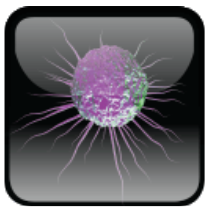
Head and neck cancer



Oxford Textbook of Oncology (3 ed.)

Edited by David J. Kerr, Daniel G. Haller, Cornelis J. H. van de Velde, and Michael Baumann

Publisher: Oxford University Press
Print Publication Date: Jan 2016
Print ISBN-13: 9780199656103
Published online: Jan 2016
DOI: 10.1093/med/9780199656103.001.0001

Head and neck cancer

Chapter: Head and neck cancer

Author(s):

Christine H. Chung, Andreas Dietz, Vincent Gregoire, Marco Guzzo, Marc Hamoir, René Leemans, Jean-Louis Lefebvre, Lisa Licitra, Adel K. El-Naggar, Brian O'Sullivan, Bing Tan, Vincent Vandecaveye, Vincent Vander Poorten, Jan Vermorken, and Michelle D. Williams

DOI: 10.1093/med/9780199656103.003.0035

Epidemiology

Head and neck squamous cell carcinoma (HNSCC) is a heterogeneous disease arising from the mucosal epithelium of the oral cavity, pharynx, and larynx. The most common risk factors for HNSCC development are tobacco and alcohol use, as well as high-risk human papillomavirus (HPV) infection [1, 2]. Concomitant use of tobacco and alcohol also appear to contribute synergistically to HNSCC carcinogenesis. Human papillomavirus-associated squamous cell carcinoma typically occurs in the oropharynx and its incidence is increasing in the Western world [3] .

HPV-negative and -positive HNSCC are demographically, biologically and clinically distinct entities with more favourable outcomes associated with HPV-positive tumours of the oropharynx [4, 5, 6].

Molecular biology of head and neck cancer

Molecular progression

Human papillomavirus-negative HNSCC develops predominantly in smokers, and a stepwise progression of molecular alterations in the squamous epithelium has been well-established (see Figure **35.1**) [7] . It is currently believed that the molecular progression model associated with the phenotypic transformation of normal epithelium to dysplasia and invasive carcinoma constitute stepwise genetic and epigenetic alterations that include gene amplification, deletion, mutation, and methylation [7]. Although the primary events remained unknown, the early alterations associated with increased genomic instability in the squamous mucosal field comprise of frequent loss of heterozygosity, functional loss of tumour suppressors and/or a functional gain of oncogenic activity [7].

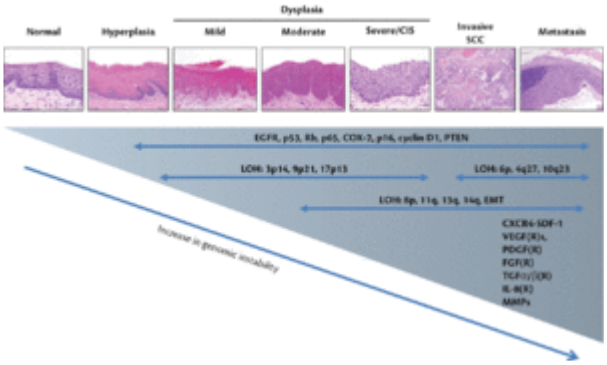


Fig. 35.1
Molecular progression of human papillomavirus-negative head and neck squamous cell carcinoma. Each step is associated with increased genomic instability or aneuploidy involving frequent loss of heterozygosity (i.e. chromosome 3p14, 9p21, 17p13, 8p, 11q, 13q, 14q, 6p, 4q27 and 10q23), functional loss of tumour suppressors (i.e. p53, NOTCH1, p16, PTEN and pRb) and/or functional gain of oncogenes (i.e. cyclin D1, EGFR, RAS and PI3K).

In contrast to the HPV-negative HNSCC, the molecular progression of HPV-associated cancer remains largely unknown. HPVs are small, non-enveloped DNA viruses, and their genome encodes various oncoproteins (E5, E6, and E7) and two capsid proteins (L1 and L2) for virion

production [8] . The integration of the virus and the human genome entails the disruption of the early exons of the HPV leading to the activities of the E6 and E7, as the critical drivers of carcinogenesis through the degradation of p53 and pRb, respectively (see Figure **35.2**) [9, 10]. Loss of p53 and pRb, two potent tumour suppressors, initiates genomic instability and leads to cell cycle deregulation [9]. Although the E6 and E7 are clearly deleterious, the simple expression of these oncoproteins is not sufficient to transform reticular epithelial crypt cells into invasive cancer. Additional genetic aberrations must be acquired. Thus, the genetic alterations required for further malignant transformation after initial HPV infection still need to be elucidated.

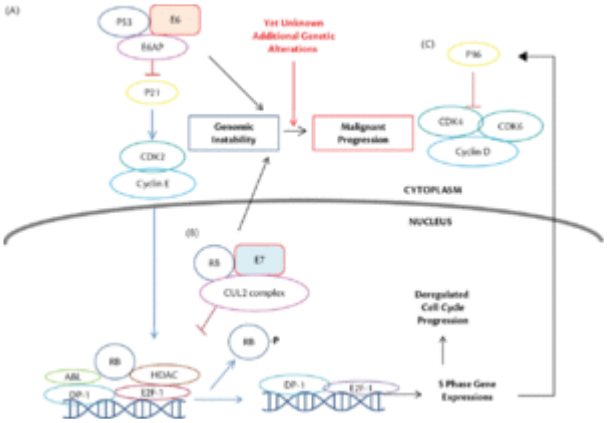


Fig. 35.2
Carcinogenesis induced by human papillomavirus. (A) E6-mediated degradation of p53; (B) E7-mediated degradation of pRb; and (C) upregulation of p16 through feedback loop induced by pRb loss and uncontrolled cell cycle progression.

Loss of tumour suppressor genes

Based on the current genomic data, it is clear that the majority of HNSCC-related mutations or deletions occur within critical tumour suppressors, resulting in loss of function. Additionally, these alterations are particularly inherent to HPV-negative disease. Among the compromised tumour suppressors, *TP53* and *CDKN2A* (p16) are well established as poor prognostic biomarkers in HNSCC.

Wild type p53 is involved in a wide range of cellular processes including autophagy, DNA damage response, cell cycle regulation, senescence, apoptosis, and ATP generation by oxidative phosphorylation [11]. Mutated p53 accumulates in the nucleus as its altered tertiary structure does not allow for proper folding, ubiquitination, and degradation. Recent

data indicate mutations that affect p53 DNA binding (disruptive mutations) are associated with worst clinical outcome compared to non-disruptive mutations. However, the presence of any *TP53* mutation is associated with worse outcome compared to wild-type *TP53* patients treated with surgery for curative intent [12]. Thus, further delineation of TP53 mutant functional complexity is of critical importance for the incorporation of these biomarkers into the development of novel HNSCC therapeutics [11].

Another important tumour suppressor gene in HNSCC is *CDKN2A*, which encodes p16. *CDKN2A* is located at Chr 9p21 and inhibits the kinase activity of CDK4 and CDK6, which induces cell cycle arrest [13]. p16 protein expression is cell cycle dependent and is focally expressed in only 5–10% of normal squamous epitheIium. In HNSCC, p16 function is frequently lost by either mutation, gene/chromosome deletion, or promoter hyper-methylation of the *CDKN2A* gene [14]. Collectively, deregulation of p16 can occur in up to 90% of HPV-negative HNSCC, while p16 up-regulation is observed in HPV-positive tumours due to E7-related pRb loss (see Figure **35.2**) [9, 15]. This results in diffuse over-expression of p16 in tumour cells and is considered a reliable surrogate biomarker for HPV positivity in oropharyngeal HNSCC.

Gain of oncogenic function

HNSCC-specific oncogene characterization is important for targeted therapies. Three common oncogenic alterations are observed in HNSCC: *CCND1* (cyclin D1), *EGFR*, and *PIK3CA*. Although these modifications are shared between HPV-positive and -negative HNSCC, differences in the frequency of their distribution are evident. In HPV-negative tumours, *CCND1, EGFR*, and *PIK3CA* mutation/amplification are seen in 32%, 15%, and 34%, respectively [16]. Meanwhile, the same alterations occur in 8%, 3%, and 56% of HPV-positive tumours [16], respectively [15]. Consequently, these data may have therapeutic implications and further clinical research targeting these alterations is required.

Genetic characterization

Recent whole exome sequencing studies of HNSCC have further validated the separation of HPV-negative and -positive HNSCC into molecularly distinct entities [5, 6]. When tumours were stratified by HPV status, HPV-positive tumours had significantly fewer mutations compared to HPV-negative tumours (4.8 versus 20.6 mutations per tumour). Commonly mutated genes included *TP53, NOTCH1, CDKN2A, HRAS, PTEN*, and *PIK3CA* [5, 6]. Of these, *TP53* is the most commonly mutated gene,

disrupted in 62–78% of HPV-negative tumours while it was not detected in HPV-positive tumours to any appreciable degree [5, 6]. These mutations would functionally disrupt epithelial differentiation and cell cycle regulations and lead to an increase in cellular proliferation. Additional mutations were observed in pathways that regulate nuclear polarity, calcium sensing, and suppression of apoptosis, which would collectively arrest maturation and provide a proliferative advantage [5] .

Molecular and growth factor characterization

At the expression level, Chung, et al. described four subtypes of HNSCC based on gene expression with distinct molecular characteristics: Group 1 tumours with high EGFR and ligand (TGFA) expression demonstrating significant EGFR activation; Group 2 tumours demonstrating epithelial-to-mesenchymal transition (EMT) with high expression of vimentin; Group 3 tumours with normal mucosal epithelium-like features; and Group 4 tumours with an up-regulation of xenobiotic metabolism, mostly observed in heavy smokers [17]. Subsequently, these four subtypes were validated by two independent datasets and each group was termed the Basal, Mesenchymal, Atypical, and Classical subtypes, respectively [15, 18]. The Atypical subtype included the majority of the HPV-positive HNSCC. In addition, various aspects of the HPV-negative HNSCC progression model could be associated with the subtypes defined above [18].

In addition, a recent gene expression study enriched with HPV-positive HNSCC (44% compared to 10–19% in other studies) revealed that tumours in the Atypical subtype can be further subdivided into two groups, resulting in five potential molecular subtypes of HNSCC [19]. Current evidence suggests the Atypical subtype should be reclassified as HPV-Mesenchymal and HPV-Classical subtypes due to the gene expression these tumours share with the Mesenchymal and Classical subtypes. However, these tumours that are aetiologically distinct harbour HPV-specific gene expression. Further delineation of the molecular characteristics associated with HNSCC through functional genomics is expected greatly to advance the development of targeted therapeutics by identifying and characterizing subtype-specific prognostic and predictive biomarkers.

Summary of molecular biology of head and neck cancers

Using the current technological advancements in genomic analysis, we have gained comprehensive knowledge and insight into the molecular biology of HNSCC. In every respect, HNSCC is a heterogeneous disease which has now been molecularly characterized into five subtypes. Predominantly, these alterations are defined by tumour suppressor loss in

HPV-negative disease, which is associated with poor prognosis and therapeutic challenges. In contrast, HPV-positive patients have good overall prognosis; however, a subset of these patients associated with worse outcome has been identified. The challenge facing future investigations is efficiently to translate what we have learned with these tools into clinically meaningful advancements in patient treatment. These are challenging goals and will require the concerted effort of HNSCC investigators from a variety of disciplines.

Pathology of head and neck tumours

The histopathologic neoplastic entities of the head and neck region are widely diverse and complex. The most common tumours arise from lining epithelium, salivary glands, and sinonasal sites. This section will focus on the most frequently encountered malignancies at these locations.

Squamous mucosal tumorigenesis

Carcinoma arising from the squamous and metaplastic mucosal lining of the head and neck sites can be broadly classified into conventional and viral-associated squamous carcinoma.

Conventional squamous carcinoma

Squamous tumorigenesis develops from the squamous mucosa of the larynx and sinonasal sites, of the oral cavity, larynx, and squamous metaplasia of respiratory epithelium [20]. These lesions are typically seen in relatively older individuals with history of exposure to and/or abuse of tobacco products and alcohol. Squamous carcinoma at these sites is typically preceded by premalignant lesions [21]. The incidence of progression of these lesions to invasive carcinoma varies considerably from patient to patient and it is currently believed to range from 10–45% [21, 22].

Premalignant squamous lesions

The progression of premalignant lesions to invasive squamous carcinoma is a multistep process resulting from progressive accumulation of genetic and epigenetic alterations [22, 23, 24] leading to invasive carcinoma (Figure **35.1**).

Squamous carcinoma

Histopathologically, squamous carcinoma are classified into conventional and non-conventional forms. The conventional form is the most dominant, and is graded based on the level of squamous manifestations and keratin differentiation into well, moderate, and poorly differentiated. The

pathologic features associated with aggressive outcome include finger-like invasive pattern, perineural invasion, depth of invasion, and distance of tumour to resection margins.

There are several less frequent phenotypic variants of squamous carcinoma; some are also shared with viral associated carcinoma of the oro- and nasopharyngeal sites (see Table 35.1 and Figure **35.3**).

Table 35.1 Head and neck squamous subtypes

Factor	Verrucous	Papillary	Basaloid	Sarcomatoid
Age	>50	30–50	>50	30–50
Grade	Low	Low	High	High
Sex	>Male	>Male	>Male	>Male
Gross	Exophytic	Exophytic	Endophytic	+/−polypoid
Site	Oral, larynx	Larynx, nasal cavity	Hypo-, oro-pharynx	Larynx, lip, oral cavity
Viral	No	?	Yes in oropharynx	No
Metastasis	No	Low	High	High when endophytic

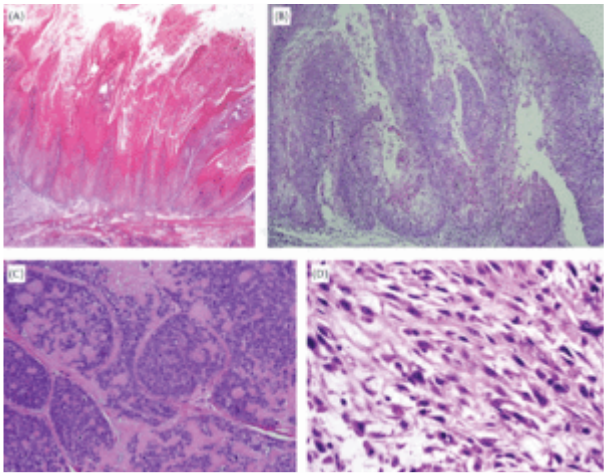


Fig. 35.3
Non-conventional squamous carcinoma subtypes in head and neck. (A) Verrucous carcinoma; (B) papillary; (C) basaloid; (D) sarcomatoid.

Verrucous carcinoma (VC)

VC is a locally aggressive, well-differentiated squamous carcinoma characterized by a warty-like appearance and broad-base rete ridges with downward growth into the stroma. In its pure form this lesion does not metastasize while hybrid verrucous and conventional squamous carcinoma may retain the potential for metastasis. The differentiation of these lesions is from verrucous hyperplasia and is difficult on small biopsies or partial excisions. The distinction can be made, however, by en bloc excision of the lesion with the adjacent mucosal shoulders. Both lesions should be excised completely.

Papillary squamous carcinoma

This is a rare type of squamous carcinoma that is generally restricted to certain locations including the larynx and the nasal cavity. It is characterized by papillae lined by neoplastic cells and an exophytic appearance with and without invasion. Evidence from an association with high- and low-risk human papilloma virus (HPV) infection has been reported.

Basaloid squamous carcinoma

This is a high-grade variant that typically presents in the pyriform sinus, tonsils/oropharyngeal sites. In non-oropharyngeal sites they are negative for HPV and associated with premalignant non-invasive lesions. The significance of recognizing this variant is important in the differential

diagnosis with solid adenoid cystic carcinoma, basal cell carcinoma, small-round-cell tumours, and melanoma on small biopsy materials. A selective panel of immunohistochemical markers can be used to establish the diagnosis.

Sarcomatoid squamous carcinoma

This rare form assumes sarcoma-like morphology and represents a transformation of conventional squamous carcinoma. The most common presentation is in the larynx, which may present as an exophytic polypoid mass or with deeply infiltrative endophytic growth. These lesions may cause differential diagnostic challenges with sarcoma, spindle cell melanoma, and pseudosarcomatous lesions. Immunohistochemical positivity for keratin may allow for the exclusion of sarcoma and melanoma. Negative results, however, may occur and close interaction between pathologists and head and neck surgeons are critical to the diagnosis and management of these lesions.

Viral associated head and neck carcinoma

These entities are commonly seen as undifferentiated/basaloid squamous carcinoma morphologies. Both arise in neighbouring structures that are lined by respiratory or squamous epithelium that covers and overlies lymphoid rich stroma. The distinctions between these forms may often be arbitrary if the tumour presents at the boundary of the naso- and oro pharynx.

Nasopharyngeal carcinoma

The nasopharyngeal carcinoma is linked to the Epstein–Barr virus (EBV) especially in endemic locations (see Figure **35.4**). Occasionally both EBV and HPV testing may be required for their differentiating. These tumours are histologically classified by WHO into keratinizing (type I) and undifferentiated subtypes (types II and III).

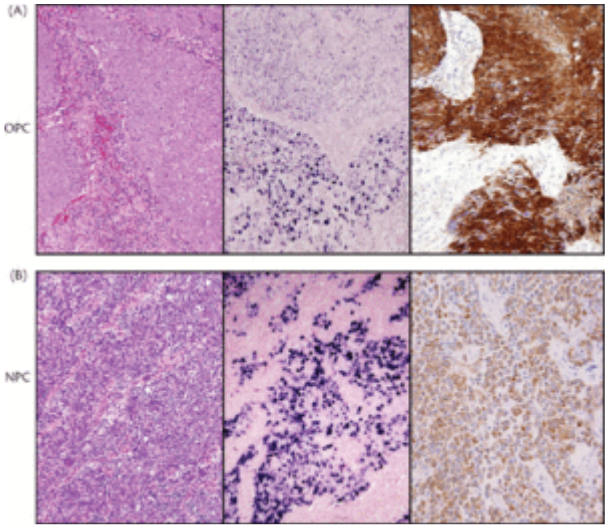


Fig. 35.4
Oropharyngeal (OPC) and nasopharyngeal carcinoma (NPC). (A) Light microscopic, HPV in-situ positivity in tumour cell nuclei, and p16 immunostaining note strong homogeneous (cytoplasmic and nuclear) positivity in tumour; (B) light microscopic and EBV (EBER, Epstein–Barr virus-encoded small RNA) in-situ image of typical undifferentiated squamous carcinoma highlighted also by keratin.

HPV-associated squamous cell carcinoma (oropharyngeal)

In contrast, to conventional squamous carcinoma which accounts for only a subset of tumours in this region, this form occurs in a different demographic population and frequency varies by country. The vast majority of these tumours are non-keratinizing/basaloid squamous carcinoma but keratinizing squamous carcinoma may also occur at these sites. The most common locations are at the base of the tongue and tonsils. These sites are characterized by invagination of squamous epithelium within the lymphoid stroma. Tumour, therefore, arise in the hidden crypts at these sites especially the tonsils. Conventional premalignant dysplastic lesions, therefore, are rarely identified. Not uncommonly, because of their location, a neck metastasis may precede the identification of the primary and may show cystic features. The majority of these cases are caused by occult primary at the base of the tongue or the tonsils. Tonsillectomy is therefore advised if the primary tumour cannot be identified by imaging. HPV in situ hybridization of high-risk variants of HPV and immunostaining by p16 are sufficient to confirm the diagnosis [25] (see Figure **35.4**).

Pathology evaluation

Intraoperative evaluation

Frozen sections are central to the evaluation of depth of invasion and of oral and lingual lesions, and in assessing the status of margins. Margins assessment requires a close cooperation between surgeon and specialized pathologist. Margins can be submitted from the defect by the surgeon or by the pathologist from the specimen. Intraoperative assessment is considered the final evaluation of margins. It is generally acceptable that a distance of 5 mm from the edge of the tumour to closet margin is a safe margin [26]. The final pathologic evaluation of the primary tumour should include positive or negative statements of the following features: size, differentiation, pattern of invasion, depth of invasion, perineural involvement, status of margins, and distance from nearest margin. If lymph node dissection is performed, the report should include the type of dissection, the number of positive and negative nodes per level, the size of the largest positive node, and whether extra-nodal extension is present or absent [27, 28, 29]. Other information that can also be included such a degree of immune response and vascular invasion. Since large numbers of squamous carcinoma undergo induction and/or adjuvant therapy prior to resection, the pathologic measurement should be adjusted to reflect the therapeutic effect on the resected tumour [30].

Pathologic reporting

Primary

The pathology report of conventional squamous carcinoma must include certain gross and microscopic features for accurate staging and clinical management. Typically the initial diagnosis is based on a core or biopsy of the index lesion. The biopsy evaluation should include the phenotype, the differentiation status, the presence or lack of submucosal invasion, and, if present, the depth.

The report of surgically excised specimens must include the following information: the histologic type, differentiation status, size of the tumour (three-dimensional), depth of invasion, perineural involvement, pattern of invasion (finger-like/pushing), distance of the closest margin (in mm), and involvement of adjacent structures cartilage/bone, and skeletal muscle.

Lymph node dissection

Close cooperation between the surgeon and the pathologist handling the case is critical to accurate orientation and proper reporting of the node status. Neck lymph nodes should either be submitted intact and then oriented on a template, or submitted as individual levels separately by the surgeon. The latter method is preferred.

Reporting should include the following information:

1. Total number of lymph nodes identified and the number of positive nodes.
2. The location/level of each positive node and the total lymph nodes in that level.
3. The size of the largest positive node.
4. The presence or absence of extracapsular spread (focal or extensive).

Sinonasal and paranasal sinuses

The spectrum of tumours arising in the sinonasal region is diverse arising from specialized Schneiderian respiratory mucosa, seromucous glands, and underlying supporting cells giving rise to some distinctly unique tumour types in this region (Figures **35.5** and **35.6**). As sinonasal tumours except squamous carcinoma are rare, careful morphologic evaluation and more importantly immunophenotyping to confirm lineage is usually required [31].

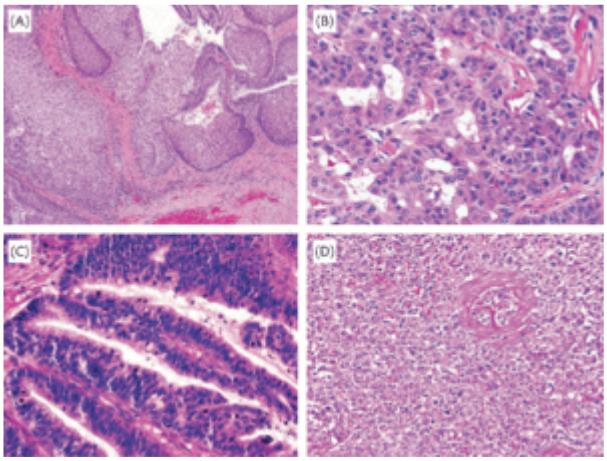


Fig. 35.5
Morphologically diverse sinonasal malignancies. (A) Squamous carcinoma (left) rising in an inverted Schneiderian papilloma (right); (B) non-enteric sinonasal adenocarcinoma, low-grade; (C) High-grade enteric sinonasal adenocarcinoma (intestinal/colonic type); (D) NK/T-cell lymphoma (angiocentric).

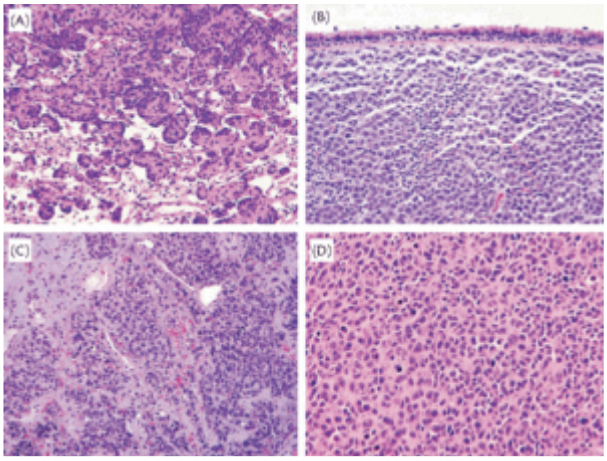


Fig. 35.6
Sinonasal ‘small’ round cell tumours morphologically overlap particularly on small biopsies. (A) Olfactory neuroblastoma with prominent Homer Wright ‘pseudorosettes’; (B) sinonasal mucosal melanoma; (C) sinonasal undifferentiated carcinoma; (D) rhabdomyosarcoma, alveolar subtype.

NUT midline carcinoma (a genetic subtype of squamal cell carcinoma (SCC))

This molecularly defined tumour (rearrangement of the NUT gene on Chr 15) is favoured to be a subtype of SCC. Often midline, though not exclusively, this highly aggressive malignancy requires ancillary testing (immunohistochemistry or fluorescence in situ hybridization [FISH]) for definitive classification which is essential for prognostic implications [32].

Adenocarcinoma

Adenocarcinomas of the sinonasal region comprise 10–20% of sinonasal malignancies and are divided into three categories based on differentiation: enteric (intestinal type), non-enteric, and salivary. They are compared in Table 35.2. Prognosis is based on the tumour subtype, grade (if applicable), and stage at presentation.

Table 35.2 Clinicopathologic features of sinonasal adenocarcinomas

Factor	Salivary	Non-salivary	
		Intestinal	Seromucinous type
Origin	Minor salivary gland	Respiratory mucosa	Minor salivary gland
Age (years)	30 to 70	60 to 70	30 to 70
Gender	Equal	> Males	Equal
Prognosis	Subtype/ stage ~50%	Grade/stage	Grade/stage
Recurrence	High (60%)	High	Yes
Risk factors	?	Wood & leather workers	?
Caveats	Classified as in major salivary glands	Usually high grade	Usually low-grade
		Exclude metastatic colon	

Sinonasal undifferentiated carcinoma (SNUC)

This rare, aggressive tumour of still debated origin often presents as locally advanced disease morphologically showing high-grade features including frequent mitoses and prominent necrosis (see Figure **35.6C**). The differential includes squamous carcinoma (often keratinizing), nasopharyngeal carcinoma (usually EBV+), neuroendocrine carcinoma, high-grade adenocarcinoma, as well as the ‘small blue cell tumours’ [33]. A comparison of the clinicopathologic features of undifferentiated carcinomas is shown in Table 35.3.

Table 35.3 Clinicopathologic features of undifferentiated carcinomas of the skull base

Feature	SNUC	NEC	NPC
Grade	High	High	High
Incidence	Rare	Rare	<0.5%
M/F	3:1	?	3:1
LN mets	30%	?	Common
Mortality	80%	50–60%	50–60%
Risk factor	?	?	EBV
Site	Nasal cavity & sinuses	Maxillary sinus	Nasopharynx
IHC/ marker	Keratin 7	Synaptophysin/ chromogranin, keratin	EBV (EBER in situ)

Abbreviations: EBER, Epstein–Barr virus-encoded small RNA; F, female; IHC, immunohstiochemistry; LN, lymph node; M, male; mets, metastases; NEC, neuroendocrine carcinoma; NPC, nasopharyngeal carcinoma.

Olfactory neuroblastoma (aesthesioneuroblastoma)

The most common neuroendocrine tumour in the sinonasal region is olfactory neuroblastoma (ONB) often a polypoid mass in the region of the cribriform plate [34] (Figure **35.6A**). The Hyam's grading system (I–IV) utilizes histologic tumour features of differentiation to define risk (necrosis, mitoses, pleomorphism, architecture, rosettes, gland formation, matrix, and calcification). However, this system is currently undergoing revalidation to exclude the newer pathologic entity of SNUC [35]. As one of the 'small round blue cell' primitive tumours, ONB must be differentiated from rhabdomyosarcoma, Ewing's sarcoma, mucosal melanoma, and the rare pituitary adenoma extending to this region. Clinicopathologic features of the small-round-cell tumours and the

Immunohistochemical evaluation essential to confirm tumour lineage for treatment are highlighted in Table 35.4.

Table 35.4 Clinicopathologic and immunohistochemical markers useful in the differential diagnosis of undifferentiated skull-base neoplasms

Feature	ONB	Ewing/ PNET	Rhabdo	Lymph-oma	NEC	Melanoma
Age (yrs)	10–20+50	<30	<20	50–60	>40	>50
Site	Cribriform plate	Maxillary	Any	Any	Any	Any
Markers:						
Keratin	-/focal	–	–/rare	–	+	–/rare
Synap	+	–/rare	–/rare	–	+	–/rare
HMB45	–	–	–	–	–	+
CD99	–	+	+/–	–	–	–
Desmin	–	–	+	–	–	–
Myogenin	–	–	+	–	–	–
S–100	Focal	–	–	–	Focal	+
CD45	–	–	–	+	–	–
Molecular	?	t(11:22)	t(2;13)*	EBV+^	?	C-kit 10–15%ʹ BRAF 5%ʹ

‘up to 50% of alveolar subtype may expression keratin and neuroendocrine markers; desmin is a sensitive screening marker’ [39].

* translocation in the alveolar subset of rhabdomyosarcoma.

^ NK/T-cell lymphoma associated with Epstein–Barr virus (EBV).

ʹ molecular profile of mucosal melanoma differs from cutaneous/sun-exposed melanoma.

Abbreviations: ONB, olfactory neuroblastoma; PNET, peripheral neuroectodermal tumour; rhabdo, rhabdomyosarcoma; synap, synaptophysin.

Non-epithelial tumours of the head and neck

Mucosal melanoma

Mucosal melanomas of the upper aerodigestive tract are histologically variable (small cells, rhabdoid, spindled, and pleomorphic), overlapping other tumour types particularly in the sinonasal region [36]. Risk factors, staging, and molecular profile are distinct for mucosal melanomas contrary to skin origin (see Table 35.4 and Figure **35.6B**).

Sarcoma

Essentially any sarcoma may arise in the head and neck, larynx, sinonasal, and skull base regions including chondrosarcomas, osteosarcomas, rhabdomyosarcoma, Ewing's sarcoma, and chordomas, as well as rare subtypes including mesenchymal chondrosarcoma, which morphologically mimics a small-round-cell tumour in the sinonasal region [37]. Pathologic review by an experienced pathologist, in conjunction with the clinical history and radiographs, aids in a timely optimized diagnosis for treatment of these rare entities.

Rhabdomyosarcoma

Rhabdomyosarcoma, a primitive malignant tumour of skeletal muscle derivation, accounts for 45% of all head and neck sarcomas with the orbit and nasopharynx being most common. There are three subtypes with variability in differential age of onset, site predilection, and prognosis. The embryonal subtype (including spindled and botryoid variants) represents the majority of cases in children. The alveolar subtype is the prevalent morphology seen in the sinonasal region, often shows a molecular translocation, and may express aberrant markers leading to misdiagnosis [38, 39] (see Table 35.4 and Figure **35.6C**). Pleomorphic rhabdomyosarcoma is rare in adults and mimics other high-grade tumours including carcinomas, melanomas and other sarcomas.

Lymphoma

The spectrum of lymphomas may involve the head and neck, often presenting in lymphoid-rich areas (tonsil, base of tongue, nasopharynx, neck and parotid lymph nodes). Three prominent subtypes of lymphoma occur in the sinonasal region: B-cell derived, T-cell derived (EBV-), and NK/T-cell (angiocentric) lymphoma, which is an EBV-positive tumour of

the sinonasal region often presenting as a midline destructive process [40] (see Figure **35.5D**). Lymphomas must be differentiated from other tumours and non-tumorous conditions (Wegener's granulomatosis and cocaine abuse), which may show similarly presenting destructive symptoms.

Salivary gland tumours

Salivary gland tumours represent approximately 10% of all head and neck neoplasms [41, 42]. Histopathologically, they comprise of widely varied subtypes with often overlapping features that may lead to differential diagnostic difficulties. The WHO classification of these neoplasms recognizes numerous benign and malignant subtypes. The primary assessment of salivary neoplasms is generally by fine needle aspiration cytology. This procedure is less sensitive in differentiating benign and malignant tumours. It is very helpful, however, in excluding reactive metastatic, infectious, and lymphoreticular malignancies. Primary benign and malignant salivary neoplasms are primarily managed by surgery. The pathological evaluation of the received mass may require intraoperative evaluation for assessment of malignancy and margins.

Pleomorphic adenoma

The most common benign tumour encountered clinically is pleomorphic adenoma. These tumours may not uncommonly recur or develop carcinoma. Careful histologic examination of the cellularity and malignant transformation is necessary. Of the 24 well-recognized salivary carcinomas, mucoepidermoid, adenoid cystic, and adenocarcinoma are the most common.

Mucoepidermoid carcinoma (MEC)

MEC is the most common salivary malignancy in both adults and children. It is formed of epidermoid, transitional, and mucinous cells and graded into low, intermediate, and high based on the presence of cystic, cellular, and cytological features. The low grade is predominantly cystic and runs a benign course if completely excised. The intermediate and high-grade MEC are more aggressive and may recur and/or develop metastasis. Therefore, grading of these tumours is important for management.

Adenoid cystic carcinoma (ACC)

This is the second most common salivary malignancy and the most biologically relentless subtype [43, 44, 45, 46]. Histologically, the tumour is generally composed of dual epithelial and myoepithelial cell formations

to form tubular, cribriform, and solid patterns. At least two of these forms exist in a given tumour. The presence of a solid component is considered an ominous feature. ACC tumours are not graded and their dominant pattern typically reflects the clinical course. ACC invariability manifest perineural invasion.

Adenocarcinoma/salivary duct carcinoma

This is generally a high-grade malignancy with poor prognosis. They may present as de novo or as a malignant transformation of pleomorphic adenoma [41, 47, 48]. This entity is characterized by a remarkable morphologic and normal resemblance to mammary duct carcinoma. The following pathologic features are critical to the management of patients with these neoplasms: tumour type, grade if appropriate, size, perineural involvement, and encapsulation and margins status. In general, the tumour type and adverse features including perineural invasion, soft tissue extension, and margins status determine the postoperative therapy.

Imaging techniques for head and neck tumours

Ultrasound

Main applications include salivary and thyroid gland and lymph nodes. For salivary and thyroid gland lesions, ultrasound should aim to differentiate benign from malignant lesions, guide biopsy or the need for further imaging evaluation by computed tomography (CT) or magnetic resonance imaging (MRI), respectively, assessing lesion number and location, texture and/or cystic content, and providing an anatomical background for nuclear imaging [49, 50]. Usually, ultrasound-guided fine needle aspiration cytology (FNAC) or biopsy is mandatory for definitive diagnosis. Ultrasound (US) is the primary modality for nodal staging in thyroid cancer and complementary in HNC. In papillary thyroid cancer, an accuracy of 89% can be obtained in 6 mm lymph nodes (see Figure **35.7**) [51]. In HNC, US has variable accuracy compared to CT and MRI; which can be increased by additional FNAC, reaching specificities of 100% and sensitivities to 73% [52, 53].

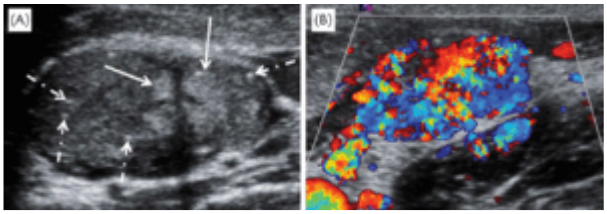


Fig. 35.7
Patient with papillary thyroid cancer. (A) ultrasound shows lymph node with heterogeneous reflective architecture (arrows) and dispersed microcalcifications (dashed arrows); (B) marked hypervascularity of the lymph node can be seen at Colour Doppler ultrasound. Diagnosis is compatible with metastatic lymph node.

Computed tomography–magnetic resonance imaging

CT is performed after injection of an iodinated contrast agent using multidetector technology. MRI is performed with high-resolution T1- and T2-weighted sequences. T1-weighted imaging is repeated after contrast injection with Gadolinium. Recently, functional diffusion-weighted MRI (DWI) is progressively included in the imaging protocol. Technical advances enable MRI to cover the entire head and neck, similarly to CT [54]. CT and MRI balance each other’s advantages and disadvantages. CT has a short examination time, and has straightforward execution. MRI shows superior contrast resolution, absent radiation exposure, and allows easy integration of functional imaging.

CT is preferred for evaluation of laryngeal, hypopharyngeal, and oropharyngeal cancer, while MRI is preferred for sinonasal, nasopharyngeal, oral, salivary gland and thyroid cancer, as well as skull base tumours and sarcomas.

Pretreatment imaging

Imaging should provide information about the anatomic subsite of the tumour, deep tumour extent over the (sub)mucosa, muscles, and skeleton, and the neurovascular bundles and nodal stage. CT better depicts subtle cortical skeletal invasion whereas MRI is stronger for detecting bone marrow infiltration [55, 56]. MRI surpasses CT to detect perineural spread for which imaging signs include obliteration of fat in or widening of the bony foramina and enlargement and contrast-enhancement of the affected nerves. Muscle invasion is best evaluated by CT or T1-weighted MRI.

In laryngeal and hypopharyngeal cancer, anatomical parameters predict local control after radiotherapy. Pretreatment tumour volume in supraglottic, glottis, and hypopharyngeal cancers identifies patients with higher likelihood of local control to radiotherapy, with tumour volume showing an inverse correlation to local control [57, 58, 59, 60]. CT-determined cartilage abnormalities are not an independent predictor of outcome [60]. In patients with supraglottic and glottic carcinoma examined by MRI, invasion of the pre-epiglottic space, thyroid and cricoid cartilage, and hypopharynx are strong predictors of local outcome post radiotherapy [61, 62].

For detection of nodal metastases, sensitivities between 48% and 97% and specificities between 39% and 96% [63] are reached using the criterion of 10 mm for short axis diameter. Morphological criteria like necrosis and extracapsular spread improve sensitivity but are rare in subcentimetric nodal metastases. Therefore, anatomical imaging criteria lack sufficient accuracy to stage the N0-neck.

Post-treatment imaging

Tumour recurrence appears as a contrast-enhancing soft tissue mass originating at the irradiated primary site or along the resection margin [64]. In contrast, mucosal necrosis is characterized by absent contrast enhancement and sometimes the occurrence of gas bubbles (see Figure **35.8**). Laryngeal necrosis shows variable soft tissue swelling, fluid around the necrotic cartilage and/or cartilage fragmentation, collapse, dislocation, lysis or sclerosis [64].

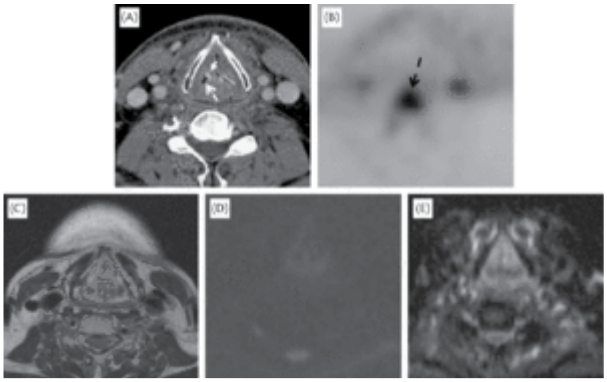


Fig. 35.8
Patient four months after chemoradiotherapy for laryngeal cancer: (A) CT-scan shows diffuse swelling of the soft tissues, dislocation and sclerosis of the right arytenoid (arrow) and small air bubbles adjacent to the arytenoid (dashed arrow). (B) ^{18}F-FDG-PET shows marked hypermetabolism in the larynx not able to distinguish tumour recurrence from inflammation. (C) T2-weighted MRI shows diffuse laryngeal hyperintensity indicating oedema. (D) No focal abnormalities are seen at the b1000 DWI while the (E) calculated ADC-map is bright. Histopathology showed laryngeal necrosis.

Combining post-treatment baseline and three-months CT or MRI during follow-up improves detection of tumour recurrence in laryngeal and hypopharyngeal cancer. CT can detect tumour recurrence with sensitivity of 83% and specificity of 95% [64]. In contrast, for oropharyngeal cancer, CT scan six weeks post treatment does not have major incremental value to clinical evaluation. MRI six to eight weeks post treatment can predict local control with 48% sensitivity and 85% specificity [51].

For lymphadenopathies, CT eight weeks post treatment may avoid neck dissection. A decrease ratio of more than 50% measured on CT imaging tends to result in a negative hemineck, while high negative predictive value (NPV) up to 95% can be reached based on nodal diameter and absence of focal lucency. However, anatomical imaging criteria suffer from low discriminative value in enlarged lymph nodes [65, 66].

Functional CT and MRI

Functional CT and MRI provide a surrogate marker for perfusion (CT perfusion and perfusion MRI) and cellularity (DWI).

Perfusion imaging is acquired by continuous scanning during contrast injection. Main applications include prediction and early response

assessment. Pretreatment CT perfusion may predict response after induction chemotherapy, chemoradiation or surgery [66]. CT perfusion after 40 and 70 Gy of radiation in patients treated with chemoradiation allows treatment monitoring [67]. Pretreatment perfusion MRI parameters are predictive for outcome in stage IV nodal disease and differentiate complete versus partial response to chemoradiation at six months follow-up [68].

DWI probes water mobility changes related to tissue cellularity, quantified by the apparent diffusion coefficient (ADC) being used for nodal staging, post-treatment imaging and response assessment [54]. DWI shows sensitivities between 83% and 98% and specificities between 97% and 87% for detecting nodal metastases [54, 69]. For detecting post-(chemo)radiotherapeutic recurrence, DWI shows sensitivities between 84% and 94% and specificities between 90% and 100% (Figures **35.8** and **35.9**) [70, 71]. For response assessment during chemoradiation, absent ADC-changes (ΔADC) relative to baseline, one week, two weeks, and fours weeks during CRT were predictive for tumour recurrence during six months follow-up, respectively. At two years follow-up, significant increase of ADC was a strong predictor of clinical remission [72, 73]. Sensitivities to predict tumour relapse ranged from 86% to 100% and specificities from 83% to 96%. In a study, evaluating the ΔADC, three weeks after completion of chemoradiation, DWI showed a positive predictive value (PPV) of 89% and negative predictive value (NPV) of 100% to predict local control and PPV of 70% and NPV of 96% to predict nodal regional control [74].

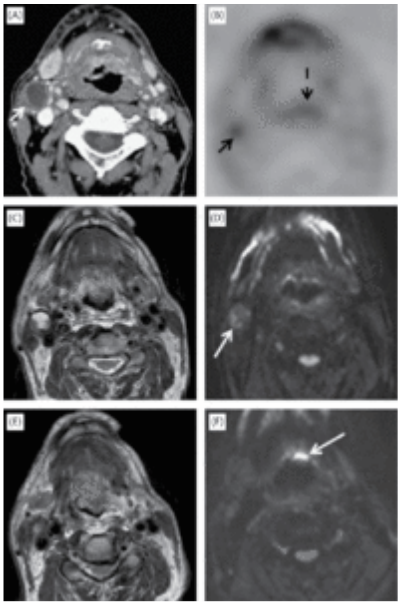


Fig. 35.9
Patient five months after chemoradiotherapy for supraglottic laryngeal cancer shows (A,B) metastatic adenopathy in level 2 of the right neck at PET/CT. Inflammatory changes are seen in the tonsillar area (dashed arrow). (C) T2-weighted and (D) DWI confirm the adenopathy where the viable tumour deposits appear hyperintense at DWI (bright; arrow). In correlation to (E) contrast-enhanced MRI, (F) DWI shows a small hyperintense lesion in the left epiglottis suspect for recurrent primary tumour; confirmed at biopsy after endoscopy.

^{18}F-FDG PET/CT

^{18}F-FDG is the most commonly used tracer for clinical PET imaging and has gained major advances with hybrid PET/CT, integrating metabolical and morphological information. Typically, PET/CT is initiated 60 to 90 minutes after injection of the radiotracer after scanning the CT portion. High-dose CT with intravenous contrast is recommended. A dedicated CT of the head and neck can be performed prior to whole body imaging, increasing sensitivity for detecting small lesions such as small nodal metastases [75].

Pretreatment imaging

In general, PET or PET/CT improves the detection of primary tumours reaching sensitivities and specificities of 95% and 92% compared to 68% and 69% for CT [76]. PET detects unknown primaries in 10% to 60% of patients with neck lymphadenopathy [77]. In patients with negative

physical examination and MRI, PET detects up to 27% of unknown primaries. Baseline FDG-PET characteristics may hold prognostic value. Patients with high FDG uptake have significantly lower control rate (55% versus 86%) and disease-free survival (42% versus 72%) than patients with low uptake [78].

For nodal staging, PET increases sensitivity ranging between 70% to 100% and specificity between 82% and 94% for PET compared to contrast-enhanced CT showing sensitivities between 48% and 97% and specificities between 39% and 96% [78]. PET complements anatomical imaging by detecting subcentimetre lymphadenopathy. However, the low spatial resolution of PET restricts its use in the N0 neck.

Staging of distant metastases is a core application for PET/CT (Figure **35.10**). PET can detect unknown distant metastases in up to 10% of patients during screening [79]. In addition, PET/CT can detect synchronous lung or upper digestive tract tumours. In a study by Schwartz et al., FDG-PET detected distant metastases or second primary in 30% of patients [80]. In a prospective multicentre study by Lonneux et al, FDG-PET detected unknown metastases or second primary tumours in 13 of 233 patients [81].

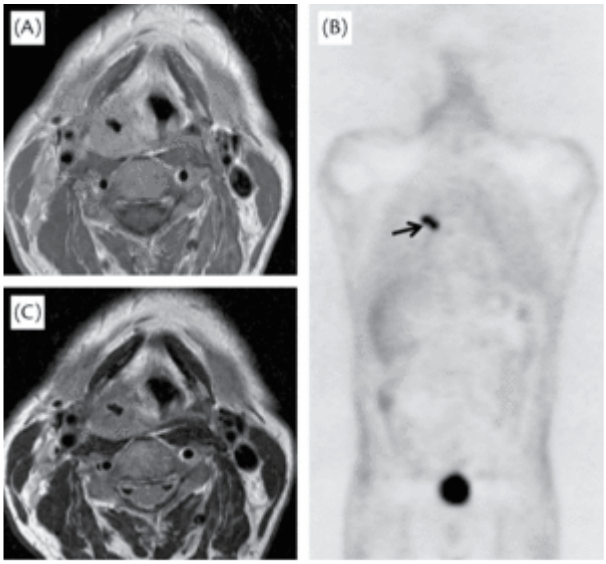


Fig. 35.10
Patient presenting with new diagnosis of (A) and (B) right-sided pyriform sinus cancer with multiple lymphadenopathies in the right neck at T1-weighted contrast enhanced MRI and T2-weighted MRI. (C) Additional ^{18}F-FDG-PET shows hypermetabolic lymph node in the right hilum of the lung (arrow) confirmed as nodal metastasis after endobronchial ultrasound guided biopsy.

Post-treatment imaging and response assessment

^{18}F-FDG-PET/CT more accurately detects tumour recurrence than anatomical imaging with sensitivities between 83% and 100% and specificities between 61% and 94% compared to 38% to 75% sensitivities and 44% to 100% specificities for CT or MRI [77]. It is generally considered that ^{18}F-FDG-PET two to four months post treatment allows better assessment of possible tumour recurrence than scanning at an earlier phase [77]. Four months ^{18}F-FDG-PET is a better predictor of tumour recurrence, while the specificity of ^{18}F-FDG-PET decreases significantly when performed earlier than 12 weeks post chemoradiation (see Figure **35.8**) [81, 82]. For imaging surveillance post chemoradiation, ^{18}F-FDG-PET shows sensitivities between 93% and 100%, with specificities between 63% and 94% [83].

Data on ^{18}F-FDG-PET response assessment during non-surgical treatment are relatively scarce. ^{18}F-FDG-PET four weeks after start of radiotherapy shows an NPV of 100% but a low PPV of only 17% to predict local control [84]. In ^{18}F-FDG-PET before and one to three weeks after radical non-

surgical treatment, high metabolic ratio post treatment is associated with 62% complete remission rate and 35% five-years' overall survival, while a low metabolic ratio is correlated to a 96% complete remission rate and a 72% overall survival [85].

Summary of imaging for head and neck tumours

Various imaging techniques are available for diagnostic evaluation of head and neck cancer patients, and the choice of imaging technique is usually based on clinical presentation and stage as well as patient tolerance and technique availability. Ultrasound, CT, and MRI remain the primary imaging modalities for HNC, providing lesion characterization, staging, and prognostication. Functional imaging improves the diagnostic yield in HNC.

Tumours of the nasal cavity and paranasal sinuses

Introduction to tumours of the nasal cavity and paranasal sinuses

Tumours of the nasal cavity and paranasal sinuses are rare and include a wide spectrum of malignancies, squamous cell carcinoma being the most frequent in the adult population and sarcoma in children. They account for 0.2–0.8 of all malignant tumours and 3% of those arising in the head and neck. Males are twice as affected as females. The peak incidence ranges between 50 to 70 years of age [86, 87]. Sinonasal tumours originate most frequently in the maxillary sinus (60%) followed by the nasal cavity (20–30%), ethmoid sinus (10–15%), and sphenoid sinus and frontal sinuses (less than 1%). Differences in histology distribution relate to the site of occurrence. Moreover, adenocarcinoma prevails in the ethmoid sinus in all the European series [88, 89], whereas the American series often report a higher prevalence of squamous cell carcinoma [90, 91].

Wood and leather workers have an increased risk of developing an ethmoid adenocarcinoma (5- to 50-fold). Tobacco smokers have a consistent association with sinonasal cancer and particularly with SCC. Exposure to formaldehyde, diisopropyl sulfate, or thorium oxide (Thorotrast), a radioactive thorium-containing contrast material used for radiographic study of the maxillary sinuses represents an additional risk factor [92]. These tumours tend to spread from one sinus to another through the foramina and fissures of the surrounding bone and show vascular, perineural, and lymphatic extension. Finally, they can involve the whole sinus complex and extend to vital structures such as the carotid artery, the cavernous sinus, the orbit skull base, and the brain.

Sinonasal tumours are usually asymptomatic in an early stage. Tumours often masquerade as a chronic inflammatory condition until they are advanced. The extension of the disease at diagnosis and the complexity of the anatomic field make the treatment of these tumours a challenging task.

Complete surgical resection followed by radiotherapy or radiochemotherapy are widely recognized as the gold standard for these tumours. Despite refinement of surgical techniques and more sophisticated chemoradiation protocols, the prognosis of these tumours continues to be disappointing.

Diagnosis and staging

Sinonasal tumours are often diagnosed at an advanced stage. Initial symptoms are generally non-specific including nasal obstruction, moderate epistaxsis, and hypoanosmia. Once the neoplasm increases in volume, the clinical appearance depends on structures that have been involved by tumour extension. Swelling of the cheek or palate and loose teeth may be associated with oral cavity invasion; diplopia, impaired ocular motion, and proptosis when the orbit is invaded; trismus when tumour extends to the masticatory space and pterygoid; neurologic deficit, headache or cerebrospinal leakage when tumour erodes the skull base and involves dura and brain.

Bone destruction is found in up to 80% of the cases. About 60% of ethmoidal tumours present with intracranial involvement [93] and 66–82% show orbital wall invasion [94]. Orbital invasion occurs in 60–80% of maxillary sinus malignancies and in about 45% of nasal tumours. Cervical lymph node enlargement can also be detected.

Biopsy is mandatory to define the nature of the lesion and to plan the proper clinical approach. The exact definition of the anatomical margins of the tumour has significant implication for staging, treatment selection and prognosis. Consequently computed CT and MRI of the head and neck along with investigations to demonstrate distant metastases are always required. CT scans provide important evaluation of bony cortical erosion and information about the extent of the tumour through the surrounding bone such as orbital floor, lamina papiracea, cribriform plate, hard palate, and skull base. Better distinction of the tumour from the adjacent soft tissue can be achieved with MRI. In particular, MRI gives better indication about tumour invasion of the orbital contents, carotid artery encasement, perineural invasion and perineural tumour spread, dura mater, and brain and cavernous sinus involvement. MRI and CT scan are both useful to asses posterior spread of tumour into the pterygopalatine fossa [95]. Paranasal tumours are staged according to TNM–AJCC

classification (TNM, 7thed.). In 2005 Cantù and coworkers validated on a large series of patients a new classification (INT classification) for malignant ethmoid tumours based on the most commonly accepted prognostic factors. This classification does not include N status but in comparison with the TNM staging system seems to provide a better prognostic discrimination among T classification [96].

Treatment

The choice of treatment strictly depends on site and extension of the disease and histology. Surgery associated with radiation or radio-chemotherapy therapy is the gold standard in many cases.

For certain tumours with very poor prognosis such as melanoma, neuroendocrine carcinomas including undifferentiated carcinoma (SNUC) and sarcomas, the role of surgery is questionable. Usually, these malignancies are well treated with radiochemotherapy therapy and surgery is considered for palliation or sometimes for rescue after locoregional recurrences.

Surgery

Limited tumours of the maxillary sinus or nasal vestibule can usually be treated with surgery alone. Advanced tumours of the maxillary sinus are treated according to the extension and location of the neoplasm with an anterior craniofacial resection or tailored maxillectomy. The surgical management of the orbital involvement is still controversial. Any attempt should be made preoperatively to distinguish between erosion of the bony orbital wall, involvement of the periosteum, and deeper penetration involving the orbital soft tissue. The orbital contents can usually be spared when there is no invasion of orbital fat and musculature or involvement of the orbital apex [94].

The invasion of the pterygopalatine fossa and the infratemporal fossa can be dominated by an anterolateral craniofacial approach. Ethmoid tumours growing far from the lamina cribrosa can be treated by transfacial ethmoidectomy. Ketcham in 1963 described the technique of craniofacial resection for a large tumour involving the nasal cavity and the ethmoid sinus approaching or involving the skull base [97]. For many years this combined transcranial-transfacial approach remained the gold standard of anterior skull base tumours [93, 98]. In the late 1990s, these tumours were also treated by an innovative endoscopic technique with or without craniotomy [99, 100]. The comparison between the techniques in terms of outcome and complications is difficult to make. However, recent reports seem to support that endoscopic resection results in a low complication rate and acceptable disease-free survival in selected cases.

The current contraindications to classical craniofacial resection are far less stringent compared to those outlined by Ketcham in his experience. Large brain involvement, encasement/invasion of the internal carotid artery, extensive skull base erosion, and invasion of the cavernous sinus are usually considered a contraindication for surgery.

The contraindications for endoscopic surgery are extensive lacrimal pathway infiltration, involvement of the anterior wall and lateral portion of the frontal sinus, hard palate, nasal bone, and infiltration of the bony walls of the maxillary sinus, with the exception of the medial one.

Neck dissection is indicated only when positive nodes have been clinically detected.

Radiotherapy

Depending on the location and the histopathology of the tumour, treatment using radiation therapy is either in the definitive or adjuvant setting. Because multiple critical normal tissues are located within or near the skull base (e.g., frontal and temporal lobes of the brain, the optic chiasm, the cranial nerves, the orbits, the lacrimal glands, and the brainstem), radiotherapy techniques are focused on treating the tumour while minimizing toxicities and complications. Using conventional radiotherapy techniques, the lacrimal apparatus and the optic pathway structures (retina, optic nerves, chiasm) often received doses equal to the target prescription dose. Conventional radiation therapy for sinonasal cancer resulted in significant ocular toxicity [101, 102]. Local control rates of 90–70% in stages T1–T2 and below 50% in stages T3–T4 were, however, achieved with prescription doses of 56–75 Gy [103].

In this framework, the use of intensity modulated radiation therapy (IMRT) has progressively emerged as the method of choice. IMRT allows selective under-dosage of organs at risk by creating concave dose distributions around the optic pathway structures together with steep cranial, lateral, and caudal gradients outside the planning target volumes to spare the lacrimal apparatus and the central nervous system. In a series of 62 patients with sinonasal tumours (ethmoid sinus, maxillary sinus, and nasal cavity) with adenocarcinoma and squamous cell carcinoma, the four-year actuarial local control after surgery and IMRT was above 80% for patients with T1-T4aN0M0 disease [104]. Eleven patients had T4b tumours with invasion of the dura or brain through the cribriform plate. Fatal relapses occurred within a year after treatment in all of those patients. IMRT implementation was clearly not able to reverse the dismal local control rates that are known to exist in stage T4b with cribriform plate invasion. In this series, severe dry-eye syndrome could be

avoided in almost all patients if attempted. Severe optic pathway injury occurred in about 5% of patients. Such complication rates were much lower in comparison to patients previously treated in the same institution prior to the implementation of the IMRT technique.

Chemotherapy

Overall, there are very few reports on the use of chemotherapy in sinonasal carcinomas, and sinonasal squamous cell cancer is not included in the typical head and neck prospective randomized trials on chemotherapy (and/or radiotherapy). Nevertheless, the principles of chemotherapy as outlined in the section on locoregionally advanced larynx and hypopharynx cancer and the section on recurrent/metastatic squamous cell carcinoma of the head and neck are also applicable for sinonasal squamous cell carcinoma. Different schedules have been used in the locoregionally advanced disease setting, but regimens most often applied were platinum based, with a response rate ranging from 36% to 87% [105, 106, 107]. Survival figures of different treatments of advanced squamous cell carcinoma of the paranasal sinuses have not changed significantly in the last 20 years. Local recurrence at the primary site and distant metastases are the most common patterns of treatment failure. New approaches should therefore focus on these issues. The incorporation of induction chemotherapy (ICT) in the multimodality treatment of advanced cancer of the paranasal sinuses has shown some promise in this regard [106, 107]. Tumour response to ICT in such patients was suggested to be predictive of treatment outcome and prognosis, giving, moreover, a reasonable chance of organ preservation [106]. Data from the Milan Cancer Institute suggests that sinonasal adenocarcinomas are also chemosensitive, and that patients with such tumours might also be candidates for primary chemotherapy [108]. In the subgroup of patients with ethmoidal intestinal-type adenocarcinomas it was found that those patients who reached a pathologic complete response showed significantly less recurrences in follow-up than those who did not. Moreover, they found that p53 status could be a promising biomarker to predict response to chemotherapy [109, 110].

Sinonasal malignancies with neuroendocrine differentiation (with the exception of esthesioneuroblastomas (ENB) might also benefit from trimodality management, given the higher rates of systemic failure for patients with SNUC, sinonasal neuroendocrine tumours (SNEC) and those with small-cell cancers (smCC) than for those with ENB [111, 112]. In contemporary studies cisplatin is the drug of choice when given concurrently with radiation, and taxane/platinum based regimens for induction, such as TPF (docetaxel, cisplatin, 5-fluorouracil).

A different approach for adenocarcinoma (often found in patients with a woodworker's history) of the ethmoid sinus has been described by the Rotterdam group [113], using a techniques modified from that originally described by Sato et al in 1970 [113, 114]. Surgical debulking performed via an extended anterior maxillary antrostomy is followed by a combination of repeated topical chemotherapy (5-fluorouracil) and necrotomy [113]. Of the 62 patients treated, eight (13%) required additional radiotherapy for local recurrence, while one patient needed surgery for regional lymph node metastases. Results were surprisingly good. Adjusted disease-free survival at five and ten years was 87% and 74%, respectively. Periorbital swelling occurred in 40%, cerebrospinal fluid leakage in 8%, and meningitis in one patient. A similar observation has been made by another research group [115].

Prognosis

Histology, tumour stage, margin status (where applicable), and site of occurrence affect the prognosis of sinonasal malignancies.

Despite the improvement of surgical techniques and novel radiochemotherapy regimens, the prognosis of these malignancies remains poor with an overall treatment five-years' survival ranging between 30% and 50%. Esthesioneuroblastoma has the best prognosis of all paranasal sinus tumours with a five-year disease-free survival (DFS) of up to 84% to 100%. The prognosis is good for minor salivary gland tumours and low-grade sarcomas with a five-year DFS of about 70%, while patients with adenocarcinoma have a better DFS than those with squamous cell carcinoma (52% versus 43.6%). Sinonasal undifferentiated carcinoma show a five-year DFS less than 20%, while all the patients with mucosal melanoma die of disease within two years after treatment. Intracranial and orbital involvement are also significant predictors. The tumour invasion of the skull base, dura, and brain progressively decreases the five-year DFS from 55.1% to 28.4%. Orbital invasion correlates with poor prognosis with a five-year DFS of 75% in patients with no orbital involvement compared with a DFS when there is periosteum/bone involvement of 40.7%. The importance of a proper surgical approach is well demonstrated by the effect of surgical margins status on disease-specific survival. Complete removal of the tumour with clear margins results in a five-year DFS of 68% compared with less than 30% when surgical margins are positive at histology [98].

Nasopharyngeal carcinoma

Introduction and epidemiology

Nasopharyngeal carcinoma (NPC) differs in many respects from other mucosal head and neck cancers. Its complicated location juxtaposed to the central skull base, and extremely high propensity to develop lymph node metastases in surgically inaccessible sites (e.g., retropharyngeal) means that the role for surgery in initial treatment is limited. The geographic and ethnic distribution is also distinct with the overwhelming majority of patients presenting in Asia, particularly in southern China (including Hong Kong, where the incidence is 25 cases per 100,000 per year, compared to 1–3 per 100,000 in Europe and North America) [116, 117], with high rates also found in Indonesia and neighbouring countries. Unexpected and intermediate rates are also evident among Inuit peoples of North America and certain regions in North Africa and the Mediterranean littoral regions. While all ages and gender are at risk, the peak is in the 40–60-year range in high-risk regions and bimodal peaks at 15–24 and 65–79 years in low-risk regions [118]. The incidence is two-to-threefold higher in men compared to women. A multifactorial aetiology includes inherited genetic predisposition, viral infection, and exposure to dietary/environmental factors in the first decade of life.

Histopathology classification of the nasopharynx includes non-keratinizing, keratinizing, and basaloid types according to the World Health Organization (2005) system. Most patients, especially in high-risk regions, have the non-keratinizing type, which is almost invariably associated with EBV, irrespective of patient ethnicity. It is further subclassified into undifferentiated and differentiated subtypes, although this distinction confers no obvious clinical significance. Human papillomavirus and/or smoking may contribute to cases in lower risk populations [119].

Presentation and primary disease assessment

The most common presenting symptom is a painless enlarging upper neck mass, classically in level 2, but any regional lymph node area is a candidate for involvement. Retropharyngeal nodes are very common and usually require imaging to detect them. Level 1 and parotid lymph nodes may be uncommonly involved. The primary tumour is often asymptomatic or may be associated with blood-stained postnasal secretion and nasal obstruction. Symptoms of tinnitus or impaired hearing are frequent and should prompt specific workup in an Asian patient. More advanced presentations may include aural pain or discharge, headache, facial numbness, diplopia, trismus, dysphagia, and dysarthria.

Initial assessment involves a detailed history and physical examination with special focus on cranial nerves (sixth being most common). Diagnosis is often established by nasopharyngoscopy and biopsy in the ambulatory setting. Preferred initial imaging is MRI, but if unavailable, contrast-enhanced CT is an alternative. Unfortunately, CT is less effective in evaluating perineural intracranial extension without bone erosion, cavernous sinus involvement, and in differentiating retropharyngeal nodal disease from posterolateral extension of primary disease.

Additional staging and supportive approaches

Audiometry and dental assessment are required. Additional workup should include complete blood count, serum biochemistry (including liver and renal function tests) to address disease-related issues but to also prepare for the use of chemotherapy. This should include hepatitis screening in risk patients, since polymerase inhibitors to block hepatitis B replication may be needed to address associated compromise in delivering chemotherapy. For stage III–IV, metastatic workup should include PET with CT; a CT of chest and abdomen and isotope bone scan may be used instead. Pre- and post-treatment plasma/serum load of EBV-DNA measured by copy number can prognosticate in the early phase of management, including attention to the rate of clearance of the viral load [120]. EBV copy number may also augment traditional TNM staging with evidence that it may surpass the prognostic value of some subsets of anatomic stage [121]. This test also facilitates early detection of disease recurrence, especially distant metastasis [122]. Serum EBV serology to assess the IgA response to the viral capsid antigen may be useful for screening and diagnosis, but studies suggest less value for prognostication and post-treatment surveillance [123, 124].

Radiotherapy for NPC

Definitive IMRT, generally with chemotherapy, is the primary treatment for NPC because it is radiosensitive and its anatomic location makes surgery technically difficult. This results from the need to eradicate insidious disease in the base of skull and to address the retropharyngeal nodes. Initially, institutional reports more than a decade ago showed dramatically improved tumour control with IMRT compared to historical expectation. These investigators demonstrated four-year estimates of locoregional and distant progression-free rates of 98% and 66% respectively [125] which has effectively changed the standard of care for this disease while recognizing that distant disease remained the predominant problem. These observations were coupled with the observation of dramatic reversal of xerostomia rates, due to the salivary sparing capability of IMRT, with only very few suffering from grade 3

xerostomia after two years. The Radiation Therapy Oncology Group (RTOG) confirmed these results in a multicentre single-arm phase II trial showing two-year locoregional, and distant metastasis-free rates of 89.3%, and 84.7%, respectively. Only two patients complained of grade 3 xerostomia at one year [126].

Subsequently, randomized phase II trials were designed to demonstrate the ability of IMRT to ameliorate normal tissue-related sequelae (xerostomia and quality of life) in early disease [127, 128] but were underpowered to address efficacy. Locally advanced disease was presumably not included in these randomized studies due to the challenges in protecting adjacent critical anatomy with non-IMRT techniques. However, these results were recently corroborated in a large phase III trial involving 616 patients that also showed a survival advantage (80% versus 67%, $p = 0.001$) for IMRT compared to two-dimensional conformal treatment (2D-CRT) [129]. The five-year actuarial local control rate was 90.5%, 91%, and 81.5% for IMRT versus 84.7%, 80%, 62.2% for 2D-CRT for all cases, T3, and T4, respectively, with corresponding improvements in xerostomia and hearing loss favouring IMRT.

General treatment approaches

Early disease

Stage I disease should be treated by radiotherapy alone (preferably IMRT) with an excellent expectation of outcome.

In stage II, concurrent chemoradiotherapy is often recommended without induction or adjuvant chemotherapy. Supporting data are limited but evident from a single randomized trial [130]; however, concerns remain since many low-risk patients can be safely treated by radiotherapy alone.

Locally advanced disease

Concurrent chemotherapy

Stage III IVB disease is universally accepted as requiring combined modality treatment with both IMRT and chemotherapy. In the only individual patient data (IPD) meta-analysis of chemotherapy in NPC (MAC-NPC), an 18% risk reduction in overall survival, representing a five-year absolute reduction in death of 6% from 56% to 62%, was seen [131]. The main contribution was from concurrent chemotherapy (risk reduction of 40% with only modest contributions from induction and adjuvant chemotherapy). Other literature-based meta-analyses and the embodied contributing clinical trials have also supported this. There is therefore no

doubt that concurrent cisplatin-based chemotherapy in addition to radiotherapy is absolutely necessary if the best chances of disease control and survival are to be achieved. However, controversies continue regarding the other aspects of treatment sequencing which are the focuses of future clinical trials.

Adjuvant chemotherapy

The need for subsequent adjuvant chemotherapy, a traditional component of management, has recently been challenged by a negative phase III multicentre randomized trial that compared concurrent chemoradiotherapy with or without adjuvant chemotherapy in locoregionally advanced disease [132]. Progress may be realized from the design of future biomarker-guided trials that stratify patients at completion of concurrent chemoradiotherapy according to residual EBV load before randomization to address the need for and intensity of adjuvant chemotherapy in different risk groups. Multicentre trials of this kind will also require attention to collaborative efforts to harmonize such quantitative plasma EBV DNA assays [133].

Induction chemotherapy

Induction chemotherapy is attractive in very advanced disease because its pre-emptive use may eradicate micro-metastasis while also reducing the size of overt gross locoregional disease; this may permit safer delivery of high-dose radiotherapy to ensuing gross disease close to critical structures (e.g., brainstem, optic chiasm), but should not reduce the dose to the elective target regions at risk of harbouring microscopic disease [134]. However, an ongoing concern is whether full-dose induction chemotherapy could compromise the delivery of the essential concurrent phase in terms of total dose of chemotherapy, numbers of cycles, and the delivery of radiotherapy to its intended completion, and whether such compromises are meaningful from a clinical outcomes perspectives. These are the focus of ongoing randomized trials that especially address newer agents, such as taxanes that were not traditionally used for induction approaches in NPC. Promising results are suggested by a small phase II randomized trial that compared neoadjuvant docetaxel and cisplatin versus cisplatin alone [135].

Very advanced disease

Stage IVC requires individualized approaches. Radical treatment should be considered for patients with good performance status and disease confined to oligometastasis [136, 137, 138].

Management of treatment failure

Patients should be closely monitored because early detection of recurrence significantly affects the chance of survival. Aggressive salvage should be considered for patients with local/regional recurrence or oligometastasis.

Management of local and/or regional failure

Options for local failure include surgery, external beam re-irradiation (EBRT), brachytherapy, stereotactic radiosurgery, chemotherapy, and photodynamic therapy. The choice of treatment is determined by the extent and location of the tumour, the availability of local resources and expertise.

Surgery is generally considered the treatment of choice if the tumour is resectable. For small and superficial recurrence, resection via the endoscopic approach, or by transoral robotic surgery, is preferred [139]. When the tumour extends across the midline or invades the parapharyngeal space, open surgical approach is indicated; approaches include a lateral infratemporal approach, and inferior transpalatal, transmaxillary, and transcervical approaches [139, 140, 141]. For regional failure, neck dissection is indicated. When resection margins are positive or there is extracapsular disease, post-operative re-irradiation is recommended.

If salvage surgery is not feasible, re-irradiation with or without concurrent chemotherapy may be considered. Smaller than usual radiotherapy fraction sizes delivered twice daily may reduce late toxicity.

Brachytherapy has shown good results for small recurrences with a five-year control of 62% [142]. With radioactive gold implants five-year local control of 70% and overall survival of 64% are achieved [140, 143].

Stereotactic radio surgery can be delivered in one fraction or fractionated. Local control rates do not differ significantly from the results of brachytherapy, but there is a wide range [143]. In addition, severe complications including massive epistaxis, cranial nerve palsies, and temporal lobe necrosis occur. Tumours near the fossa of Rosenmuller and foramen lacerum have the highest risk of haemorrhage due to the location of the carotid artery. Complication rates for fractionated stereotactic surgery are marginally lower than stereotactic surgery, but survival rates do not differ. Long-term results are awaited to evaluate superiority.

A relative new approach is photodynamic therapy (PDT). After intravenous administration of a photosensitive drug, illumination of the tumour will result in cell death with a penetration depth of 0.5–1 cm.

Although only small studies are available, preliminary results are promising [144, 145]. Pain is the worst side effect and sometimes ‘sunburn’ is evident if the patient is exposed to sunlight too soon. A gradual return to sun exposure over two to three weeks is necessary.

Management of distant metastasis

Distant metastasis is the main form of failure. For oligometastasis, surgery, radiation and chemotherapy can be used, and cure is possible in a small subset of patients [138]. For extensive metastasis, palliative chemotherapy with/without radiotherapy to symptomatic sites can be considered. When patients are chemo-naive, cisplatinum-based regimens give the best responses. Otherwise combinations of platinum-based chemotherapy with gemcitabine, capecitabine, or docetaxel could be used [146].

Tumours of the oral cavity

Introduction to tumours of the oral cavity

Therapy of squamous cell carcinoma of the oral cavity (OCSCC), including tumours of the anterior two-thirds of the tongue, hard palate and buccal mucosa, upper and lower alveolar process, and lips is an interdisciplinary task but mainly guided by primary surgical approaches. Radiotherapy and systemic therapies have additional character and are relevant (but not leading) parts in therapy concepts. Therefore, the main task for decision-making in therapy for OCSCC is to answer the question whether the tumour is resectable (with good functional outcome after reconstruction) or not. The following section is related to the German evidence-based clinical Guidelines [147] which are based on the current literature until 2012, analysed for evidence according to the evidence-graduation system of the Scottish Intercollegiate Guidelines Network (SIGN [148]). Furthermore, diagnostics and treatment strategies are based on the criteria of GCP (good clinical practice) which are currently emphasized and recommended in high-evidence-level clinical trials.

Role of surgery

Due to the diagnostic procedure, the role of surgery is to confirm the histological entity of the lesion. Therefore, biopsies have to be taken in the marginal sites of the lesion including panendoscopy in total anaesthesia to exclude metachronous or secondary primary carcinomas of the upper aerodigestive tract. The pathologist should be provided with sufficient information including extension and clear localization of the lesion including clinical TNM (UICC) definition of the staging result. The pathological report must include histological analysis according to the

WHO classification: grading, depth of invasion [149], lymphatic, blood vessel, and perineural microinvasion, and other locally infiltrated structures [150]. After completion of the staging procedure, the individual tumour situation should be presented and discussed at the interdisciplinary tumour board (minimum composition of the entire board: medical (or clinical) oncologist, radiation oncologist, radiologist, pathologist, and head and neck surgeon). In case the patient has an acceptable performance status and resectable disease, surgery is recommended as first-choice treatment and first-step procedure in multimodality treatment concepts in OCSCC. Criteria for reasonable resectability are: individual situation of the patient, accessibility of clear resection margins (R0 resection margin according to TNM, UICC), and predictable post-operative quality of life after surgery including functional reconstruction. According to GCP the best available tumour distance to the resection margin should measure not less than 3–5 mm at the formalin fixed resection specimen and there should be a palpable approximately 1 cm tumour border in the patient while in surgery. In the case of R+ or a less than 3 mm resection margin described in the pathology report, localized re-resection is recommended. Continuity of the mandible should be preserved if no infiltration of the bone intra-operatively and in pretherapeutic imaging has been shown. Techniques of reconstruction should be planed related to the individual oncologic situation and as an integrated part of the primary surgical procedure. The extent of reconstruction should be balanced in relation to functional and aesthetic outcomes. For reconstruction of the oral cavity microvascular free flaps have been shown to be feasible and are recommended worldwide for excellent defect closure and functional outcomes. In OCSCC, 20–40% of neck nodes present occult metastases in the neck at level I–III, less often at level IV,V. Consequently, surgical treatment of the neck is recommended according to the worldwide accepted Robbins neck dissection classification guidelines [151]. Additional to invasive definitive OCSCC, squamous intraepithelial neoplasia 3 (SIN 3) lesions also have to be surgically treated since the probability of malignant transformation is nearly 90% [152].

Role of radiation oncology

In OCSCC, the main role of radiotherapy is in the adjuvant setting since response to primary radiotherapy and concurrent chemoradiation is poor compared to the other head and neck sites. Adjuvant radiotherapy is following the degree of the resection margins (R0, R1, R2) or the extent of the primary tumour (>T3) and the N+–neck situation according to the post-surgical staging results. The more recent metanalysis, conducted on all head and neck sites, showed that there is a significant improvement of overall survival and event-free survival by adding systemic therapy to

radiation, and this is true both for the curative and the post-operative setting with a five-year overall survival benefit of 6.5%. It was also shown that cisplatin alone, given concomitantly with radiation, is able to achieve the same results as a combination of antineoplastic drugs [153]. In this context, concomitant chemoradiation is considered the state-of-the-art treatment when surgery is not feasible, or post-operatively when high-risk features are present in the pathological report, such as R1 or R0 <5mm (intermediate risk) resection or the presence of nodal disease with extracapsular spread. It should be recognized that this form of treatment may be associated with severe toxicity, and for this reason its indication should be reviewed on an individual basis by an expert multidisciplinary team.

Potential role of primary systemic therapy

Only a small benefit was shown by induction chemotherapy that included cisplatin and fluorouracil (PF). Based on these encouraging results, induction chemotherapy was further studied by adding a third drug: taxotere to PF (TPF). The triple regimen was superior to PF in terms of overall survival; however, we still lack the evidence that induction chemotherapy is adding to standard locoregional treatment [154]. For this reason this is not considered a standard treatment. Induction chemotherapy has been specifically used in advanced operable oral cavity cancer where patients were treated either with induction chemotherapy followed by surgery and radiation, or surgery followed by radiation. The first randomized study included PF [155] and a more recent one TPF [156]. Both trials were negative with respect to the primary endpoint, which was overall survival, but there was an interesting signal of the potential role of response to induction chemotherapy in terms of sparing mandibulectomies and/or post-operative radiation. In both studies patients achieving a major pathological response with induction chemotherapy had the best prognosis. This observation has been done in other neoplasms treated with induction chemotherapy, such as breast cancer and osteosarcomas. It is clear that a better recognition of chemosensitive patients, for example by exploiting high-throughput techniques together with better drugs, is warranted for future treatment developments.

Tumours of the oropharynx

Introduction and clinical assessment

Oropharyngeal cancer (OPC) originates from the mucosa of the oropharynx, which includes the base of tongue and vallecula anteriorly, the posterior oropharyngeal wall, the tonsillar region and lateral

oropharyngeal walls, and the soft palate and uvula superiorly. The incidence is approximately ten per 100,000 inhabitants. They are classified into two disease entities: smoking/alcohol-related and human papillomavirus-related (HPV-positive) OPC squamous cell carcinomas. The former generally have well to moderately differentiated keratinizing morphology, whereas HPV-associated lesions are typically poorly differentiated with a non-keratinizing or basaloid morphology (see also the section ‘Pathology of head and neck tumours’).

Frequent initial symptoms are a sensation of a foreign body in the throat or pharyngitis, followed by otalgia or odynophagia. Palpable lymph nodes in the neck are very frequent and may be the first and sole symptom. The traditional smoking/alcohol-related case often has a larger primary tumour size, less advanced nodal disease, and a correspondingly less advanced stage group. In contrast the HPV-positive case will generally have a smaller and less infiltrative primary but more extensive nodal disease (and often cystic appearance that may erroneously be considered a ‘branchial cleft cyst’).

The initial workup requires a comparative evaluation of the local extension with endoscopy, often under general anaesthesia, and imaging. For details on imaging, see ‘Imaging techniques for head and neck tumours’.

Epidemiology and disease behaviour

The past decades have witnessed an unprecedented worldwide increase in the emergence of the HPV-positive cases. The traditional form is generally seen in a more debilitated population with less social support and with ongoing comorbidities largely related to lifestyle and the exposure to alcohol and tobacco. The HPV-positive cancers occur in younger patients with a much better performance status, and less intense or even minimal tobacco/alcohol consumption. Males are more commonly affected in both diseases. Aetiology through the sexual transmission of the HPV 16 or 18 viruses is suggested in these lesions.

Irrespective of treatment modality, the HPV-positive variant has a better prognosis, except for distant metastases. Concern has been raised that contemporary treatments developed for the traditional form of the disease may be ‘over-treating’ the more favourable HPV-associated variant. As a consequence, although treatment does not differ at present, de-intensification clinical trials are in design or ongoing to address treatment options for the different risk groups of HPV-positive and HPV-negative OPC. These include studies addressing the role of radiotherapy alone, transoral surgical techniques (including laser or robotic surgery), and different forms of systemic treatment.

Contemporary standard for locally advanced disease: chemotherapy and radiation

The interaction between chemotherapy and radiation specifically in locoregionally advanced OPC has only been studied to a limited extent. There is a single phase III trial that showed a survival benefit to using induction chemotherapy prior to local treatments [157], and only two trials showed survival improvement with the use of concurrent chemoradiation (CCRT) when compared with conventional radiotherapy alone [158, 159]. Although specific data on OPC are limited, the literature is replete with trials where the oropharynx is the predominant subsite, thereby underpinning the results of the meta-analysis of chemotherapy in head and neck cancer (MACH-NC) reported by Pignon et al. [160, 153]. This meta-analysis showed a significant interaction between the timing of chemotherapy and outcome (CCRT being superior to either induction or adjuvant regimens) and provides the foundation for considering CCRT as the contemporary gold standard for management in the locally advanced (stage III/IV) OPC, irrespective of the HPV status.

An alternative strategy for improving the outcome of ‘favourable’ locally advanced head and neck cancer is targeting the EGFR based on the improvement in survival from cetuximab delivered concurrently with radiotherapy compared to radiotherapy alone in a randomized trial [161]. Approximately 60% of this trial’s population comprised OPC, which was also the subgroup with the most benefit from concurrent cetuximab in this setting, and with a toxicity profile that seemed to be less than that expected from traditional concurrent chemotherapy. While the latter has been disputed, approaches using cetuximab have led initial attempts to reduce toxicity and de-intensify treatments for the HPV-associated cancers by potentially replacing concurrent cisplatin with cetuximab or other anti-EGFR agents in ongoing trials. Another approach is using induction chemotherapy to select patients for a reduced radiotherapy dose (e.g., the completed single arm ECOG 1308 phase II trial). The induction strategy provides an intriguing possibility for the subset of the HPV-positive population with the greatest risk of distant metastasis, now the leading cause of death for this disease. An induction chemotherapy strategy (e.g., a combination of docetaxel, cisplatin, and 5-fluorouracil (TPF)) with response assessment to minimize or omit concurrent chemotherapy seems a strategy that could be incorporated into future trials when one considers the impact of this approach on distant metastases, as shown in a more recent MACH-NC analysis, 39% of which consisted of OPC (although not HPV-specific) [154].

Risk-stratified management

Considering OPC as a single group of tumours has proved problematic. In the first publication of the RTOG 0129 trial, Ang and colleagues reported that HPV negative status, >10 pack-year tobacco exposure, T4, and N2b-N3 status were adverse predictors for overall and progression-free survival for OPC, and three risk groups could be constructed using these parameters based on risk of death in patients undergoing concurrent chemoradiotherapy [4] . Subsequently O'Sullivan and colleagues performed a similar analysis on an institutional cohort of prospectively compiled HPV-positive stage III/IV patients but addressed distant metastasis risk, rather than survival outcomes alone, in patients treated with either radiotherapy alone or CCRT [162]. Risk of distant metastases was significantly associated with T4 category disease, the degree of nodal involvement, and the same intriguing relationship with smoking history observed in RTOG 0129. Thus, heavy or light smokers with T1–T3, N0–N2a disease seemed relatively immune to the risk of distant metastases whether or not chemotherapy was used, but a smoking history of >10 pack years was important in N2b disease, and N2c and N3 disease were at risk of distant metastases irrespective of smoking history. Recognition of such characteristics has begun to guide contemporary clinical trial designs with several evolved protocols emerging that address different risk groups based on whether the patients belong to a favourable risk group with minimal risk of distant metastases, or require more intense locoregional treatment.

The only phase III randomized trial of an intensive concomitant boost altered fractionation RT alone regimen compared to CCRT with cisplatin in OPC of unknown HPV status was recently reported, and found no difference in DFS or OS [163]. In fact, tolerance was better with altered fractionation and a subset analysis suggested that the efficacy of altered fractionation appeared more pronounced in stage III disease. However, in stage IV, CCRT with cisplatin fared better and was most obvious in more extensive lymph node disease. Garden et al. recently reported a large single institution experience, also of unknown HPV status, indicating that low volume disease (e.g., T1–T2, N1–N2), has extremely favourable outcome with RT alone (exceeding 90%) despite being nominally classified as stage III or IV [164]. Thus, radiotherapy alone may provide very effective control for low-volume 'locally advanced' HPV-positive cases, but as the nodal disease stage increases, especially among heavy smokers, outcome is compromised due predominantly to the risk of distant metastases in the HPV-positive population, though the risk may be mitigated with chemotherapy [162].

Radiotherapy approaches

IMRT is usually used because of its ability to relatively spare normal tissues, most obviously salivary tissues. Pharyngeal constrictor muscles and mandibular regions can often be protected to some degree as well. Eisbruch et al. reported an RTOG multicentre single-arm phase II study of IMRT in OPC which validated one of the major reasons for using IMRT, the reliable and important ability to protect salivary function while achieving high locoregional control [165]. This benefit was confirmed in the PARSPORT trial, a UK multicentre randomized controlled study of IMRT versus conventional radiotherapy in pharyngeal cancer patients (85% OPC), showing reduced incidence of xerostomia with IMRT and significantly better recovery of saliva secretion with improvements in associated quality of life [166].

Contemporary radiotherapy approaches typically employ treatment intensification by the use of chemotherapy as discussed earlier, or hyperfractionation with dose intensification supported by meta-analysis data [167]. In addition, the observed benefit of moderately accelerated radiotherapy was also found to be independent of HPV status in the DAHANCA 6 and 7 trials, suggesting that this strategy should be maintained if the intensity of chemotherapy is reduced [168].

Surgery for oropharyngeal tumours

Although most oropharyngeal tumours are treated by a non-surgical approach, surgery remains important, either for initial treatment or salvage. Careful attention to the goals and needs of each case will provide the rationale, and indication for different surgical approaches for the primary site are summarized below. Elective neck surgery must also be considered if there is doubt about disease eradication, based on clinical and imaging initially or eight to 12 weeks following radiotherapy.

Transoral surgery is an attractive approach for tumours limited to the site of origin. Electrocautery was used initially followed by the laser CO_2 knife in the mid-70s, which became the most common approach. Although providing alternatives to open surgery in selected cases, these techniques remained limited due to the restricted access to the base of the tongue and the glossotonsillar sulcus. More recently, transoral robotic surgery (TORS) has been developed, providing excellent global visualization, with a magnified three-dimensional view, allowing access to difficult areas, and this has expanded the indications for using TORS [169].

There are two main approaches to open surgery: firstly, the mandibular swing approach that provides the same access to the lateral oropharynx as the traditional hemi-mandibulectomy but preserving the mandibular

arch via the osteosynthesis performed after tumour resection. Submandibular approaches represent the second group. Thus resection of the posterior wall of the oropharynx may be performed via the opening of the larynx by anterior access between the hyoid bone and the base of tongue. Vallecular tumours may be resected by a supraglottic laryngectomy extended to the base of tongue.

Although limited resections do not ordinarily require reconstruction, reconstruction underpins the ability to undertake much modern head and neck surgery. Improvements in reconstructive surgery have substantially reduced the post-surgical functional and cosmetic sequelae. Local mucosal flaps (such as the FAMM, facial artery musculo-mucosal, flap) may be used in some cases. Pedicled flaps (dorsal flap, trapezius flap, or the most commonly used, the major pectoralis myo-cutaneous flap) have significantly improved volume and surface reconstruction as well as prevention of post-operative complications in the case of salvage surgery in irradiated fields. The introduction of microvascularized free flaps was an important milestone in oropharyngeal surgery. Some flaps are able to reconstruct a mucosal surface (radial forearm free flap) or tongue volume (dorsal free flap, anterolateral thigh free flap) or the mandible (iliac crest free flap, scapular free flap, or preferably the fibula free flap) [170].

Tumours of the larynx and hypopharynx (including organ preservation)

Introduction and clinical assessment

The large majority of larynx and hypopharynx cancers are SCC. The few other cases comprise glandular carcinomas, sarcomas, melanomas, and lymphomas. The annual world incidence of head and neck cancer is estimated to be nearly 700,000 and globally, with some variations between countries, 20–25% are larynx cancers and 10% are hypopharynx cancers. The incidence of larynx cancer is decreasing in North America and in Western Europe; it is stable or slightly increasing in other countries. The incidence of hypopharynx cancer seems rather stable [171]. The incidence is much higher in males (85–90%) with a peak incidence between 50 and 60 years.

The larynx is divided in three levels: the glottis (true vocal cords), the supraglottic (epiglottis, aryepiglottic folds, false vocal cords, and the ventricles), and the subglottis (between the glottis and the trachea). The hypopharynx is divided into pyriform fossae, the post-cricoid area, and the posterior wall. These cancers are the result of tobacco consumption possibly associated with alcohol abuse for supraglottic and hypopharyngeal cancers.

The presenting symptoms are a sore throat, dysphonia, or a referred otalgia. Dysphagia and dyspnoea occur later. Metastatic lymph nodes are frequent in supraglottic and hypopharyngeal cancers. The initial workup consists of a clinical examination, an endoscopy under general anaesthesia (in 95%; and with biopsy), and imaging. CT is the most useful imaging for detecting in depth extension (cartilages, paraglottic spaces, pre-epiglottic space) and metastatic lymph nodes that are missed by the clinical examination. For details on imaging, see section ‘Imaging techniques for head and neck tumours’. Staging should be carried out according to the TNM classification of malignant tumours, with stage groupings I, II, III, IVA, IVB, and IVC.

Management issues

When the initial workup is completed all cases must be discussed during a tumour board meeting (including surgeons, radiation oncologists, medical oncologists, radiologists, pathologists, etc.) in order to select the most appropriate treatment for each patient. Treatment choices depend on patient characteristics (age, occupation, comorbidities) and preferences, tumour characteristics, as well as local expertise and resources.

Early disease

For early disease, the choice is between conservative surgery or radiotherapy, which seem comparable in outcome (although never prospectively compared), while chemotherapy has no role to play.

Locoregionally advanced disease

For advanced disease, the choice is between ‘mutilating’ surgery (with or without post-operative irradiation) or definitive irradiation with or without chemotherapy or biotherapy (cetuximab), and with surgery in reserve as salvage therapy. There is no randomized study comparing both attitudes that could help in selecting one or the other. Clearly the choice is mainly institution-dependent and must be considered in the light of clinical trials on larynx preservation (see below). For more advanced and unresectable disease, the choice is between irradiation alone with different fractionation schedules and chemo- or bioradiotherapy under different settings. Such approaches are frequently studied in the framework of clinical research.

Recurrent/metastatic disease

For recurrent and/or metastatic disease, for each case one should consider whether a potentially curative option (surgery or re-irradiation)

is still feasible. For other options see ‘Management of recurrent and/or metastatic squamous cell carcinoma of the head and neck’.

Treatment options

Surgical options

There is a large surgical armamentarium for laryngeal and hypopharyngeal cancers [172]. Transoral CO_2 laser is a widely accepted approach for early diseases pending an excellent endoscopic access and a complete view of the tumour in all directions. This type of surgery is sometimes advocated for larger tumours, particularly in Germany, but is directly linked to the surgeon’s expertise. More recently, TORS has been proposed by some teams but should be considered at the moment to be experimental, requiring larger series and cost-effectiveness evaluation.

Open partial surgery ranges from very limited resections (such as cordectomy, epiglottectomy, or lateral pharyngectomy) to large resections (such as supracricoid partial laryngectomy or supracricoid hemi-laryngopharyngectomy) allowing the surgeon to cope with all local extensions.

Total laryngectomy is required for large tumours and may be associated with either partial or circumferential pharyngectomy, requiring either pedicled or free flaps for closure.

A neck dissection is systematically performed (except for tumours confined to true vocal cords).

Radiation therapy options

For early-stage tumours (T1–N0), a standard fractionation regimen delivering a therapeutic dose of 64–66 Gy and a prophylactic neck dose in the order of 50 Gy in daily fractions of 2 Gy, five times a week is recommended. For T1 glottic carcinoma, a dose of 60–64 Gy to the glottic larynx without nodal irradiation is standard. For moderately advanced tumours (T2–N0 or N1), hyperfractionation or accelerated fractionation schedules have shown to be more effective than standard radiotherapy [168]. For these tumour stages, there is no compelling evidence for the use of induction or concomitant systemic treatment (chemotherapy or biotherapy). For locally advanced disease (T3 or T4, more than N1), a therapeutic dose of 70 Gy in daily fractions of 2 Gy, five times a week, and a prophylactic dose of 50 Gy are recommended, in particular when concomitant chemotherapy or biotherapy is used [153]. In case of contraindication to systemic treatment, the use of hyperfractionation,

accelerated fractionation, or simultaneous integrated boost radiation therapy is recommended.

Post-operative RT is recommended in the case of inadequate resection margins, T3 or T4 tumour, multiple positive lymph nodes, and in the case of extracapsular spread of disease [173, 174]. Typically, a dose of 60–66 Gy will be delivered with daily fractions of 2 Gy, five times a week. In case of R1 resection and/or presence of extracapsular extension, the use of CCRT has been demonstrated to be superior to radiation alone [175].

Regarding the radiation technique, as demonstrated in randomized trials, the use of IMRT should be standard to decrease the incidence of late morbidity, especially the incidence of xerostomia [167]. For T1 glottic, however, conformal radiation therapy still remains a standard. Consensus guidelines on target volume selection and delineation for a state-of-the-art delivery of IMRT have been provided [176].

However, even in the IMRT era, the use of modified fractionation regimens and the use of CCRT or bioradiotherapy (BRT) is associated with an increased incidence of acute and late toxicity compared to standard radiotherapy alone, with unexplained deaths reported in up to 10% of cases with adequate follow-up after CCRT [177]. Variables that seem to correlate with the development of late severe toxicity are older age, advanced T stage, larynx/hypopharynx site, and neck dissection after CCRT [177]. These alarming data need specific attention and are a further plea to treat head and neck cancer patients in referral centres that meet all the requirement for an optimal care for such patients.

Chemotherapy and biotherapy options

The role of chemotherapy is slowly moving towards a more prominent position within the different treatment paradigms in patients with squamous cell carcinoma of the head and neck. The use of CCRT is generally accepted as a standard therapy post-surgery in high-risk patients (see above), in patients with resectable disease, when the anticipated functional outcome and/or prognosis is so poor that multilating surgery is not justified, and in patients with unresectable disease [178]. The optimal chemotherapy regimen for that approach is cisplatin 100 mg/m^2 days on 1, 22, and 43 during RT. CCRT improves survival and locoregional control over RT alone in patients with locoregionally advanced squamous cell carcinoma of the head and neck [153, 179]. Alternative non-surgical approaches in such patients are BRT with cetuximab (the only approved anti-EGFR monoclonal antibody) and the use of induction chemotherapy (ICT) before local therapies. The addition of cetuximab to RT improved survival and locoregional control

over RT alone in one single randomized phase III study [161]. The hazard ratios for survival with RT plus cetuximab versus RT alone were comparable to those reported for CCRT versus RT alone in nearly 10,000 patients included in the MACH-NC meta-analysis [153]. However, there has been no direct comparison between RT plus cetuximab and CCRT in phase III reported. Despite that, there are sufficient data available suggesting that compliance with RT plus cetuximab seems to be better than with CCRT. The MACH-NC meta-analysis indicates that the role of ICT is less than that of platinum-based CCRT. However, the optimal ICT was not part of that analysis. The optimal ICT regimen has been defined by two major phase III trials, TAX 323 and TAX 324, both showing improved survival and progression-free survival with docetaxel, cisplatin and 5-fluorouracil (TPF) compared to PF in patients with resectable and unresectable locoregionally advanced head and neck cancer [180, 181]. In addition, a more recent meta-analysis on TPF versus PF indicated significantly less distant metastases and significantly less locoregional failure with TPF [154]. However, a direct comparison of CCRT versus TPF induction followed by RT has not been performed. So far, randomized trials of sequential therapy, i.e. ICT followed by CCRT versus CCRT alone, have not shown a clear benefit for the sequential approach and this approach should not be considered standard therapy for the moment. It is also unclear whether replacing 5-fluorouracil with cetuximab in the triple regimen might lead to better outcome. Further studies for both approaches are needed. With respect to larynx preservation procedures, platinum-based chemotherapy given during RT (CCRT), preceding RT (ICT→RT), or alternating with RT are all acceptable approaches (see below).

Larynx preservation

At the beginning of the twentieth century two major options were available: surgery (partial or total) and external beam irradiation. Up until the 1980s the surgeons tried to extend the indications of partial surgery with larger procedures and to improve rehabiliation after total laryngectomy with voice prostheses. At the same time radiation oncologists improved the efficacy of irradiation with a better delineation of the irradiated area and with modification of the fractionation. But there was no direct comparison of total laryngectomy and definitive irradiation.

In the 1980, the results of studies with ICT using the PF combination concluded that ICT was able to produce notable tumour regression and that this regression was predicting a high radiosensitivity [182]. This supported the initiation of a period of challenging clinical research on larynx preservation.

The first two adequately powered trials validating the concept of larynx preservation were the Veterans trial in the US for laryngeal cancer and the EORTC 24891 trial in Europe for hypopharyngeal cancer. Both trials compared total laryngectomy with ICT (with PF) followed by RT in good responders or by total laryngectomy in poor responders [183, 184]. Both survival and disease control were found similar in both arms of the respective studies and 56% of patients could retain their larynx in the ICT arm.

The next two trials compared ICT (with PF) to alternating chemoradiotherapy (EORTC 24954 in laryngeal and hypopharyngeal cancer), and ICT (with PF) to cisplatin-based CCRT and to RT alone (RTOG 91-11 in laryngeal cancer) [185, 186]. The first trial failed to find any difference in survival or larynx preservation between both arms. The long-term results of the RTOG 91-11 trial concluded that induction PF followed by RT and CCRT showed similar efficacy for the composite endpoint of laryngectomy-free survival. Locoregional control and larynx preservation were significantly improved with CCRT compared with the ICT arm or the RT alone arm. Overall survival did not differ significantly, although there was a trend towards a worse outcome with CCRT relative to ICT and deaths not attributed to laryngeal cancer were higher with CCRT (30.8% versus 20.8% with ICT and 16.9% with RT alone) [187].

The fifth trial compared two ICT regimens (TPF versus PF) in patients with locally advanced laryngeal and hypopharyngeal cancer as an alternative to total laryngectomy (GORTEC 2000-01). Responding patients received RT with or without additional chemotherapy. Larynx preservation was significantly higher in the TPF arm of the study (70.3% versus 57.5%), without any difference in overall survival [188].

The last trial compared CCRT and biotherapy (RT + cetuximab) in patients responding to ICT with TPF (GORTEC TREMPLIN trial). The overall toxicity was substantial, there was no signal that one arm could be superior to the other, or in favour of RT alone as found in the previous trials [189].

Evidently, the optimal approach for larynx preservation has still not been identified. Several treatment options are available, each with different levels of tolerability but little difference in outcome. CCRT with three courses of cisplatin and TPF induction followed by RT in good responders is the treatment now mostly used. Superiority of one over the other can only be assessed by a randomized trial.

Squamous cell carcinoma of unknown primary site

Introduction to squamous cell carcinoma

Cervical nodal metastasis from clinically undetectable SCC primary sites accounts for approximately 3% of all head and neck malignancies [190], and most frequently manifests in the upper jugular and mid-jugular lymph nodes. Histologically, SCC accounts for the majority of cases, particularly when masses are situated in the upper two-thirds of the neck, and generally indicates an origin from a hidden primary somewhere in the head and neck region. It constitutes a favourable-risk cancer of unknown primary (CUP) group compared to patients with less favourable histologies, such as adenocarcinomas.

Diagnostic workup

Physical examination, including comprehensive nasofibroscopy and endoscopic assessment under general anaesthesia conducted by experienced otolaryngologists or head and neck surgeons, detects primary head and neck SCC in over 50% of patients presenting with cervical lymph node metastases [191]. Locoregional imaging should ideally be performed before endoscopy as it may identify suspicious mucosal areas guiding biopsy sampling. Systematic tonsillectomy has been advocated by some authors as up to 45% of occult primary have been reported [190]. The role of FDG-PET has been extensively studied over the last few years, with detection rate of a primary tumour in up to 30% of patients, and a systematic review has recommended its routine use in patient management [192]. To optimize the yield of guided biopsies, FDG-PET/CT should be performed before the endoscopy. This examination, however, needs to be considered as an adjunct to comprehensive clinical examination, and not as a replacement. Another advantage of FDG-PET examination is that it gives the metastatic workup a higher accuracy than CT or MRI [192].

For pathological confirmation of the disease in the neck, fine needle aspirate is the preferred modality. In case of repetitive negative examination, a surgical procedure removing the entire node, possibly followed by a neck node dissection, is recommended. For pathological examination, in case of poorly differentiated or undifferentiated carcinoma, EBV testing should be routinely performed to exclude the presence of an undifferentiated carcinoma, which has a different prognosis and requires a different treatment approach. HPV testing could also be performed, although no study has so far demonstrated that HPV-positive SCC should be differently managed than HPV-negative SCC. More advanced molecular techniques performed on the lymph node and the random mucosal biopsies have been described, but so far none of

these studies has profoundly altered the clinical management of patients with CUP [193].

The staging of CUP follows the staging of the neck for head and neck primaries. It should, however, be emphasized that the 'T'-site should be classified as 'T0' and not as 'Tx', the latter depicting a primary tumour staging that has not been performed, rather than a staging which did not identify any primary tumour.

Therapeutic strategies

In the past, treatment of CUP commonly consisted of lymph node dissection and elective irradiation of the putative mucosal sites and bilateral neck plus supraclavicular nodes. Recently, however, primary concomitant chemoradiotherapy, followed by a selective neck node dissection only in case of residual node disease, has been introduced. In addition, the dogma that radiotherapy for CUP should always include irradiation of both sides of the neck and the oropharyngeal, hypopharyngeal, and laryngeal mucosa has been challenged.

Neck node dissection with or without post-operative radiotherapy

In non-CUP series, for limited disease in the neck (i.e. pN1), neck node dissection procedures (typically selective neck node dissection or modified radical neck node dissection) without post-operative radiotherapy in the absence of extracapsular extension has shown control above the clavicles in the order of 95% plus (see review in [194]). Applied to selected CUP patients, such policy has shown high neck control, but with a significantly higher rate of emergence of primary tumours in the untreated mucosa compared to patients who benefited from post-op or primary radiotherapy [195]. In this series from Denmark, however, there was no difference in disease-specific survival among patient groups. It will always remain impossible to differentiate between the emergence of the putative primary and a subsequent head and neck primary, which typically occurs with a frequency of 1–2% per year.

For patients treated by surgery for a known primary tumour and who presented with multiple nodes and/or capsular rupture, post-operative radiotherapy or chemoradiotherapy (in case of capsular rupture) has been recognized as evidence-based practice [196]. There is thus no reason not to apply such policy to patients with CUP. The question of prophylactic treatment on both sides of the neck and the oropharyngeal, hypopharyngeal, and laryngeal mucosa however still remains unanswered.

Primary radiotherapy

In non-CUP series, it is recognized that radiotherapy alone yields a high rate of regional control above the clavicle around 90–95% for patients with N1 disease (see review in [194]). For patients with advanced neck disease, it has also been reported that altered fractionation radiotherapy or concomitant chemoradiotherapy followed by selective neck node dissection for residual disease yielded neck control rate in the same order of magnitude than after primary neck node dissection. Along this line, there has been a progressive change in the management of patients with CUP towards more use of primary radiotherapy or concomitant chemoradiotherapy. In a large retrospective review of 1726 patients with CUP treated either by surgery and post-operative radiotherapy or chemoradiotherapy (based on extracapsular extension) or by primary chemoradiotherapy, no statistically significant difference in five-year overall survival was observed between the two groups [197]. In this latter series, as reported in non-CUP series, the extent of the nodal disease and the presence of extracapsular extension were strong independent prognostic factors.

Indications for post-radiotherapy neck node dissection

The use of radiotherapy or concomitant chemoradiotherapy as primary treatment modality raises the question of the role of node dissection following radiotherapy for patients with N2–N3 disease at initial diagnosis. Residual neck mass may be present in up to 30–60% of patients after completion of chemoradiotherapy. For those patients, irrespective of the neck stage, there seems to be a consensus in the literature favouring an immediate neck node dissection because of the low probability of achieving a neck control with salvage surgery when recurrence develops [198]. For patients with complete neck response after radiotherapy or chemoradiotherapy, there are currently many arguments supporting the position that systematic planned neck dissection is no longer justified, and many institutions have switched to neck dissection for residual disease in the neck only [199]. Improvement in assessing the neck status with imaging has contributed enormously to this change in paradigm. Very high negative predictive values of CT, MRI, and more recently FDG-PET have indeed been reported for assessing the neck after radiotherapy or concomitant chemoradiotherapy [200, 201]. All the data mentioned above are from series of patients with a known primary tumour; there is however no reason not to extrapolate them to the situation of the CUP patients.

Target volumes in radiotherapy

As already alluded, the choice of the appropriate target volumes for radiotherapy of CUP remains controversial. First, the potential gain with comprehensive radiotherapy in controlling the putative primary carcinoma should be weighed, even in the new IMRT area, against its effect on quality of life resulting from increased acute and persistent morbidity such as xerostomia. Second, as already mentioned, it is possible that a head and neck carcinoma detected later in this patient subset is actually a second primary tumour instead of the putative cancer. Last, the possibility of conservative surgical approaches and the feasibility of re-irradiating the head and neck region (especially in the non-treated areas) are being recognized should a cancer emerge after ipsilateral radiotherapy. In the series from Denmark, although the rate of subsequent mucosal primary was higher in patients who did not receive comprehensive radiotherapy on both side of the neck and on the mucosa, no difference in disease-specific survival could be observed [195]. When all data from small retrospective series are put together totalling up to 1000 patients, no difference in the rate of subsequent head and neck primaries could be detected between patients who got surgery alone, unilateral radiotherapy, or bilateral radiotherapy including the head and neck mucosa (personal data).

Conclusion

The diagnosis of CUP is made after exclusion of the presence of a mucosal primary. There are two mains options for the primary treatment of CUP: either a neck node dissection followed by post-operative radiotherapy or chemoradiotherapy, or a primary radiotherapy or chemoradiotherapy depending on the nodal stage, followed in case of residual neck disease by a selective neck dissection (see Figure **35.11**). There is no data to suggest the superiority of one over the other. For radiotherapy, unilateral neck or bilateral neck, including the oropharyngeal, hypopharyngeal, and laryngeal mucosa are possible options. There is no definite data to demonstrate the superiority of one over the other, but owing to the reduced toxicity of unilateral irradiation, and the possibility of salvage treatment in case of emergence of a mucosal primary and/or a contralateral neck node development, the former is becoming the preferred option.

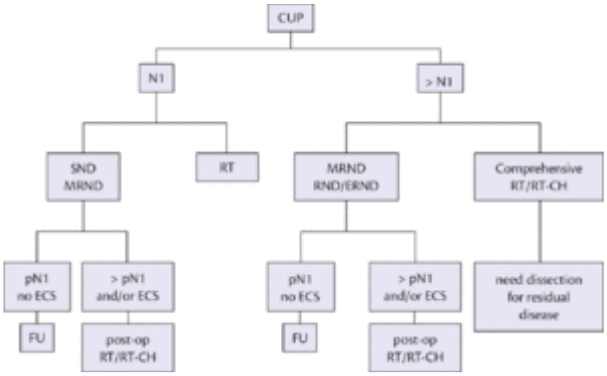


Fig. 35.11
Treatment algorithm of carcinoma of unknown primary (CUP).

Abbreviations: ECS, extracapsular spread; ERND, extended radical neck dissection; FU, follow-up; MRND, modified radical neck dissection; RND, radical neck dissection; RT, radiotherapy; RT-CH, concomitant chemoradiotherapy; SND, selective neck dissection.

Recurrent and/or metastatic squamous cell carcinoma of the head and neck

Extent of the problem

Squamous cell carcinoma of the head and neck (SCCHN) is in great majority a locoregional complex disease, with evidence of dissemination in 10% or less at first presentation. Therefore, achieving adequate locoregional disease control of this primary disease, whether by surgery, radiation (with or without the additional use of systemic treatment), or a combination of these, is of central importance when managing patients with SCCHN. Failing to do so will lead to persistant disease (disease left behind after completion of primary treatment), recurrent disease (to be differentiated from second primary tumours (SPTs) in time and location [202]) and/or distant metastases. Moreover, past and current lifestyle choices in many cases increase the risk for new primary cancers even when the initial tumour has been cured. According to the MACH-NC data from 50 CCRT trials and 30 ICT trials, the rates of local and/or regional recurrences (LRRs) at five years were 50.8% and 47.5% in the experimental arms, respectively, and 60.1% and 46.5% in the control (RT alone) arms of the trials, respectively [203]. The corresponding rates of distant metastases (DM) were below 20%. Factors to be considered when choosing treatment in these circumstances include the extent of the recurrence, the type of initial curative treatment and the time interval between that treatment and the recurrence, the patient’s performance

status comorbidities and preferences after being well informed. Curative intent strategies in case of local and/or regional recurrences will be possible only in 50% or less [204].

Retreatment strategies

Surgery

Salvage surgery is the treatment of choice for all patients with resectable LRRs or second primary tumours and sufficient good health, and therefore should be considered first at all times. Goodwin reported that based on a meta-analysis of 32 studies a survival rate of 39% could be expected at five years with salvage surgery [205]. However, the best chances of cure were in those patients with early-stage recurrent tumours and in those with recurrent cancer of the larynx, whereby the treated site seemed to be of less importance than the recurrence stage [205]. Unfortunately, those with limited tumour bulk (after adequate staging with PET or PET/CT) who are also medically fit comprise only 20% or less of the LRRs. Consultation with a radiologist and a careful examination under general anaesthesia is needed. Not only the extent of the recurrence is of importance but also the original extent of the tumour, since it is generally considered mandatory to excise the original extent of the tumour with a generous margin to obtain microscopic radicality. Major salvage surgery nearly always requires flap reconstruction for adequate wound healing and to permit the best post-operative function and quality of life. After (chemo-)radiotherapy, microvascular surgery is often possible and probably still the favoured method, especially for oral and oropharyngeal cancers because pedicled flaps may result in less optimal wound healing and yield inferior functional results. Tonsillar defects can often be reconstructed well with a relatively thin fasciocutaneous flap, whereas base-of-tongue reconstruction often requires an intermediate thickness flap. Laryngectomy defects require a free or pedicled flap as reinforcement of the suture line or as a patch. As to surgery for isolated residual or recurrent disease in the neck, there is a tendency to perform (super)selective neck dissections that remove only the level(s) that contain disease. This does not seem to compromise control of disease, obviates the need for flap surgery, and limits complication rates. Most authors reserve salvage neck surgery for those patients that have evidence of regional recurrence, and refrain from planned neck dissections even for the higher N stages. Salvage laryngectomy for laryngeal cancer recurrence offers survival in the range of 35–66%, albeit with a substantial risk of complications [206, 207, 208]. Good function outcome can be expected; the vast majority of patients are able to produce speech using a voice prosthesis, and have a ‘normal’ or ‘soft’ diet. Major salvage surgery for other sites yields results that are

less favourable (27–40% survival) and likewise carry a fairly high complication rate [205]. Positive surgical margins are the main negative prognostic factor in multivariate analysis, pointing to the great importance of appropriate selection of patients. Regional control after salvage neck dissection can be achieved at five years in the order of 80% [209].

Re-irradiation

Proper selection of patients for re-irradiation is also of major importance. Only those with no or insignificant organ dysfunction and comoribities should be considered candidates for re-irradiation [210]. If possible, the functional status of the patient should be assessed by using standardized measures, such as the Charlson comobidity index or ACE-27 grading [204]. Favourable prognostic factors are the possibility of removing the recurrence beforehand, having a long interval between the recurrence and the initial treatment, and being able to give an adequate radiation dose, while prior CCRT is an unfavourable condition [211].

Patients with resectable recurrences or new primary cancers in a previously irradiated area who undergo salvage surgery should be considered for re-irradiation plus concurrent systemic treatment (whether cytotoxic or non-cytotoxic) when histopathology is showing high-risk features such as positive margins or extracapsular extension. This will lead to a better locoregional control rate, but at the expense of a higher toxicity (grade 3–4 late toxicity in >1/3 of patients and up to 8% treatment-related deaths) and no clear survival advantage compared to no post-operative reirradiation [205, 212, 213]. Expected OS rates at two years are in the order of 40–50% [205].

Patients with unresectable disease, as expected, do less well. Reviews have suggested that one-quarter to one-third of the patients will be free of locoregional disease at two years and two-year OS will be in the order of 10–30%. Grade 3–4 late toxicity in these cases will occur in up to 40%, and nearly 10% of patients will have treatment-related deaths. In general, a radiation dose in the range of ≥60 Gy is recommended, delivered by using conventional fractionation (1.8–2 Gy/fx), hyperfractionation or hypofractionation (in case of stereotactic RT). General advice is to irradiate the gross tumour volume with a sufficient margin (around 5 mm) and no elective treatment of adjacent regions.

Alternative local therapies

Photodynamic therapy involves the use of a light-sensitive drug or photosensitizer (given systemically or topically), in combination with light of a visible wavelength, to destroy the target cells. Patients with early

recurrences in the oral cavity, nasopharynx, and larynx might be candidates for such treatment when conventional treatments are not available or not appropriate [214, 215]. In addition electrochemotherapy (ECT) can be seen as an alternative. ECT is the local application of pulses of electric current to tumour tissue to render the cell membranes permeable to otherwise non-permeant or poorly permeant anticancer drugs, thereby facilitating a potential localized cytotoxic effect [216, 217]. However, experience with ECT is still rather limited and the optimal indication is rather uncertain. Both approaches suffer from lack of comparative data versus adequate salvage surgery or re-irradiation.

Systemic treatment

Unfortunately, most patients with recurrent/metastatic (R/M) SCCHN are only eligible for palliative treatment. Treatment options in these patients include supportive care only or supportive care plus single-agent chemotherapy, combination chemotherapy, or targeted therapies, either alone or in combination with cytotoxic agents. Negative prognostic factors for survival are a poor performance status, severe weight loss, tumours originating in the oral cavity or hypopharynx, well/moderately differentiated disease, and prior radiotherapy [218]. Response to cytotoxic chemotherapy also proves to be a favourable characteristic and is of prognostic significance. SCCHN is a chemosensitive disease, as is evident from responses observed with various drugs of different classes of cytotoxic agents [219]. The four most extensively studied single cytotoxic agents are bleomycin (which is hardly used anymore), methotrexate, 5-fluorouracil, and cisplatin. Newer agents from the same or other classes of cytotoxic agents also sometimes showed promising results, but when tested in randomized trials never surpassed the efficacy of methotrexate or cisplatin alone. Taxanes (when combined with platinum compounds) seem more favourable than 5-fluorouracil in the R/Ms disease setting, because they induce less mucositis, a troublesome side effect in particular in patients that have been previously treated with radiation. Table 35.5 summarizes the development of systemic therapy in R/M SCCHN and shows that 30 years after the first use of cisplatin in this disease, survival advantage was observed for the first time when platinum-based cytotoxic chemotherapy was combined with cetuximab, a chimeric IgG1 monoclonal antibody (MoAb) targeting the EGFR [220]. The safety profile of this PFE (platinum/5-FU/Erbitux®) regimen was quite acceptable, with no negative effect on quality of life and an improved response that coincided with a better symptom control [221].

Table 35.5 Development of chemotherapy in R/M SCCHN. 1977: cisplatin shows efficacy in first-line SCCHN

Research group	N	Regimen	ORR (%)	Median OS (months)	Significant OS benefit
Grose et al. 1985	100	Methotrexate Cisplatin	16 8	5.0 4.5	No
Forastiere et al. 1992	277	Cisplatin + 5-FU Carboplatin + 5-FU Methotrexate	32* 21 10	6.6 5.0 5.6	No
Clavel et al. 1994	382	CABO Cisplatin + 5-FU Cisplatin	34* 31* 15	7.3 7.3 7.3	No
Gibson et al. 2005	218	Cisplatin + 5-FU Cisplatin + paclitaxel	27 26	8.7 8.1	No
Vermorken et al. 2008	442	Platinum + 5-FU Platinum + 5-FU + Cetuximab	20 36*	7.4 10.1*	Yes

*significant.

CABO, cisplatin, methotrexate, bleomycin, vincristine.

Recent taxane/platinum/cetuximab combinations suggest that further response and survival improvement might be possible, but a phase III trial is necessary to prove this [222]. Unfortunately, phase III trials with other EGFR targeting agents, whether MoAbs (zalutumumab, panitumumab, nimotuzumab) or reversible selective EGFR tyrosine kinase inhibitors (TKIs, such as erlotinib and gefitinib), failed to show significant survival benefit [223]. Therefore, cetuximab is the only

targeted agent approved for use in R/M SCCHN in first-line in combination with platinum/5-FU, and in some countries also in platinum-refractory disease in second-line cases. Response rate with cetuximab is rather low, while EGFR expression generally is high. Identification of biomarkers predicting response to cetuximab and other anti-EGFR therapeutics is pressing, as well as unravelling of the underlying mechanisms of resistance [224]. In line with this are studies with a new generation of irreversible small molecule pan-EGFR inhibitors as well as dual targeting MoAbs and a mixture of MoAbs targeting non-overlapping epitopes on the EGFR with the hope of overcoming resistance and to further improve outcome [223]. In addition, other targeted agents, such as c-Met inhibitors, IGF-1R inhibitors, antiangiogenic agents, drugs that block the PI3K/Akt/mTOR pathway, drugs that block the STAT pathway, and drugs that target nuclear and regulatory mechanisms, such as proteasome inhibitors, HDAC inhibitors, and heat shock protein inhibitors are all being studied. It is clear that combinations or sequential targeted therapies needs to be further studied and that identification of predictive markers should get high priority.

Salivary gland cancer and paragangliomas

Salivary gland cancer

Epithelial malignancies of the paired major (parotid, submandibular, and sublingual) and minor salivary glands (MiSG) are most complicated, due to their low incidence. The incidence in the US is ten patients per 10^6 per year. In Europe, Belgium, the Netherlands, the UK, and Finland have approximately six to seven new cases per 10^6 per year. Up to 70% arise in the parotid, 10–25% in the MiSG; the rest are submandibular carcinomas, with sublingual carcinomas being very rare [225].

Clinical presentation—imaging—pretreatment tissue diagnosis

Most parotid tumours present as an asymptomatic peri-auricular lump. Malignancy is suspected by rapid volume increase, pain, enlarged cervical lymph nodes, fixation to deep structures or facial skin, or facial nerve (VIIN) dysfunction. Surgery with or without adjuvant therapy being the treatment of choice, the workup evaluates the likelihood of malignancy and the extent and location of a tumour. Imaging is needed when tumour mobility is impaired, the tumour is >4 cm, and there is any sign of malignancy. MRI outperforms CT for the retromandibular parotid, the stylomastoid foramen area, and for identifying perineural extension. PET with or without CT is performed to exclude distant metastases. The resulting information, summarized in the TNM classification, combined

with other clinical, histopathological, patient, and tumour characteristics, determines treatment options [226].

A submandibular gland cancer patient mostly presents with a slow-growing, painless mass under the jaw, occasionally with distortion of the floor of the mouth. Pain (30%) suggests local tissue extension. Cervical lymphadenopathy is present in 25% of patients. Radiological evaluation of submandibular salivary gland cancer (SGC) does not differ from the parotid subsite as mentioned above.

MiSG carcinomas (MiSGCs) are found throughout the entire upper aerodigestive tract and symptoms depend upon the anatomical site involved. Most frequently the oral cavity and oropharynx are affected, with the classical presentation of a painless submucosal swelling, sometimes altering denture positioning. In the nose and pharynx, MiSGC mostly causes obstructive symptoms. Pain is reported in one in four, regional metastasis in one in six patients [227]. To estimate the anatomical involvement, imaging (CT +/– MRI) is mandatory. For MiSGC an incisional biopsy provides the histological information needed to plan further treatment. As for major SGC, the TNM-components and stage grouping are the strongest prognosticators [225].

Before embarking on treatment, for major SGC, FNAC reasonably differentiates between malignant and benign lesions (accuracy 79%). Even if FNAC suggests benign disease, removal of the tumour for further histopathology remains mandatory. In MiSGC, the submucosal tumour is accessible for incisional biopsy, providing a more representative specimen for histopathologic subclassification. The caveat to interpreting these biopsies is that many of the 24 SGC types (Table 35.6) have overlapping histological features. Increasingly, molecular biological studies are performed, on the incisional biopsy material as well [225, 228].

Table 35.6 The WHO 2005 histologic classification of malignant salivary gland tumours

Type WHO	Abbreviation
1. Acinic cell carcinoma	AcCC
2. Mucoepidermoid carcinoma	MEC
3. Adenoid cystic carcinoma	AdCC
4. Polymorphous low grade adenocarcinoma	PLGA
5. Epithelial myoepithelial carcinoma 6. Clear cell carcinoma, Not Otherwise Specified (NOS)	
7. Basal cell adenocarcinoma	
8. Sebaceous carcinoma	
9. Sebaceous lymphadenocarcinoma 10. Cystadenocarcinoma 11. Low grade cribriform cystadenocarcinoma 12. Mucinous adenocarcinoma	
13. Oncocytic carcinoma	
14. Salivary duct carcinoma	SDC
15. Adenocarcinoma NOS	ACNOS
16. Myoepithelial carcinoma	
17. Carcinoma in pleomorphic adenoma 18. Carcinosarcoma 19. Metastasizing pleomorphic adenoma	
21. Small cell carcinoma 22. Large cell carcinoma	
23. Lymphoepithelial carcinoma	

24. Sialoblastoma

Treatment: surgery yields post-operative histopathological information

For parotid cancer the best chance of cure follows primary excision, the extent of which depends on the tumour size, the relationship to the VIIN, and extraparotid tissue invasion. For the majority of cancers with a normal functioning VIIN that are located in the superficial parotid lobe (80%), a standard superficial parotidectomy is adequate. Tumours >4 cm, located in the parapharyngeal or deep lobe, or with VIIN involvement should have a total or radical parotidectomy, considering that in high-stage, high-grade parotid cancer, the intraparotid lymph nodes may harbour metastatic disease. Alternatively, one may choose to rely on post-operative radiotherapy to control these possible microscopic deep lobe lymph node deposits [229]. In the same way, it is accepted that microscopical disease left behind on a non-involved spared VIIth branch can be controlled by post-operative radiotherapy. Regional metastasis is seen in one in three patients with parotid cancer, involves mostly levels II, III, and IV, and requires a (modified) radical neck dissection, removing levels I to V; radicality towards the non-lymphatic structures (nerve XI, jugular vein, sternocleidomastoid muscle) depends on proximity of the lymph node metastasis. In pN+ patients, radiotherapy improves locoregional control and survival [230, 231]. In patients with a cN0 neck at presentation, elective treatment (elective neck dissection or radiotherapy) depends on risk factors for occult neck disease (tumour size >4 cm, histology with clinical high-grade behaviour, age >54, perilymphatic and extraparotid extension) [8] . In our practice, we fine-tune the surgical approach to the N0 neck using preoperative USgFNAC and perioperative frozen section of the level II lymph nodes; if the latter reveal macrometastases, a modified neck dissection follows [226]. The MD Anderson approach is elective radiotherapy to the cN0 neck in high-risk patients, relying on definitive histopathology of the resected primary, because the indications for elective neck treatment concur with the indications for post-operative radiotherapy to the primary, and because pre- and perioperative typing of SGC is difficult (accuracy 51–62%) [232].

For submandibular gland cancer, treatment has shifted in the last decades from aggressive surgery, including the submandibular gland in a radical neck dissection, often with en bloc excision of the floor of mouth

and lower rim of the mandible as monotherapy [233], to more limited surgery, supplemented by post-operative radiotherapy (level I–II–III dissection comprising the submandibular gland, only to be extended if disease extension dictates so) [234, 235].

For MiSGC, the treatment of choice is resection of the primary with free margins, resection margin status being the most important prognosticator, correlating strongly with anatomical extent and histological type [225]. The neck in MiSGC should be only addressed surgically for cN+ disease, for a cN0 neck when the risk of subclinical disease exceeds 20%, or when the neck is surgically entered as an approach to the primary [227]. Except in high-grade MEC, the occult metastasis rate is too low to justify elective treatment. For patients with pN+ disease, post-operative radiotherapy improves locoregional control and survival [231].

Following resection, the pathologist types the tumour using the 2005 WHO classification (Table 35.6) and identifies grade and negative prognostic factors such as perineural, vascular, and perilymphatic growth, and involved margins. Increasingly, molecular markers including chromosomal translocations with their protein products, improve accurate histological diagnosis. Some tumours express androgen receptors (AR) that could be also therapeutically exploited. There is no clear relationship between histotypes and biological behaviour, as commented by Leivo [236]. In population-based studies, the majority of major SGC are acinic cell carcinoma (AcCC) (15–17%), adenoid cystic carcinoma (AdCC) (16–27%), and MEC (14.5–19.2%). For MiSGC, AdCC (32–71%) and MEC (15–38%) outnumber adenocarcinoma not otherwise specified (ACNOS), AcCC, polymorphous low-grade adenocarcinoma (PLGA), epithelial myoepithelial carcinoma, and carcinoma ex-pleomorphic adenoma [225, 226].

Post-operative radiotherapy for parotid and submandibular carcinomas

Indicated in stage III and IV disease, and in case of adverse histopathological factors (perineural and vascular invasion, close or positive margins, high-grade pathology), IMRT is now the ‘standard of care’ that minimizes complications. Typically a dose of 60 Gy in 30 fractions of 2 Gy in six weeks will be delivered on the parotid bed and the neck node levels (when pathologically invaded). In case of AdCC infiltrating the facial nerve, a comprehensive coverage of the nerve up to the base of the skull is recommended. The Dutch Head and Neck Oncology Cooperative Group found a 9.7-fold reduction of local recurrence in patients receiving combined surgery and radiotherapy as compared to surgery-only patients. Post-operative radiotherapy can only

be omitted for stage I–II lesions in AcCC and low-grade MEC if complete resection does not reveal adverse pathological factors [226]. For high-risk major SGC, two reports recently suggested the benefit of a post-operative platinum-based concomitant chemoradiation scheme [237, 238].

Post-operative radiotherapy for MiSGC

For MiSGC, post-operative radiotherapy to the primary site is recommended for most patients, only to be omitted in ‘clear margin’ stage I and II disease without lymphovascular or perineural invasion [225, 227, 231].

Radiotherapy and chemotherapy in unresectable disease

For patients who are inoperable, who refuse surgery, or who have an unresectable tumour, primary photon-based radiotherapy (dose of 66 to 70 Gy) results in 17–57% locoregional control at ten years. In a randomized trial conducted 30 years ago, neutron radiotherapy reached up to 75% five-year local control, especially for AdCC, but remains unattractive because of no survival benefit and severe late side effects [239]. More recently, encouraging results have been reported with the use of heavy ion therapy (carbon ion), which combines both the biological advantage of neutrons and an exquisite dose distribution [240].

In SGC chemotherapy remains of palliative use only, resulting in a temporary benefit in about 20% of treated patients. The most active drugs are cisplatin and doxorubicin [241, 242, 243]. Taxanes are not active in AdCC. In this latter histotype it is worthwhile suggesting a watchful approach in indolent diseases. Table 35.7 lists the targeted therapies that have been explored clinically. Unfortunately, none has significantly improved results.

Table 35.7 Molecular targets and corresponding therapies studied in salivary gland carcinoma

Molecular target	Salivary gland carcinoma type	Molecular therapy
c-KIT	AdCC	imatinib
ErbB–1	All types	cetuximab gefinitib
ErbB–2	All types	trastuzumab lapatinib
VEGF –family	AcCC	axinitib
NFκB – proteasomes degrading its inhibitor (I-κB)-α	AdCC	bortezomib

AR expressing tumours might be treated with androgen deprivation.

Treatment results according to site

The treatment results for parotid carcinoma in major treatment centres, listed in Table 35.8, have to be appreciated in their specific context of stage, percentage high-grade, treatment period and corresponding treatment regimens, patient inclusion criteria, and adequacy of follow-up. Many univariate and multivariate statistical analyses have focused on prognostic factors in SGC to fine-tune the individual patient's prognostic estimate [226].

Table 35.8 Disease-specific survival (DSS) for Parotid Carcinoma (multiple histologies together)

Research group	Publication year	Number of patients	DSS five years	DSS ten years
Spiro	1986	623	55%	47%
Spiro et al.	1989	62	63%	47%
Kane et al.	1991	194	69%	68%
Poulsen et al.	1992	209	71%	65%
Leverstein et al.	1998	65	75%	67%
Therkildsen et al.	1998	251	76%	72%
Renehan et al.	1999	103	78%	65%
Vander Poorten et al.	1999	168	59%	54%
Harbo et al.	2002	152	57%	51%
Godballe et al.	2003	85	52%	
Vander Poorten et al.	2003	231	62%	
Lima et al.	2005	126	72%	69%
Mendenhall et al.	2005	224		57%

Vander Poorten et al.	2009	237	69%	58%

Reproduced with permission from Vander Poorten V. et al., Diagnosis and management of parotid carcinoma with a special focus on recent advances in molecular biology, *Head and Neck*, Volume 34, Issue 3, pp. 429–440, Copyright © 2012 John Wiley and Sons Ltd.

Treatment results for submandibular gland cancer have increased recently as compared to the earlier series where post-operative radiotherapy was not yet customary. The five-year disease-free survival (DSS) of 61% and the ten-year DSS of 51% in Amsterdam [234] are similar to the findings in Toronto with a five-year DSS of 60% and a ten-year DSS of 48% [244].

For MiSGC, five-year survival ranges from 66% to 80% and ten-year survival from 56% to 70%, whereas initial tumour control is expected to be 56–62%. MSGCs overall do not imply a poorer prognosis than their submandibular and parotid counterparts, although specific subsites (e.g., the skull base) imply a worse outcome [225].

Summary

Every step in the management of SGC is complicated: the clinical and radiological evaluation, the pathology, the ablative and reconstructive surgery, the radiotherapy and eventual chemotherapy, and the management of complications. The best care can undoubtedly be provided when these patients are centralized in specialized tertiary referral centres.

Cervical paragangliomas

Cervical paragangliomas (PG) are highly vascular soft tissue tumours, originating from the paraganglia receptors in the vascular adventitia. They follow the course of cranial nerve X in the skull base and the parapharyngeal space lower down. With decreasing frequency they arise from the carotid body, jugular, tympanic, and vagal locations. The incidence of these rare head and neck tumours remains unclear, since most are benign tumours, not registered by cancer registries. About 6–19% are reportedly malignant, evidenced only by imaging studies showing local invasion, regional or distant metastasis, since the histological appearance of malignant PG is identical to that of benign tumours [245].

Genetics

About nine in ten PGs are sporadic; in one in ten patients a mutation in the succinate dehydrogenase (SDH) subunits (SDHD, SDHB, SDHC) genes typically causes development of multifocal PG at age <40, and in combination with pheochromocytomas [246].

Clinical presentation—workup

Most patients with carotid PG present with an asymptomatic pulsatile neck mass which patients report to vary in volume. At other sites, symptoms of PG reflect the cranial nerves they interfere with, ranging from vague pain through hearing loss, pulsatile tinnitus (n VIII), velopharyngeal insufficiency (n IX), chronic cough, dysphagia, dysphonia, aspiration (n X) and shoulder weakness (n XI). Up to 3% of PGs secrete catecholamines, detected by urinalysis. CT+/–MRI+/–MR angiography of the head and neck are so typical (salt and pepper appearance, flow voids, splaying of the carotid bifurcation for carotid body tumours, anterior displacement of both internal and external carotid artery in vagal paraganglioma) that they are sufficient for diagnosis, obviating a (hazardous) biopsy. Imaging studies reveal location, extent, relation to the great vessels, and eventual coexistent PG at other sites. For the latter, a somatostatin receptor scanning (octreotide scan) is also useful.

Treatment and outcome

There are three valid options to choose from. The slow growth rate, with half of the tumours not showing volume increase during long-term follow-up, supports an initial wait-and-scan policy for many patients [247, 248]. Alternatively, in volume-increasing lesions, both surgery and radiotherapy (IMRT: moderate-dose RT of 44–50 Gy over 22–25 fractions or in selected very small skull base lesions, stereotactic radiosurgery) are valid options [245, 249]. Given the potential complications, surgery is usually reserved for limited PG where minimal morbidity is expected. Typically, these are the 70% of carotid body tumours that are Shamblin class I (small and easily dissected from the vessels) and class II (glomus tumour partially surrounds the vessels). For all other tumours (class III carotid body tumours and vagal—jugular –tympanic PG), new post-operative cranial deficits are hard to avoid. A recent review looking at ‘all surgically treated carotid PG’ observed 22% new cranial nerve deficits, 3% stroke, and 1% peroperative deaths [250]. The same authors reviewed the literature on vagal and jugular PG and concluded that on average 1 extra post-operative cranial nerve deficit is observed per patient operated, as opposed to eight post-treatment cranial nerve deficits per 100 patients treated with RT, at a comparable local control rate of 80–90% for both modalities. Ten-year local control rates using RT of 94% and higher are

reported [251, 252]. It can be concluded that RT has comparable tumour control and significantly less morbidity than surgery. A choice for surgery should put in the balance the patient's age, tumour size, predicted tumour growth, and cranial nerve function in order maximally to safeguard quality of life.

Further reading

Bauer DE, Mitchell CM, Strait KM, Lathan CS, Stelow EB et al. Clinicopathologic features and long-term outcomes of NUT midline carcinoma. Clinical Cancer Research 2012; 18(20): 5773–5779.

Bisdas S, Rumboldt Z, Surlan-Popovic K, Baghi M, Koh TS et al. Perfusion CT in squamous cell carcinoma of the upper aerodigestive tract: long-term predictive value of baseline perfusion CT measurements. American Journal of Neuroradiology 2010; 31: 576–581.

Cordes B, Williams MD, Tirado Y, Bell D, Rosenthal DI et al. Molecular and phenotypic analysis of poorly differentiated sinonasal neoplasms: an integrated approach for early diagnosis and classification. Human Pathology 2009; 40(3): 283–292.

Dauer EH, Lewis JE, Rohlinger AL, Weaver AL, Olsen KD. Sinonasal melanoma: a clinicopathologic review of 61 cases. Otolaryngology Head and Neck Surgery 2008; 138(3): 347–352.

de Bondt RB, Nelemans PJ, Hofman PA, Casselman JW, Kremer B et al. Detection of lymph node metastases in head and neck cancer: a meta-analysis comparing US, USgFNAC, CT and MR imaging. European Journal of Radiology 2007; 64: 266–272.

Di Martino E, Nowak B, Hassan HA, Hausmann R, Adam G et al. Diagnosis and staging of head and neck cancer: a comparison of modern imaging modalities (positron emission tomography, computed tomography, color-coded duplex sonography) with panendoscopic and histopathologic findings. Archives of Otolaryngology—Head & Neck Surgery 2000; 126: 1457–1461.

Ducic Y, Young L, McIntyre J. Neck dissection: past and present. Minerva Chirurgica 2010; 65(1): 45–58.

Ejaz A, Wenig BM. Sinonasal undifferentiated carcinoma: clinical and pathologic features and a discussion on classification, cellular differentiation, and differential diagnosis. Advances in Anatomic Pathology 2005; 12: 134–143.

El-Naggar AK, Westra WH. p16 expression as a surrogate marker for HPV-related oropharyngeal carcinoma: a guide for interpretative relevance and consistency. Head & Neck 2012; 34(4): 459–461.

Etges A, Pinto DS Jr, Kowalski LP, Soares FA, Araújo VC. Salivary duct carcinoma: immunohistochemical profile of an aggressive salivary gland tumour. Journal of Clinical Pathology 2003; 56(12): 914–918.

Frates MC, Benson CB, Charboneau JW, Cibas ES, Clark OH et al. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Radiology 2005; 237: 794–800.

Frierson HF Jr, El-Naggar AK, Welsh JB, Sapinoso LM, Su AI et al. Large scale molecular analysis identifies genes with altered expression in salivary adenoid cystic carcinoma. American Journal of Pathology 2002; 161(4): 1315–1323.

Hermans R. Posttreatment imaging in head and neck cancer. European Journal of Radiology 2008; 66: 501–511.

Hermans R, Van den Bogaert W, Rijnders A, Doornaert P, Baert AL. Predicting the local outcome of glottic cancer treated by definitive radiation therapy: value of computed tomography determined tumor parameters. Radiotherapy & Oncology 1999; 50: 39–46.

Howlett DC. High resolution ultrasound assessment of the parotid gland. British Journal of Radiology 2003; 76: 271–277.

Ingeholm P, Theilgaard SA, Buchwald C, Hansen HS, Francis D. Esthesioneuroblastoma: a Danish clinicopathological study of 40 consecutive cases. APMIS 2002; 110(9): 639–645.

Kane SV, Gupta M, Kakade AC, D’ Cruz A. Depth of invasion is the most significant histological predictor of subclinical cervical lymph node metastasis in early squamous carcinomas of the oral cavity. European Journal of Surgical Oncology 2006; 32(7): 795–803.

Kim S, Loevner L, Ouon H, Sherman E, Weinstein G et al. Diffusion-weighted magnetic resonance imaging for predicting and detecting early respons to chemoradiation therapy of squamous cell carcinomas of the head and neck. Clinical Cancer Research 2009; 15: 986–994.

King AD. Imaging for staging and management of thyroid cancer. Cancer Imaging 2008; 8: 57–69.

Lango MN, Andrews GA, Ahmad S, Feigenberg S, Tuluc M et al. Postradiotherapy neck dissection for head and neck squamous cell carcinoma: pattern of pathologic residual carcinoma and prognosis. Head & Neck 2009; 31(3): 328–337.

Li S, Feng X, Li T, Zhang S, Zuo Z et al. Extranodal NK/T-cell lymphoma, nasal type: a report of 73 cases at MD Anderson Cancer Center. American Journal of Surgical Pathology 2013; 37(1): 14–23.

Ljumanović R, Langendijk JA, Schenk B, Van Wattingen M, Knol DL et al. Supraglottic carcinoma treated with curative radiation therapy: identification of prognostic groups with MR imaging. Radiology 2004; 232: 440–448.

Lonneux M, Hamoir M, Reychler H, Maingon P, Duvillard C et al. Positron emission tomography with [18F]fluorodeoxyglucose improves staging and patient management in patients with head and neck squamous cell carcinoma: a multicenter prospective study. Journal of Clinical Oncology 2010; 28: 1190–1195.

Lonneux M, Lawson G, Ide C, Bausart R, Remacle M et al. Positron emission tomography with fluorodeoxyglucose for suspected head and neck tumor recurrence in the symptomatic patient. Laryngoscope 2000; 110: 1493–1497.

Myers JN, Greenberg JS, Mo V, Roberts D, Extracapsular spread. A significant predictor of treatment failure in patients with squamous carcinoma of tongue. Cancer 2001 15; 92(12): 3030–3036.

O'Neill JP, Bilsky MH, Kraus D. Head and neck sarcomas: epidemiology, pathology, and management. Neurosurgery Clinics of North America 2013; 24(1): 67–78.

Pameijer FA, Mancuso AA, Mendenhall WM, Parsons JT, Kubilis MS. Can pretreatment computed tomography predict local control in T3 squamous cell carcinoma of the glottis larynx treated with definitive radiotherapy? International Journal of Radiation Oncology Biology Physics 1997; 37: 1011–1021.

Vandecaveye V, De Keyzer F, Nuyts S, Deraedt K, Dirix P, Hamaekers P, Vander Poorten V, Delaere P, Hermans R. Detection of head and neck squamous cell carcinoma with diffusion weighted MRI after (chemo)radiotherapy: correlation between radiologic and histopathologic findings. Int J Radiat Oncol Biol Phys. 2007; 67: 960–971.

Kim S, Loevner L, Ouon H et al. Diffusion-weighted magnetic resonance imaging for predicting and detecting early respons to chemoradiation

therapy of squamous cell carcinomas of the head and neck. Clin Cancer Res 2009; 15: 986–994.

Quon A, Fischbein NJ, McDougall IR, Le QT, Loo BW Jr et al. Clinical role of 18F-FDG PET/CT in the management of squamous cell carcinoma of the head and neck and thyroid carcinoma. Journal of Nuclear Medicine 2007; 48(Suppl. 1): 58S–67S.

Rao PH, Roberts D, Zhao YJ, Bell D, Harris CP et al. Deletion of 1p32-p36 is the most frequent genetic change and poor prognostic marker in adenoid cystic carcinoma of the salivary glands. Clinical Cancer Research 2008; 14(16): 5181–5187.

Schöder H, Yeung HW. Positron emission imaging of head and neck cancer, including thyroid carcinoma. Seminars in Nuclear Medicine 2004; 34: 180–197.

Schwartz DL, Rajendran J, Yueh B, Coltrera M, Anzai Y et al. Staging of head and neck squamous cell cancer with extended-field FDG-PET. Archives of Otolaryngology—Head & Neck Surgery 2003; 129: 1173–1178.

Shukla-Dave A, Lee NY, Jansen JF, Thaler HT, Stambuk HE et al. Dynamic contrast-enhanced magnetic resonance imaging as a predictor of outcome in head-and-neck squamous cell carcinoma patients with nodal metastases. International Journal of Radiation Oncology Biology Physics 2012; 82: 1837–1844.

Thoeny HC, De Keyzer F, King AD. Diffusion-weighted MR imaging in the head and neck. Radiology 2012; 263: 19–32.

Tshering Vogel DW, Zbaeren P, Geretschlaeger A, Vermathen P, De Keyzer F et al. Diffusion-weighted MR imaging including bi-exponential fitting for the detection of recurrent or residual tumour after (chemo)radiotherapy for laryngeal and hypopharyngeal cancers. European Radiology 2013; 23: 562–569.

van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa; present concepts of management. Oral Oncology 2010; 46(6): 423–425.

Vandecaveye V, De Keyzer F, Dirix P, Lambrecht M, Nuyts S et al. Applications of diffusion-weighted magnetic resonance imaging in head and neck squamous cell carcinoma. Neuroradiology 2010; 52: 773–784.

Vandecaveye V, De Keyzer F, Nuyts S, Deraedt K, Dirix P et al. Detection of head and neck squamous cell carcinoma with diffusion weighted MRI

after (chemo)radiotherapy: correlation between radiologic and histopathologic findings. International Journal of Radiation OncologyBiology Physics 2007; 67: 960–971.

Yamamoto Y, Wong TZ, Turkington TG, Hawk TC, Coleman RE. Head and neck cancer: dedicated FDG PET/CT protocol for detection—phantom and initial clinical studies. Radiology 2007; 244: 263–272.

Yeung AR, Liauw SL, Amdur RJ, Mancuso AA, Hinerman RW et al. Lymph node-positive head and neck cancer treated with definitive radiotherapy: can treatment response determine the extent of neck dissection? Cancer 2008; 112: 1076–1082.

References

1. Maier H, Dietz A, Gewelke U, Heller WD, Weidauer H. Tobacco and alcohol and the risk of head and neck cancer. Clnical Investigations 1992; 70(3–4): 320–327.

2. D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C et al. Case-control study of human papillomavirus and oropharyngeal cancer. New England Journal of Medicine 2007; 356(19): 1944–1956.

3. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. Journal of Clinical Oncology 2011; 29(32): 4294–4301.

4. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI et al. Human papillomavirus and survival of patients with oropharyngeal cancer. New England Journal of Medicine 2010; 363(1): 24–35.

5. Stransky N, Egloff AM, Tward AD, Kostic AD, Cibulskis K et al. The mutational landscape of head and neck squamous cell carcinoma. Science 2011; 333(6046): 1157–1160.

6. Agrawal N, Frederick MJ, Pickering CR, Bettegowda C, Chang K et al. Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1. Science 2011; 333(6046): 1154–1157.

7. Haddad RI, Shin DM. Recent advances in head and neck cancer. New England Journal of Medicine 2008; 359(11): 1143–1154.

8. zur Hausen H. Papillomaviruses and cancer: from basic studies to clinical application. Nature Reviews Cancer 2002; 2(5): 342–350.

9. Chung CH, Gillison ML. Human papillomavirus in head and neck cancer: its role in pathogenesis and clinical implications. Clinical Cancer Researchearch 2009; 15(22): 6758–6762.

10. Howard JD, Chung CH. Biology of human papillomavirus-related oropharyngeal cancer. Seminars in Radiation Oncology 2012; 22(3): 187–193.

11. Maslon MM, Hupp TR. Drug discovery and mutant p53. Trends in Cellular Biology 2010; 20(9): 542–555.

12. Poeta ML, Manola J, Goldwasser MA, Forastiere A, Benoit N et al. TP53 mutations and survival in squamous-cell carcinoma of the head and neck. New England Journal of Medicine 2007; 357(25): 2552–2561.

13. Lukas J, Parry D, Aagaard L, Mann DJ, Bartkova J et al. Retinoblastoma-protein-dependent cell-cycle inhibition by the tumour suppressor p16. Nature 1995; 375(6531): 503–506.

14. Ha PK, Califano JA. Promoter methylation and inactivation of tumour-suppressor genes in oral squamous-cell carcinoma. Lancet Oncology 2006; 7(1): 77–82.

15. Hayes DN, Grandis JR, El-Naggar AK. The Cancer Genome Atlas Network: comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature 2015; 517: 576–582

16. cBioportal for Cancer Genomics, <>.

17. Chung CH, Parker JS, Karaca G, Wu J, Funkhouser WK et al. Molecular classification of head and neck squamous cell carcinomas using patterns of gene expression. Cancer Cell 2004; 5(5): 489–500.

18. Walter V, Yin X, Wilkerson MD, Cabanski C, Zhao N et al. Molecular subtypes in head and neck cancer exhibit distinct patterns of chromosomal gain and loss of canonical cancer genes. PLOS One 2013; 8(2):e56823.

19. Keck MK, Zuo Z, Khattri A, Brown CD, Stricker T et al. Integrative analysis of head and neck cancer identifies two biologically distinct HPV and three non-HPV subtypes earch 2015 Feb 15; 21(4): 870–881

20. Barnes L, Eveson JW, Reichart P et al eds. Head and Neck Tumours. Lym: IARC, 2005.

21. Napier SS, Speight PM. Natural history of potentially malignant oral lesions and conditions: an overview of the literature: an overview of the literature. Journal of Oral Pathology & Medicine 2008; 37(1): 1–10.

22. van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa; present concepts of management. Oral Oncology 2010; 46(6): 423–425.

23. Slaughter DP, Southwick HW, Smejkal W. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. Cancer 1953; 6(5): 963–968.

24. Lee JJ, Hong WK, Hittelman WN, Mao L, Lotan R et al. Predicting cancer development in oral leukoplakia: ten years of translational research. Clinical Cancer Research 2000 May; 6(5): 1702–1710.

25. El-Naggar AK, Westra WH. p16 expression as a surrogate marker for HPV-related oropharyngeal carcinoma: a guide for interpretative relevance and consistency. Head & Neck 2012; 34(4): 459–461.

26. Kane SV, Gupta M, Kakade AC, D’ Cruz A. Depth of invasion is the most significant histological predictor of subclinical cervical lymph node metastasis in early squamous carcinomas of the oral cavity. European Journal of Surgical Oncology 2006; 32(7): 795–803.

27. Myers JN, Greenberg JS, Mo V, Roberts D, Extracapsular spread. A significant predictor of treatment failure in patients with squamous carcinoma of tongue. Cancer 2001 15; 92(12): 3030–3036.

28. Woolgar JA, Scott J. Prediction of cervical lymph node metastasis in squamous cell carcinoma of the tongue/floor of mouth. Head & Neck 1995; 17(6): 463–472.

29. Ducic Y, Young L, McIntyre J. Neck dissection: past and present. Minerva Chirurgica 2010; 65(1): 45–58.

30. Lango MN, Andrews GA, Ahmad S, Feigenberg S, Tuluc M et al. Postradiotherapy neck dissection for head and neck squamous cell carcinoma: pattern of pathologic residual carcinoma and prognosis. Head & Neck 2009; 31(3): 328–337.

31. Cordes B, Williams MD, Tirado Y, Bell D, Rosenthal DI et al. Molecular and phenotypic analysis of poorly differentiated sinonasal neoplasms: an integrated approach for early diagnosis and classification. Human Pathology 2009; 40(3): 283–292.

32. Bauer DE, Mitchell CM, Strait KM, Lathan CS, Stelow EB et al. Clinicopathologic features and long-term outcomes of NUT midline carcinoma. Clinical Cancer Research 2012; 18(20): 5773–5779.

33. Ejaz A, Wenig BM. Sinonasal undifferentiated carcinoma: clinical and pathologic features and a discussion on classification, cellular differentiation, and differential diagnosis. Advances in Anatomic Pathology 2005; 12: 134–143.

34. Ingeholm P, Theilgaard SA, Buchwald C, Hansen HS, Francis D. Esthesioneuroblastoma: a Danish clinicopathological study of 40 consecutive cases. APMIS 2002; 110(9): 639–645.

35. Hyams VJ, Batsakis JG, Michaels L eds. Olfactory neuroblastoma. In Hyams VJ, Baksakis JG, Michaels L eds, Tumors of the Upper Respiratory Tract and Ear. Washington, DC: Armed Forces Institute of Pathology, 1988, 240–248.

36. Dauer EH, Lewis JE, Rohlinger AL, Weaver AL, Olsen KD. Sinonasal melanoma: a clinicopathologic review of 61 cases. Otolaryngology Head and Neck Surgery 2008; 138(3): 347–352.

37. O'Neill JP, Bilsky MH, Kraus D. Head and neck sarcomas: epidemiology, pathology, and management. Neurosurgery Clinics of North America 2013; 24(1): 67–78.

38. Ahmed AA, Tsokos M. Sinonasal rhabdomyosarcoma in children and young adults. International Journal of Surgical Pathology 2007 Apr; 15(2): 160–165.

39. Bahrami A, Gown AM, Baird GS, Hicks MJ, Folpe AL. Aberrant expression of epithelial and neuroendocrine markers in alveolar rhabdomyosarcoma: a potentially serious diagnostic pitfall. Modern Pathology 2008; 21(7): 795–806.

40. Li S, Feng X, Li T, Zhang S, Zuo Z et al. Extranodal NK/T-cell lymphoma, nasal type: a report of 73 cases at MD Anderson Cancer Center. American Journal of Surgical Pathology 2013; 37(1): 14–23.

41. Spiro IJ, Wang CC, Montgomery WW. Carcinoma of the parotid gland: analysis of treatment results and patterns of failure after combined surgery and radiation therapy. Cancer 1993; 71(9): 2699–2705.

42. Spiro RH. Salivary neoplasms: overview of a 35-year experience with 2,807 patients. Head & Neck Surgery 1986; 8(3): 177–184.

43. Mani RS, Chinnaiyan AM. Triggers for genomic rearrangements: insights into genomic, cellular and environmental influences. Nature Reviews Genetics 2010; 11(12): 819–829.

44. Frierson HF Jr, El-Naggar AK, Welsh JB, Sapinoso LM, Su AI et al. Large scale molecular analysis identifies genes with altered expression in salivary adenoid cystic carcinoma. American Journal of Pathology 2002; 161(4): 1315–1323.

45. Rao PH, Roberts D, Zhao YJ, Bell D, Harris CP et al. Deletion of 1p32-p36 is the most frequent genetic change and poor prognostic marker in adenoid cystic carcinoma of the salivary glands. Clinical Cancer Research 2008; 14(16): 5181–5187.

46. Jeng YM, Lin CY, Hsu HC. Expression of the c-kit protein is associated with certain subtypes of salivary gland carcinoma. Cancer Letters 2000; 154(1): 107–111.

47. Murrah VA, Batsakis JG. Salivary duct carcinoma. Annals of Otology, Rhinology & Laryngology 1994; 103(3): 244–247.

48. Etges A, Pinto DS Jr, Kowalski LP, Soares FA, Araújo VC. Salivary duct carcinoma: immunohistochemical profile of an aggressive salivary gland tumour. Journal of Clinical Pathology 2003; 56(12): 914–918.

49. Howlett DC. High resolution ultrasound assessment of the parotid gland. British Journal of Radiology 2003; 76: 271–277.

50. Frates MC, Benson CB, Charboneau JW, Cibas ES, Clark OH et al. Management of thyroid nodules detected at US: Society of Radiologists in Ultrasound consensus conference statement. Radiology 2005; 237: 794–800.

51. Ojiri H, Mendenhall WM, Mancuso AA. CT findings at the primary site of oropharyngeal squamous cell carcinoma within 6–8 weeks after definitive radiotherapy as predictors of primary site control. International Journal of Radiation Oncology Biology Physics 2002; 52: 748–754.

52. King AD. Imaging for staging and management of thyroid cancer. Cancer Imaging 2008; 8: 57–69.

53. de Bondt RB, Nelemans PJ, Hofman PA, Casselman JW, Kremer B et al. Detection of lymph node metastases in head and neck cancer: a meta-analysis comparing US, USgFNAC, CT and MR imaging. European Journal of Radiology 2007; 64: 266–272.

54. Vandecaveye V, De Keyzer F, Dirix P, Lambrecht M, Nuyts S et al. Applications of diffusion-weighted magnetic resonance imaging in head and neck squamous cell carcinoma. Neuroradiology 2010; 52: 773–784.

55. Brockenbrough JM, Petruzzelli GJ, Lomasney L. 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: 113–117.

56. Imaizumi A, Yoshino N, Yamada I, Nagumo K, Amagasa T et al. A potential pitfall of MR imaging for assessing mandibular invasion of squamous cell carcinoma in the oral cavity. American Journal of Neuroradiology 2006; 27: 114–122.

57. Mancuso AA, Mukherji SK, Schmalfuss I, Mendenhall W, Parsons J et al. Preradiotherapy computed tomography as a predictor of local control in supraglottic carcinoma. Journal of Clinical Oncology 1999; 17: 631–637.

58. Pameijer FA, Mancuso AA, Mendenhall WM, Parsons JT, Kubilis MS. Can pretreatment computed tomography predict local control in T3 squamous cell carcinoma of the glottis larynx treated with definitive radiotherapy? International Journal of Radiation Oncology Biology Physics 1997; 37: 1011–1021.

59. Pameijer FA, Mancuso AA, Mendenhall WM, Parsons JT, Mukherji SK et al. Evaluation of pretreatment computed tomography as a predictor of local control in T1/T2 piriform sinus carcinoma treated with definitive radiotherapy. Head & Neck 1998; 20: 159–68.

60. Hermans R, Van den Bogaert W, Rijnders A, Doornaert P, Baert AL. Predicting the local outcome of glottic cancer treated by definitive radiation therapy: value of computed tomography determined tumor parameters. Radiotherapy & Oncology 1999; 50: 39–46.

61. Ljumanović R, Langendijk JA, Schenk B, Van Wattingen M, Knol DL et al. Supraglottic carcinoma treated with curative radiation therapy: identification of prognostic groups with MR imaging. Radiology 2004; 232: 440–448.

62. Ljumanovic R, Langendijk JA, van Wattingen M, Schenk B, Knol DL et al. MR imaging predictors of local control of glottic squamous cell carcinoma treated with radiation alone. Radiology 2007; 244: 205–212.

63. de Bondt RB, Nelemans PJ, Hofman PA, Casselman JW, Kremer B et al. Detection of lymph node metastases in head and neck cancer: a meta-

analysis comparing US, USgFNAC, CT and MR imaging. European Journal of Radiology 2007; 64: 266–272.

64. Hermans R. Posttreatment imaging in head and neck cancer. European Journal of Radiology 2008; 66: 501–511.

65. Yeung AR, Liauw SL, Amdur RJ, Mancuso AA, Hinerman RW et al. Lymph node-positive head and neck cancer treated with definitive radiotherapy: can treatment response determine the extent of neck dissection? Cancer 2008; 112: 1076–1082.

66. Bisdas S, Rumboldt Z, Surlan-Popovic K, Baghi M, Koh TS et al. Perfusion CT in squamous cell carcinoma of the upper aerodigestive tract: long-term predictive value of baseline perfusion CT measurements. American Journal of Neuroradiology 2010; 31: 576–581.

67. Surlan-Popovic K, Bisdas S, Rumboldt Z, Koh TS, Strojan P. Changes in perfusion CT of advanced squamous cell carcinoma of the head and neck treated during the course of concomitant chemoradiotherapy. American Journal of Neuroradiology 2010; 31: 570–575.

68. Shukla-Dave A, Lee NY, Jansen JF, Thaler HT, Stambuk HE et al. Dynamic contrast-enhanced magnetic resonance imaging as a predictor of outcome in head-and-neck squamous cell carcinoma patients with nodal metastases. International Journal of Radiation Oncology Biology Physics 2012; 82: 1837–1844.

69. Thoeny HC, De Keyzer F, King AD. Diffusion-weighted MR imaging in the head and neck. Radiology 2012; 263: 19–32.

70. Vandecaveye V, De Keyzer F, Nuyts S, Deraedt K, Dirix P et al. Detection of head and neck squamous cell carcinoma with diffusion weighted MRI after (chemo)radiotherapy: correlation between radiologic and histopathologic findings. International Journal of Radiation Oncology Biology Physics 2007; 67: 960–971.

71. Tshering Vogel DW, Zbaeren P, Geretschlaeger A, Vermathen P, De Keyzer F et al. Diffusion-weighted MR imaging including bi-exponential fitting for the detection of recurrent or residual tumour after (chemo)radiotherapy for laryngeal and hypopharyngeal cancers. European Radiology 2013; 23: 562–569.

72. Kim S, Loevner L, Ouon H, Sherman E, Weinstein G et al. Diffusion-weighted magnetic resonance imaging for predicting and detecting early respons to chemoradiation therapy of squamous cell carcinomas of the head and neck. Clinical Cancer Research 2009; 15: 986–994.

73. Vandecaveye V, Dirix P, De Keyzer F, de Beeck KO, Vander Poorten V et al. Predictive value of diffusion-weighted magnetic resonance imaging during chemoradiotherapy for head and neck squamous cell carcinoma. European Radiology 2010; 20: 1703–1714.

74. Vandecaveye V, Dirix P, De Keyzer F, Op de Beeck K, Vander Poorten V et al. Diffusion-weighted magnetic resonance imaging early after chemoradiotherapy to monitor treatment response in head-and-neck squamous cell carcinoma. International Journal of Radiation Oncology Biology Physics 2012; 82: 1098–1107.

75. Yamamoto Y, Wong TZ, Turkington TG, Hawk TC, Coleman RE. Head and neck cancer: dedicated FDG PET/CT protocol for detection—phantom and initial clinical studies. Radiology 2007; 244: 263–272.

76. Di Martino E, Nowak B, Hassan HA, Hausmann R, Adam G et al. Diagnosis and staging of head and neck cancer: a comparison of modern imaging modalities (positron emission tomography, computed tomography, color-coded duplex sonography) with panendoscopic and histopathologic findings. Archives of Otolaryngology—Head & Neck Surgery 2000; 126: 1457–1461.

77. Schöder H, Yeung HW. Positron emission imaging of head and neck cancer, including thyroid carcinoma. Seminars in Nuclear Medicine 2004; 34: 180–197.

78. Allal AS, Dulguerov P, Allaoua M, Haenggeli CA, El-Ghazi el A et al. Standardized uptake value of 2-[(18)F] fluoro-2-deoxy-D-glucose in predicting outcome in head and neck carcinomas treated by radiotherapy with or without chemotherapy. Journal of Clinical Oncology 2002; 20: 1398–1404.

79. Quon A, Fischbein NJ, McDougall IR, Le QT, Loo BW Jr et al. Clinical role of 18F-FDG PET/CT in the management of squamous cell carcinoma of the head and neck and thyroid carcinoma. Journal of Nuclear Medicine 2007; 48(Suppl. 1): 58S–67S.

80. Schwartz DL, Rajendran J, Yueh B, Coltrera M, Anzai Y et al. Staging of head and neck squamous cell cancer with extended-field FDG-PET. Archives of Otolaryngology—Head & Neck Surgery 2003; 129: 1173–1178.

81. Lonneux M, Hamoir M, Reychler H, Maingon P, Duvillard C et al. Positron emission tomography with [18F]fluorodeoxyglucose improves staging and patient management in patients with head and neck

squamous cell carcinoma: a multicenter prospective study. Journal of Clinical Oncology 2010; 28: 1190–1195.

82. McGuirt WF, Williams DW 3rd, Keyes JW Jr, Greven KM, Watson NE Jr et al. A comparative diagnostic study of head and neck nodal metastases using positron emission tomography. Laryngoscope 1995; 105: 373–375.

83. Lonneux M, Lawson G, Ide C, Bausart R, Remacle M et al. Positron emission tomography with fluorodeoxyglucose for suspected head and neck tumor recurrence in the symptomatic patient. Laryngoscope 2000; 110: 1493–1497.

84. Kishino T, Hoshikawa H, Nishiyama Y, Yamamoto Y, Mori N. Usefulness of 3’-deoxy-3’-18F-fluorothymidine PET for predicting early response to chemoradiotherapy in head and neck cancer. Journal of Nuclear Medicine 2012; 53: 1521–1527.

85. Brun E, Kjellén E, Tennvall J, Ohlsson T, Sandell A et al. FDG PET studies during treatment: prediction of therapy outcome in head and neck squamous cell carcinoma. Head & Neck 2002; 24: 127–135.

86. Sisson GA, Becket SP. Cancer of the nasal cavity and paranasal sinuses In Suen JY, Myers EN ed., Cancer of the Head and Neck. New York: Churchill Livingstone, 1981, 242–279.

87. Carrau R, Myers E, Johnson J. Paranasal sinus carcinoma, diagnosis, treatment andprognosis. Oncology 1992; 6: 43–50.

88. Cheesman A, Lund V, Howard D. Craniofacial resection for tumors of the nasal cavity and paranasal sinuses. Head & Neck Surgery 1986; 8: 429–435.

89. Lund V, Harrison D. Craniofacial resection for tumors of the nasal cavity and paranasal sinuses. American Journal of Surgery 1988; 156: 187–190.

90. Irish J, Gullane P, Gentili F, Freeman J, Boyd JB et al. Tumors of the skull base: outcome and survival analysis of 77 cases. Head & Neck 1994; 16(1): 3–10.

91. Shah J, Kraus D, Arbit E, Galicich J, Strong E. Craniofacial resection for tumor involving the anterior skull. Otolaryngology—Head & Neck Surgery 1992; 106: 387–393.

92. Cantu G, Solero CL, Mariani L, Lo Vullo S, Riccio S et al. Intestinal type adenocarcinoma of the ethmoid sinus in wood and leather workers: a retrospective study of 153 cases. Head & Neck 2011; 33(4): 535–542.

93. Cantu G, Solero CL, Miceli R, Mattana F, Riccio S et al. Anterior craniofacial resection for malignant paranasal tumors: a monoinstitutional experience of 366 cases. Head & Neck 2012; 34(1): 78–87.

94. Suarez C, Ferlito A, Lund VJ, Silver CE, Fagan JJ et al. Management of the orbit in malignant sinonasal tumors. Head & Neck 2008; 30(2): 242–250.

95. Singh N, Eskander A, Huang, Curtin H, Bartlett E et al. Imaging and resectability issues of sinonasal tumors. Expert Review of Anticancer Therapy 2013; 13(3): 297–312.

96. Cantu G, Solero C. L, Miceli R, Bolzoni Villaret A et al. Which classification for ethmoid malignant tumors involving the anterior skull base? Head & Neck 2005; 27(3): 224–231.

97. Ketcham AS, Wilkins RH, Van Buren JM, Mariani L, Mattavelli F et al. A combined intracranial facial approach to the paranasal sinuses. American Journal of Surgery 1963; 106: 698–703.

98. Ganly I, Patel SG, Singh B, Kraus DH, Bridger PG et al. Craniofacial resection for malignant paranasal sinus tumors: report of an international collaborative study. Head & Neck 2005; 27(7): 575–584.

99. Nicolai P, Battaglia P, Bignami M, Bolzoni Villaret A, Delù G et al. Endoscopic surgery for malignant tumors of the sinonasal tract and adjacent skull base: a 10-year experience. American Journal of Rhinology 2008; 22(3): 308–316.

100. Batra PS, Luong A, Kanowitz SJ, Sade B, Lee J et al. Outcomes of minimally invasive endoscopic resection of anterior skull base neoplasms. Laryngoscope 2010; 120(1): 9–16.

101. Parsons JT, Bova FJ, Fitzgerald, Mendenhall WM, Million RR. Severe dry-eye syndrome following external beam irradiation. International Journal of Radiation Oncology Biology Physics 1994; 30; 775–780.

102. Parsons JT, Bova FJ, Mendenhall WM, Million RR, Fitzgerald CR. Response of the normal eye to high dose radiotherapy. Oncology (Huntington) 1996; 10; 837–847.

103. Dulguerov P, Jacobsen MS, Allal, Lehmann W, Calcaterra T et al. Nasal and paranasal sinus carcinoma: are we making progress? A series of 220 patients and a systematic review. Cancer 2001; 92; 3012–3029.

104. Duthoy W, Boterberg T, Claus, Ost P, Vakaet L et al. Postoperative intensity-modulated radiotherapy in sinonasal carcinoma: clinical results in 39 patients. Cancer 2005; 104; 71–82.

105. Licitra L, Locati LD, Bossi P, Cantù G. Head and neck tumors other than squamous cell carcinoma. Current Opinions in Oncology 2004; 16: 236–241.

106. Hanna EY, Cardenas AD, DeMonte F, Roberts D, Kupferman M et al. Induction chemotherapy for advanced squamous cell caricnoma of the paranasal sinuses. Archives of Otolaryngology—Head & Neck Surgery 2011; 137(1): 78–81.

107. Lee MM, Vokes EE, Rosen A, Witt ME, Weichselbaum RR et al. Multimodality therapy in advanced paranasal sinus caricnoma: superior long-term results. Cancer Journal from Scientific American 1999; 5(4): 219–223.

108. Licitra L, Locati LD, Cavina R, Garassino I, Mattavelli F et al. Primary chemotherapy followed by anterior craniofacial resection and radiotherapy for paranasal cancer. Annals of Oncology 2003; 14: 367–372.

109. Licitra L, Suardi S, Bossi P, Locati LD, Mariani L et al. Prediction of TP53 status for primary cisplatin, fluorouracil, and leucovorin chemotherapy in ethmoid sinus intestinal-type adenocarcinoma. Journal of Clinical Oncology 2004; 22: 4901–4906.

110. Bossi P, Perrone F, Miceli R, Cantù G, Mariani L et al. TP53 status as guide for the management of ethmoid sinus intestinal-type adenocarcinoma. Oral Oncology 2013; 49: 413–419.

111. Rosenthal DI, Barker JL, El-Naggar AK, Aggarwal JP, Kane SV et al. Sinonasal malignancies with neuroendocrine differentiation. Patterns of failure according to histologic phenotype. Cancer 2004; 101: 2567–2573.

112. Mourad WF, Hauerstock D, Shourbaji RA, Hu KS, Culliney B et al. Trimodality management of sinonasal undifferentiated carcinoma and review of the literature. American Journal of Clinical Oncology 2013; 36: 584–588.

113. Knegt PP, Ah-See KW, vd Velden LA, Kerrebijn J. Adenocarcinoma of the ethmoidal sinus complex: surgical debulking and topical fluorouracil may be the optimal treatment. Archives of Otolaryngology—Head & Neck Surgery 2001; 127: 141–146.

114. Sato Y, Morita M, Takahashi H, Watanabe N, Kirikae I. Combined surgery, radiotherapy, and regional chemotherapy of the paranasal sinuses. Cancer 1970; 25; 571–579.

115. Almeyda R, Capper J. Is surgical debridement and topical 5-fluorouracil the optimum treatment for woodworkers' adenocarcinoma of the ethmoid sinuses? A case-controlled study of a 20 years experience. Clinical Otolaryngology 2008; 33(5): 435–441.

116. Van Dijk BA, Gatta G, Capocaccia R, Pierannunzio D, Strojan P et al. Rare cancers of the head and neck area in Europe. European Journal of Cancer 2012; 48: 783–796.

117. Chang ET, Adami HO. The enigmatic epidemiology of nasopharyngeal carcinoma. Cancer Epidemiology, Biomarkers & Prevention 2006; 15: 1765–1777.

118. Bray F, Haugen M, Moger TA, Tretli S, Aalen OO et al. Age-incidence curves of nasopharyngeal carcinoma worldwide: bimodality in low-risk populations and aetiologic implications. Cancer Epidemiology, Biomarkers & Prevention 2008; 17: 2356–2365.

119. Robinson M, Suh YE, Paleri V, Devlin D, Ayaz B et al. Oncogenic human papillomavirus-associated nasopharyngeal carcinoma: an observational study of correlation with ethnicity, histological subtype and outcome in a UK population. Infectious Agents and Cancer 2013; 8: 30.

120. Hsu CL, Chang KP, Lin CY, Chang HK, Wang CH et al. Plasma Epstein–Barr virus DNA concentration and clearance rate as novel prognostic factors for metastatic nasopharyngeal carcinoma. Head & Neck 2012; 34: 1064–1070.

121. Leung SF, Zee B, Ma BB, Hui EP, Mo F et al. Plasma Epstein-Barr viral deoxyribonucleic acid quantitation complements tumor-node-metastasis staging prognostication in nasopharyngeal carcinoma. Journal of Clinical Oncology 2006; 24: 5414–5418.

122. Hsu CL, Chan SC, Chang KP, Lin TL, Lin CY et al. Clinical scenario of EBV DNA follow-up in patients of treated localized nasopharyngeal carcinoma. Oral Oncology 2013; 49: 620–625.

123. Twu CW, Wang WY, Liang WM, Jan JS, Jiang RS et al. Comparison of the prognostic impact of serum anti-EBV antibody and plasma EBV DNA assays in nasopharyngeal carcinoma. International Journal of Radiation Oncology Biology Physics 2007; 67: 130–137.

124. Feng M, Wang W, Fan Z, Fu B, Li J et al. Tumor volume is an independent prognostic indicator of local control in nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy. Radiation Oncology 2013; 8: 208.

125. Lee N, Xia P, Quivey JM, Chau RM, Suen JJ et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. International Journal of Radiation Oncology Biology Physics 2002; 53: 12–22.

126. Lee N, Harris J, Garden AS, Straube W, Glisson B et al. Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225. Journal of Clinical Oncology 2009; 27: 3684–3690.

127. Kam MK, Leung SF, Zee B, Chau RM, Suen JJ et al. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. Journal of Clinical Oncology 2007; 25: 4873–4879.

128. Pow EH, Kwong DL, McMillan AS, Wong MC, Sham JS et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. International Journal of Radiation Oncology Biology Physics 2006; 66: 981–991.

129. Peng G, Wang T, Yang KY, Zhang S, Zhang T et al. A prospective, randomized study comparing outcomes and toxicities of intensity-modulated radiotherapy vs. conventional two-dimensional radiotherapy for the treatment of nasopharyngeal carcinoma. Radiotherapy & Oncology 2012; 104: 286–293.

130. Chen QY, Wen YF, Guo L, Liui H, Huang P-Y et al. Concurrent chemoradiotherapy vs radiotherapy alone in stage II nasopharyngeal carcinoma: phase III randomized trial. Journal of the National Cancer Institute 2011; 103: 1761–1770.

131. Baujat B, Audry H, Bourhis J, et al. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. International Journal of Radiation Oncology Biology Physics 2006; 64: 47–56.

132. Chen L, Hu CS, Chen XZ, Chan AT, Onat H et al. Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial. Lancet Oncology 2012; 13: 163–171.

133. Le QT, Zhang Q, Cao H, Cheng AJ, Pinsky BA et al. An international collaboration to harmonize the quantitative plasma Epstein-Barr virus DNA assay for future biomarker-guided trials in nasopharyngeal carcinoma. Clinical Cancer Research 2013; 19: 2208–2215.

134. Lee WM, Ng WT, Chan OS, et al. If concurrent-adjuvant chemoradiotherapy is beneficial for locoregionally advanced nasopharyngeal carcinoma, would changing the sequence to induction-concurrent achieve better outcome? Journal of Radiation Oncology 2012; 1: 107–115.

135. Hui EP, Ma BB, Leung SF, King AD, Mo F et al. Randomized phase II trial of concurrent cisplatin-radiotherapy with or without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma. Journal of Clinical Oncology 2009; 27: 242–249.

136. Lin H, Lin H, Cai X, Jin T, Guo LB et al. Chemotherapy plus radiotherapy makes curability a possibility in nasopharyngeal carcinoma patients with distant metastasis at diagnosis. Head & Neck Oncology 2013; 5: 1.

137. Ma J, Wen ZS, Lin P, Wang X, Xie FY. The results and prognosis of different treatment modalities for solitary metastatic lung tumor from nasopharyngeal carcinoma: a retrospective study of 105 cases. Chinese Journal of Cancer 2010; 29: 787–795.

138. Fandi A, Bachouchi M, Azli N, Taamma A, Boussen H et al. Long-term disease-free survivors in metastatic undifferentiated carcinoma of nasopharyngeal type. Journal of Clinical Oncology 2000; 18: 1324–1330.

139. Hao SP, Tsang NM. Surgical management of recurrent nasopharyngeal carcinoma. Chang Gung Medical Journal 2010; 33: 361–369, 2010.

140. Wei WI, Kwong DL. Current management strategy of nasopharyngeal carcinoma. Clinical & Experimental Otorhinolaryngology 2010; 3: 1–12.

141. Wei WI, Sham JS. Nasopharyngeal carcinoma. Lancet 365: 2041–2054, 2005.

142. Suarez C, Rodrigo JP, Rinaldo A, Langendijk JA, Shaha AR et al. Current treatment options for recurrent nasopharyngeal cancer. European Archives of Otorhinolaryngology 2010; 267: 1811–1824.

143. Chua DT, Wei WI, Sham JS, Hung KN, Au GK. Stereotactic radiosurgery versus gold grain implantation in salvaging local failures of nasopharyngeal carcinoma. International Journal of Radiation Oncology Biology Physics 2007; 69: 469–474.

144. Indrasari SR, Timmermans AJ, Wildeman MA, Karakullukcu MB, Herdini C et al. Remarkable response to photodynamic therapy in residual T4N0M0 nasopharyngeal carcinoma: a case report. Photodiagnosis and Photodynamic Therapy 2012; 9: 319–320.

145. Wildeman MA, Nyst HJ, Karakullukcu B, Tan BI. Photodynamic therapy in the therapy for recurrent/persistent nasopharyngeal cancer. Head & Neck Oncology 2009; 1: 40.

146. Bensouda Y, Kaikani W, Ahbeddou N, Rahhali R, Jabri M et al. Treatment for metastatic nasopharyngeal carcinoma. European Annals of Otorhinolaryngology–Head & Neck Diseases 2011; 128: 79–85.

147. Wolff K-D, Bootz F, Beck J, Bikowski K, Böhme P et al. Carcinoma of the oral cavity [Mundhöhlenkarzinom, Diagnostik und Therapie des Mundhöhlenkarzinoms] AWMF-Register-Number 007-100OL, Version 2.0 11.2012.

148. Scottish Intercollegiate Guidelines Network (SIGN), <>.

149. O'Brien CJ, Lauer CS, Fredricks S, Clifford AR, McNeil EB et al. Tumor thickness influences prognosis of T1 and T2 oral cavity cancer—but what thickness? Head & Neck 2003; 25(11): 937–945.

150. Royal College of Pathologists. Standards and Datasets for Reporting Cancers: Datasets for Histopathology Reports on Head and Neck Carcinomas and Salivary Neoplasms, 2nd ed. London: Royal College of Pathologists, 2005. Available from url: , accessed on 21 May 2015.

151. Robbins KT, Clayman G, Levine PA, Medina J, Sessions R et al. Neck dissection classification update: revisions proposed by the American Head and Neck Society and the American Academy of Otolaryngology—Head and Neck Surgery. Archives of Otolaryngology—Head & Neck Surgery 2002; 128(12117328): 751–758.

152. Küffer R, Lombardi T. Premalignant lesions of the oral mucosa: a discussion about the place of oral intraepithelial neoplasia (OIN). Oral Oncologyog 2002; 38(2): 125–130.

153. Pignon JP, le Maitre A, Maillard E, Bourhis J on behalf of the MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH_NC): an update on 93 randomised trials and 17,346 patients. Radiotherapy and Oncology 2009; 92: 4–14.

154. Blanchard P, Bourhis J, Lacas B, Posner MR, Vermorken JB et al. Taxane-cisplatin-fluorouracil as induction chemotherapy in locally advanced head and neck cancers: an individual patient data meta-analysis of the meta-analysis of chemotherapy in head and neck cancer group. Journal of Clinical Oncology 2013; 31(23): 2854–2860.

155. Licitra L, Grandi C, Guzzo M, Mariani L, Lo Vullo S et al. Primary chemotherapy in resectable oral cavity squamous cell cancer: a randomized controlled trial. Journal of Clinical Oncology 2003; 21(2): 327–333.

156. Zhong LP, Zhang CP, Ren GX, Guo W, William WN Jr et al. Randomized phase III trial of induction chemotherapy with docetaxel, cisplatin, and fluorouracil followed by surgery versus up-front surgery in locally advanced resectable oral squamous cell carcinoma. Journal of Clinical Oncology 2013; 31(6): 744–751.

157. Domenge C, Hill C, Lefebvre JL, De Raucourt D, Rhein B et al. Randomized trial of neoadjuvant chemotherapy in oropharynx carcinoma. French Groupe d'Etude des Tumeurs de la Tête et du Cou (GETTEC). British Journal of Cancer 2000; 83: 1594–1598.

158. Denis F, Garaud P, Bardet E, Alfonsi M, Sire C et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. Journal of Clinical Oncology 2004; 22: 69–76.

159. Fallai C, Bolner A, Signor M, Gava A, Franchin G et al. Long-term results of conventional radiotherapy versus accelerated hyperfractionated radiotherapy versus concomitant radiotherapy and chemotherapy in locoregionally advanced carcinoma of the oropharynx. Tumori 2006; 92: 41–54.

160. Pignon JP, Bourhis J, Domenge C, De Raucourt D, Rhein B et al. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 2000; 355: 949–955.

161. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. New England Journal of Medicine 2006; 354: 567–578.

162. O'Sullivan B, Huang SH, Siu LL, Waldron J, Zhao H et al. Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. Journal of Clinical Oncology 2013; 31: 543–550.

163. Rishi A, Ghoshal S, Verma R, Oinam AS, Patil VM et al. Comparison of concomitant boost radiotherapy against concurrent chemoradiation in locally advanced oropharyngeal cancers: a phase III randomised trial. Radiotherapy & Oncology 2013; 107: 317–324.

164. Garden AS, Kies MS, Morrison WH, Weber RS, Frank SJ et al. Outcomes and patterns of care of patients with locally advanced oropharyngeal carcinoma treated in the early 21st century. Radiation Oncology 2013; 8: 21.

165. Eisbruch A, Harris J, Garden AS, Chao CK, Straube W et al. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early-stage oropharyngeal cancer (RTOG 00-22). International Journal of Radiation Oncology Biology Physics 2010; 76: 1333–1338.

166. Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncology 2011; 12: 127–136.

167. Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet 2006; 368: 843–854.

168. Lassen P, Eriksen JG, Krogdahl A, Therkildsen MH, Ulhøi BP et al. The influence of HPV-associated p16-expression on accelerated fractionated radiotherapy in head and neck cancer: evaluation of the randomised DAHANCA 6&7 trial. Radiotherapy & Oncology 2011; 100: 49–55.

169. Adelstein DJ, Ridge JA, Brizel DM, et al. Transoral resection of pharyngeal cancer: summary of a National Cancer Institute Head and Neck Cancer Steering Committee Clinical Trials Planning Meeting, November 6–7, 2011, Arlington, Virginia. Head & Neck 2012; 34: 1681–1703.

170. Bozec A, Poissonet G, Chamorey E, Casanova C, Laout C et al. Quality of life after oral and oropharyngeal reconstruction with a radial forearm free flap: propsective study. Journal of Otolaryngology—Head & Neck Surgery 2009; 38: 401–408.

171. Curado MP, Edwards B, Storm H, Ferlay J, Heanue M et al eds. Cancer Incidence in Five Continents, vol. IX. IARC Scientific Publications No. 160. Lyon, France: International Agency for Research on Cancer, 2007.

172. Chevalier D, Lefebvre JL. Laryngeal cancer. In Anniko M, Bernal-Sprekelsen M, Bonkowsky V, Bradley PJ eds. Otorhinolaryngology, Head and Neck Surgery, European Manuel of Medicine. Berlin-Heidelberg: Springer-Verlag, 2010, 499–502.

173. Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre JL et al. European Organization for Research and Treatment of Cancer Trial 22931. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. New England Journal of Medicine 2004; 350: 1945–1952.

174. Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH et al. Radiation Therapy Oncology Group 9501/Intergroup. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. New England Journal of Medicine 2004; 350: 1937–1944.

175. Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head & Neck 2005; 27: 843–850.

176. Grégoire V, Ang K, Budach W, Grau C, Hamoir M et al. Delineation of the neck node levels for head and neck tumors: A 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. Radiotherapy & Oncology 2013; 110(1): 172–181.

177. Machtay M, Moughan J, Trotti A, Garden AS, Weber RS et al. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. Journal of Clinical Oncology 2008; 26: 3582–3589.

178. Gregoire V, Lefebvre JL, Licitra L, Felip E. Squamous cell carcinoma of the head and neck. EHNS-ESMO-ESTRO Clinical Practice Guidelines

for diagnosis, treatment and follow-up. Annals of Oncology 2010; 21(Suppl. 5): v184–v186.

179. Blanchard P, Baujat B, Holostenco V, Baey C, Bauhis J et al. Meta-analysis of chemotherapy in head and neck (MACH-NC): a comprehensive analysis by tumour site. Radiotherapy & Oncology 2011; 100: 33–40.

180. Vermorken JB, Remenar E, van Herpen C. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. New England Journal of Medicine 2007; 357; 1695–1704.

181. Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winquist E et al. Cisplatin and fluorouracil alone or with docetxe l in head and neck cancer. New England Journal of Medicine 2007; 357: 1705–1715.

182. Ensley JF, Jacobs JR, Weaver A, Kinzie J, Crissman J et al. Correlation between response to cisplatinum-combination chemotherapy and subsequent radiotherapy in previously untreated patients with advanced squamous cell cancers of the head and neck. Cancer 1984; 54(5): 811–814.

183. The Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. New England Journal of Medicine 1991; 324: 1685–1690.

184. Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collette L et al. Larynx preservation in pyriform sinus cancer: Preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. Journal of the National Cancer Institute 1996; 88: 890–899.

185. Lefebvre JL, Horiot J, Rolland F, Tesselaar M, Leemans CR et al. Phase III study on larynx preservation comparing sequential versus alternating chemoradiotherapy in hypopharynx and larynx cancer. Journal of the National Cancer Institute 2009; 101: 142–152.

186. 21. Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. New England Journal of Medicine 2003; 349: 2091–2098.

187. Forastiere AA, Zhang G, Weber RS, Maor MH, Goepfert H et al. Long-term results of RTOG 91-11: a comparison of three non-surgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. Journal of Clinical Oncology 2013; 31: 845–852.

188. Pointreau Y, Garaud P, Chapet S, Sire C, Tuchais C et al. Randomized trial of induction chemotherapy with cisplatin and5-fluorouracil with or without docetaxel for larynx preservation. Journal of the National Cancer Institute 2009; 101: 498–506.

189. Lefebvre JL, Pointreau Y, Rolland F, Alfonsi M, Baudoux A et al. Induction chemotherapy followed by either cemoradiotherapy or bioradiotherapy for larynx preservation: the TREMPLIN randomized phase II study. Journal of Clinical Oncology 2013; 31: 853–859. Erratum in Journal of Clinical Oncology 2013; 31: 1702.

190. Strojan P, Ferlito A, Medina JE, Woolgar JA, Rinaldo A et al. Contemporary management of lymph node metastases from an unknown primary to the neck: I. A review of diagnostic approaches. Head & Neck 2013; 35(1): 123–132.

191. Cianchetti M, Mancuso AA, Amdur RJ, Werning JW, Kirwan J et al. Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. Laryngoscope 2009; 119: 2348–2354.

192. Yoo J, Henderson S, Walker-Dilks C. Evidence-based guideline recommendations on the use of positron emission tomography imaging in head and neck cancer. Clinical Oncology (Royal College of Radiologists) 2013; 25(4): e33–e66.

193. Hasina R, Lingen MW. Head and neck cancer: the pursuit of molecular diagnostic markers. Semin Oncol 2004 Dec; 31(6): 718–725.

194. Grégoire V, Duprez Th, Lengelé B, Hamoir M. Management of the neck. In: Gunderson LL, Tepper JE eds, Clinical Radiation Oncology. Philadelphia: Churchill Livingstone, 2007, 827–852.

195. Grau C, Johansen LV, Jakobsen J, Geertsen P, Andersen E et al. Cervical lymph node metastases from unknown primary tumours. Results from a national survey by the Danish Society for Head and Neck Oncology. Radiotherapy & Oncology 2000 May; 55(2): 121–129.

196. Bernier J, Pfister DG, Cooper JS. Adjuvant chemo- and radiotherapy for poor prognosis head and neck squamous cell carcinomas. Critical Reviews Oncology Hematology 2005; 56(3): 353–364.

197. Balaker AE, Abemayor E, Elashoff D, St John MA. Cancer of unknown primary: does treatment modality make a difference? Laryngoscope 2012; 122(6): 1279–1282.

198. Narayan K, Crane CH, Kleid S, Hughes PG, Peters LJ. Planned neck dissection as an adjunct to the management of patients with advanced neck disease treated with definitive radiotherapy: for some or for all? Head Neck 1999; 21: 606–613.

199. Hamoir M, Ferlito A, Schmitz S, Hanin FX, Thariat J et al. The role of neck dissection in the setting of chemoradiation therapy for head and neck squamous cell carcinoma with advanced neck disease. Oral Oncology 2012; 48: 203–210.

200. Bar-Ad V, Mishra M, Ohri N, Intenzo C. Positron emission tomography for neck evaluation following definitive treatment with chemoradiotherapy for locoregionally advanced head and neck squamous cell carcinoma. Reviews on Recent Clinical Trials 2012; 7(1): 36–41.

201. Clavel S, Charron MP, Bélair M, Delouya G, Fortin B et al. The role of computed tomography in the management of the neck after chemoradiotherapy in patients with head-and-neck cancer. International Journal of Radiation Oncology Biology Physics 2012; 82: 567–573.

202. Warren S, Gates O. Multiple primary malignant tumors: a survey of the literature and a statistical study. American Journal of Cancer 1932; 16: 1358–1414.

203. Blanchard P, Baujat B, Holostenco V, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): a comprehensive analysis by tumour site. Radiation Oncology 2011; 100: 33–40

204. Strojan P, Corry J, Eisbruch A, Vermorken JB, Mendenhall WM et al. Recurrent and second primary squamous cell carcinoma of the head and neck: when and how to re-irradiate. Head & Neck 2013; 37(1):134–150.

205. Goodwin WJ JR. Salvage surgery for patients with recurrent squamous cell carcinoma of the upper aerodigestive tract: when do the ends justify the means? Laryngoscope 2000; 110(3 Pt 2 Suppl. 93): 1–18.

206. Stoeckli SJ, Pawlik AB, Lipp M, Huber A, Schmid S. Salvage surgery after failure of nonsurgical therapy for carcinoma of the larynx and hypopharynx. Archives of Otolaryngology—Head & Neck Surgery 2000; 126: 1473–1477.

207. Parsons JT, Mendenhall WM, Stringer SP, Cassisi NJ, Million RR. Salvage surgery following radiation failure in squamous cell carcinoma of the supraglottic larynx. International Journal of Radiation Oncology Biology Physics 1995; 32: 605–609.

208. Van der Putten L, de Bree R, Kuik DJ, Rietveld DH, Buter J et al. Salvage laryngectomy: oncological and functional outcome. Oral Oncology 2011; 47: 296–301.

209. Van der Putten L, van den Broek GB, de Bree R, van den Brekel MW, Balm AJ et al. Effectiveness of selective and radical neck dissection for regional pathological lymphadenopathy after chemoradiation. Head & Neck 2009; 31: 593–603.

210. Tanvetyanon T, Padhya T, McCaffrey J, Zhu W, Boulware D et al. Prognostic factors for survival after salvage reirradiation of head and neck cancer. Journal of Clinical Oncology 2009; 27: 1983–1991

211. Choe KS, Haraf DJ, Solanski A, Cohen EE, Seiwert TY et al. Prior chemoradiotherapy adversely impacts outcomes of recurrent and second primary head and neck cancer treated with concurrent chemotherapy and reirradiation. Cancer 2011; 117(20): 4671–4678.

212. Paleri V, Kelly CG. Re-irradiation with concurrent chemotherapy in re current head and neck cancer: a decision analysis model based on a systemic review. Clin Otolaryngol 2008; 33: 331–337

213. Sher DJ, Haddad RI, Norris CM Jr, Posner MR, Wirth LJ et al. Efficacy and toxicity of re-irradiation using intensity-modulated radiotherapy for recurrent or second primary head and neck cancer. Cancer 2010; 116: 4761–4768.

214. Nyst HJ, Tan IB, Stewart FA, Balm AJ. Is photodynamic therapy a good alternative to surgery and radiotherapy in the treatment of head and neck cancer? Photodiagnostic Photodynamic Therapy 2009; 6(1): 3–11.

215. Stoker SD, van Diessen JN, de Boer JP, Karakullukcu B, Leemans CR et al. Current treatment options for local residual nasopharyngeal caricnoma. Current Treatment Options in Oncology 2013; 14(4): 475–791.

216. Tijink BM, De Bree R, Van Dongen GA, Leemans CR. How we do it: Chdemo-eletroporation in the head and neck for otherwise untreatable patients. Clinical Otolaryngology 2006; 31(5): 447–451.

217. Mevio N, Bertino G, Occhini A, Scelsi D, Tagliabue M et al. Electrochemotherapy for the treatment of recurrent head and neck cancers: preliminary results. Tumori 2012; 98(3): 308–313

218. Argiris A, Li Y, Forastiere A. Prognostic factors and long-term survivorship in patients with recurrent or metastatic carcinoma of the head and neck. Cancer 2004; 101 (10): 2222–2229

219. Vermorken JB, Specenier P. Optimal treatment for recurrent/metastatic head and neck cancer. Annals of Oncology 2010; 21 (Suppl. 7): vii252–vii261

220. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. New England Journal of Medicine 2008; 359 (11): 1116–1127.

221. Mesia R, Rivera F, Kawecki A, Rottey S, Hitt R et al. Quality of life of patients receiving plastinum-based chemotherapy plus cetuximab first line for recurrent and/or metastatic squamous cell carcinoma of the head and neck. Annals of Oncology 2010; 21 (10): 1967–1973.

222. Guigay J, Fayette J, Dillies A-F, Sire C, Kerger JN et al. Cetuximab, docetaxel, and cisplatin (TPEx) as first-line treatment in patients with recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): final results of phase II trial GORTEC 2008-03. Journal of Clinical Oncology 2012; 30 (15S): 357s (abstract#5505).

223. Schmitz S, Ang KK, Vermorken J, Haddad R, Suarez C et al. Targeted therapies for squamous cell carcinoma of the head and neck: current knowledge and future directions. Cancer Treat Rev 2013; 40(3): 390–404.

224. Boeckx C, Baay M, Wouters, Specenier P, Vermorken JB et al. Anti-epidermal growth factor receptor therapy in head and neck squamous cell carcinoma: focus on potential molecular mechanisms of drug resistance. Oncologist 2013; 18(7): 850–864,

225. Vander Poorten V, Hunt J, Bradley PJ et al. Recent trends in the management of minor salivary gland carcinoma. Head Neck 2013.

226. Vander Poorten V, Bradley PJ, Takes RP, Rinaldo A, Woolgar JA, et al. Diagnosis and management of parotid carcinoma with a special focus on recent advances in molecular biology. Head Neck 2012; 34: 429–440.

227. Vander Poorten VLM, Balm AJM, Hilgers FJM, Tan IB, Keus RB et al. Stage as major long term outcome predictor in minor salivary gland carcinoma. Cancer 2000; 89: 1195–1204.

228. Barnes L, Eveson JW, Reichart P, Sidranski P. Pathology and genetics of head and neck tumours. World Health Classification of Tumours. In IARC, ed. Lyon: IARC press; 2005;210.

229. Kirkbride P, Liu FF, O'Sullivan B et al. Outcome of curative management of malignant tumours of the parotid gland. Journal of Otolaryngology 2001; 30: 271–279.

230. Armstrong JG, Harrison LB, Spiro RH, Fass DE, Strong EW et al. Malignant tumors of major salivary gland origin: a matched-pair analysis of the role of combined surgery and postoperative radiotherapy. Archives of Otolaryngology – Head and Neck Surgery 1990; 116: 290–293.

231. Terhaard CH, Lubsen H, Rasch CR, Levendag PC, Kaanders HH et al. The role of radiotherapy in the treatment of malignant salivary gland tumors. International Journal of Radiation Oncology Biology Physics 2005; 61: 103–111.

232. Frankenthaler RA, Byers RM, Luna MA, Callender DL, Wolf P et al. Predicting occult lymph node metastasis in parotid cancer. Archives of Otolaryngology – Head and Neck Surgery 1993; 119: 517–520.

233. Conley J, Myers E, Cole R. Analysis of 115 patients with tumors of the submandibular gland. Annals of Otology, Rhinology & Laryngology 1972; 81: 323–330.

234. Vander Poorten VLM, Balm AJM, Hilgers FJM, Tan IB, Loftus-Coll BM et al. Prognostic factors for long term results of the treatment of patients with malignant submandibular gland tumors. Cancer 1999; 85: 2255–2264.

235. Weber RS, Byers RM, Petit B, Wolf P, Ang K et al. Submandibular gland tumors. Adverse histologic factors and therapeutic implications. Archives of Otolaryngology – Head and Neck Surgery 1990; 116: 1055–1060.

236. Leivo I. Insights into a complex group of neoplastic disease: advances in histopathologic classification and molecular pathology of salivary gland cancer. Acta Oncologica 2006; 45: 662–668.

237. Tanvetyanon T, Qin D, Padhya T, McCaffrey J, Zhu W et al. Outcomes of postoperative concurrent chemoradiotherapy for locally advanced major salivary gland carcinoma. Archives of Otolaryngology – Head and Neck Surgery 2009; 135: 687–692.

238. Pederson AW, Salama JK, Haraf DJ, Witt ME, Stenson KM et al. Adjuvant chemoradiotherapy for locoregionally advanced and high-risk salivary gland malignancies. Head and Neck Oncology 2011; 3: 31.

239. Laramore GE, Krall JM, Griffin TW, Duncan W, Richter MP et al. Neutron versus photon irradiation for unresectable salivary gland tumors: final report of an RTOG-MRC randomized clinical trial. Radiation Therapy Oncology Group. Medical Research Council. International Journal of Radiation Oncology Biology Physics 1993;27:235–240.

240. Jensen AD, Nikoghosyan AV, Lossner K, Herfarth KK, Debus J et al. IMRT and carbon ion boost for malignant salivary gland tumors: interim analysis of the COSMIC trial. BMC Cancer 2012; 12: 163.

241. Licitra L, Cavina R, Grandi C et al. Cisplatin, doxorubicin and cyclophosphamide in advanced salivary gland carcinoma: a phase II trial of 22 patients. Annals of Oncology 1996; 7: 640–642.

242. Laurie SA, Ho AL, Fury MG, Sherman E, Pfister DG. Systemic therapy in the management of metastatic or locally recurrent adenoid cystic carcinoma of the salivary glands: a systematic review. Lancet Oncology 2011; 12: 815–824.

243. Laurie SA, Licitra L. Systemic therapy in the palliative management of advanced salivary gland cancers. Journal of Clinical Oncology 2006;24:2673–2678.

244. Bissett RJ, Fitzpatrick PJ. Malignant submandibular gland tumors. A review of 91 patients [published erratum appears in American Journal of Clinical Oncology 1988; 11(4): 514]. American Journal of Clinical Oncology 1988; 11: 46–51.

245. Mendenhall WM, Amdur RJ, Vaysberg M, Mendenhall CM, Werning JW. Head and neck paragangliomas. Head & Neck 2011; 33: 1530–1534.

246. Martin TP, Irving RM, Maher ER. The genetics of paragangliomas: a review. Clinical Otolaryngology 2007; 32: 7–11.

247. van der Mey AG, Frijns JH, Cornelisse CJ, Brons EN, van Dulken H et al. Does intervention improve the natural course of glomus tumors? A series of 108 patients seen in a 32-year period. Annals of Otology, Rhinology & Laryngology 1992; 101: 635–642.

248. Langerman A, Athavale SM, Rangarajan SV, Sinard RJ, Netterville JL. Natural history of cervical paragangliomas: outcomes of observation of 43 patients. Archives of Otolaryngology – Head and Neck Surgery 2012; 138: 341–345.

249. Foote RL, Pollock BE, Gorman DA, Schomberg PJ, Stafford SL et al. Glomus jugulare tumor: tumor control and complications after stereotactic radiosurgery. Head & Neck 2002; 24: 332–338.

250. Suarez C, Rodrigo JP, Mendenhall WM, Hamoir M, Silver CE et al. Carotid body paragangliomas: a systematic study on management with surgery and radiotherapy. European Archives of Oto-Rhino-Laryngology 2013.

251. Verniers DA, Keus RB, Schouwenburg PF, Bartelink H. Radiation therapy, an important mode of treatment for head and neck chemodectomas. European Journal of Cancer 1992; 28A: 1028–1033.

252. Suarez C, Rodrigo JP, Bodeker CC, Llorente JL, Silver CE et al. Jugular and vagal paragangliomas: systematic study of management with surgery and radiotherapy. Head & Neck 2013; 35(8): 1195–1204.