy should be individualized based on patient characteristics (PS, goals of therapy).

- **The preferred chemoradiotherapy approach for fit patients with locally advanced disease remains concurrent cisplatin and radiotherapy.**
- **Cisplatin-based induction chemotherapy can be used, followed by radiation-based locoregional treatment (ie, sequential chemoRT). However, an improvement in overall survival with the incorporation of induction chemotherapy compared to proceeding directly to state-of-the-art concurrent chemoRT (cisplatin preferred, category 1) has not been established in randomized studies.**
- **Cisplatin-based induction chemotherapy followed by high-dose, every-3-week cisplatin chemoradiotherapy is not recommended due to toxicity concerns.[1,2]**
- **After induction chemotherapy, multiple options can be used for the radiation-based portion of therapy. Radiotherapy alone versus radiotherapy plus weekly carboplatin or cetuximab are among the options.**

Squamous Cell Cancers

Lip, Oral Cavity, Oropharynx, Hypopharynx, Glottic Larynx, Supraglottic Larynx, Ethmoid Sinus, Maxillary Sinus, Occult Primary:

- **Primary systemic therapy + concurrent RT**
  - **High-dose cisplatin[3,4] (preferred) (category 1)**
  - **Cetuximab[5] (category 1 for oropharynx, hypopharynx, or larynx; category 2B for lip, oral cavity, ethmoid sinus, maxillary sinus, occult primary)**
  - **Carboplatin/infusional 5-FU (category 1)[6,7]**
  - **5-FU/hydroxyurea[8]**
  - **Cisplatin/paclitaxel[8]**
  - **Cisplatin/infusional 5-FU[9]**
  - **Carboplatin/paclitaxel[10] (category 2B)**
  - **Weekly cisplatin 40 mg/m² (category 2B)[11,12]**
- **Postoperative chemoradiation**
  - **Cisplatin[13-18] (category 1 for high-risk** non-oropharyngeal cancers)**

Nasopharynx:

- **Chemoradiation followed by adjuvant chemotherapy**
  - **Cisplatin + RT followed by cisplatin/5-FU[19-20] or carboplatin/5-FU[21] (category 2B for carboplatin/5-FU)**
- **Cisplatin + RT without adjuvant chemotherapy (category 2B)[22]**

Lip, Oral Cavity, Oropharynx, Hypopharynx, Glottic Larynx, Supraglottic Larynx, Ethmoid Sinus, Maxillary Sinus, Occult Primary:

- **Induction*/Sequential chemotherapy**
  - **Docetaxel/cisplatin/5-FU[23-25] (category 1 if induction is chosen)**
  - **Paclitaxel/cisplatin/infusional 5-FU[26]**
  - **Following induction, agents used with concurrent chemoradiation typically include weekly carboplatin, weekly cisplatin (category 2B), or weekly cetuximab[1,27,28]**

Nasopharynx:

- **Induction/Sequential chemotherapy**
  - **Docetaxel/cisplatin/5-FU[29]**
  - **Docetaxel/cisplatin (category 2B)[30]**
  - **Cisplatin/5-FU[24]**
  - **Cisplatin/epirubicin/paclitaxel**
  - **Following induction, agents to be used with concurrent chemoradiation typically include weekly cisplatin[20] or carboplatin[27]**

*The categories of evidence and consensus for induction therapy vary depending on site. (See disease-specific site in the Head and Neck Table of Contents)
**Adverse features: extranodal extension and/or positive margins.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CHEM-A
1 OF 5

PRINCIPLES OF SYSTEMIC THERAPY

- The choice of systemic therapy should be individualized based on patient characteristics (PS, goals of therapy).
- Unless otherwise specified, regimens listed below can be used for either nasopharyngeal or non-nasopharyngeal cancer.

Recurrent, Unresectable, or Metastatic (with no surgery or RT option)

- First-Line Combination Therapy Options:
  - Cisplatin or carboplatin/5-FU/cetuximab[30] (non-nasopharyngeal) (category 1)
  - Cisplatin or carboplatin/docetaxel[31] or paclitaxel[32]
  - Cisplatin/cetuximab[33] (non-nasopharyngeal)
  - Cisplatin/5-FU[32,34]
  - Cisplatin or carboplatin/docetaxel/cetuximab[35] (non-nasopharyngeal)
  - Cisplatin or carboplatin/paclitaxel/cetuximab[36,37] (non-nasopharyngeal)
  - Cisplatin/gemcitabine[39,40] (category 1) (nasopharyngeal)
  - Carboplatin/cetuximab[41] (nasopharyngeal)
- First-Line Single-Agent Options:
  - Cisplatin[33,42]
  - Carboplatin[43]
  - Paclitaxel[44]
  - Docetaxel[45,46]
  - 5-FU[42]
  - Methotrexate[47,48]
  - Cetuximab[49] (non-nasopharyngeal)
  - Gemcitabine[50] (nasopharyngeal)
  - Capecitabine[51]

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 9 of 12, September 2018) am 27.09.2018

#	Suchfrage
1	MeSH descriptor: [Head and Neck Neoplasms] explode all trees
2	MeSH descriptor: [Neoplasms, Squamous Cell] explode all trees
3	((((((((((((((((((((((((("head") or "neck") or "Upper Aerodigestive Tract") or "UADT") or "esophageal") or "esophagus") or "facial") or "face") or "mouth") or "oral") or "gingival") or "lip*") or "palatal") or "salivary") or "tongue") or "otorhinolaryngologic") or "ear*") or "laryngeal") or " larynx") or "nose") or "nasal") or “nasopharyngeal”) or "pharyngeal") or "pharynx") or "parathyroid") or "thyroid") or "trachea*"):ti (Word variations have been searched)
4	(cancer* or tum*r* or carcinoma* or neoplas* or adenocarcinoma* or sarcoma* or lesions*):ti,ab,kw
5	#2 and #3
6	#1 or #5
7	#3 and #4
8	#6 or #7
9	#8 with Cochrane Library publication date from Sep 2013 to Sep 2018
10	#9 in Cochrane Reviews and Cochrane Protocols

Systematic Reviews in Medline (PubMed) am 27.09.2018

#	Suchfrage
1	(head and neck neoplasms/therapy[mh:noexp])
2	esophageal Neoplasms/therapy[mh]
3	Facial Neoplasms/therapy[mh]
4	Mouth Neoplasms/therapy[mh]
5	Otorhinolaryngologic Neoplasms/therapy[mh]
6	Parathyroid Neoplasms/therapy[mh]
7	Thyroid Neoplasms/therapy[mh]
8	"tracheal neoplasms/therapy"[mh]
9	#2 or #6 or #7
10	#9 AND "neoplasms, squamous cell"[mh]
11	#10 OR #8 OR #5 OR #4 OR #3 OR #1
12	((head[ti] OR neck[ti] OR “Upper Aerodigestive Tract”[ti] OR UADT[ti] OR esophageal[ti] OR esophagus[ti] OR facial[ti] OR face[ti] OR mouth[ti] OR oral[ti] OR gingival[ti] OR lip[ti] OR lips[ti] OR palatal[ti] OR salivary[ti] OR tongue[ti] OR otorhinolaryngologic[ti] OR ear*[ti] OR laryngeal[ti] OR larynx[ti] OR nose[ti] OR nasal[ti] OR nasopharyngeal[ti] OR pharyngeal[ti] OR pharynx[ti] OR parathyroid[ti] OR thyroid[ti] OR trachea*[ti]))
13	(((((((tumor[ti]) OR tumors[ti]) OR tumour*[ti]) OR carcinoma*[ti]) OR adenocarcinoma*[ti]) OR neoplas*[ti]) OR sarcoma*[ti]) OR cancer*[ti]) OR lesions*[ti]

#	Suchfrage
14	squamous cell[tiab]
15	#12 AND #13 AND #14
16	((((((((((treatment*[tiab]) OR therapy[tiab]) OR therapies[tiab]) OR therapeutic[tiab]) OR monotherap*[tiab]) OR polytherap*[tiab]) OR pharmacotherap*[tiab]) OR effect*[tiab]) OR efficacy[tiab]) OR treating[tiab]) OR treated[tiab]) OR management[tiab]) OR drug*[tiab]
17	#15 AND #16
18	#17 AND pubmednotmedline[sb]
19	#11 OR #18
20	(#19) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))
21	(#20) AND ("2013/09/01"[PDAT] : "3000"[PDAT])
22	(#21) NOT "The Cochrane database of systematic reviews"[Journal]
23	(#22) NOT retracted publication[ptyp]

Leitlinien in Medline (PubMed) am 27.09.2018

#	Suchfrage
1	("head and neck neoplasms/therapy"[mh])
2	"neoplasms, squamous cell/therapy"[mh]
3	((head[ti] OR neck[ti] OR “Upper Aerodigestive Tract”[ti] OR UADT[ti] OR esophageal[ti] OR esophagus[ti] OR facial[ti] OR face[ti] OR mouth[ti] OR oral[ti] OR gingival[ti] OR lip[ti] OR lips[ti] OR palatal[ti] OR salivary[ti] OR tongue[ti] OR otorhinolaryngologic[ti] OR ear*[ti] OR laryngeal[ti] OR larynx[ti] OR nose[ti] OR nasal[ti] OR nasopharyngeal[ti] OR pharyngeal[ti] OR pharynx[ti] OR parathyroid[ti] OR thyroid[ti] OR trachea*[ti]))
4	#2 AND #3
5	#1 OR #4
6	(((((((tumor[ti]) OR tumors[ti]) OR tumour*[ti]) OR carcinoma*[ti]) OR adenocarcinoma*[ti]) OR neoplas*[ti]) OR sarcoma*[ti]) OR cancer*[ti]) OR lesions*[ti]
7	#3 AND #6
8	#7 AND pubmednotmedline[sb]
9	#5 OR #8
10	(#9) AND ((Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[ti] OR recommendation*[ti]) NOT (letter[ptyp] OR comment[ptyp])))
11	(#10) AND ("2013/09/01"[PDAT] : "3000"[PDAT])
12	(#11) NOT retracted publication[ptyp]

Referenzen

1. **Alberta Provincial Head and Neck Tumour Team.** Nasopharyngeal cancer treatment [online]. Edmonton (CAN): Alberta Health Services (AHS); 2013. [Zugriff: 01.10.2018]. (Clinical Practice Guideline Band HN-003, Version 1). URL: https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-hn003-nasopharyngeal.pdf.

2. **Alberta Provincial Head and Neck Tumour Team.** Oral cavity cancer [online]. Edmonton (CAN): Alberta Health Services (AHS); 2014. [Zugriff: 01.10.2018]. (Clinical Practice Guideline; Band HN-002, Version 1). URL: http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-hn002-oral-cavity.pdf.

3. **Garcia-Leon FJ, Garcia-Estepa R, Romero-Tabares A, Gomez-Millan Borrachina J.** Treatment of advanced laryngeal cancer and quality of life. Systematic review. Acta Otorrinolaringol Esp 2017;68(4):212-219.

4. **Grégoire V, Leroy R, Heus P, Hooft L, Van de Wetering F, Spijker R, et al.** Oropharyngeal, hypopharyngeal and laryngeal cancer: diagnosis, treatment and follow-up [online]. Brüssel (BEL): Belgian Health Care Knowledge Centre (KCE); 2015. [Zugriff: 01.10.2018]. (KCE Report; Band 256). URL: https://kce.fgov.be/en/oropharyngeal-hypopharyngeal-and-laryngeal-cancer-diagnosis-treatment-and-follow-up.

5. **Grégoire V, Leroy R, Heus P, Van de Wetering F, Scholten R, Verleye L, et al.** Oral cavity cancer: diagnosis, treatment and follow-up [online]. Brüssel (BEL): Belgian Health Care Knowledge Centre (KCE); 2014. [Zugriff: 01.10.2018]. (KCE Report; Band 227). URL: https://kce.fgov.be/en/oral-cavity-cancer-diagnosis-treatment-and-follow-up.

6. **Iglesias Docampo LC, Arrazubi Arrula V, Baste Rotllan N, Carral Maseda A, Cirauqui Cirauqui B, Escobar Y, et al.** SEOM clinical guidelines for the treatment of head and neck cancer (2017). Clin Transl Oncol 2018;20(1):75-83.

7. **National Comprehensive Cancer Network (NCCN).** Head and neck cancers. Version 2.2018 [online]. Fort Washington (USA): NCCN; 2018. [Zugriff: 01.10.2018]. (NCCN Clinical Practice Guidelines in Oncology). URL: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf.

8. **Pastor M, Lopez Pousa A, Del Barco E, Perez Segura P, Astorga BG, Castelo B, et al.** SEOM clinical guideline in nasopharynx cancer (2017). Clin Transl Oncol 2018;20(1):84-88.

9. **Quon H, Vapiwala N, Forastiere A, Kennedy EB, Adelstein DJ, Boykin H, et al.** Radiation therapy for oropharyngeal squamous cell carcinoma: American Society of Clinical Oncology Endorsement of the American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline. J Clin Oncol 2017;35(36):4078-4090.

10. **Scottish Intercollegiate Guidelines Network (SIGN).** Management of primary cutaneous squamous cell carcinoma. A national clinical guideline [online]. Edinburgh (GBR): SIGN; 2014. [Zugriff: 01.10.2018]. (SIGN publication; Band 140). URL: https://www.sign.ac.uk/assets/sign140.pdf.

11. **The Head and Neck Cancer Disease Site Group.** Epidermal growth factor receptor (EGFR) targeted therapy in stage III and IV head and neck cancer [online]. 12.2017. Toronto (CAN): Cancer Care Ontario (CCO); 2015. [Zugriff: 01.10.2018]. (Program in Evidence-based Care,

Evidence-Based Series; Band 5-12 Version 3). URL: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/576?redirect=true.