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# Human Papillomavirus Associated Oropharyngeal Carcinoma- Diagnosis and Management

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## Abstract

Head and neck squamous cell carcinomas arise from the mucosa of the upper aerodigestive tract and is often driven by risk factors like tobacco and alcohol consumption. Most of the time patients present with locally advanced stages and the outcome is poor, despite recent advances in multi-modality treatment. The epidemiology of the disease has changed over the last decade with the introduction of a separate clinical entity; Human Papillomavirus (HPV) associated head and neck cancer. The tumorigenesis is different from that of tobacco and alcohol-driven malignancies. These tumors have a better response to treatment owing to their inherent genetic makeup and carry an excellent prognosis. The current school of thought is to reduce the long-term morbidities associated with various treatment modalities, as these patients tend to survive longer. The best management of HPV-associated oropharyngeal cancer is under active investigation.

**Keywords:** human papilloma virus, oropharyngeal cancer, squamous cell carcinoma, treatment, prognosis

## 1. Introduction

HPV is currently a well-recognized and emerging risk factor for head and neck squamous cell carcinoma. HPV associated oropharyngeal carcinoma have distinct clinical behavior and outcome. This led to a paradigm shift in the research and trend towards De-escalating treatment strategies. The rationale of these trials is to prove that the de-intensified treatment modality has same efficacy with less morbidity compared to standard of treatment. This chapter tries to elaborate on the epidemiology, onco-genesis, testing for HPV, treatment approaches and different clinical trials addressing the issue.

## 2. Epidemiology

Oropharyngeal carcinoma represents 0.9% of all cancers and its incidence is increasing with an estimate of 173,495 new cases in 2018 [1]. Epidemiological

studies have demonstrated that there has been a reduction in the incidence of laryngeal, hypopharyngeal, and oral cavity cancers since 1980, following a reduction in tobacco use in developed countries [2]. Oropharyngeal cancer incidence initially remained constant, then started rising [2, 3]. Later it was correlated to HPV-associated cancers in the tonsillar region and base of the tongue. There is a geographical variation in the incidence of oropharyngeal carcinoma with the increasing incidence of HPV associated cancers in the developed countries [4]. Among men the rising incidence of HPV associated oropharyngeal cancer was noticed in the United States, Australia, Canada, Japan and Slovakia and among women it was noticed in Denmark, Estonia, France, Netherlands, Poland, Slovakia and United Kingdom [4]. These patients tend to be younger and follow a biphasic distribution, which peaks around 30 and 55 years [5]. Male gender preponderance has been noted in many studies. In the ICON-S database median age of the HPV positive cases was 57 years and 84% of patients were male [5].

3. Clinical characteristics of HPV associated oropharyngeal cancer

HPV-associated Oropharyngeal Squamous cell Carcinoma (OPSCC) has different demographic and biological features when compared to HPV negative cancers [6]. These patients tend to be younger, with little or no tobacco exposure, and associated with certain sexual behaviors like oral sex. They have different molecular alterations. **Table 1** shows a comparison between clinical and biological profiles of HPV positive and HPV negative oropharyngeal carcinoma. The synergetic mechanism of HPV with tobacco and alcohol is unknown. The subset of OPSCC patients with significant smoking history may harbor TP53 and EGFR mutations and their outcomes are similar to HPV negative head and neck cancers.

Characteristics	HPV positive	HPV negative
Age	younger	older
Gender	3:1 men	3:1 men
Socioeconomic status	high	low
Risk factors	sexual behavior	tobacco, alcohol
Co factors	immunosuppression, marijuana use	diet, hygiene
Incidence	increasing	decreasing
Survival	better	worse
Predilection site	tonsil, base of tongue	none
Histology	basaloid/poorly differentiated	keratinized
T-Stage	lower T-stage	higher T stage
Nodal status	higher, often cystic nodes	lower
Field cancerization	unknown	present
Genetics	P53 inactivated by E6	P53 is mutated
	Rb inactivated by E7	Rb inactivated by cyclin D1Amplification
	P 16 over expressed	Inactivation of p 16

**Table 1.**  
*Major differences between HPV positive and negative oropharyngeal cancers.*

4. Human papillomavirus and carcinogenesis

A systematic review by Kriemer et al. has described the presence of HPV DNA in head and neck cancers [7]. Approximately 150 HPV subtypes have been reported. HPV 16 is associated with >90% of HPV associated oropharyngeal cancers [7]. HPV is a circular, double stranded DNA virus of 55 nm. Multiple sexual partners and/ or higher frequency of oral sex may increase the risk of HPV infection and later malignant transformation. Tonsillar crypts provide large epithelial surface and deep invaginations of the mucosal surface are thought to favor the capture and processing of viral antigens. The epithelial basal cells are the target cells of the virus, where the viral DNA undergoes uncoating and is transported to the nucleus. In high risk HPV infection E6 and E7 proteins are produced from the supra basal layers. In HPV induced carcinogenesis, E6 and E7 oncoproteins deregulates cell cycle and apoptosis by acting on p53 [8]. P53 is a tumor suppressor gene which controls G1 transition to S phase in the cell cycle at G1 check point by inducing the expression of cyclin inhibitors p16, p21 and p27 which in turn will block cyclin dependent kinases and progression of the cell cycle at G1/S transition. Inactivation, of p53 gene causes increased cell proliferation. Rb family of proteins governs the check point between G1 and S Phase. In normal cell cycle hypo phosphorylated Rb forms a complex with E2F and makes it unavailable for the DNA synthesis. E7 oncoprotein inactivate Rb family of proteins that causes over expression of E2F thereby produces increased cell proliferation [9].

5. Principles of HPV testing for oropharyngeal carcinoma

All patients diagnosed with OPSCC should undergo testing for HPV status. Biopsy from the primary lesion or FNAC from an involved node is sufficient for HPV testing. The gold standard is the demonstration of HPV E6/E7 mRNA expression in clinical specimens, which is often impractical. Demonstration of HPV DNA, by polymerase chain reaction (PCR), has high sensitivity, but specificity is low as cross-contamination can occur. In situ hybridization (ISH) technique allows the identification of a single viral copy and is more specific. In the HPV carcinogenesis, E7 mediated Rb inhibition leads to induction of demethylases resulting in overexpression of p16<sup>INK4A</sup>, which is a cyclin-dependent kinase inhibitor. Hence the immunohistochemistry (IHC) test for P 16 is used as a surrogate marker for HPV status. Various methods for testing the HPV status is summarized in **Table 2**. Infection with non-HPV subtypes or low viral copy numbers cannot be detected by IHC and there can be a 7% disparity between HPV ISH and IHC reports. In the case of an equivocal P16, further testing by ISH can clarify the HPV status. Work up for patients includes thorough history taking, with documentation on pack-years smoked, and clinical examination (inspection, palpation, and endoscopy evaluation to see the extent of the lesion). Imaging using CT or MRI

Tumor tissue	Serum
<ul style="list-style-type: none"><li>• Testing for viral load(Viral DNA) In situ-hybridization</li></ul>	<ul style="list-style-type: none"><li>• Antibody testing (Cumulative viral load) L1</li></ul>
Polymerase Chain Reaction	Capsid protein
<ul style="list-style-type: none"><li>• Gene expression E6,E7 mRNA</li></ul>	<ul style="list-style-type: none"><li>• Expressed oncoprotein E6, E7</li></ul>
<ul style="list-style-type: none"><li>• Surrogate Immunohistochemistry-P<sub>16</sub></li></ul>	

**Table 2.**  
*Various methods used for testing HPV status.*

neck aids in staging detects regional lymphadenopathy including retropharyngeal nodes. MRI neck in treatment position is particularly useful in delineation of the primary lesion for radiotherapy planning. The primary lesions of HPV positive OPSCC often had well-defined borders on imaging with a cystic nodal disease with or without necrosis. A chest X-ray is advisable to assess the baseline pulmonary function. Additionally, they need a dental evaluation for radiotherapy planning. All patients should undergo nutrition, speech, and swallowing evaluation, and smoking cessation counseling should be given if needed. Pre-anesthesia workup is needed if planning for surgery.

6. New staging system

As the number of HPV-associated OPSCC increased the 7th AJCC staging system lost its ability to differentiate between stages. There was an overlap of survival among different stages of HPV positive oropharyngeal carcinoma. Based on

Clinical and Pathological T categories
• T1 Tumour 2 cm or less in greatest dimension
• T2 Tumour more than 2 cm but not more than 4 cm
• T3 Tumour more than 4 cm in or extension to lingual surface of epiglottis
• T4 Tumour invades any of the following: larynx, deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), medial pterygoid, hard palate, mandible, lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base; or encases carotid artery
Clinical N categories
N0 No regional lymph node metastasis
N1 Unilateral metastasis, in lymph node(s), all 6 cm or less
N2 Contralateral or bilateral metastasis in lymph node(s), all 6 cm or less in greatest dimension
N3 Metastasis in lymph node(s) greater than 6 cm in dimension
Clinical
Stage I T1,T2 N0,1 M0
Stage II T1,T2 N2 M0
T3 N0,N1,N2M0
Stage III T1-T4 N3 M0
T4 Any N M0
Stage IV Any T Any N M1
Pathological N categories
Nx-regional nodes cannot be assessed
pN0-No regional lymph node metastasis
pN1-Metastasis in 4 or few lymphnodes
pN2-Metastasis in more than 4 lymphnodes
There is no T4b in the current classification and carcinoma in-situ is removed as there is absence of a distinct basement membrane in the epithelium of Waldeyers ring.
Extra capsular extension is not included in the pathological classification and there is no pN3 status.

Table 3.  
New classification for HPV positive carcinoma oropharynx based on AJCC Cancer Staging Manual, 8th [11].



accumulating evidence of prognostic value for HPV-positive OPSCC new staging system was refined [5, 10]. The new AJCC 8th staging system for HPV positive oropharyngeal carcinoma is summarized in **Table 3** [11].

7. HPV status and treatment response

There are many factors attributed to the survival advantage for p16 positive oropharyngeal carcinoma. Many of the patients are younger, they have fewer comorbidities and less chance of field cancerization given reduced smoking history. HPV-positive tumours may harbour fewer or different genetic alterations. HPV-positive tumours have higher radio sensitivity, due to compromised DNA repair capacity [12]. Other studies have reported intrinsic radiation sensitivity and increased apoptosis following radiation exposure [13]. The immunologic response may play a role in the improved response to radiotherapy and chemotherapy in HPV-positive tumors.

The survival advantage noted for HPV positive OPSCC in the radiotherapy setting has been summarized in **Table 4**. Retrospective analysis of the HPV positive subgroup in the RTOG 0129 trial reported a strong association between HPV status and good survival [19]. They risk stratified the patients as having a low, intermediate, or high risk of death based on the combination of tumor HPV status, pack-years of tobacco smoking, and cancer stage. In the low-risk group, which included

Study	N	Subsite	% HPV	Treatment	Survival HPV + ve	Survival HPV – ve	P value
ECOG 2399 [14]	96	oropharynx + larynx	40	induction chemotherapy + chemo radiation	95%	62%	0.005
DAHANCA 5 [15]	156	all head and neck sites	22	radiotherapy + concurrent Nimorazole	62%	26%	0.003
TROG 02.02 [16]	172	oropharynx	57	chemo radiation with or without Tirapazamine	91%	74%	0.004
TAX 324 [17]	111	oropharynx	50	induction chemotherapy + chemo radiation	79%	31%	0.0001
RTOG 9003 [18]	190	oropharynx	39	standard fractionation versus altered fractionation radiotherapy	49%	19.6%,	<0.0001
RTOG 0129 [19]	323	oropharynx	64	accelerated RT vs. Standard RT + concurrent chemotherapy	82.4%,	57.1%	<0.001
DAHANC A6, 7 [20]	769	all head and neck sites	23	five or six fractions of radiotherapy per week +Nimorazole	62%	47%	0.0001

**Table 4.**  
Major randomized trials that have reported survival benefit for HPV positive subset.

HPV positive and non-smokers, 3-year disease-free survival (DFS) was 93% when compared to <50% in the high-risk group which included the HPV negative and smokers. The intermediate-risk group included HPV positive patients with smoking history and HPV negative non-smokers. This led to the thought for de-intensification of the multimodality approach for low-risk category patients. In the post-op setting, the German radiation oncology group study showed a better correlation of HPV positive status with oropharyngeal carcinoma subsite and better outcomes in the patients undergoing adjuvant chemoradiation for locally advanced head and neck cancers [21]. Retrospective analysis of IMCL-9815 study, where patients were treated with radiotherapy with or without Cetuximab, the overall survival was better for p16 positive patients [22]. In the abovementioned trials, a better prognosis for HPV positive oropharyngeal carcinoma was independent of treatment modality. The association of HPV positive status with improved outcome was restricted to the oropharyngeal primary site [23].

## **8. De-escalating treatment intensity**

The treatment options for early-stage OPSCC includes radical radiotherapy versus surgery (resection of the primary+/- ipsilateral or bilateral neck dissection). For locally advanced oropharyngeal carcinoma primary treatment is radical chemoradiation or induction chemotherapy followed by radical chemoradiation with or without salvage surgery. The primary lesion and involved node with a margin are treated to a dose of 66-70Gy in 33-35 fractions and prophylactic nodal stations will receive 54 Gy in 30 fractions. With the introduction of intensity-modulated radiotherapy (IMRT) dose to dysphagia aspiration, related structures can be minimized. Cisplatin 80-100 mg/m<sup>2</sup> once in 3 weeks is the standard concurrent chemotherapy schedule. For primary lesions of the oropharynx, surgical clearance is an issue, considering the complex anatomy and proximity to critical structures. Reconstruction is difficult and retropharyngeal nodes cannot be surgically removed. Bilateral neck dissection should be considered for lesions over the base of the tongue, soft palate, posterior pharyngeal wall, or tonsillar lesion invading the base of the tongue. Functional outcome is better with radiotherapy. In advanced-stage disease, surgery is often followed by adjuvant therapy which will lead to increased morbidity and decreased quality of life. Major factors deciding the treatment modality include performance status of the patient, location of the primary lesion, expertise available, morbidities associated with each treatment option, and patient preference. Since HPV-positive oropharyngeal carcinoma patients tend to be younger and have prolonged survival, there is a potential to improve the quality of life through reducing the treatment-related toxicities. Application of this knowledge has led to multiple de-escalating strategies.

### **8.1 Minimally invasive surgery**

The development of minimally invasive surgical techniques like transoral laser microsurgery (TLM) and transoral robotic surgery (TORS) has changed the surgical management for early oropharyngeal carcinoma. No prospective randomized studies are supporting the use of TORS over conventional surgery for oropharyngeal carcinoma. Small series report better swallowing outcomes in selected oropharyngeal carcinoma patients treated with less invasive surgery with or without neck dissection, followed by adjuvant therapy [24]. Complications include postoperative haemorrhage and the need for temporary tracheostomy.

ORATOR trial is the first phase 2 randomized trial comparing radiotherapy with transoral robotic surgery and neck dissection for early stage oropharyngeal squamous cell carcinoma [25]. Patients with T1–T2, N0–2 ( $\leq 4$  cm) OPSCC tumor types were randomized to radiotherapy arm (70 Gy, with chemotherapy, if N1–2) or TORS plus neck dissection (with or without adjuvant chemoradiotherapy, based on pathology). In the surgery arm, 24% of patients received postoperative chemo-radiotherapy. The initial report showed swallowing related quality of life score was better in the radiotherapy group after one year follow up. The ongoing ORATOR II trial is testing the overall survival between radiotherapy arm versus surgery [26].

Few other trials are assessing whether the swallowing function can be improved following minimally invasive surgery like Trans Oral Robotic Surgery (TORS) and to prove non-inferiority of reducing the intensity of adjuvant treatment in terms of overall survival. **Table 5** shows de-intensification trials after surgical intervention. The aim of the ECOG 3311 study was to find out whether the dose of adjuvant radiotherapy can be reduced in the intermediate risk patients [27]. 2-year Progression free survival was not affected by observation alone in the low risk group and reduced dose radiotherapy in the intermediate risk group. Pathos trial examines whether swallowing function is better in patients undergoing transoral resection of HPV-positive OPSCC with reduced adjuvant treatment and results are awaited [28]. The rationale behind ADEPT trial is to find out is it safe to avoid concurrent chemotherapy in patients with extracapsular extension following minimally invasive surgery [29].

In the ECOG 3311 trial, the negative margin was defined as 3 mm or greater and adjuvant radiotherapy was offered to those with,  $<3$  mm margin [27]. For transoral resection, the chance of positive margin is likely for the base of tongue tumors than Tonsillar tumors. In transoral laser microsurgery, the tumor may be removed in multiple pieces and it may be difficult to commend on the margin status. In many recent studies, the margin is generally considered clear unless involved [24].

Trial	Phase	N	Inclusion criteria (HPV + ve OPSCC)	Intervention (following TORS+ neck dissection)	Outcome
ECOG 3311 [27]	II	511	resectable stage III–IVB	A.Low risk- observation B.Intermediate risk- 50Gy/25 fractions or 60Gy/30 fractions C.High risk– Chemo radiation 66Gy/33 fractions	2-year PFS A-93.9% B- 95.0% C- 95.9%
PATHOS trial [28]	III	1100	resectable T1–T3, N0–2b. excludes active smokers with N2b disease	Intermediate risk- 50Gy/25 fractions or 60Gy/30 fractions High risk–60Gy/30 fractions or 60Gy/30 fractions + weekly Cisplatin	Awaited
ADEPT [29] (NCT01687413)	III	500	resectableT1–4a with negative margin pN positive with ECE	RT 60Gy/30 fractions or RT 60Gy/30 fractions + weekly Cisplatin	Awaited

TORS:Trans oral robotic surgery; ECE: extracapsular extension.

**Table 5.**  
Trials addressing the role of minimal invasive surgery and reduced dose radiotherapy.



Currently, it is proven that the number of involved nodes is more prognostic than extranodal extension in resected oropharyngeal carcinoma and has been incorporated in the pathological staging of AJCC 8th edition [30]. Some authors have tried omitting chemotherapy in high-risk patients with extranodal extension, to reduce the toxicity associated with triple modality treatment [31]. In the absence of evidence, this practice is not recommended. Routman has reported resected oropharyngeal cancer patients without high-risk features have an 11% risk of failure, whereas those with ECE had a 53% risk of recurrence [32]. This implicates the role of adjuvant radiotherapy in this setting. The role of adjuvant radiotherapy in resected HPV positive oropharyngeal cancer with intermediate-risk patients (PNI, LVI, T3 to T4, or N2 diseases) needs further clarification. The basic principle of oncology is to limit the number of modalities used for treatment to reduce long term morbidities. Long-term data are needed for further refinement of the best management strategy.

## 8.2 Non-surgical de-intensification strategies

De-intensification strategies employing reducing the dose or volume of radiation therapy have the potential to reduce gastric tube dependence, osteoradionecrosis, dysphagia, xerostomia, dental decay, hypothyroidism, carotid stenosis, etc. which include the following

- a. Replace Cisplatin with Cetuximab (along with radiotherapy).
- b. Neoadjuvant chemotherapy followed by decreased radiotherapy dose/volume
- c. Chemo-radiation with decreased radiotherapy and chemotherapy doses.
- d. Omitting chemotherapy.
- e. Protons instead of photons.

### 8.2.1 Replace cisplatin with cetuximab

In the subset analysis of Bonners trial, the benefit of Cetuximab plus RT was restricted to the oropharyngeal subsite [33]. It was later hypothesized to replace Cisplatin with Cetuximab in this favorable group. The three major trials which looked into this aspect were RTOG1016, De-Escalate HPV, and the TROG study (Summarized in **Table 6**).

Results from both RTOG 1016 trial and De-Escalate HPV trial show that HPV positive disease has a good prognosis, there was no difference of toxicity between the two arms, better overall survival and less recurrence with Cisplatin plus RT arm and Cisplatin plus RT remains the standard of care in low-risk HPV positive disease. The result of the TROG 12.01 study is awaiting [36].

### 8.2.2 Neoadjuvant chemotherapy followed by decreased radiotherapy dose/volume

E1308 was a phase II trial, in which patients were selected to reduced RT dose based on complete clinical response to neoadjuvant chemotherapy with Cisplatin + Paclitaxel + Cetuximab [37]. Those who achieved complete clinical response was treated to an RT dose of 54Gy in 27 fractions, 5 days a week with concurrent cetuximab for 6 weeks, and those patients who achieved a partial response or stable disease was treated to a

Trial	Phase	N	Inclusion criteria (HPV-positive OPSCC)	Intervention	Results
RTOG 1016 [34]	III	706	T1–2, N2a–3 or T3–4, any N	Accelerated RT(70Gy) + cetuximab vs. RT+ 3 weekly Cisplatin	5 year survival 77.9% vs. 84.6% p = 0.5056(non- inferiority)
De-ESCALaTE HPV [35]	III	334	T3N0–T4N0, T1N1–T4N3 excludes > N2b, >10 PY	Conventional RT+ Cetuximab vs. RT + weekly Cisplatin	2-year survival 89.4% vs. 97.5% (p = 0.001)
TROG 12.01 [36]	III	200	Stage III (excluding T1–2, N1) or IV (excluding T4, N3, or M1) if ≤10 PY. If >10 PY, only N0 – 2A	RT+cetuximab vs. RT+ weekly Cisplatin	Awaited

PY: pack years.

**Table 6.**  
*Trials replacing Cisplatin with Cetuximab.*

dose of 69.3 Gy in 33 fractions, 5 days a week with concurrent Cetuximab for 7 weeks. After a median follows up of 35.4 months, the 2-year progression-free survival was 80% in the reduced RT group with improved swallowing and nutritional status.

The Quarterback trial is another trial that is looking into this aspect. It is a phase III randomized trial comparing reduced dose (IMRT,56Gy in 28 fractions with concurrent Carboplatin weekly) and standard-dose radiotherapy (IMRT,70Gy in 35 fractions with concurrent Carboplatin weekly) for locally advanced HPV oropharyngeal carcinoma after neoadjuvant chemotherapy with TPF (Cisplatin, Docetaxel, and 5-Fluorouracil) regimen [38]. The primary endpoint is progression-free survival and results are awaited.

Another study has tried reducing the radiation therapy volume, keeping the radiation dose unchanged [39]. Following induction chemotherapy (Cisplatin, Paclitaxel, Cetuximab ± Everolimus), patients with >50% reduction received radiotherapy to gross disease only. Whereas patients with <50% reduction received radiotherapy to gross disease and next elective nodal station. Two -year PFS was 93.1% in the responders versus 74% in the non-responders.

In the OPTIMA trial, both dose reduction and volume de-escalation were tried where radiation was limited to the first echelon of uninvolved nodes [40]. After 3 cycles of neoadjuvant chemotherapy (Carboplatin+ nab-Paclitaxel), low-risk patients with ≥50% response received 50 Gy RT, low-risk patients with 30%–50% response, and high-risk patients with ≥50% response received 45 Gy RT + concurrent chemotherapy and patients with the lesser response received 75Gy + concurrent chemotherapy. Two-year progression survival was not compromised compared to historical control.

8.2.3 Chemoradiation with decreased radiotherapy and chemotherapy doses

In a phase II trial, favourable risk HPV associated oropharyngeal carcinoma patients were randomized to receive 60Gy intensity-modulated radiation therapy

with concurrent weekly Cisplatin (30 mg/m<sup>2</sup>) followed by biopsy from the primary site and planned neck dissection of the initially involved site [41]. The primary endpoint of the study, pathological complete response was 86% and was associated with less toxicity. Few drawbacks of this study are that they included early-stage cases, short follow-up (14 months), and planned neck dissection which was unnecessary in some patients. In the follow up study, with the same IMRT dose 60 Gy in 30 fractions, multiple chemotherapy options were there (weekly regimens with Cisplatin 30 to 40 mg/m<sup>2</sup> (first choice), Cetuximab 250 mg/m<sup>2</sup> (second choice), Carboplatin AUC 1.5 and paclitaxel 45 mg/m<sup>2</sup>) and chemotherapy was omitted for patients with T0-2 N0-1 disease, ≤ 10 pack-years smoking history [42]. The neck dissection was advised based on positive PET/CT done after 10–16 weeks. The results are awaited.

#### 8.2.4 Omitting chemotherapy

In the HN 002 trial, patients with stage T1- T2, N1-N2b or T3, N0-N2b, p16 positive oropharyngeal carcinoma patients were randomized to receive either IMRT 60 Gy/30 fractions over 6 weeks, or IMRT with concurrent weekly Cisplatin 40 mg/m<sup>2</sup> [43]. Estimated 2-year survival and late toxicity were similar and acute toxicity were more in the chemotherapy arm.

#### 8.2.5 Protons instead of photons

The goal of the trial was to compare the side effects of 2 radiation treatments; intensity-modulated photon beam therapy 70Gy(RBE) in 33 fractions, with intensity-modulated proton beam therapy, 70Gy(RBE) in 33 fractions. The estimated study completion date is 2024 [44].

### 9. Unknown primary with cervical node metastasis

If p16 positive in lymph node specimen, it is staged as per p16 positive oropharynx carcinomas and treated accordingly.

### 10. Immunotherapy

Immunotherapy as sole therapy has reported a delay in progression in metastatic HPV positive oropharyngeal carcinoma [45]. Combining Checkpoint inhibitors like anti-programmed cell death 1 (PD-1) with tumor vaccine has some shown benefit in a recurrent setting in phase II trials [46].

### 11. Post-treatment surveillance

Following the completion of treatment, the patient should be evaluated clinically once in 3 months for the initial 2 years, once in 6 months for 5 years, and yearly thereafter. Persisting symptoms, radiating pain to the ear, etc. warrants local recurrence. Negative PET/CT scan obtained between 3 and 6 months after completion of treatment and at 12 months post-treatment is associated with a good prognosis. Considering the low recurrence rate in HPV positive OPSCC and the cost involved, it's not a routine investigation that is followed.

## 12. Treatment of recurrent and metastatic disease

Salvage surgery or irradiation if feasible should be considered for recurrent disease. Palliative chemotherapy with platinum doublets can be considered if local treatment not feasible. Clinical trials are ongoing with targeted agents, immunotherapy as sole treatment versus combination therapy.

## 13. Conclusion

HPV associated oropharyngeal carcinoma is on the rise. A lot of research is happening in this field to refine the best treatment for this separate clinical entity with the vision to reduce long term morbidities. Mature data with long term follow up is needed to change the current practice. At present, HPV-positive oropharyngeal carcinoma patients should not be treated with de-intensification protocols outside the clinical trial setting.

## Conflict of interest

“The authors declare no conflict of interest.”

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