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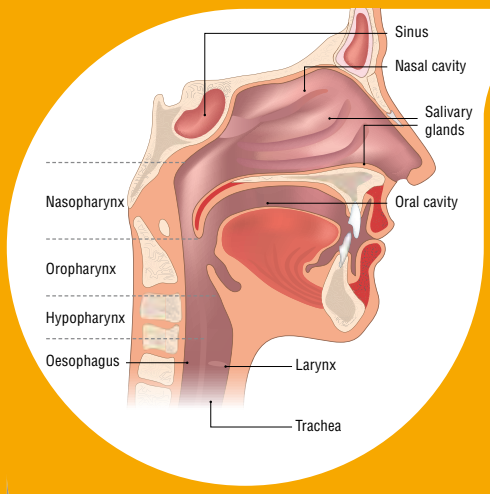
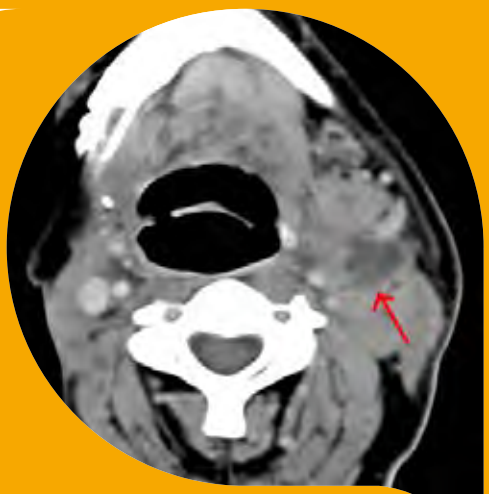
HEAD & NECK CANCERS

ESSENTIALS *for* CLINICIANS

edited by
Lisa Licitra
Michalis V Karamouzis





ESMO Press

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Essentials for Clinicians

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Edited by

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Preface

The complexity and heterogeneity of Head and Neck Cancers (HNCs) would seemingly only conflict with the concise and practical format of ESMO's *Essentials for Clinicians* book series. Overcoming this incongruity (particularly in Section A: "What every oncologist should know") allows readers to really appreciate the 'mission' of this ESMO initiative: to extend knowledge to every oncologist of tumours commonly considered a field of special interest for a few highly-specialised professionals. This objective arises from existing needs.

First, HNCs, though classified as rare cancers, together represent a very large group of malignancies, lying around fifth in terms of absolute worldwide incidence (this volume also includes thyroid cancers). Second, although highly-selected expertise is needed to optimally comply with the complex multidisciplinary health care provision in this cancer setting, we believe that education is pivotal in supporting the role of the medical oncologist within the management team.

Section B: "More advanced knowledge" has been properly thought out to cater for oncologists dedicated to HNCs. Notably, this section seeks to address some unmet needs or particular aspects of the therapeutic management of HNCs. This includes discussion of rarer subtypes of HNC (e.g. nasopharyngeal cancer, salivary gland cancers) and other challenges (e.g. supportive therapies, new emerging agents), no less important in the treatment of HNCs.

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Abbreviations

3D-CRT	Three-dimensional conformal radiotherapy
ACC	Adenoid cystic carcinoma
ADCC	Antibody dependent cell-mediated cytotoxicity
AJCC	American Joint Committee on Cancer
AR	Androgen receptor
ATC	Anaplastic thyroid carcinoma
ChT	Chemotherapy
ChT-RT	Chemoradiotherapy
CS	Cavernous sinus
Ct	Calcitonin
CT	Computed tomography
DARS	Dysphagia/aspiration related structures
DTC	Well-differentiated thyroid carcinoma
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ENE	Extranodular extension
ENT	Ear, nose and throat
ESA	Erythropoiesis-stimulating agent
FDA	Food and Drug Administration
FNA	Fine needle aspiration
FTC	Follicular thyroid carcinoma
G-CSF	Granulocyte colony-stimulating factor
Gy	Gray
H&E	Haematoxylin & eosin
Hb	Haemoglobin
HNC	Head and neck cancer
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
IChT	Induction ChT
IG	Intermediate grade
IGRT	Image-guided radiotherapy
IHC	Immunohistochemistry
IMRT	Intensity modulated radiotherapy
ISH	*In situ* hybridisation
LB	Lobectomy
LG	Low grade
mAb	Monoclonal antibody
MEC	Mucoepidermoid carcinoma
MRI	Magnetic resonance imaging
MTC	Medullary thyroid carcinoma
mTOR	Mechanistic target of rapamycin
MTX	Methotrexate
NPC	Nasopharyngeal carcinoma
OPC	Oropharyngeal cancer
ORR	Overall response rate
OS	Overall survival
OSC	Oropharyngeal squamous cell carcinoma
PDTC	Poorly differentiated thyroid carcinoma
PET	Positron emission tomography
PFS	Progression-free survival
PI3K	Phosphatidylinositol 3 phosphate
PS	Performance status
pRB	Retinoblastoma protein
PTC	Papillary thyroid carcinoma
QoL	Quality of life
Rb	Retinoblastoma
RS	Relative survival
RT	Radiotherapy
SCC	Squamous cell carcinoma
SDC	Salivary duct carcinoma
SGC	Salivary gland cancer
SIB	Simultaneous integrated boost
SRT	Stereotactic radiotherapy
TC	Thyroid carcinoma
Tg	Thyroglobulin
TgAb	Thyroglobulin autoantibodies
TGCA	The Cancer Genome Atlas
TK	Tyrosine kinase
TKI	Tyrosine kinase inhibitor
TLMS	Transoral laser microsurgery
TLR	Toll-like receptor
TNM	Tumour-node-metastasis
TORS	Transoral robotic surgery
TPF	Docetaxel-cisplatin-fluorouracil
TSG	Tumour suppressor gene
TSH	Thyroid stimulating hormone
TTx	Total thyroidectomy
US	Ultrasound
VC	Verrucous carcinoma
VEGF	Vascular endothelial growth factor
WBS	Whole body scan
WHO	World Health Organisation

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Michalis Karamouzis & Lisa Licitra

A

What every oncologist should know

1 Epidemiology, risk factors and pathogenesis of squamous cell tumours

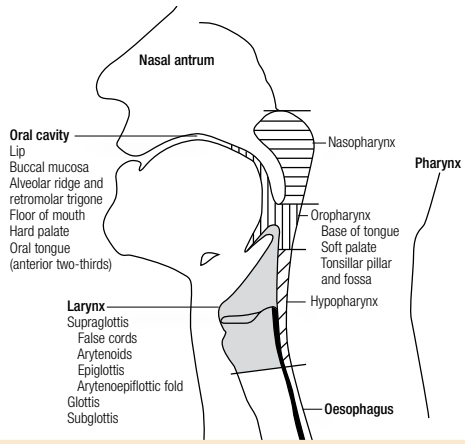
Epidemiology

Head and neck squamous cell carcinoma (HNSCC) encompasses a variety of tumours originating in the lip, oral cavity, hypopharynx, oropharynx, nasopharynx or larynx.

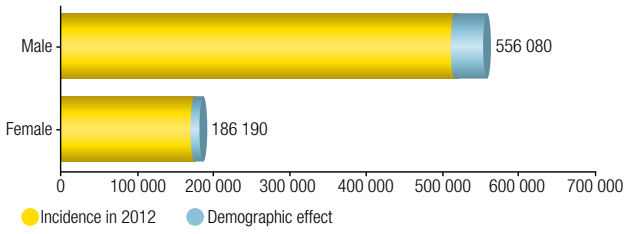
It is the sixth most common malignancy worldwide, accounting for approximately 6% of all cancer cases, responsible for an estimated 1%–2% of all cancer deaths.

Oral cavity and laryngeal cancers are the most common head and neck cancers globally (age-adjusted standardised incidence rate 3.9 and 2.3 per 100 000, respectively).

Anatomical sites and subsites of the head and neck. The approximate distribution of head and neck cancer is oral cavity, 44%; larynx, 31%; and pharynx, 25%



World
Lip, oral cavity, larynx, nasopharynx, other pharynx
Number of new cancers in 2015 (all ages)



HNSCC is predicted to account for 742 270 new cases and 407 037 deaths worldwide, for the year 2015. It is the most common cancer in Central Asia.

In the United States, more than 54 000 new cases were diagnosed in 2014, resulting in an annual incidence of 15 per 100 000, with 12 000 deaths attributed to the disease.

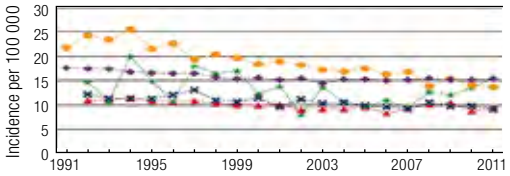
In Europe, HNSCC incidence and mortality rates are higher, with approximately 140 000 new cases diagnosed in 2014, corresponding to an annual incidence of 43/100 000.

HNSCC incidence trends have been strongly influenced by patterns of tobacco use over time and across countries.

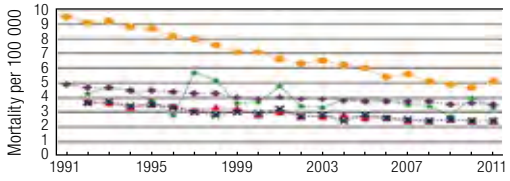
In the USA, overall incidence of oral cavity and pharyngeal cancers began decreasing 30 years ago and stabilised in 2003. Overall incidence of laryngeal cancer began declining in the 1990s.

In Eastern Europe and China (high tobacco consumption rates), a rise in HNSCC is anticipated. Infection with human papillomavirus (HPV) is responsible for a growing ratio of oropharyngeal tumours.

U.S. Head and neck cancer incidence



U.S. Head and neck cancer mortality



Whites · African Americans · Hispanics* · Asians/Pacific Islanders* · American Indians/Alaska Natives*

*Incidence and mortality data not available before 1992.

REVISION QUESTIONS

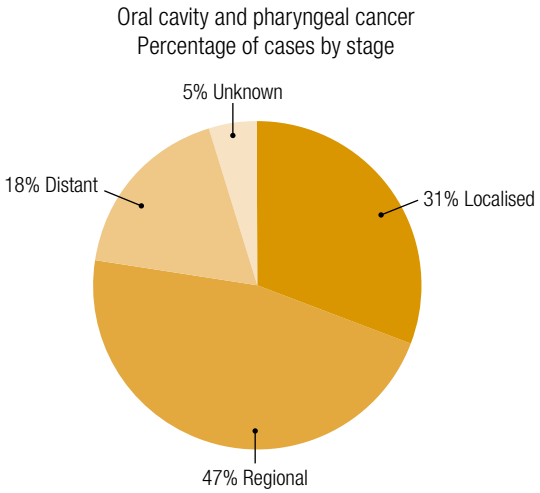
1. Which is the most common head and neck cancer globally?
2. What is the trend of HNSCC incidence in the USA and Europe in the last 20 years?
3. What is the percentage of deaths due to head and neck cancer among all cancer-related deaths?

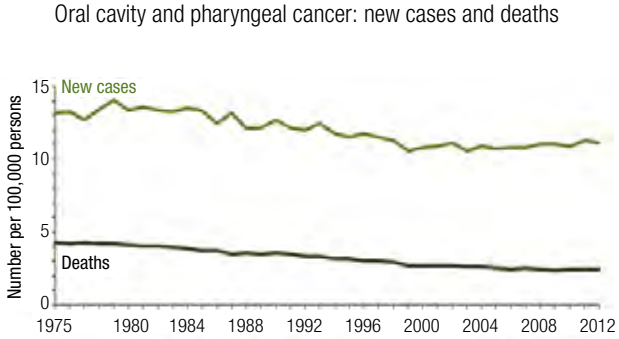
Clinical features and survival rates

Survival in HNSCC is predicted primarily by anatomical site, stage and HPV status, with other pathological and clinical factors influencing prognosis to a lesser degree.

In the recent EUROCARE population-based study, five-year relative survival was poorest for hypopharyngeal cancer (25%) and highest for laryngeal cancer (59%).

For oral cavity and pharyngeal cancer, 31% of cases are localised at the time of diagnosis. For laryngeal cancer, 55% of patients are diagnosed with localised disease.





For oral cavity and pharyngeal cancer, 5-year survival rates have increased from 57% in 1992 to 65.1% in 2003. Death rates have not changed over 2003–2012.

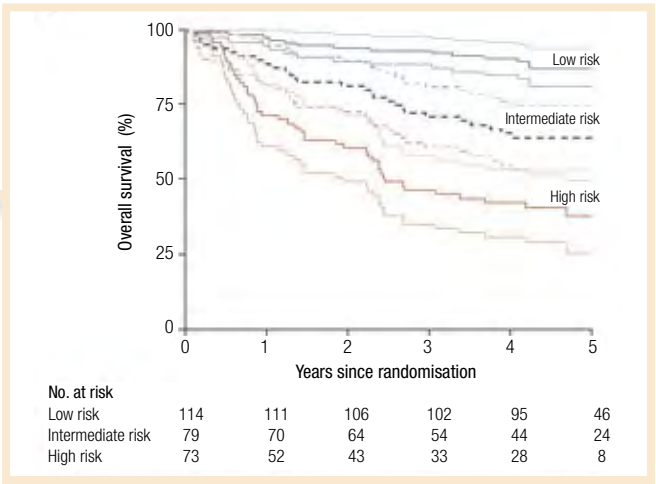
For cancer of the larynx, 5-year survival rates have not changed significantly over the past 30 years.

The survival improvement is greatest for tonsil cancer (39.7% to 69.8%). This trend is attributed to HPV-positive tumour status, which is a strong predictor for survival.

High cure rates are reported for localised and locoregional disease. However, the 3-year survival rate does not exceed 40% in a subset of patients with localised HNSCC.

HPV-positive oropharyngeal cancer (OPC) patients show better response to treatment, and survival is improved by approximately 50%. Improvement in survival is reduced in smokers.

Despite advances in multimodality treatment, survival rates for recurrent/metastatic disease remain dismal.



REVISION QUESTIONS

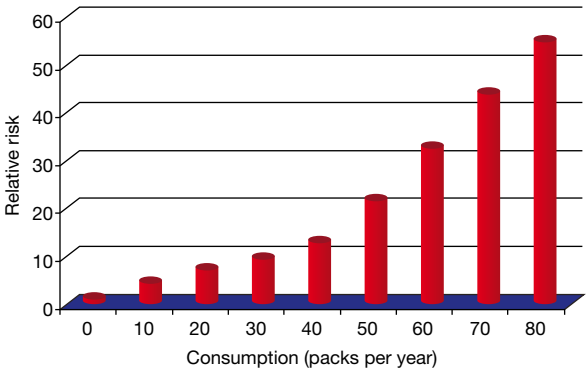
1. What is the 5-year survival rate of head and neck cancer in Europe by anatomical site?
2. What is the trend of survival rates for oral cavity and pharyngeal cancer and cancer of the larynx in the past 20 years?
3. What is the 3-year survival rate of head and neck cancer according to stage?

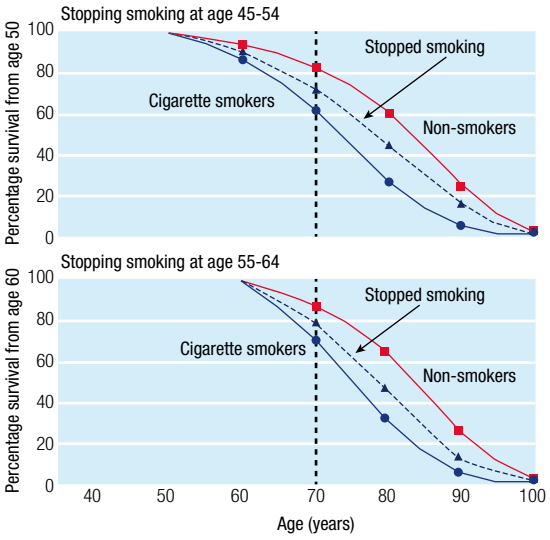
Risk factors

Tobacco: Approximately 90% of patients with HNSCC have a history of tobacco use.

Compared to non-smokers, tobacco users have a 4–5-fold increased risk for cancer in the oral cavity, oropharynx and hypopharynx and a 10-fold increased risk of laryngeal cancer.

Risk of HNSCC is related to the frequency, intensity and duration of tobacco consumption; association is dose-dependent.





Smoking cessation may reduce risk of HNSCC. Risk decreases with time since smoking cessation.

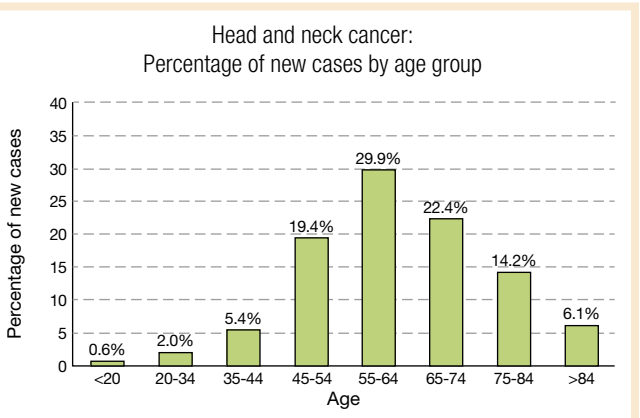
Smokeless (chewing) tobacco increases the risk of cancer of the oral cavity. In India and Sudan, 50%–60% of oral cavity cancers are attributed to smokeless tobacco.

It is estimated that tobacco smoking increases the risk of HPV infection and persistence; therefore it may contribute to development of HPV-positive OPC.

Alcohol: Alcohol use independently increases the risk of HNSCC, with 1%–4% of cases attributed to alcohol alone. It specifically increases the risk of hypopharyngeal cancer.

It acts synergistically with tobacco, resulting in an approximately 35-fold increase in HNSCC risk in heavy smokers (>2 packs/day) and drinkers (>4 drinks/day).

Gender, age: Men have a 2- to 5-fold greater risk of HNSCC than women. HNSCC risk also increases with age, with a median age of diagnosis in the late 60s and 70s.



REVISION QUESTIONS

1. What percentage of patients with HNSCC have a history of tobacco use?
2. Which type of head and neck cancer has the strongest association with tobacco?
3. How much is the risk of HNSCC increased by the combined effect of tobacco and alcohol?

Risk factors (continued)

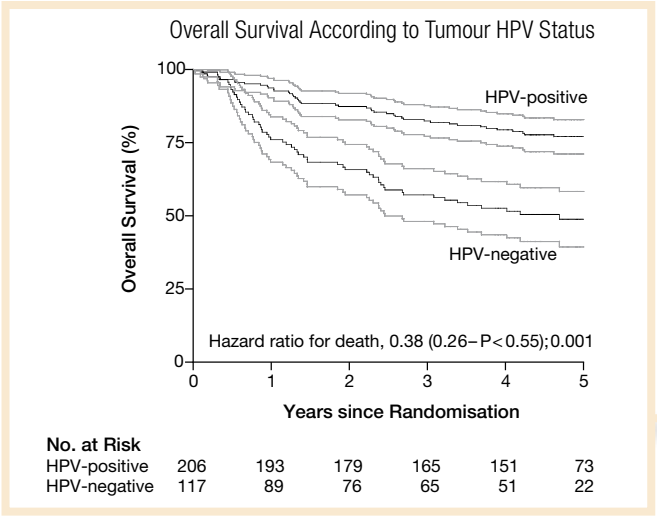
HPV infection: It is the cause of a distinct subset of HNSCCs that occur primarily in the oropharynx. The proportion of HPV-positive (HPV+) OPCs is growing.

HPV Type 16 (HPV16) is responsible for more than 90% of HPV+ OPCs. The time from first oral HPV infection to the development of cancer is estimated to be more than a decade.

Measures of sexual behaviour (number of vaginal and oral partners, history of genital warts) have been associated with HPV+ OPC.

Parameter	HPV-	HPV+
Gender	2-3 fold more common in men	4-5 fold more common in men
Age at diagnosis	Median age late 60s and 70s	Median age early 50s
Race		More common in Whites
Smoking	90% smoking history	50%-65% smoking history
Sexual behaviour	Not a significant risk factor	Number or oral and vaginal sex partners is an important risk factor
Site	Oral cavity and larynx most commonly	Oropharynx HPV+ <20% at other sites
Clinical picture	Varies	Early T stage, enlarged nodes
Incidence trends	Decreasing	Increasing
Survival rates	All sites: 65% 5-year survival Oropharynx: 25% 5-year survival	60%-80% 5-year survival

HPV-, Human papillomavirus negative; HPV+, human papillomavirus positive.



HPV, Human papillomavirus.

Patients with HPV+ OPC are less likely to be smokers than HPV-negative (HPV-) patients. However, approximately 50% of patients with HPV+ OPC have a history of tobacco use.

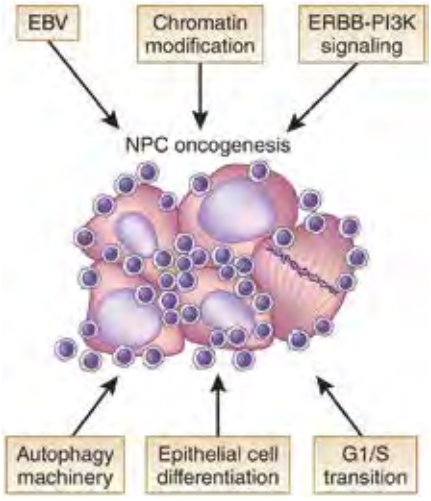
Individuals with HPV+ OPC tend to be male and white, although these characteristics do not predict HPV positivity. In addition, they present at a younger age at diagnosis.

HPV+ OPC is characterised by an earlier T stage at presentation but with extensive nodal involvement. However, prognosis is better compared with tobacco-related HNSCC.

Incidence patterns by ethnic origin have changed over time. Incidence of HNSCC in Black people has been declining since the 1990s and is currently lower than in White people.

Other risk factors for HNSCC include immunosuppression (organ transplant recipients, human immunodeficiency virus), systemic diseases (lichen) and genetic diseases (Fanconi anaemia).

Nasopharyngeal and paranasal sinus cancers are associated with the Epstein-Barr virus (EBV). Nasopharyngeal cancer is common in endemic areas (Southern China, Northern Africa).



EBV, Epstein-Barr virus; NPC, nasopharyngeal cancer.

REVISION QUESTIONS

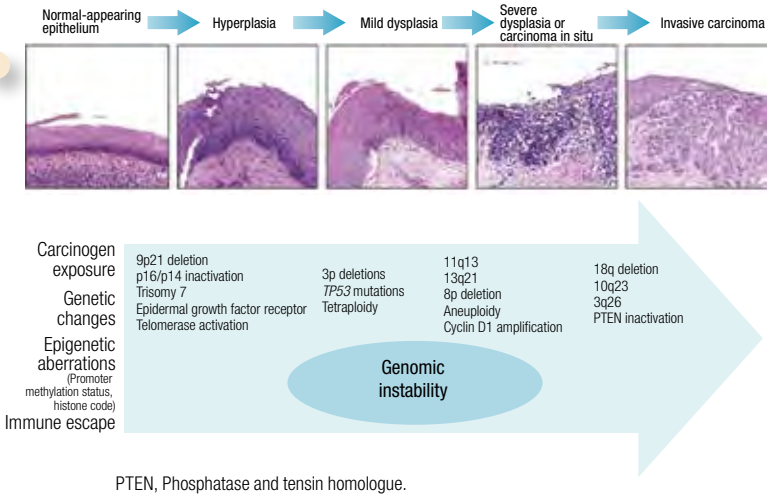
1. Which type of HPV is associated with the majority of HPV+ OPCs?
2. What are the clinical features of HPV+ OPC?
3. Which virus is associated with nasopharyngeal cancer?

Pathogenesis

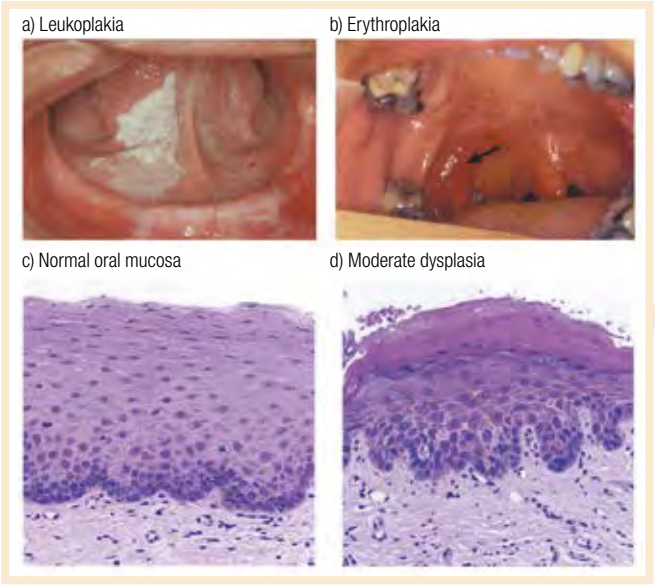
Transformation of normal mucosa into invasive HNSCC follows a molecular progression model of multistep carcinogenesis.

Loss of genetic material from chromosome region *9p21* and inactivation of *p16* tumour suppression gene are the earliest alterations identified at transition to hyperplastic mucosa.

Subsequent transition to dysplasia is characterised by loss of *3p* and *17p* and by *p53* inactivation. Loss of *11q, 13q* and *14q* precedes transition to carcinoma *in situ*.



PTEN, Phosphatase and tensin homologue.



Loss of *6p*, *8p* and *4q* is identified during transformation to invasive HNSCC. Tobacco-related HNSCC is associated with mutation of *p53* and downregulation of p16 protein.

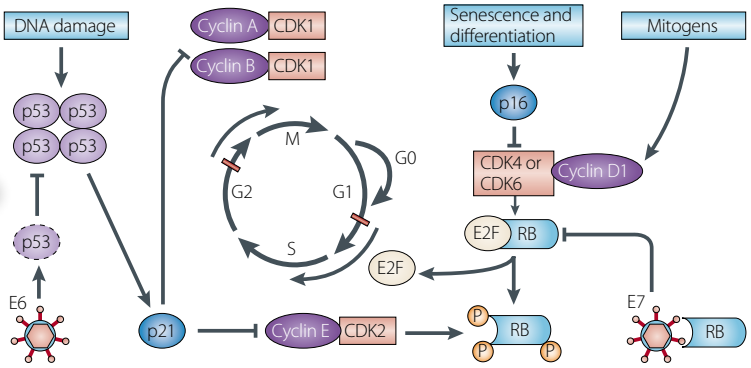
Leukoplakia and erythroplakia are the precursors of invasive HNSCC in the oral mucosa. Leukoplakia appears as white plaques and erythroplakia as a red zone of mucosa.

Field carcinogenesis refers to carcinogen distribution over large areas in upper aerodigestive tracts, due to continuous exposure, rendering mucosa a potential site for cancer.

HPV infection carcinogenesis: The integration of HPV DNA into the host genome disrupts the expression of factor E2, the transcriptional repressor of E6 and E7 viral proteins.

E6 and E7 encode oncoproteins that bind and degrade p53 and retinoblastoma (Rb) tumour suppressors, respectively. Degradation of Rb induces expression of p16^{INK4A}.

Rb is a negative regulator of p16 protein; low Rb levels lead to p16 upregulation. HPV+ OPC is typically *p53* and *Rb1* wild-type and demonstrates high p16 protein levels.



REVISION QUESTIONS

1. Which molecular abnormalities are associated with tobacco-related HNSCC?
2. What are the molecular features of HPV+ OPC?
3. What are the premalignant lesions of invasive squamous cancer in the oral mucosa?

Summary: Epidemiology, risk factors and pathogenesis of squamous cell tumours

- HNSCC encompasses a heterogeneous group of upper aerodigestive malignancies originating in the lip, oral cavity, pharynx and larynx
- It is the sixth most common cancer worldwide, accounting for 1%–2% of all cancer-related deaths
- Historically, HNSCC has been associated with tobacco smoking and alcohol use
- Globally, the incidence of tobacco-related HNSCC is associated with patterns of tobacco use and is decreasing in countries with declining rates of tobacco consumption
- In the past decade, infection with high-risk HPV and especially with HPV16 has been implicated in the pathogenesis of a growing subset of HNSCCs, mainly those arising from the oropharynx
- HPV-related OPC represents a distinct entity in terms of biology and clinical behaviour
- Five-year survival rates for all stages of HNSCC is approximately 65%. High cure rates are reported with localised and locoregional disease, but prognosis is dismal for recurrent or metastatic disease
- For HNSCC, malignant transformation of normal mucosa to invasive carcinoma follows a molecular progression model of multistep carcinogenesis
- Tobacco-related HNSCC demonstrates mutation of the *p53* gene and downregulation of the p16 protein
- On the contrary, HPV-associated OPC is typically characterised by wild-type *p53* and *Rb* genes and upregulation of p53 protein levels

Further Reading

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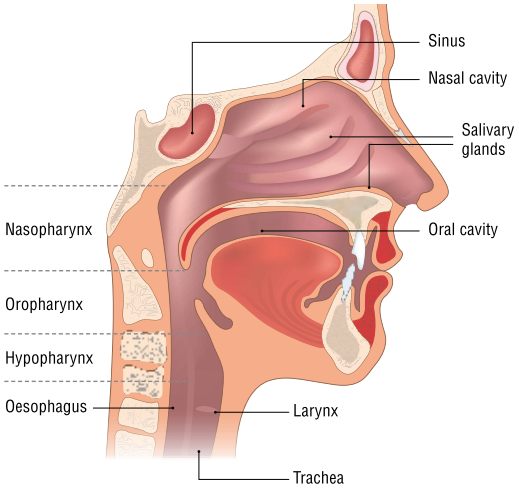
2 Diagnosis and staging of squamous cell tumours

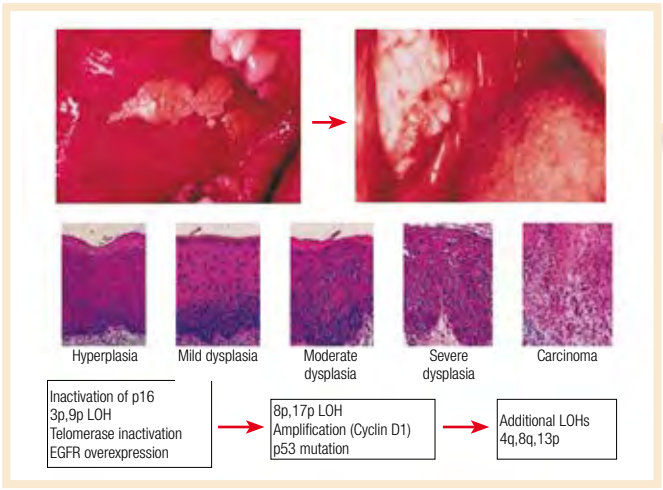
Natural history

Head and neck squamous cell carcinoma (HNSCC) arises from the upper aerodigestive mucosa, which holds important functional roles such as respiration, swallowing, speech and hearing.

HNSCC is a heterogeneous disease with different anatomical sites: oral cavity, oropharynx, hypopharynx, larynx, nasopharynx and sinus.

An understanding of the anatomical origins of HNSCC is essential for an appropriate diagnosis, treatment and follow-up.





EGFR, Epidermal growth factor receptor; LOH, loss of heterogeneity.

HNSCC is the final stage of a process of progressive steps: from hyperplasia to dysplasia, carcinoma *in situ* and to invasive carcinoma.

Limitless replicative potential of head and neck cancer cells is often caused by abrogation of p53 and retinoblastoma pathways that perturb cell regulation.

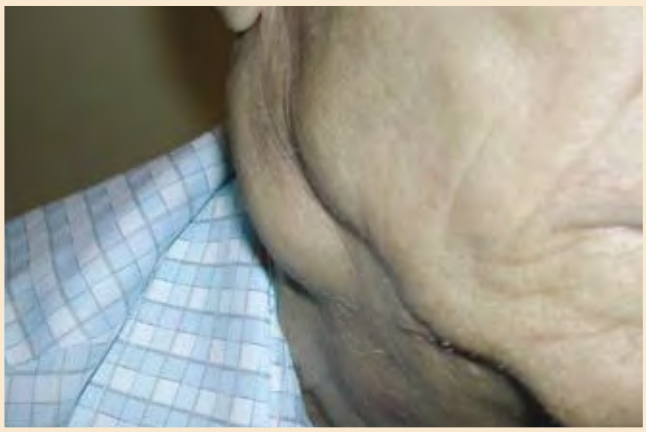
Some HNSCC become independent from growth factors, due to somatic change in the epidermal growth factor receptor (EGFR) signalling pathway.

Carcinomas usually originate in the mucosa; they initially grow by local infiltration. Locoregional invasion occurs early into muscles, and later into bones and nerves.

Lymphatic dissemination patterns depend on the degree of differentiation, tumour size and primary tumour site. 5% of patients present only with neck lymphadenopathy.

Haematological spread occurs later (10%–12%). Lung followed by bones are the organs more commonly affected. Spread occurs more often in hypopharyngeal cancer.

Cervical lymphadenopathy in a patient



REVISION QUESTIONS

1. What are the most relevant molecular changes from dysplasia to invasive carcinoma?
2. Which is the organ most frequently affected by distant metastases?
3. Can severe dysplasia generate distant metastases?

Symptoms and physical examination

A confirmed screening test to detect premalignant lesions in the head and neck is not yet available. Clinical symptoms vary and depend on the location of the tumour.

A detailed history of previous malignancies, treatments, patient's comorbidities, family history, birth place and ethnicity should be carried out.

Social situation and occupational history is needed. Tobacco and alcohol consumption should be investigated to help in the cessation of toxic habits.

Clinical symptoms related to primary tumour site

Location	Symptom
Oral cavity	-Oral cavity injury -Oral pain -Dysphagia -Swelling
Oropharynx	-Dysphagia -Odynophagia: sore throat -Otalgia -Globus sensation -Cervical nodes
Larynx	-Hoarseness -Cough -Dysphonia -Shortness of breath -Cervical nodes
Hypopharynx	-Dysphagia -Odynophagia -Dysphonia -Cervical nodes

Levels of cervical lymph node description

Levels	Location
IA	Submental nodes
IB	Submandibular nodes
IIA	Upper jugular: anterior to spinal accessory nerve
IIB	Upper jugular: posterior to spinal accessory nerve
III	Middle jugular nodes
IV	Lower jugular nodes
VA	Posterior triangle: above the inferior border of the cricoid
VB	Posterior triangle: below the inferior border of the cricoid
VI	Anterior compartment
VII	Superior mediastinal nodes

Physical examination should include: Eastern Cooperative Oncology Group (ECOG) performance status, oral cavity inspection, endoscopy, neurological, cardiac and pulmonary examination, and complete blood tests.

Assessment of regional lymph node status is essential in the evaluation of head and neck cancer patients. Lymph node group classification includes 7 levels.

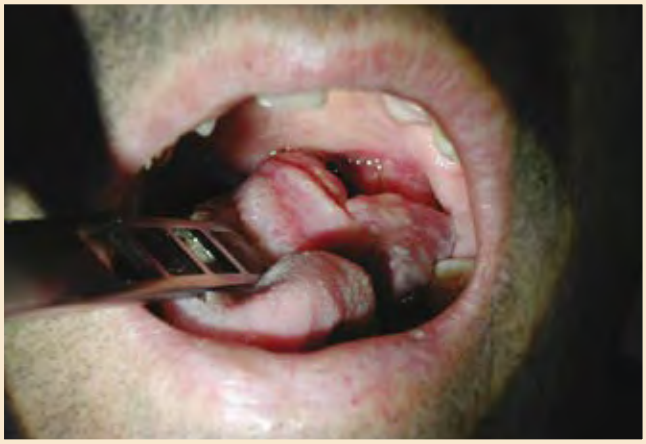
At the time of diagnosis, in case of respiratory or digestive symptoms, the coexistence of other tumours should be excluded (10%–15% synchronous tumours).

Indirect laryngoscopy by mirror is very useful to examine the vallecula and base of tongue, but a flexible endoscope is the best option.

Chewing, swallowing, breathing and phonation should be explored. Stability of the airway must be assessed; bleeding or obstructing mass may require tracheotomy.

Special assessment is required of dentistry, nutrition, social situation, physiotherapy and psycho-oncology needs during diagnosis, following treatment and follow-up.

Patient with a base of the tongue tumour

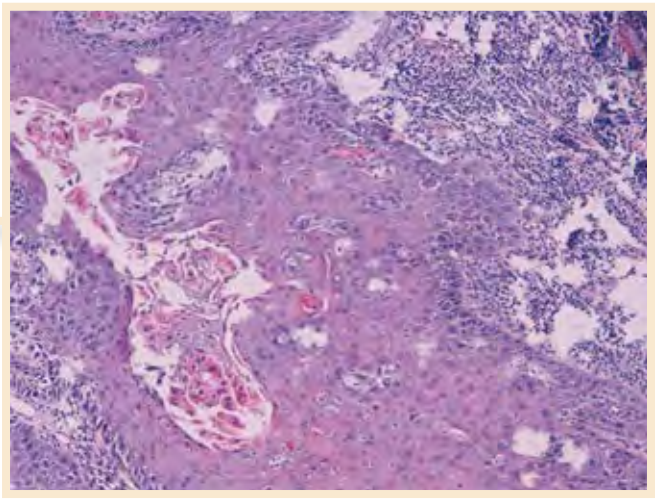


REVISION QUESTIONS

1. Which is the area of the head and neck most frequently affected by hoarseness?
2. If an enlarged lymph node appears in the middle jugular area, to which lymph node group are we referring?
3. What is the percentage of synchronous tumours?

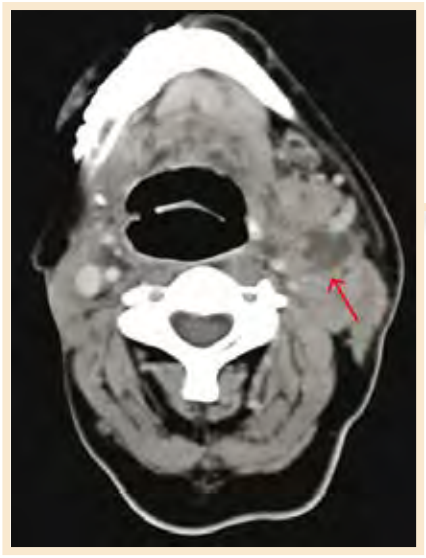
Histological confirmation and extension study

Final diagnosis is provided by histological examination of the primary tumour. If not possible, a puncture of one of the affected lymph nodes should be performed. Biopsy is always better than fine needle aspiration.



80% of head and neck cancers are squamous cell carcinomas. Pathological diagnosis should be made according to the World Health Organisation classification.

Human papillomavirus (HPV) testing (p16 immunohistochemistry and other biomarkers if possible, such as HPV DNA polymerase chain reaction/*in situ* hybridisation) should be conducted for oropharyngeal cancer.



Computed tomography (CT) or cervico-facial magnetic resonance imaging (MRI) are needed to explore tumour extension.

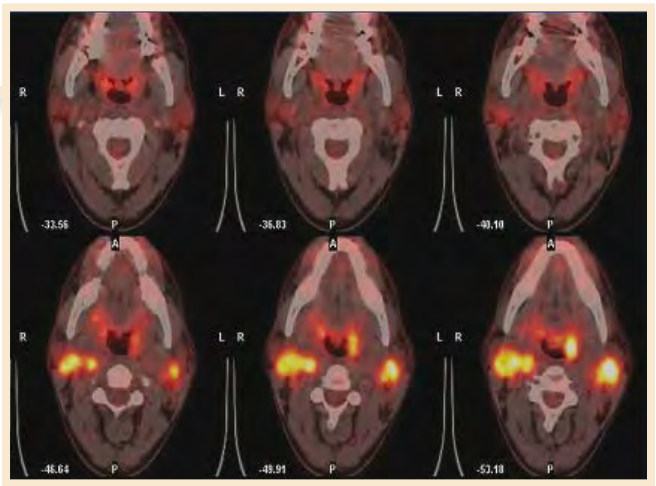
A head and neck endoscopic work-up with multiple biopsies may be needed to find the primary tumour and to visualise the oropharynx, larynx and hypopharynx.

Chest CT is recommended in advanced stages, while abdominal CT or bone study are recommended in the presence of signs or symptoms of disease distant spread.

Positron emission tomography (PET)/CT is superior to both CT/MRI to detect cervical lymph nodes, distant metastases and second primary tumours resulting in alteration of treatment.

PET/CT is suggested for initial staging of oral cavity, oropharyngeal, hypopharyngeal, glottic and supraglottic cancers in Stages III-IV disease.

PET/CT has limitations in spatial resolution, to detect nodal necrosis, as well as in the detection of osteomedullary invasion of the mandible and jawbone.



REVISION QUESTIONS

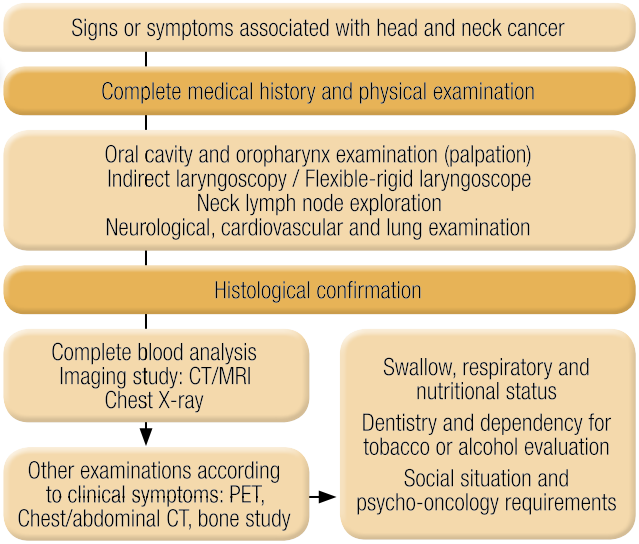
1. What is the anatomical location most frequently affected by HPV?
2. When is chest CT recommended?
3. What are the limitations of PET/CT imaging in head and neck cancer diagnosis?

Diagnostic algorithm and staging

A diagnostic algorithm for head and neck cancer patients is shown here. Persistent symptoms should always be explored.

A multidisciplinary team is required to optimise diagnosis, clinical work-up and treatment decisions for head and neck cancer patients.

Squamous head and neck cancers should be staged according to the tumour-node-metastasis (TNM) system and grouped into categories, according to the American Joint Committee on Cancer (AJCC) classification.



CT, Computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

Lymph node involvement

- N0: no regional lymph node metastasis
- N1: metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension without extranodal extension
- N2a: metastasis in a single ipsilateral lymph node, 3-6 cm in greatest dimension without extranodal extension
- N2b: metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension without extranodal extension
- N2c: metastases in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension without extranodal extension
- N3a: Metastasis in a lymph node more than 6 cm in greatest dimension without extranodal extension
- N3b: Metastasis in a single or multiple lymph nodes with clinical extranodal extension

T definitions are different, depending on the T location.

T is usually based on the size of the tumour, local invasion and its relation to adjacent anatomical structures affected.

The definition of category N (lymph node involvement) is the same for all locations of head and neck cancer (except for nasopharyngeal cancer and HPV-related/ p16-positive oropharyngeal cancer, which have their own TNM classifications) .

Category M for the presence of distant metastasis:
M0: no distant metastasis
M1: distant metastasis present

Histological grade as shown in the table opposite.

When surgery is performed, pathological stage should be described (e.g. pT2pN1).

Histological grade

- G1: well differentiated
- G2: moderately differentiated
- G3: poorly differentiated
- G4: undifferentiated

REVISION QUESTIONS

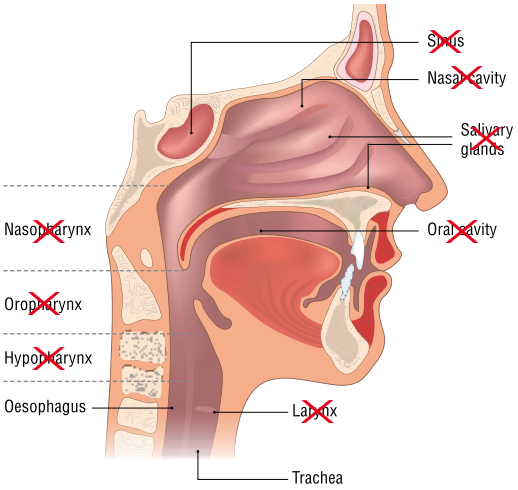
1. Does the multidisciplinary head and neck unit need to participate in the head and neck cancer initial clinical work-up?
2. Is the histological grade part of the TNM classification system?
3. Is the N classification similar for all tumours?

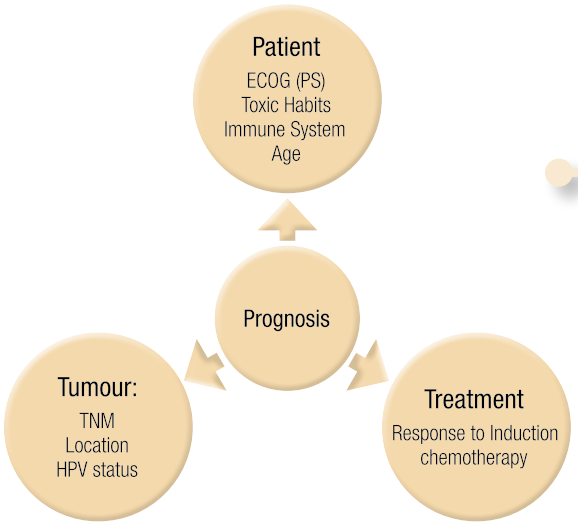
Unknown primary tumour; prognostic factors

Squamous cell carcinoma of an unknown primary of the head and neck is defined as metastatic in the lymph nodes without any evidence of primary tumour.

It accounts for 3%–7% of all head and neck cancers. A complete clinical examination and imaging should be performed, including panendoscopy with biopsies.

Epstein-Barr virus (nasopharynx) and HPV (oropharynx) should be tested on the biopsy sample to direct clinical and radiological primary tumour identification.





ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; PS, performance status; TNM, tumour-node-metastasis.

Patient-related factors include: Eastern Cooperative Oncology Group (ECOG) performance status, advanced age, gender, tobacco use and immune system status.

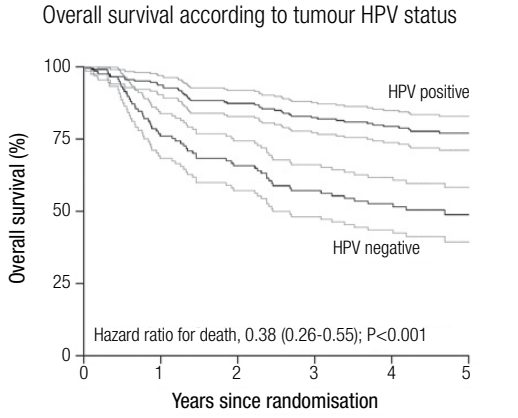
The stage of the tumour based on TNM is the most important factor for prognosis and survival. The location of the tumour is also important: hypopharynx has the worst prognosis whereas glottis has the best.

Treatment-related factors: response to induction chemotherapy and radiotherapy is the most important.

HPV-related oropharyngeal squamous cell carcinoma (OSC) has distinct epidemiology, clinical and molecular characteristics.

Most HPV-related OSC patients respond better to treatment and have better survival than non-related patients.

HPV detection should be performed for OSC to assess prognosis, but no changes in the therapeutic approach should yet be made, unless participating in a clinical trial.



HPV, Human papillomavirus.

REVISION QUESTIONS

1. What are the viral tests that should be performed in a squamous cell carcinoma of unknown primary of the head and neck?
2. What is the location of the tumour with the worst prognosis in the head and neck area?
3. Should we apply any therapeutic change when HPV-related OSC is diagnosed?

Summary: Diagnosis and staging of squamous cell tumours

- HNSCC is a heterogeneous disease with different anatomical sites
- The head and neck area has important functional roles, such as respiration, swallowing, speech and hearing
- Clinical symptoms are varied and depend on the location of the primary tumour
- A complete medical history and physical examination (flexible endoscope) are needed
- Dental status, nutritional status, social situation, rehabilitation and psychological needs should be assessed
- The definitive diagnosis is provided by histology of the primary tumour, if possible
- CT or MRI are needed to explore tumour extension. PET/CT may be necessary for better assessment
- A multidisciplinary team is required to optimise initial diagnostic work-up, treatment, supportive care, and follow-up decision-making
- Squamous head and neck cancer should be staged by the TNM system
- HPV-related OSC has distinct epidemiology, molecular and clinical characteristics

Further Reading

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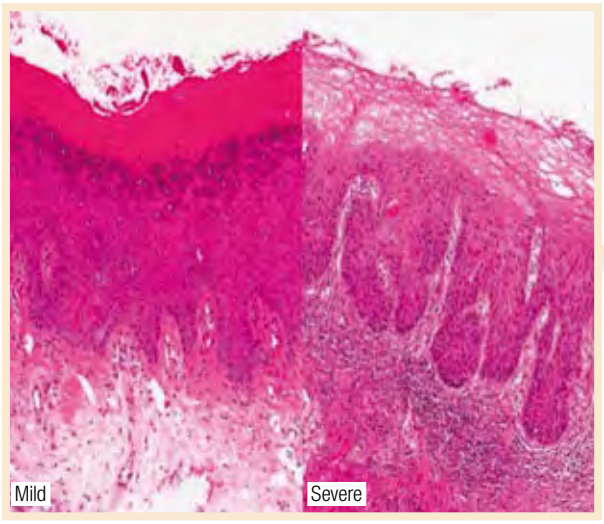
3 Histopathological and molecular characterisation of squamous cell tumours

Introduction – epithelial dysplasia and early squamous cell carcinoma

In cases of suspected squamous cell carcinoma (SCC), specimens are examined macroscopically prior to tissue processing and histopathological analysis.

Sampled tissue is dehydrated and paraffin-embedded. Then 2–5 µm sections are cut on a microtome. Routine staining is performed with haematoxylin & eosin (H&E).

Additional staining techniques, including periodic acid–Schiff, immunohistochemistry (IHC) and *in-situ* hybridisation (ISH) techniques, may also be used for diagnostic purposes.



Epithelial dysplasia is regarded as potentially malignant and is diagnosed by the presence of architectural and cytological changes within the epithelium.

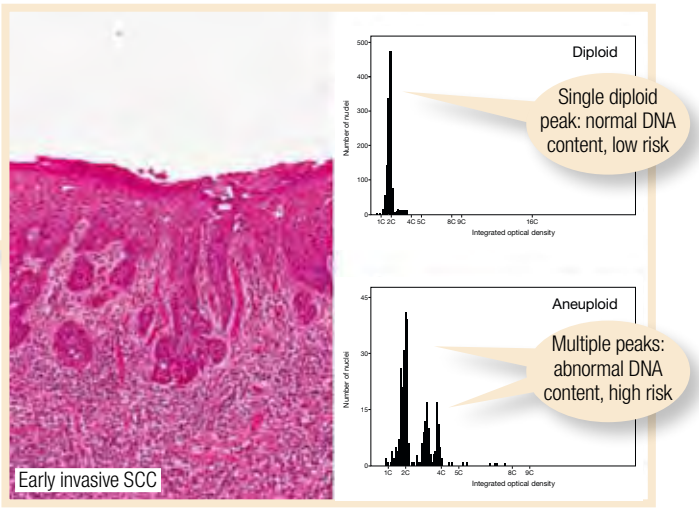
Conventional grading systems separate epithelial dysplasia into mild, moderate, severe and carcinoma *in situ*, based on the degree and extent of changes.

Features of dysplasia include nuclear and cellular pleomorphism, abnormal mitoses and keratinisation, altered cellular polarity and drop-shaped rete pegs.

Widespread accumulation of genomic abnormalities within the epithelium is known as "field change", from which dysplasia and primary SCC may arise. Despite adequate resection of primary tumours, field change may result in development of subsequent SCCs.

The severity of dysplasia is the most useful guide to the risk of SCC development, but other tests, such as DNA ploidy or loss of heterozygosity, may be useful.

Early invasive SCC is characterised by penetration of the basement membrane and invasion of the underlying stroma, and can be difficult to diagnose.



SCC, Squamous cell carcinoma.

REVISION QUESTIONS

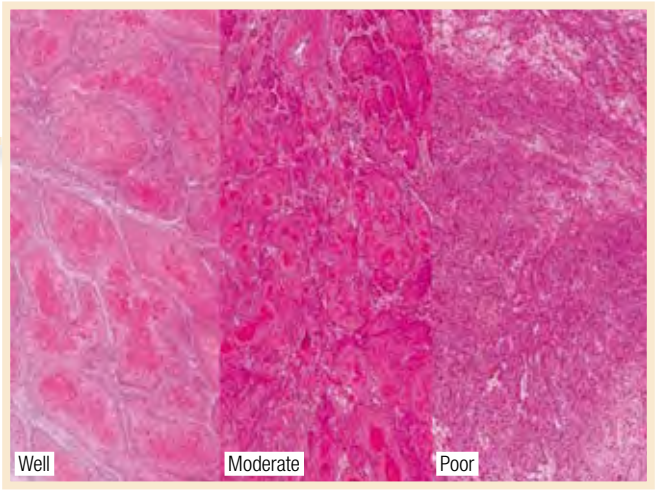
1. How are SCC specimens processed?
2. What cytological atypia are seen in epithelial dysplasias?
3. What is meant by the term "field change" and why is it important?

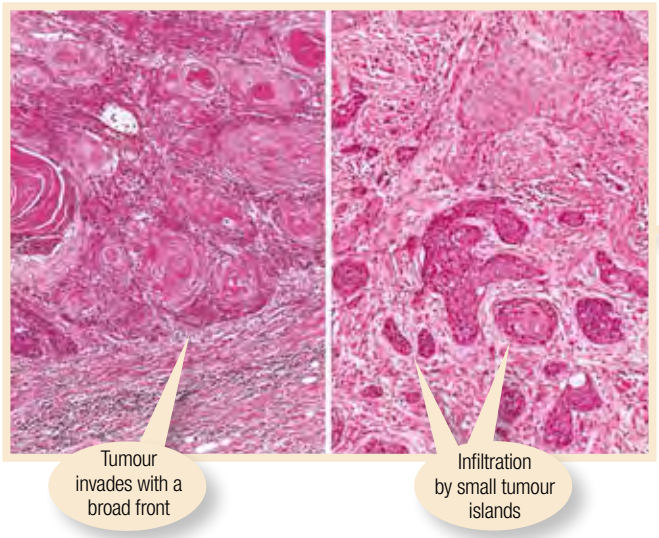
Histopathology of squamous cell carcinoma

SCC is graded based on its resemblance to squamous epithelium and can be subject to inter-examiner variation.

Well-differentiated SCCs are obviously squamous with recognisable intracellular bridges and keratinisation. The majority of SCCs are moderately differentiated.

Poorly differentiated SCCs show little to no keratinisation and may require IHC for cytokeratins to confirm their epithelial origin.





Morphological characteristics of the invasive front of squamous carcinoma are used as a prognostic factor and are indicative of the tumour's aggressiveness.

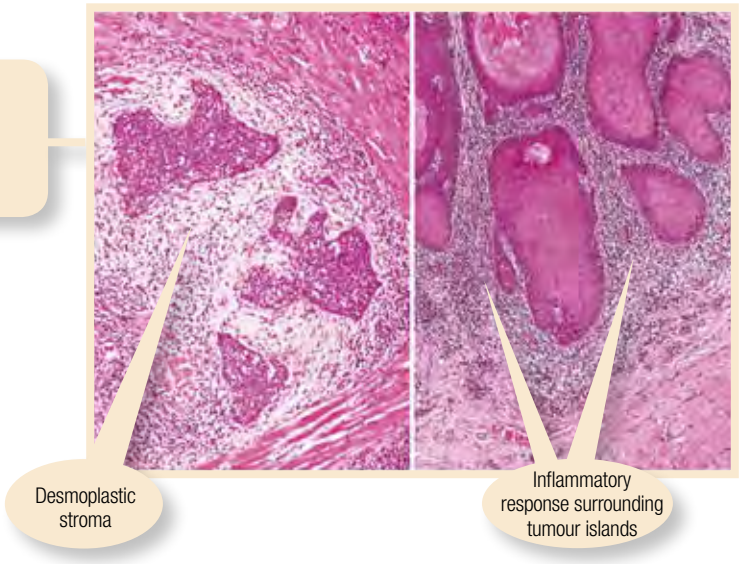
SCC comprising large solid sheets with a broad front is regarded as possessing a cohesive invasive front, and has a more favourable outcome.

Tumours with diffusely infiltrating small islands ahead of the main tumour body are non-cohesive and have an increased likelihood of metastasis and poorer outcome.

Interactions between tumour and host immune and stromal cells result in the formation of the tumour microenvironment, which contributes to tumourigenesis.

Proliferation of stromal fibroblasts and production of a desmoplastic fibrous stroma is often seen surrounding islands of SCC, and is related to poor prognosis.

Variable host-immune responses may be seen surrounding tumour islands, usually dominated by infiltrates of lymphocytes and plasma cells.



REVISION QUESTIONS

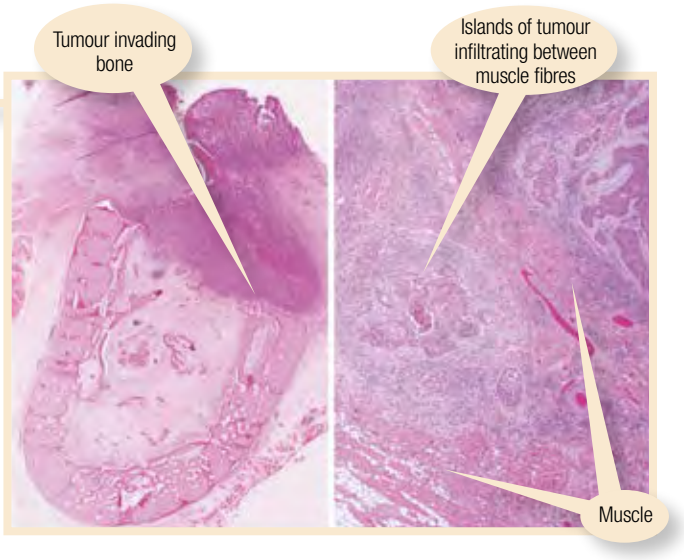
1. How is SCC graded? How is this determined?
2. How does the invasive front influence the prognosis of SCC?
3. What is meant by the tumour microenvironment and why is it important?

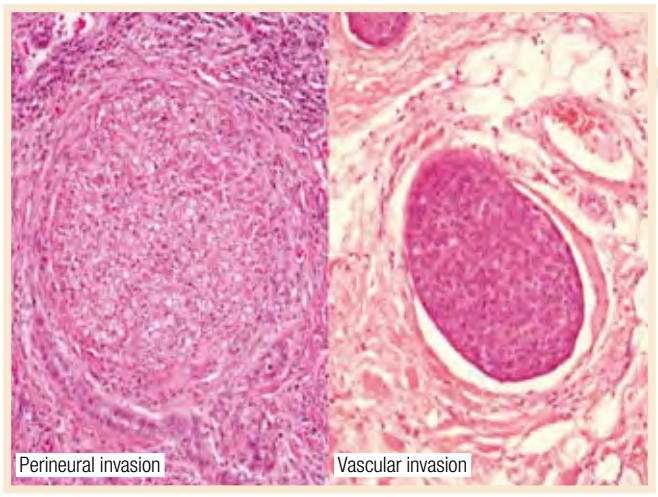
Histopathology of squamous cell carcinoma (continued)

As a tumour grows, local invasion of surrounding tissues is influenced by anatomical features. Tumour can infiltrate sizeable distances along muscle fibres.

Oral SCC frequently invades bone by spread down the periodontal ligament or through the alveolar crest. Subsequent spread occurs through marrow spaces.

Bone invasion is an important prognostic factor for SCC and upgrades the staging of the disease to T4, irrespective of the tumour size or depth of invasion.





SCC can spread by vascular and lymphatic invasion, as well as infiltration along the nerve sheath within the perineural space.

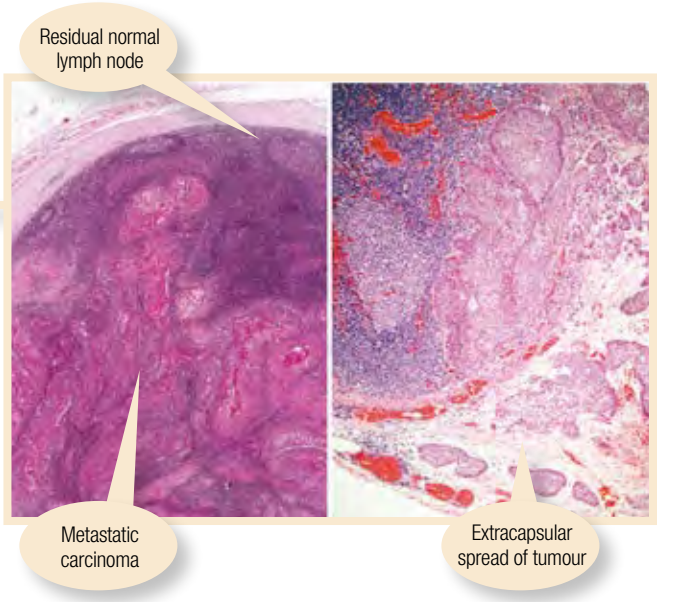
Perineural infiltration has implications in tumour management and is associated with increased locoregional recurrence and poorer prognosis.

SCC may infiltrate along and invade blood vessels. Vascular invasion is another adverse prognostic factor due to its role in tumour metastases.

Lymphatic spread from the primary tumour to regional lymph nodes is variable but often relates to the site, size and invasive front of the tumour.

The extent and distribution of lymph node metastases, including extracapsular extension of tumour, is a reliable adverse prognostic factor.

Lymphatic drainage of the head and neck is relatively predictable, but sentinel lymph node biopsy may aid staging and treatment planning in clinically N0 necks.



REVISION QUESTIONS

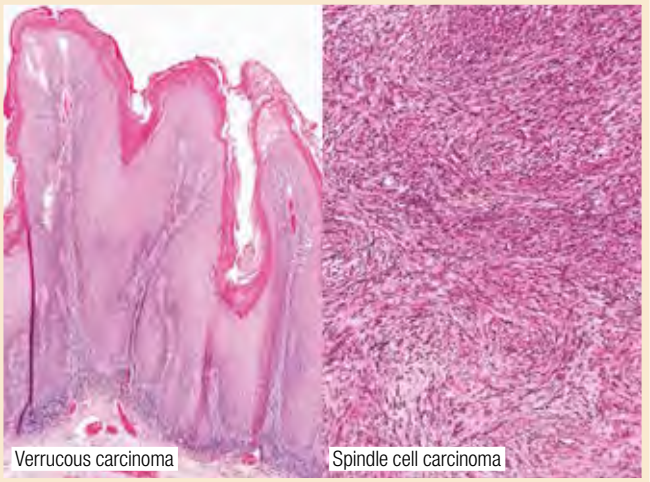
1. Why is identification of bone invasion an important determinant in SCC?
2. List three routes of SCC spread and how they impact prognosis.
3. What is sentinel lymph node biopsy? Why would it be carried out?

Variants of squamous cell carcinoma and aids to diagnosis

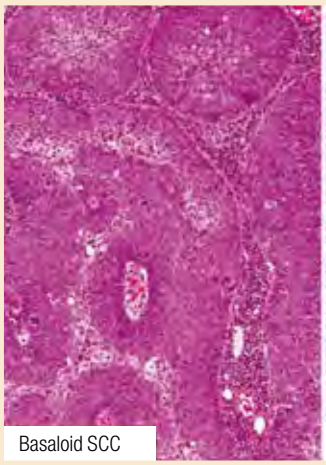
Verrucous carcinoma (VC) is a low-grade variant of SCC. It usually presents as a slow-growing wart-like growth on the cheek and gingivae of older males.

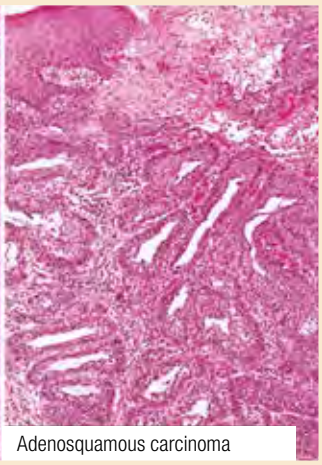
VC is locally invasive, has a high recurrence rate but rarely metastasises. Histologically, there are keratin projections, bulbous rete pegs and little cellular atypia.

Spindle cell carcinoma is a high-grade biphasic tumour with SCC and malignant spindle cell components, which expresses epithelial and mesenchymal markers.


Verrucous carcinoma

Spindle cell carcinoma


Basaloid SCC


Adenosquamous carcinoma

Basaloid SCC arises predominantly in the upper respiratory tract and is characterised by its aggressive behaviour.

Histologically, basaloid SCC comprises both squamous and basaloid elements. There is a higher association of human papillomavirus (HPV) infection with basaloid variants of SCC.

Other rare variants include acantholytic SCC, papillary SCC and adenosquamous SCC.

In most cases, the H&E-stained section is sufficient, but in some circumstances, such as very poorly differentiated tumours, it is essential to prove it is SCC.

IHC may be used to aid diagnosis. The technique uses antibodies against markers of interest to show their expression in the tumour.

The main uses of IHC are to demonstrate cytokeratin expression, but other antibodies are used in some circumstances, as shown in the table.

IHC Antibody	Use in Head and Neck SCC
Pancytokeratin (AE1/AE3)	In poorly differentiated and anaplastic lesions to detect squamous differentiation
Cytokeratin 5/6	May suggest squamous origin in poorly differentiated and anaplastic lesions
p63	May suggest squamous origin in poorly differentiated and anaplastic lesions
p16	Overexpression of p16 is associated with HPV-positive SCC
TTF-1	Expression of TTF-1 in neck nodes may indicate a metastasis of lung origin
Neuroendocrine markers: Chromogranin A, Synaptophysin, CD56	In basaloid and undifferentiated SCC to exclude neuroendocrine carcinoma and small cell carcinoma

HPV, Human papillomavirus; IHC, immunohistochemistry; SCC, squamous cell carcinoma.

REVISION QUESTIONS

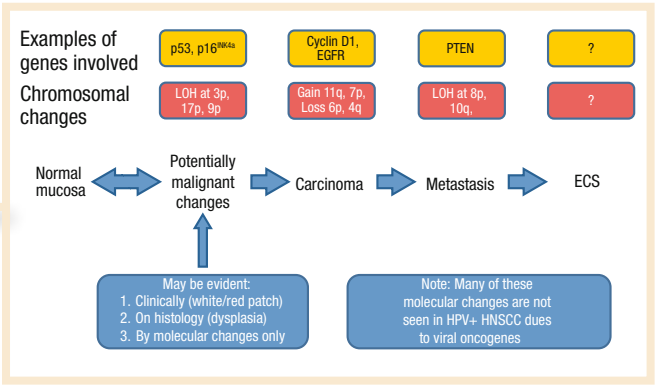
1. How does VC differ from conventional SCC?
2. What virus is strongly associated with the basaloid variant of SCC?
3. List three variants of SCC most commonly found in the upper respiratory tract.

Molecular characterisation

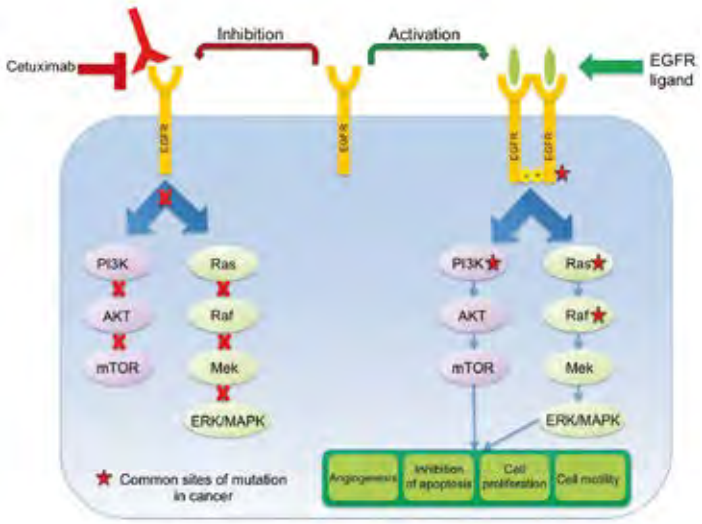
Molecular characterisation by next generation sequencing of SCC has identified some common genetic changes, but SCC is very heterogeneous.

Proto-oncogenes have normal cell functions, but when altered can lead to tumour development. Examples include *Cyclin D1* and epidermal growth factor receptor *(EGFR)*. *EGFR* is often amplified in SCC, leading to uncontrolled cell growth.

Tumour suppressor genes (TSGs) are involved in cell growth and division and are inactivated in SCC. Examples include *TP53*, *p16 (CDKN2a)* and *Notch1*.



ECS, Extracapsular spread; EGFR, epidermal growth factor receptor; HNSCC, head and neck squamous cell carcinoma; LOH, loss of heterogeneity; PTEN, phosphatase and tensin homologue.



EGFR, Epidermal growth factor receptor; mTOR, mechanistic target of rapamycin.

TP53 encodes p53 protein, which has a role in genome stability. *TP53* is commonly mutated in SCC and its detection in margins may indicate risk of recurrence.

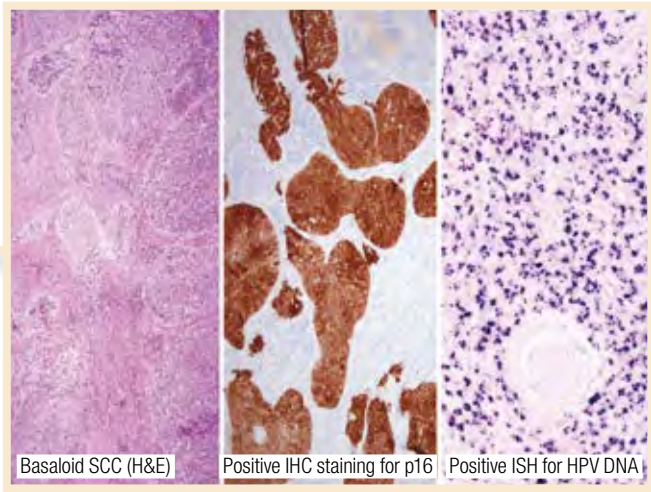
Cetuximab is an EGFR-inhibiting monoclonal antibody used for treatment of SCC, and was the first United States Food and Drug Administration (FDA)-approved targeted therapeutic in head and neck SCC.

Groups of mutations that frequently occur together are termed "tumour signatures" and may be useful in the development of future diagnostic biomarkers.

HPV types 16 and 18 have been identified as causative factors in oropharyngeal carcinoma. Viral proteins E6 and E7 inactivate TSGs.

p16 is encoded by *CDKN2A* and is involved in cell cycle regulation. IHC for *p16* is used as an initial screen for HPV-related carcinoma.

DNA and RNA ISH probes directed against HPV oncoproteins E6/E7 can also be used to confirm HPV-related carcinoma.



H&E, Haematoxylin & eosin; HPV, human papillomavirus; IHC, immunohistochemistry; ISH, *in situ* hybridisation; SCC, squamous cell carcinoma.

REVISION QUESTIONS

1. What is meant by the terms "oncogene" and "tumour suppressor gene"? Give examples of each.
2. What is the clinical significance of identification of gene mutations in the treatment of SCC?
3. Which molecular techniques can be used to identify HPV-related SCC?

Summary: Histopathological and molecular characterisation of squamous cell tumours

- Epithelial dysplasia is characterised by cellular and architectural changes within the epithelium and is graded as mild, moderate, severe or carcinoma *in situ*
- SCC is graded into well, moderately and poorly differentiated, dependent on its resemblance to squamous epithelium
- The morphology of the invasive front of SCC is linked to the tumour's aggressiveness and has prognostic value
- SCC is locally invasive but can spread by perineural, vascular and lymphatic invasion
- Bone invasion by SCC is an adverse prognostic factor and upgrades the TNM disease staging to T4
- Lymph node metastasis indicates poor prognosis, particularly if there is extracapsular extension of tumour
- The World Health Organisation recognises distinct histological variants of SCC
- Verrucous carcinoma and basaloid squamous cell carcinoma have a higher association with HPV
- Oncogenes and TSGs are involved in cancer progression. Their identification can be used to develop new targeted agents
- Immunohistochemistry (p16) and ISH are techniques that can be used to identify HPV-related SCC

Further Reading

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4 Site- and stage-driven treatment strategy in non-metastatic disease

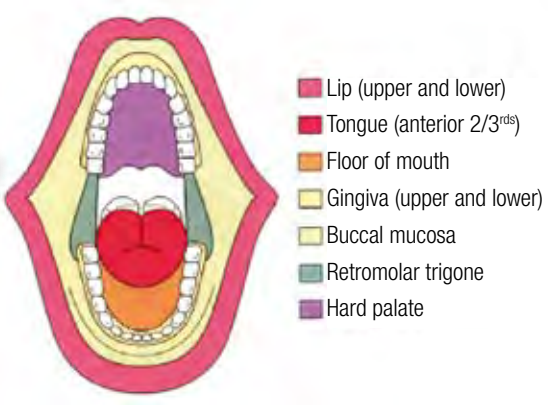
Oral cavity | Lip, floor of the mouth, oral tongue, buccal mucosa, upper and lower gingiva, hard palate (including retromolar trigone)

Stage I tumours can be treated with surgery or radiotherapy (RT), e.g. brachytherapy. If transoral resection without functional sequelae is feasible, surgery is preferred.

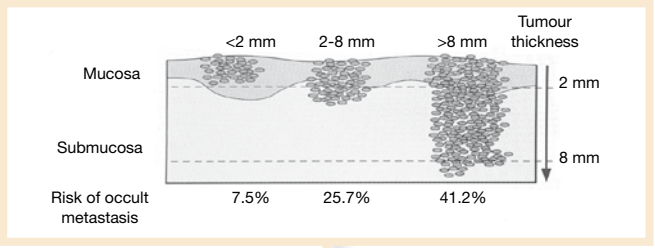
In Stage II tumours, surgery is the standard of care. For lesions <3 cm, infiltration <1 cm and tumour thickness <4 mm, RT can be considered if there is adequate distance from bone structures.

In Stage III-IV tumours, surgery usually followed by RT +/- chemotherapy (ChT) is preferred. In unresectable disease, concomitant chemoradiotherapy (ChT-RT) is the standard of care.

Oral cavity subsites: anatomical classification



Predictive value of tumour thickness in squamous cell carcinoma of the tongue and floor of the mouth



In clinically negative neck disease, prophylactic neck dissection can be avoided in T1 lesions and T2 lesions of the hard palate, upper lip and upper gingiva. Strict follow-up is advised.

Prophylactic neck dissection should always be indicated if primary tumour infiltration depth is >3 mm in T1-T2 lesions. Prophylactic neck surgery is mandatory in all T3-T4 lesions arising from the oral cavity.

Surgery is preferred for prophylactic neck treatment; RT can be considered in selected cases (e.g. if postoperative RT on T is indicated, or in case of anaesthetic contraindications).

3–5 year overall survival (OS) for Stage I-II tumours after radical treatment is 70%–85%. In Stage III-IV tumours, 5-year OS is ~50%.

The local control rate is 60%, with significant variation by stage and site.

Neoadjuvant ChT showed no improvement in OS, thus it can be considered only within clinical trials.

Postoperative RT is indicated in case of pathological minor risk factors:

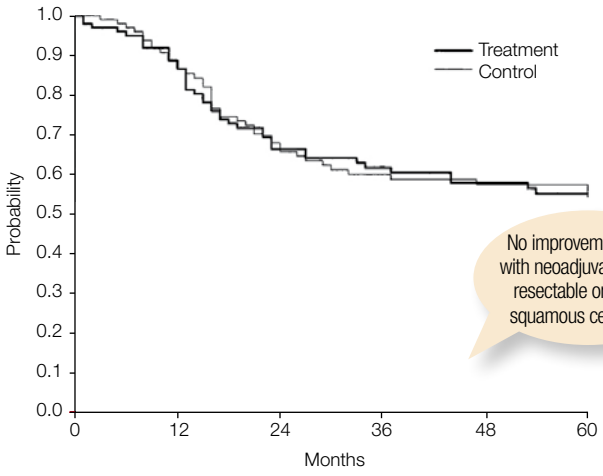
- Poor differentiation grade (G3)
- Perineural and/or vascular invasion
- Number of pathologically positive lymph nodes (≥2)
- pT3, pT4

In selected non-radical excision, re-excision can be considered.

Concurrent ChT-RT is indicated in case of pathological major risk factors:

- R1 resection (resection with microscopic residual disease)
- Lymph node extranodular extension (ENE)

Overall survival curves by treatment arm



No improvement in OS with neoadjuvant ChT in resectable oral cavity squamous cell cancer

ChT, Chemotherapy; OS, overall survival.

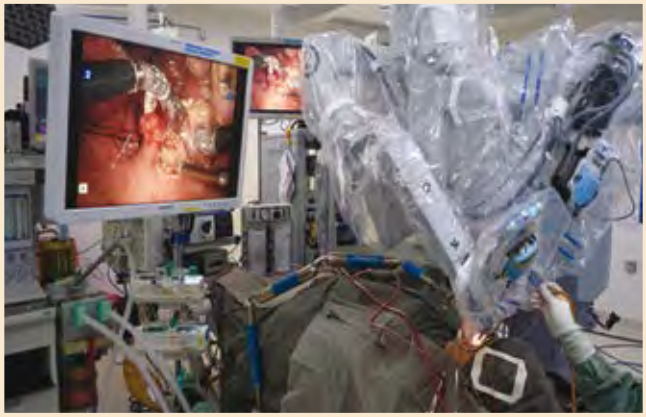
REVISION QUESTIONS

1. What is the standard treatment in locally advanced (Stage III-IV) unresectable oral cavity cancer?
2. What is the best management strategy in T1 radically resected oral tongue cancer with infiltration depth >3 mm?
3. What is the 5-year OS rate in Stage III-IV oral cavity cancer?

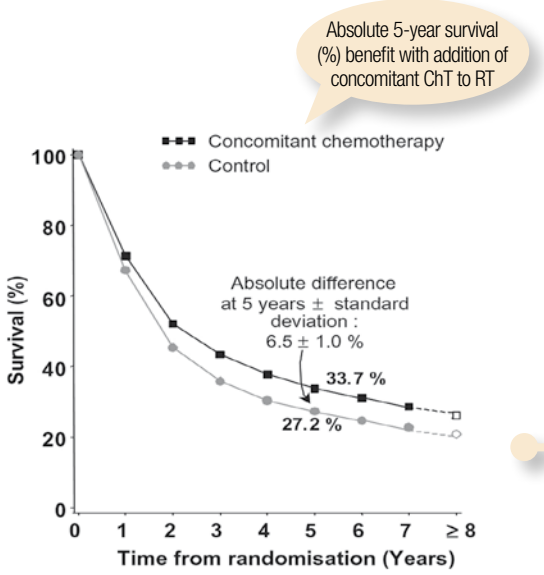
Oropharynx | Soft palate, base of tongue, tonsillar area

Tumours, clinically staged as T1-T2 N0, can be equally treated with radical surgery or RT, though RT is generally preferred for better functional outcome.

New conservative surgical techniques (e.g. transoral robotic surgery [TORS] and transoral laser microsurgery [TLMS]) have shown promising results in terms of functional outcome, but surgical expertise is needed.



Prophylactic treatment of clinically negative neck disease is always indicated, as any lesion arising in the oropharynx has a risk of subclinical neck disease >20%.



ChT, Chemotherapy; RT, radiation therapy.

Postoperative RT is indicated in case of pathological minor risk factors:

- Poor differentiation grade (G3)
- Perineural and/or vascular invasion
- Number of pathologically positive lymph nodes (≥2)
- pT3, pT4

In selected cases of non-radical excision, a re-excision can be considered.

Concurrent ChT-RT is indicated in case of pathological major risk factors:

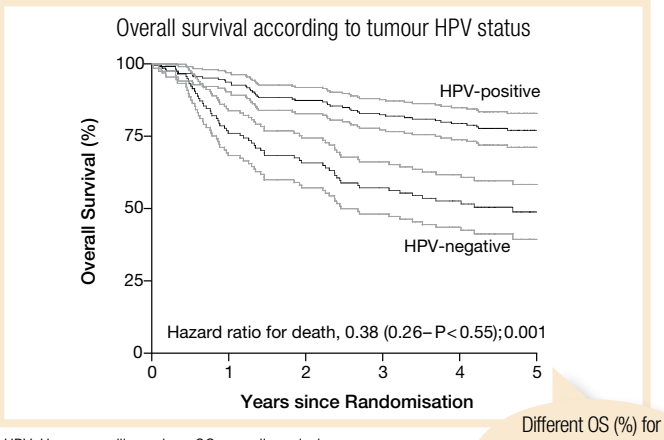
- R1 resection
- Lymph node ENE

Tumours, clinically staged as T3-T4 N0 or any T and N+, may be generally treated with RT associated with platinum-based ChT. Bioradiation (bio-RT; cetuximab plus RT) is an alternative approved option. However, ChT-RT is preferred because a formal comparison between these two therapeutic options is still needed. Bio-RT is advisable for patients unfit to receive cisplatin.

When concurrent chemo- or bio-RT is not feasible, altered fractionation RT (accelerated or hyperfractionated, with highest survival benefit for the latter) should be considered.

Several prognostic factors have been established: human papillomavirus (HPV) tumoural status, smoking history and clinical stage. Early stage HPV-related tumours have a 5-year OS of 90%, therefore there are many ongoing clinical trials aimed at treatment deintensification. At present, the treatment of HPV-positive oropharynx remains unchanged (see above).

Neoadjuvant ChT showed no improvement in OS, thus it can be considered only within clinical trials.



HPV, Human papillomavirus; OS, overall survival.

Different OS (%) for oropharyngeal cancer patients with HPV-positive and HPV-negative tumours

REVISION QUESTIONS

1. What is the standard of care in locally advanced oropharyngeal cancer?
2. What is the prognostic impact of HPV-related oropharyngeal cancer?
3. What is the role of neoadjuvant ChT in oropharyngeal cancer?

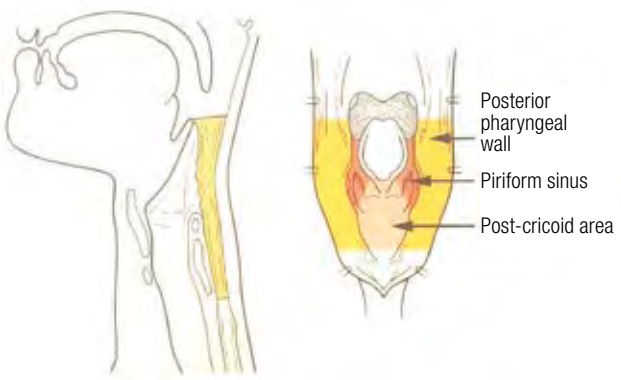
Hypopharynx | Posterior pharyngeal wall, post-cricoid/pharyngo-oesophageal junction, piriform sinus

Stage I-II tumours can be equally treated with surgery or RT. RT is preferred to extensive surgery due to the functional outcomes but conservative surgery, if feasible, is an alternative.

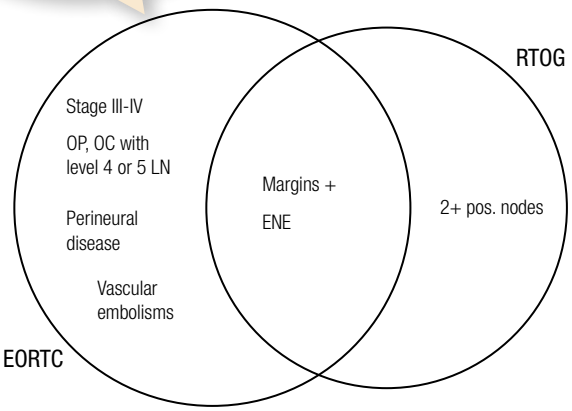
Resectable Stage III-IV tumours can be cured with surgery followed by RT +/- ChT. Unresectable tumours are treated with chemo-/bio-RT.

Prophylactic treatment of clinically negative neck disease is always indicated, as any lesion of the hypopharynx has a risk of subclinical neck disease >20%.

Hypopharynx subsites: anatomical classification



Pathological major risk factors for postoperative concomitant ChT-RT in radically resected HNSCC



ChT-RT, Chemoradiotherapy; ENE, lymph node extranodular extension; EORTC, European Organisation for Research and Treatment of Cancer; HNSCC, head and neck squamous cell carcinoma; LN, lymph node; OC, oral cavity; OP, oropharynx; RTOG, Radiation Therapy Oncology Group.

Postoperative RT is indicated in case of pathological minor risk factors:

- Poor differentiation grade (G3)
- Perineural and/or vascular invasion
- Number of pathologically positive lymph nodes (≥2)
- pT3, pT4

In case of non-radical excision, a re-excision can be considered.

Concurrent ChT-RT is indicated in case of pathological major risk factors:

- R1 resection
- Lymph node ENE

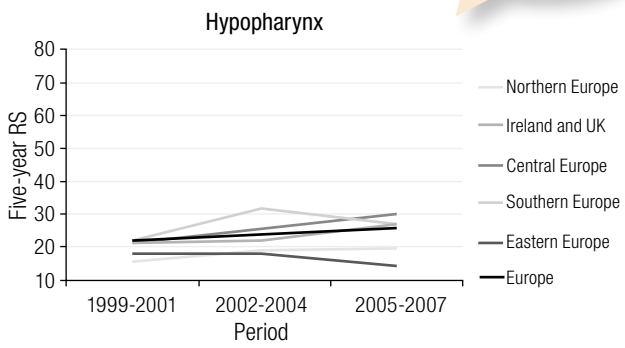
In patients who are candidates for total laryngectomy, an organ preservation multimodality strategy can be adopted.

Carefully selected patients can be treated with concurrent definitive ChT-RT or with induction ChT (IChT), followed by exclusive RT (IChT → RT) in responding patients. IChT → RT is associated with a better long-term survival but a lower organ preservation rate.

The standard regimen for IChT is docetaxel-cisplatin-fluorouracil (TPF), while cisplatin is the standard chemotherapeutic agent for ChT-RT.

The 5-year OS for Stage I-II tumours is 70%–80%. In Stage III-IV tumours, prognosis is dismal with a 5-year OS of about 30%.

5-year relative survival rate (RS, %) in hypopharyngeal cancer patients across European regions



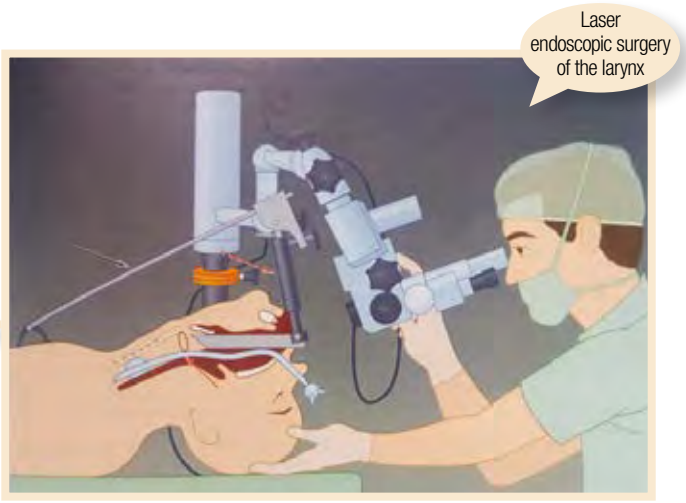
REVISION QUESTIONS

1. What is indicated in case of lymph node ENE?
2. What is the standard ChT regimen before RT in the organ-preservation strategy?
3. What is the prognosis of locally advanced (Stage III-IV) hypopharyngeal cancer?

Larynx | Supraglottic: infra- and supra-hyoid epiglottis, aryepiglottic fold (laryngeal side), arytenoid, false vocal cords; glottic: true vocal cords, anterior and posterior commissure; subglottic

Supraglottic tumours:
Stage I-II tumours can be equally treated with conservative surgery (endoscopic or open) or exclusive RT. When radicality is expected, surgery is preferred.

Glottic tumours:
Stage I-II tumours can be equally treated with conservative surgery (laser endoscopic) or RT. For T1 tumours, RT is equivalent to or better than surgery in terms of quality of the voice. RT is preferred in case of anterior commissure involvement and subglottic extension.



Subglottic tumours:
Stage I-II tumours are treated with exclusive RT.

In presence of inadequate margins (<5 mm in open surgery and <2–3 mm in endoscopic surgery), another treatment (RT or endoscopic surgery) is needed.

In T2, T3 supra- or glottic tumours that are candidates for total laryngectomy, an organ preservation multimodality strategy can be adopted. Data on this strategy in subglottic tumours are not available, but it could be considered in selected cases (e.g. T3N0).

Prophylactic treatment of clinically negative neck disease is indicated in selected cases of supraglottic subsite (e.g. T2).

In T4 patients, surgery followed by RT +/- ChT is considered state of the art. Unresectable tumours are treated with chemo-/bio-RT.

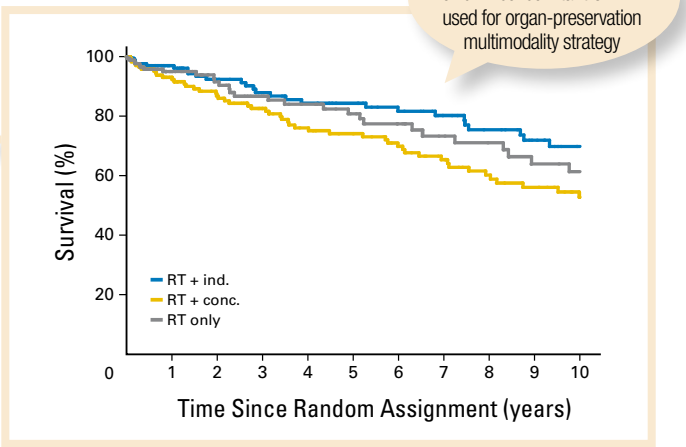
Postoperative RT is indicated in case of pathological minor risk factors:
- Poor differentiation grade (G3)
- Perineural and/or vascular invasion
- Number of pathologically positive lymph nodes (≥2)
- pT3, pT4

In case of non-radical excision, a re-excision can be considered.

Concurrent ChT-RT is indicated if pathological major risk factors:
- R1 resection
- Lymph node ENE

The organ preservation multimodality strategy includes concurrent definitive ChT-RT or IChT followed by exclusive RT in responding patients (IChT → RT). IChT → RT is associated with a better long-term survival but a lower organ preservation rate. The standard regimen for IChT is TPF, while cisplatin is the standard chemotherapeutic agent for ChT-RT.

The local control rate is about 80%–95% in early stage supraglottic and glottic tumours and 60%–70% in early stage subglottic tumours. In advanced stage disease, the local control rate is about 60% with surgery + RT (+/- ChT) or organ preservation strategy.



ChT-RT, Chemoradiotherapy; RT, radiotherapy.

REVISION QUESTIONS

1. When is RT preferred to surgery in the treatment of early stage glottic tumours?
2. Which laryngeal cancers can be treated with an organ preservation strategy?
3. What are the results of this strategy?

Summary: Site- and stage-driven treatment strategy in non-metastatic disease

- In early stage disease, Stage I-II (cT1-2N0), of HNSCC, surgery or RT are equally good therapeutic options
- In early stage oral cancers, if a transoral resection is feasible without significant sequelae, surgery might be preferred to RT
- In early stage oral cancers, in case of clinically negative neck disease, prophylactic neck dissection should be performed if the primary tumour infiltration depth is >3 mm
- In locally advanced disease, Stage III-IV (cT3-4N-/N+) HNSCC, concurrent ChT-RT is the standard of care. For larynx or hypopharynx, ChT-RT may be also suggested in resectable cases as an organ-preservation approach, but only for unresectable disease in oral cavity
- In concurrent ChT-RT, ChT consists of platinum-based regimens (cisplatin preferred to carboplatin). No differences between thrice- or once-weekly schedules have been demonstrated
- Bio-RT (cetuximab plus RT) is an alternative approved therapeutic option, advisable for patients unfit to receive cisplatin
- Altered fractionation RT (accelerated or hyperfractionated) should be considered when ChT-RT or bio-RT are not feasible
- IChT with the TPF regimen, followed by RT +/- ChT, is a real alternative therapy (vs ChT-RT or bio-RT) only in larynx or hypopharynx subsites as a multimodality organ-preservation strategy; otherwise it may be an option only within clinical trials
- Postoperative ChT-RT is indicated in case of major risk factors (R1 resection and/or lymph node ENE)
- HPV is a validated positive prognostic factor only for the oropharyngeal subsite

Further Reading

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Principles of surgery of squamous cell tumours

5

Principles and goals in head and neck surgery

Early head and neck squamous cell carcinoma (HNSCC) can usually be treated with either surgery or radiotherapy. Multimodality treatment of HNSCC (required in advanced cases) has drawbacks such as toxicities, reduced functional outcome and treatment failure and is contraindicated in patients with many comorbidities.

Lefebvre and Ang (2009) established a list of guidelines for better outcome specification after organ-preservation therapy in patients with laryngeal and hypopharyngeal cancer, which should be used in further clinical trials.

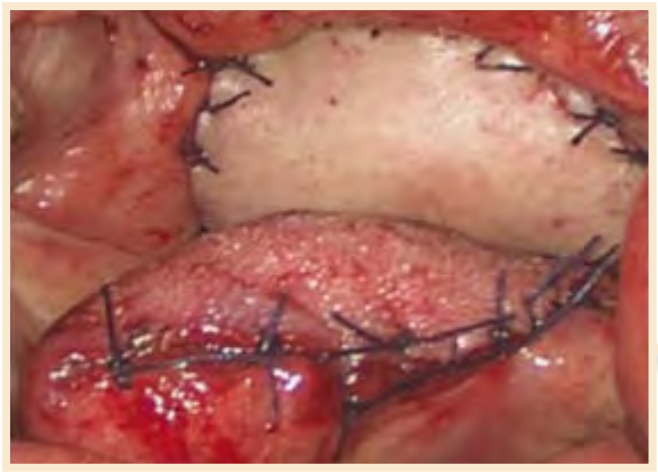
These guidelines describe a new endpoint: "laryngo-oesophageal dysfunction-free survival", implicating the highly important issue of late functional outcome.

Summary of some key recommendations (Lefebvre and Ang 2009)

Patient selection	Eligible patients should have T2 or T3 laryngeal (glottic or supraglottic) or hypopharyngeal squamous cell carcinoma not considered for partial laryngectomy Exclusion criteria should include laryngeal dysfunction (defined as pretreatment tracheotomy, tumour-related dysphagia requiring feeding tube, or recurring pneumonia within the preceding 12 months requiring hospitalisation). Patients aged >70 years should also be considered
Assesments	Baseline assessments for speech and swallowing function (e.g. a barium oesophagram) may be useful for longitudinal comparison Assessment of voice should be done with a simple, validated instrument (e.g. Voice Handicap Index-10 or Voice-Related Quality of Life) at 1 and 2 years
Endpoints	The primary endpoint should combine assessment of survival and preservation of organ function, as in the new composite endpoint laryngo-oesophageal dysfunction (LED)-free survival (includes death, local relapse, total or partial laryngectomy, tracheotomy at ≥2 years, or feeding tube at ≥2 years) Recommended secondary endpoints include freedom from LED, overall survival, progression-free survival, locoregional control, time to tracheotomy, time to laryngectomy, time to discontinuation of feeding tube, and quality of life/patient-reported outcomes
Tissue banking and biomarker assessment	Recommended proof-of-principle correlative biomarker studies for near-term trials include EGFR (total, p-EGFR, and *EGFRvIII*) defined by immunohistochemistry, excision repair cross-complementation group 1 gene, E-cadherin and β-catenin, epiregulin and amphiregulin, and *TP53* mutation

EGFR, Epidermal growth factor receptor.

Reconstruction with a radial forearm flap



HNSCC treatment guidelines are based on phase III trials and meta-analyses, with an excess of chemoradiotherapy (ChT-RT) studies at the expense of surgical trials.

Due to the disproportion between surgical and non-surgical trials, it is difficult to set up clinical recommendations for HNSCC treatment based on the evidence.

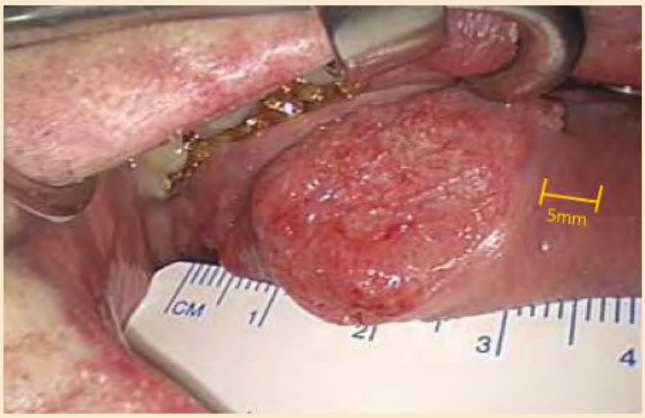
Well-established and proven standards in surgery of HNSCC are defined as state-of-the-art tumour resection and reconstruction procedures.

Instruments for evaluating best surgical practice are different from methodological standards in non-surgical phase II or III trials.

The inclusion of the minimal distance between tumour tissue and resection margins into the current R-classification would be useful. The R-classification is used and is recommended by the American Joint Committee on Cancer (AJCC) / Tumour Node Metastasis (TNM) system.

In HNSCC surgery, a distance of 5 mm at minimum (except in tumours of the vocal cord) is highly recommended.

Minimal distance of 5 mm between tumour and resection margin



REVISION QUESTIONS

1. Which outcome-defining endpoint was proposed by Lefebvre and Ang?
2. From which field do the majority of high-impact publications on HNSCC come: surgery or ChT-RT?
3. How wide is an oncological-sufficient resection margin in HNSCC?

Principles and goals in head and neck surgery (continued)

Standardised neck dissection should be included in the tumour stage-related surgical concept.

Neck lymph nodes are divided into levels according to the Robbins classification.

Primary surgery and additional adjuvant treatment of HNSCC is always recommended if R0 resection is possible.

Robbins classification of lymph node levels	
Level Ia and Ib	Submental and submandibular lymph nodes
Level IIa and Ib	Upper jugular lymph nodes
Level III	Middle jugular group
Level IV	Lower jugular group
Level Va and Vb	Posterior triangle group
Level VI	Anterior compartment group

Tumour board

The choice of either surgery or non-surgical primary approaches is mainly based on clinical experience and medical culture.

Several studies showed that patients treated in high-volume centres have a better outcome than those treated in low-volume centres.

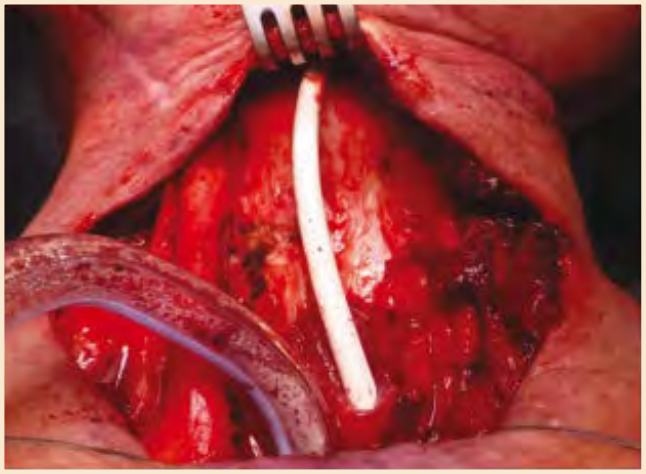
The treatment decision should be based on an interdisciplinary view (tumour board) on best survival, late functional outcome and patient's needs.

Head and neck oncology is experiencing a renaissance in surgery, due to new techniques, less radical approaches and better reconstruction, and also to late toxicity problems after primary ChT-RT.

The dense anatomical structures in the head and neck, coupled with limited soft tissue redundancy, must be allowed for in surgical planning.

A consequent oncologically sound resection must be performed, even if a larger or more challenging reconstructive defect may result.

Operative finding after pharyngo-laryngectomy



REVISION QUESTIONS

1. Which lymph node levels are defined according to Robbins?
2. Who should make decisions about cancer treatment?
3. What are the reasons for the renaissance in primary and salvage surgery of HNSCC?

Goals of reconstruction: wound healing, vital structure protection, function and cosmesis

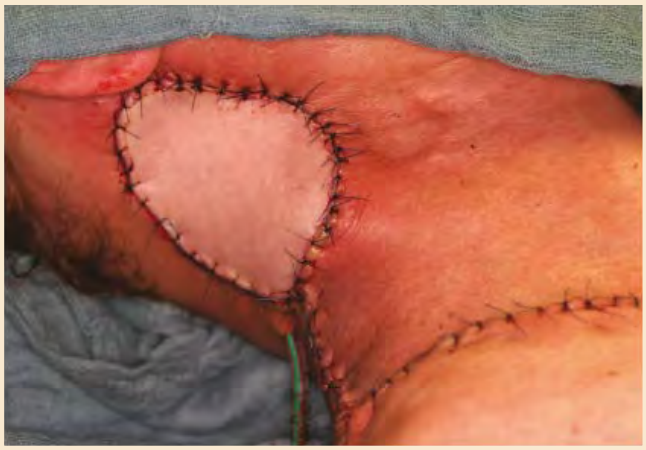
The first principle in reconstructive surgery applies to the creation of a defect. The repair follows a sequence often referred to as the "reconstructive ladder".

Reconstructive ladder
Primary closure
Skin grafts
Local flaps
Distant pedicled flaps
Microvascular tissue transfer

Wound management should begin with the simplest technique first, and then progress to more complex rearrangement and transfers, as needed.

The strategy ultimately chosen should provide the best functional and cosmetic outcomes for patients, yet pose the least surgical risk.

Reconstruction with a pectoralis major flap

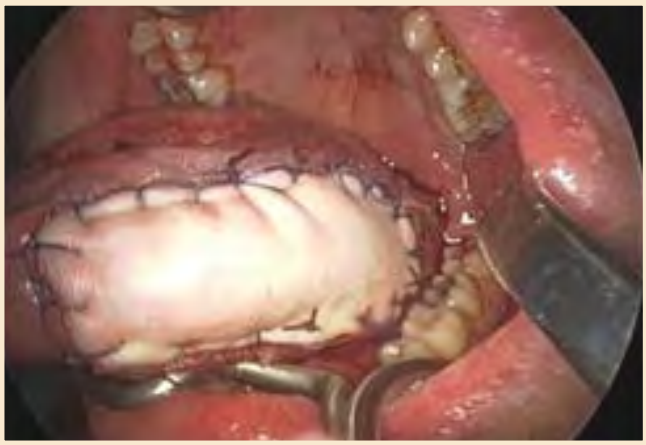


The reconstruction of a surgical defect follows a generalised set of principles applied to the patient's anatomical and functional deficit(s).

These principles allow the surgeon to reconstruct a wide variety of defects to achieve optimal functional and aesthetic outcomes for patients.

Before a patient is taken to the operating room, the defect and functional and aesthetic results should be known and accepted by both the patient and surgeon.

Reconstruction of the tongue with a radial forearm flap



The overarching goal of reconstructive surgery is to create new tissue arrangements that serve in place of native structures.

Surgery of the head and neck poses unique challenges in achieving reconstructive results that go beyond simple wound healing.

The reconstructive surgeon must preserve a patient's ability to eat, speak, swallow and breathe, in addition to yielding a good aesthetic outcome and quality of life.

REVISION QUESTIONS

1. What is meant by the term "reconstructive ladder"?
2. What methods of tissue repair do you know?
3. What is the goal of reconstructive surgery?

Goals of reconstruction: wound healing, vital structure protection, function and cosmesis (continued)

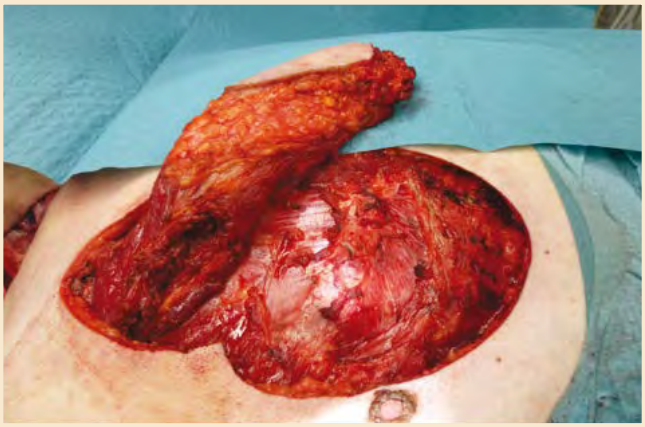
A "flap" refers to tissue that is moved from a donor to a recipient site and carries its own blood supply. The main types are pedicled and microvascular free flaps.

These two flaps differ from each other in that pedicled free flaps remain connected to their native blood supply, either random or axial.

Microvascular free flaps are tissue units with axial vessels, completely separated from their donor site and connected to a vein and artery at the defect.

Radial forearm flap

Pectoralis major myocutaneous flap



Pedicled flaps are best suited to defects requiring tissue bulk for a multilayer tissue closure in which minimal tissue folding is required.

A pedicled flap offers some advantages in head and neck reconstruction, as exemplified by the pectoralis major myocutaneous flap, popularised in 1979.

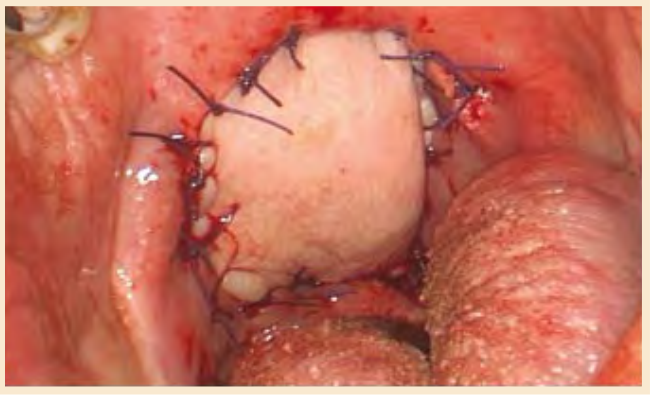
Pedicled flaps can be inset into a wound in a single step, and bring with them a robust and reliable blood supply.

Microvascular free tissue transfers offer distinct advantages in reconstruction for use in scalp, facial, oral, pharyngeal and osteocutaneous defects.

The ability to mould and sculpt microvascular free flaps to three-dimensional forms allows them to be used in a multitude of settings.

The radial forearm free flap has become a workhorse flap in head and neck reconstruction, especially for soft-tissue replacement. Postoperative radiotherapy can start two to three weeks after the operation, depending on wound healing.

Reconstruction of the soft palate with a radial forearm flap



REVISION QUESTIONS

1. How does a flap differ from a graft?
2. What are the advantages of pedicled flaps?
3. What are the advantages of microvascular free flaps?

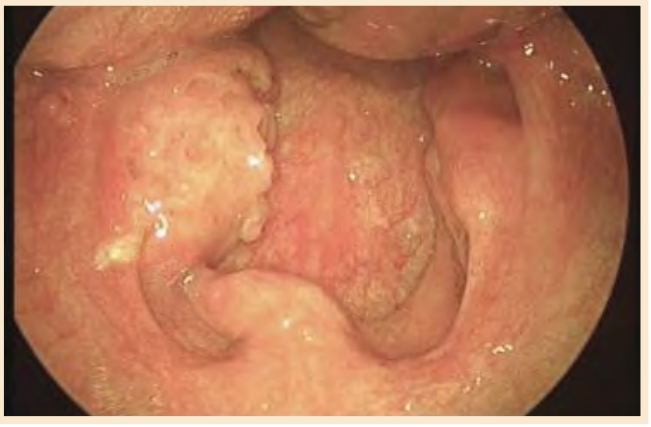
Transoral surgery triggered by HPV16 in oropharyngeal cancer treatment

In North America and Western Europe, the incidence of human papillomavirus (HPV) 16-related HNSCC of the oropharynx is increasing dramatically.

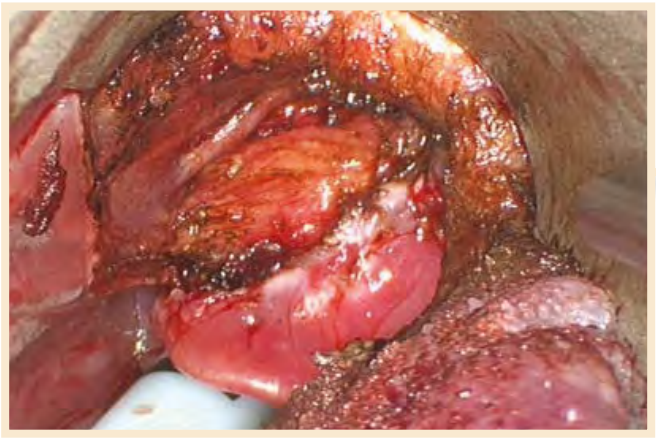
Today, there are no data showing by direct comparison the superiority of surgical or non-surgical treatment in HPV-positive disease.

Current data show that HPV16-positive oropharyngeal cancer patients do much better than HPV16-negative patients, regardless of receiving surgery or ChT-RT.

Tonsil cancer



Intraoperative finding after laser resection of cancer of the base of tongue

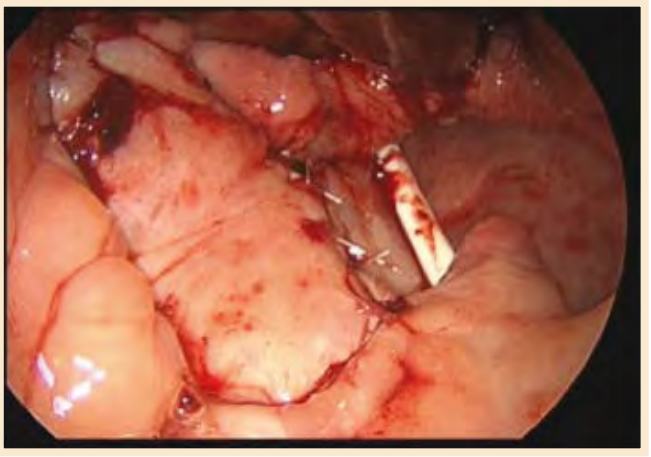


Transoral Robotic Surgery (TORS) is used in routine treatment for lesions of the tonsillar region and base of tongue in many US centres, with good results.

In Europe, TORS is in strong competition with Transoral Laser Microsurgery (TLMS). Use of TLMS is limited, especially in the base of tongue lesions, but is highly efficient in well-trained hands in most head and neck regions.

Evidence for the superiority of TORS over TLMS does not exist, and reimbursement policies in Europe do not cover its costs.

Reconstruction with a radial forearm flap



The small volume of the oropharynx and limited tissue redundancy restrict reconstructive options. Healing by secondary intention may cause unwanted scarring.

An open wound may pose risk to surrounding structures if a communication exists between the oropharynx and deep neck.

Skin grafts can be used to restore superficial tissue loss. More involved defects of the oropharynx or soft palate are best treated with a regional or free flap.

REVISION QUESTIONS

1. Are there any data showing the superiority of surgical or non-surgical treatment in HPV-positive disease?
2. What are the advantages of TORS compared with TLMS?
3. What reconstructive options do we have for covering oropharyngeal defects?

Summary: Principles of surgery of squamous cell tumours

- The field of head and neck surgery has advanced enormously
- Head and neck oncology is currently experiencing a renaissance in primary and salvage surgery
- New techniques and late toxicity problems after primary ChT-RT dominate the interdisciplinary view on therapy of HNSCC
- The surgeon must not compromise the complete excision of neoplastic disease, even if a larger or more challenging reconstructive defect may result
- The type of flap which offers the best functional and cosmetic outcome should be used for coverage of defects
- Microvascular free tissue transfers offer distinct advantages in reconstruction
- No evidence for superiority of TORS over TLMS exists
- Health insurance policies in Europe do not cover the costs of TORS; therefore this technique is not recommended for first-choice routine treatment
- Current evidence is not in favour of abandoning primary surgery in HPV16-positive patients with oropharyngeal cancer, nor of changing routine treatment options beyond clinical trials
- Future concepts also have to include surgical aspects, which have to be reflected within new clinical trial approaches

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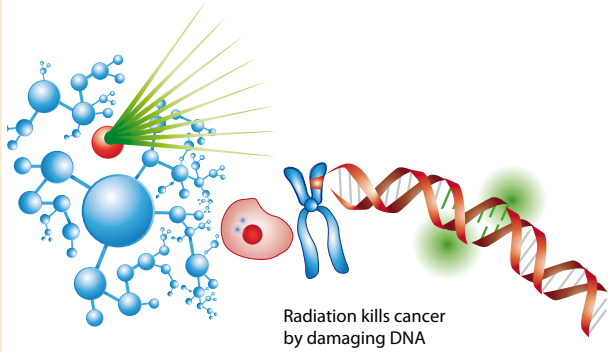
Principles of radiotherapy of squamous cell tumours 6

Introduction; general principles of radiotherapy

Radiotherapy (RT) plays an important role in the management of head and neck cancers.

RT is given either as a sole curative modality or combined with systemic treatment (such as chemotherapy [ChT], hypoxia modifiers or monoclonal antibodies). RT can also be given as an adjuvant treatment following surgery (either as a sole modality or in combination with ChT).

For some head and neck cancer subsites, RT offers the chance for organ sparing and function preservation by avoiding the use of surgery.



Radiation kill cells primarily by causing ionisation, which leads to single strand or double strand DNA damage. If the DNA damage cannot be repaired by cellular DNA repair mechanisms, the injury leads to cell death.

Normal cells have a greater capacity to repair the DNA damage compared with malignant cells, leading to preferential cancer cell death.

The aim of RT is to deliver adequate dose to the tumour to eradicate the cancer cells, while ensuring the dose delivered minimises acute and long-term damage to the surrounding normal tissue.

Radiation dose is measured in Gray (Gy), which is the absorption of 1 Joule of energy per kilogram of water.

Photons tend to cause more sparse ionising cell changes compared to particles such as protons and other heavy particles, which have higher linear energy transfer, resulting in dense ionisation along the track.

Most RT is delivered through an external source such as a linear accelerator, but sometimes can be given by brachytherapy, which delivers radiation directly into (interstitial), or adjacent to (intracavity), the tumour.

REVISION QUESTIONS

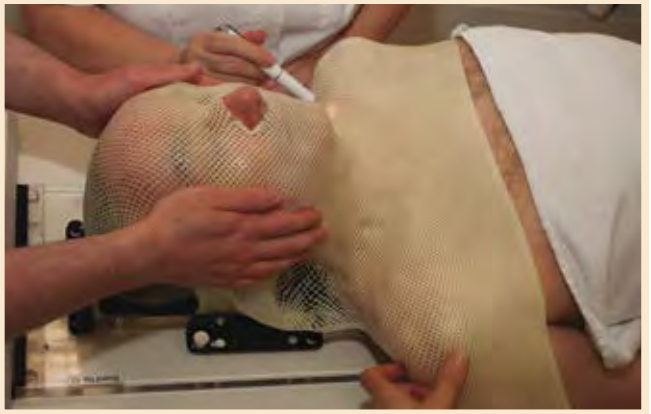
1. What are the treatment modalities for head and neck cancer?
2. How does radiation kill cancer cells?
3. How does radiation allow for organ sparing and function preservation?

Preparation for radiotherapy

As head and neck cancers affect the organs that influence eating, swallowing, speech, vision and hearing, which are in close proximity to critical structures such as the brainstem, spinal cord and temporal lobes, accurate delivery of radiation to the cancer while sparing the organs at risk is critical in head and neck cancer RT.

To facilitate this, patients are accurately immobilised with individualised thermoplastic moulds that effectively restrict patient movement from the top of the head to the shoulders.

Immobilisation of a patient with a mould



Patient being set up for treatment

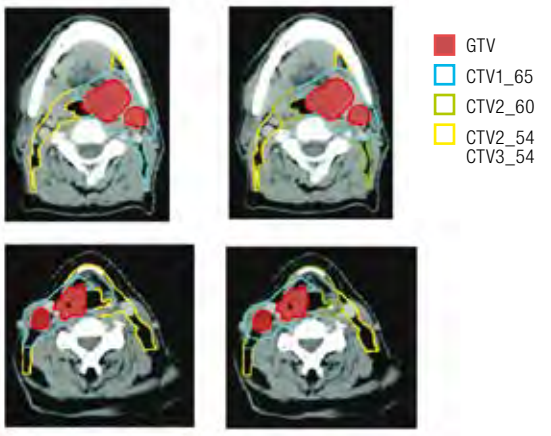
The patients then undergo a planning computed tomography (CT) scan with intravenous contrast, to allow accurate delineation of the cancer and the organs at risk.

Magnetic resonance imaging (MRI) and positron emission tomography (PET)/CT scans can also be used as adjunct to the planning process.

Once the planning imaging has been acquired, the oncologist carefully delineates the cancer and the areas and nodal regions at risk of microscopic spread. The organs at risk are also delineated.

The dosimetrist then carefully plans the treatment using sophisticated computer-based planning systems to optimise the doses that will be delivered to these different areas.

Treatment contouring and planning



GTV: All gross disease on imaging or exam; CTV1: "Microscopic margin"; CTV2: "High risk" nodal volumes and mucosal sites; CTV3: "Elective" uninvolved nodal regions at risk for microscopic disease

REVISION QUESTIONS

1. Why are patients immobilised with a mould for RT?
2. What imaging do patients receive in order for the radiation oncologist to plan RT?
3. What are the areas the oncologist has to delineate to plan RT?

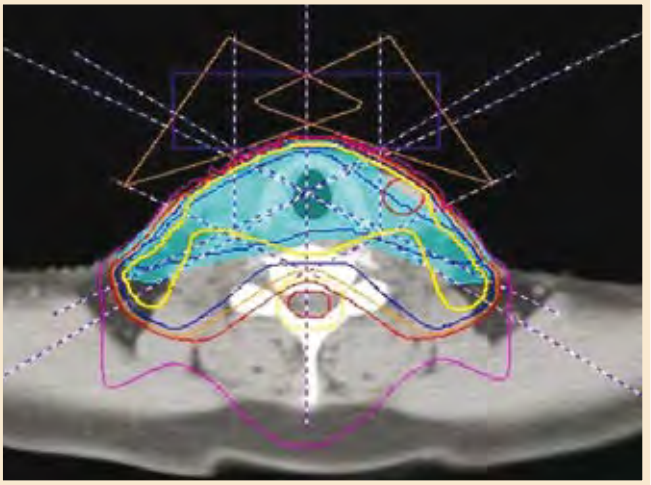
Preparation for radiotherapy (continued)

Three-dimensional conformal radiotherapy (3D-CRT) refers to the delivery of RT that conforms to the target volume and the patient's anatomy.

The ability to spare the critical organs is further improved by modulating multiple non-uniform beams with a technique known as intensity modulated RT (IMRT).

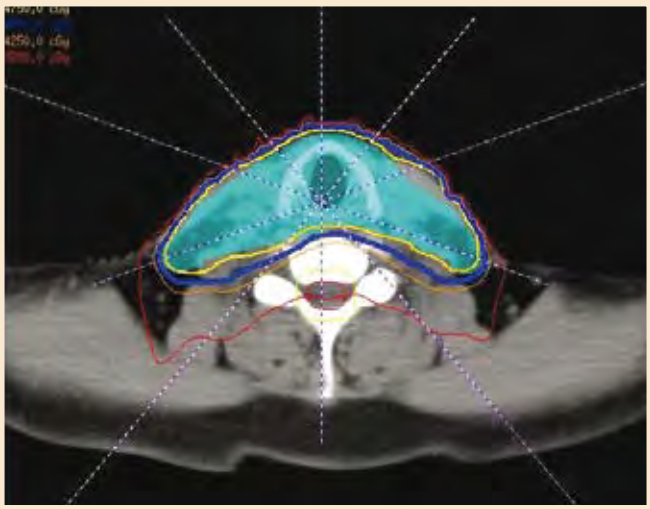
Randomised trials have shown that IMRT reduces certain long-term side effects compared to 3D-CRT (Nutting 2011).

3D-CRT: Blue indicates the target. Yellow line is 95% isodose



CRT, Conformal radiotherapy.

IMRT: Coverage of target better than 3D-CRT



CRT, Conformal radiotherapy; IMRT, intensity modulated radiotherapy.

IMRT can be delivered much faster through a rotational arc IMRT, which allows the treatment head to continuously modulate the delivered dose as it is moving around the patient.

To ensure that the treatment is accurately delivered, image-guided radiotherapy (IGRT) is delivered with the use of 3D cross-sectional imaging during treatment to minimise set up inaccuracies.

The concept of image-guided adaptive RT is currently in development. This technique incorporates re-planning of the RT based on anatomical and volume changes of the cancer, and the organs at risk during treatment.

Since RT can affect a patient's dentition, eating and swallowing, it is advisable for patients to be reviewed by a dentist, dietician and speech & language therapist prior to RT.

To reduce the risk of osteoradionecrosis, any teeth that are likely to require extraction in the future are best extracted prior to starting RT.

Patients are also advised to stop smoking and given smoking cessation treatment. For more detailed information, please refer to Chapter 11.

Acute side effects of head and neck RT

Lethargy, xerostomia, mucositis, dermatitis, pain, thickened secretions, dysphagia, nausea, loss of taste, malnutrition, oedema

Chronic side effects of head and neck RT

Xerostomia, fibrosis, dysphagia, osteoradionecrosis, restriction of movement, shrinkage of tissue

RT, Radiotherapy.

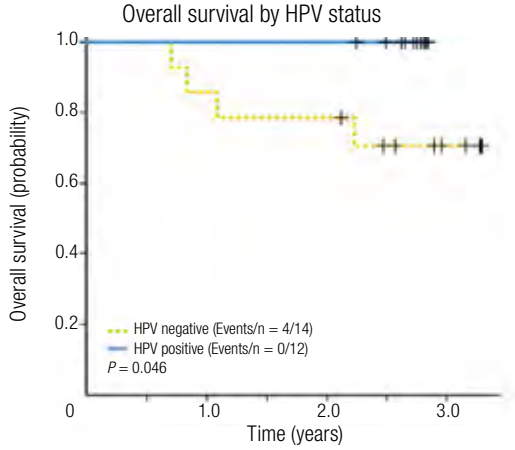
REVISION QUESTIONS

1. How is IMRT better than 3D-CRT?
2. How can an oncologist ensure that treatment is accurately delivered?
3. What other allied health professionals are needed to help care for a patient undergoing head and neck RT?

Radiotherapy indications, dose and fractionation

RT is often given as the definitive treatment for some head and neck subsites such as oropharynx, hypopharynx, nasopharynx and larynx, with good local control.

Local control with RT depends on the physical size of the tumour as well as the biological characteristics of the cancer. For instance, studies have shown that cancers which are human papillomavirus (HPV)-positive have better prognosis and local control (Ang 2010).



HPV, Human papillomavirus.

Risk factors for recurrence:

- Close or positive microscopic margins
- Perineural invasion
- Vascular invasion
- Presence of lymph node metastasis
- Presence of extracapsular spread

RT can also be given as a postoperative treatment in most head and neck subsites where it is felt that there is a risk of postoperative recurrence.

Delay of more than 6 weeks after surgery before starting postoperative RT is also a poor prognostic factor. For further details please refer to Chapter 4.

RT is often given in multiple fractions (traditionally 5 fractions per week) to take advantage of the radiological differences in cancer and normal tissue response to radiation. There is evidence of dose response in head and neck cancer.

The international conventional dose of RT is a radiobiological equivalent dose of around 70 Gy in 35 fractions (over 7 weeks) for definitive RT, and around 60 Gy in 30 fractions (over 40 days) to 66 Gy in 33 fractions (over 45 days) for postoperative RT. There is, however, considerable variation to this practice.

Using IMRT, different target regions can be treated with different doses in the same number of fractions, a concept known as simultaneous integrated boost (SIB). Some centres may boost a particular target area with additional dose after completion of treatment to the other target areas.

Interruptions to the RT schedule, which increase the overall treatment time, are to be avoided if possible, as uncompensated treatment gaps have been shown to reduce local control.

Compensation for unavoidable or unscheduled interruptions to RT

- Twice-daily fractions, minimum 6 hours interval
- Weekend treatment
- Use of biologically equivalent dose in fewer fractions to achieve planned overall time
- Additional fractions where compensation cannot be achieved within the original planned time

RT, Radiotherapy.

Radiotherapy indications, dose and fractionation (continued)

Studies have shown altered fractionation improves local control with increase in early toxicities (Overgaard et al 1998).

The MARCH meta-analysis of altered fractionation trials has shown that altered fractionation can give better local control on the primary (6.4% benefit in 5 years), although its impact on nodal control is less pronounced (Bourhis et al 2006). There is an absolute benefit in overall survival of 3.4%.

However, the benefit of altered fractionation is not seen when concurrent ChT is given with RT (Nyugen-Tan 2014).

Altered fractionation strategies have been tested in head and neck cancer

The main approaches are:

i. Hyperfractionation (giving multiple small fractions per day to a higher than conventional total dose). For example, 80.5 Gy in 70 fractions, twice daily fractions over 47 days

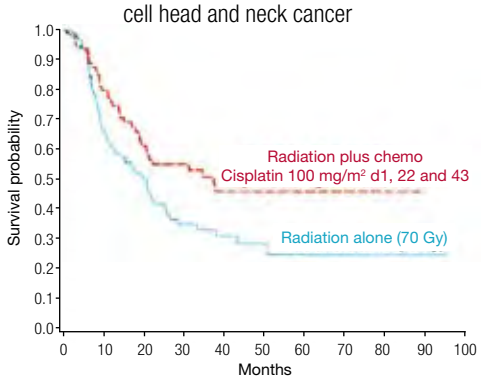
ii. Accelerated fractionation (giving conventional or lower total doses over a shorter overall treatment time). For example, 70 Gy in 35 fractions over 40 days

REVISION QUESTIONS

1. What affects the local control of cancers by RT?
2. In the postoperative setting, what risk factors predict cancer relapse?
3. Why are treatment gaps in RT detrimental?

Radiotherapy with concomitant systemic therapy

An intergroup comparison of standard radiation therapy and concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer



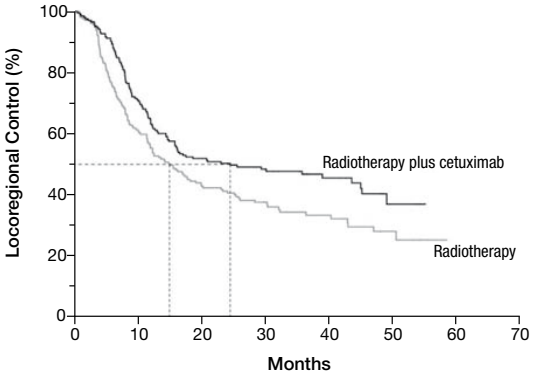
For patients with advanced head and neck squamous carcinoma (Stage 3, 4a, 4b), the addition of concomitant systemic treatment has been shown to be beneficial in terms of local control and overall survival (Pignon et al 2009). Cisplatin is most commonly used.

In the postoperative setting, the addition of ChT has been shown to improve survival in those patients with evidence of extracapsular nodal spread or positive excision margins (Bernier et al. 2005).

Most head and neck squamous carcinomas over-express epidermal growth factor receptor (EGFR). The concomitant use of a monoclonal antibody against EGFR, cetuximab, has also been shown to be beneficial (Bonner et al 2006).

However, when cetuximab is added to cisplatin-based concurrent chemoradiotherapy, there is no improvement of outcome, but increased toxicities (Ang et al 2014).

Hypoxia modifiers such as nimorazole, when added to RT, have also been shown to improve locoregional control and cancer-related deaths. There is a non-statistically significant trend towards improved overall survival (Overgaard et al 1998).



No. at Risk

Radiotherapy	213	122	80	51	30	10
Radiotherapy plus cetuximab	211	143	101	66	35	9

REVISION QUESTIONS

1. Which stages benefit from the addition of concomitant systemic treatment?
2. What are the concomitant systemic options?
3. Are there any benefits in adding two different types of concomitant systemic agent?

Summary: Principles of radiotherapy of squamous cell tumours

- RT is an effective modality in the treatment of head and neck cancer
- The aim of RT is to deliver an adequate dose to kill cancer cells, but minimise the dose to normal tissues to reduce long-term complications
- RT requires accurate target immobilisation and treatment planning
- RT gives good local control and allows for organ preservation
- For advanced stage cancers, the addition of concomitant systemic treatment improves local control and overall survival
- In the postoperative setting, RT reduces the risk of locoregional relapse and improves overall survival in cases with high risk of relapse
- Altered fractionation has been shown to improve local control
- Emerging technologies with IMRT and IGRT improve the outcome for patients
- RT can result in various side effects, some acute, some long term
- Patients on RT require the assistance of allied health professionals such as dentist, dietician and speech and language therapist, to optimise their function and help with patients' compliance to treatment

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Treatment of recurrent or metastatic disease

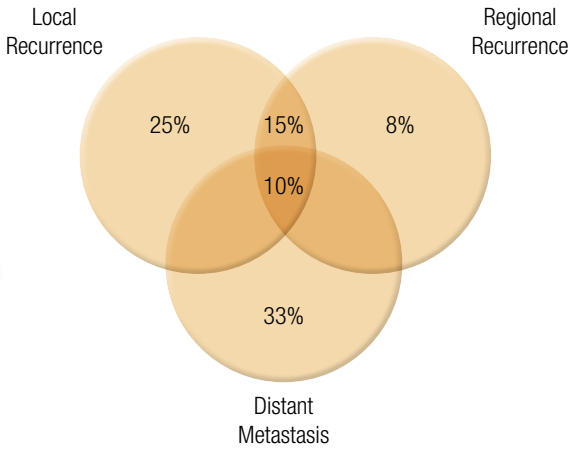
7

Introduction

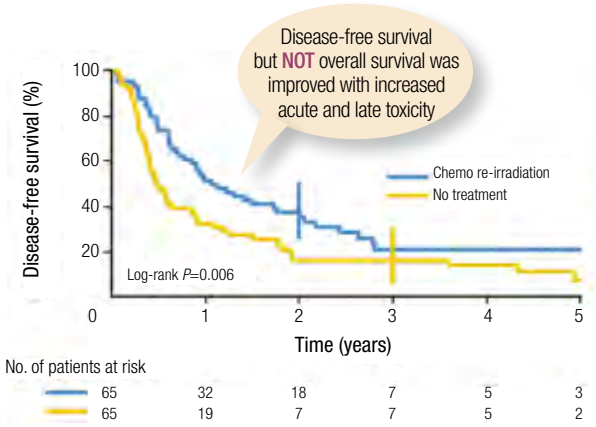
About one half of the patients treated for Stage III and IV disease will develop locoregional relapse or have locally persistent disease.

About one third of the patients treated for earlier stage disease will develop distant metastases.

Locoregional or distant relapses are usually detected in two thirds of cases within the first 2 years after prior treatment.



Postoperative re-irradiation combined with chemotherapy after salvage surgery compared with salvage surgery alone in head and neck carcinomas



Surgery is recommended for resectable recurrent or persistent disease. Adjuvant (radio/chemo) therapy should be considered, if feasible, after local salvage surgery.

If the local recurrence is considered unresectable and the patient did not have prior radiotherapy (RT), then RT with or without systemic therapy is recommended.

For patients not candidates for curative-intent surgery and/or RT, the treatment is the same as for patients with metastatic disease.

For patients with metastatic disease, systemic therapy remains the standard-of-care.

Performance status (PS) at relapse is the strongest predictive factor of clinical outcome.

The main treatment objectives are to prolong survival and/or provide symptom palliation.

Factors associated with clinical outcome in patients with recurrent and/or metastatic squamous cell head and neck cancer

Patient-related
Poor performance status
Presence of comorbidity
Poor cognitive functioning
Lack of social support
Ongoing carcinogen use
Tobacco
Betel quid
Alcohol
Disease-related
Advanced stage, bulky locoregional or metastatic disease
History of aggressive disease
Hypercalcaemia of malignancy
Treatment-related
Prior treatment
Lack of or minimal response to treatment

REVISION QUESTIONS

1. What is the incidence of recurrent and/or metastatic disease?
2. Are surgery and RT used in recurrent disease?
3. Which are the main factors associated with clinical outcome?

Single-agent chemotherapy

Comparison of chemotherapy (ChT) versus supportive care has not been evaluated in well-designed randomised clinical trials.

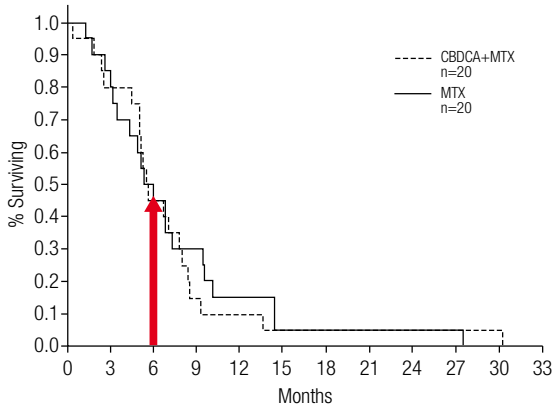
Cisplatin monotherapy versus no treatment resulted in a 10-week median survival prolongation in a small study.

Various chemotherapeutic agents are active as single-agent treatment.

Active single agents in the treatment of recurrent and/or metastatic squamous cell head and neck cancer with response rate >15%

Cisplatin
Carboplatin
5-Fluorouracil
Methotrexate
Vinblastine
Bleomycin
Ifosfamide
Doxorubicin
Cyclophosphamide
Hydroxyurea
Pemetrexed

A comparison of carboplatin plus methotrexate versus methotrexate alone in patients with recurrent and/or metastatic squamous cell head and neck cancer



CBDCA, Carboplatin; MTX, methotrexate.

Single-agent ChT achieves less than 10% response rate and shows no significant survival improvement.

The addition of platinum agents to methotrexate (MTX) is not superior to MTX alone.

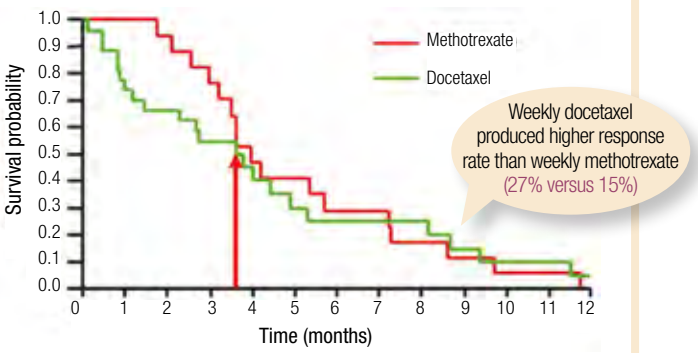
Single-agent cisplatin and MTX are both considered standard-of-care single-agent treatment options.

Paclitaxel and docetaxel have produced responses of 20% to 40% in phase II clinical trials.

There are limited data on paclitaxel compared with docetaxel, as well as between taxanes and other agents.

Taxanes can be used as single-agent treatment in patients with renal dysfunction, for whom cisplatin and MTX are difficult to use.

Comparison of docetaxel versus methotrexate in patients with recurrent squamous cell head and neck cancer



REVISION QUESTIONS

1. Is single-agent ChT or supportive care better?
2. Is there a standard single-agent treatment?
3. What is the therapeutic index of taxanes?

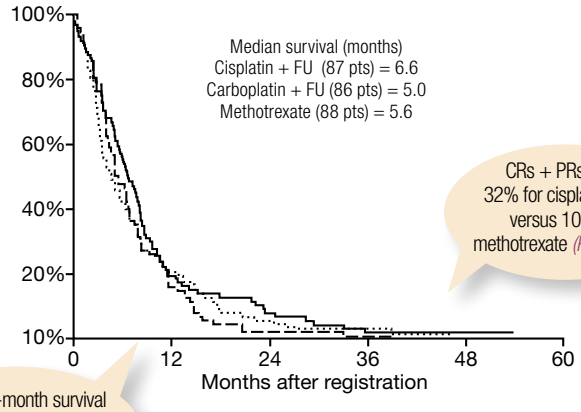
Combination chemotherapy

Combination ChT is associated with higher response rates than single-agent therapy.

Combination ChT has not produced better survival outcomes compared with monotherapy.

Combination chemotherapy is associated with more high-grade toxicity.

Comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate for patients with recurrent and/or metastatic squamous cell head and neck cancer

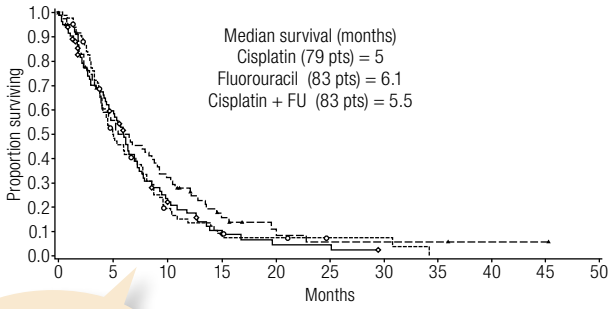


CRs + PRs were 32% for cisplatin + FU versus 10% for methotrexate *(P = 0.001)*

At least 9-month survival was 31% for cisplatin + FU, 30% for carboplatin + FU and 27% for methotrexate

CR, Complete remission; FU, fluorouracil; PR, partial remission.

Comparison of cisplatin and fluorouracil as single agents and in combination for patients with recurrent and/or metastatic squamous cell head and neck cancer



Patients with poorly differentiated tumours and better PS had superior survival

FU, Fluorouracil; PS, performance status.

Cisplatin-based combinations have been compared with single agents in phase III clinical trials.

Cisplatin-fluorouracil combination is considered the standard-of-care reference regimen.

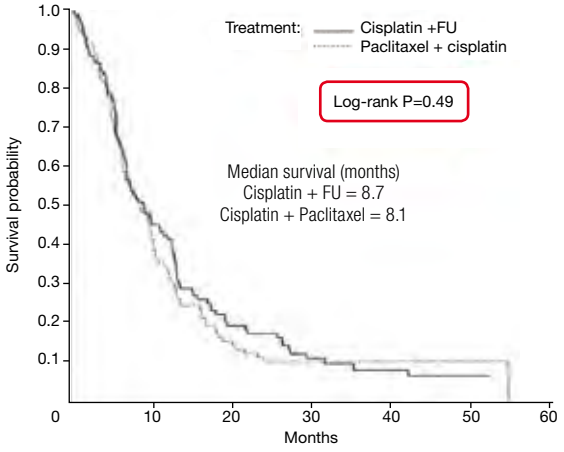
Cisplatin-based combinations have resulted in median survival of 6 to 9 months, and 1-year survival rate of 20% to 40%.

The combination of taxanes with platinum compounds has produced high response rates and median survival of 5–12 months in phase II clinical trials.

Paclitaxel-cisplatin combinations failed to show significant differences regarding response rate and overall survival compared with cisplatin-fluorouracil.

Triple-agent schedules containing a taxane, a platinum compound and other agents (e.g. cetuximab) have given high response rates and promising survival outcomes in phase II trials.

Comparison of cisplatin plus fluorouracil versus cisplatin plus paclitaxel for recurrent and/or metastatic squamous cell head and neck cancer



FU, Fluorouracil.

REVISION QUESTIONS

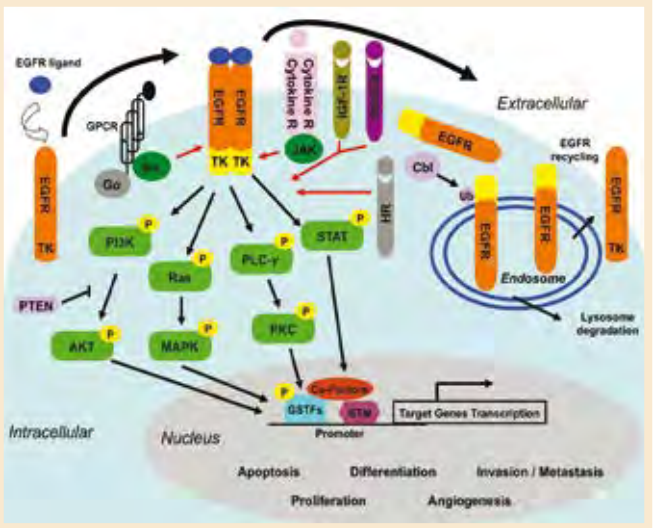
1. Is mono- or polychemotherapy better?
2. What is the clinical benefit of combination ChT?
3. Is there a role for taxanes in combination strategy?

EGFR inhibitors

Epidermal growth factor receptor (EGFR) is over-expressed in 80%–100% of head and neck squamous cell carcinomas.

Increased EGFR expression has been correlated with worse clinical outcome.

EGFR dimerisation causes activation of the receptor-linked tyrosine kinase (TK), recruitment of signalling complexes and phosphorylation (activation) of multiple downstream cascades.



EGFR, Epidermal growth factor receptor; IGF, insulin growth factor; PTEN, phosphatase and tensin homologue; TK, tyrosine kinase.

Phase III studies evaluating EGFR inhibitors in recurrent and/or metastatic squamous cell head and neck cancer

Agent	Treatment	Primary endpoint	Results	Source
Cetuximab	Cisplatin plus cetuximab or placebo	PFS	4.2 versus 2.7 months (*P*=0.07) OS: 9.2 versus 8 months (*P*=0.21)	Burtness et al JCO 2005
Cetuximab	Platinum/5-FU ± cetuximab (Extreme Trial)	OS	10.1 versus 7.4 months (*P*=0.036)	Vermorken et al NEJM 2008
Panitumumab	Cisplatin/5-FU ± panitumumab (Spectrum Trial)	OS	11.1 versus 9 months (*P*=0.14)	Vermorken et al Lancet Oncol 2013
Gefitinib	Gefitinib 250 mg or 500 mg versus methotrexate	OS	5.6 versus 6 versus 6.7 months (*P*=0.12 & 0.39)	Stewart et al JCO 2009
Gefitinib	Docetaxel plus gefitinib 250 mg or placebo	OS	7.3 versus 6 months (*P*=0.60)	Argiris et al JCO 2013

5-FU, 5-Fluorouracil; EGFR, epidermal growth factor receptor; OS, overall survival; PFS, progression-free survival.

EGFR targeting can be done either with monoclonal antibodies targeting the extracellular domain, or with small molecule TK inhibitors (TKIs) targeting the intracellular domain.

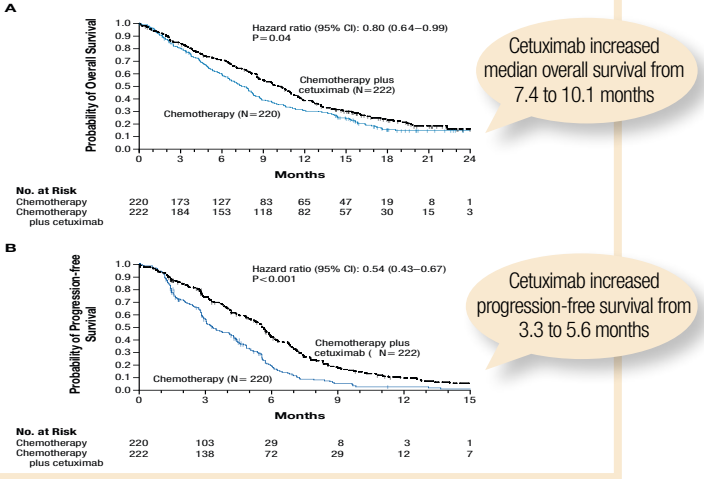
Some phase III clinical trials have been evaluating EGFR inhibitors.

Cetuximab is the only EGFR inhibitor that has shown overall survival benefit.

The addition of cetuximab to cisplatin-fluorouracil ChT is the standard first-line treatment, as it resulted in a 2.7 month increase of median survival and a 2.3 month prolongation of progression-free survival.

Cetuximab-associated Grade 3/4 side effects are skin toxicity, hypomagnesaemia and infusion-related reactions.

Cetuximab 500 mg/m^2 every 2 weeks can be safely administered in combination with ChT, and as maintenance single-agent treatment until disease progresses.



Cetuximab increased median overall survival from 7.4 to 10.1 months

Cetuximab increased progression-free survival from 3.3 to 5.6 months

CI, Confidence interval.

REVISION QUESTIONS

1. What is the role of EGFR in head and neck carcinogenesis?
2. What are the main EGFR-targeting strategies?
3. How has cetuximab changed the treatment landscape?

Second-line therapy

Phase II clinical trials have evaluated various drugs.

Overall, clinical trials showed a response rate up to 20%.

No significant benefit was found regarding response duration, progression-free survival and overall survival.

Activity of selected agents in second-line treatment in recurrent and/or metastatic squamous cell head and neck cancer

Agent	Response rate (%)	Median survival (months)
Paclitaxel	9	8
Docetaxel	11	6.5
Capecitabine	20	7.5
Cetuximab	13	6
Gefitinib	3-11	6-8
Erlotinib	4	6
Sunitinib	3	3.5
Cabazitaxel	0	5
Pembrolizumab	18.5	NR

NR, Not reached.

Major criteria for the selection of second-line treatment in patients with recurrent and/or metastatic squamous cell head and neck cancer

Patient-related
- Poor performance status
- Presence of comorbidity
- Poor cognitive functioning
- Lack of social support

Disease-related
- Bulky locoregional and/or metastatic disease
- Oropharyngeal primary site
- Prior RT
- Tumour differentiation

Treatment-related
- Prior first-line treatment
- Toxicity of previous treatment
- Disease-free interval
- Treatment-free time period

RT, Radiotherapy.

The choice of therapy should be based on patient-related factors, factors related to disease outcome and previous treatments.

Best supportive care is an acceptable treatment option in patients with poor PS.

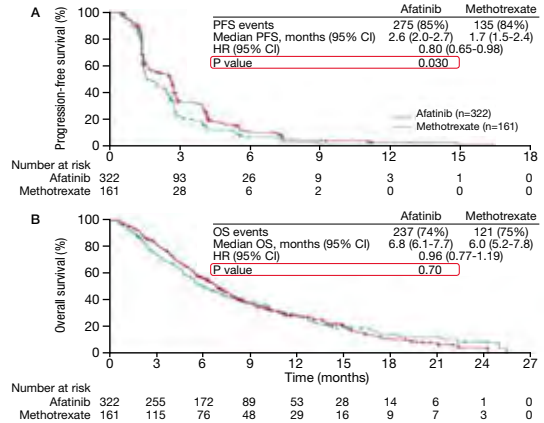
New immunotherapy drugs (anti-PD-1 antibodies) have shown survival benefit in second-line treatment and represent a standard-of-care option.

EGFR TKIs (gefitinib) have been tested in phase III clinical trials in patients after platinum failure, with discouraging results.

Afatinib (a new oral irreversible ERBB-receptor family blocker) has improved progression-free survival compared with methotrexate.

Various novel agents are being evaluated in this clinical setting.

Afatinib versus methotrexate as second-line treatment in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck



CI, Confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

REVISION QUESTIONS

1. What is the standard-of-care second-line treatment?
2. What are the factors that govern treatment decisions?
3. Are there new effective agents?

Summary: Treatment of recurrent or metastatic disease

- Locoregional relapses and/or distant metastases are frequent in head and neck cancer patients
- Locoregional or distant relapses are usually detected in two thirds of cases within the first 2 years after prior treatment
- The main treatment objectives in this patient group are to prolong survival and/or provide symptom palliation
- Recurrent disease after multimodal local treatment is generally considered incurable if the patient cannot be salvaged by surgery and/or additional RT
- PS predicts patients' clinical outcome
- Platinum-based ChT in combination with cetuximab is considered the standard-of-care in fit patients
- Cisplatin, methotrexate and taxanes can be used as single-agent treatment
- Combination ChT has not produced better survival outcomes compared with single-agent treatment
- Anti-PD-1 immunotherapy drugs represent a standard-of-care second-line treatment
- Based on the improvement in knowledge of squamous cell head and neck cancer molecular biology, new compounds are currently being investigated

Further Reading

Argiris A, Ghebremichael M, Gilbert J, et al. Phase III randomized, placebo-controlled trial of docetaxel with or without gefitinib in recurrent or metastatic head and neck cancer: an Eastern Cooperative Oncology Group trial. J Clin Oncol 2013; 31:1405–1414.

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Urba S, van Herpen CM, Sahoo TP, et al. Pemetrexed in combination with cisplatin versus cisplatin monotherapy in patients with recurrent or metastatic head and neck cancer: final results of a randomized, double-blind, placebo-controlled, phase 3 study. Cancer 2012; 118:4694–4705.

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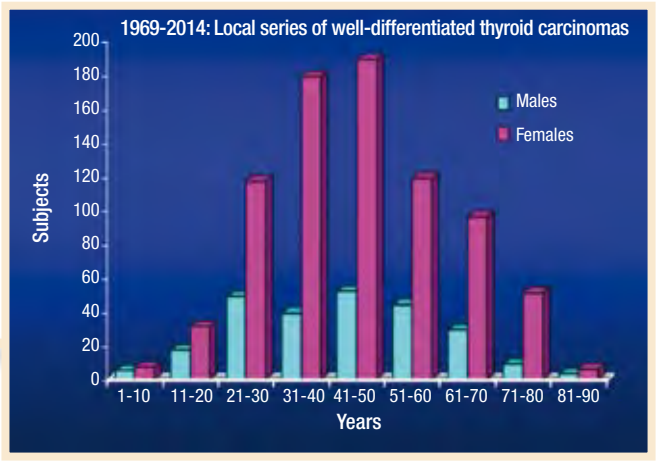
Thyroid carcinomas

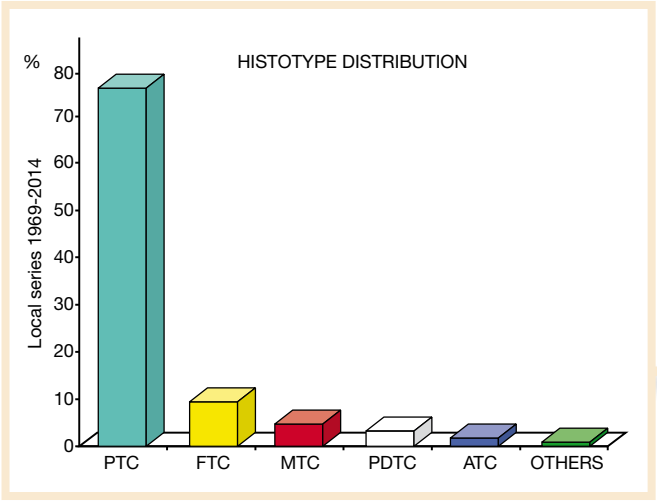
Epidemiology and pathogenesis

Thyroid carcinomas (TCs) are rare (3.6% of all human tumours) but are the most frequent endocrine malignancies. Their incidence has been growing in the last decades.

This increased incidence is essentially due to the detection of small carcinomas, <1 cm, likely to be a consequence of the wide use of neck ultrasound (US).

Female/male ratio is 4/1; the median age at diagnosis is 45–50 years; children are rarely affected. The only risk factor recognised so far is exposure to ionising radiation.





ATC, Anaplastic thyroid carcinoma; FTC, follicular thyroid carcinoma; MTC, medullary thyroid carcinoma; PDTC, poorly differentiated thyroid carcinoma; PTC, papillary thyroid carcinoma.

TCs are classified as: (1) well differentiated (DTC); (2) poorly differentiated (PDTC); (3) anaplastic (ATC); (4) medullary (MTC); (5) other non-epithelial.

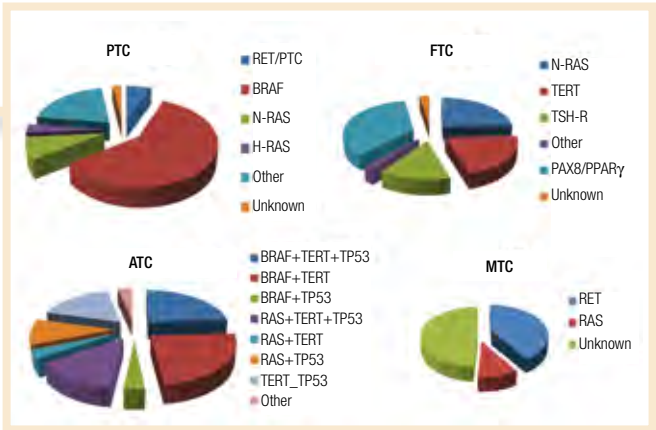
DTC, PDTC and ATC originate from follicular cells and the degree of differentiation is related to the ability to produce thyroglobulin, take up iodine and respond to thyroid stimulating hormone (TSH).

DTC are the most frequent and are categorised into papillary (PTC, 80%) and follicular (FTC, 10%). PDTC, ATC and MTC are rare (5%, 2% and 5%–7%, respectively).

The most frequent oncogenic alterations in PTC are *RET/PTC* rearrangements (20%) and *BRAFV600E* mutation (45%). Other rarer alterations have recently been found.

The most frequent oncogenic alterations in PDTC and ATC are *p53* and *TERT* promoter point mutations. Other oncogenic alterations have been described.

The most frequent oncogenic alterations in MTC are *RET* activating point mutations, which are found as germinal in hereditary cases, and somatic in sporadic cases.



ATC, Anaplastic thyroid carcinoma; FTC, follicular thyroid carcinoma; MTC, medullary thyroid carcinoma; PTC, papillary thyroid carcinoma.

REVISION QUESTIONS

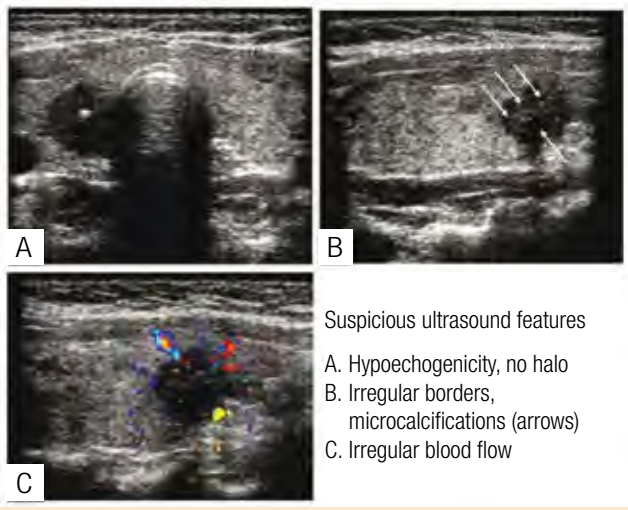
1. How frequent are TCs?
2. Which is the most frequent histotype?
3. What is the most frequent oncogenic alteration in ATC?

Clinical presentation; prognosis

In the majority of cases, TC presentation is a single thyroid nodule or a nodule in the context of a multinodular goitre identified by neck palpation or US.

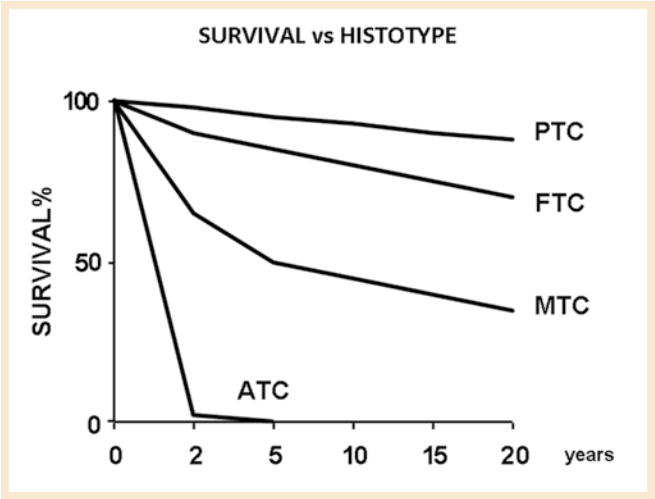
Only 5% of thyroid nodules are malignant. These latter have peculiar US features, but the diagnosis of malignancy is performed by fine needle aspiration.

No presurgical serum markers are known for DTC, PDTC and ATC, while elevated levels of pre-surgical serum calcitonin (Ct) are diagnostic of MTC.



Suspicious ultrasound features

A. Hypoechogenicity, no halo
B. Irregular borders, microcalcifications (arrows)
C. Irregular blood flow



ATC, Anaplastic thyroid carcinoma; FTC, follicular thyroid carcinoma; MTC, medullary thyroid carcinoma; PTC, papillary thyroid carcinoma.

The prognosis of TC is correlated with the degree of differentiation: while PTC and FTC patients are long survivors, ATC patients rarely survive >6 months.

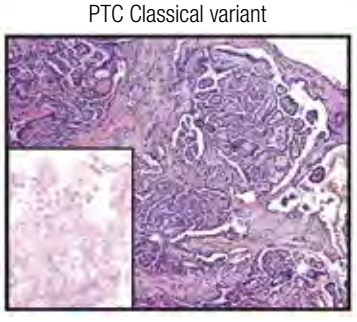
At multivariate analysis, the poor prognostic factors for both survival and recurrence are either an advanced age (>65) or stage (Stage III and IV) at diagnosis.

The prognosis of MTC, either when sporadic or familial, is greatly dependent on the stage at diagnosis, and definitive cure can be obtained only if intrathyroidal.

Among PTCs, the histological variant also plays a prognostic role: the follicular variant is the “good”, the classical is the “bad” and the tall cells is the “ugly”.

Controversial data are reported on the prognostic role of *BRAFV600E* mutation, which is, indeed, more frequent in the tall cell variant and older patients.

A bad prognostic role in terms of both recurrence and survival is recognised for somatic *RET* point mutations in sporadic MTC, particularly for the *M918T RET* mutation.



PTC Variants:
a. Classical
b. Follicular
c. Tall cells
} Most frequent

d. Solid
e. Sclerosing
f. Columnar
g. Warthin like
} Rare

PTC, Papillary thyroid carcinoma.

REVISION QUESTIONS

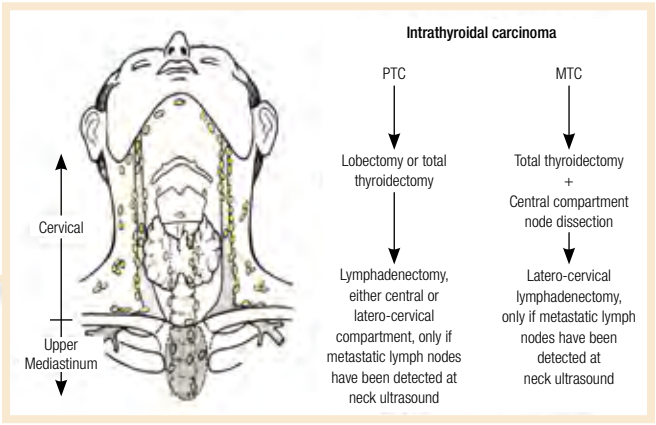
1. Which diagnostic tool is able to identify TC in a nodule?
2. Is the prognosis for ATC as good as for DTC?
3. Why is it important to know the histological variant of a PTC?

Initial treatment

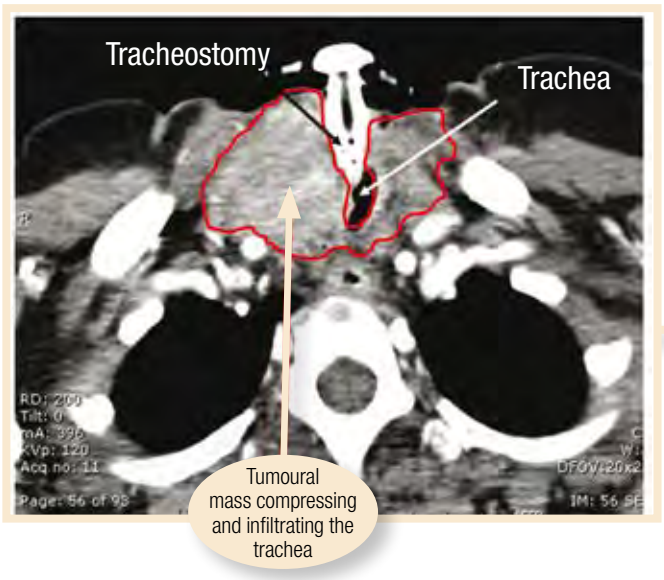
According to the recent publication of the international guidelines for the treatment of TC, surgery can be either a hemithyroidectomy (or lobectomy [LB]) or a total thyroidectomy (TTx).

Prophylactic node dissection is not indicated in DTC. Lymph node surgery, either of the central or lateral compartments, is due if US shows node metastases.

If MTC is diagnosed before surgery, TTx and prophylactic central neck node dissection are always indicated.



MTC, Medullary thyroid carcinoma; PTC, papillary thyroid carcinoma.

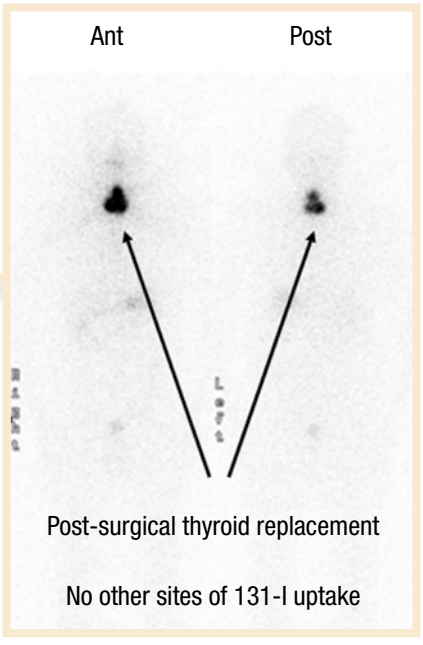


Surgical complications of LB or TTx that must be taken into consideration are vocal cord palsy and hypoparathyroidism, both of which can be transient or permanent.

PDTC and ATC are usually locally very advanced with infiltration of other neck structures, which makes surgery rarely complete. R2 debulking is still useful.

Tracheal compression or infiltration may require a tracheostomy or, whenever possible, an endotracheal stent or laser treatment of the infiltrating tissue.

After TTx, DTC with an intermediate or high risk of recurrence should be treated with radioiodine (131-I), after stimulation with recombinant TSH. A post 131-I whole body scan (WBS) will show the sites of iodine uptake.



PDTC and ATC patients with local infiltration should be locally treated with external radiotherapy, with palliative intent.

131-I therapy does not play any role in MTCs since they derive from parafollicular C cells, which have a neuroendocrine origin and are not able to take up iodine.

REVISION QUESTIONS

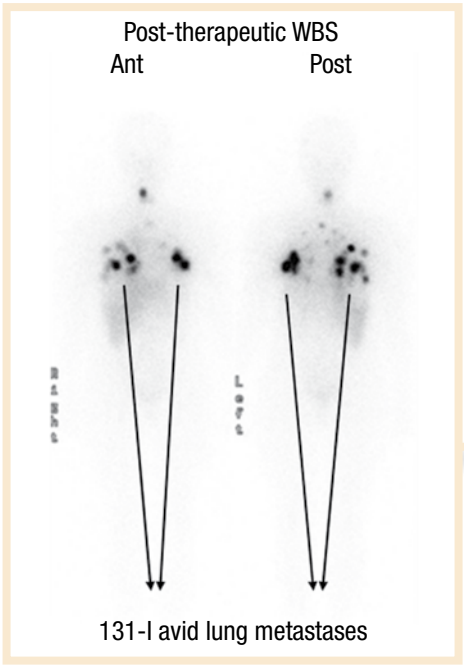
1. What is the initial surgical treatment of DTC?
2. Is prophylactic node dissection always indicated in DTC and MTC?
3. Why can MTC not be treated with 131-I?

Follow-up

The follow-up of DTC and MTC is based on the periodical measurement of thyroglobulin (Tg) plus its autoantibodies (TgAb) and Ct, respectively, associated with neck US.

DTC patients treated with TTx and 131-I will likely have low or undetectable serum Tg, and the patient will be considered as "cured" if neck US is also negative.

DTC patients treated with LB or TTx but not 131-I will likely have detectable serum Tg: the trend of increase, decrease or stabilisation will be considered thereafter.

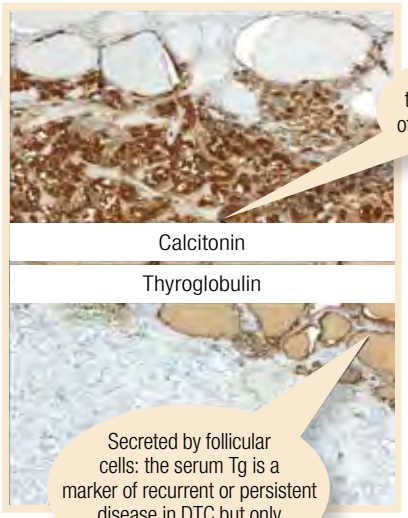


WBS, Whole body scan.

MTC patients with a postoperative undetectable basal or stimulated serum Ct have a risk of recurrence of 10% and 3%, respectively. Neck US should also be performed.

Patients with a post-TTx serum Ct detectable but <150 pg/ml are rarely positive at conventional imaging, but these patients must be monitored every 6–12 months.

Neck US, computed tomography (CT) scan of the chest, and magnetic resonance imaging (MRI) of the liver and brain are indicated to check the possible sites of metastasis in MTC patients with high levels of Ct.

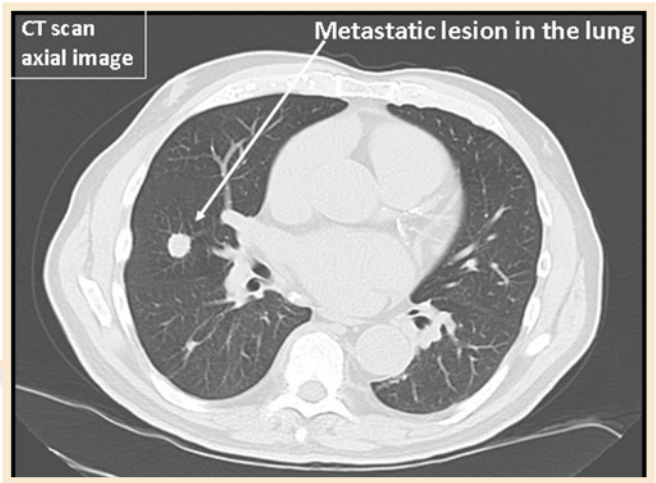


Ct, Calcitonin; DTC, differentiated thyroid carcinoma; MTC, medullary thyroid carcinoma; Tg, thyroglobulin

Biochemical, clinical and US monitoring should be performed in DTC patients: every 18 months in patients considered as cured, more frequently (6–12 months) if biochemical evidence (detectable levels of serum Tg) or evidence of metastatic lesions at imaging is still present.

If necessary, 131-I treatment can be repeated, at least until there is evidence of clinical benefit and evidence of lesions still able to take up 131-I.

When a post-131-I WBS is negative, and the possibility of iodine contamination can be excluded, no more 131-I treatments should be administered.



CT, Computed tomography.

REVISION QUESTIONS

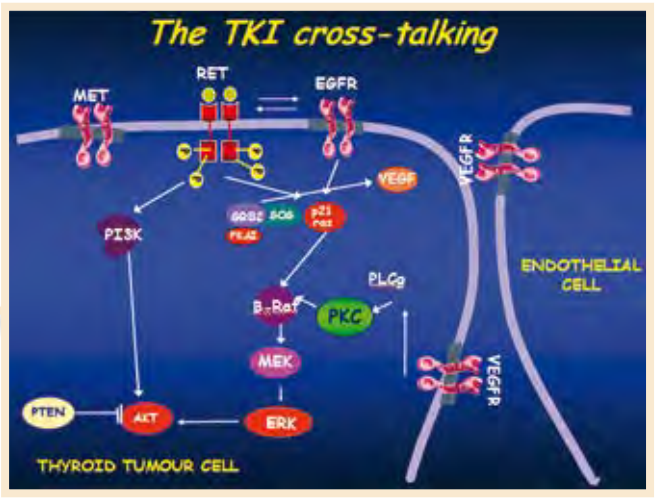
1. What are the post-surgical serum markers for DTC and MTC?
2. What should you do if the serum level of Tg suggests persistence of disease in DTC?
3. What is the risk of recurrence in MTC patients with an undetectable level of basal Ct?

Treatment of advanced cases

Radioiodine-refractory advanced and progressive DTC were orphan of any therapy until a few years ago. Chemotherapy (mainly doxorubicin) was ineffective.

Similarly, no chemotherapy has been shown to be effective in advanced and symptomatic MTCs, which, moreover, cannot be treated with 131-I due to their nature.

RET, RAS and *BRAF* mutations represent the major rationale for treatment of advanced DTC and MTC with tyrosine kinase inhibitors (TKIs) targeted against these activated receptors.



TKI, Tyrosine kinase inhibitor.

DRUG (Reference)	TC	PTS (n)	PR (%)	SD >6 months	PFS (median months)	AE >30% of patients
Vandetanib (Wells et al 2012)	MTC	331	45	87	ne	Diarrhoea Skin rash Nausea Hypertension
Cabozantinib (Elisei et al 2013)	MTC	330	28	ne	11.2	Diarrhoea H-F syndrome Weight loss Anorexia Nausea Fatigue
Sorafenib (Brose et al 2013)	DTC	417	12.2	42	10.8	H-F syndrome Alopecia Skin rash Fatigue Weight loss Hypertension Anorexia
Lenvatinib (Schlumberger et al 2015)	DTC	392	64.8	29.8	18.3	Hypertension Diarrhoea Anorexia Weight loss Nausea Stomatitis

AE, Adverse event; DTC, well-differentiated thyroid carcinoma; H-F, hand and foot; MTC, medullary thyroid carcinoma; PFS, progression-free survival; PR, partial remission; PTS, patients; SD, stable disease; TC, thyroid carcinoma.

Sorafenib and lenvatinib have been investigated in advanced DTC in phase III studies: the primary end point was progression-free survival (PFS) in patients treated with drug versus placebo.

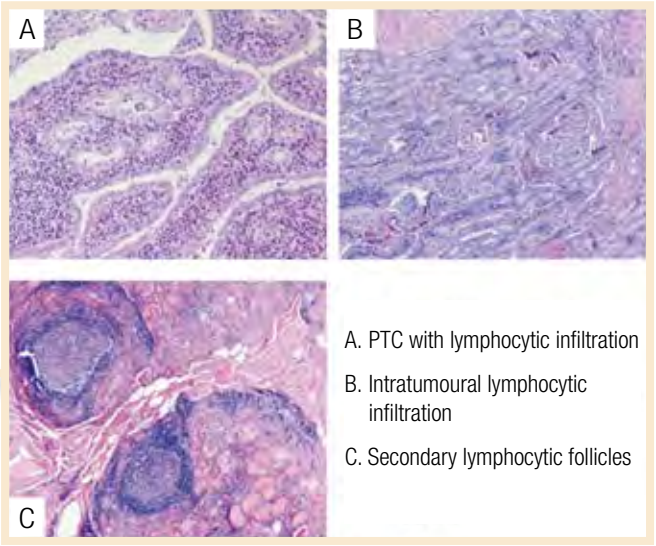
Similarly, vandetanib and cabozantinib have been studied in advanced/progressive MTC. In these studies also, the primary endpoint was PFS in the 2 arms.

The 4 studies demonstrated a significant increase of PFS in patients treated with the drugs. After these studies sorafenib and lenvatinib, as well as vandetanib and cabozantinib, were approved for advanced/progressive DTC and MTC, respectively.

ATCs are still orphan of any drug and are almost invariably lethal. In the near future a phase II/III study with lenvatinib should start in several countries.

Other therapeutic strategies are under evaluation, such as the use of selumetinib, a MEK inhibitor, to re-induce the lost ability to take up 131-I.

Immunotherapies, used alone or in combination with lenvatinib, are under consideration on the basis of the frequent association of TC with lymphocytic infiltration.



PTC, Papillary thyroid carcinoma.

REVISION QUESTIONS

1. What is the rationale for the use of TKIs in TC?
2. Have some TKIs been approved for the treatment of advanced DTC and MTC?
3. Which other therapeutic strategies are under investigation?

Summary: Thyroid carcinomas

- TC is a rare malignancy but its occurrence is still increasing worldwide
- Females are affected 4 times more often than males, and ionising radiation exposure is the only well recognised risk factor
- No presurgical serum markers are known for DTC, while high levels of serum Ct are diagnostic of MTC
- The most common oncogenic alterations are *BRAFV600E* and *RET/PTC* rearrangements in DTC, and *RET* point mutations in MTC
- The prognostic factors for both recurrence and survival are advanced age and/or an advanced stage at diagnosis
- Thyroidectomy is the initial treatment of thyroid carcinoma. Lymphadenectomy should be performed only if there is evidence of metastatic lesions at neck US
- 131-I treatment is performed in DTC cases with an intermediate or high risk of recurrence, while it cannot be used in MTC or in ATC
- DTC and MTC patients can be followed by measuring serum Tg and Ct, respectively. Neck US is fundamental in their follow-up
- New targeted therapies have recently been approved for the treatment of advanced and progressive DTC and MTC
- ATC is still orphan of successful therapies, and are still lethal

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B

More advanced knowledge

9 Nasopharyngeal carcinoma

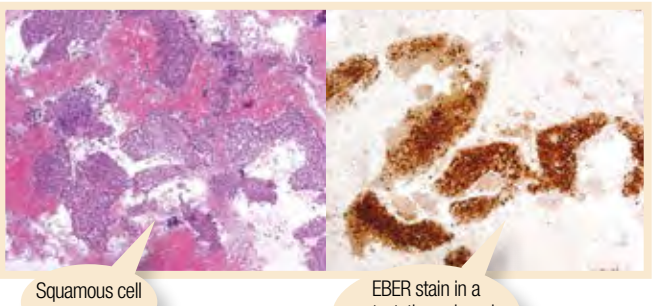
Histology; key physical signs; staging

Histology

Squamous cell carcinoma may be found in low-incidence populations (Western Europe) related to smoking, with less favourable prognosis than keratinising carcinoma.

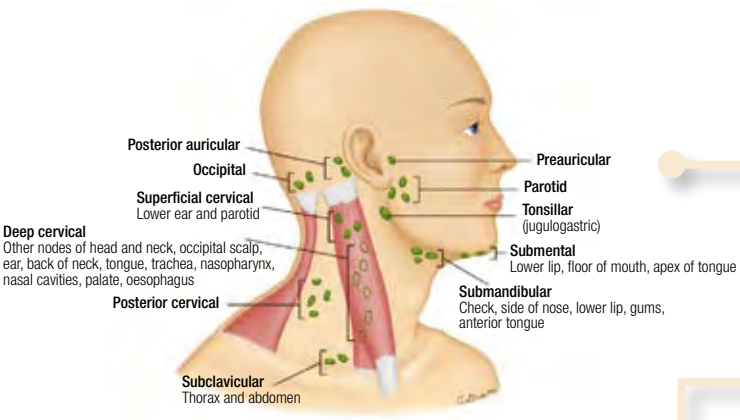
Non-keratinising carcinoma predominates in intermediate-incidence/endemic regions (Mediterranean basin, South-east Asia), consistently associated with Epstein-Barr virus (EBV).

EBV-based diagnostic tools for nasopharyngeal carcinoma (NPC): in tissue (e.g. EBER stain in a metastatic neck node) and in blood (e.g. EBV DNA and EBV antibodies).

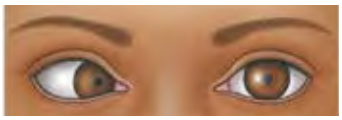


NPC, Nasopharyngeal carcinoma.

Lymph nodes of the head and neck



Left VI cranial nerve palsy



Physical signs

Cervical lymphadenopathy (common):
Proceed from upper (N1, 2) to lower (N3) neck direction. Retropharyngeal nodal metastases (N1) detection requires magnetic resonance imaging (MRI). Determine prognosis and therapy decision.

Cranial nerve palsy (uncommon):
Confers T4 stage. V and VI nerves most commonly involved. Coronal MRI shows nasopharynx tumour extending superiorly to left cavernous sinus (CS), causing V and VI nerve palsies.

Work-up & staging

Consider MRI of nasopharynx and neck.
Metastatic screening: positron emission tomography (PET) scan may be considered for locoregionally advanced disease (e.g. N3).
Dental assessment: ear, nose and throat (ENT) assessment (need for intervention of middle ear effusion); nutritional assessment.

Stage I	Stage II
T = nasal, oropharyngeal N = nil	T = parapharyngeal N = one side upper-mid neck
Stage III	**Stage IVA**
T = skull base N = both sides upper-mid neck	T = intracranial, cranial nerves N = lower neck or >6 cm

REVISION QUESTIONS

1. What is the application of EBV-based blood markers in the management of NPC?
2. What is the pattern of lymph node metastases in NPC and how is this reflected by the staging?
3. Cranial nerve palsies can be one of the presenting symptoms of NPC. Which are the most commonly involved cranial nerves?

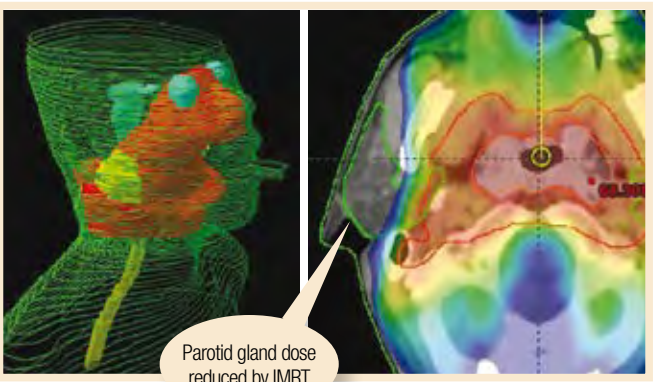
Treatment

Stage I, II disease

Radiotherapy (RT) alone. Role of concurrent chemotherapy (ChT) for Stage II is optional.

RT directed to nasopharynx, skull base, cervical lymphatics on both sides (lower neck spared for N0 cases).

Delivered as intensity-modulated RT (IMRT): helps to reduce parotid irradiation (hence less xerostomia) and improve tumour target coverage. Meticulous delineation of targets and margins is essential. Dose: 70 Gy, although a lower dose level of 66 Gy was also used in the pre-IMRT era.



IMRT, Intensity-modulated radiotherapy.

Stage III, IVA disease

Concurrent chemotherapy with radiotherapy:

E.g. 3-weekly schedule (cisplatin 100 mg/m^2 on d1, 22, 43)

E.g. Weekly schedule (cisplatin 40 mg/m^2 weekly from d1, for 6–8 cycles)

Neoadjuvant ChT is not a standard treatment; it may be considered for locally advanced tumours encroaching on vital organs (optic chiasm, brainstem) to aim for a debulking effect, facilitating RT planning. Usually 3 courses are given with cisplatin-based ChT.

Adjuvant ChT (cisplatin 80 mg/m^2 d1, 5-fluorouracil infusion 1 g/m^2 d1, 2, 3, 4 for 3 cycles) following concurrent chemoradiation is controversial. May apply only to high-risk group defined by biomarker (EBV DNA): studies are ongoing.

Stage IVB (M1) disease

Palliative ChT is considered, and RT may also be considered for locoregional disease and oligometastases.

REVISION QUESTIONS

1. What is the recommended treatment for Stage I-II NPC?
2. What is the recommended treatment for Stage III-IV NPC?
3. What is the benefit of using the IMRT mode of RT, compared to conventional RT, in the treatment of NPC?

Follow-up; outcome; recurrence

Follow-up

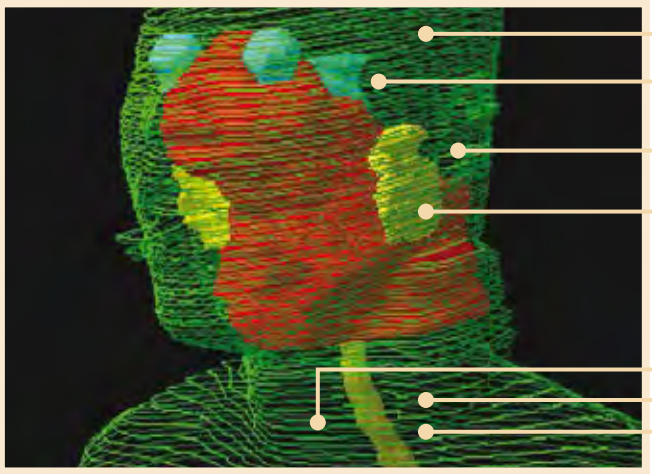
Nasopharyngoscopy and biopsy (possible false-positive biopsy before 12 weeks).

Follow-up should be more frequent in the first years post-therapy, e.g. every 3–4 months.

MRI in the early (e.g. <6 month) period may be difficult to interpret (residual thickening and small nodes at the originally affected sites). PET scan, if considered, should be performed no earlier than 3 months post-therapy.

A persistently detectable EBV DNA level after therapy strongly correlates with recurrence.

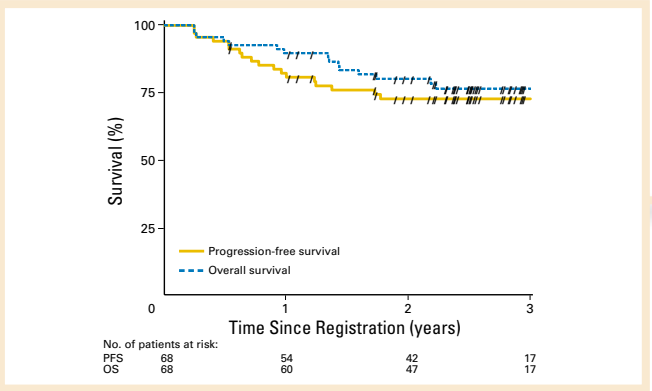
Possible long-term effects of radiotherapy



Outcome

Prognosis is more favourable than for other head and neck cancers of corresponding stage. Overall local control rates are >85%, and the main challenge is distant failure.

Clinical stage	Number of patients	5-Year disease specific survival
I	51	100.0
II	214	96.4
III	413	82.7
IVA	190	70.4



OS, Overall survival; PFS, progression-free survival.

Recurrence

Treatment of local recurrence: More options for limited recurrence (nasopharyngectomy, brachytherapy, stereotactic RT [SRT], or combinations). Some skull base recurrence can be treated by SRT, IMRT.

Treatment of distant failure: palliative ChT. A small subset of patients with oligometastases, especially if intrathoracic or limited skeletal, may have long survival.

REVISION QUESTIONS

1. What is the treatment outcome expected for EBV-associated NPC?
2. What are the common long-term side effects of RT for NPC?
3. If a patient complains of unexplained fatigue on follow-up of previously treated NPC, what treatment-related complication should be considered?

Summary: Nasopharyngeal carcinoma

- In low-incidence areas, the well-differentiated histology is common; undifferentiated carcinoma is prevalent in high-incidence regions, and associated with EBV
- The close association of EBV with cancer is exploited to develop diagnostic tools based on detection of EBV material, such as in tissue (e.g. EBER) or in blood (e.g. EBV DNA, EBV antibodies)
- Currently the most important application of tumour markers is using EBV DNA in blood to detect residual disease after therapy and recurrent disease on follow-up
- Enlarged neck nodes, typically in the upper neck, are a common presenting symptom of NPC. Cranial nerve palsies, usually of the V and VI nerves, are an uncommon presenting symptom
- MRI of the head and neck is an important staging tool
- IMRT is the mainstay of therapy, its main advantages being to minimise parotid irradiation and provide better coverage of the tumour target
- For locoregionally advanced disease (Stage III to IVA), concurrent ChT is added. For Stage II disease, this is optional
- The role of adjuvant ChT after concurrent ChT is controversial
- The role of neoadjuvant ChT is considered investigational. It may be applied in specific cases where advanced stage tumours pose complications related to RT
- Therapy outcome, especially of the undifferentiated type, is much more favourable compared with other head and neck cancers of similar stages, with 5-year survival rates around 80%–95% for Stage I-II disease, and 60%–80% for Stage III-IV

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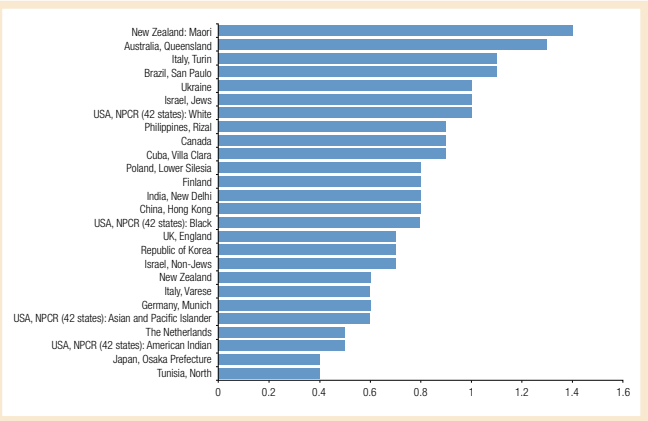
10 Salivary gland tumours

Epidemiology and histopathology

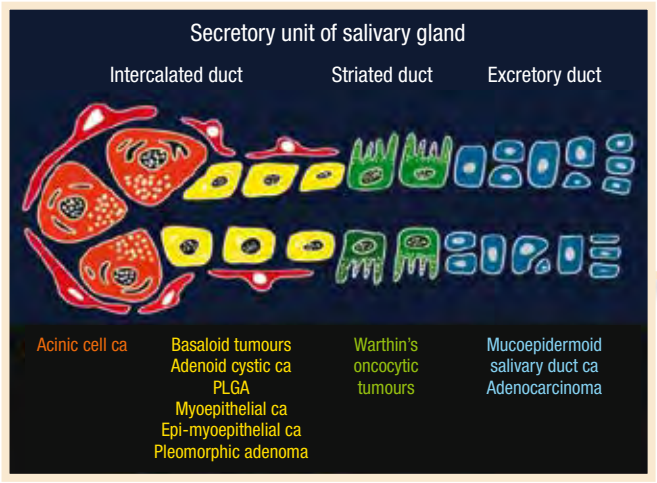
Salivary gland cancers (SGCs) are rare epithelial tumours. Worldwide annual incidence varies between <0.05 and 4 per 100 000, with an incidence of 1.2 per 100 000 in European countries. Paediatric cases are very uncommon, with an incidence of 0.8–1.4 per million in the population under 20 years old.

They are most common in the 6th-7th decades of life. Age, previous irradiation and pleomorphic adenoma diagnosed at a younger age may be related to SGC development.

Major salivary gland cancer incidence rates (age-adjusted) in several world male populations (2003-2007)



NPCR, National Program of Cancer Registries.



Ca, Cancer; PLGA, polymorphous low-grade adenocarcinoma.

Salivary glands comprise 3 pairs of major salivary glands – the parotid, the submandibular and the sublingual – and from 450 to 750 glandular structures, distributed throughout the whole head and neck region and the upper aerodigestive tract. Based on their morphology and mucous production, the latter are defined as minor salivary glands.

The new edition of the World Health Organisation (WHO) classification (2017) includes more than 20 malignant histotypes, each one characterised by a different morphology, histological grading, immunoprofile and outcome.

Mucoepidermoid carcinoma (MEC) is the most common subtype. It comprises low- (LG), intermediate- (IG) and high-grade carcinomas, the latter having the worst outcome. *CRTC1-MAML2* gene fusion is reported to have prognostic significance, but this is still controversial.

Adenoid cystic carcinoma (ACC) is an aggressive and slow-growing cancer. It is constituted of epithelial and myoepithelial cells in variable proportion, resulting in tubular, cribriform and solid growth patterns. *MYB-NFIB* fusion gene is found in about 80% of cases; its prognostic role is still currently unclear.

Malignant tumours	
Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/3
Acinic cell carcinoma	8550/3
Polymorphous adenocarcinoma	8525/3
Clear cell carcinoma	8310/3
Basal cell adenocarcinoma	8147/3
Intraductal carcinoma	8500/2
Adenocarcinoma, NOS	8140/3
Salivary duct carcinoma	8500/3
Myoepithelial carcinoma	8982/3
Epithelial-myoepithelial carcinoma	8562/3
Carcinoma ex pleomorphic adenoma	8941/3
Secretory carcinoma	8502/3
Sebaceous adenocarcinoma	8410/3
Carcinosarcoma	8980/3
Poorly differentiated carcinoma	
Undifferentiated carcinoma	8020/3
Large cell neuroendocrine carcinoma	8013/3
Small cell neuroendocrine carcinoma	8041/3
Lymphoepithelial carcinoma	8082/3
Squamous cell carcinoma	8070/3
Oncocytic carcinoma	8290/3
Uncertain malignant potential	
Sialoblastoma	8974/1

ICD-O: International Classification of Disease for Oncology; behaviour is coded /0 for benign tumours; /1 for unspecified, borderline or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia;/ 3 for malignant tumours.

REVISION QUESTIONS

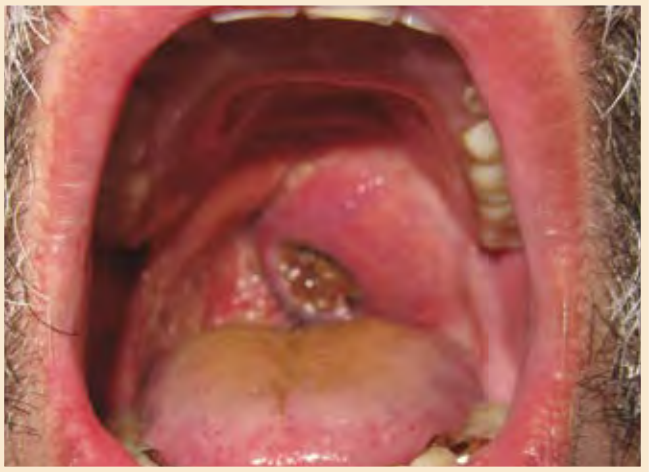
1. What is the incidence of SGCs worldwide?
2. How numerous are the salivary glands?
3. How many malignant epithelial histotypes are reported in the WHO classification?

Clinical presentation and diagnosis

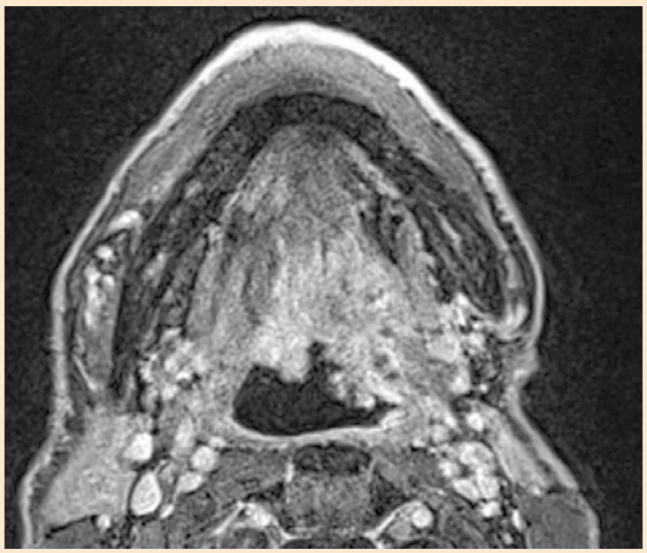
Malignancies of the major salivary glands may be clinically indistinguishable from benign tumours. The rate of malignancy increases with the reduction of gland dimension, being about 25% in parotid, 50% in submandibular and 80% in sublingual glands.

Minor SGCs arise more often in the hard palate, nasal cavity and paranasal sinuses; masses are malignant in more than 50% of cases. Typical presentation is an asymptomatic submucosal mass.

Adenocarcinoma, not otherwise specified of the hard palate



Adenoid cystic carcinoma of the tongue base, investigated by magnetic resonance imaging



Fine needle aspiration (FNA) has good accuracy (87% to 96%) for diagnosis. Open biopsy is not recommended because of the risk of seeding.

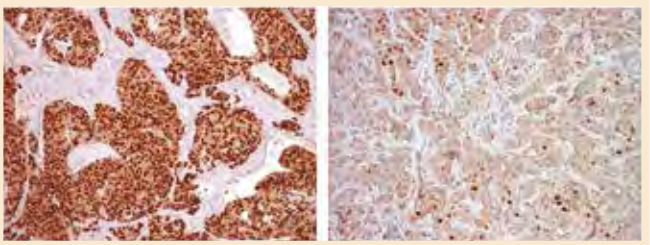
Magnetic resonance imaging (MRI) is indicated in case of (1) larger tumours (>4 cm); (2) involvement of deep lobe of parotid; (3) minor SGCs of the head and neck region. Whole body computed tomography (CT) scan or positron emission tomography (PET)/CT may be indicated in advanced stage and high-grade tumours. Thorax CT scan may be useful in locally advanced ACC.

Molecular and immunohistochemical analyses can be useful in cases of uncertain diagnosis.

MYB-NFIB gene fusion and wild-type *c-kit* are reported in about 80% of ACC; *MALM2-CRTC1* is associated with IG- and LG-MEC; *ETV6-NTRK3* fusion gene has been reported in the mammary analogue secretory carcinoma, as well as *EWSR* rearrangements. Androgen receptor (AR) and HER2 overexpression are typically found in salivary duct carcinoma (SDC).

A positive immunoreactivity for AR

AR-negative immunoreaction



AR, Androgen receptor.

REVISION QUESTIONS

1. What is the role of FNA in the diagnostic work-up?
2. Is a skilled pathologist recommended?
3. Can molecular and immunohistochemical analyses contribute to diagnosis?

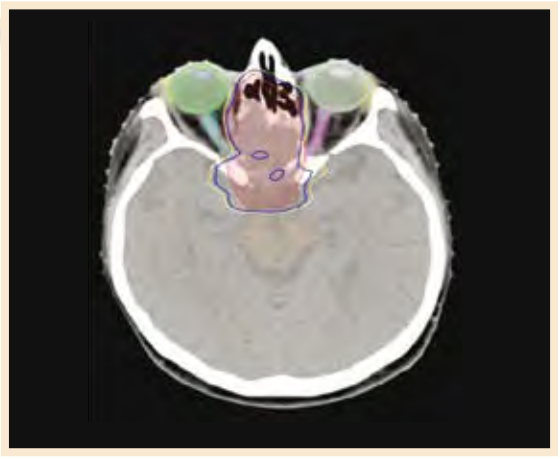
Treatment and prognosis

Radical surgery is the main treatment, followed by radiotherapy (RT) in cases of high-grade malignancies, close margins, high T stage, perineural invasion and lymph node metastases.

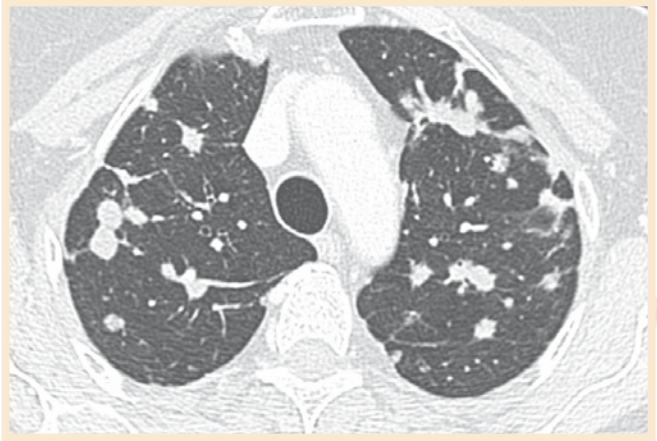
RT alone is reserved for unresectable disease. Intensity-modulated RT (IMRT) plus carbon ion boost seems to increase local control, progression-free survival (PFS) and overall survival (OS) in ACC.

Data on the efficacy of combined chemoradiotherapy in the postoperative setting and as exclusive treatment are limited.

Adenoid cystic carcinoma of ethmoid sinus (Stage T4b) treated by Volumetric Modulated Arc Therapy (VMAT) with a dose of 72 Gy. Red line: high risk target volume; Yellow line: 72 Gy; Blue line: 65 Gy



Bilateral lung metastases from adenoid cystic carcinoma



Locoregional recurrence occurs in 16%–85% of cases. It can be managed with further surgery and/or RT only in very selected cases. Re-irradiation with carbon ion therapy could play a role in this setting.

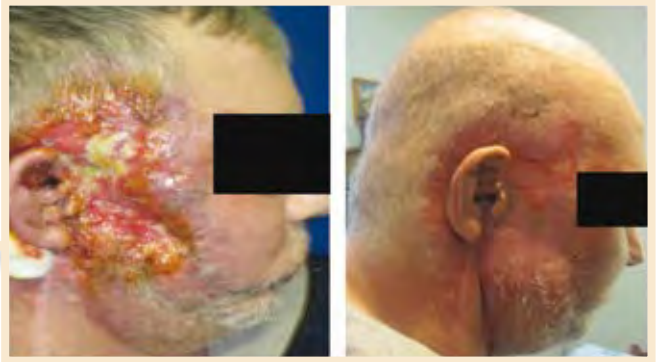
Distant metastases are the principal cause of failure, being diagnosed in 25%–55% of patients. Only 20% of patients with distant metastases are alive at 5 years.

Platinum-based chemotherapy (ChT) is recommended in metastatic patients; cisplatin plus doxorubicin has shown a higher activity with more toxicity. Single-agent ChT has demonstrated a 10%–20% response rate. No advantage for ChT has yet been demonstrated on OS.

Complete androgen blockade may be beneficial in AR-expressing cases; anti-HER2 monoclonal antibodies could be useful in HER2 3+ cases.

Several molecular-driven therapies as well as antiangiogenic compounds are currently under investigation.

Locoregional relapse of an AR-expressing salivary duct cancer: before (left) and two months after complete androgen blockade (right)



AR, Androgen receptor.

REVISION QUESTIONS

1. When is a combination of surgery and RT indicated?
2. What is the role of carbon ion radiotherapy?
3. What is the role of ChT?

Summary: Salivary gland tumours

- Salivary gland tumours are a rare and heterogeneous group of epithelial malignancies that should be managed only in referral centres
- FNA combined with ultrasound is the best tool for diagnosis
- More than 20 malignant tumours are listed in the updated WHO classification; almost every histotype is characterised by a specific immunohistochemical profile rather than a peculiar clinical history
- A skilled pathologist is needed for pathological diagnosis; a second pathological opinion in a referral centre is recommended if the diagnosis has been performed in low-volume head and neck cancer institutes
- Surgery is the mainstay of treatment both in major and minor salivary gland tumours
- Surgery plus adjuvant RT is recommended in high-grade tumours and in cases of high-risk pathological features
- RT alone is recommended in unresectable tumours; heavy-ion RT could have a role in ACC
- Retreatment by surgery or RT should always be considered in cases of locoregional relapse
- ChT is delivered in cases of systemic disease, although an improvement in PFS or OS has never been proven
- New compounds (e.g. antiangiogenic agents) are under investigation, and a randomised phase II trial (EORTC 1206) is currently ongoing to test the superiority of androgen blockade versus ChT in metastatic AR-expressing salivary gland tumours

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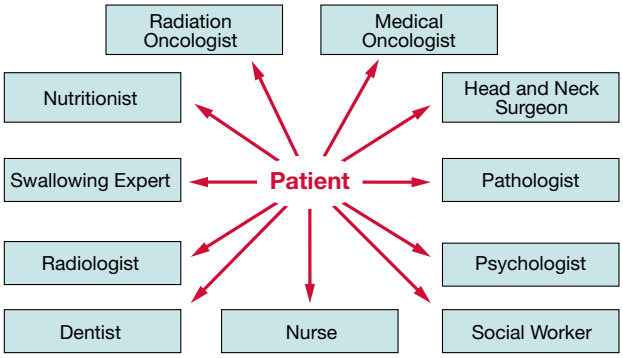
11 Individualised supportive care before and during curative treatment of head and neck tumours

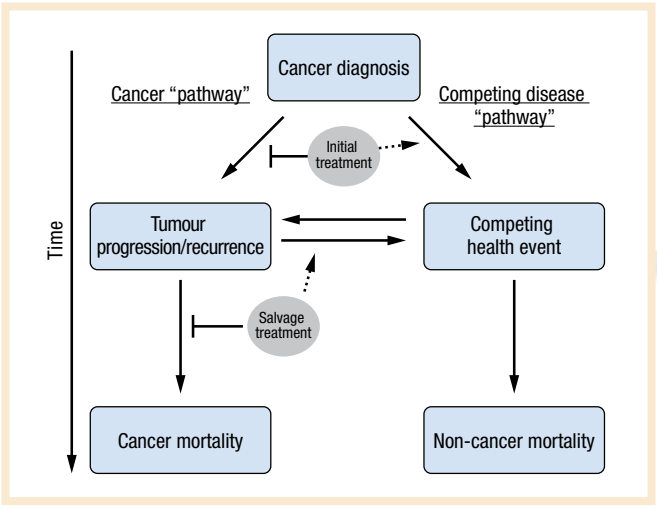
The burden of the problem

Treatment of locally advanced head and neck cancer (HNC) requires a multimodal approach, for therapeutic and supportive care decisions.

Toxicities induced by oncological therapies (surgery, chemotherapy and radiotherapy) may strongly affect patients' quality of life (QoL) and impact on treatment compliance.

Accurate patient selection and an individualised supportive care approach are mandatory before treatment initiation.





Concurrent chemoradiotherapy (ChT-RT) for HNC is associated with severe acute toxicities, which can result in a mortality rate ranging from 2% to 9.3%.

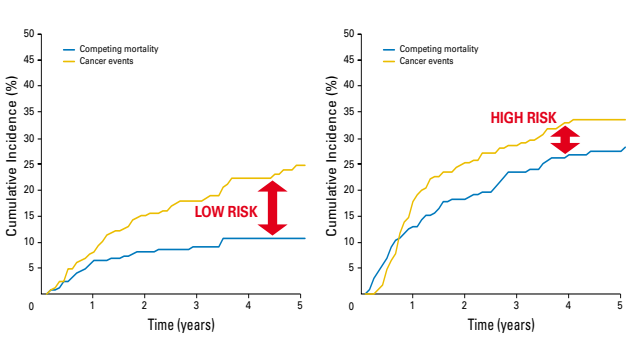
Competing event is defined as an intercurrent or treatment-related mortality.

It is not only a matter of acute toxicity, as late adverse events may compromise patients' QoL and possibly cause late death.

Risk factors for competing events: age, comorbidity, low body mass index and female sex. Low- and high-risk groups may be identified.

Within a multimodality approach, decreasing treatment toxicities is an important aim to improve patients' survival.

Supportive care may reduce acute/late effects, increase compliance and dose intensity, improve QoL, reduce costs of treatment, and possibly improve survival.



REVISION QUESTIONS

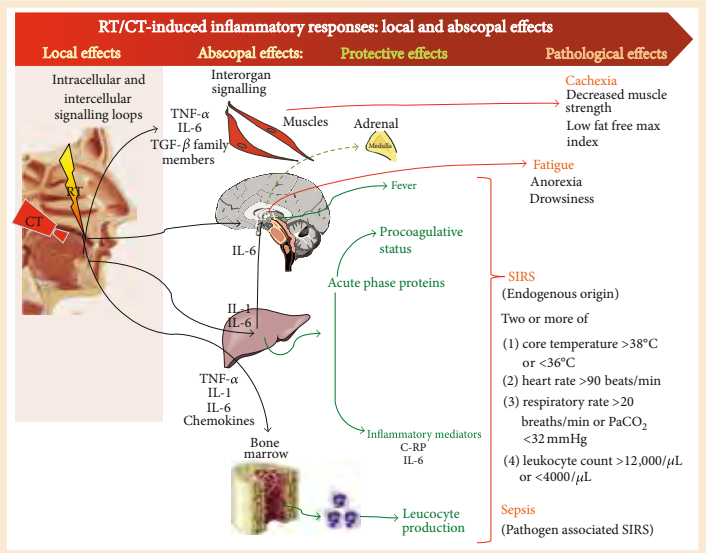
1. How should toxicities induced by treatment in HNC be managed?
2. Acute and late toxicities: what are the risk factors and impact on patients' QoL and survival?
3. What are the benefits of a strong supportive care programme?

Risk factors, mucositis and dysphagia

Head and neck cancer patients are frail, due to:

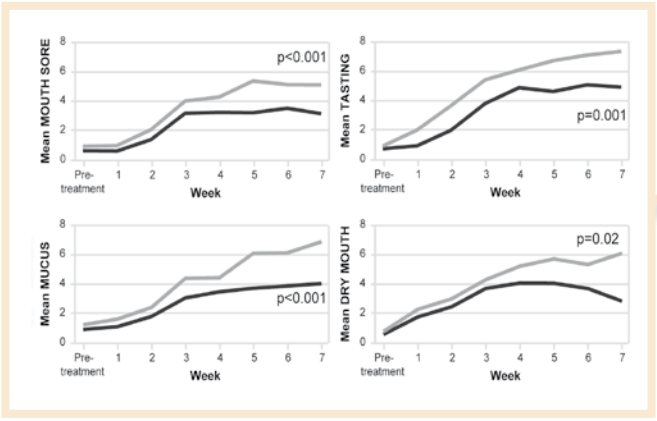
- Patient-related factors: malnutrition, poor immune status, dysphagia, comorbidities, bad oral cavity condition.
- Treatment-related factors: mucositis, dysphagia, neutropaenia/lymphopaenia, infections, dermatitis, tracheostomy.

Toxicities due to radiotherapy +/- chemotherapy or targeted therapy should be considered as a whole, with local adverse effects possibly leading to systemic complications.



C-RP, C-reactive protein; CT, chemotherapy; IL, interleukin; RT, radiotherapy; SIRS, systemic inflammatory response syndrome; TGF, transforming growth factor; TNF, tumour necrosis factor.

Differences in symptoms reported by patient with radiation alone (dark grey line) or concurrently with chemotherapy (light grey line)



Mucositis develops in 90%–100% of cases with ChT-RT (Grade 3-4 in 40%–50% of patients), consisting of inflammatory and/or ulcerative lesions of the oral and/or gastrointestinal tract. An expert dental examination is part of the patient's assessment.

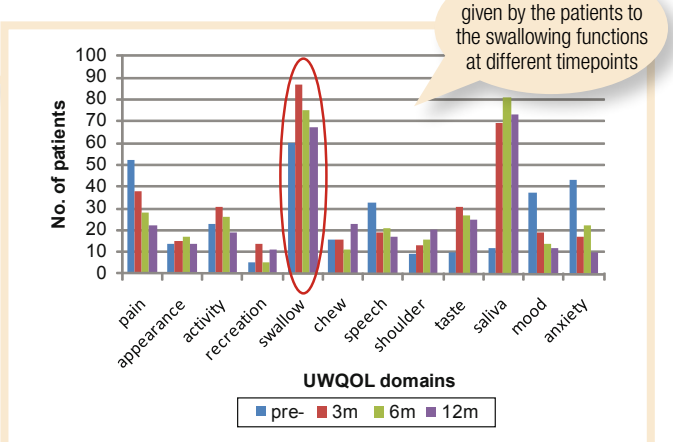
During treatment, adequate oral care is a key preventive measure, with frequent mouthwashes and soft-bristle toothbrush use. Pain due to mucositis is one of the most distressing consequences, possibly inducing nutritional deficits. Use of chemotherapy increases the risk.

Suggested preventive/therapeutic treatments are: morphine mouthwashes (0.2%), low-level laser therapy, doxepin mouthwashes and zinc supplementation. Patients should also stop smoking.

Dysphagia should be assessed before and during treatment. Patient-reported scales (i.e. MDADI) and instrumental evaluations are practical options for dysphagia screening.

It is recommended to minimise the dose to the main DARS (Dysphagia/Aspiration Related Structures) and salivary glands without reducing primary tumour radiotherapy volume doses.

Preventive swallowing exercises during ChT-RT may reduce long-term dysphagia; if enteral nutrition is adopted, patients should be encouraged to continue to swallow. Dental care is also crucial in this effort.



UWQOL, University of Washington Quality of Life Questionnaire.

REVISION QUESTIONS

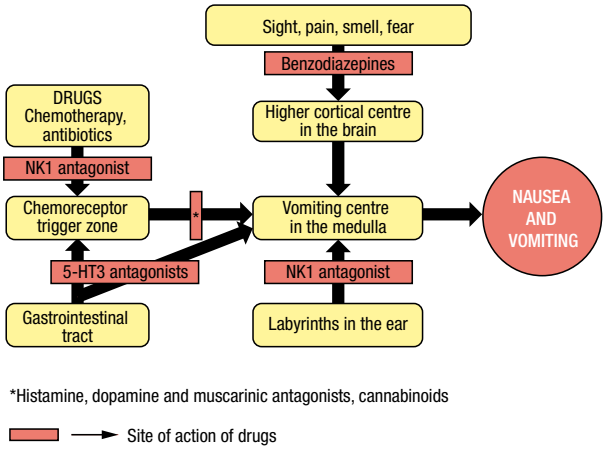
1. Why are HNC patients frail?
2. What are the preventive and therapeutic strategies for mucositis?
3. Which approaches may reduce the risk of acute and late dysphagia?

Nausea and vomiting; anaemia; leukopaenia

In head and neck squamous cell carcinoma (HNSCC), cisplatin-based chemotherapy is used in the majority of cases. Cisplatin is highly emetogenic and can cause acute (within first 24 h) and delayed (>24 h) nausea.

A 3-drug regimen with a 5-HT3 receptor antagonist, dexamethasone, and an NK1 receptor antagonist is suggested for the prevention of cisplatin-induced nausea and vomiting.

There are several factors impacting on nausea and vomiting during ChT-RT: dysgeusia, sticky saliva, employment of feeding tube, concurrent use of opioids.



Comparison of erythropoiesis-stimulating agents

Erythropoiesis stimulating agents	Epoetin alfa	Darbepoetin alfa
Primary indication	Anaemia due to: concurrent myelosuppressive chemotherapy in patients with cancer; chronic kidney disease (CKD); associated with HIV (zidovudine) therapy. Reduction of allogeneic red blood cell transfusion for elective, noncardiac, nonvascular surgery	Anaemia due to: concurrent myelosuppressive chemotherapy in patients with cancer; CKD
Route of administration	Subcutaneous or intravenous	Subcutaneous or intravenous
Half-life	4 to 13 hours (intravenous) 16 to 67 hours (subcutaneous)	Cancer, adult, subcutaneous: 74 hours (range: 24 to 144 hours) CKD, subcutaneous, non-dialysis: 70 hours (range: 35 to 139 hours) CKD, subcutaneous, dialysis: 46 hours (range: 12 to 89 hours)
Dosing: renal impairment	No dosage adjustment necessary	No dosage adjustment necessary
Excretion	Faeces (majority); urine (small amounts, 10% unchanged in normal volunteers)	Adults: 1.6 ± 1.0 ml/hour/kg
Pregnancy risk	Category C	Category C

CKD, Chronic kidney disease.

All causes of anaemia should be identified and corrected. Erythropoiesis-stimulating agents (ESAs) may be used in patients receiving chemotherapy if haemoglobin (Hb) <10 mg/dl (until reaching Hb levels of 12 mg/dl).

ESAs should be used with caution in patients with liver disease and increased risk of thromboembolic events, and are not recommended in patients treated with curative intent with radiotherapy.

Haematopoietic growth factors should be used for primary prophylaxis of chemotherapy-induced neutropaenia only if the risk of febrile neutropaenia is ≥20%.

REVISION QUESTIONS

1. Which antiemetic agents are used for prevention of cisplatin-related acute and delayed nausea?
2. When should ESAs be used with caution?
3. When should haematopoietic growth factors be used?

Skin care; infections; malnutrition

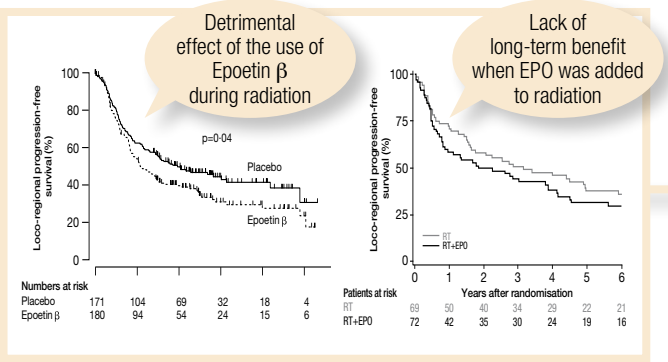
The following recommendations should be given for skin care during ChT-RT: wash with lukewarm water and mild soap, avoid microtraumas, tapes and adhesives.

Consider topical or systemic antimicrobials if positive skin cultures or documented infections are present; topical steroids should not be employed as prevention.

In the presence of toxicity Grade 3 or less, every effort should be taken not to stop the radiotherapy; with Grade 4, consider interrupting both systemic therapy and radiotherapy.

Type of RT	Toxicity grading scale	Grade 0–2 skin toxicity (%)	Grade ≥3 skin toxicity (%)
Conventional	EORTC	47	11 (Grade 3)
	RTOG	73	27 (Epidermitis)
	RTOG	94	7 (Grade 3)
Accelerated RT	WHO	Not reported	6.4 (Grade 3), 0.7 (Grade 4)
Accelerated RT with split	RTOG	85	3 (Grade 3)
Very accelerated RT	RTOG	66	33 (Epidermitis)
Accelerated RT with concomitant boost	RTOG	85	11 (Grade 3)
Hyperfractionated RT	RTOG	81	11 (Grade 3), <1 (Grade 4)
Hyperfractionated accelerated RT	EORTC	Not reported	46 (Grade 3/4)
IMRT (not randomised)	RTOG	75	18 (Grade 3), 7 (Grade 4)

EORTC, European Organisation for Research and Treatment of Cancer; IMRT, intensity-modulated radiotherapy; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; WHO, World Health Organisation.



EPO, Erythropoietin; RT, radiotherapy.

Febrile neutropaenic HNC patients should be considered at high risk for complications, requiring hospitalisation and prompt start of antibiotic intravenous therapy.

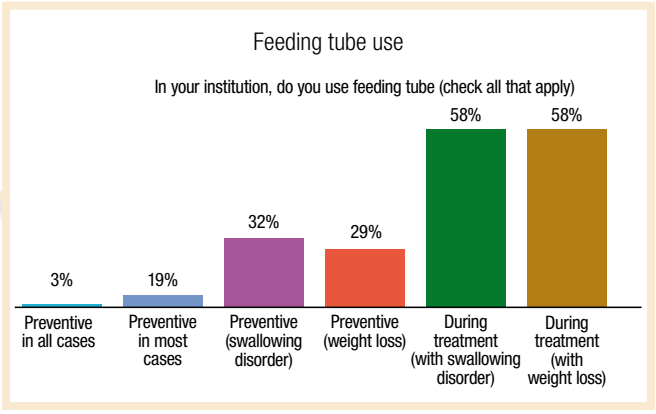
Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not indicated during ChT-RT; in case of anaemia, red blood cell transfusions should preferably be used over ESAs.

In case of suspected or confirmed sepsis, empirical antibiotic therapy should be promptly started, both anti-Gram-positive and anti-Gram-negative.

Malnutrition screening should be undertaken on all patients at diagnosis, to identify those at nutritional risk, and then be repeated at intervals.

Dietary counselling and/or supplements should be started at the beginning of oncological treatment. In selected cases, prophylactic tube feeding should be considered before starting any treatment.

During treatment, with a food intake <50% for more than 5 days despite nutrition counselling, enteral tube feeding should be used to help minimise weight loss and dehydration.



REVISION QUESTIONS

1. Which approach should be adopted in case of Grade 3 and Grade 4 skin toxicities during ChT-RT?
2. What is the preferred strategy for red and white blood series support?
3. Which criteria suggest use of enteral tube feeding during ChT-RT?

Summary: Individualised supportive care before and during curative treatment of head and neck tumours

- Treatment of locally advanced HNC requires a multimodal approach
- Accurate patient selection and individualised supportive care are mandatory
- Mortality rate, the tip of the iceberg of toxicities, may be up to 9% in HNC trials
- Supportive care may reduce acute/late effects and treatment costs, improve dose intensity and QoL
- HNC patients are frail, due to patient- and treatment-related factors
- Adequate oral care is a key preventive measure for mucositis
- Dysphagia should be assessed and prevented before and during treatment
- Cisplatin-based chemotherapy is the cornerstone of treatment. A combination of antiemetic agents is used to prevent acute and delayed nausea
- ESAs should be employed in patients with Hb <10 mg/dl only when treated with palliative intent and not when receiving curative radiotherapy
- In case of Grade 3 skin toxicity, do not stop radiotherapy; in case of Grade 4, stop systemic treatment and radiotherapy
- Febrile neutropaenic HNC patients should be hospitalised
- Malnutrition screening should be undertaken on all patients at diagnosis

Further Reading

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Emerging targets and new agents in squamous head and neck tumours

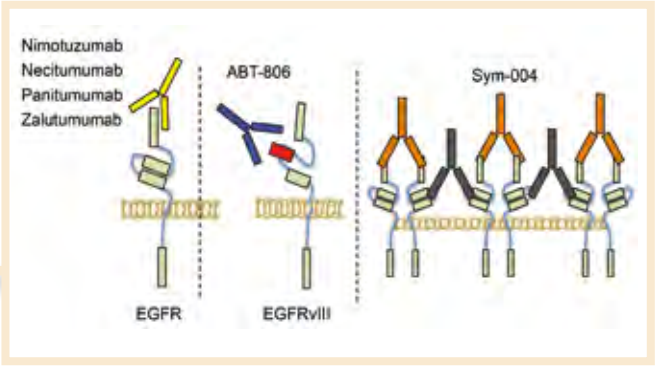
12

HER family and cell-cycle inhibitors

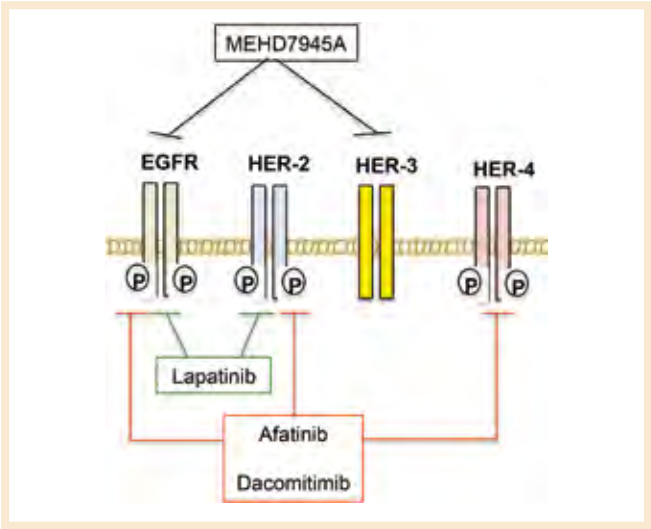
Epidermal growth factor receptor (EGFR) is overexpressed in 90% of cases of head and neck squamous cell carcinoma (HNSCC). Cetuximab, a chimaeric IgG1 anti-EGFR monoclonal antibody (mAb), improves overall survival when combined with radiotherapy or chemotherapy.

New anti-EGFR mAbs are under investigation. Necitumumab, nimotuzumab and zalutumumab are fully human IgG1 mAbs. Panitumumab is a human IgG2 mAb. ABT-806 targets an epitope exposed in EGFRvIII. Sym004 is composed of 2 anti-EGFR mAbs.

Only a minority of patients benefit from anti-EGFR mAbs: objective response rate (ORR) of single agents is around 6%–13%. Predictive biomarkers are needed.



EGFR, Epidermal growth factor receptor.

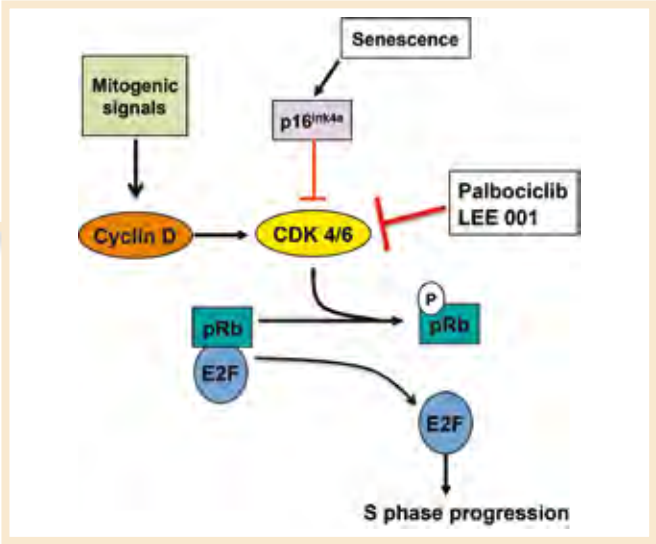


EGFR, Epidermal growth factor receptor.

Crosstalk among ErbB receptors could limit the clinical efficacy of EGFR-targeted therapies and may promote treatment resistance.

MEHD7945A is a human IgG1 mAb targeting both EGFR and HER3, resulting in comparable activity to cetuximab in a phase II trial.

Afatinib and dacomitinib are irreversible pan-HER inhibitors. Afatinib improves progression-free survival in recurrent HNSCC. Predictive biomarkers are needed.



p16^{INK4A} is inactivated in 90% and *CCND1* (encoding for cyclin D1) is amplified in 20%–30% of human papillomavirus (HPV)-negative HNSCC.

These alterations activate the cyclin-dependent kinases 4 and 6 (CDK 4/6), with phosphorylation of the retinoblastoma protein (pRb) and release of E2F transcription factor.

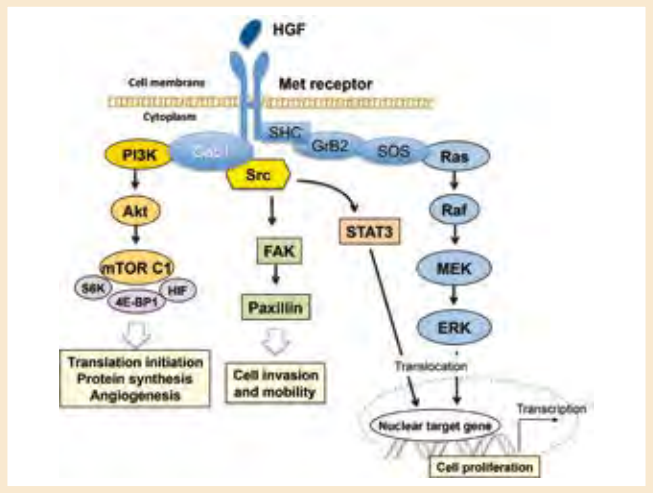
This promotes cell-cycle transition from G1 to S phase. CDK 4/6 inhibitors and other cell-cycle inhibitors are currently being investigated in p16-negative HNSCC.

REVISION QUESTIONS

1. What are the limitations of the use of anti-EGFR therapies in HNSCC?
2. What is the rationale to develop pan-HER inhibitors?
3. What are the genetic alterations that support the investigation of CDK inhibitors in HNSCC?

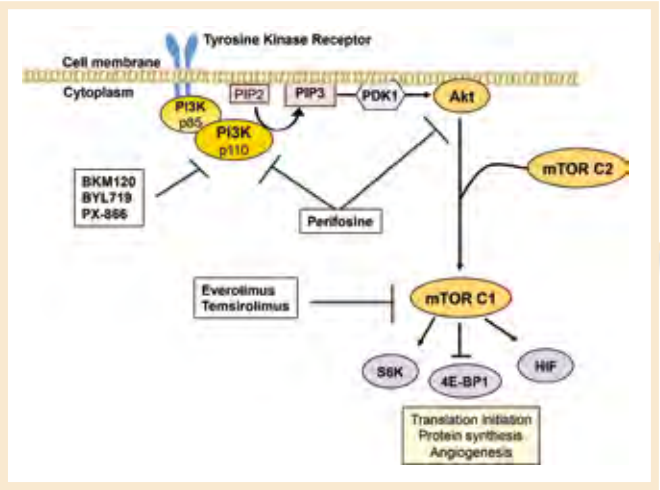
Growth factor and angiogenesis inhibitors

c-Met is overexpressed and mutated in 75% and 14% of HNSCC, respectively. Excessive activation of c-Met is implicated in cetuximab resistance.



Two tyrosine kinase inhibitors (TKIs), dasatinib and saracatinib, targeting the non-receptor tyrosine kinase Src are currently under evaluation in cetuximab-pretreated HNSCC patients.

Silencing of tumour suppressor genes caused by hypermethylation is an epigenetic mechanism implicated in HNSCC. Demethylating agents such as decitabine are under investigation.



The phosphatidylinositol 3 phosphate (PI3K)/Akt/mechanistic target of rapamycin (mTOR) pathway is frequently activated in HNSCC.

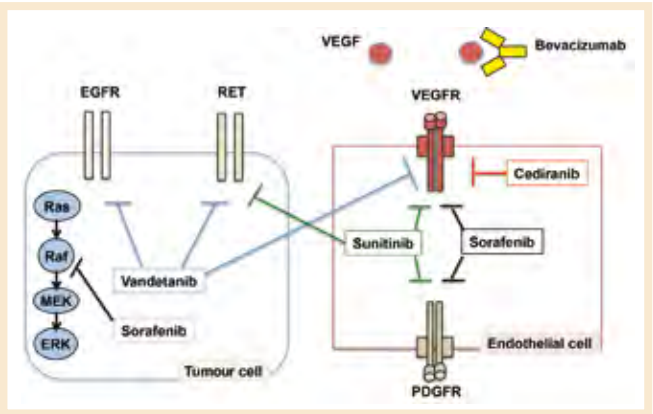
PI3KCA amplification/mutations are found in 34% and 56% of HPV-negative and -positive HNSCC, respectively. Around 20% of HPV-positive HNSCC have an activating *PI3KCA* mutation.

PI3K inhibitors (BKM120, BYL19, PX-866), perifosine (PI3K and AKT inhibitor), and mTOR inhibitors (everolimus, temsirolimus) are examples of agents under investigation.

Increased expression of vascular endothelial growth factor (VEGF) is associated with resistance to EGFR inhibitors and with poor prognosis in HNSCC, suggesting that angiogenesis is a reliable target.

Combination strategies against the EGFR family and angiogenesis are being investigated. Vandetanib targets EGFR, RET and VEGFR2, and was shown *in vitro* and *in vivo* to overcome cisplatin and radioresistance in HNSCC.

Anti-VEGF agents that are being or have been evaluated: the mAb bevacizumab targeting VEGF, and different TKIs such as sunitinib, sorafenib and cediranib. Bleeding, ulceration and fistulae are known adverse events of these compounds.



EGFR,Epidermal growth factor receptor; PDGFR, platelet-derived growth factor receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

REVISION QUESTIONS

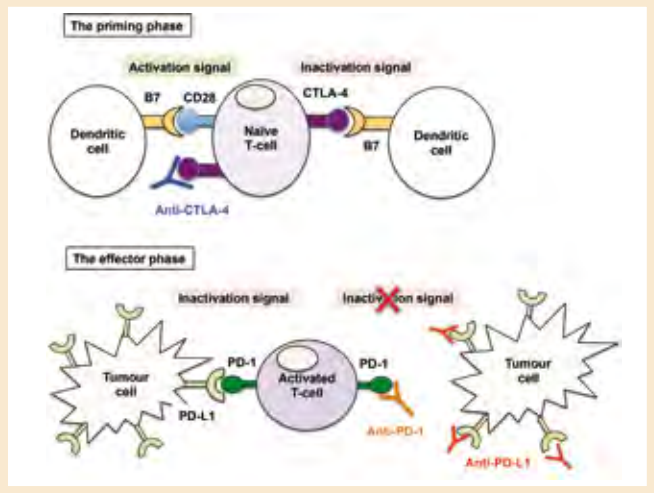
1. Why could Met inhibitors be interesting to use in HNSCC therapeutics?
2. Which pathway is frequently altered in HPV-positive HNSCC?
3. What are the risks of anti-VEGF therapy in HNSCC?

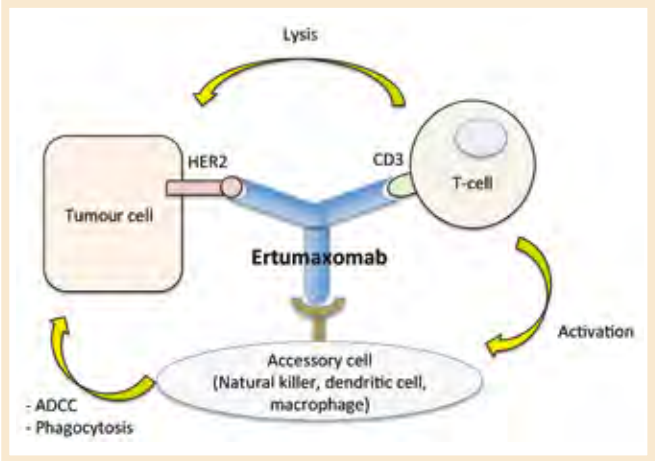
Immunotherapy and personalised treatment

Naive T-cells are activated by dendritic cells that present the tumour antigens. After activation, T-cells express CTLA-4 and bind to B7, thus blocking immune response.

The activated T-cells will recognise the antigen on the tumour cells to initiate cell killing, but this can be blocked by the PD-1/ PD-L1 pathway.

PD-1/PD-L1 inhibitors are under investigation. Nivolumab (anti-PD1) has been shown to improve survival in patients who progress after platinum therapy.





ADCC, Antibody dependent cell-mediated cytotoxicity

Cytokines and toll-like receptors (TLRs) amplify the natural killer cell capacity for cytolysis. Interleukin-12 and VTX-2337, a TLR agonist, are under investigation.

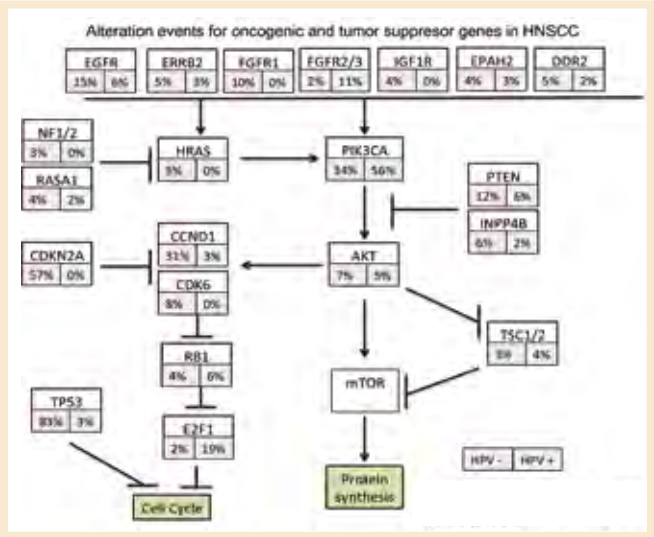
New mAbs such as ertumaxomab block the EGFR family and stimulate immune effector cells, enhancing antibody dependent cell-mediated cytotoxicity (ADCC).

Lenalinomide is a thalidomide analogue with antiangiogenic and immunomodulatory effects, supposed to enhance the ADCC of cetuximab.

The Cancer Genome Atlas (TCGA) work has identified other genetic alterations that may also be targeted by new compounds.

The fibroblast growth factor receptor family genes are altered in around 10%. *EphA2* and *DDR2* could be targeted by dasatinib. RAS, *NF1/2, RASA1, PTEN, INPP4B, TSC1/2, AKT* also appear as potential targets.

Gene expression profiling identified 3 HNSCC supergroups called inflamed/mesenchymal (I/M), basal (B) or classical (CL). HPV+ HNSCC are part of the I/M and CL groups.



HNSCC, Head and neck squamous cell carcinoma.

REVISION QUESTIONS

1. Explain the main mechanism of action of anti-CTLA-4 mAbs.
2. Explain the main mechanism of action of mAbs targeting the PD-1/PD-L1 pathway.
3. What is the objective response rate of mAbs targeting the PD-1/PD-L1 pathway?

Summary: Emerging targets and new agents in squamous head and neck tumours

- Up to 90% of HNSCC express high levels of EGFR
- Overexpression of EGFR as well as high EGFR gene copy number are associated with poor prognosis
- Cetuximab improves overall survival, either as curative treatment in combination with radiation therapy, or as palliative treatment in combination with chemotherapy
- Only a minority of patients derive long-term benefit from anti-EGFR treatment, emphasising the importance of developing novel treatment strategies
- Potentially more potent anti-EGFR compounds as well as combination strategies are under investigation to improve treatment efficacy
- $p16^{INK4A}$ is inactivated in 90% of HNSCC and CCND1 is amplified in 20%-30% of HPV-negative HNSCC. Therefore, there is a strong rationale to investigate cell-cycle inhibitors in HNSCC
- The PI3K/Akt/mTOR pathway is frequently activated in HNSCC
- HPV-positive HNSCC have frequent PI3KCA hotspot mutations
- Immune checkpoint inhibitors are under investigation with an ORR around 15%–20% in phase II trials, especially with agents targeting the PD-1/PD-L1 pathway

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Appendix 1: WHO Classification, 4th Edition (2017)

Tumours of the nasal cavity, paranasal sinuses and skull base

Carcinomas

- Keratinizing squamous cell carcinoma
- Non-keratinizing squamous cell carcinoma
- Spindle cell (sarcomatoid) squamous cell carcinoma
- Lymphoepithelial carcinoma
- Sinonasal undifferentiated carcinoma
- NUT carcinoma
- Neuroendocrine carcinoma
- Adenocarcinoma
  - Intestinal-type adenocarcinoma
  - Non–intestinal-type adenocarcinoma

Teratocarcinosarcoma

Sinonasal papillomas

- Sinonasal papilloma, inverted type
- Sinonasal papilloma, oncocytic type
- Sinonasal papilloma, exophytic type

Respiratory epithelial lesions

- Respiratory epithelial adenomatoid hamartoma
- Seromucinous hamartoma

Salivary gland tumours

- Pleomorphic adenoma

Malignant soft tissue tumours

- Fibrosarcoma
- Undifferentiated pleomorphic sarcoma
- Leiomyosarcoma
- Rhabdomyosarcoma
- Angiosarcoma
- Malignant peripheral nerve sheath tumour
- Biphenotypic sinonasal sarcoma
- Synovial sarcoma

Borderline / low-grade malignant soft tissue tumours

- Desmoid-type fibromatosis
- Sinonasal glomangiopericytoma
- Solitary fibrous tumour
- Epithelioid haemangioendothelioma

Benign soft tissue tumours

- Leiomyoma
- Haemangioma
- Schwannoma
- Neurofibroma

Other tumours

- Meningioma
- Sinonasal ameloblastoma
- Chondromesenchymal hamartoma

Haematolymphoid tumours

- Extranodal NK/T-cell lymphoma
- Extraosseous plasmacytoma

Neuroectodermal / melanocytic tumours

- Ewing sarcoma / primitive neuroectodermal tumours
- Olfactory neuroblastoma
- Mucosal melanoma

Tumours of the nasopharynx

Nasopharyngeal carcinoma

Nasopharyngeal papillary adenocarcinoma

Salivary gland tumours

- Adenoid cystic carcinoma
- Salivary gland anlage tumour

Benign and borderline lesions

- Hairy polyp
- Ectopic pituitary adenoma
- Craniopharyngioma

Soft tissue tumours

- Nasopharyngeal angiofibroma

Haematolymphoid tumours

Notochordal tumours

- Chordoma

Tumours of the hypopharynx, larynx, trachea and parapharyngeal space

Malignant surface epithelial tumours

- Conventional squamous cell carcinoma
- Verrucous squamous cell carcinoma
- Basaloid squamous cell carcinoma
- Papillary squamous cell carcinoma
- Spindle cell squamous cell carcinoma
- Adenosquamous carcinoma
- Lymphoepithelial carcinoma

Precursor lesions

- Dysplasia
- Squamous cell papilloma & squamous cell papillomatosis

Neuroendocrine tumours

- Well-differentiated neuroendocrine carcinoma
- Moderately differentiated neuroendocrine carcinoma
- Poorly differentiated neuroendocrine carcinoma

Salivary gland tumours

- Adenoid cystic carcinoma
- Pleomorphic adenoma
- Oncocytic papillary cystadenoma

Soft tissue tumours

- Granular cell tumour
- Liposarcoma
- Inflammatory myofibroblastic tumour

Cartilage tumours

- Chondroma and chondrosarcoma

Haematolymphoid tumours

Tumours of the oral cavity and mobile tongue

Malignant surface epithelial tumours

- Squamous cell carcinoma

Oral potentially malignant disorders & oral epithelial dysplasia

- Oral potentially malignant disorders
- Oral epithelial dysplasia
- Proliferative verrucous leukoplakia

Papillomas

- Squamous cell papilloma
- Condyloma acuminatum
- Verruca vulgaris
- Multifocal epithelial hyperplasia

Tumours of uncertain histogenesis

- Congenital granular cell epulis
- Ectomesenchymal chondromyxoid tumour

Soft tissue and neural tumours

- Granular cell tumour
- Rhabdomyoma
- Lymphangioma

Haemangioma
Schwannoma and neurofibroma
Kaposi sarcoma
Myofibroblastic sarcoma

Oral mucosal melanoma

Salivary type tumours

Mucoepidermoid carcinoma
Pleomorphic adenoma

Haematolymphoid tumours

CD30-positive T-cell lymphoproliferative disorder
Plasmablastic lymphoma
Langerhans cell histiocytosis
Extramedullary myeloid sarcoma

Tumours of the oropharynx (base of tongue, tonsils, adenoids)

Squamous cell carcinoma

Squamous cell carcinoma, HPV-positive
Squamous cell carcinoma, HPV-negative

Salivary gland tumours

Pleomorphic adenoma
Adenoid cystic carcinoma
Polymorphous adenocarcinoma

Haematolymphoid tumours

Hodgkin lymphoma
Burkitt lymphoma
Follicular lymphoma
Mantle cell lymphoma
T-lymphoblastic leukaemia/lymphoma
Follicular dendritic cell sarcoma

Tumours and tumour-like lesions of the neck and lymph nodes

Tumours of unknown origin

Carcinoma of unknown primary
Merkel cell carcinoma
Heterotopia-associated carcinoma

Haematolymphoid tumours

Cysts and cyst-like lesions

Branchial cleft cyst
Thyroglossal duct cyst
Ranula
Dermoid and teratoid cysts

Tumours of salivary glands

Malignant tumours

Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Acinic cell carcinoma
Polymorphous adenocarcinoma
Clear cell carcinoma
Basal cell adenocarcinoma
Intraductal carcinoma
Adenocarcinoma, NOS
Salivary duct carcinoma
Myoepithelial carcinoma
Epithelial–myoepithelial carcinoma
Carcinoma ex pleomorphic adenoma
Secretory carcinoma
Sebaceous adenocarcinoma
Carcinosarcoma
Poorly differentiated carcinoma
Lymphoepithelial carcinoma
Squamous cell carcinoma
Oncocytic carcinoma
Sialoblastoma

Benign tumours

Pleomorphic adenoma
Myoepithelioma
Basal cell adenoma
Warthin tumour
Oncocytoma
Lymphadenoma
Cystadenoma
Sialadenoma papilliferum
Ductal papillomas
Sebaceous adenoma
Canalicular adenoma and other ductal adenomas

Non-neoplastic epithelial lesions

Sclerosing polycystic adenosis
Nodular oncocytic hyperplasia
Lymphoepithelial sialadenitis
Intercalated duct hyperplasia

Benign soft tissue lesions

Haemangioma
Lipoma/sialolipoma
Nodular fasciitis

Haematolymphoid tumours

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

Odontogenic and maxillofacial bone tumours

Odontogenic carcinomas

Ameloblastic carcinoma
Primary intraosseous carcinoma, NOS
Sclerosing odontogenic carcinoma
Clear cell odontogenic carcinoma
Ghost cell odontogenic carcinoma

Odontogenic carcinosarcoma

Odontogenic sarcomas

Benign epithelial odontogenic tumours

Ameloblastoma
  Ameloblastoma, unicystic type
  Ameloblastoma, extraosseous/peripheral type
  Metastasizing ameloblastoma
Squamous odontogenic tumour
Calcifying epithelial odontogenic tumour
Adenomatoid odontogenic tumour

Benign mixed epithelial & mesenchymal odontogenic tumours

Ameloblastic fibroma
Primordial odontogenic tumour
Odontoma
Dentinogenic ghost cell tumour

Benign mesenchymal odontogenic tumours

Odontogenic fibroma
Odontogenic myxoma/myxofibroma
Cementoblastoma
Cemento-ossifying fibroma

Odontogenic cysts of inflammatory origin

Radicular cyst
Inflammatory collateral cysts

Odontogenic and non-odontogenic developmental cysts

- Dentigerous cyst
- Odontogenic keratocyst
- Lateral periodontal cyst and botryoid odontogenic cyst
- Gingival cysts
- Glandular odontogenic cyst
- Calcifying odontogenic cyst
- Orthokeratinized odontogenic cyst
- Nasopalatine duct cyst

Malignant maxillofacial bone and cartilage tumours

- Chondrosarcoma
- Mesenchymal chondrosarcoma
- Osteosarcoma

Benign maxillofacial bone and cartilage tumours

- Chondroma
- Osteoma
- Melanotic neuroectodermal tumour of infancy
- Chondroblastoma
- Chondromyxoid fibroma
- Osteoid osteoma
- Osteoblastoma
- Desmoplastic fibroma

Fibro-osseous and osteochondromatous lesions

- Ossifying fibroma
- Familial gigantiform cementoma
- Fibrous dysplasia
- Cemento-osseous dysplasia
- Osteochondroma

Giant cell lesions and simple bone cyst

- Central giant cell granuloma
- Peripheral giant cell granuloma
- Cherubism
- Aneurysmal bone cyst
- Simple bone cyst

Haematolymphoid tumours

- Solitary plasmacytoma of bone

Tumours of the ear

Tumours of the external auditory canal

- Squamous cell carcinoma
- Ceruminous adenocarcinoma
- Ceruminous adenoma

Tumours of the middle and inner ear

- Squamous cell carcinoma
- Aggressive papillary tumour
- Endolymphatic sac tumour
- Otosclerosis
- Cholesteatoma
- Vestibular schwannoma
- Meningioma
- Middle ear adenoma

Paraganglion tumours

- Carotid body paraganglioma
- Laryngeal paraganglioma
- Middle ear paraganglioma
- Vagal paraganglioma

Appendix 2: Selected treatment schedules

Squamous cell carcinomas

A. Locally advanced disease (systemic therapy plus radiotherapy)

Regimen	Chemotherapy	Dose	Route	Schedule
High-dose cisplatin [1, 2]	Cisplatin	100 mg/m²	i.v.	Day 1
				q 3 weeks for 3 cycles
Weekly cisplatin [3, 4]	Cisplatin	40 mg/m²	i.v.	Weekly
Cetuximab [5]	Cetuximab	Initially 400 mg/m² and then 250 mg/m²	i.v.	Weekly
CF [6-8]	Carboplatin or cisplatin	70 mg/m² 60 mg/m²	i.v.	Days 1–4 Day 1
	5-FU	600–800 mg/m²	i.v. (C.I.)	Days 1–4
				q 3 weeks for 3 cycles
CP [9, 10]	Carboplatin or cisplatin	100 mg/m² 20 mg/m²	i.v.	Weekly
	Paclitaxel	30–45 mg/m²	i.v.	Weekly
5-FU / Hydroxyurea [9]	Hydroxyurea	1 g	p.o.	2/day
	5-FU	800 mg/m²	i.v.	Daily

B. Recurrent, unresectable or metastatic disease (with no surgery or radiotherapy option)
B.1. Combination chemotherapy

Regimen	Chemotherapy	Dose	Route	Schedule
Cetuximab-based chemotherapy, 1st line [11]	Cetuximab	Initially 400 mg/m² and then 250 mg/m²	i.v.	Weekly
	Carboplatin or cisplatin	AUC=5 100 mg/m²	i.v.	Day 1
	5-FU	1000 mg/m²	i.v. (C.I.)	Days 1–4
				q 3 weeks for 6 cycles Cetuximab maintenance in pts with PR / SD
PF, 1st line [12]	Cisplatin	100 mg/m²	i.v.	Day 1
	5-FU	1000 mg/m²	i.v. (C.I.)	Days 1–4
				q 3–4 weeks
CP, 1st line [12]	Cisplatin	75 mg/m²	i.v.	Day 1
	Paclitaxel	175 mg/m²	i.v.	Day 1
				q 3 weeks
TP, 1st line [13]	Cisplatin	75 mg/m²	i.v.	Day 1
	Docetaxel	75 mg/m²	i.v.	Day 1
				q 3 weeks
TC, 1st line [14]	Carboplatin	AUC=6	i.v.	Day 1
	Docetaxel	65 mg/m²	i.v.	Day 1
				q 3 weeks
TPEx, 1st line [15]	Cetuximab	Initially 400 mg/m² and then 250 mg/m²	i.v.	Weekly
	Cisplatin	75 mg/m²	i.v.	Day 1
	Docetaxel	75 mg/m²	i.v.	Day 1
				q 3 weeks for 4 cycles Cetuximab maintenance in patients with PR/SD
CE, 1st line [16, 17]	Cisplatin	75–100 mg/m²	i.v.	Day 1
	Cetuximab	Initially 400 mg/m² and then 250 mg/m²	i.v.	Weekly
				q 3–4 weeks

B.2. Single-agent chemotherapy

Regimen	Chemotherapy	Dose	Route	Schedule
Nivolumab, 2nd line [18]	Nivolumab	3 mg/kg	i.v.	Day 1
				q 2 weeks
Methotrexate, 2nd line [19, 20]	Methotrexate	40–60 mg/m^2	i.v.	Weekly
Pembrolizumab, 2nd line [21]	Pembrolizumab	200 mg	i.v.	Day 1
				q 3 weeks
Cisplatin, 2nd line [22]	Cisplatin	100 mg/m^2	i.v.	Day 1
				q 3 weeks
5-FU, 2nd line [22]	5-FU	1000 mg/m^2	i.v. (C.I.)	Days 1–4
				q 3 weeks
Docetaxel, 2nd line [23]	Docetaxel	75 mg/m^2	i.v.	Day 1
				q 3 weeks
Paclitaxel, 2nd line [24]	Paclitaxel	80 mg/m^2	i.v.	Weekly
Cetuximab, 2nd line [25]	Cetuximab	Initially 400 mg/m^2 and then 250 mg/m^2	i.v.	Weekly
Vinorelbine, 2nd line [26]	Vinorelbine	30 mg/m^2	i.v.	Weekly
Capecitabine, 2nd line [27]	Capecitabine	1250 mg/m^2	p.o.	Days 1–14
				q 3 weeks

Abbreviations: 2/d, twice a day; 5-FU, 5-fluorouracil; AUC, area under the curve; C.I., continuous infusion; i.v., intravenous; p.o., oral; PR, partial response; SD, stable disease.

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Nasopharyngeal carcinoma

A. Locally advanced disease: concurrent chemotherapy plus radiotherapy

Regimen	Chemotherapy	Dose	Route	Schedule
High-dose cisplatin [1, 2]	Cisplatin	100 mg/m^2	i.v.	Days 1, 22 and 43
Weekly cisplatin [3-5]	Cisplatin	40 mg/m^2	i.v.	Weekly for 6-8 cycles
Carboplatin [6]	Carboplatin	100 mg/m^2 or AUC=2	i.v.	Weekly for 6-8 cycles

B. Locally advanced disease: induction / neoadjuvant chemotherapy

Regimen	Chemotherapy	Dose	Route	Schedule
PF [7-9]	Cisplatin	100 mg/m^2	i.v.	Day 1
	5-FU	1000 mg/m^2	i.v. (C.I.)	Days 1–4
				q 3 weeks
TP [10]	Cisplatin	75 mg/m^2	i.v.	Day 1
	Docetaxel	75 mg/m^2	i.v.	Day 1
				q 3 weeks
TC [11]	Carboplatin	AUC=6	i.v.	Day 1
	Paclitaxel	70 mg/m^2	i.v.	Days 1, 8 and 15
				q 3 weeks
GP [12]	Cisplatin	75 mg/m^2	i.v.	Day 1
	Gemcitabine	1000 mg/m^2	i.v.	Days 1 and 8
				q 3 weeks
TPF (Asian doses) [13]	Cisplatin	60 mg/m^2	i.v.	Day 1
	Docetaxel	60 mg/m^2	i.v.	Day 1
	5-FU	600 mg/m^2	i.v. (C.I.)	Days 1–5
				q 3 weeks
TPF (European doses) [14]	Cisplatin	75 mg/m^2	i.v.	Day 1
	Docetaxel	75 mg/m^2	i.v.	Day 1
	5-FU	750 mg/m^2	i.v. (C.I.)	Days 1–4
				q 3 weeks

C. Locally advanced disease: adjuvant chemotherapy

Regimen	Chemotherapy	Dose	Route	Schedule
PF or CF [1, 6]	Cisplatin or carboplatin	80 mg/m^2 AUC=5	i.v.	Day 1
	5-FU	1000 mg/m^2	i.v. (C.I.)	Days 1–4
				q 4 weeks x3

D. Recurrent, unresectable or metastatic disease (with no surgery or radiotherapy option)
D.1. Combination chemotherapy

Regimen	Chemotherapy	Dose	Route	Schedule
PF or CF [15-17]	Cisplatin or carboplatin	75 mg/m^2 AUC=5	i.v.	Day 1
	5-FU	1000 mg/m^2	i.v. (C.I.)	Days 1–4
				q 3 weeks
GP [15, 16]	Cisplatin	75 mg/m^2	i.v.	Day 1
	Gemcitabine	1000 mg/m^2	i.v.	Days 1 and 8
				q 3 weeks
CP [16]	Cisplatin	75 mg/m^2	i.v.	Day 1
	Paclitaxel	175 mg/m^2	i.v.	Day 1
				q 3 weeks
TC [18]	Carboplatin	AUC=5	i.v.	Day 1
	Paclitaxel	175 mg/m^2	i.v.	Day 1
				q 3 weeks
TP [19]	Cisplatin	75 mg/m^2	i.v.	Day 1
	Docetaxel	75 mg/m^2	i.v.	Day 1
				q 3 weeks

D.2. Single-agent chemotherapy

Regimen	Chemotherapy	Dose	Route	Schedule
Gemcitabine [20]	Gemcitabine	1000–1250 mg/m^2	i.v.	Days 1 and 8
				q 3 weeks
Capecitabine [21]	Capecitabine	1250 mg/m^2	p.o.	Days 1–14
				q 3 weeks
Paclitaxel [22]	Paclitaxel	175 mg/m^2	i.v.	Day 1
				q 3 weeks
Docetaxel [23]	Docetaxel	75 mg/m^2	i.v.	Day 1
				q 3 weeks

Abbreviations: AUC, Area under the curve; C.I., continuous infusion; i.v., intravenous; p.o., oral.

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Salivary gland carcinomas

A. Recurrent, unresectable or metastatic disease (with no surgery or radiotherapy option)
A.1. Adenoid cystic carcinoma

Regimen	Chemotherapy	Dose	Route	Schedule
CAP [1-4]	Cyclophosphamide	500 mg/m^2	i.v.	Day 1
	Doxorubicin	50 mg/m^2	i.v.	Day 1
	Cisplatin	50 mg/m^2	i.v.	Day 1
				q 3 weeks
Cisplatin [5]	Cisplatin	100 mg/m^2	i.v.	Day 1
				q 3–4 weeks
Epirubicin [6]	Epirubicin	30 mg/m^2	i.v.	Day 1
				Weekly
Vinorelbine [7]	Vinorelbine	30 mg/m^2	i.v.	Day 1
				Weekly

A.2. Non-adenoid cystic carcinoma*

Regimen	Chemotherapy	Dose	Route	Schedule
CAP [4, 8]	Cyclophosphamide	500 mg/m^2	i.v.	Day 1
	Doxorubicin	50 mg/m^2	i.v.	Day 1
	Cisplatin	50 mg/m^2	i.v.	Day 1
				q 3 weeks
Gemcitabine plus cisplatin [9]	Gemcitabine	1000 mg/m^2	i.v.	Days 1–8
	Cisplatin	70 mg/m^2	i.v.	Day 1
				q 3 weeks
Vinorelbine plus cisplatin [10]	Vinorelbine	25 mg/m^2	i.v.	Days 1–8
	Cisplatin	80 mg/m^2	i.v.	Day 1
				q 3 weeks
Carboplatin plus paclitaxel [11]	Carboplatin	AUC=6	i.v.	Day 1
	Paclitaxel	200 mg/m^2	i.v.	Day 1
				q 3 weeks
Paclitaxel [12]	Paclitaxel	200 mg/m^2	i.v.	Day 1
				q 3 weeks

*This definition includes histotypes different from adenoid cystic carcinoma
Abbreviations: AUC, Area under the curve; i.v., intravenous.

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Image sources

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