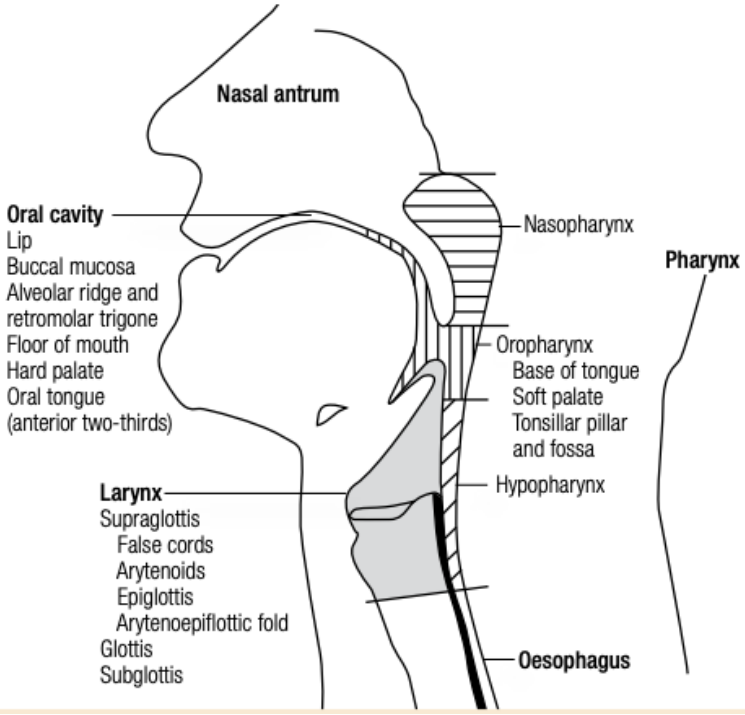
Head and Neck Cancer

General Overview

- Cancers originating in the anatomical structures of the mouth, nose, paranasal sinuses, naso-, oro-and hypopharynx, larynx, salivary glands, external auditory canal and the neck.
- Incidence has increased, particular oropharyngeal cancer because of the prevalence of HPV infection and HPV-induced malignancies.
- 6th most common cancer worldwide, accounting for 1% – 2% of all cancer-related deaths
- Risk factors: male sex, HPV infection, EBV infection, smoking, alcohol consumption (synergism resulting in a relative 35 fold increase in incidence) and exposure to certain toxins (Nikkel, asbestos, wood dust etc)
- Histology:
    - According to anatomical site
    - Primarily Squamous cell carcinoma (SCC)
    - Adenocarcinoma can be found in the salivary glands, sinuses or nasal cavity.
    - More seldom are SNUCs to be regarded as undifferentiated or badly differentiated tumors of the nasal cavity or paranasal sinuses.
- Symptoms: Related to anatomical site, however first signs are frequently caused by lymphatic spread to the neck.
- Lymphatic drainage: 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.
- HPV induced oral cavity and oropharyngeal cancer are a distinctive entity in terms of biology / TNM staging and (better) outcome.

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%



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.

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

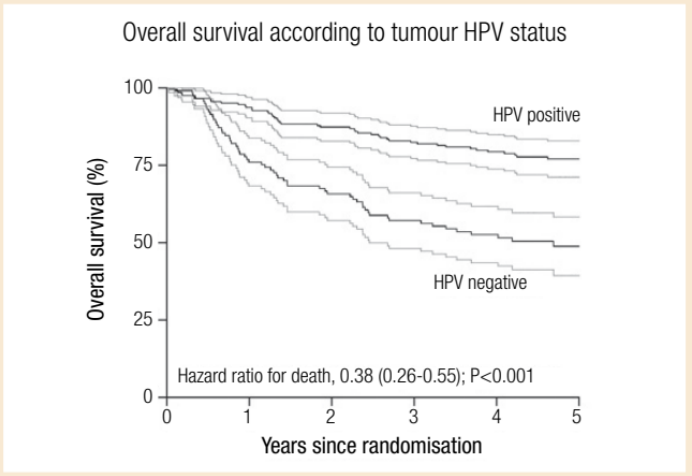
Staging (AJCC Version 8) and Prognosis

- 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) .

Lymph node involvement

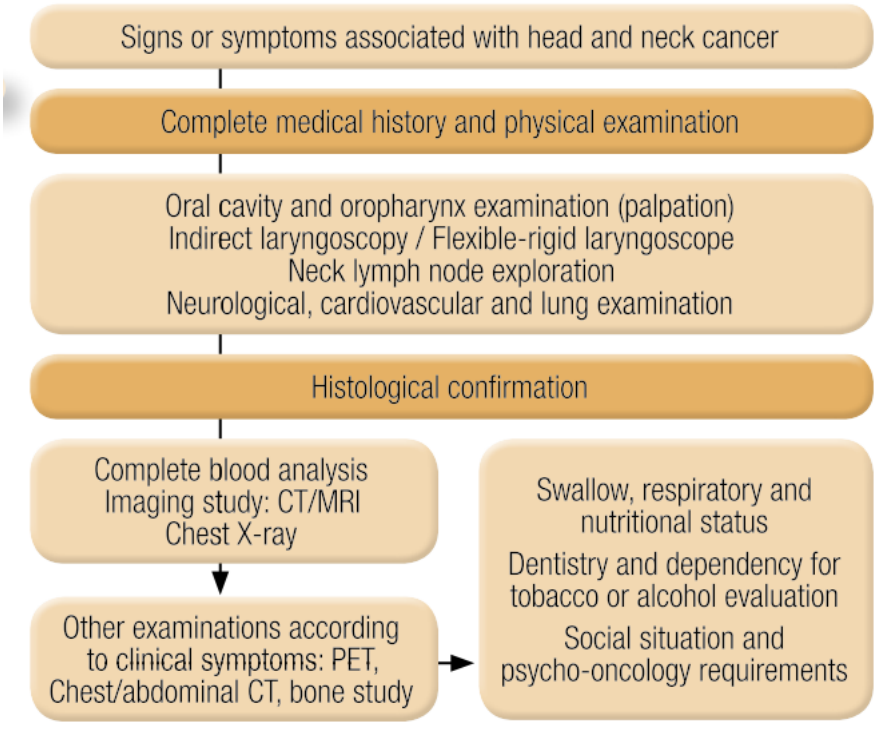
- N0: no regional lymph node metastasis
- N1: metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension without extranodal extension
- N2a: metastasis in a single ipsilateral lymph node, 3-6 cm in greatest dimension without extranodal extension
- N2b: metastases in multiple ipsilateral 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

- Prognosis:
  - Dependent on tumor site and differentiation / grading
  - Hypopharynx : 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%.
  - HPV – induced oro-pharyngeal tumors are known to have a better prognosis.



Diagnostic algorithm

- Multidisciplinary team
- Persistent symptoms
- Solitary persistent lymph nodes
- KO + fiber endoscopy
- CT or MRI
- PET/CT



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

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

Oral cavity and oropharyngeal carcinoma

- Local excision in stages I – II.
- 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.
- Post operative 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)

Hypopharynx

- 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%.
- 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
- 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-cisplatinfluorouracil (TPF), while cisplatin is the standard chemotherapeutic agent for ChT-RT.

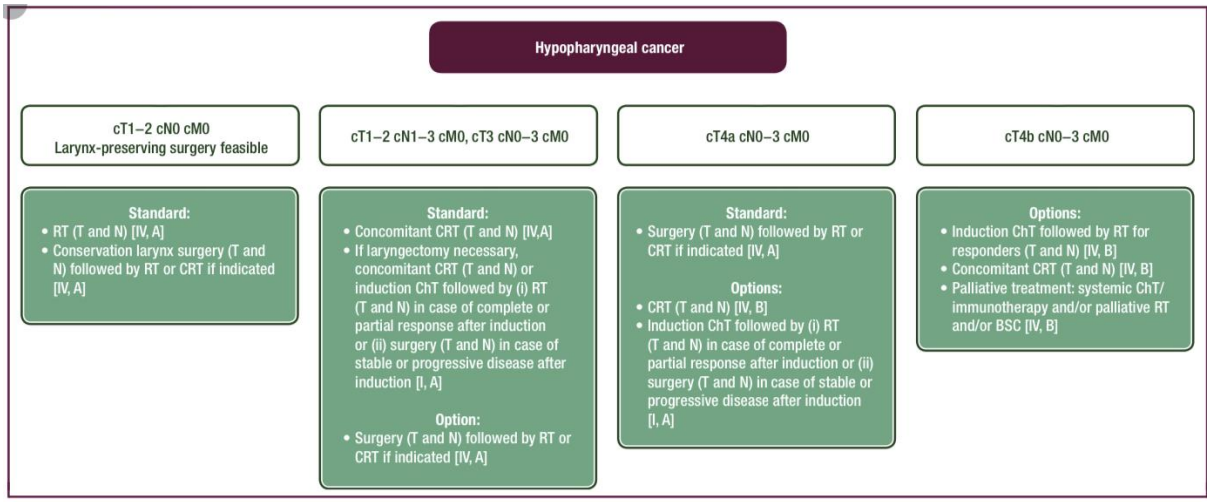


Figure 4. Management of hypopharyngeal cancer (stage I–IVB).
BSC, best supportive care; ChT, chemotherapy; CRT, chemoradiotherapy; M, metastasis; N, node; RT, radiotherapy; T, tumour.

Larynx

- Supraglottic tumors: 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 tumors: 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 (
- In case of T3 / T4 tumors : patients that are candidates for total laryngectomy, an organ preservation multimodality strategy can be adopted.
- 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

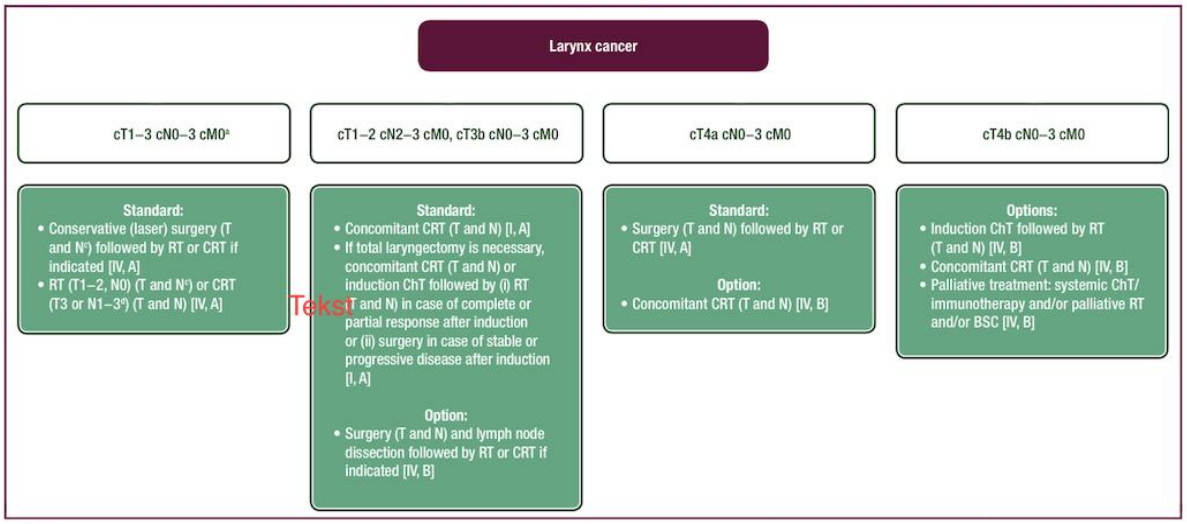


Figure 2. Management of laryngeal cancer (stage I–IVB).
BSC, best supportive care; ChT, chemotherapy; CRT, chemoradiotherapy; M, metastasis; N, node; RT, radiotherapy; T, tumour.
[a] Not requiring total laryngectomy.
[b] Requiring total laryngectomy.
[c] cT1–2N0 glottic cancer does not require neck dissection or neck RT.
[d] Altered fractionation (accelerated or hyperfractionated) RT is a valid option for selected T3 or T3N1.

Treatment: 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
- Dependent on CPS scores : Pembrolizumab in monotherapy or Platinum-based ChT in combination with pembrolizumab 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

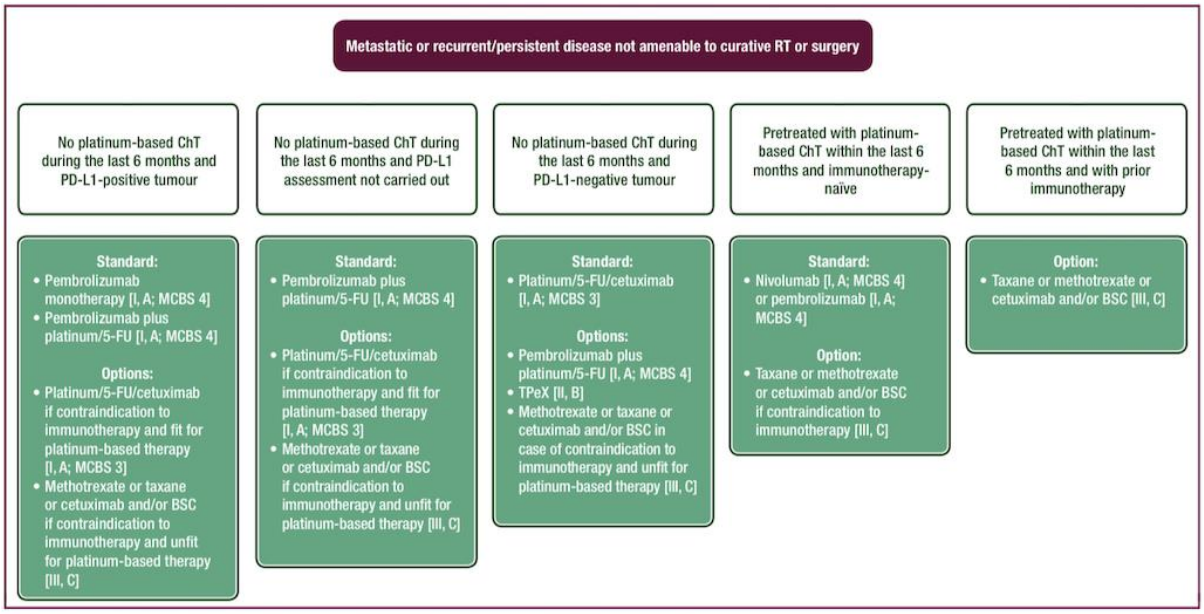


Figure 5. Management of recurrent and/or metastatic disease not amenable to curative RT or surgery.
5-FU, 5-fluorouracil; BSC, best supportive care; ChT, chemotherapy; CRT, chemoradiotherapy; M, metastasis; N, node; PD-L1, programmed death-ligand 1; RT, radiotherapy; T, tumour; TPeX, cisplatin/docetaxel/cetuximab.

Nasopharynx

- TNM-classification / prognosis
- N0
  - T1-2
  - Chemoradiotherapy
  - T3-4
  - Induction chemotherapy + chemoradiotherapy.
- N+
  - T1-4
  - (Induction chemotherapy) + chemoradiotherapy
  - In case of negative PET-CT after 3 months, wait and see and repeat PET-CT after 12 months. In case of positve PETCT: lymphnode resection.
- Recurrence nasopharynx carcinoma
  - No standard treatment.

References

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- Burtness B.et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. 2019, 394, 10212:1879-1964.