

ONCOLOGY KNOWLEDGE HUB · FOR HEALTH PROFESSIONALS

Head & Neck Cancer

A mini review for clinicians

For postgraduate residents (medical, radiation and surgical oncology, ENT and head and neck surgery, oral and maxillofacial surgery, dentistry, medicine), practising clinicians and medical students

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Updated 10 October 2026. Educational summary written in our own words from current guidelines and primary trials; no drug doses; not advice for an individual patient. Verify current guidelines and Indian regulatory approvals before treatment decisions. Patients and families: please see the patient guides at drharitha.co.in.

Head & Neck Cancer

Oral cavity · Oropharynx (HPV) · Larynx · Hypopharynx · Nasopharynx (EBV) · PD-L1 CPS · Key points for clinicians · Last updated 11 October 2026

01 At a glance

- Lip and oral cavity cancer is the **commonest cancer in Indian men**: roughly 1.4 lakh new cases and 80,000 deaths a year (GLOBOCAN 2022), about a third of the world total. Worldwide, head and neck cancer causes about 900,000 cases and over 400,000 deaths a year; men outnumber women 2–4 to 1.
- More than 90% are **squamous cell carcinomas**. The site decides the cause, the first symptom and the route of spread: the **oral cavity** (tobacco chewing, areca nut; buccal–gingival cancers in India), the **oropharynx** (tonsil and base of tongue; HPV-driven in 70–80% in the West but a minority in India) and the **larynx and hypopharynx** (smoking and alcohol). The **nasopharynx** is a distinct, EBV-driven disease, rare in India except in the north-east (see section 06).
- **Stage drives cure**: about 70–90% of patients with stage I–II disease are alive at 5 years, usually after a single treatment (surgery or radiotherapy). Two-thirds of Indian patients present with stage III–IV disease, which needs two or three modalities and costs function as well as money.
- Since 2024 the treatment map has moved: **perioperative pembrolizumab** for resectable PD-L1-positive disease ([KEYNOTE-689](#) ^[1]), **nivolumab added to postoperative chemoradiation** for HPV-negative high-risk disease ([NIVOPOSTOP](#) ^[2]) and **immunotherapy first line** for recurrent or metastatic disease ([KEYNOTE-048](#) ^[3]).
- The avoidable harms in Indian practice are **delay before the biopsy** (ulcers treated with ointments, neck nodes treated as tuberculosis, hoarseness treated as a cold), **unplanned radiotherapy gaps**, and **teeth extracted after radiotherapy**.

Figure 1. Three working groups. More than 90% of head and neck cancers are squamous cell carcinomas; the site decides the cause, the first symptom, the route of spread and the first treatment. Proportions are approximate (Indian hospital-based registries).



02 Clinical presentation, common traps & genetic causes

Who is at risk

Factor	Size of risk	Clinical note
Smoked tobacco (cigarettes, bidis, cigars, pipes)	5- to 25-fold in heavy smokers; dose-dependent; excess risk fades over about 20 years after stopping	Larynx, hypopharynx, oropharynx and oral cavity (INHANCE ^[4]).
Smokeless tobacco and areca nut (gutka, khaini, zarda, mawa, pan, pan masala)	Areca nut alone is an independent carcinogen; effect multiplies with tobacco and alcohol	The main cause of buccal mucosa and gingivobuccal cancers in India; also oral submucous fibrosis (Guha 2014 ^[5]).
Alcohol	Five- to sixfold at >50 g/day; multiplies tobacco risk	Spirits carry more risk than wine in some studies; alcohol-containing mouthwash used heavily adds a little.
HPV (mainly type 16)	Causes most tonsil and base-of-tongue cancers in high-income countries	Younger, often non-smoking patients with small primaries and cystic neck nodes; much less common in India.
Epstein-Barr virus	Nasopharyngeal carcinoma	Undifferentiated cancer in a neck node: test EBER and look at the nasopharynx.
Poor oral hygiene, chronic trauma	Modest independent risk (INHANCE ^[6])	Sharp teeth and ill-fitting dentures are not proven causes, but they hide and irritate lesions: examine under them.
Immunosuppression, Fanconi anaemia, prior head and neck RT	Higher and earlier risk	Fanconi anaemia: cancers at a young age and extreme sensitivity to RT and cisplatin.
Oral potentially malignant disorders	Erythroplakia highest risk; leukoplakia and oral submucous fibrosis lower but real	Biopsy the reddest or thickest area; stop tobacco and areca nut; follow up for life.

How head and neck cancers present

Site	Typical first symptom	What to know
Oral cavity	Non-healing ulcer, white or red patch, lump, loose tooth, ill-fitting denture, trismus	Buccal cancers are often treated as infection or trauma and seldom present as T1. Numb lip or chin means mandibular nerve invasion.
Oropharynx	Sore throat, pain on swallowing, referred earache; painless neck lump (HPV)	A cystic neck "branchial cyst" in an adult over 40 is a metastasis until proven otherwise. Palpate the base of tongue.
Larynx (glottis)	Hoarseness	Hoarseness >3 weeks in a smoker needs laryngoscopy, not antibiotics. Glottic cancer is found early and rarely spreads to nodes.
Larynx (supraglottis), hypopharynx	Pain or difficulty swallowing, referred earache, neck mass, late stridor	Usually late and node-positive; weight loss and aspiration common.

Site	Typical first symptom	What to know
Nasopharynx	Neck node (often level II or V, bilateral), unilateral serous otitis media, nasal block or bleeding, double vision or facial numbness	EBV-driven; MRI and nasoendoscopy; treated with radiotherapy and chemotherapy, not surgery (see section 06, nasopharyngeal carcinoma).
Any site	Neck mass without an obvious primary	FNAC first; never excise a neck node before examining the upper aerodigestive tract.

Figure 3. When to examine and biopsy. Most delays in India happen before the first biopsy: ulcers treated with ointments, neck nodes treated as TB, and hoarseness treated as a cold.

- **The two-week rule:** any ulcer, patch or lump in the mouth that persists 2 weeks after removing an obvious irritant needs a biopsy. Repeated courses of antibiotics, antifungals or ointments only buy the tumour time.
- **"Oral TB" and "TB lymphadenitis":** tuberculosis of the tongue and neck exists, but a hard, painless node in a tobacco user is cancer until FNAC says otherwise. Start antituberculous treatment only on microbiological or histological proof.
- **Trismus in an areca nut chewer** may be oral submucous fibrosis, a cancer in the masticator space, or both. Examine carefully and image if mouth opening is falling or one-sided.
- **Second primary cancers:** field cancerisation means up to 1 in 5 survivors develops another tobacco- or alcohol-related tumour (head and neck, oesophagus, lung). Examine the whole upper aerodigestive tract at diagnosis.
- **HPV-positive cancer is not only for the young non-smoker:** it also occurs in older people and in smokers, and heavy smoking (more than about 10 pack-years) erodes its better prognosis ([Gillison 2012](#) ^[7]).

SHARE WITH PATIENTS: PRESENTATION AND MYTHS

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

[🇮🇳 Telugu–English handout: mouth and throat cancer warning signs, and the 2-minute mouth self-check \(తెలుగు · English\)](#)

[Only smokers get mouth and throat cancer?](#)

[Chewing tobacco is safer than smoking cigarettes?](#)

[Pan masala without tobacco is completely safe?](#)

[A mouth ulcer that doesn't hurt can't be cancer?](#)

[White or red patches inside the mouth are always harmless?](#)

[A change in voice that won't go away is always due to a cold?](#)

[A painless swelling in the neck is never serious?](#)

03 Screening, workup & staging essentials

Screening

- There is no screening test for pharyngeal or laryngeal cancer. For the mouth, **visual oral examination** works: in the Kerala cluster-randomised trial (over 190,000 people aged 35+, three rounds by trained health workers), screening reduced oral cancer deaths by 27% overall and by 29% in tobacco or alcohol users, despite real-life compliance ([Sankaranarayanan 2005](#) ^[8]). India's NP-NCD programme offers it from age 30.
- Opportunistic screening costs nothing: look in the mouth of every tobacco or areca nut user at every visit, including under dentures, and teach the 2-minute self-check (see the patient handout).
- Oral brush cytology, toluidine blue and autofluorescence devices do not replace a biopsy of a suspicious lesion. No drug prevents oral cancer in people with leukoplakia: retinoids and other agents tried in trials are not recommended outside studies.

Workup before treatment

Figure 4. From suspicion to a treatment plan. Biopsy before imaging is fine for an obvious oral lesion, but image before biopsy for deep or laryngeal tumours so the scan is not distorted; never excise a neck node without first looking for a primary.

Step	What to do	Why
Examination	Inspect and palpate the mouth and oropharynx; flexible nasolaryngoscopy; examination under anaesthesia when the extent is unclear	Defines T; looks for synchronous second primaries
Biopsy	Punch or incisional biopsy of the primary; FNAC of a node (core or excision only after the primary search when lymphoma is a question)	Open neck–node biopsy before definitive treatment can worsen control
Imaging of the primary and neck	Contrast CT (bone, larynx cartilage) or MRI (oral tongue, soft tissue, perineural spread, nasopharynx)	Depth, bone invasion, ENE, retropharyngeal nodes
Distant staging	CT chest for all; PET–CT for stage III–IV, heavy smokers and unknown primary	Lung metastases and second lung primaries; PET–CT also finds occult nodes
Pathology	Grade, DOI, PNI, LVI, margins; p16 for every oropharynx cancer; PD–L1 CPS for resectable stage III–IVA and for recurrence	p16 changes staging; CPS opens immunotherapy
Fitness	Performance status, nutrition, creatinine clearance, audiogram, comorbidity, social support	Decides cisplatin versus alternatives and the feasibility of 7 weeks of daily treatment
Dental and swallowing	OPG, extractions, fluoride trays; speech and swallow baseline	Prevents osteoradionecrosis and preserves function

Figure 5. TNM at a glance (simplified from AJCC 8th edition). Depth of invasion, not thickness, now sets the oral cavity T category; ENE moves a neck to N3b; HPV-associated oropharynx cancer has its own, kinder table.

Figure 6. Where each site drains. Levels II–IV carry most nodal disease; midline primaries (base of tongue, soft palate, supraglottis) need both sides of the neck treated.

- **Depth of invasion** is measured from the basement membrane of adjacent normal mucosa, not tumour thickness. It sets the T category (DOI >5 mm = at least T2; >10 mm = T3) and predicts nodal spread: patients with nodal metastases had a mean DOI of 5.6 mm versus 3.8 mm in those without.
- **Mandible:** bone invasion is hard to see before surgery. Edentulous jaws are invaded more easily (no tooth socket barrier); even minimal cortical invasion in an edentulous jaw usually needs a segmental resection.
- **Oropharynx:** test p16 in every case; confirm HPV by DNA/RNA if the decision depends on it. Discordant results (p16+ but HPV–, or the reverse) have survival close to HPV–negative cancer ([EPIC-OPC \[9\]](#)).
- **Larynx:** record vocal cord mobility (mobile, impaired, fixed), cartilage invasion on CT and subglottic extension; these decide T stage and whether larynx preservation is possible.
- **Unknown primary** (squamous cancer in a neck node): p16 and EBER on the node, PET-CT before any biopsy under anaesthesia, then panendoscopy with bilateral tonsillectomy and directed biopsies; transoral lingual tonsillectomy finds many hidden base-of-tongue primaries. N1 without ENE: surgery or RT alone; N2b or more: chemoradiation to both necks and the likely mucosal sites.
- **PET-CT timing:** after chemoradiation, wait 12 weeks; earlier scans give false positives.

04 Biomarkers that change treatment

In this section: [HPV-associated versus HPV-negative cancer: a side-by-side guide](#) · [Biomarkers that change treatment](#)

HPV-associated versus HPV-negative cancer: a side-by-side guide

HPV-driven and tobacco-driven squamous cancers of the oropharynx look alike under the microscope but are different diseases: different causes, molecular routes, patients, stage tables, prognosis and late-effect burden. The treatment backbone is still the same outside trials. This guide compares them point by point. HPV accounts for 70–80% of oropharyngeal cancer in North America and Europe; in India it is a minority (about 1 in 8 in the ConCERT trial), and many Indian HPV-positive patients also use tobacco.

Figure 7. Two diseases in one site. HPV status changes the stage and the prognosis but, outside trials, not the treatment; replacing cisplatin with cetuximab was worse in two randomised trials, and dose de-escalation remains investigational.

1. Molecular pathogenesis

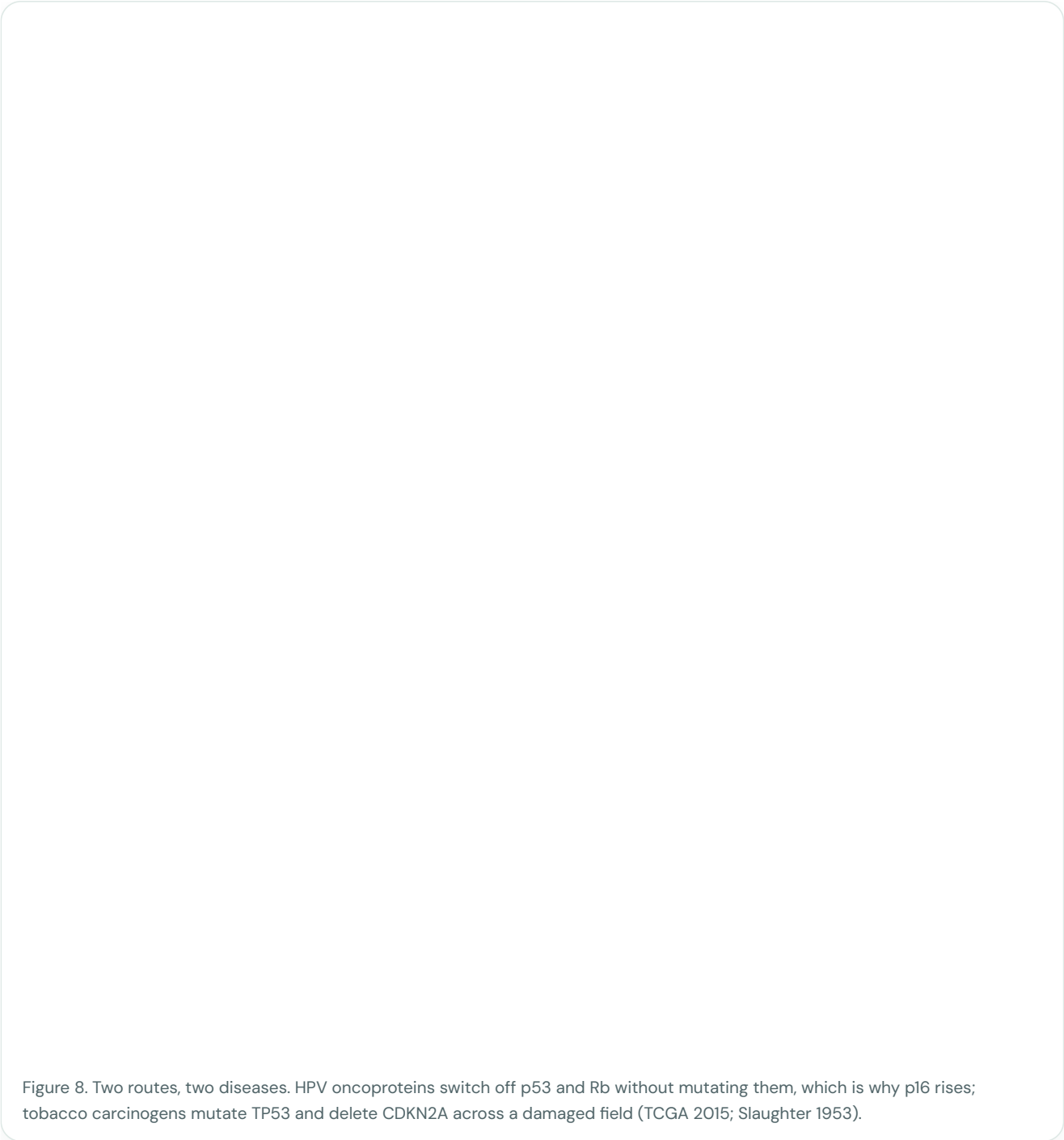


Figure 8. Two routes, two diseases. HPV oncoproteins switch off p53 and Rb without mutating them, which is why p16 rises; tobacco carcinogens mutate TP53 and delete CDKN2A across a damaged field (TCGA 2015; Slaughter 1953).

Feature	HPV-associated	HPV-negative (tobacco, areca nut, alcohol)
Cause and latency	Persistent oral infection with high-risk HPV (HPV-16 in most); acquired sexually, cancer usually >10 years later. E6 antibodies appear years before diagnosis.	Carcinogen exposure over decades; risk rises with dose and falls slowly after stopping.
Where it starts	Reticulated crypt epithelium of the palatine and lingual tonsils (tonsil, base of tongue), where the basal layer is exposed.	Any mucosal site; the whole exposed field (mouth, pharynx, larynx, oesophagus, lung) is at risk.
p53	Protein degraded by viral E6; the TP53 gene is usually wild type.	TP53 mutated in most tumours, often early (p53 IHC abnormal in dysplasia).
Rb and p16	Rb inactivated by E7 → loss of feedback → p16 strongly over- expressed (hence p16 IHC as surrogate).	CDKN2A (p16) deleted or silenced; Rb pathway activated through CCND1 (cyclin D1) amplification.

Feature	HPV-associated	HPV-negative (tobacco, areca nut, alcohol)
Other genomic changes (TCGA ^[10] 2015 ^[10])	Fewer copy-number changes; PIK3CA mutation or amplification common; TRAF3 loss and E2F1 gain characteristic.	Chromosome 3p, 9p and 17p loss and 11q13 gain; EGFR amplification, FAT1 and NOTCH1 loss; marked chromosomal instability.
Field cancerisation	Limited; second primaries much rarer.	Typical: dysplastic or genetically altered mucosa beyond the tumour explains synchronous and metachronous primaries (Slaughter 1953 ^[11] , Braakhuis 2002 ^[12]).
Tumour microenvironment	Often T-cell inflamed; better oxygenated in many tumours.	More hypoxic and immune-excluded; hypoxia is a key cause of radioresistance.
Why it responds	Wild-type p53 can still trigger apoptosis after radiation; viral antigens attract immune attack.	Mutant p53, hypoxia and repair pathways blunt radiation and chemotherapy.
Blood marker	Circulating tumour HPV DNA is detectable and falls with treatment (research tool for surveillance).	No validated blood marker.

- **How HPV transforms a cell:** the circular viral genome usually integrates into host DNA at the E2 gene; losing E2 removes the brake on E6 and E7. E6 (with E6-associated protein) sends p53 for degradation, so damaged cells keep dividing and escape apoptosis; E7 releases E2F from Rb and inactivates p21 and p27, driving S-phase entry. Persistent E6/E7 expression is needed to keep the cancer growing.
- **Why p16 is a good surrogate:** with Rb disabled, the cell over-produces p16 in a futile attempt to stop the cycle. In tobacco-driven cancer the opposite happens: CDKN2A is deleted, so p16 is low. That is why strong, diffuse p16 in an oropharyngeal cancer means HPV in most cases, but p16 outside the oropharynx often does not.
- **Why HPV cancers do better:** intact (non-mutated) p53 still mediates radiation-induced apoptosis, tumours are often less hypoxic and are immunogenic (viral antigens). Smoking adds tobacco-type mutations and erodes this advantage ([Gillison 2012](#) ^[7], [MARCH-HPV](#) ^[13]).
- **Field cancerisation in tobacco cancer:** genetically altered clones spread laterally through the mucosa before invasion. This explains second primaries, local recurrences after "clear" margins, and why stopping tobacco matters even after cure.
- **Epidemiology of the virus:** oral HPV DNA is found in about 7% of adults (HPV-16 in 1%), three times more often in men, and is linked to the number of oral sex partners ([D'Souza 2007](#) ^[14], [Gillison 2008](#) ^[15]). Most infections clear; long-term partners of patients are not at increased risk (oral HPV in 4%) ([D'Souza 2014](#) ^[16]).

2. Clinical presentation, diagnosis and staging

Feature	HPV-associated oropharynx	HPV-negative oropharynx
Age (ICON-S)	Median 57 years; rising in older adults	Median 61 years
Sex	About 84% men	About 76% men
Exposures	Often never or light smokers; more sexual (including oral sex) partners	Heavy tobacco and alcohol; areca nut in India
First symptom	Painless neck lump, often cystic; may be the only finding (unknown primary)	Sore throat, odynophagia, referred otalgia, weight loss

Feature	HPV-associated oropharynx	HPV-negative oropharynx
Primary and nodes (7th ed.)	Small primary (T1–T2 in 64%) with bulky nodes (N2–N3 in 69%)	Larger primary (T1–T2 in 44%); N2–N3 in 51%
Other second cancers	Fewer synchronous (1 vs 9%) and metachronous (6 vs 13%) primaries	Field cancerisation: head and neck, oesophagus, lung
Staging	AJCC 8th HPV table: most are stage I–II despite large nodes (ICON-S ^[17])	Standard oropharynx table: most stage III–IV
Outcome after chemoradiation (RTOG 0129)	8-year OS 71%; locoregional failure 20%	8-year OS 30%; locoregional failure 52%
Distant metastasis	About 10% (not significantly fewer); lung most common	About 16%
After relapse	Median survival 2.6 years (Fakhry 2014 ^[18])	Median survival 0.8 years

- **The classic HPV presentation:** a fit man in his 50s with a painless, often cystic level II node and a small or invisible tonsil or base-of-tongue primary. A "branchial cyst" in an adult is a metastasis until proven otherwise; never excise it before examining and imaging the pharynx.
- **Testing:** p16 IHC on every oropharyngeal squamous cancer and every squamous neck node of unknown primary (strong, diffuse nuclear and cytoplasmic staining in ≥70% of cells; [ASCO/CAP 2018](#) ^[19]). Confirm with HPV DNA or RNA (ISH or PCR) when the decision depends on it: about 10% of p16-positive tumours are HPV-negative, and discordant tumours have 5-year survival of 53–55% compared with 81% when both tests are positive ([EPIC-OPC](#) ^[9]). p16 on fine-needle aspirates is less sensitive (only a third met the threshold in one series): use a cell block or HPV PCR.
- **Do not test p16 routinely** in oral cavity, laryngeal or hypopharyngeal cancer: HPV is present in a minority (about 11–17% in US data) and has no treatment implication there.
- **Staging:** the AJCC 8th edition HPV table (from [ICON-S](#) ^[17]) down-stages node-positive disease: T1–T2 with ipsilateral nodes ≤6 cm is stage I. Explain this to patients: "stage I" with a large neck node is still treated with full curative intent, and the stage numbers cannot be compared with HPV-negative stages.
- **Prognostic groups:** HPV status, pack-years and nodal stage define risk ([Ang 2010](#) ^[20]); retropharyngeal nodes, PIK3CA mutation and continued smoking worsen outcome in HPV-associated disease.

Figure 9. HPV status and pack-years together predict outcome. These risk groups shaped de-escalation trials, which so far enrol mainly low-risk patients; outside trials, treatment is not reduced.

3. Management compared

Setting	HPV-associated	HPV-negative	Evidence
T1–T2, NO or a single node ≤3 cm	RT alone (non-smoker, no adverse nodal features) or TORS + neck dissection; chemoradiation if smoker or adverse features	RT or transoral/open surgery + neck dissection; adjuvant therapy more often needed	ORATOR ^[21] , NCCN
Locoregionally advanced	Cisplatin chemoradiation; avoid trimodality (surgery then CRT)	Cisplatin chemoradiation, or surgery + adjuvant RT/CRT when function allows	MACH-NC 2021 ^[22]
Radiosensitiser	Cisplatin (weekly or 3-weekly). Cetuximab is worse : 5-year OS 78 vs 85%, 2-year OS 89 vs 98%, LRF 23 vs 9%	Cisplatin; cetuximab not compared directly but weaker	RTOG 1016 ^[23] , De-ESCALaTE HPV ^[24] , ARTSCAN III ^[25]
Cisplatin-ineligible	Carboplatin-based or weekly docetaxel; RT alone if frail	Same	Patil 2023 ^[26]
Perioperative immunotherapy	No reliable data: only about 4% of KEYNOTE-689 patients were HPV-positive, and NIVOPOSTOP had very few	Pembrolizumab (CPS ≥1, resectable III–IVA) or nivolumab with postoperative cisplatin–RT	KEYNOTE-689 ^[1] , NIVOPOSTOP ^[2]

Setting	HPV-associated	HPV-negative	Evidence
Postoperative high risk (ENE, positive margin)	Cisplatin-RT remains standard; the benefit of adding cisplatin for ENE alone is debated	Cisplatin-RT (± nivolumab)	ECOG 3311 ^[27] , EORTC 22931 ^[28]
Treatment reduction	Investigational: lower adjuvant RT dose after TORS, reduced-dose CRT, RT alone in selected low-risk patients, induction-selected dose reduction, hypoxia-guided de-escalation	Not applicable	See table below
Recurrent/metastatic	Same systemic therapy; PD-1 inhibitors work regardless of HPV (nivolumab median OS 9.1 vs 4.4 months in p16+ in CheckMate 141). Resect or ablate isolated lung metastases in selected patients.	Same systemic therapy	KEYNOTE-048 ^[3] , CheckMate 141 ^[29]
Surveillance	Same schedule; ctHPV DNA promising (two consecutive positives predicted recurrence in 94%; negative predictive value ~100%) but not standard	Same schedule; second-primary vigilance and lung CT for smokers	Chera 2020 ^[30] , PET-NECK ^[31]

- **The rule outside trials:** treat HPV-associated cancer by its stage and site with the same standard options as HPV-negative cancer; use cisplatin, not cetuximab; avoid trimodality treatment by choosing the route least likely to need it.
- **Choosing RT or TORS in early disease:** both cure most patients. TORS suits small, accessible, lateralised primaries with limited nodal disease where pathology is unlikely to show ENE or positive margins; otherwise RT-based treatment avoids surgery followed by full chemoradiation.
- **Treatment de-escalation** remains investigational; the trials below show both the promise (less toxicity) and the risk (more failures). Offer it only within a trial.

Trial	Design	Result	Message
ECOG 3311 ^[27]	TORS, then risk-based adjuvant therapy; intermediate risk randomised to 50 vs 60 Gy	3-year PFS 95 vs 94%; grade ≥3 toxicity 15 vs 25%; better quality of life with 50 Gy. Low risk (no adjuvant): PFS 97%	Lower-dose adjuvant RT is promising after TORS
NRG-HNO02 ^[32]	Non/light smokers; 60 Gy RT alone (accelerated) vs 60 Gy + weekly cisplatin	2-year PFS 88 vs 91%; locoregional failure 10 vs 3%; RT-alone arm missed its target	Chemotherapy still matters at reduced dose
ORATOR ^[21]	RT (± chemo) vs TORS + neck dissection (± adjuvant)	3-year OS 87 vs 88%; swallowing QoL slightly better with RT; 71% of TORS patients still needed full-dose RT	TORS did not reduce total treatment for most
ORATOR2	Reduced-dose RT (60 Gy + cisplatin) vs TORS + reduced adjuvant RT	2-year OS 100 vs 89%; closed early after two TORS-related deaths	Surgical de-escalation carries its own risks
MC1273 ^[33] / MC1675	After surgery: 30–36 Gy twice daily + docetaxel vs 60 Gy + cisplatin	Late grade ≥3 toxicity ~2 vs 7%; better swallowing; PFS 87 vs 95% (early)	Less toxicity, possible loss of control
Chera 2019 ^[34]	Single-arm: 60 Gy ± reduced-dose cisplatin, low-smoking patients	2-year PFS 86%, OS 95%; no grade ≥3 events reported; no permanent feeding tubes	Hypothesis-generating

Trial	Design	Result	Message
E1308, OPTIMA	Induction chemotherapy, then RT dose by response	Good control in low-risk (<10 pack-years, ≤T3/N2b); toxicity rose with RT dose	Response-adapted dosing is investigational
Lee 2024 ^[35]	Hypoxia PET selects non-hypoxic tumours for lower dose	Feasible with high control in a phase II study	Biology-guided selection under study

4. Toxicity and survivorship compared

Issue	HPV-associated	HPV-negative
Who carries the burden	Younger patients who will usually be cured: decades of living with late effects (dysphagia, xerostomia, fibrosis, osteoradionecrosis, hearing loss)	Older patients with more comorbidity; non-cancer deaths and second cancers compete with late effects
Acute toxicity	Same as for any oropharyngeal chemoradiation; cetuximab swaps hearing, kidney and GI toxicity for skin and infusion reactions, without being safer overall	Same; poorer baseline nutrition and lung function in heavy smokers
Swallowing	Avoid trimodality treatment; DO-IMRT and swallow exercises; de-escalation trials report better swallowing	Late dysphagia and aspiration more often; continued smoking and alcohol worsen them
Jaw and teeth	Osteoradionecrosis risk after oropharyngeal IMRT remains real; dental care for life	Same, often with poorer dentition at baseline
Second primaries	Uncommon	Up to 1 in 5 survivors; lung CT if ≥20 pack-years
Psychosocial	Anxiety about a sexually transmitted cause, partners and disclosure; reassure with facts	Stigma of tobacco and alcohol; addiction support
Follow-up length	Late recurrences and late effects justify long follow-up; ctHPV DNA under study	Intensive for 2–3 years, then lifelong for second primaries

- **What to tell patients and partners:** HPV is very common and most people clear it; the cancer is not caught by kissing or ordinary contact; long-term partners do not need special tests, and studies have not found them to be at increased risk. HPV vaccination of children (girls and boys where available) before sexual debut prevents infection with cancer-causing types.
- **Prevention:** a nine-valent vaccine is approved in the US for preventing HPV-associated oropharyngeal cancer, and vaccinated young adults have far less oral HPV infection. India now has its own HPV vaccine and a programme for adolescent girls (Dr. Haritha to confirm current scope).
- **Indian practice:** test p16 in every oropharyngeal cancer (it changes stage and counselling), but do not de-escalate; many p16-positive Indian patients smoke or chew tobacco and belong to the intermediate-risk group.
- **HPV outside the oropharynx:** p16 or HPV positivity in oral cavity, larynx or hypopharynx may carry a modestly better prognosis but has no treatment implications.

Biomarkers that change treatment

- **p16/HPV** is the only biomarker that changes staging. In RTOG 0129, 3-year survival was about 82% with HPV-positive and 57% with HPV-negative oropharynx cancer ([Ang 2010](#) ^[20]). Outside trials it does **not** change

treatment: replacing cisplatin with cetuximab was worse in [RTOG 1016](#) ^[23] (5-year OS 78 vs 85%) and [De-^{\[24\]} ESCALaTE HPV](#) ^[24] (2-year OS 89 vs 98%). **p16 outside the oropharynx** is common and does not mean HPV-driven cancer; do not test oral cavity or larynx routinely.

- **PD-L1 combined positive score (CPS)** counts PD-L1-staining tumour cells, lymphocytes and macrophages per 100 tumour cells (22C3 assay). CPS ≥ 1 opens perioperative pembrolizumab and first-line pembrolizumab; CPS ≥ 20 identifies those who can have pembrolizumab alone ([KEYNOTE-048](#) ^[31]).
- **Pathological risk features** are the biomarkers that decide adjuvant therapy most often: positive margins and extranodal extension (chemoradiation) versus pT3–T4, multiple nodes, perineural and lymphovascular invasion (RT alone).
- **EGFR** is overexpressed in most head and neck cancers, but its level does not predict benefit from cetuximab and is not tested.
- **Not useful in routine practice:** tumour mutational burden, HRAS, PIK3CA and other NGS findings outside trials; serum markers (SCC antigen, CYFRA 21-1) for diagnosis or follow-up.
- Biology explains radioresistance: tumour hypoxia (well-oxygenated cells are 2.5–3 times more radiosensitive), rapid repopulation during gaps, continued smoking and low haemoglobin. Hypoxic sensitisers such as nimorazole improved locoregional control in a meta-analysis ([Overgaard 2011](#) ^[36]) but are not used widely; erythropoiesis-stimulating agents worsened outcomes ([DAHANCA 10](#) ^[37]).

05 Local therapy: surgery & radiotherapy

Surgery

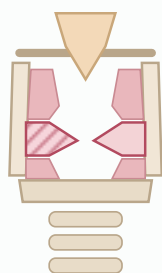
Figure 10. What the head and neck surgeon offers. Margin status and extranodal extension on the final pathology decide adjuvant therapy, so the operation and the reconstruction are planned with the radiation oncologist from day one.

- **Oral cavity: surgery first** for almost every resectable tumour; it gives pathological staging (DOI, margins, nodes) and causes less long-term morbidity than radiotherapy to the mouth. Plan a 1 cm mucosal margin to reach a final margin >5 mm; re-excise close (<2 mm) or involved margins in early disease rather than relying on RT.
- **Elective neck dissection in the clinically node-negative neck:** in a Tata Memorial trial of 500 patients with early oral cancer (mostly tongue), elective dissection improved 3-year survival from 67.5% to 80% and disease-free survival from 45.9% to 69.5% compared with watch-and-wait ([D'Cruz 2015](#) ^[38]). The benefit was clearest with DOI >3 mm. Selective dissection of levels I–III (IV for tongue) is standard.
- **Sentinel node biopsy** is an alternative in expert centres for T1–T2 cNO tumours: in [Senti-MERORL](#) ^[39], 5-year neck control and survival matched elective dissection, with less shoulder morbidity. Less reliable for floor of mouth.
- **Neck by site:** tongue and floor of mouth DOI >3 mm → elective neck (bilateral if near the midline); DOI ≤1 mm and lateralised → observe; 1–3 mm → SLNB or elective dissection; T1 lower lip → observe; buccal, gingiva, retromolar trigone, hard palate → elective dissection.

- **Buccal mucosa:** deceptively easy-looking but hard to clear; the buccal space allows early deep spread to skin. Reconstruct the cheek lining (free flap for all but the smallest defects) or severe trismus follows; jaw exercises are part of treatment.
- **Mandible:** marginal mandibulectomy keeps continuity when tumour abuts but does not enter medullary bone; segmental resection for invasion, reconstructed with a vascularised fibula (or scapula) and plate. Primary reconstruction is standard; an anterior defect left unreconstructed causes the "Andy Gump" deformity.
- **Transoral surgery** (robotic, TORS, or laser, TLM) for selected T1–T2 oropharynx and supraglottic cancers avoids mandibulotomy. Choose it only when margins are likely clear and adjuvant chemoradiation unlikely; triple-modality treatment is the worst outcome for swallowing. In [ORATOR](#) ^[21] swallowing quality of life at 1 year was slightly better after RT than after TORS with neck dissection, below the clinically meaningful threshold.
- **Larynx:** transoral laser cordectomy for early glottic cancer; open partial laryngectomy for selected cases; total laryngectomy for T4a with cartilage destruction or a non-functional larynx, and for salvage. Voice after laryngectomy: tracheo-oesophageal puncture with voice prosthesis, electrolarynx or oesophageal speech.
- **Neck in oropharynx/larynx:** levels II–IV (bilateral for midline primaries); comprehensive dissection for N2–N3; glottic T1–T2: no elective neck.
- Reconstruction choices: radial forearm (tongue, floor of mouth, soft palate), anterolateral thigh (large soft-tissue defects), fibula or scapula (mandible, maxilla), pectoralis major as a robust regional flap. Free-flap success rates are 93–99% in experienced hands.

Larynx and hypopharynx surgery: types, pros and cons, outcomes

The operation is chosen by tumour extent, cord mobility, cartilage invasion, lung function (partial operations mean some aspiration while swallowing is learnt) and the patient's priorities for voice, swallowing and the stoma. Organ preservation with chemoradiation and these operations are complementary: a surgeon able to offer salvage surgery must be part of the plan from the start.



Transoral laser cordectomy

REMOVES

Tumour on the vocal cord, through the mouth

KEEPS

Rest of the larynx; no neck wound; no tracheostomy

Glottic Tis–T1 (selected T2)



Supraglottic laryngectomy

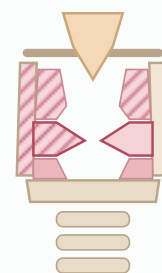
REMOVES

Epiglottis and false cords (above the vocal cords)

KEEPS

Both vocal cords and the natural voice

Supraglottic T1–T2; good lung function



Vertical partial laryngectomy

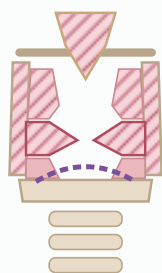
REMOVES

One side of the larynx with its cartilage

KEEPS

The other cord; natural airway after healing

Selected T1–T2 glottic when laser access is poor



Supracricoid laryngectomy

REMOVES

Both cords and the thyroid cartilage

KEEPS

Cricoid and at least one arytenoid; no permanent stoma

Selected T2–T3, limited T4a; expert centres



Total laryngectomy

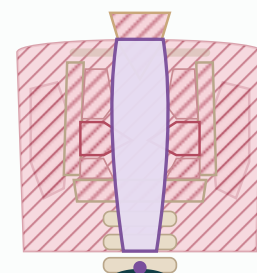
REMOVES

Whole larynx; trachea brought out as a neck stoma

KEEPS

Swallowing; speech with a voice valve

T4a, dead larynx, salvage after RT



Total laryngopharyngectomy

REMOVES

Larynx and the surrounding pharynx

KEEPS

Swallowing via a flap or jejunum tube

Advanced hypopharynx and post-cricoid cancer

■ Tissue removed
 ■ Cartilage kept
 ■ Reconstruction (flap or jejunum)
 ○ Stoma with voice valve
 --- Pexy

Figure 11. Larynx and hypopharynx operations, from least to most (schematic, front view). Partial operations keep the voice and natural airway but need good lung function and swallowing rehabilitation; total laryngectomy and laryngopharyngectomy give the best local control for destroyed or non-functioning organs at the cost of a permanent stoma.

Procedure	Best suited to	Advantages	Disadvantages	Outcomes and function (approximate, from surgical series)
Transoral laser cordectomy (TLM)	Glottic Tis–T1, selected T2; good laryngeal exposure	Single short admission; no neck wound or tracheostomy; can be repeated; keeps RT in reserve	Needs a good view of the whole tumour; anterior commissure involvement raises recurrence; deeper cordectomy gives a breathier voice	T1 local control about 85–95%, larynx preservation above 95% with salvage; voice similar to RT after superficial cordectomy, poorer after deep resection

Procedure	Best suited to	Advantages	Disadvantages	Outcomes and function (approximate, from surgical series)
Vertical partial laryngectomy (open)	Selected T1–T2 glottic when laser access is poor	Natural voice and airway kept; complete pathology	Temporary tracheostomy; rough voice; largely replaced by laser surgery and RT	Local control comparable to RT in selected series; most patients decannulated
Supraglottic laryngectomy (transoral or open)	Supraglottic T1–T2 (selected T3 with pre-epiglottic spread), mobile cords, good lung function	Keeps normal voice; one-stage treatment of the primary and neck	Early aspiration while swallowing is relearned; bilateral neck dissection needed; often adjuvant RT	Local control about 85–90% for T1–T2; most return to an oral diet after swallow rehabilitation
Supracricoid partial laryngectomy (CHP/CHPE)	Selected T2–T3 and limited T4a glottic or supraglottic; at least one mobile arytenoid; no major subglottic extension; FEV1 adequate	Avoids a permanent stoma; preserves speech and swallowing	Rough, breathy voice; temporary tracheostomy and feeding tube; aspiration pneumonia risk; long rehabilitation; needs an expert team	Local control about 90% or more in experienced series; most patients decannulated and eating by mouth within weeks to months
Total laryngectomy + voice prosthesis	T4a with cartilage destruction or extralaryngeal spread; non-functioning larynx; salvage after RT/CRT	Best local control for destroyed larynx; no aspiration; swallowing usually good	Permanent stoma; loss of natural voice and smell; pharyngocutaneous fistula; stoma and humidifier care; social impact	Fluent tracheo-oesophageal speech in roughly 70–90%; fistula about 10–20% after primary surgery and up to about 30% after salvage (a muscle or free flap onlay lowers it)
Total laryngopharyngectomy (± oesophagectomy) with free jejunum, tubed flap or gastric pull-up	Advanced hypopharynx and post-cricoid cancer; salvage	Removes bulky disease; reconstruction restores swallowing in most	Major surgery; fistula, stricture, flap failure; adjuvant RT usually needed; voice by prosthesis	Most resume an oral diet; strictures in a minority need dilatation; long-term survival limited by distant spread in advanced hypopharyngeal cancer
Partial pharyngectomy (transoral or open)	Selected small pyriform sinus or posterior pharyngeal wall tumours	Larynx preserved	Few suitable patients; usually followed by RT	Good local control in selected early tumours; function similar to RT alone

- **Comparing routes for early glottic cancer:** laser surgery and RT give similar local control and laryngeal preservation; laser is one short procedure and keeps RT for later, RT avoids anaesthesia and suits anterior commissure tumours. Choose with the patient by access, voice needs and travel.
- **Larynx preservation versus total laryngectomy** for T3: survival is similar ([VA Larynx^{\[40\]}](#), [RTOG 91-11^{\[41\]}](#)); for the pyriform sinus, [EORTC 24891^{\[42\]}](#)); for T4a with cartilage destruction, or a larynx that no longer protects

the airway, laryngectomy gives better results.

- **Voice after laryngectomy:** a tracheo-oesophageal voice prosthesis (primary or secondary puncture) is the most natural option; electrolarynx and oesophageal speech are alternatives. Speech therapy should meet the patient before surgery.
- Figures in this table are approximate ranges from surgical series and guidelines, given for counselling; outcomes depend heavily on case selection and the experience of the team. *Flagged for Dr. Haritha's review.*

Radiotherapy

Figure 12. Radiotherapy schedules (illustrative). Head and neck squamous cancers repopulate fast during treatment gaps, so time matters as much as dose.

- **IMRT is standard:** it spared salivary function compared with conventional RT in randomised trials, including a Tata Memorial trial ([PARSPORT](#) ^[43], [Gupta 2012](#) ^[44]); dysphagia-optimised IMRT improved patient-reported swallowing ([DARS](#) ^[45]). Daily image guidance allows tighter margins.
- **Altered fractionation** without chemotherapy improves survival over standard RT (hyperfractionation most; [MARCH](#) ^[46], [Bourhis 2006](#) ^[47]), but does not replace concurrent chemotherapy; with cisplatin, give once-daily RT.

- **Time matters:** start postoperative RT within 6 weeks and finish within about 100 days of surgery ([Ang^{\[48\]} 2001^{\[48\]}](#)); avoid gaps during definitive RT. Continued smoking during RT lowers response and survival.
- **Definitive RT for oral cancer** is reserved for those who cannot have surgery: it controls the primary less well and carries a higher risk of osteoradionecrosis. Brachytherapy boosts suit small, accessible tumours in experienced centres.
- **Glottic T1:** small-field RT with slightly larger fractions gives local control comparable to laser surgery and spares the other cord; altered fractionation improves control. Supraglottic and subglottic tumours need bilateral elective nodal RT.
- **After definitive (chemo)RT:** clinical review at 4–6 weeks, PET-CT at 12 weeks; neck dissection only for residual disease or an unequivocally positive PET. In [PET-NECK^{\[31\]}](#) (564 patients with N2–N3 disease), PET-CT surveillance gave the same 2-year survival as planned neck dissection and avoided most operations. Salvage surgery for residual primary disease.
- Protons may spare normal tissue further (lower feeding-tube rates in one trial) but are costly and not standard.
- **Re-irradiation** for recurrence or a second primary in an irradiated field: salvage surgery first if possible; postoperative re-irradiation only for high-risk pathology; re-irradiation with chemotherapy (or SBRT) for selected unresectable recurrences at experienced centres. Treatment deaths approach 10% and severe toxicity up to 50%: select carefully by prior dose, interval, volume and fitness.

SHARE WITH PATIENTS: SURGERY AND RADIOTHERAPY

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

[Telugu–English handout: mouth, teeth, food and swallowing during head and neck radiotherapy \(తెలుగు-English\)](#)

[A biopsy makes mouth or throat cancer spread?](#)

[Every mouth cancer needs removal of the whole jaw or tongue?](#)

[Radiotherapy to the head and neck always leaves you permanently unable to swallow?](#)

[If a patient can't have surgery, the cancer can't be cured?](#)

o6 Systemic therapy: indications & options

In this section: [Nasopharyngeal carcinoma](#) · [Quick-reference tables](#)

Indications and options only; no doses. Benefits are given in absolute terms where possible. Trial names link to the primary publications.

Chemotherapy with radiotherapy (locally advanced disease)

Figure 13. Three routes for locally advanced disease. Concurrent chemoradiation adds about 6.5% absolute 5-year survival over radiotherapy alone (MACH-NC); the choice of route is about function as much as cure.

- **Concurrent chemoradiation** improved overall survival over RT or surgery alone in 71 trials (10,680 patients): absolute gain 6.5% at 5 years, 3.6% at 10 years, from fewer locoregional failures ([MACH-NC 2021](#) ^[22]). There was **no benefit over age 70** (HR 0.97); RT alone is usual for older or frail patients.
- **Cisplatin is the sensitiser**, weekly or every 3 weeks, aiming at a cumulative dose of at least 200 mg/m². In the Indian ConCERT trial (270 patients, mostly oropharynx), weekly cisplatin had non-inferior locoregional control with less severe mucositis (41 vs 54%) and kidney injury (4 vs 18%). Earlier, a Tata Memorial trial using a lower weekly dose found 3-weekly cisplatin better in the postoperative oral cavity setting ([Noronha](#) ^[49] [2018](#) ^[49]); weekly dosing must be full-dose to work.
- **Cisplatin-ineligible** (creatinine clearance <50 mL/min, hearing loss, neuropathy, ECOG 2, >10% weight loss): in a Tata Memorial trial of 356 such patients, adding weekly low-dose docetaxel to RT improved 2-year

overall survival from 42% to 51% and DFS from 30% to 42%, with more mucositis ([Patil 2023](#) ^[26]).

Carboplatin-based regimens are alternatives.

- **Cetuximab** with RT beat RT alone (3-year OS 55 vs 45%; [Bonner 2006](#) ^[50], [5-year update](#) ^[51]) but is inferior to cisplatin ([RTOG 1016](#) ^[23], [De-ESCALaTE HPV](#) ^[24], [ARTSCAN III](#) ^[25]), adds nothing to cisplatin-RT ([RTOG 0522](#) ^[52]) and is not used with RT in older or frail patients.
- **Induction chemotherapy** (TPF) beat PF in [TAX 324](#) ^[53] (5-year OS 52 vs 42%) and [TAX 323](#) ^[54] (median 18.8 vs 14.5 months), but adding induction to chemoradiation did not improve survival in [PARADIGM](#) ^[55] or [DeCIDE](#) ^[56]. Use it selectively: larynx/hypopharynx preservation (response selects patients for RT), bulky N2c–N3 disease, borderline–resectable oral cancer, or when RT will be delayed. Neutropenia is frequent: G-CSF and/or antibiotic prophylaxis.
- **Larynx preservation:** in the [VA Larynx](#) ^[40] trial (332 patients), induction cisplatin–5FU then RT in responders gave the same 2-year survival as laryngectomy (68%) and preserved the larynx in 64%; [EORTC](#) ^[42] [24891](#) ^[42] showed the same for pyriform sinus cancer. In [RTOG 91-11](#) ^[41] (547 patients), both concurrent cisplatin–RT and induction then RT improved 5-year laryngectomy-free survival over RT alone (47 and 44 vs 34%); concurrent therapy gave the best locoregional control (68 vs 55%), but 10-year survival trended lower (28 vs 39% with induction), suggesting more non-cancer deaths ([long-term report](#) ^[57]). After TPF induction, cisplatin- or cetuximab-RT gave similar larynx preservation in [TREMLIN](#) ^[58]. T4a tumours with gross cartilage destruction, both cords destroyed or a non-functioning larynx do better with laryngectomy.
- **Checkpoint inhibitors added to definitive chemoradiation** have failed: avelumab ([JAVELIN Head and Neck 100](#) ^[59]), pembrolizumab (KEYNOTE-412) and pembrolizumab instead of cetuximab with RT in cisplatin-unfit patients ([PembroRad](#) ^[60]).

Immunotherapy around surgery

- **Perioperative pembrolizumab** ([KEYNOTE-689](#) ^[1]): in resectable stage III–IVA oral cavity, larynx, hypopharynx or HPV-negative oropharynx cancer, two neoadjuvant doses before surgery and pembrolizumab with and after postoperative RT ($\pm$ cisplatin) improved 3-year event-free survival (about 60 vs 46% in CPS ≥ 1 ; HR 0.73 overall). Overall survival is immature and pathological complete response was only about 3%. About 60% had oral cavity cancer. Benefit was confined to CPS ≥ 1 .
- **Nivolumab with postoperative chemoradiation** ([NIVOPOSTOP](#) ^[2]): after resection with high-risk features (ENE, involved margin, ≥ 4 nodes or multiple PNI), adding nivolumab to cisplatin-RT and then 6 months of nivolumab improved 3-year DFS (63 vs 53%; HR 0.76) through better locoregional control, regardless of PD-L1. Grade ≥ 3 toxicity 74 vs 68%. Very few HPV-positive patients: use only for HPV-negative disease. OS immature.
- These two strategies have not been compared; choose one per patient (pembrolizumab started before surgery continues after it). Cost limits access in India: discuss trial and assistance programmes openly.

Adjuvant therapy after surgery

Figure 14. Adjuvant treatment follows the pathology report. Only positive margins and extranodal extension benefited from adding cisplatin in both EORTC 22931 and RTOG 9501.

- In [EORTC 22931](#) ^[28], adding cisplatin to postoperative RT improved 5-year overall survival from 40% to 53%; in [RTOG 9501](#) ^[61] locoregional control improved but survival did not. A pooled analysis showed the benefit was confined to **positive margins and extranodal extension** ([Bernier 2005](#) ^[62]; [RTOG 9501 at 10](#) ^[63] **years** ^[63]).
- Weekly cisplatin with postoperative RT was non-inferior to 3-weekly and less toxic in [JCOG1008](#) ^[64] (3-year OS 72 vs 59%; less neutropenia, hearing loss and kidney injury).
- Intermediate-risk features (pT3–T4, ≥2 nodes without ENE, PNI, LVI, levels IV–V, close margins) → RT alone; cetuximab with RT improved DFS but not OS and doubled late severe toxicity.
- **Early oral cancer:** re-excision for close or involved margins rather than RT; RT for pN+ disease, bone invasion and DOI >4 mm with other risk features.

Recurrent or metastatic disease

Figure 15. First-line choices by PD-L1 combined positive score (CPS). Immunotherapy prolongs overall survival and gives a small group durable control; response rates alone underestimate its value.

- **First, ask whether the recurrence is curable:** resectable local or isolated neck recurrence without distant spread → salvage surgery (elective bilateral neck dissection for recurrent larynx and pharynx cancers), with postoperative re-irradiation only for high-risk pathology; unresectable → re-irradiation with chemotherapy in selected patients at experienced centres. Distinguish a second primary from a recurrence (biopsy; especially a new lung lesion). Palliative systemic therapy is for the rest.
- **Pembrolizumab first line** ([KEYNOTE-048](#) ^[3], [4-year update](#) ^[65]): pembrolizumab with platinum–5FU beat cetuximab–platinum–5FU in all patients (median OS 13 vs 11 months; 4-year OS 19 vs 5%). Pembrolizumab alone was better in CPS ≥1 (4-year OS 17 vs 6%), driven by CPS ≥20 (median 15 vs 11 months), with a lower response rate (17 vs 36%), early progression in some, and far less grade ≥3 toxicity (17 vs 69%).
- **EXTREME** (platinum–5FU–cetuximab, then cetuximab maintenance) improved median OS from 7.4 to 10.1 months ([EXTREME](#) ^[66]) and remains the choice when immunotherapy is unsuitable. Nivolumab–ipilimumab did not beat it ([CheckMate 651](#) ^[67]).
- **Platinum-refractory disease** (progression within 6 months of platinum): nivolumab (median OS 7.7 vs 5.1 months; 1-year OS 34 vs 20%; [CheckMate 141](#) ^[29]) or pembrolizumab (median 8.4 vs 6.9 months; [KEYNOTE-040](#) ^[68]) over methotrexate, docetaxel or cetuximab.
- **Indian evidence for low-cost care:** oral metronomic methotrexate–celecoxib (± erlotinib) is active and well tolerated ([Patil 2019](#) ^[69]); adding **low-dose nivolumab** to metronomic chemotherapy improved overall survival in a randomised Tata Memorial trial ([Patil 2023](#) ^[70]), a pragmatic option where full-dose immunotherapy is unaffordable.

- Later lines: taxanes, cetuximab, methotrexate, platinum rechallenge after a long interval. Offer palliative care early; many patients need help with pain, bleeding, airway, feeding and wound care.

SHARE WITH PATIENTS: TREATMENT MYTHS

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

<u>🇮🇳 Telugu–English handout: mouth, teeth, food and swallowing during head and neck radiotherapy (తెలుగు-English)</u>	<u>Every head and neck cancer patient needs chemotherapy?</u>
<u>If cancer spreads to the neck lymph nodes, it is automatically stage IV and can't be cured?</u>	<u>All head and neck cancers are caused by HPV?</u>

Figure 16. Side effects that shape survivorship, mapped to the organs at risk. Most can be reduced before treatment starts: dental clearance, fluoride trays, swallowing and jaw exercises, and stopping tobacco.

Nasopharyngeal carcinoma: a distinct disease

Nasopharyngeal carcinoma (NPC) differs from other head and neck cancers in cause, histology, spread and treatment: it is driven by Epstein–Barr virus in most patients, is exquisitely sensitive to radiotherapy and chemotherapy, cannot be removed surgically at diagnosis, and spreads to distant sites more often. It is endemic in southern China and South–East Asia; in India it is uncommon except in the north–eastern states, so most Indian clinicians see it rarely and should refer to a centre that treats it regularly.

Cause, pathology and biology

- **Histology** (WHO): non–keratinising carcinoma (differentiated or undifferentiated) is EBV–associated and dominates endemic regions; keratinising squamous carcinoma is less EBV–linked, more tobacco– and alcohol–related, less radiosensitive and relatively commoner outside endemic areas; basaloid squamous carcinoma is rare.
- **Risk factors**: EBV, a diet rich in salt–preserved fish and meats (nitrosamines), family history (a first–degree relative raises risk several–fold), occupational wood dust and formaldehyde, and tobacco for the keratinising type.
- **EBV as a tumour marker**: tumour cells carry EBV (EBER in–situ hybridisation on biopsy or a neck node identifies a nasopharyngeal origin). Plasma EBV DNA before treatment reflects tumour burden and predicts outcome; detectable levels after treatment predict relapse ([Lin 2004](#) ^[71], [Lee 2021](#) ^[72]). In endemic regions plasma EBV DNA screening found earlier–stage cancers ([Chan 2017](#) ^[73]); it is not a screening test for low–incidence populations such as most of India. Assays are not yet standardised.

Presentation and workup

- **Typical presentation**: a painless upper neck mass (the commonest first sign; often level II or V and bilateral), nasal obstruction or blood–stained nasal discharge, **unilateral serous otitis media or hearing loss in an adult**, and cranial nerve palsies from skull base spread (abducens: double vision; trigeminal: facial numbness or pain). Bimodal age: adolescents and young adults, and people in their 50s and 60s.
- **Trap**: an adult with one–sided "glue ear" or a level V node treated repeatedly with antibiotics or antituberculous drugs. Look at the nasopharynx with a flexible scope before any neck node is excised.
- **Workup**: nasopharyngoscopy and biopsy; **MRI of the nasopharynx, skull base and neck** (better than CT for skull base, parapharyngeal and intracranial spread, perineural disease and retropharyngeal nodes); PET–CT for stage III–IV or bulky nodes (distant metastases are commoner than in other head and neck cancers); baseline plasma EBV DNA where available; dental, audiology, ophthalmic and endocrine (pituitary, thyroid) baselines before RT.

Category	AJCC 8th edition (simplified)
T1	Nasopharynx, or extension to oropharynx or nasal cavity, without parapharyngeal involvement
T2	Parapharyngeal space and/or adjacent soft tissue (medial or lateral pterygoid, prevertebral muscles)
T3	Bony skull base, cervical vertebra, pterygoid structures and/or paranasal sinuses
T4	Intracranial extension, cranial nerves, hypopharynx, orbit, parotid and/or soft tissue beyond the lateral pterygoid
N1	Unilateral cervical and/or uni– or bilateral retropharyngeal nodes, ≤6 cm, above the caudal border of the cricoid

Category	AJCC 8th edition (simplified)
N2	Bilateral cervical nodes, ≤6 cm, above the caudal border of the cricoid
N3	Any node >6 cm and/or extending below the caudal border of the cricoid
Stage groups	I: T1N0 · II: T2N0 or T0–2N1 · III: T3 or N2 · IVA: T4 or N3 · IVB: M1

Treatment

Setting	Standard approach	Notes	Evidence
Stage I	IMRT alone to the nasopharynx and elective neck	Surgery has no role for the primary; IMRT preserves salivary function	Kam 2007 ^[74]
Stage II	IMRT; add concurrent cisplatin for N1, bulky T2 or high EBV DNA	Low-risk T2N0 or T1N1 with low EBV DNA may need RT alone	Chen 2011 ^[75]
Stage III–IVA	Induction gemcitabine–cisplatin (or TPF), then cisplatin–IMRT	Concurrent cisplatin is the core; adding chemotherapy before or after improves control of distant disease	Zhang 2019 ^[76] , Sun ^[77] 2016 ^[77] , MAC– ^[78] NPC ^[78]
High risk after chemoradiation	Metronomic capecitabine for 1 year	N2–N3 or T4 disease, or detectable EBV DNA after treatment	Chen 2021 ^[79]
Local recurrence	Endoscopic nasopharyngectomy if resectable; otherwise hyperfractionated re-IMRT	Experienced centres only; late toxicity of re-RT is the main risk	Liu 2021 ^[80] , You ^[81] 2023 ^[81]
Metastatic, first line	Gemcitabine–cisplatin plus a PD-1 inhibitor (toripalimab, camrelizumab or tislelizumab)	Oligometastatic disease: consider local RT to the primary and metastases after response	Zhang 2016 ^[82] , JUPITER-02 ^[83] , CAPTAIN-1st ^[84]

- **Radiotherapy is the backbone:** IMRT to about 70 Gy to gross disease with elective coverage of both necks and the retropharyngeal nodes. IMRT gave better salivary function than older techniques ([Kam 2007](#)^[74]) and allows high doses next to the brainstem, optic apparatus and temporal lobes.
- **Concurrent cisplatin** for locoregionally advanced disease was established by [Intergroup 0099](#)^[85] (chemoradiation plus adjuvant chemotherapy vs RT alone; large survival gain) and confirmed by the [MAC–](#)^[78] [NPC meta-analysis](#)^[78], in which adding chemotherapy to RT improved overall survival, most with concurrent plus induction or adjuvant chemotherapy.
- **Induction chemotherapy:** gemcitabine–cisplatin before chemoradiation improved recurrence-free and overall survival ([Zhang 2019](#)^[76]); TPF improved failure-free survival ([Sun 2016](#)^[77]). This "induction then chemoradiation" sequence is now standard for stage III–IVA in fit patients, unlike other head and neck sites where induction rarely improves survival.
- **Adjuvant:** one year of metronomic capecitabine after chemoradiation improved failure-free survival in high-risk patients (3-year about 85 vs 76%) with mild toxicity ([Chen 2021](#)^[79]); a practical, low-cost option.
- **Recurrent or metastatic disease:** gemcitabine–cisplatin is the chemotherapy backbone (better PFS and OS than cisplatin–5FU; [Zhang 2016](#)^[82]). Adding a PD-1 inhibitor improved PFS and OS (toripalimab: median PFS 21.4 vs 8.2 months in the final analysis; [JUPITER-02](#)^[83], [final OS](#)^[86], camrelizumab: [CAPTAIN-1st](#)^[84]). Unlike other head and neck cancers, a PD-L1 CPS threshold is not used. Long survival is possible in oligometastatic disease with chemotherapy and local RT.

- **Local recurrence:** endoscopic nasopharyngectomy gave longer survival and fewer severe late effects than re-irradiation for resectable recurrences ([Liu 2021](#) ^[80]); when re-RT is needed, hyperfractionated IMRT reduced severe late toxicity and improved survival compared with once-daily re-RT ([You 2023](#) ^[81]).

Follow-up and late effects specific to NPC

- MRI of the nasopharynx about 3 months after RT, then with clinical examination and nasoendoscopy; plasma EBV DNA where it was detectable at baseline.
- Late effects need lifelong checks: hearing loss (cisplatin and RT to the middle ear), hypothyroidism and **hypopituitarism** (yearly endocrine tests), temporal lobe necrosis, cranial neuropathy, carotid stenosis, trismus, xerostomia and dental decay.
- Family members of patients from endemic regions may ask about screening: advise prompt assessment of neck lumps, nasal bleeding or one-sided hearing loss; routine screening is not advised in low-incidence settings.

Quick-reference tables

Quick-reference tables (also printable as one PDF from the Printable Teaching Resources page). No chemotherapy doses; check current approvals and product information.

Table A. Pathology and biomarker tests that change management

Test	Where it matters	How tested	What it changes	Key evidence
p16 (surrogate for HPV)	Every oropharyngeal squamous cancer; neck node of unknown primary	IHC: strong, diffuse nuclear and cytoplasmic staining in ≥70% of cells; confirm with HPV DNA/RNA (ISH or PCR) when decisions hinge on it; FNA cell blocks under-call p16	Selects the HPV staging table; better prognosis; points the unknown-primary search to tonsil and base of tongue	Ang 2010 ^[20] , EPIC-OPC 2023 ^[9]
p16/HPV discordance	Oropharynx cancers tested both ways	p16 IHC plus HPV DNA/RNA	p16+/HPV- or p16-/HPV+ behaves close to HPV-negative disease (5-year OS about 55% vs 81% when both positive): do not de-escalate	EPIC-OPC 2023 ^[9]
Depth of invasion (DOI)	Oral cavity, above all oral tongue	Measured from the basement membrane of adjacent normal mucosa (not tumour thickness)	Sets T category (>5 mm = at least T2, >10 mm = T3); DOI >3 mm → elective neck treatment; >4 mm favours adjuvant RT	AJCC 8th; D'Cruz ^[38] 2015 ^[38]
Margins	Every resection	Clear >5 mm; close 1–5 mm (oral cavity <2 mm in some guidance); involved = tumour at ink	Involved: re-excise or postoperative chemoradiation; close: re-excise (early oral) or RT	Bernier 2005 ^[62]

Test	Where it matters	How tested	What it changes	Key evidence
Extranodal extension (ENE)	Every neck dissection	Pathology: tumour through the node capsule (record major vs minor if possible)	Adds cisplatin to postoperative RT (± nivolumab in HPV-negative disease); upstages to pN3b in non-HPV sites	EORTC 22931 ^[28] , RTOG 9501 ^[61] , NIVOPOSTOP ^[2]
PNI, LVI, grade, nodal number	Resected specimens	Pathology synoptic report	Intermediate risk → postoperative RT alone; ≥2 nodes is a weaker reason for chemotherapy	Bernier 2005 ^[62]
PD-L1 combined positive score (CPS)	Resectable stage III–IVA (perioperative pembrolizumab) and recurrent/metastatic disease	22C3 assay; CPS = PD-L1+ positive tumour cells and immune cells ÷ tumour cells × 100	CPS ≥1: pembrolizumab-based first line; CPS ≥20: pembrolizumab alone is an option; CPS ≥1 needed for KEYNOTE-689 benefit	KEYNOTE-048 ^[3] , KEYNOTE-689 ^[1]
EBV DNA / EBER	Nasopharynx; neck node of unknown primary with undifferentiated histology	EBER ISH on tissue; plasma EBV DNA	Points to nasopharynx; plasma EBV DNA for prognosis and follow-up (see Nasopharyngeal carcinoma , section O6)	—
Cisplatin fitness	Before chemoradiation	Creatinine clearance, audiogram, neuropathy, performance status, age, weight loss	Ineligible: RT alone (older/unfit) or RT + weekly docetaxel / carboplatin; avoid cetuximab in HPV-positive disease	Patil 2023 ^[26] , RTOG 1016 ^[23]

Table B. Treatment by setting (no doses)

Setting	Standard	Alternatives / notes	Evidence
Oral cavity T1–T2 NO	Wide excision (margin >5 mm) + elective neck dissection if DOI >3 mm (SLNB in expert centres)	DOI ≤1 mm lateralised: observe neck; close margin: re-excision; RT only if surgery not possible	D'Cruz 2015 ^[38] , Senti- ^[39] , MERORL ^[39]
Oral cavity T3–T4a or N+	Resection + neck dissection + reconstruction → adjuvant RT ± cisplatin	CPS ≥1: perioperative pembrolizumab option; borderline resectable: TPF induction then reassess	KEYNOTE-689 ^[1] , EORTC 22931 ^[28]
Oropharynx T1–T2 NO–N1	Definitive RT or transoral surgery + neck dissection	Choose the route that is least likely to need a second or third modality	ORATOR ^[21]
Oropharynx stage III–IV (HPV+ or –)	Cisplatin chemoradiation (weekly or 3-weekly)	Cisplatin-ineligible: carboplatin-based or weekly docetaxel; never cetuximab in HPV+; TORS for selected small primaries	RTOG 1016 ^[23] , De- ^[24] , ESCALaTE HPV ^[24] , Noronha 2018 ^[49]
Glottic T1–T2	RT (small field, slightly hypofractionated) or transoral laser surgery	No elective neck treatment; voice outcomes similar	NCCN; EHNS–ESMO–ESTRO guideline

Setting	Standard	Alternatives / notes	Evidence
Supraglottic T1–T2	RT or transoral surgery with bilateral elective neck (II–IV)	Open supraglottic laryngectomy for selected cases	NCCN
Larynx/hypopharynx stage III–IVA, larynx preservation wanted	Cisplatin chemoradiation, or TPF induction → RT in responders	T4a with cartilage destruction or a non-functional larynx: total laryngectomy + adjuvant RT	RTOG 91-11 ^[41] , VA ^[40] , Larynx ^[40] , TAX ^[53] , 324 ^[53]
Postoperative: positive margin or ENE	RT + cisplatin (weekly preferred)	HPV-negative: add nivolumab (NIVOPOSTOP); cisplatin-ineligible: RT ± weekly docetaxel	JCOG1008 ^[64] , NIVOPOSTOP ^[2] , Patil ^[26] , 2023 ^[26]
Postoperative: intermediate risk	RT alone, within 6 weeks of surgery	Cetuximab with RT improved DFS but not OS and doubled severe toxicity	Ang 2001 ^[48]
Unfit, ≥70 years or comorbid	RT alone (accelerated or hyperfractionated if feasible)	Hypofractionated palliative RT for symptoms	MACH-NC 2021 ^[22] , MARCH meta-analysis ^[46]
Recurrent/metastatic, first line, CPS ≥1	Pembrolizumab alone (CPS ≥20) or with platinum–5FU	Rapid progression: add chemotherapy regardless of CPS	KEYNOTE-048 ^[3] , KEYNOTE-048 update ^[65]
Recurrent/metastatic, CPS <1 or IO not possible	Platinum + 5FU or taxane ± cetuximab (EXTREME) ± pembrolizumab	Frail: single-agent taxane, methotrexate or oral metronomic regimens	EXTREME ^[66] , Patil ^[69] , 2019 ^[69]
Platinum-refractory (<6 months)	Nivolumab or pembrolizumab	Low-dose nivolumab with metronomic chemotherapy improved survival in an Indian trial	CheckMate 141 ^[29] , KEYNOTE-040 ^[68] , Patil 2023 ^[70]
Nasopharyngeal carcinoma (stage III–IVA)	Induction gemcitabine–cisplatin (or TPF) → cisplatin–IMRT; metronomic capecitabine if high risk	Stage I: IMRT alone; metastatic: gemcitabine–cisplatin + PD-1 inhibitor; local recurrence: endoscopic surgery or hyperfractionated re-IMRT	Zhang 2019 ^[76] , Chen ^[79] , 2021 ^[79] , JUPITER- ^[83] , 02 ^[83]
Isolated local recurrence	Salvage surgery if resectable	Re-irradiation (IMRT or SBRT) in selected patients at experienced centres	NCCN

Table C. Before, during and after treatment: supportive care checklist

When	What	Why
Before	Dental assessment and OPG; extract unsalvageable teeth ≥10–14 days before RT; fluoride trays	Extractions in irradiated bone are the main trigger for osteoradionecrosis
Before	Dietitian: baseline weight, BMI, swallowing; plan feeding route (prophylactic tube in selected high-risk patients)	Weight loss >10% predicts toxicity and treatment breaks
Before	Speech and swallowing assessment; start swallow and jaw exercises	Preventive exercises improve swallowing outcomes whatever the timing (PRO-ACTIVE)
Before	Stop tobacco and areca nut; alcohol counselling; quitline 1800- 11-2356	Continued smoking lowers response and survival and raises toxicity
Before	Audiogram, creatinine clearance, hepatitis B screen, TSH baseline	Cisplatin eligibility; baseline for late hypothyroidism

When	What	Why
During	Weekly review: mucositis, pain (step up to opioids early), weight, hydration, skin	Avoid unplanned RT breaks: every lost day lowers local control
During	Salt-and-soda rinses several times a day; soft, non-spicy food; treat oral candida	Mucositis is unavoidable; good care limits it
During	Fever on cisplatin/TPF: same-day neutropenia check; G-CSF ± antibiotic prophylaxis with TPF	Febrile neutropenia in about 1 in 8 on TPF
After	Clinic + scope per schedule; PET-CT at 12 weeks after CRT for node-positive disease	Earlier PET gives false positives
After	TSH every 6–12 months; dental review 6-monthly; fluoride for life	Hypothyroidism and radiation caries are common and silent
After	Swallow, jaw (trismus) and shoulder physiotherapy; lymphoedema care	Late dysphagia and trismus can appear years later
After	Screen for depression and suicide risk; return-to-work and family support	Head and neck survivors carry a high psychological burden

Table D. Managing common side effects

Problem	Usual cause	Prevent	Act when
Oral mucositis	RT ± chemotherapy	Oral hygiene, salt-soda rinses, IMRT, stop tobacco	Cannot swallow liquids or pain uncontrolled: admit, IV fluids, opioids, feeding tube
Xerostomia	RT to parotid/submandibular glands	Parotid-sparing IMRT (PARSPORT)	Saliva substitutes, sips of water, sugar-free gum; pilocarpine in selected patients
Radiation caries, osteoradionecrosis	Xerostomia; extractions after RT	Fluoride trays for life; extractions before RT; atraumatic dentistry later	Exposed bone >3 months: oral surgery referral; pentoxifylline-tocopherol or surgery for advanced cases
Dysphagia, aspiration	RT to pharyngeal constrictors, surgery	Swallow exercises; keep eating by mouth when safe; DO-IMRT (DARS)	Cough with meals, chest infections: video-fluoroscopy or FEES; dilatation for stricture
Trismus	RT to masticator muscles, surgery	Jaw-stretch exercises from day one	Mouth opening <35 mm: structured therapy (stacked spatulas, devices)
Hearing loss, tinnitus	Cisplatin, RT near the ear	Baseline audiogram; switch agent if hearing falls	Hearing aids; consider weekly schedule or alternative sensitiser
Kidney injury, hypomagnesaemia	Cisplatin	Hydration, magnesium, avoid nephrotoxins	Creatinine rise: hold and reassess eligibility
Acneiform rash, infusion reaction	Cetuximab	Skin care, sun protection, premedication	Grade 3 rash: hold and treat; anaphylaxis: stop permanently
Immune-related effects	Pembrolizumab, nivolumab	Baseline TSH, LFT, glucose; patient alert card	Diarrhoea, breathlessness, rash, fatigue: grade and treat early (steroids as per guidelines)
Hypothyroidism	Neck RT, immunotherapy	TSH every 6–12 months	Raised TSH: thyroxine replacement

Problem	Usual cause	Prevent	Act when
Neck fibrosis, lymphoedema, shoulder drop	Neck dissection (nerve XI), RT	Nerve-sparing dissection; early physiotherapy	Manual lymph drainage, shoulder rehabilitation
Weight loss	All of the above	Weekly weights; early dietitian; tube before >10% loss	Rapid loss or dehydration: feeding tube, admission

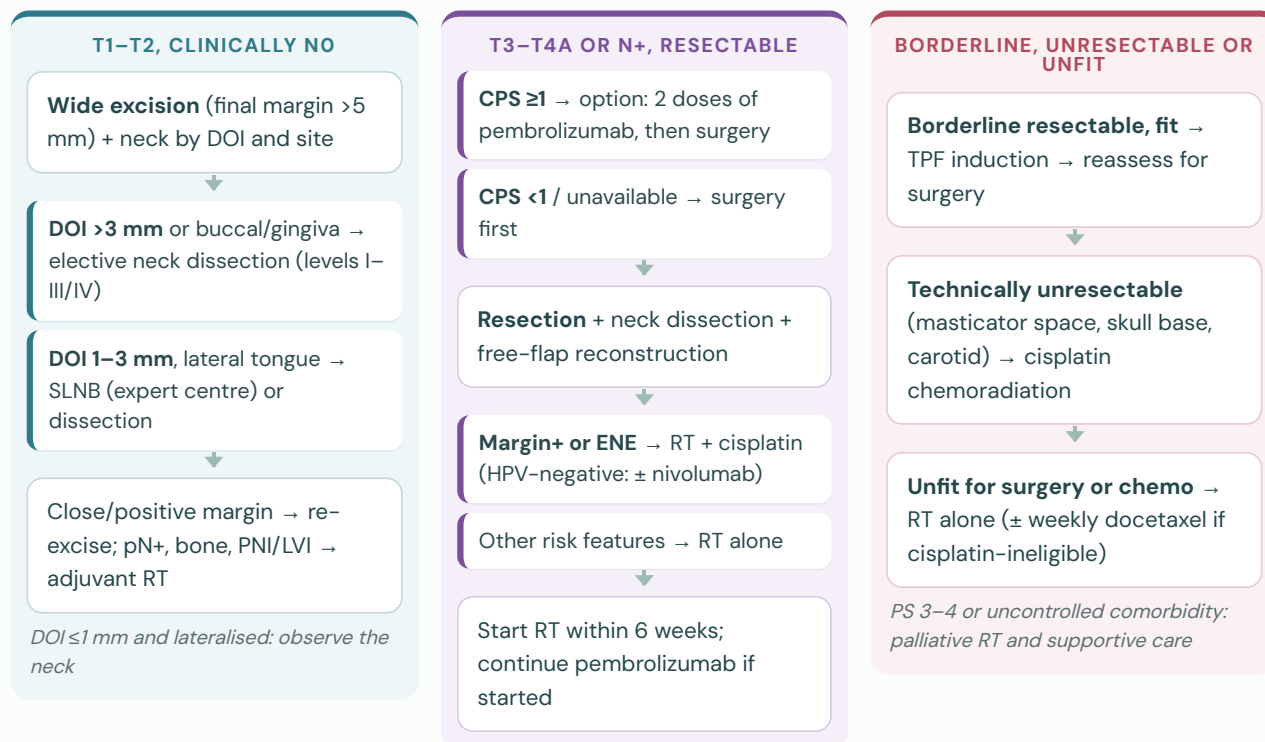
07 Management algorithms

These decision paths pull together sections O2–O6. Colours: teal for early disease, purple for intermediate paths, rose for advanced or high-risk paths. Algorithms 3 and 4 give site-specific detail for laryngeal and hypopharyngeal cancer.

ALGORITHM 1

Oral cavity cancer

Biopsy-proven oral SCC: CT or MRI of the primary and neck · CT chest (PET-CT if stage III–IV) · DOI estimate · dental OPG · nutrition · tobacco cessation · PD-L1 CPS if stage III–IVA · tumour board

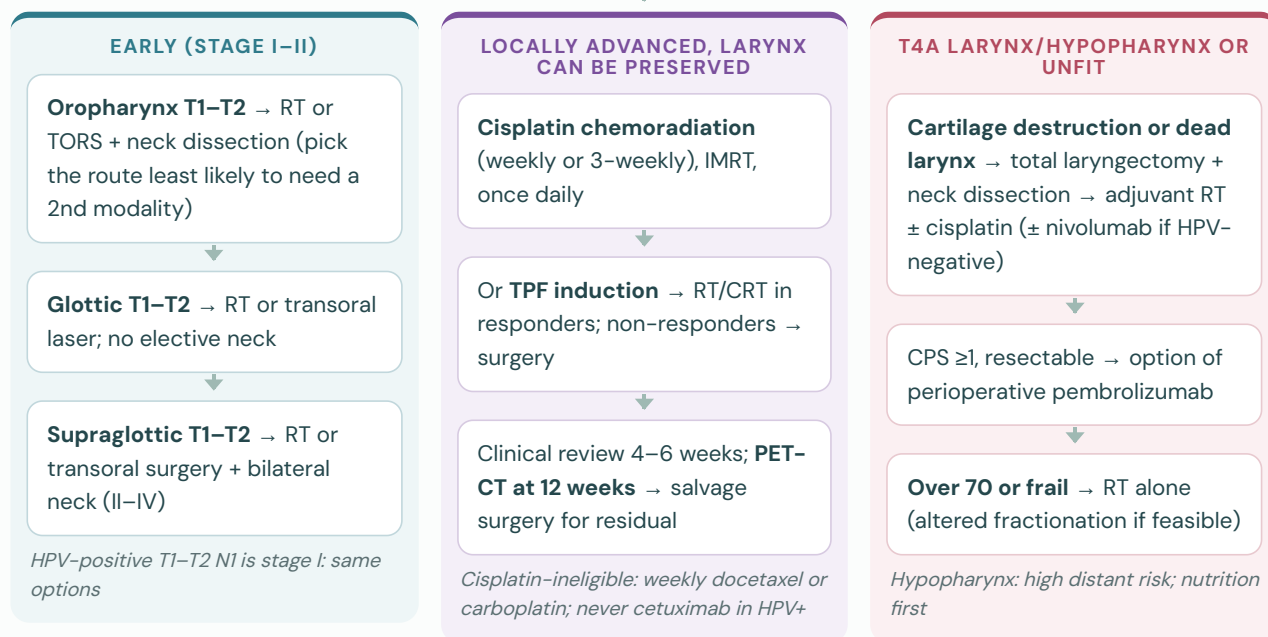


All patients: dental clearance before RT · swallow and jaw exercises · weight weekly · PET-CT at 12 weeks only after definitive (chemo)RT · TSH every 6–12 months after neck RT · stop tobacco and areca nut for life.

ALGORITHM 2

Oropharynx, larynx and hypopharynx

Biopsy-proven SCC: p16 (oropharynx) · CT/MRI neck + CT chest or PET-CT · laryngoscopy (cord mobility) · audiogram, creatinine clearance · dental · nutrition · swallow baseline · tumour board

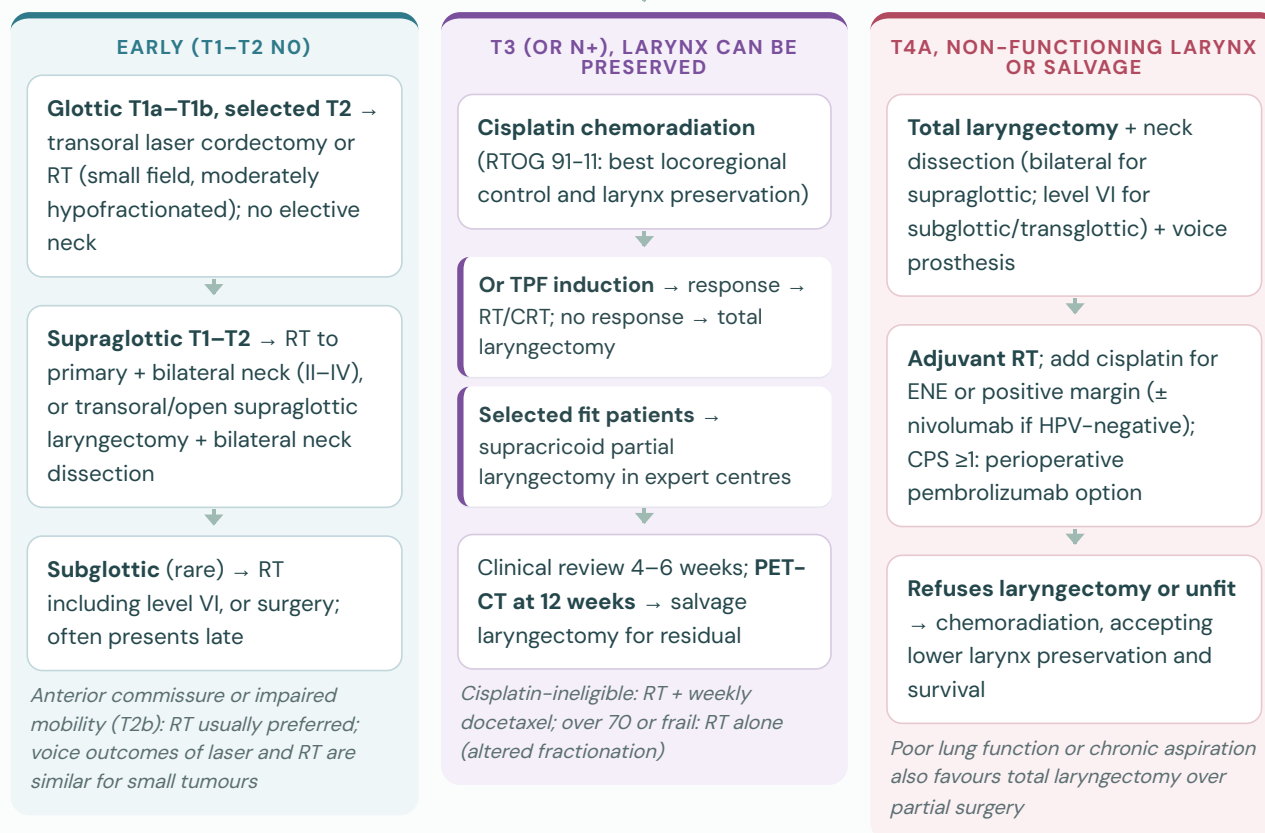


All patients: stop smoking (quitline 1800-11-2356) · avoid treatment gaps · swallow exercises before RT · voice rehabilitation after laryngectomy · TSH 6–12-monthly · yearly low-dose chest CT if ≥20 pack-years.

ALGORITHM 3

Laryngeal cancer (glottic, supraglottic, subglottic)

Biopsy-proven laryngeal SCC: laryngoscopy (stroboscopy for early glottic) · cord mobility · CT neck for cartilage and pre-epiglottic/paraglottic spread · CT chest (PET-CT if stage III–IV) · lung function, voice and swallow baseline · dental · tumour board with a surgeon who offers partial and total laryngectomy

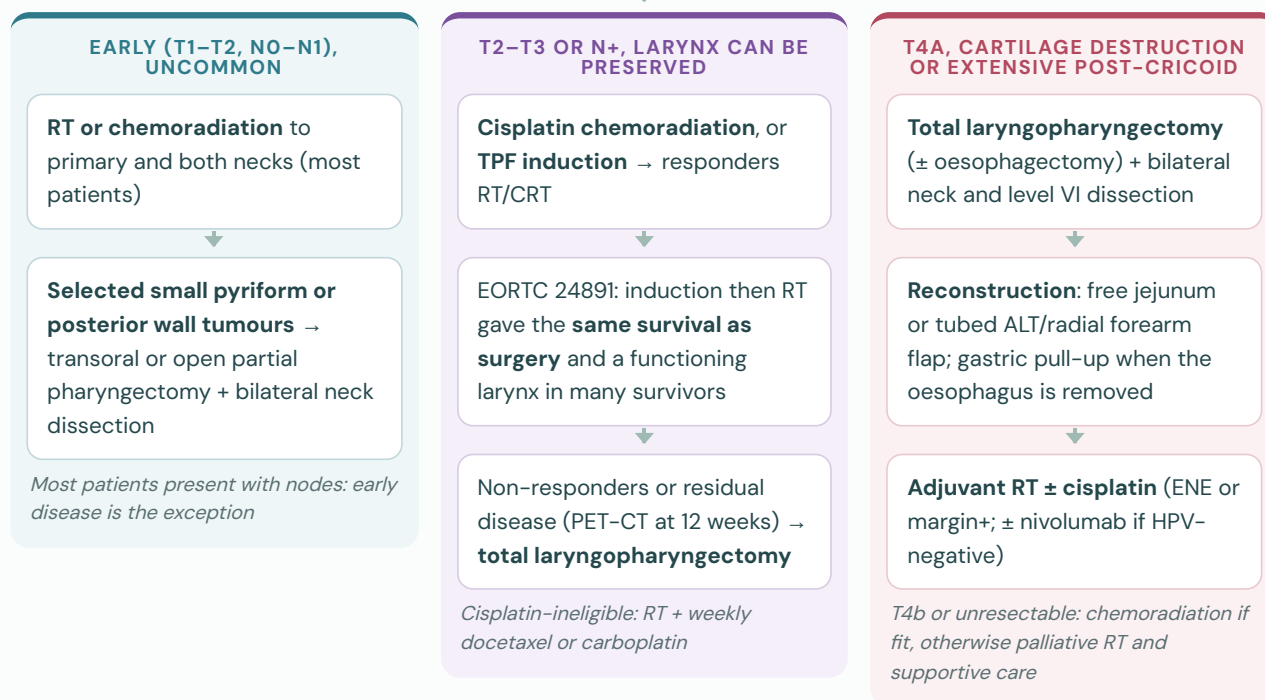


All patients: stop smoking (quitline 1800–11–2356) · speech and swallow therapy before and after treatment · stoma care and humidification after laryngectomy · TSH 6–12-monthly after neck RT · yearly low-dose chest CT if ≥20 pack-years.

ALGORITHM 4

Hypopharyngeal cancer (pyriform sinus, post-cricoid, posterior wall)

Biopsy-proven hypopharyngeal SCC: panendoscopy with oesophagoscopy (synchronous oesophageal cancer) · CT/MRI neck · PET-CT (high distant risk) · **nutrition first** (feeding tube if weight loss or aspiration) · lung function · dental · tumour board

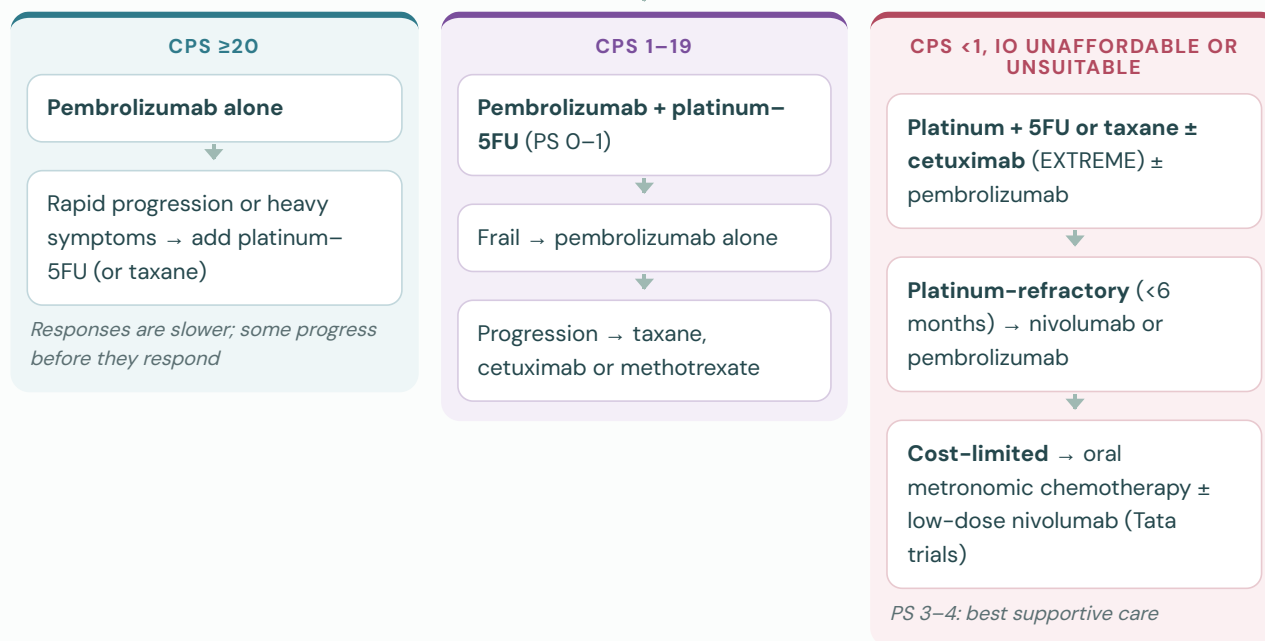


All patients: nutrition and weight weekly · speech rehabilitation (voice prosthesis) · stricture dilatation if swallowing narrows · surveillance of the oesophagus and lungs for second primaries · TSH 6–12-monthly.

ALGORITHM 5

Recurrent or metastatic disease

Recurrence suspected: biopsy · PET-CT · is it curable? (isolated local/neck → salvage surgery or re-irradiation at an experienced centre) · PD-L1 CPS · performance status · goals of care

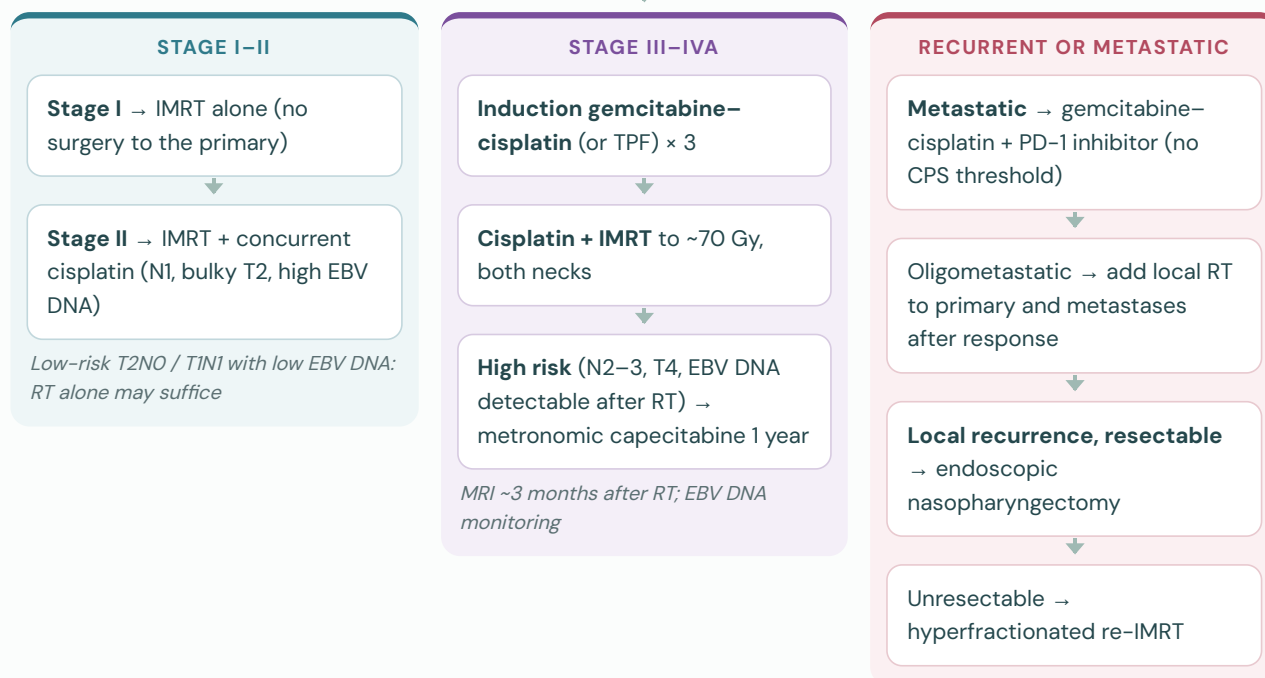


All patients: early palliative care · pain, bleeding and airway plans · nutrition and feeding route decisions with the family · trials where available · carboplatin rather than cisplatin after previous cisplatin.

ALGORITHM 6

Nasopharyngeal carcinoma

Biopsy-proven NPC (EBER positive): nasoendoscopy · MRI nasopharynx, skull base and neck · PET-CT if stage III–IV or bulky nodes · plasma EBV DNA · dental, audiology, endocrine and eye baselines · tumour board in an experienced centre



All patients: refer to a centre that treats NPC regularly · yearly TSH and pituitary tests, hearing checks · watch for temporal lobe necrosis, cranial neuropathy and carotid stenosis · dental care for life.

o8 Survivorship, follow-up & reducing recurrence

Figure 17. When relapses happen (illustrative shapes, not to scale). About 80–90% of recurrences appear within 2–3 years, so follow-up is most intensive then; second primary cancers continue for life.

Figure 18. A simple follow-up rhythm (NCCN, American Cancer Society survivorship guideline). Imaging is a baseline at about 12 weeks; afterwards the examination and the patient's symptoms drive tests.

Follow-up protocol (NCCN, American Cancer Society)

Interval	What	Also
Year 1	Clinic with examination and flexible scope every 1–3 months	Baseline imaging of primary and neck about 12 weeks after treatment (PET-CT after chemoradiation)
Year 2	Every 2–4 months	Imaging only for symptoms or a hard-to-examine site
Years 3–5	Every 4–6 months	TSH every 6–12 months after neck RT; dental review 6-monthly
After 5 years	Yearly, for life	Late effects, second primaries; low-dose chest CT yearly if ≥20 pack-years and fit

- **Second primaries and lifestyle:** up to 20% of survivors develop a second tobacco- or alcohol-related cancer. Stopping tobacco and areca nut is the most effective step after treatment; offer cessation support at every visit (quitline 1800-11-2356).
- **Teeth and jaw:** lifelong fluoride, 6-monthly dental review, atraumatic dentistry; osteoradionecrosis affects about 5–7% after IMRT and most cases follow extractions in irradiated bone. Trismus affects up to a third: jaw exercises.
- **Swallowing:** keep eating by mouth when safe; start or continue swallow exercises; late radiation-associated dysphagia can appear years later ([Hutcherson 2012](#) ^[87]). 10–25% of survivors depend on tube feeding in some series.
- **Thyroid:** TSH every 6–12 months after neck RT; hypothyroidism is common and silent.
- **Neck and shoulder:** lymphoedema (face and neck), fibrosis and shoulder dysfunction after neck dissection: physiotherapy and manual lymph drainage.

- **Mind and family:** survivors face high rates of depression, anxiety and suicide; disfigurement, speech and eating changes affect work and marriage. Screen at every visit; involve counsellors and support groups ([ACS^{\[88\]} guideline^{\[88\]}](#)).
- **Shared care with the family doctor and dentist:** give them the follow-up plan, red flags (new ulcer, lump, pain, bleeding, hoarseness, swallowing change, breathlessness) and the TSH schedule.

SHARE WITH PATIENTS: FOLLOW-UP

Plain-language myth pages written for patients and families. Send them from the clinic to reinforce what you discussed.

[📄 Telugu–English handout: mouth, teeth, food and swallowing during head and neck radiotherapy \(తెలుగు-English\)](#)

[After successful treatment, follow-up isn't necessary?](#)

[If I stop chewing tobacco, my cancer risk becomes zero straight away?](#)

Figure 19. A four-week target from first visit to treatment. Longer intervals from diagnosis to treatment are linked with worse survival in large observational studies; in India most of the delay happens before the biopsy.

09 Landmark trials

Figure 20. How to read a survival curve (illustrative). Use the absolute gap at a fixed time and overall survival, not the median or PFS alone, when weighing benefit against toxicity and cost.

- **MACH-NC (2021)** ^[22]: 107 trials, 19,805 patients → concurrent chemoradiation +6.5% absolute 5-year survival; no gain over 70; induction or adjuvant chemotherapy alone does not improve survival → concurrent cisplatin-RT is the backbone.
- **EORTC 22931** ^[28] / **RTOG 9501** ^[61]: postoperative RT ± cisplatin → benefit confined to positive margins and ENE → defines high-risk adjuvant therapy.
- **D'Cruz (2015)** ^[38]: elective vs therapeutic neck dissection in early oral cancer (Tata Memorial, 500 patients) → 3-year OS 80 vs 67.5% → elective neck dissection when DOI >3 mm.
- **Senti-MERORL** ^[39]: sentinel node biopsy vs elective dissection (cT1–T2N0 oral/oropharynx) → equal 5-year survival, less shoulder morbidity → SLNB in expert centres.
- **KEYNOTE-689** ^[1]: perioperative pembrolizumab in resectable stage III–IVA disease → 3-year EFS about 60 vs 46% in CPS ≥1; OS immature → new option for PD-L1-positive resectable disease.

- **NIVOPOSTOP** ^[2]: nivolumab + postoperative cisplatin-RT in high-risk resected disease → 3-year DFS 63 vs 53% → option for HPV-negative high-risk disease.
- **VA Larynx** ^[40] and **RTOG 91-11** ^[41]: induction chemotherapy or chemoradiation instead of laryngectomy → larynx preserved without survival loss → organ preservation became standard.
- **PET-NECK** ^[31]: PET-CT surveillance vs planned neck dissection after chemoradiation for N2–N3 → same survival, far fewer operations → PET-CT at 12 weeks decides.
- **TAX 324** ^[53]: TPF vs PF induction → 5-year OS 52 vs 42% → if induction is used, use TPF; **PARADIGM** ^[55] and **DeCIDE** ^[56] found no survival gain from adding it to chemoradiation.
- **RTOG 1016** ^[23] and **De-ESCALaTE HPV** ^[24]: cetuximab vs cisplatin with RT in HPV-positive oropharynx cancer → worse survival with cetuximab → do not de-escalate outside trials.
- **Tata docetaxel trial (2023)** ^[26]: RT ± weekly docetaxel in cisplatin-ineligible patients → 2-year OS 51 vs 42% → an affordable sensitiser.
- **KEYNOTE-048** ^[3]: pembrolizumab ± chemotherapy vs EXTREME first line → longer survival (4-year OS 19 vs 5% with chemotherapy) → immunotherapy first line by CPS.
- **CheckMate 141** ^[29]: nivolumab after platinum → 1-year OS 34 vs 20% → PD-1 inhibitors for platinum-refractory disease.
- **Tata low-dose nivolumab trial (2023)** ^[70]: low-dose nivolumab + metronomic chemotherapy vs metronomic chemotherapy → better overall survival → an access-driven option for Indian practice.
- **PARSPORT** ^[43] and **DARS** ^[45]: parotid-sparing and dysphagia-optimised IMRT → less dry mouth and better swallowing → function is an endpoint too.

10 Practice pearls & pitfalls

- A non-healing ulcer or patch for more than 2 weeks after removing an irritant needs a biopsy, not another ointment.
- A painless, hard or cystic neck node in an adult is metastatic cancer until proven otherwise: FNAC, then look for the primary; do not excise it first.
- Hoarseness for more than 3 weeks in a smoker means laryngoscopy.
- Measure DOI and treat the neck: elective neck dissection saves lives in early oral cancer when DOI exceeds 3 mm (D'Cruz).
- Re-excite close margins in early oral cancer; radiotherapy is a poor substitute for a clear margin.
- In edentulous patients the mandible is invaded more easily; plan segmental resection and fibula reconstruction early.
- Test p16 in every oropharynx cancer, but do not use it to de-escalate treatment outside a trial.
- Never replace cisplatin with cetuximab in HPV-positive oropharynx cancer; use carboplatin or docetaxel if cisplatin is impossible.
- Glottic T1–T2 cancers do not need elective neck treatment; supraglottic cancers need both sides of the neck.
- Weekly cisplatin works only at full dose; count the cumulative dose (aim ≥ 200 mg/m²).
- Over 70 or frail: radiotherapy alone; chemotherapy added no survival in MACH-NC.
- Extract hopeless teeth before radiotherapy, not after; prescribe fluoride for life.
- Every day of unplanned RT break costs control: solve pain, nutrition and transport problems before they cause a gap.
- PET-CT after chemoradiation at 12 weeks, not earlier.
- Check PD-L1 CPS early: it decides perioperative pembrolizumab and first-line therapy at recurrence.
- Where full-dose immunotherapy is unaffordable, low-dose nivolumab with metronomic chemotherapy is evidence-based (Tata Memorial).
- Ask about tobacco, areca nut and alcohol at every visit for life; cessation is treatment.

11 Case vignettes: lines of management

Eight cases, written for postgraduates and practising clinicians. Read the presentation, decide on diagnosis, workup and plan, then open the line of management. No doses are given.

CASE 1 Oral tongue · early · DOI

A tongue ulcer treated with gels for three months

46 years, man

Lateral tongue, 1.8 cm

cNO, DOI ~4 mm on MRI

A 46-year-old shopkeeper who chews gutka has a painful ulcer on the left lateral tongue next to a sharp molar. Two dentists prescribed gels and smoothed the tooth; it persisted for 3 months. Examination: 1.8 cm indurated ulcer, no palpable nodes. Punch biopsy: moderately differentiated SCC.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

STAGING

MRI of the oral cavity and neck: DOI about 4 mm, no suspicious nodes; CT chest clear. Dental review; tobacco cessation.

2

SURGERY

Partial glossectomy with a 1 cm planned margin and an ipsilateral selective neck dissection (levels I–IV), because DOI is above 3 mm.

3

PATHOLOGY

pT2 (DOI 6 mm), margins clear at 7 mm, 0 of 28 nodes, no PNI or LVI: stage II.

4

AFTER SURGERY

No adjuvant therapy. Follow-up 1–3-monthly in year 1; stop gutka permanently (the field is at risk).

TEACHING POINTS

- Two weeks is the limit for an unexplained mouth ulcer: biopsy.
- DOI, not size alone, drives T stage and elective neck treatment.
- Elective neck dissection improved survival in early oral cancer (D'Cruz).

See: Sections 02, 03, 05 · Algorithm 1 · [D'Cruz 2015](#) ^[38], [Senti-MERORL](#) ^[39]

CASE 2 Buccal mucosa · pN1 · adjuvant RT

A cheek ulcer in a long-time khaini user

52 years, woman

Buccal mucosa, 3.5 cm

Oral submucous fibrosis

A 52-year-old agricultural worker who has used khaini and pan for 30 years has a 3.5 cm ulceroproliferative lesion of the right buccal mucosa. Mouth opening is two fingers (submucous fibrosis). A 1.5 cm mobile level IB node is palpable. Biopsy: SCC.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

STAGING

Contrast CT face and neck: no bone invasion, no masticator space involvement; one 1.6 cm level IB node without ENE. CT chest clear. Dental clearance; dietitian.

2

SURGERY

Wide excision with a margin of the buccal pad and skin preserved, modified neck dissection, radial forearm free flap to reline the cheek.

3 PATHOLOGY

pT3 (DOI 11 mm), margins clear (6 mm), 1 of 32 nodes positive (2 cm, ENE negative), PNI present.

4 ADJUVANT

Postoperative RT (about 60 Gy) to the primary and neck, starting within 6 weeks; no chemotherapy (no positive margin or ENE). Jaw-stretch exercises during and after RT to prevent trismus.

TEACHING POINTS

- Buccal cancers spread deep early; reconstruct the lining or trismus follows.
- Adjuvant RT alone for intermediate-risk features; cisplatin only for margins or ENE.
- Submucous fibrosis makes examination and follow-up harder: train the patient in self-examination.

See: Sections 02, 05, 06 · Algorithm 1 · [Bernier 2005](#) ^[62], [Ang 2001](#) ^[48]

CASE 3 Gingivobuccal T4a · CPS ≥1 · ENE**A loose tooth that was extracted**

58 years, man

Lower gum, bone invasion

cN2b, CPS 15

A 58-year-old man had a loose lower molar extracted; the socket never healed and a growth appeared. Examination: 4 cm lesion of the lower gingivobuccal sulcus with chin numbness and two palpable ipsilateral nodes. Biopsy: SCC; PD-L1 CPS 15.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1 STAGING

CT: erosion into the medullary mandible (T4a), two nodes (N2b). PET-CT: no distant spread. Stage IVA. Fit, PS 1.

2 OPTIONS AT THE TUMOUR BOARD

Surgery first, or two doses of neoadjuvant pembrolizumab followed by surgery and pembrolizumab with and after adjuvant RT (KEYNOTE-689, CPS ≥1). Cost and access discussed; he chooses the pembrolizumab route through an assistance programme.

3 SURGERY

Composite resection with segmental mandibulectomy, comprehensive ipsilateral neck dissection, fibula free flap with plate.

4 PATHOLOGY

pT4a, margins clear, 3 nodes positive, one with extranodal extension.

5 ADJUVANT

RT with cisplatin (ENE) plus pembrolizumab, then maintenance pembrolizumab. (Had he not received neoadjuvant pembrolizumab, nivolumab with cisplatin-RT would be the NIVOPOSTOP option for this HPV-negative, ENE-positive disease.)

TEACHING POINTS

- A non-healing extraction socket is a classic presentation of gingival cancer.
- Bone invasion → segmental resection and free-flap reconstruction.
- ENE → chemoradiation; checkpoint inhibitors now extend the options before or after surgery.

See: Sections 04–06 · Algorithm 1 · [KEYNOTE-689](#) ^[1], [NIVOPOSTOP](#) ^[2], [EORTC 22931](#) ^[28]

CASE 4 Oropharynx · HPV-associated · stage I**A painless neck lump in a non-smoker**

44 years, man

Never-smoker

p16-positive

A 44-year-old software engineer notices a painless, soft 3 cm lump below the right angle of the jaw, treated as a branchial cyst. FNAC: squamous carcinoma, p16 strongly positive. Examination: small firm area in the right tonsil.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1**STAGING**

PET-CT: 1.5 cm right tonsil primary, one cystic ipsilateral node (2.8 cm), nothing else. HPV-associated cT1 N1 = AJCC 8th stage I. HPV DNA confirmed.

2**OPTIONS**

Definitive RT alone (a single node ≤ 3 cm; chemotherapy is added for larger or multiple nodes in many guidelines) or transoral robotic surgery with neck dissection, choosing the route least likely to need a second modality. ORATOR showed similar swallowing outcomes.

3**IF CHEMORADIATION IS CHOSEN**

Cisplatin, not cetuximab: cetuximab gave worse survival in RTOG 1016 and De-ESCALaTE.

4**FOLLOW-UP**

PET-CT at 12 weeks after RT; examination schedule; smoking advice for life; partners do not need special testing.

TEACHING POINTS

- A cystic neck mass in an adult is a metastasis until proven otherwise.
- HPV-associated cancer has its own staging and a better prognosis.
- Do not de-escalate outside trials.

See: Sections O2–O4 · Algorithm 2 · [Ang 2010](#) ^[20], [RTOG 1016](#) ^[23], [ORATOR](#) ^[21]

CASE 5 Glottic T1a · voice**Hoarseness treated as a cold for two months**

63 years, man

Smoker, 40 pack-years

Mobile cords

A 63-year-old auto driver has been hoarse for 2 months after a cold; two courses of antibiotics did not help. Flexible laryngoscopy: an irregular lesion on the middle third of the left vocal cord, both cords mobile. Biopsy: SCC.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1**STAGING**

CT neck: no cartilage invasion, no nodes. T1a NO, stage I. Chest CT: emphysema, no lesion.

2**OPTIONS**

Transoral laser cordectomy or small-field RT (slightly hypofractionated). Both give high local control and similar voice; no elective neck treatment.

3**PLAN**

He chooses RT to avoid anaesthesia. Smoking cessation started before treatment (continued smoking lowers control).

4 FOLLOW-UP

Laryngoscopy every 1–3 months in year 1; yearly low-dose chest CT (heavy smoker); recurrence after RT → salvage surgery.

TEACHING POINTS

- Hoarseness >3 weeks in a smoker = laryngoscopy.
- Early glottic cancer rarely spreads to nodes: treat the cord only.
- Smoking cessation is part of treatment and prevents second lung cancers.

See: Sections 02, 05 · Algorithms 2 and 3 · [MARCH](#)^[46]

CASE 6 Larynx T3 · organ preservation**A fixed vocal cord and a wish to keep his voice**

57 years, man

Supraglottic, fixed cord

cN1

A 57-year-old teacher has hoarseness, pain on swallowing and a left earache. Laryngoscopy: supraglottic tumour extending to the glottis with a fixed left cord. CT: paraglottic spread, no cartilage destruction; one 2.5 cm ipsilateral node. Biopsy: SCC. He wants to keep his voice.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1 STAGING

T3 N1, stage III. PET-CT: no distant disease. Creatinine clearance 85 mL/min, normal audiogram, PS 0.

2 LARYNX PRESERVATION

Cisplatin chemoradiation with IMRT to the larynx and both necks (RTOG 91-11), or TPF induction then RT in responders. Laryngectomy with adjuvant RT remains an equal-survival alternative.

3 SUPPORTIVE CARE

Swallow exercises from week 1, dietitian, dental review; feeding tube if weight falls.

4 RESPONSE

PET-CT at 12 weeks: complete response. If residual disease had been found, salvage laryngectomy would be the next step.

TEACHING POINTS

- T3 larynx can often be preserved without losing survival.
- T4a with cartilage destruction does better with laryngectomy.
- Salvage surgery must be available before choosing organ preservation.

See: Sections 05–06 · Algorithms 2 and 3 · [VA Larynx](#)^[40], [RTOG 91-11](#)^[41], [TAX 324](#)^[53]

CASE 7 Hypopharynx · cisplatin-ineligible**An older man who cannot have cisplatin**

71 years, man

Pyriform sinus T3N2b

CrCl 42 mL/min, hearing loss

A 71-year-old retired farmer has dysphagia and 9 kg weight loss. Endoscopy: right pyriform sinus tumour. CT: T3 N2b. Creatinine clearance 42 mL/min; uses a hearing aid. PS 1. Biopsy: SCC, p16 negative.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

NUTRITION FIRST

Dietitian; nasogastric or gastrostomy feeding before treatment; dental review.

2

SENSITISER

Cisplatin is contraindicated (kidney function, hearing). Options: RT with weekly low-dose docetaxel (Tata trial: 2-year OS 51 vs 42%) or carboplatin-based chemoradiation; RT alone if frailty increases. Cetuximab is a weaker choice.

3

RADIOTHERAPY

IMRT, once daily, no gaps; weekly review of weight, mucositis and pain.

4

AFTER TREATMENT

PET-CT at 12 weeks; swallow rehabilitation; TSH monitoring; goals-of-care discussion given the high distant risk of hypopharyngeal cancer.

TEACHING POINTS

- Age alone does not decide, but chemotherapy adds little over 70: weigh fitness carefully.
- Weekly docetaxel is an evidence-based, affordable sensitiser when cisplatin is impossible.
- Hypopharyngeal cancer presents late and malnourished: feed before you treat.

See: Sections 06, 08 · Algorithms 2 and 4 · [Patil 2023](#) ^[26], [MACH-NC 2021](#) ^[22]

CASE 8 Recurrent/metastatic · CPS ≥20 · access**Lung nodules eight months after chemoradiation**

60 years, man

Oral cavity cancer

CPS 25

Eight months after surgery and adjuvant cisplatin-RT for an oral tongue cancer, a 60-year-old man has cough. CT: multiple lung nodules; biopsy confirms metastatic SCC (rather than a new lung primary). PD-L1 CPS 25. PS 1. Family income is limited.

Before you open the answer: what is the likely diagnosis, what must be done before treatment, and what is the plan?

1

IS IT CURABLE?

Multiple lung metastases: no; aim for longer life with good quality.

2

BEST EVIDENCE

Pembrolizumab alone (CPS ≥20: median OS 15 vs 11 months over EXTREME, with far less toxicity); add chemotherapy if symptoms progress fast.

3

IF FULL-DOSE IMMUNOTHERAPY IS UNAFFORDABLE

Low-dose nivolumab with oral metronomic chemotherapy (Tata Memorial trial, improved survival), or metronomic chemotherapy alone; EXTREME-type chemotherapy if fit.

4

PALLIATIVE CARE

Introduced at the same visit: symptom control, home care, and discussion of goals with the family.

TEACHING POINTS

- Biopsy a new lung lesion: second primary or metastasis changes treatment.
- CPS decides first-line immunotherapy.
- Evidence-based, lower-cost options exist and should be offered openly.

See: Sections 06, 07 · Algorithm 5 · [KEYNOTE-048](#) ^[3], [Patil 2023](#) ^[70], [Patil 2019](#) ^[69]

12 References & guidelines

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- NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers (current version); ASCO guideline on management of the neck in oral cavity and oropharynx cancer (2019); ESMO and EHNS-ESMO-ESTRO guidelines for head and neck squamous cell carcinoma.
- American Cancer Society head and neck cancer survivorship care guideline; MASCC/ISOO mucositis guidance.
- Indian context: National Programme for Prevention and Control of Non-Communicable Diseases (NP-NCD) oral cancer screening; GLOBOCAN 2022 (India); Tata Memorial Centre randomised trials cited above.
- Cross-checked in October 2026 against 39 UpToDate topic reviews (epidemiology and risk factors; HPV-associated cancer; diagnosis and staging; overview of treatment; early oral cavity, oropharynx and larynx; locoregionally advanced oral cavity and oropharynx; chemoradiation approaches; adjuvant RT/chemoradiation; general principles of RT; radiation resistance; complications during treatment; mandibular and palatal reconstruction; speech and swallowing rehabilitation; quality of life; long-term survivors; recurrent and metastatic disease; plus, in a second batch, larynx and hypopharynx (early and advanced), unknown primary, management of the neck after RT, surveillance, re-irradiation, local recurrence, second primaries, chemoprevention and screening, late complications, dose and fractionation, pathology, HPV virology, epidemiology and treatment, treatment protocols, HIV and malignancy, sarcomas, alcohol, and sexual health). Facts only, in our own words; primary sources cited.
- Not covered by the supplied topics and written from guidelines or memory, flagged for Dr. Haritha's review: India incidence figures and stage distribution; ConCERT (abstract, no PubMed record yet); KEYNOTE-412 (abstract); NP-NCD screening age; extraction timing before RT.
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Educational summary for health professionals, written in our own words from current guidelines and primary trials. No chemotherapy doses

are given. Verify current guidelines, Indian regulatory approvals and individual patient factors before treatment decisions.