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Overview

Oropharyngeal Cancers in the East and the West – Implications of Aetiopathogenesis on Prognosis and Research

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Abstract

There has been a surge in human papillomavirus (HPV)-positive oropharyngeal cancers (OPCs) in the West. Although the prognosis of HPV-positive OPC is good, de-escalation strategies have so far not been able to confirm comparable cancer control. We examine the strategies implemented across the globe to safely reduce toxicities in HPV-positive disease. HPV-negative OPC has a poorer prognosis and is more prevalent in Eastern countries. We outline the intensification strategies currently used in HPV-negative cancers, with an aim to better prognosis. With recent improvements in clinical trial frameworks in Eastern countries such as India, we discuss areas where joint collaborative research between Western and Eastern countries could further improve outcomes in OPC.

Key words: East; HPV; oropharyngeal cancer; West

Statement of Search Strategies Used and Sources of Information

A search of English language publications on PubMed with the keywords of 'HPV', 'human papillomavirus', 'oropharyngeal cancer' and associated medical subject headings (MeSH) was performed, with filters for clinical trials and with special reference for studies from India. Papers describing 1. Oropharyngeal Cancer management strategies and 2. HPV stratified management of oropharyngeal cancer were selected for further review. The clinicaltrials.gov resource was searched for ongoing studies in oropharyngeal cancer with treatments based on HPV status.

Changing Epidemiology of Oropharyngeal Cancers

The surge in incidence of oropharyngeal cancers (OPC) in Western countries has been attributed to human papillomavirus (HPV) [1–4]. Various sociocultural issues, including oral sex practices, are thought to have driven this increased incidence of HPV-related OPCs [5]. The implementation of gender-neutral vaccination programmes in many Western countries is expected to dramatically reduce the incidence of HPV-related OPC in the West over the next few decades.

By contrast, Indian OPC patients present primarily in the late fifth and sixth decades of life [6]. Although there is a paucity of literature on the prevalence of HPV in OPCs in India, it seems to be driven predominantly by tobacco rather than HPV. Nair *et al.* [7] have summarised a number of studies from India that have looked at the association between HPV and head and neck cancers. However, only three studies reported on substantial numbers of OPC cases. Table 1 summarises the characteristics of OPC patients reported in those studies.

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Table 1
Oropharyngeal Cancer reported from India

Author (date)	Number of oropharyngeal cancers	HPV detection method	HPV prevalence	Other risk factors and prognostic groups
Bahl *et al.* [8] Prospective observational study	105	Consensus PCR and reverse line-blot hybridisation assay	22.8%	• 83% of HPV-positive patients current or former smokers. No difference between HPV-positive and HPV-negative • 58%of HPV-positive patients reported a history of oral or anal sex, compared with 29% of HPV-negative patients • No difference in T and N categories between HPV-positive and HPV-negative
Murthy *et al.* [9] Retrospective analysis of patients recruited in multiple clinical trials, with a plan to correlate HPV status with prognosis	100	P16 IHC and PCR	20% p16-positive 39.6% HPV-positive by PCR	• 73.5% of p16-positive patients were current or former smokers • Lack of concordance between p16 IHC-positive and HPV-positive by PCR (only 39% of HPV-positive patients were p16-positive, 76% p16-positive were HPV-positive) • Trend towards lower T stage and higher N stage in p16-positive patients • Among non-smokers, p16-positive showed trend towards better outcomes
Sannigrahi *et al.* [10] Prospective observational study	87	PCR with consensus primers, HPV-16 E7 mRNA expression, selective IHC	34.4% all HPV 15% HPV16	• 84% of HPV-positive patients were smokers

HPV, human papillomavirus; IHC, immunohistochemistry; PCR, polymerase chain reaction; RNA ribonucleic acid.

The proportion of tobacco users among head and neck cancer patients reported in the above studies remained close to 80%. A compilation of data from three epidemiological surveys revealed that although there was a modest decrease of 5% in the prevalence of cigarette and bidi smoking between 1998 and 2015, this has not reduced the absolute numbers of tobacco users, which has risen by 27 million to 108 million people [11]. In many Eastern countries, especially in South-East Asian countries like India, there is a higher incidence of the use of smokeless tobacco than smoked tobacco [12]. Smokeless tobacco, while clearly recognised as a predisposing factor for the high incidence of oral cancers, has also been found to be associated with an increased risk of OPC [13].

Sexual practices (the number of sexual partners and oral sex) are associated with HPV-positive OPC [14]. There is a paucity of data on the prevalence of oral sexual practice in OPC patients in Eastern countries [15]. One of the few prospective observational studies from India that has collected data on sexual practices in India suggests that HPV-positive patients have more lifetime sexual partners and a higher prevalence of high-risk sexual activity [8].

Prognostic Factors in Oropharyngeal Cancer. Can They be Predictive?

The biology of HPV-positive OPC versus HPV-negative OPC is quite different, as is its response to standard curative treatment using radiotherapy and concurrent chemotherapy [1,16]. One of the largest case series published on OPC from the pre- HPV era is from India [6]. This series of more than 600 OPC patients suggested that adverse prognosticators of local/regional control and disease-free survival outcomes included poor performance status at presentation, tobacco use, multiple lymph nodes or lymph node size greater than 3 cm. Interestingly, the analysis suggested that patients receiving a radiation dose of more than 66 Gy had improved disease-free survival compared with those receiving a lower dose.

One of the earliest and pivotal studies in OPC is RTOG 0129. This study compared an altered fractionation regimen with conventional radiotherapy doses in OPC. Although the study did not report any benefits of altered fractionation over conventional fractionated radiotherapy, an analysis of prognostic factors was carried out. In 266 patients with complete data and follow-up, Ang *et al.* [16] reported that a greater nodal burden, larger tumour size, smoking history and p16-negative status strongly predicted for a poor overall survival and disease-free survival in OPCs. A retrospective review of outcomes based on a patient's HPV status (positive $n = 18$) within the randomised IMCL-9815 study, comparing radiotherapy with or without cetuximab, showed an improved prognosis with cetuximab over and above radiotherapy, irrespective of their HPV status [17]. Similar to the report by Ang *et al.* [16], patients with p16-positive disease had a better overall survival, irrespective of the intervention with cetuximab together with radiotherapy [17]. A combined analysis of 815 patients with OPC from five randomised controlled studies (RTOG 9003, DAHANCA 6&7, RTOG 0129, ARTSCAN) confirmed better overall and progression-free survival (PFS) for p16-positive OPC [18].

HPV positivity was therefore established as a strong prognosticator for OPC, leading to a change in the tumour, node, metastasis (TNM) staging system of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) staging systems for HPV-positive and HPV-negative OPCs in the eighth edition [19]. However, whether HPV positivity was a predictive factor for radiotherapy response was yet to be proven. Concurrent cisplatin and radiotherapy (CTRT) still remains the standard of care for locally advanced head and neck cancers, but the treatment is associated with significant acute and late toxicities [20,21]. Therefore, with a higher disease burden and prognostically inferior cancers, patients in the East may need intensification strategies in contrast to OPC in the West, which is HPV driven with a better prognosis.

Research Strategies for HPV-negative and HPV-positive Oropharyngeal Carcinoma

Future improvements in treatment outcomes in OPC are dependent on the results of modern research targeting the two biologically heterogeneous disease types based on their HPV status. With data strongly suggesting excellent outcomes for HPV-positive OPC, de-escalation strategies are being evaluated [22]. In the more treatment-refractory OPC cancers, not driven by HPV, intensification strategies are being explored [23].

Strategies Aimed at Improving Outcomes in HPV-positive Oropharyngeal Carcinoma

Given the above information, it is clear that, apart from known clinical prognosticators, HPV has been considered an important independent variable that affects survival in OPC. However, whether HPV positivity is a predictive factor for radiotherapy response remains to be proven. With increased acute and moderate long-term toxicities after standard CTRT [21], strategies to reduce morbidities without compromising survival needed to be explored in HPV-positive OPC. A study carried out at our institution in India showed that with a baseline 5-year survival of 90%, a 5% incremental benefit in survival was thought to be important enough by 87% of patients to accept the additional toxicity of CTRT over radiotherapy alone [24]. At 3 months after the completion of treatment, however, the proportion of patients who would accept the toxicity of CTRT for a 5% benefit reduced to 50%, confirming the need for a less morbid treatment option in cancers with a good prognosis.

Research on HPV-positive OPC with a high probability of survival post-treatment therefore needed a balanced de-escalation strategy that would allow lower morbidity with similar disease control rates.

Substituting Cisplatin with Cetuximab with Radiotherapy

Although cisplatin–radiotherapy showed an increased acute toxicity to achieve a higher survival over radiation only in locally advanced head and neck cancers, survival following cetuximab was not compromised by higher mucosal toxicities [25,26]. Randomised studies were therefore formulated to ascertain if cetuximab–radiotherapy can replace cisplatin–radiotherapy in good prognosis HPV-positive OPC. Table 2 highlights the results of the studies. Both the RTOG 1016 and the de-ESCALaTE HPV studies failed to show non-inferiority of cetuximab–radiotherapy compared with cisplatin–radiotherapy, with poorer overall survival and higher recurrence rates associated with cetuximab–radiotherapy [27,28]. Cisplatin–radiotherapy therefore remains the standard-of-care in HPV-positive OPC.

Reducing Radiotherapy Dose Intensity

The simplest strategy to improve the toxicity of CTRT is to reduce the dose of radiotherapy. The NRG HN002 study is a randomised study of low-dose intensity-modulated radiation in both arms (60 Gy) with or without cisplatin. This is a bold study, assuming that a 10 Gy reduction in radiotherapy dose is unlikely to affect control rates in patients with HPV-positive OPC. Another strategy of radiotherapy dose escalation considers radiotherapy dose stratification after endoscopic surgery to the primary and neck [29]. A stratified risk model for HPV-positive OPC patients based on disease burden after surgery has been used to stratify radiotherapy dose prescription in the Eastern Cooperative Group study (ECOG 3311) [30]. The initial data safety monitoring committee (DSMC) review of the results of the study has been reported to be safe and longer follow-up data are awaited [31].

Substituting Concurrent with Neoadjuvant Chemotherapy

Due to increased morbidity with CTRT, investigators have tried de-intensifying the radiation dose and substituting concurrent with induction chemotherapy. A phase II study [32] tried using paclitaxel and carboplatin followed by concurrent paclitaxel and radiotherapy in locally advanced OPC and laryngeal cancers. The strategy was successful in organ preservation in 84% of OPC at 3 years. With a better understanding of OPC cancer biology, a phase II study [33] used HPV p16 as a biomarker and reduced-dose radiotherapy (45 and 50 Gy) following induction chemotherapy (carboplatin and nab-paclitaxel). Another phase II study [34] has reported initial results using three cycles of paclitaxel, cisplatin and cetuximab followed by 54 Gy radiation together with weekly cetuximab if patients developed a complete clinical response after chemotherapy. The trial reported PFS of 80% at around 3 years, but in patients with a smaller disease volume (<T3, unilateral small nodes) and non-smokers the PFS was as high as 94%. A phase III randomised study (QUARTERBACK Trial) [35] started recruiting patients responding to induction docetaxel, cisplatin and fluorouracil to concurrent carboplatin and standard-dose

Table 2
Completed studies investigating substitution of concurrent cisplatin with cetuximab in human papillomavirus (HPV)-positive oropharyngeal cancer

Study	Number of oropharyngeal cancers treated within study	HPV detection method	Year of reported outcome	Median follow-up	Outcome	Toxicity
De-ESCALaTE HPV [27]	334	HPV p16-positive oropharyngeal cancer	2019	2 years	Two-year overall survival cisplatin–radiotherapy versus cetuximab–radiotherapy 97.5% versus 89.4% ($P = 0.01$)	No difference in all grade or grade 3/4 toxicities
RTOG 1016 [28]	849	HPV p16-positive oropharyngeal cancer	2019	4.5 years	Five-year overall survival cisplatin–radiotherapy versus cetuximab–radiotherapy 84.6% versus 77.9% ($P = 0.02$)	No difference in reported CTCAE grade 3/4 adverse events

radiotherapy versus reduced-dose radiotherapy. The results of this study are awaited. The strategy of substituting CTRT with induction and reduced-dose radiotherapy is interesting. However, the following points need careful analysis with the use of this strategy: (a) do control rates in the longer term (at least 5 years of follow-up) remain similar in both arms; (b) is the global quality of life after protracted treatment after induction chemotherapy going to be better compared with CTRT; (c) the proportion of HPV-positive patients who do not respond to a lower radiotherapy dose needs careful analysis, given the very high control rates of these patients to standard CTRT. Table 3 summarises the strategies being explored in ongoing studies in HPV-positive OPCs.

Strategies in HPV-negative Patients

Although the bulk of recent trials in North America and Europe have focussed on HPV-positive cancers, with the intention of de-intensifying treatment and reducing toxicities without compromising survival, there has been less of a focus on HPV-negative cancers. The prognosis for locally advanced HPV-negative cancers is poor, and in the countries where they are predominant (including India), there is a strong case for designing trials that focus on this subset.

We have outlined below the different approaches that can be taken, highlighting studies that have looked at treatment-related associations with HPV status and the ongoing trials that are mainly focussed on HPV-negative and poor prognostic groups. Ongoing studies are summarised in Table 4. The results of these approaches will define how HPV-negative OPC will be treated in the future.

Table 3
Selected ongoing studies exploring de-escalation strategies in human papillomavirus (HPV)-positive oropharyngeal cancers

Study description	Clinicaltrials.gov ID
Substituting cetuximab for cisplatin with radiotherapy	
TROG 12.01 – Weekly cisplatin–radiotherapy versus weekly cetuximab–radiotherapy - phase III RCT	NCT01855451
Reducing dose of radiotherapy	
NRG HN002- Reduced dose IMRT with or without weekly cisplatin - phase II RCT	NCT02254278
Transoral surgery followed by low-dose or standard-dose radiotherapy with or without chemotherapy in treating patients with HPV-positive stage III–IVA oropharyngeal cancer (ECOG 3311)	NCT01898494
The Quarterback Trial: Reduced dose radiotherapy for HPV-positive oropharynx cancer (if responding to induction therapy)	NCT01706939

IMRT, intensity-modulated radiotherapy; RCT, randomised controlled trial.

Radiotherapy Dose Escalation

Dose escalation with radiotherapy for locoregionally advanced head and neck cancers has traditionally been challenging due to concerns about acute and late toxicities. With the advent of highly conformal techniques it has been possible to target complex tumour volumes while maintaining lower doses to critical structures, including the spinal cord and brainstem, dysphagia- and aspiration-related structures and salivary glands. A dose-escalation study in stage II/III non-bulky tumours, including OPCs, showed feasibility and some early success [36]. In laryngo-hypopharyngeal cancers, the ART DECO study also showed feasibility with limited late toxicity [37]. Further advances in the form of metabolic imaging-based treatment planning [38,39] has opened new doors in more advanced disease by allowing a more accurate definition of a boost volume. Most of the metabolic target volume-directed studies in advanced cancers are ongoing. ARTFORCE is a phase II randomised controlled trial comparing chemoradiation or bioradiation with standard radiotherapy doses versus a metabolically redistributed adapted dose of 64–80 Gy in 35 fractions (NCT01504815) in HPV unselected advanced cancers. More recently, designed studies have focused on the HPV-negative subgroup in oropharyngeal cancers. At our centre, the INTELHOPE study is a randomised phase II study of dose escalation to an FDG positron emission tomography-based metabolic target volume (73.5 Gy versus 66 Gy in 30 fractions) to HPV-negative OPC (NCT02757222). Other studies include the C-ART-2 randomised phase II study of adaptive dose escalation by positron emission tomography-guided dose painting by numbers in advanced head and neck cancers, including HPV-negative OPC (NCT01341535). Dynamic contrast-enhanced magnetic resonance imaging-based dose escalation is being used in poor-prognosis unresectable head and neck cancers, including HPV-negative or high-risk HPV-positive cancers and laryngopharyngeal cancers (NCT02031250). One of the arms of the multi-armed CompARE randomised controlled trial in the UK is examining dose-escalated radiotherapy to 64 Gy in 25 fractions and concomitant cisplatin versus standard of care (ISRCTN41478539). The results of these studies will inform us about the feasibility, technical nuances and effectiveness of this approach.

Intensifying Concurrent Chemotherapy

Within the existing paradigm of radiotherapy with concurrent platinum-based chemotherapy, a pooled analysis of two institutional datasets ($n = 659$) of OPC, laryngopharyngeal and unknown primary cancers assessing chemotherapy dose intensity found that although there was no effect of dose intensity in HPV-positive cancers, there was a meaningful impact on HPV-negative cancers. The 3-year overall survival in HPV-negative patients who received <200, 200 and >200 mg/m^2 was 52, 60 and 72%, respectively ($P = 0.001$) [40]. Therefore, treatment regimens in HPV-negative cancers must ensure that platinum dose intensity is maintained.

Table 4
Selected ongoing studies in human papillomavirus (HPV)-negative or poor prognostic HPV-positive patients

Study description	Clinicaltrials.gov ID
Radiotherapy dose escalation	
INTELHOPE - randomised phase II study of PET-guided dose escalation of 73.5 Gy vs 66Gy in 30 fractions	NCT02757222
C-ART-2 - randomised phase II study of adaptive dose escalation by PET-CT guided dose-painting by numbers.	NCT01341535
DCE-MRI-based dose escalation for poor-prognosis and neck cancer - randomised phase II study	NCT02031250
CompARE - pragmatic randomised phase III study including a dose-escalation arm of 64Gy in 25Fr	ISRCTN 41478539
Hypoxia modification	
NIMRAD - randomised placebo-controlled phase III study in cisplatin and cetuximab ineligible patients with concurrent nimorazole	NCT01950689
DAHANCA 33 - phase II study of hypoxia-PET guided dose escalation with concurrent cisplatin and nimorazole	NCT02976051
EGFR directed therapy	
TRYHARD - randomised phase II study of the addition of lapatinib with cisplatin–radiotherapy vs cisplatin-radiotherapy alone	NCT01711658
PARP inhibition	
Phase I study of Olaparib concurrent with radiotherapy	NCT02229656
ORCA-2 - phase I study of olaparib with concurrent cisplatin–radiotherapy	NCT02308072
Partially randomized Phase II study of induction veliparib with carboplatin and paclitaxel in stage IVA/IVB cancers	NCT01711541
CDK4 inhibition	
Los-Tres-Paso - phase II study of palbociclib neoadjuvant and adjuvant along with concurrent cisplatin/cetuximab with radiotherapy	NCT03389477
Phase I/II study of palbociclib concurrent with cetuximab–radiotherapy	NCT03024489
Phase II study of cetuximab ± palbociclib in recurrent metastatic cancers - phase II study	NCT02499120
Immunotherapy	
DURTRE-RAD - randomised phase II trial of addition of durvalumab ± tremelimumab to radiotherapy	NCT03624231
Phase I/Ib study of addition of durvalumab–radiotherapy prior to surgery	NCT03635164
CompARE - single arm pragmatic randomized phase III trial of durvalumab neoadjuvant and adjuvant to cisplatin–radiotherapy	ISRCTN 41478539

CDK4, cyclin D kinase 4; DCE-MRI, dynamic contrast enhanced-magnetic resonance imaging; EGFR, epidermal growth factor receptor; PARP, poly (ADP-ribose) polymerases; PET, positron emission tomography.

Adding Hypoxia Modifiers

Hypoxic radioresistance is well recognised and several trials have attempted hypoxia modification using a number of different approaches. In the DAHANCA 5 study evaluating the addition of nimorazole versus placebo concurrently with radiotherapy, nimorazole was found to improve outcomes. In a subset analysis of patients (331/440) in whom p16 status was retrospectively evaluable, it was found that nimorazole improved outcomes in the HPV-negative patients, but had no effect in HPV-positive patients [41].

Similarly, in the TROG 02.02 randomised trial comparing cisplatin-based chemotherapy with or without tirapazamine, although there was no overall benefit with the addition of tirapazamine, there was a trend towards benefit in the subset of patients who had p16-negative tumours [42].

Ongoing studies with nimorazole, such as the randomised NIMRAD trial for patients ineligible for cisplatin or cetuximab (NCT01950689) and the phase II DAHANCA 33 trial of image-guided dose-escalated hyperfractionated radiotherapy with cisplatin and nimorazole (NCT02976051), in hypoxic HPV-negative OPC and advanced laryngeal and pharyngeal cancers, will shed further light on the utility of hypoxia modification in advanced head and neck cancer.

Epidermal Growth Factor Receptor-Directed Therapies

Cetuximab has shown benefit against radiotherapy alone in the definitive setting with the IMCL-9815 trial [25], as well as against cisplatin and 5-fluorouracil in the recurrent/metastatic setting in the EXTREME trial [43]. In an analysis of patients recruited in these two studies, HPV or p16 status was prognostic of outcomes, but was not predictive of benefit from the drug [44]. However, the addition of cetuximab to cisplatin and radiation in the definitive setting did not improve outcomes, regardless of epidermal growth factor receptor (EGFR) status [45].

Lapatinib is an EGFR/Her-2 dual inhibitory tyrosine kinase inhibitor. In a randomised phase II trial assessing the benefit of lapatinib in addition to chemoradiation in unresected stage III/IVA–B cancer, lapatinib improved complete response rates and PFS, with the greatest benefit in HPV-negative tumours (median PFS $>$ 20.4 months with lapatinib versus 10.9 months with placebo) [46]. This is now being tested in the randomised phase II TRYHARD trial in HPV-negative OPC and laryngopharyngeal cancers (NCT01711658).

Poly (ADP-ribose) Polymerase Inhibition

Poly (ADP-ribose) polymerases (PARPs) are enzymes involved in DNA base excision repair. In preclinical models, PARP inhibitors have been shown to sensitise tumours to

radiotherapy and chemotherapy-induced DNA damage [47]. Human studies of PARP inhibitors concurrent with radiotherapy or chemoradiotherapy have been initiated. A phase I study of olaparib, a PARP inhibitor, concurrent with radiotherapy in stage II/III HPV-negative OPC and laryngeal cancers is currently underway in the Netherlands (NCT02229656). ORCA-2 is another phase I study in the UK assessing olaparib with cisplatin-based chemoradiotherapy in head and neck cancers, including HPV-negative OPC (NCT02308072). A third study is a phase I/II partially randomised study looking at neoadjuvant paclitaxel, carboplatin and veliparib prior to concomitant chemoradiation in stage IVA/B head and neck cancers, including HPV-negative OPC (NCT01711541).

Cyclin D kinase 4 Inhibition

Cyclin D kinase 4 (CDK4) is a key regulator of the G1-S transition in the cell cycle. Palbociclib is an orally active, highly selective inhibitor of CDK4/6 with the ability to block (Retinoblastoma protein) Rb phosphorylation. Although the greatest clinical progress has been made in the treatment of metastatic breast cancer, it has been found that palbociclib has activity in head and neck cancers in a phase I trial in patients resistant to platinum or cetuximab [48]. Given that HPV-positive cancers have high levels of p16 and low levels of Rb, CDK4/6 inhibitors are predicted to be ineffective in these cancers. Ongoing human trials are evaluating the role of palbociclib in advanced head and neck cancer. The Los Tres Paso trial is a phase II study investigating the addition of neoadjuvant and adjuvant palbociclib with radiation concurrent with cisplatin or cetuximab specifically in HPV/p16-negative head and neck cancers (NCT03389477). Palbociclib is also being investigated in the concurrent setting with radiotherapy and cetuximab in locoregionally advanced head and neck cancers in a phase I/II study (NCT03024489). In the recurrent or metastatic setting, a phase II study is investigating the addition of palbociclib to cetuximab (NCT02499120).

Immunotherapy

Immunotherapy has made inroads into the treatment of advanced head and neck cancer with the anti-PD-1 monoclonal antibodies nivolumab and pembrolizumab. The activity of immunotherapeutic agents has been more pronounced in tumours where the mutational load is high. It would therefore be expected that HPV-negative cancers would have higher response rates with immunotherapy. However, this has not been borne out in published research. In the Keynote-012 randomised phase II trial assessing pembrolizumab, the response rates were higher in the HPV-positive cancers (32% versus 14%) [49]. Similarly, in patients with recurrent or metastatic disease in the Checkmate-141 randomised phase III trial assessing nivolumab, the response rates were higher in p16-positive patients (15.9% versus 8.0% if p16 positive versus p16 negative) [50].

Durvalumab is an anti-PD-L1 monoclonal antibody that has improved survival in stage III lung cancer when used an adjuvant treatment after chemoradiation therapy [51]. Several trials are testing durvalumab in the treatment of head and neck cancer. The DURTRE-RAD study is testing the addition of durvalumab ± tremelimumab (an anti-CTLA4 monoclonal antibody) to radiotherapy in HPV-negative cancers (NCT03624231). The safety of durvalumab and radiotherapy prior to surgery in HPV-negative squamous cancers is being tested in a phase IA/IB trial (NCT03635164). Again, the CompARE study is examining the role of durvalumab as a neoadjuvant and adjuvant treatment option after CTRT in the curative setting (NCT41478539).

With the recent announcement of a lack of benefit of durvalumab (±tremelimumab) in advanced recurrent/metastatic head and neck cancers that have failed on platinum-based chemotherapy in the phase III EAGLE study [52], it remains to be seen whether durvalumab will have an impact in poor-prognosis non-metastatic disease.

Implications of the Studies in the East and the West

HPV/p16 status has been a strong prognosticator of outcomes in OPC. Patients in the West, being HPV-positive, are being offered de-escalation strategies, whereas curative treatment in the East requires intensification. The de-escalation strategy of substituting cisplatin with cetuximab and radiotherapy unfortunately seems to result in higher local recurrence rates and is therefore ineffective. Stratified radiotherapy dose reduction after surgery or chemotherapy will probably result in fewer radiotherapy-related toxicities. However, it is important to ensure that this benefit is not at the expense of higher local relapses.

It is clear that there is a paucity of clinical trials exploring specific strategies for OPC originating from the East, and representation of Eastern patients in studies originating in the West has also been poor. Historically, treatment pathways have been formulated across the globe based on established evidence primarily involving populations from Western countries. Geographical differences have been associated with differences in the prevalence of specific prognosticators, like HPV and OPC. This, together with lower socioeconomic strata, poorer tolerance to CTRT [53] and emerging radiogenomic variability, highlights the importance of appropriate representation of patients from the East in clinical trials. The reasons for non-representation in clinical trials are multifactorial. Although large patient numbers in clinics and lower numbers of trained clinical staff seem to affect the overall initiation of investigator-led studies from India, recent pivotal research in cancers such as oral cavity cancer [54] and ongoing studies like INTEL-HOPE [55] could provide more representative data from India. Funding sources for a middle/low income group country like India are often more difficult as the emphasis is on providing high-quality treatment for most patients. Multicentric international collaborative trials are few, mainly restricted by the sponsors' willingness to include Eastern centres. It is essential to consider the cost of treatment when initiating research with newer agents, both in de-intensification and intensification strategies. This is

especially important in low and middle income group countries, like India.

Recently the clinical trial framework in India has had a significant makeover, becoming more patient friendly, requiring sound ethical approvals and centres having to undergo accreditation [56]. With more centres from India contributing to research on head and neck cancers [53,54,57,58], investigators should be able to convince Western sponsors to include the Eastern population for more representative results.

Conflicts of interest

There are no conflicts of interest.

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