

Head & neck cancer: biomarkers, treatment by setting, supportive care and side effects

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A. Pathology and biomarker tests that change management

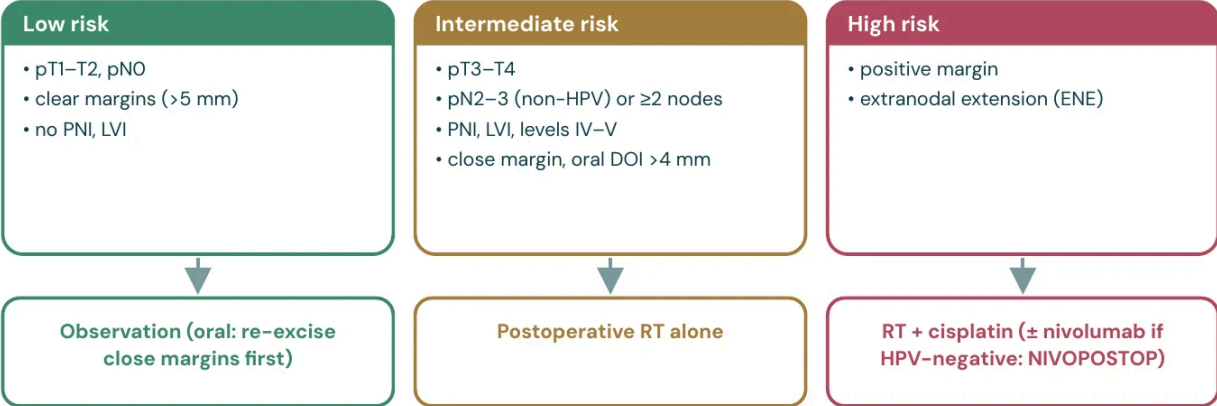
Feature	HPV-associated (p16+)	HPV-negative (p16-)
Typical patient	Younger, often never-smoker	Older, smoker and drinker
Primary	Small tonsil or base-of-tongue tumour	Larger, infiltrative
Neck	Early, often cystic nodes	Nodes later, solid
Test	p16 IHC (≥70% of cells) ± HPV DNA/RNA	p16 negative
Staging	AJCC 8th HPV table (more stage I-II)	Standard oropharynx table
3-year survival (RTOG 0129)	~82%	~57%
Standard treatment	Same as HPV-negative outside trials	CRT or surgery ± adjuvant

Smoking above ~10 pack-years erodes the HPV advantage. In India HPV-driven oropharynx cancer is a minority (about 1 in 8 oropharynx cancers in the Indian ConCERT trial). Discordant p16/HPV results behave like HPV-negative disease.

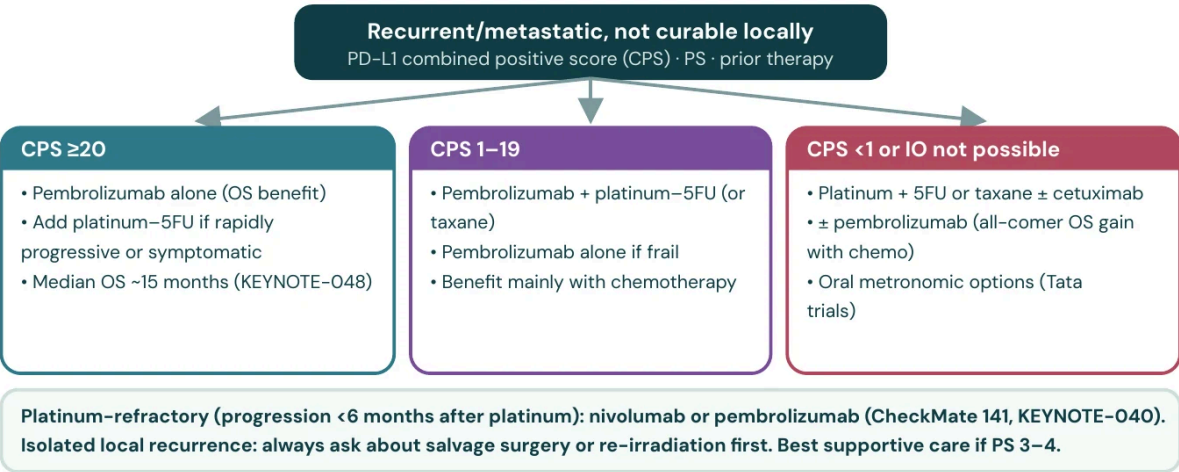
Test	Where it matters	How tested	What it changes	Key evidence
p16 (surrogate for HPV)	Every oropharyngeal squamous cancer; neck node of unknown primary	IHC: strong, diffuse nuclear and cytoplasmic staining in ≥70% of cells; confirm with HPV DNA/RNA (ISH or PCR) when decisions hinge on it; FNA cell blocks under-call p16	Selects the HPV staging table; better prognosis; points the unknown- primary search to tonsil and base of tongue	Ang 2010 , EPIC-OPC 2023
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
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 2015
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

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 ($\pm$ nivolumab in HPV-negative disease); upstages to pN3b in non-HPV sites	EORTC 22931, RTOG 9501, NIVOPOSTOP
PNI, LVI, grade, nodal number	Resected specimens	Pathology synoptic report	Intermediate risk $\rightarrow$ postoperative RT alone; ≥ 2 nodes is a weaker reason for chemotherapy	Bernier 2005
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 $\div$ tumour cells $\times$ 100	CPS ≥ 1 : pembrolizumab– based first line; CPS ≥ 20 : pembrolizumab alone is an option; CPS ≥ 1 needed for KEYNOTE–689 benefit	KEYNOTE–048, KEYNOTE–689
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, RTOG 1016

B. Treatment by setting (no doses)



Cisplatin-ineligible: RT alone or RT + weekly docetaxel (Tata trial). Start RT within 6 weeks of surgery. Perioperative pembrolizumab (KEYNOTE-689, CPS ≥1) continues after surgery when it was given before. HPV-associated ENE: cisplatin-RT (no nivolumab data).



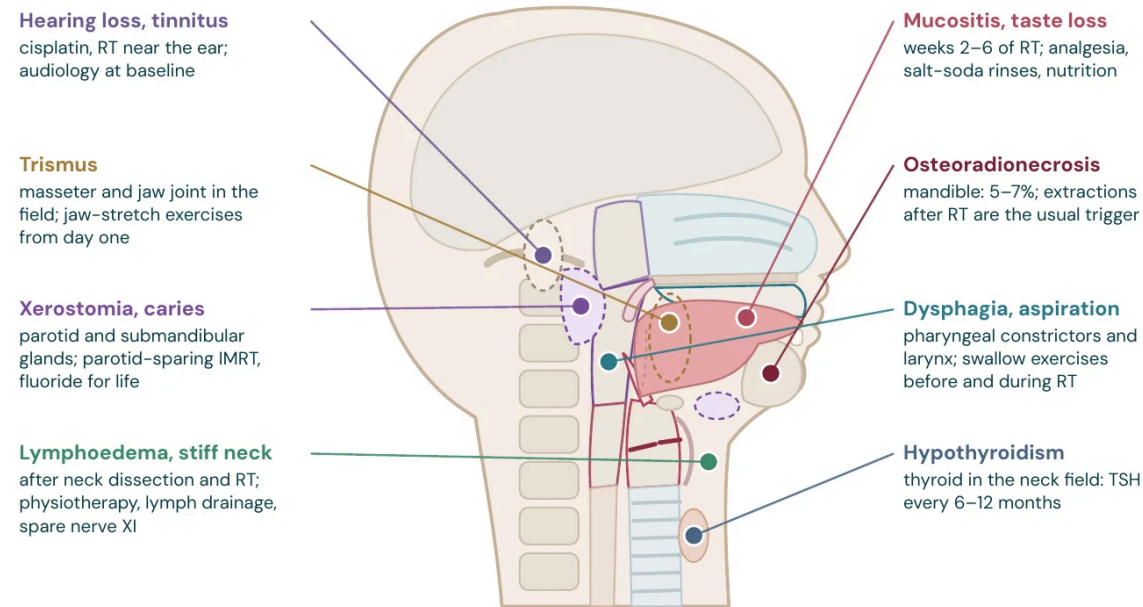
Setting	Standard	Alternatives / notes	Evidence
Oral cavity T1–T2 NO	Wide excision (margin >5 mm) + elective neck dissection if DOI >3 mm (SLNB in expert centres)	DOI ≤1 mm lateralised: observe neck; close margin: re-excise; RT only if surgery not possible	D'Cruz 2015 , Senti- MERORL

Setting	Standard	Alternatives / notes	Evidence
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 , EORTC 22931
Oropharynx T1–T2 N0–N1	Definitive RT or transoral surgery + neck dissection	Choose the route that is least likely to need a second or third modality	ORATOR
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 , De– ESCALaTE HPV , Noronha 2018
Glottic T1–T2	RT (small field, slightly hypofractionated) or transoral laser surgery	No elective neck treatment; voice outcomes similar	NCCN; EHNS–ESMO–ESTRO guideline
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 , VA Larynx , TAX 324
Postoperative: positive margin or ENE	RT + cisplatin (weekly preferred)	HPV–negative: add nivolumab (NIVOPOSTOP); cisplatin–ineligible: RT ± weekly docetaxel	JCOG1008 , NIVOPOSTOP , Patil 2023
Postoperative: intermediate risk	RT alone, within 6 weeks of surgery	Cetuximab with RT improved DFS but not OS and doubled severe toxicity	Ang 2001
Unfit, ≥70 years or comorbid	RT alone (accelerated or hyperfractionated if feasible)	Hypofractionated palliative RT for symptoms	MACH-NC 2021 , MARCH meta- analysis
Recurrent/metastatic, first line, CPS ≥1	Pembrolizumab alone (CPS ≥20) or with platinum–5FU	Rapid progression: add chemotherapy regardless of CPS	KEYNOTE-048 , KEYNOTE-048 update
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 , Patil 2019
Platinum–refractory (<6 months)	Nivolumab or pembrolizumab	Low–dose nivolumab with metronomic chemotherapy improved survival in an Indian trial	CheckMate 141 , KEYNOTE-040 , Patil 2023
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 , Chen 2021 , JUPITER- 02
Isolated local recurrence	Salvage surgery if resectable	Re–irradiation (IMRT or SBRT) in selected patients at experienced centres	NCCN

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
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

D. Managing common side effects



Dashed outlines: ear, parotid, masseter and submandibular gland lie lateral to the midline and are projected for orientation.
Cisplatin: hearing, kidney, nausea · Cetuximab: acneiform rash, infusion reactions · Immunotherapy: thyroid, skin, colitis, pneumonitis

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

Problem	Usual cause	Prevent	Act when
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
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