Diagnosis and Management of HPV+VE Ca Oropharynx

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Introduction

- 10% of all H&N Ca and holds 18th rank in GLOBOCON 2020.
- Plays an essential role in swallowing, speech and protection of airway.
- Natural history of disease remains the same – (despite evolution in technology)- OPSCC tends to be less well differentiated and have a higher incidence of lymphatic involvement.
- Historically RT has been the preferred therapy mode because of its organ function preservation properties with a 5 year control rate of 80% or > for T1T2 NO-1 Lesions even in Pre IMRT ERA.
- ***Patients with cT1-T2 and cN0-N1 tumors are potential candidates for single modality therapy***
- Use of robotic Sx was reported by Weinstein et al in 2010. Role reemerged after HPV +ve good prognosis pts .

Table 3. Main differences among patients with HPV-related and non-related head and neck squamous cell carcinoma

	HNSCC HPV-non related	HNSCC HPV-related
Risk factor	Alcohol, tobacco	Number of oral sex partners
Age	Older	Younger
Incident trends	Mostly decreasing	Increasing
Head and neck tumor location	Anyone	Base of the tongue, tonsil
Stage	Anyone	Small T, large N involvement
Radiological image	Anyone	Cystic nodal involvement
Histopathological features	Keratinising	Baseloid, Non-keratinising
Tumor differentiation	Anyone	Undifferentiated
Biology and genetic alterations:		
CDKN2A	Common	Rare
$p16^{INK4a}$ overexpression	Rare	Common
EGFR	Common (amplification)	Rare
p53	Common	Rare (p53 degradation by E6)
pRb	Rare	Rare (pRb degradation by E7)
PIK3CA	Common	Common (APOBEC)
TRAF3	Rare	Common
Outcomes	Worse OS and PFS	Better OS and PFS
Metastatic dissemination	Yes	Rarely
Comorbidity	Yes	No
Second primary tumors	Yes	No
Prevention strategies	Quitting smoking and drinking	Vaccination (in development)

HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; OS, overall survival; PFS, progression free survival.

Table 2. New TNM staging system classification for HPV-related OPSCC patients 8th edition, developed by The International Collaboration on Oropharyngeal Cancer Network for Staging (ICON-S)

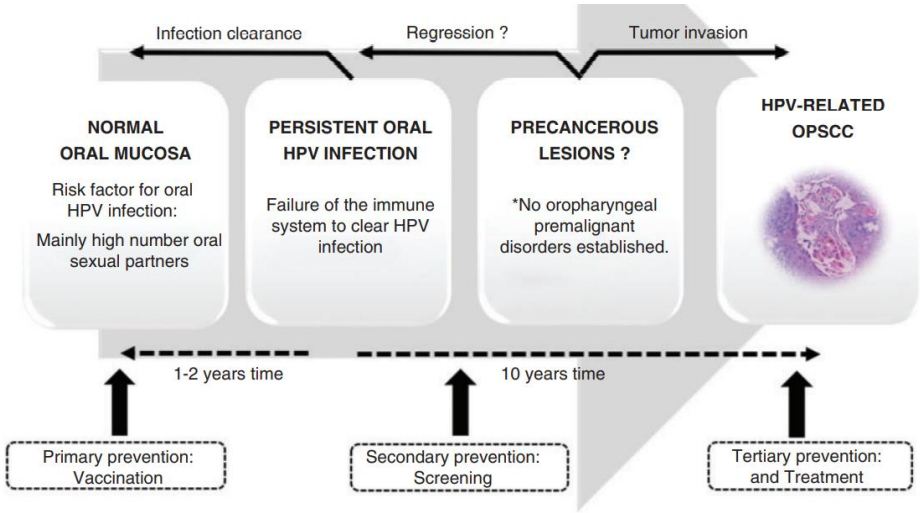
Characteristics	7th edition TNM	8th edition TNM ICON-S [81]
Stage classifications	Stage I (T1N0) Stage II (T2N0) Stage III (T3N0 or T1-T3N1) Stage IVa (T4aN0-1 or T1-T4aN2) Stage IVb (T4b or T1-T4bN3) Stage IVc (M1)	Stage I (T1-T2N0-N1) Stage II (T1-T2N2 or T3N0-N2) Stage III (T4 or N3) Stage IV (M1)
5 years OS by stage	NA	I: 88% II: 81% III: 65%
Main N (lymph node) differences	N1: metastasis in a single ipsilateral lymph nodes, <3 cm N2a: metastasis in a single ipsilateral lymph node >3 cm but <6 cm. N2b: metastasis in multiple ipsilateral lymph nodes, <6 cm N2c: metastasis in bilateral or contralateral lymph nodes, <6 cm	N1: ipsilateral metastasis in lymph node(s), <6 cm N2: bilateral or contralateral metastasis in lymph node(s), <6 cm[a]
Main T (tumor) differences	T4a: tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate or mandible T4b: tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base or encases carotid artery	T4: tumor invades any of the following: larynx, deep/extrinsic muscle of tongue, medial pterygoid, hard palate, mandible, lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base or encases carotid artery[b]

HPV, human papillomavirus; ICON-S: The International Collaboration on Oropharyngeal cancer Network for Staging; M: metastasis; N: lymph node; NA: Not applicable; OPSCC, oropharyngeal squamous cell carcinoma; OS, overall survival T, tumor.

[a]Because 5-years OS was similar among N1, N2a and N2b, they re-termed the N categories.

[b]Because 5-years OS was similar among T4a and T4b, they were no longer subdivided and it was re-termed as T4.

HPV – Pathogenesis



- Transmitted via orogenital contact, HPV infects the basal epithelial layer of the oropharyngeal mucosa and integrates itself into the host genome. The HPV oncoproteins E6 and E7 bind and degrade the host p53 and Rb tumor suppressor proteins, respectively, inhibit cell death pathways, and promote cellular proliferation.
- pts with p16INK4apositive but HPV-DNA-negative OPSCC showed a significantly less favourable survival than patients with p16INK4a-positive and HPV-DNA-positive tumours ($P < 0.001$). This consideration should be taken into account for describing HPV-related OPSCC patients candidates for de-escalation treatment clinical trials.

Good Prognosis of HPV+ve OPSCC leads to changes in AJCC STAGING (8th Edition)

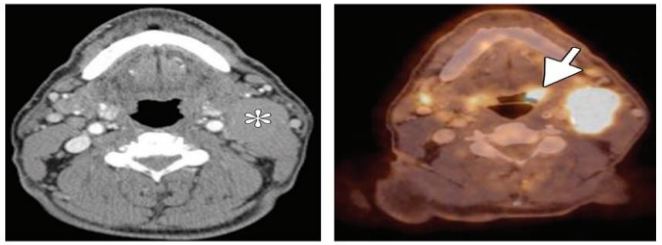


Figure 1. p16-positive OPSCC in a 66-year-old man with a large mobile left neck mass that was non-responsive to homeopathy and at fine-needle aspiration was determined to be SCC. Axial contrast-enhanced CT image (**a**) and corresponding PET/CT image (**b**) show a large solid level IIA nodal mass (* in **a**) and asymmetric focal intense fluorodeoxyglucose (FDG) avidity (arrow in **b**) in the left glossotonsillar sulcus, which biopsy showed to be the primary site, designated T1. For p16-negative OPSCC without clinical evidence of extranodal extension (ENE), the large ipsilateral node (which is >3 cm but ≤6 cm) would be designated N2a with final prognostic grouping of stage IVA. For p16-positive OPSCC, as the tumor was determined to be at pathologic analysis, the unilateral large node is N1, the final staging is T1N1, and the prognostic grouping is stage I.

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Head and Neck Cancers

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Table 3 — Continued
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Oropharynx (p16-) and Hypopharynx (8th ed., 2017)
(Not included: P16-positive (p16+) oropharyngeal cancers and nasopharyngeal cancer)

Regional Lymph Nodes (N):
Pathological N (pN) - Oropharynx (p16-) and Hypopharynx

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); *or* larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); *or* in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in single ipsilateral node 3 cm or smaller in greatest dimension and ENE(+); *or* a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); *or* in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+); *or* a single contralateral node of any size and ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+) *or* a single contralateral node of any size and ENE(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

Distant Metastasis (M)
M0 No distant metastasis
M1 Distant metastasis

Histologic Grade (G)
GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

Prognostic Stage Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N0,N1,N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

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Table 4
American Joint Committee on Cancer (AJCC)
TNM Staging System for HPV-Mediated (p16+) Oropharyngeal Cancer (8th ed., 2017)
(Not including: P16-negative (p16-) cancers of the oropharynx)

Primary Tumor (T)

T0	No primary identified
T1	Tumor 2 cm or smaller in greatest dimension
T2	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3	Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced local disease Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond*

Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.

Regional Lymph Nodes (N)
Clinical N (cN)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One or more ipsilateral lymph nodes, none larger than 6 cm
N2	Contralateral or bilateral lymph nodes, none larger than 6 cm
N3	Lymph node(s) larger than 6 cm

Pathological N (pN)

NX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in 4 or fewer lymph nodes
pN2	Metastasis in more than 4 lymph nodes

Distant Metastasis (M)
M0 No distant metastasis
M1 Distant metastasis

Histologic Grade (G)
No grading system exists for HPV-mediated oropharyngeal tumors

Prognostic Stage Groups

Clinical

Stage I	T0,T1,T2	N0,N1	M0
Stage II	T0,T1,T2	N2	M0
	T3	N0,N1,N2	M0
Stage III	T0,T1,T2,T3	N3	M0
	T4	N0,N1,N2,N3	M0
Stage IV	Any T	Any N	M1

Pathological

Stage I	T0,T1,T2	N0,N1	M0
Stage II	T0,T1,T2	N2	M0
	T3,T4	N0,N1	M0
Stage III	T3,T4	N2	M0
Stage IV	Any T	Any N	M1

Panel Recommendations For HPV Diagnosis And Management In HNSCC

Parameters	Recommendations
Clinical features[a]	Nontobacco using female/male High-risk sexual behavior Early T-stage with advanced N-stage Cystic nodal metastases on radiological imaging Nonkeratinizing or basaloid SCC on histopathology
Primary sites to be tested[b]	Oropharynx Carcinoma unknown primary with neck nodes
p16 IHC test[c]	Good surrogate for HPV infection Use a validated kit[d] ≥50% (preferably ≥70%) nuclear/cytoplasmic staining for a positive test
Counseling[e]	Pre- and post-test counseling to be considered Psychosocial impact of HPV testing must be borne in mind
Treatment	Standard treatment should be offered No role of de-escalation outside clinical trial setting
Vaccination	Not recommended routinely[f]

The Prevalence And Clinicopathological Correlation Of HPV In H&N SCC In India: A Systematic Review Article

- Studies conducted across India show the prevalence of HPV in H&N Cancers ranging from 0- 86.6%.
- Some studies reported that HPV +ve HNSCC is more common in younger age, presents with advanced stage disease, and with nodal metastasis.
- As opposed to western literature HPV +ve HNSCC in India is associated with a WD tumor grade.
- ***There is no difference in t/t outcome and survival among HPV +ve and – ve HNSCC.***
- Rather than debate over TORS/RT , we require Tobacco control program to improve survival- The primary Goal of t/t .

Cancer Treatment and Research Communications 26 (2021) 100301

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NCCN Guidelines Version 2.2022
Cancer of the Oropharynx (p16 [HPV]-positive)

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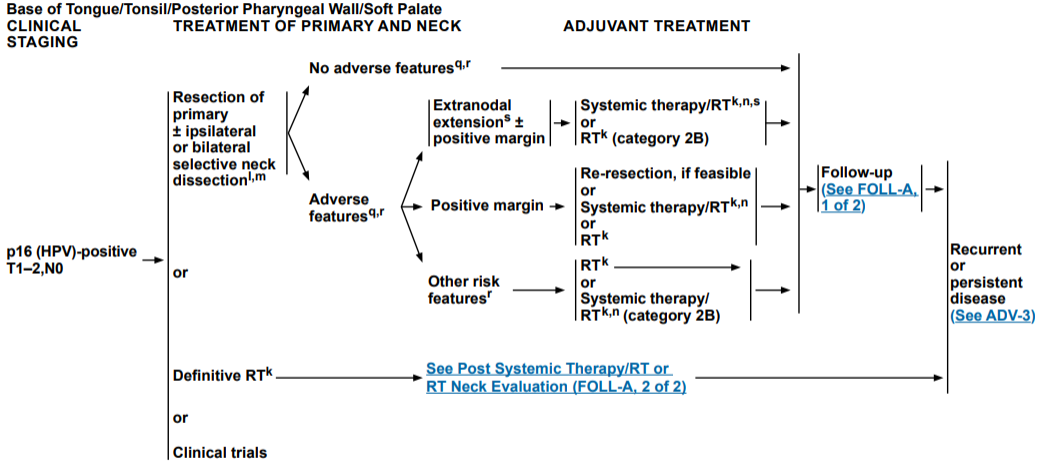
Base of Tongue/Tonsil/Posterior Pharyngeal Wall/Soft Palate



[k] See Principles of Radiation Therapy (ORPH-A).
[l] See Principles of Surgery (SURG-A).
[m] Tumors in the base of tongue, posterior pharyngeal wall, and soft palate require consideration of bilateral neck treatment as do tumors of the tonsil invading the tongue base.
[n] See Principles of Systemic Therapy for Non-Nasopharyngeal Cancers (SYST-A).
[q] Pathologic staging criteria differ from clinical staging criteria in HPV-mediated oropharyngeal cancer. For pathologic stage following resection, see AJCC 8th edition for appropriate staging criteria (ST-7).
[r] Adverse features: extranodal extension, positive margins, close margins, pT3 or pT4 primary, one positive node >3 cm or multiple positive nodes, nodal disease in levels IV or V, perineural invasion, vascular invasion, lymphatic invasion (see Discussion). The definition of an adverse feature in the context of HPV+ disease is an area of active research. This includes the presence and extent of extranodal extension, and the number of involved nodes.
[s] The recommendations for patients at high risk with extranodal extension + positive margins are based on randomized studies involving patients for whom the HPV status of their tumors was not specified.

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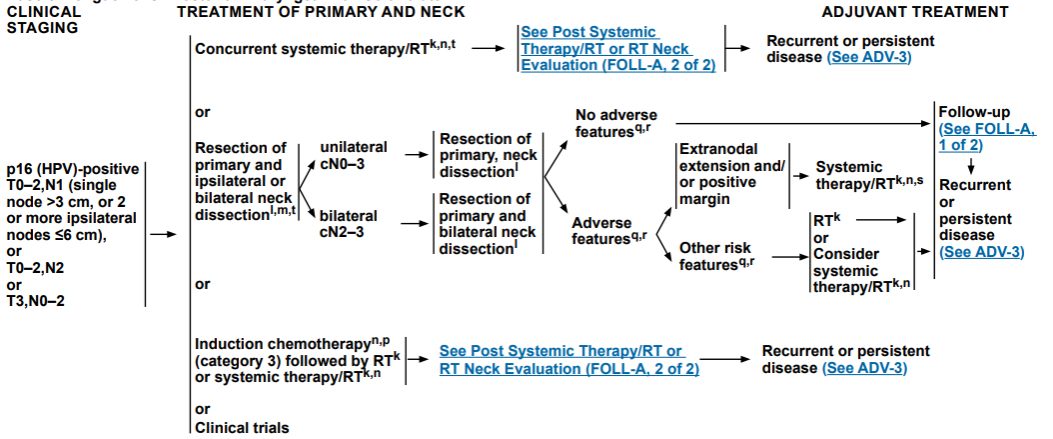

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[p] See Discussion on induction chemotherapy.
[q] Pathologic staging criteria differ from clinical staging criteria in HPV-mediated oropharyngeal cancer. For pathologic stage following resection, see AJCC 8th edition for appropriate staging criteria (ST-7).
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[s] The recommendations for patients at high risk with extranodal extension + positive margins are based on randomized studies involving patients for whom the HPV status of their tumors was not specified.
[t] For those with clinical evidence of fixed or matted nodes or obvious extranodal extension, resection is not recommended and concurrent systemic therapy/RT is preferred.

ONLY RCT- RT Versus TORS & ND For OPSCC (ORATOR): An Open-label, Phase 2, Randomised Trial

- 68 pts from six hospitals in Australia and Canada 10/08/2012-9/06/2017.
- Neutropenia 18% vs none , hearing loss 38% vs 15%, and tinnitus 35%vs 6% reported in the RT group than in the TORS plus ND group.
- > cases of trismus in the TORS plusND group 26% vs one 3% .
- The MC adverse events in the RT group were dysphagia (n=6), hearing loss (n=6), and mucositis (n=4), all grade 3, and in the TORS plus ND group, dysphagia (n=9, all grade 3) and there was ***one death caused by bleeding after TORS***.
- Pts treated with RT showed superior swallowing-related QOL scores 1 year after t/t,. Pts with OPSCC should be informed about both t/t options.
- RT is preferred by less dysphagia, < pain and pain medication use,

< Trismus & shoulder impairment & No bleeding.

www.thelancet.com/oncology Published online August 12, 2019 http://dx.doi.org/10.1016/S1470-2045(19)30410-3

Assessment Of Toxic Effects And Survival In T/T Deescalation With RT Vs TORS For Hpv-associated OPSCC The ORATOR2 Phase 2 RCT

- Objective To assess a primary RT approach vs a primary TORS approach in t/t deescalation for HPV-related OPSCC.
- This international, multicenter, open-label parallel-group phase 2 RCT was conducted at 9 tertiary academic cancer centers in Canada and Australia and enrolled patients with T1-T2N0-2 p16–positive OPSCC between February 13, 2018, and November 17, 2020.

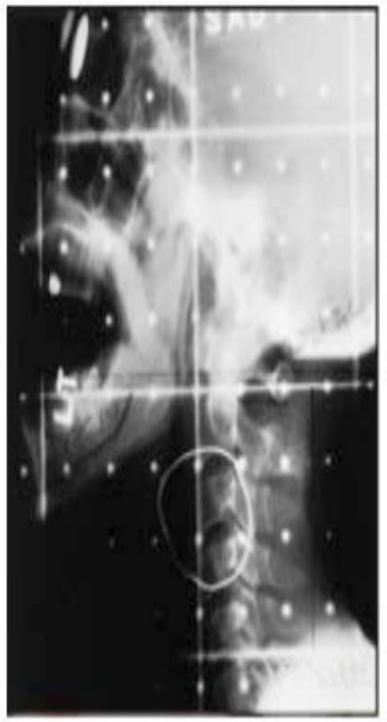
Utilizing primary RT as a de-escalation strategy in pts with HPV+ve OPSCC resulted in efficacious oncologic outcomes, according to findings from the phase 2 ORATOR 2 trial presented at the 2021 American Society for Radiation Oncology Annual Meeting (ASTRO).

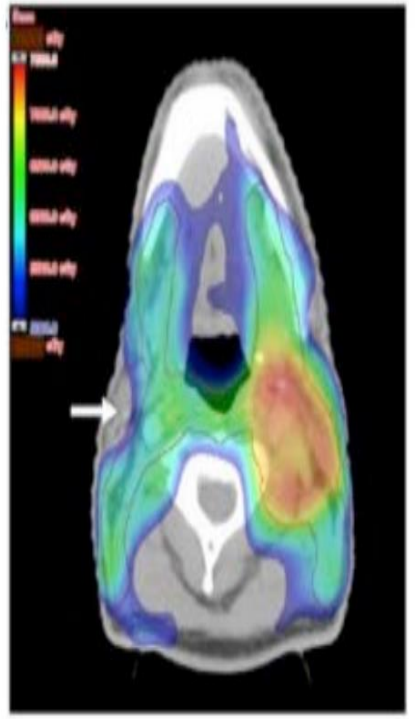
- There were 4 events for the PFS end point, also all in the TOS and ND arm, which included the 3 mortality events and 1 local recurrence
- MD Anderson Dysphagia Inventory scores at 1 year were similar between arms (85.7 [15.6] and 84.7 [14.5], respectively)
- Patients had up to 3 years of follow-up. (Median 17 months)
- In this RCT , TOS was associated with an unacceptable risk of grade 5 toxic effects, but patients in both trial arms achieved good swallowing outcomes at 1 year
- Sx poses a higher risk of peri-t/t mortality, a heavier financial burden, as well as a longer treatment period for patients if adjuvant RT is needed (71% Of pts).

JAMA Oncol. 2022;8(6):1-7. doi:10.1001/jamaoncol.2022.0615

Modern T/T Outcomes For Early T-stage OPSCC Treated With IMRT At A Tertiary Care Institution

- A total of 198 patients were identifed, of which 82% were male and 73% were HPV +ve.
- 68% of pts experienced a grade 2 toxicity, 48% a grade 3 and 4% a grade 4.
- The most frequent toxicities were dysphagia, neutropenia and ototoxicity.
- The rates of gastrostomy tube dependence at 1 and 2 years were 2.5% and 1% respectively.
- There were no grade 5 (fatal) toxicities. HPV+ve pts experienced 5-year OS (86% vs 64%, p=0.0026)
- **Rate of salvage sx is less than 3%.**
- DO-IMRT & BIGART alongwith AFRT has a proven potential to improve the therapeutic ratio further.





Di Gravio et al. Radiat Oncol (2020) 15:261

RT versus SX in Early-Stage HPV-Positive Oropharyngeal Cancer

Table 4. Summary of late toxicity in primary radiotherapy vs. surgery arms

Toxicity	Radiotherapy (n=60)		Surgery (n=106)	
	Grade 1-2	≥ Grade 3	Grade 1-2	≥ Grade 3
Aspiration	0	0	3 (2.8)	1 (0.9)
Dysphagia	4 (6.7)	0	10 (9.4)	3 (2.8)
Lymphedema	0	0	4 (3.8)	0
Neck fibrosis	2 (3.3)	0	15 (14.2)	0
Oral cavity bleeding	0	0	1 (0.9)	1 (0.9)
Oral pain	0	0	4 (3.8)	0
Otalgia	0	0	2 (1.9)	0
Sensory neuropathy	1 (1.7)	0	5 (4.7)	0
Shoulder pain	1 (1.7)	0	16 (15.1)	0
Tinnitus	1 (1.7)	0	4 (3.8)	0
Trismus	0	0	3 (2.8)	0
Ulceration	0	0	1 (0.9)	0
Xerostomia	9 (15.0)	0	14 (13.2)	0

Values are presented as number (%).

No differences in OS, PFS, and LC between upfront RT and Sx in stage I-II hpv+OPC . However, most early-stage hpv+OPC patients undergoing surgery received adjuvant (CC)RT(73.6%)

Cancer Res Treat. 2022;54(2):406-416

Contraindications Of TORS

Tumor Related

VASCULAR

- Tonsillar involvement with a retropharyngeal carotid artery
- Tumor located at the midline of the tongue base or vallecula
- Tumor located adjacent to the carotid bulb or internal carotid artery
- Carotid artery enveloped by tumor or metastatic lymph nodes

FUNCTIONAL

- Tumor resection requiring ≥50% of the deep tongue base musculature or posterior pharyngeal wall
- Resection of the tongue base and entire epiglottis

ONCOLOGICAL

- Stage T4b
- Unresectable neck disease
- Multiple distant metastases
- Neoplastic-related trismus
- Prevertebral fascia involvement
- Mandible or hyoid involvement
- Tumor extension to lateral neck soft tissues
- Involvement of the eustachian tube

RT Practically no contraindication

Non – Oncological

- A medical condition that precludes stopping antiplatelet medications or anticoagulants.
- As with all surgical approaches, any systemic disease associated with unacceptable morbidity or mortality during GA or during the postop period.
- Non-cancer related trismus which prevents robotic access via the oral cavity. (common in Tobacco chewing population of India)
- Cervical spine disease that interferes with necessary patient positioning during TORS
- Narrow arched mandible

Eur Arch Otorhinolaryngol (2015) 272:1551–1552

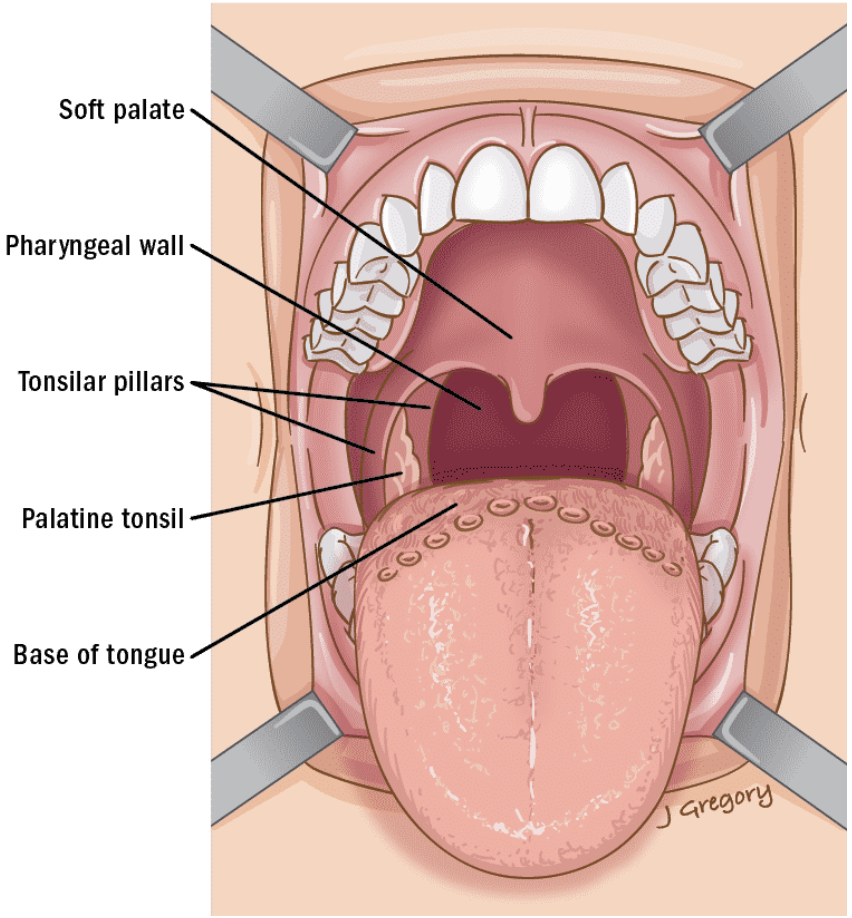
- FROM 2010 TO 2022 – TORS is investigational and struggling hard for Ideal Case Selection for single modality therapy to treat OPSCC - Far away from reality in our country .

- ROL - we were unable to identify a group where TORS is superior .

OROPHARYNX – All SUBSITES Can Be Effectively Treated By RT AS A SINGLE MODALITY IN EARLY STAGE

Table 2. Cancer of the oropharynx: Suggested Classification

1. Anterior or glosso-epiglottic	Antero-inferior	Base of tongue vallecula fossae lingual surface of epiglottis
	Antero-superior	Anterior faucial pillars
2. Lateral or Tonsillar		Tonsil supratonsillar fossa Velo tonsillar region Linguo(glosso) tonsillar sulcus
3. Posterior or pharyngo-nasal	Postero-superior	Oral surface of soft palate uvula Posterior faucial pillars
	Postero-lateral	Postero-lateral walls posterior wall



RT alone as per altered fractionation RTOG 9003 Level 1 evidence is a reasonable option .very cost effective and backbone of curative cancer care in LMIC.

Radiotherapy For Early Stage Oropharynx Cancer

- Time tested
- Evidence based
- Effective
- Assessable and Feasible
- Noninvasive and Safe
- With a promising future ahead with ongoing deintensification trial and advancement in radiotherapy technique including proton beam .
- **Reduced-Dose RT for HPV-Associated OPCA(NRG Oncology HN002)**

Deescalation Strategies

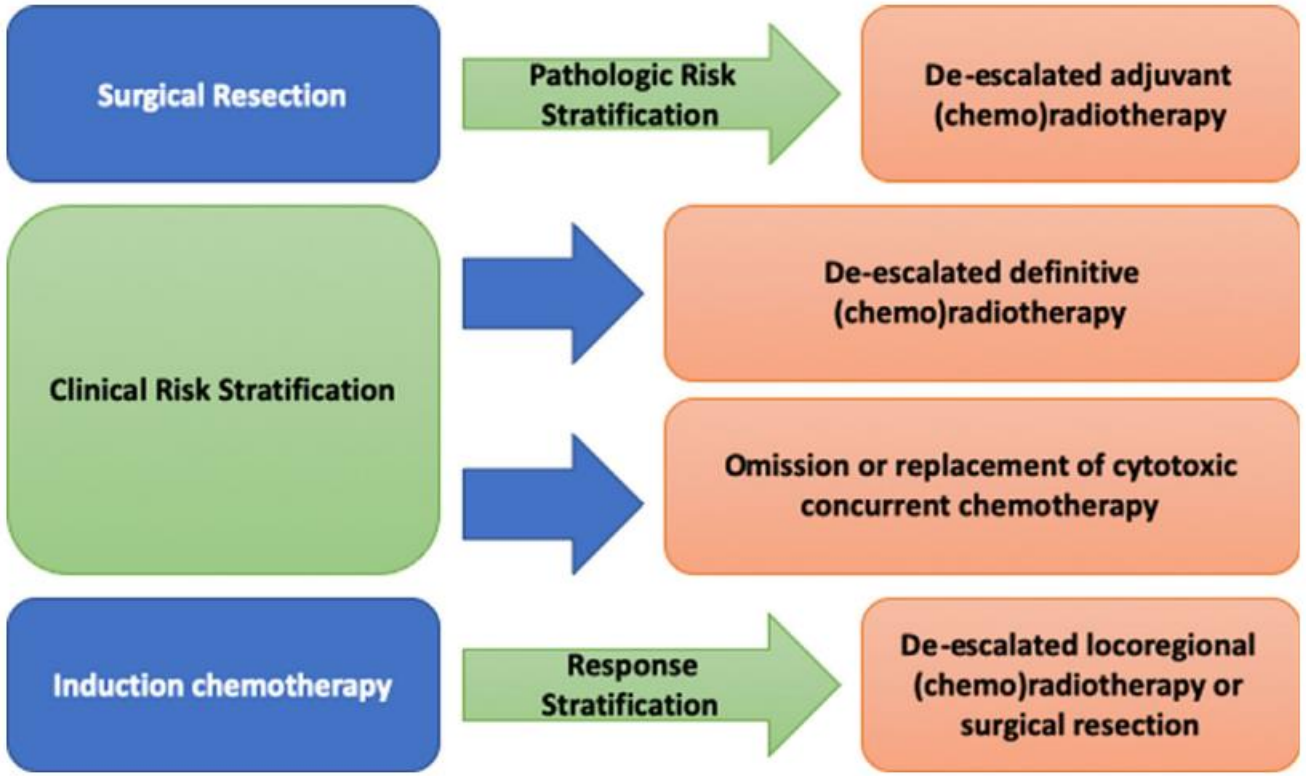
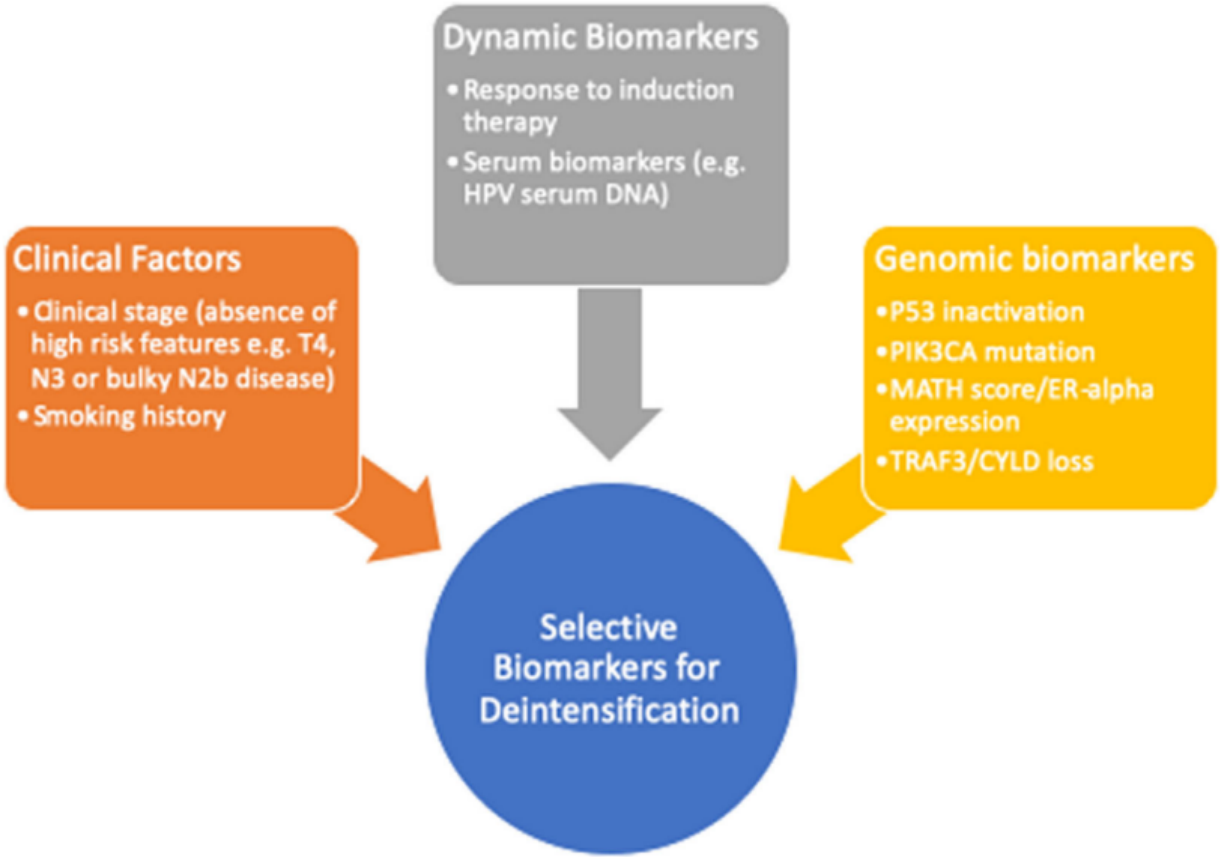


Figure 1. Approaches to de-escalation in head and neck squamous cell carcinoma.

Biomarker selection for t/t deintensification in head & neck SCC .



Review De-Escalation Strategies for HPV-Associated Oropharyngeal SCC—Where Are We Now?

Table 1. Overview of both published and ongoing treatment de-escalation clinical trials for human papillomavirus-associated oropharyngeal squamous cell carcinoma.

Study Name	NCT Code	Phase	Status	Eligibility	De-Escalation Strategy	Outcomes
Upfront surgery and pathology-based adjuvant therapy						
ORATOR	NCT01590355	II	Complete	T1–T2, N0–2 OPSCC (7th edition)	Patients randomized to: 1. Surgical arm: TOS and ND ± adjuvant therapy (60 Gy RT or 64 Gy RT and chemotherapy) 2. RT: 70 Gy ± high dose cisplatin (carboplatin or cetuximab if unfit)	Surgery group (n = 34): 16 patients received adjuvant RT, 8 patients received adjuvant CRT RT group (n = 34): 2 patients withdrew, 23 patients received concomitant CRT RT group had a better one-year swallowing-related quality of life, however, not a clinically meaningful difference ~4 Year follow-up
ORATOR2	NCT03210103	II	Complete, no published results	T1–2, N0–2 potentially resectable HPV-related OPSCC (8th edition)	Patients are risk stratified by smoking history, then randomized to de-intensified 60 Gy RT ± weekly cisplatin or TOS and ND ± adjuvant 50 Gy RT	Surgery group (n = 31), RT group (n = 30). Recruitment closed early due to two treatment related deaths in the surgical arm Two-year OS estimates were 89.1% in the TORS group and 100% in RT group The two-year PFS estimates were 83.5% in the TORS group and 100% in the RT group 71% Of the surgical group had grade 2–5 toxicities versus 67% of patients in the RT arm
Surgery and de-escalation of adjuvant radiotherapy						
MC1273	NCT01932697	II	Complete	Resectable HPV-related OPSCC, stage III or IV, ≤10 PY (7th edition)	All patients underwent surgery with curative intent. Post-operatively deemed high risk if ENE, LVI, PNI, ≥2 regional LN involved, any LN > 3 cm, or ≥T3 primary tumor. Stratified based on ENE: 1. ENE negative: 30 Gy and docetaxel 2. ENE positive: 36 Gy and docetaxel	Group A (n = 37) (1 distant recurrence) Group B (n = 43) (4 locoregional recurrence and 5 distant metastases) Whole cohort, two-year DMFS, PFS, and OS were 94.9%, 91.1%, and 98.7%, respectively This aggressive RT de-intensification achieved similar results as historical controls Toxicity and adverse events were improved as compared with historical controls Pre-RT QOL scores were improved at one year follow-up

Table 1. *Cont.*

Study Name	NCT Code	Phase	Status	Eligibility	De-Escalation Strategy	Outcomes
AVOID	NCT02159703	II	Complete	Resectable pT1–2, pN1–3 HPV-related OPSCC (7th edition)	All patients undergo TORS and ND on with >2 mm margins, no PNI, no LVI. All patients receive adjuvant therapy to neck only (no primary site): 1. Neck involved in disease: 60–66 Gy 2. Neck uninvolved in disease: 54 Gy With concurrent chemotherapy if ENE+	All patients received adjuvant RT at 60–66 Gy (n = 60), ENE+ received concurrent CRT (n = 13) Follow up of 2.4 years Mean primary site radiation of 36.9 Gy Recurrence: primary site (n = 1), regional recurrence (n = 1), distant metastases (n = 2) Two-year LCR 98.3%, OS 100% at the time of analysis Adverse events: late soft tissue necrosis in the primary site with conservative management (n = 2) No long-term feeding tube dependence (n = 0)
E3311	NCT01898494	II	Complete	T1–2, N1–2b HPV-related OPSCC (7th edition)	All patients undergo TOS and ND. Post-operative risk stratification: 1. Group A = Low risk = pT1–2, pN0–1 + negative margins: observation 2. Intermediate risk = negative margins, ≤1 mm ENE, 2–4 LN involved, PNI or LVI: randomized to a. Group B 50 Gy adjuvant RT b. Group B 60 Gy adjuvant RT 3. Group D high risk = positive margins, >1 mm ENE, >5 LN involved: 66 Gy adjuvant RT with concurrent cisplatin	Group A (n = 38), Group B (n = 100), Group C (n = 108), Group D (n = 131) Follow up period of 35 months No significant difference in PFS or OS: PFS 96.9% for arm A, 94.9% for arm B (50 Gy), 96.0% for arm C (60 Gy), and 90.7% for arm D OS was 100% for arm A, 99.0% for arm B, 98.1% for arm C, and 96.3% for arm D MDADI and FACT-H&N for both intermediate-risk groups were similar
SIRS	NCT02072148	II	Complete	T1, N1–2b or T2, N0–2b HPV-related OPSCC with <20 PY (7th edition)	All patients undergo TOS and ND. Post-operative risk stratification: 1. Low risk = pT1–2, pN0–2b, no high risk features: observe 2. Intermediate risk = pT1–2, pN0–2b, negative margins, LVI, PNI, <3 LNs, <1 mm ENE: 50 Gy adjuvant RT 3. High risk ≥ 3LN, positive margins, ENE+, contralateral LNs: 56 Gy adjuvant RT with concurrent cisplatin	Group A (25), Group B (15), Group C (14) Median follow up 43.9 months PFS probability was 91.3% for Group 1, 86.7% for Group 2, and 93.3% for Group 3 Global MDADI QOL scores improved with time and returned to baseline scores

Table 1. *Cont.*

Study Name	NCT Code	Phase	Status	Eligibility	De-Escalation Strategy	Outcomes
PATHOS	NCT02215265	II/III	Accrual	T1–3, N0–2b HPV-related OPSCC (7th edition)	All patients undergo TOS and ND. Post-operative risk stratification: 1. Low risk = pT1–2, no adverse features: observe 2. Intermediate risk = T1–3, N2a-b, PNI, LVI, 1–5 mm margins: randomized to adjuvant RT of 50 Gy or 60 Gy 3. High risk = positive margins (<1 mm), >1 mm ENE: randomized to adjuvant 60 Gy RT or 60 Gy RT with concurrent cisplatin	N/A
ADEPT	NCT01687413	III	Accrual	Resectable T1–4a HPV-related OPSCC, ENE positive	All patients undergo TORS and ND, nodal disease with ENE randomized to 60 Gy RT alone or with concurrent weekly cisplatin	N/A
MINT	NCT03621696	II	Complete, no published results	Stage I-III resectable HPV-related OPSCC (8th edition)	All patients undergo TOS and ND. Post-operative risk stratification: 1. Low risk = <T4, <cN3, no ENE, negative margins: 42 Gy adjuvant RT 2. Intermediate risk = <T4, <cN3, ENE, or positive margins = 42 Gy adjuvant RT with one dose cisplatin 3. High risk = T4, cN3: 60 Gy RT with concurrent cisplatin	Preliminary results available on clinicaltrials.gov
DART-HPV (follow-up phase III randomized clinical trial to MC1273)	NCT02908477	III	Complete, no published results	Resectable T1–3, N0–3, M0HPV-related OPSCC (7th edition)	Patients are randomized to: 1. CRT with 60 Gy and cisplatin if high risk or 2. Docetaxel with 30 Gy (36 Gy if high risk)	N/A

Table 1. *Cont.*

Study Name	NCT Code	Phase	Status	Eligibility	De-Escalation Strategy	Outcomes
ADAPT	NCT03875716	II	Accrual	Resectable HPV-related OPSCC, T0–2, N0–1, M0 (8th edition)	All patients undergo TOS and ND. Post-operative risk stratification: 1. Low risk = pT1–2, N0–1, minimum of 15 LNs examined, ≤2 LN involved, no ENE: observation 2. Intermediate risk = pT1–2, N0–2, >2 LNs involved, <15 LNs examined, positive LNs in levels Ib, IV, or V, ≤1 mm ENE, contralateral LNs, close margins: reduced adjuvant RT 3. High risk = pT1–4, N0–2 with >1 mm ENE and positive margins: adjuvant RT (standard dose)	N/A
DELPHI	NCT03396718	I	Accrual	Patients with resected primary and ND with indication for adjuvant therapy	Patients are randomized to: 1. Intermediate risk = HPV + pT3 and R0 +/− 1–2 LN involvement and no ECE: 54/59.4 Gy 2. High risk = HPV + with R1, pT4, 3+ nodes, and/or ECE: 60/66 Gy 3. Comparative group 1 (HPV−) = 60/66 Gy 4. Comparative group 2 (HPV+) = 60/66 Gy	N/A
	NCT03729518	II	Accrual	Resectable T1–3, N0–2c HPV-related OPSCC (7th edition)	All patients undergo TORS and ND. If post-operative pathology demonstrates <5 involved LN, patients undergo reduced adjuvant RT to nodal areas, avoiding primary site, with or without chemotherapy	N/A
	NCT02784288	I	Active, not recruiting	Potentially resectable T1–3, N0–2c HPV-related OPSCC	All patients undergo ND and biopsy of primary site. Post-operative pathology determining treatment pathway: 1. Low risk = ≤1 LN < 6 cm, no ENE, no LVI, no PNI: TOS 2. Intermediate risk = >/=2 LNs, presence of PNI/LVI, no ENE: RT 3. High risk = ENE or positive margins: concurrent CRT	N/A

Table 1. *Cont.*

Study Name	NCT Code	Phase	Status	Eligibility	De-Escalation Strategy	Outcomes
Altered regimen of chemoradiotherapy						
NRG-HN002	NCT02254278	II	Complete	T1–2, N1–2b or T3, N0–2b, HPV-related OPSCC (7th edition) with ≤10 PY	Patients are randomized to reduced dose 60 Gy IMRT with or without concomitant cisplatin	Group A = IMRT + C (n = 157) and Group B = IMRT (n = 149) Two-year PFS for Group A was 90.5%, and Group B was 87.6% One-year MDADI mean scores were 85.30 and 81.76, respectively. Two-year OS rates were 96.7% and 97.3%, respectively The IMRT-alone group did not meet acceptability criteria.
	NCT00606294 (pilot)NCT03323463	II	Complete	T1–2, N1–2c HPV-related OPSCC (7th edition)	Patients undergo pre-operative tumour resection and ^{18}F-FMISO PET for assessment of hypoxia. 1. No hypoxia = receive 30 Gy RT and cisplatin 2. Hypoxia = start CRT with repeat ^{18}F-FMISO PET in 1 week to reassess hypoxia 3. If no hypoxia: 30 Gy RT with cisplatin 4. If persistent hypoxia: 70 Gy RT with cisplatin	18 Patients included in study. 15 Patients received 30 Gy and cisplatin (6 patients had no hypoxia on initial assessment, 9 patients had no hypoxia on intra-treatment assessment) 3 Patients received 70 Gy and cisplatin Two-year locoregional control, progression-free survival, and overall survival for the de-escalated cohort per protocol were 100%, 92.9%, and 92.9%, respectively
LCC1120	NCT01530997	II	Complete	T0–3, N0-N2c, M0 HPV-related OPSCC with ≤10 PY (or >5 years tobacco-free if ≤30 PY) (7th edition)	All patients are treated with de-escalated IMRT (60 Gy) and reduced dose of weekly concurrent cisplatin. After completion of chemoradiotherapy, patients underwent at least ND with primary site biopsy to assess pathologic response	43/45 Patients completed the study protocol At a median 14 month from of treatment, no measurable tumor present on physical and radiologic examination in 64% of patients The pathologic complete response rate was 86% After a median 36-month follow-up, three-year locoregional control, distant metastasis-free survival, and overall survival rates were 100%, 100%, and 95%, respectively

Table 1. *Cont.*

Study Name	NCT Code	Phase	Status	Eligibility	De-Escalation Strategy	Outcomes
LCC1413	NCT02281955	II	Complete, results not published	T0–3, N0-N2c, M0 HPV-related OPSCC with ≤10 PY (or >5 years tobacco-free if ≤30 PY) (7th edition)	All patients are treated with de-escalated IMRT (60 Gy) and reduced dose of weekly concurrent cisplatin After completion of CRT, all patients underwent PET-CT scan in place of surgery for pathologic assessment	All patients received 60 Gy IMRT (n = 114), 80% of the patients staged to receive chemotherapy completed at least four cycles of cisplatin and 11% received cetuximab upfront due to contraindications to cisplatin The post-treatment complete response on PET-CT was 93% at the primary site and 80% in the neck All patients with residual disease at the primary site are alive and no evidence of disease Two-year locoregional control, progression-free survival, and overall survival were 95%, 86%, and 95%, respectively
LCCC1612	NCT03077243	II	Active, not recruiting	T0–3, N0–2c, M0 HPV-related OPSCC (7th edition), p53 mutation status	Patients are risk stratified by their p53 mutation status and smoking history: 1. Low risk = ≤10 PY or >10 PY without p53 mutation: 60 Gy IMRT with concurrent cisplatin 2. High risk = >10 PY with p53 mutation: 70 Gy IMRT with concurrent cisplatin	N/A
	NCT01088802 (7th edition)	II	Active, not recruiting	T1–3, any N, resectable HPV-related OPSCC	RT dose to 63 from 70 and from 58.1 Gy to 50.75 Gy	N/A
EVADER	NCT03822897	II	Active, not recruiting	T1–3, N0–1, M0 HPV-related OPSCC (8th edition)	Patients receive definitive RT (70 Gy) to primary site and reduced-dose elective nodal irradiation (56 Gy), with or without concurrent cisplatin	N/A
Targeted therapy with egfr inhibitor versus cisplatin						
RTOG1016	NCT01302834	III	Complete	T1–2, N2–3 or T3–4, N0–3 HPV-related OPSCC (7th edition)	Patients receive standard-dose 70 Gy IMRT and are randomized to receive concurrent cisplatin or cetuximab	Group A cetuximab (399) and Group B cisplatin (406). Median follow-up duration of 4.5 years Estimated five-year overall survival was 77.9% vs. 84.6%, respectively PFS was significantly lower in the cetuximab group as compared with the cisplatin group (hazard ratio 1.72)

Table 1. *Cont.*

Study Name	NCT Code	Phase	Status	Eligibility	De-Escalation Strategy	Outcomes
De-ESCALaTE HPV	NCT01874171	III	Complete	T3–4, N0, T1–4, N1–3, HPV-related OPSCC with ≤10 PY (7th edition)	Patients receive standard-dose 70 Gy RT and are randomized to receive concurrent cisplatin or cetuximab	Cisplatin group (n = 152), cetuximab group (n = 152) A significant difference in two-year overall survival of 97.5% for cisplatin versus 89.4% for cetuximab, p = 0.001, and two-year recurrence rate of 6.0% for cisplatin versus 16.1% for cetuximab, p = 0.0007
TROG12.01	NCT01855451	III	Complete	Stage III (except T1–2, N1) or stage IV (except T3, N3 or M1) with ≤10 PY. If >10 PY, must be N0–2a (7th edition)	Patients receive standard-dose 70 Gy RT and are randomized to receive concurrent cisplatin or cetuximab	Group A cisplatin (92) and Group B cetuximab (90) There was no difference in the primary endpoint of symptom severity The T-score was 4.35 in the cisplatin arm and 3.82 in the cetuximab arm The three-year failure-free survival rates were 93% and 80%, respectively
NRG HN005	NCT03952585	II	Accrual	T1–2, N1 or T3, N0–2b HPV-related OPSCC with ≤10 pack year history (8th edition)	Patients are randomized to one of three arms: 1. 70 Gy IMRT with concurrent cisplatin 2. 60 Gy IMRT with cisplatin 3. 60 Gy IMRT with cisplatin and nivolumab	N/A
Neoadjuvant chemo with consolidation surgery						
NeCTORS	NCT02760667	II	Accrual	Stage III-IV HPV-associated OPSCC (7th edition)	All patients undergo 3 cycles of neo-adjuvant chemotherapy with cisplatin and docetaxel and transoral surgery and selective ND	55 Patients were enrolled to undergo neoadjuvant chemotherapy and surgery, 2/55 required adjuvant CRT for unresectable positive margins following TORS, 0/55 required salvage RT for recurrence Five-year disease-free survival was 96.1% as compared with 67.6% for concurrent CRT
E1308	NCT01084083	II	Complete	Resectable stage III or IV HPV-related OPSCC (7th edition)	All patients undergo 3 cycles of induction chemotherapy with cisplatin, paclitaxel, and cetuximab 1. Complete clinical response: 54 Gy adjuvant RT with weekly cetuximab 2. Incomplete clinical response: 69.3 Gy adjuvant RT with weekly cetuximab	80 Patients were enrolled, 70% achieved a primary-site complete clinical response to induction chemotherapy, and 51 patients continued to cetuximab with IMRT 54 Gy After median follow-up of 35.4 months, two-year PFS and OS rates were 80% and 94%, respectively, for those who had complete initial response In the 69 Gy RT arm, there were higher rates of these same adverse events, with 47% suffering from mucositis and 29% having dysphagia

Table 1. *Cont.*

Study Name	NCT Code	Phase	Status	Eligibility	De-Escalation Strategy	Outcomes
Quarterback	NCT01706939	II	Complete	Stage III-IV HPV-related OPSCC, no distant metastases, ≤20 PY (7th edition)	All patients undergo 3 cycles of induction chemotherapy with docetaxel, cisplatin, 5-fluorouracil. Patients with partial clinical response or complete clinical response were randomized (2:1) to reduced-dose IMRT (56 Gy) or standard-dose IMRT (70 Gy), with weekly carboplatin	Group A standard-dose chemoradiotherapy (8) and Group B reduced dose chemoradiation (12) Median follow up was 56 months Three-year progression-free survival was 87.5% and 83.3%, respectively Non-inferiority of reduced CRT dosages could not be demonstrated given the limited number of enrolled participants
Quarterback II	NCT02945631	II	Accrual	Stage III-IV, M0 HPV related OPSCC, ≤20 PY, not a current smoker (7th edition)	All patients undergo 3 cycles of induction chemotherapy with docetaxel, cisplatin, 5-fluorouracil Stratified based on response: 1. Low risk = partial or complete clinical response: 56 Gy RT with concurrent carboplatin 2. High risk = no response or progression: surgery or standard 70 Gy RT with concurrent carboplatin	N/A
OPTIMA	NCT02258659	II	Complete	T1–4, N2–3 HPV-related OPSCC (7th edition)	All patients undergo 3 cycles of induction chemotherapy with carboplatin and nab-paclitaxel 1. Low-risk patients = ≤T3, ≤N2b, ≤10 pack-years: a. >50% clinical response: 50 Gy RT b. 30–50% clinical response: 45 Gy and concurrent paclitaxel c. <30% clinical response: 75 Gy and concurrent paclitaxel 2. High risk = T4 or ≥N2c or >10 pack-years: a. >50% clinical response: 45 Gy and concurrent paclitaxel b. <50% clinical response: 75 Gy and concurrent paclitaxel	62 Patients (28 low risk/34 high risk) were enrolled Of low-risk patients, 71% received 50 Gy radiation, while 21% received 45 Gy CXRT Of high-risk patients, 71% received 45 Gy CXRT With a median follow-up of 29 months, two-year PFS and OS were 95% and 100% for low-risk patients and 94% and 97% for high-risk patients, respectively

Table 1. *Cont.*

Study Name	NCT Code	Phase	Status	Eligibility	De-Escalation Strategy	Outcomes
OPTIMA-II	NCT03107182	II	Active, not recruiting	T3–4 or N2–3 HPV-related OPSCC (7th edition)	All patients undergo 3 cycles of induction chemotherapy with carboplatin and nab-paclitaxel, with additional nivolumab. Risk stratification based on staging and clinical response: 1. Low-risk patients = T1–2, N2a-b a. >50% clinical response and TORS-eligible: TORS/neck dissection +/− reduced RT b. >50% clinical response and TORS-ineligible: reduced RT (50 Gy) c. 30–50% clinical response: 50 Gy RT with concurrent cisplatin d. <30% clinical response: 75 Gy and concurrent cisplatin 2. High risk = T4, bulky N2b-2c-3, >10 pack-years: a. >50% clinical response: 50 Gy RT and concurrent cisplatin b. <50% clinical response: 75 Gy and concurrent cisplatin All patients will be offered adjuvant nivolumab for 6-months post completion of definitive therapy.	N/A
CCRO-022	NCT02048020/ NCT01716195	II	Complete	Stage III–IV HPV-related OPSCC (7th edition)	All patients undergo 2 cycles of induction chemotherapy with paclitaxel and carboplatin. 1. Low risk = complete clinical response or partial clinical response: 54 Gy adjuvant IMRT with concurrent paclitaxel 2. High risk = <partial clinical response: 60 Gy adjuvant IMRT with concurrent paclitaxel	44 Patients were enrolled, 24 (55%) patients with complete or partial responses to induction chemotherapy received 54 Gy radiation, and 20 (45%) patients with less than partial responses received 60 Gy Median follow-up was 30 months. Two-year PFS was 92%

Proton Therapy for HPV-Associated Oropharyngeal Cancers of the Head & Neck: a De-Intensification Strategy

- IMPT is a form of radiotherapy that de-intensifies t/t through dose de-escalation to normal tissues without compromising dose to the primary tumor and involved, regional lymph nodes. Preclinical studies have demonstrated that HPV-positive SCC is more sensitive to proton radiation than is HPV-negative .
- Retrospective studies comparing IMRT to IMPT for OPC suggest comparable rates of disease control and lower rates of pain, xerostomia, dysphagia, dysgeusia, gastrostomy tube dependence, and osteoradionecrosis with IMPT—all of which meaningfully affect the QOL of patients treated for HPV-associated OPC.
- Two phase III trials currently underway—the “Randomized Trial of IMPT versus IMRT for the Treatment of Oropharyngeal Cancer of the Head and Neck” and the “TOxicity Reduction using Proton bEam therapy for Oropharyngeal cancer (TORPEdO)” trial—are expected to provide prospective, level I evidence regarding the effectiveness of IMPT for such pts.

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Treatment De-escalation For HPV+ Oropharyngeal Cancer: A Systematic Review And Meta-analysis

- The primary outcome of interest was OS.
- Secondary endpoints were PFS, LRC, and DM expressed as HR.
- A total of 55 studies (from 1393 screened references) were employed for quantitative synthesis for 38 929 pts. Among n = 48 studies with data available, de-intensified t/ts reduced OS in HPV+ OPCs (HR = 1.33, 95% CI 1.17-1.52; $p < 0.01$).
- In de-escalated t/ts, PFS was also decreased (HR = 2.11, 95% CI 1.65- 2.69; $p < 0.01$). Compared with standard t/ts, reduced intensity approaches were associated with reduced locoregional and distant disease control (HR = 2.51, 95% CI 1.75-3.59; $p < 0.01$; and HR = 1.9, 95% CI 1.25-2.9; $p < 0.01$).
- CCRT improved survival in a definitive curative setting compared with RT alone (HR = 1.42, 95% CI 1.16-1.75; $p < 0.01$).
- When adjuvant t/ts were compared, standard and de-escalation strategies provided similar OS.
- In conclusion, in pts with HPV+ OPC, de-escalation t/ts should not be widely and agnostically adopted in clinical practice, as therein lies a concrete risk of offering a sub-optimal t/t to pts.

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Conclusion

- Cisplatin concurrent with standard dose RT remains the standard of care for t/t of pts with locally advanced HPV-OPC, although it is being challenged by de-escalation clinical trials.
- Multiple de-escalation strategies in pts with favorable-risk HPV-OPC have excellent short term survival outcomes, but phase III data are needed before any of these can be adopted as standard of care.
- Cetuximab with RT is inferior to cisplatin for definitive t/t of pts with HPV-OPC.
- Novel predictors of pts at risk for recurrence, such as hypoxia, circulating tumor DNA, and genomic data (PIK3CA, p53), are likely to be important for additional risk stratification in next-generation trials. Other pt factors that might impact outcomes could also be considered when designing future trials, including neutrophil/lymphocyte ratio, microbiome, body mass index, nutritional markers, and comorbidities.
- Finally, the prevention of cancer is the ultimate de-escalation strategy.
- Well-designed, large, randomized, multicenter clinical trials are needed to refine, optimize, and establish a treatment paradigm for HPV+ OPSCC that optimizes oncologic outcomes while reducing acute and chronic toxicities - A way far away in India.