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Everything You Need to Know about HPV Related OPSCC So Far…

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Abstract

Purpose: HPV-positive OPSCC is now known to have different clinicopathologic factors compared to traditional OPSCC. It tends to affect younger patients and has been shown to be chemo-radiosensitive with an excellent prognosis in contrast to HPV-negative OPSCC. In view of this, multiple different treatment de-escalation strategies have been proposed, with the aim to reduce morbidity typically associated with treatment. The current available evidence on these de-escalation policies is discussed in this retrospective literature review.

Methods: A literature search was performed on Pubmed, NCBI, Cochrane, Medline and CINAHL to identify current literature looking at de-escalation strategies for HPV related OPSCC. The identified de-escalation trials were used to discuss currently proposed de-escalation strategies. 45 papers published from 1985 to 2021 were studied. Inclusion criteria included completed and ongoing trials on management of OPSCC published in English literature. Exclusion criteria included management of oropharyngeal cancers without discussion on completed or ongoing trials. 39 papers satisfied criteria and were reviewed individually by all authors and information collated to avoid interpretation bias.

Results: ECOG 1,308 has shown de-escalation with ICT followed by cetuximab-low dose RT to be superior. NRG-HN002 found low dose Cisplatin-RT superior to AXF. De-ESCALATE and RTOG 1,016 both found Cetuximab-RT to be inferior to Cisplatin-RT with significantly worse outcomes and no significant difference in severe toxicity. ECOG 3,311 supports reducing the dose of RT after surgery.

Conclusion: The results of several clinical trials are awaited; however, the available results are not promising for de-escalation in HPV-positive OPSCC. Further validation through randomized control trials is needed prior to widespread changes in practice.

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Introduction

The HPV 16 genotype has been identified as a causative agent in many Oropharyngeal Squamous Cell Carcinomas (OPSCC), particularly at the base of tongue and tonsillar region [1]. HPV-positive OPSCC has different clinicopathologic features compared to HPV-negative OPSCC which potentially has implications for staging, treatment and prognosis [2]. HPV-positive OPSCC is associated with a 58% reduction in death rate compared to HPV-negative OPSCC [3]. Despite this, current treatment is based on stage of disease, regardless of HPV status, and multidisciplinary recommendation involving patient preference. Early stage disease is usually treated with surgery or Radiotherapy (RT) alone whilst locally advanced disease is treated with multimodality approach including Chemotherapy (CT), RT and/or surgery. Morbidity and toxicity associated with Chemoradiotherapy (CRT) treatment regimens includes carotid stenosis, gastric tube dependence, osteoradio-necrosis and xerostomia [4]. Severe late toxicity can occur in up to 43% of patients and may be permanent [5]. HPV-positive OPSCC tends to predominantly affect younger patients who are expected to survive for several decades highlighting the importance of minimizing long-term morbidity [3].

Aims

This retrospective literature review on OPSCC clinical trials (2000-2021) investigating different treatment options including de-escalation summarizes the findings from these trials to guide future clinical management. This is a current update as of October 31st, 2021.

Methods and Materials

A literature search was performed on Pubmed, NCBI, Cochrane, Medline and CINAHL to identify current literature looking at de-escalation strategies for HPV related OPSCC. The identified de-escalation trials were used to discuss currently proposed de-escalation strategies. 45 papers published from 1985 to 2021 were studied. Inclusion criteria included completed and ongoing trials on management of OPSCC published in English literature. Exclusion criteria included management of oropharyngeal cancers without discussion on completed or ongoing trials. 39 papers satisfied criteria and were reviewed individually by all authors and information collated to avoid interpretation bias.

De-Escalation Strategies

HPV-positive OPSCC has been shown to be chemo-radiosensitive with better treatment response [6] and significantly improved 5 year overall survival rate (5yr OS) compared to HPV-negative OPSCC.

ECOG 2399, found a better response rate in HPV-positive OPSCC compared to HPV-negative OPSCC (84% *vs.* 57%) following paclitaxel+carboplatin Induction Chemotherapy (ICT) then concurrent Cisplatin+RT standard fractionation (SFX 70Gy/35# 7 weeks) if a partial or complete response was observed. HPV-positive OPSCC also had a significantly better progression free survival with 2 year overall survival rate (2yr OS) of 95% compared to 62% [7].

CRT is associated with significant morbidity and toxicity. As HPV related OPSCC has been shown to be chemo-radiosensitive various treatment de-escalation strategies have been proposed for patients with HPV-positive OPSCC with the aim of reducing morbidity and toxicity associated with CRT without altering the improved Overall Survival (OS) seen in these patients who are typically young and expected to survive for many decades.

Chemotherapy: Less Toxic Systemic Agent

Cisplatin+Radiotherapy *vs.* Cetuximab+Radiotherapy

One of the strategies proposed involves substituting Cisplatin+RT with Cetuximab+RT, an EGFR targeted antibody, in HPV-positive OPSCC. Findings from Bonner et al. [8] suggest concurrent Cetuximab+RT is effective in the treatment of locally advanced head and neck SCC. Cetuximab+RT had a better outcome in patient groups with OPSCC, ≤ 65 years old, early T stage, advanced N stage and high performance score. Although HPV status of participants was not assessed specifically, the majority of patients with better outcome from Cetuximab+RT were HPV-positive OPSCC.

This has been further investigated with a number of phase 3 clinical trials comparing concurrent Cetuximab+RT with Cisplatin+RT in HPV p16 positive OPSCC, based on the assumption that Cetuximab has a comparable efficacy with lower toxicity. This includes both RTOG-1016 and de-escalate which have similar methodology allowing for direct comparison between them both [9,10].

However, findings of RTOG 1016, a multicentre, RCT, phase 3 completed trial (USA, 2019) were in striking contrast with Bonner et al. [8] and reported that the 5yr OS rate was significantly better in the Cisplatin+RT Accelerated Intensity Modulated Radiotherapy (AFX IMRT) group compared to the Cetuximab+RT AFX IMRT group (5yr OS 84.6% *vs.* 77.9%). Progression Free Survival (PFS) was significantly better in the Cisplatin+RT group compared to the Cetuximab+RT group (PFS 78.4% *vs.* 67.3%) [9].

De-escalate, a multicentre, RCT, phase 3 completed trial (UK, Ireland, Netherlands 2018) supports findings of RTOG 1016. The 2 yr OS rate for all stages were reported to be significantly better in the Cisplatin+RT SFX IMRT group compared to the Cetuximab+RT SFX IMRT group (2 yr OS 97.5% *vs.* 89.4%). In early stage HPV positive OPSCC, 2 yr OS was found to be less significant between the Cisplatin+RT group and the Cetuximab+RT group (2 yr OS 98% *vs.* 93%). However, for advanced HPV positive OPSCC, the OS was greater in the Cisplatin+RT group compared to the Cetuximab+RT group (2 yr OS 69.5% *vs.* 23%). PFS was found to be better in the Cisplatin+RT group. The 2 year recurrence rate was significantly lower in the Cisplatin+RT group compared to the Cetuximab+RT group (2 year recurrence rate 6% *vs.* 16.1%). In addition, no significant difference in rates of severe toxicity was observed between the groups [10].

TROG 12.01, a multicentre, RCT, phase 3 completed trials (Australia, NZ 2021) also supports these findings. The 3 yr Failure Free Survival (FFS) was found to be significantly better in the Cisplatin-RT group compared to the Cetuximab-RT group (3 yr FFS 93% *vs.* 80%) [11].

The results of these trials should be interpreted with caution as it included OPSCC exclusive of HPV p16 status. Hence it is invaluable to maximize use of advanced investigation tools including ISH, PCR and E6/E7 antibody to confirm OPSCC attributable to HPV. Moreover, Cetuximab+RT may not be the optimum treatment for virally induced OPSCC [12]. Both RTOG 1016 and De-escalate have shown inferior survival rates with Cetuximab+RT in HPV positive OPSCC.

The findings of the de-escalate trial were presented at ESMO Congress in 2018. As HPV-positive OPSCC patients tend to be younger with a good prognosis, de-escalation of treatment to a less toxic agent with non-inferior outcomes was investigated. Cetuximab had been proposed on the hypothesis that it is less toxic and as effective as Cisplatin-RT. However, de-escalate has disproven this and the recommendation is continued use of Cisplatin-RT in HPV-positive OPSCC, unless elderly or intolerant of platinum, as it has similar rates of toxicity to Cetuximab-RT with better survival and lower rate of locoregional recurrence and distant metastasis [13,14] (Table 1).

Intratumoural Immune Cell (ITIC) CD103 expression, a marker of tissue resident memory T cells, was later quantified on immunohistochemistry from participants in de-escalate and TROG 12.01. High risk HPV OPSCC patients with high CD103 expression (>30%) was compared with low risk HPV OPSCC patients with low CD103 expression (<30%). Cisplatin+RT was found to be good for low risk HPV OPSCC with either low or high CD103. Cetuximab+RT was found to be good for low risk HPV OPSCC with high CD103 with better 3 yr FFS (92%) and 3 yr OS (100%) independent of stage. This

Table 1: Comparison table on cetuximab studies.

Favoring Cetuximab	Less/Not in Favor of Cetuximab
1. IMCL-9815 trial [8]	1. De-escalate
	2. RTOG-1016
	3. TROG 12.01
	4. RTOG-0522 (prospective trial with mainly HPV-negative)
	5. DeLOS-II (prospective trial with mainly HPV-negative)

Table 2: Chemotherapy studies.

Name of Trial	Date Started	Date Completed	For/against De-escalation	Compared
RTOG 1016	2011	2019	Against de-escalation	Cisplatin+RT *vs.* Cetuximab+RT
De-escalate	2012	2018	Against de-escalation	Cisplatin+RT *vs.* Cetuximab+RT
TROG 12.01	2013	2021	Against de-escalation	Cisplatin+RT *vs.* Cetuximab+RT
RTOG 0522	2005	2011	Against de-escalation	Cisplatin+RT *vs.* Cetuximab+Cisplatin+RT
TROG 02.02	2002	2010	No significant difference	Cisplatin+RT *vs.* Tirapazamine+Cisplatin+RT
TAX TAXOTERE 324	1999	2011	For de-escalation	TPF ICT *vs.* PF ICT

could be targeted for de-escalation in future trials [15].

Combination chemoradiotherapy

Changes in concurrent CRT have been proposed as a de-escalation strategy. Various studies have investigated this including RTOG 0522 and TROG 02.02 [16,17] (Table 2).

RTOG 0522 a multicentre RCT, phase 3 completed trial (USA, 2011) compared concurrent Cisplatin+RT with Cetuximab+Cisplatin+RT in HPV positive OPSCC patients. Patients received a radiotherapy regimen of either AFX (72 Gy/42# 6 weeks) or AFX IMRT (70 Gy/35# 6 weeks). No significant difference in overall outcomes was found by adding Cetuximab to Cisplatin+RT. There was no significant difference in 3 yr OS in the Cetuximab+Cisplatin+RT group compared to Cisplatin+RT (3 yr OS 72.9% *vs.* 75.8%) [16].

TROG 02.02 a multicentre, randomized, phase 3 completed trials (Europe, USA, Australia, New Zealand, 2010) compared Cisplatin+RT with concurrent Tirapazamine+Cisplatin+RT SFX in both HPV p16 positive and negative OPSCC. 57% of patients recruited were HPV p16 positive. No significant improvement in 2 yr OS was found by adding Tirapazamine to Cisplatin+RT irrespective of HPV status. HPV-positive OPSCC patients had significantly better 2 yr OS compared with HPV negative OPSCC (2 yr OS 91% *vs.* 74%). Two year Failure Free Survival (FFS) was also better in the HPV p16 positive OPSCC group compared to HPV-negative OPSCC (2 yr FFS 87% *vs.* 72%). In addition, Loco-Regional Failure (LFR) rates were lower in the HPV p16 positive OPSCC group [17].

Induction chemotherapy+cisplatin-radiotherapy

ICT prior to concurrent Cisplatin+RT has been proposed as a de-escalation strategy for HPV positive OPSCC. The aim of ICT is to shrink the tumor and provide a smaller area to irradiate. The tumor response to ICT can then be used as a predictive guide to how the tumour will respond with RT.

TAX TAXOTERE 324 a multicentre, randomized, phase 3 completed trials (China, 2011) compared TPF ICT (Cisplatin+5-fluorouracil+docetaxel) with PF ICT (Cisplatin+5-fluorouracil) followed by Cisplatin+RT (70-74 Gy/35-37# 7 weeks) in both groups. The OS and PFS was significantly better in the TPF ICT group. 50% of participants recruited in the trial had HPV positive OPSCC and were found to have significantly better outcomes compared to HPV-negative OPSCC. The 5 yr OS was greater in the HPV-positive group compared to HPV-negative OPSCC (5 yr OS 82% *vs.* 35%). The 5 year PFS was also significantly greater for the HPV-positive OPSCC group compared to HPV-negative OPSCC (5 yr PFS 78% *vs.* 28%) [18].

This strategy with better outcomes and less associated toxicity can be used as a cytoreductive measure prior to considering concomitant CRT for high volume HPV-positive disease.

Radiotherapy: De-escalated RT

Other proposed de-escalation strategies include reduction of the total radiation dose for HPV positive OPSCC (Table 3).

Cartmill et al. [19] reported that morbidity associated with RT in OPSCC is dose dependent. RT to the pharyngeal constrictors adversely affects swallow and causes dysphagia, stricture formation, aspiration risk and dependence on PEG feeding. Mirghani et al. [20] and Duprez et al. [21] have shown that if more than 50% of the superior pharyngeal constrictors and more than 30% of the middle pharyngeal constrictors are exposed to the standard RT dose of 70 Gy or above then the risk of adverse effects significantly increases. Therefore, by reducing the RT dose to 52 Gy to 55 Gy, or, by reducing the RT field to completely avoid the superior and middle pharyngeal constrictors, where possible, this should significantly reduce the severity of adverse effects. Intensity Modulated Radiotherapy (IMRT) is more targeted and its development has been associated with reduced RT associated morbidity. A number of clinical trials have been published or continue to investigate reduction of RT dose comparing standard 70 Gy with de-escalated 54 Gy to 56 Gy [22-24]. These trials recruited patients based on their ISH or PCR positive status.

ECOG 1308 a multicentre, non-randomized, phase 2 completed trial (USA, 2014) compared con-current Cetuximab+SFX IMRT (69 Gy/33#) with Cetuximab+low dose IMRT (54 Gy/27#) in stage III/IV HPV positive OPSCC patients. Following ICT (Paclitaxel, Cisplatin and Cetuximab) participants were restaged and if showing a partial or complete response to ICT they received concurrent Cetuximab+SFX IMRT or Cetuximab+low dose IMRT (54 Gy/27#). The Cetuximab-

Table 3: Radiotherapy studies.

Name of Trial	Date Started	Date Completed	For/against De-escalation	Compared
TORPEdO	2020	Ongoing	Awaited	IMPT *vs.* IMRT
ECOG 1308	2010	2014	For de-escalation	Cetuximab+SFX IMRT *vs.* Cetuximab+low dose IMRT
RTOG 9003	1991	2010	For de-escalation	SFX *vs.* hyper-FX RT *vs.* AFX-S *vs.* AFX-C
RTOG 0129	2002	2010	No significant difference in outcomes	Cisplatin+SFX RT *vs.* AFX-C RT
NRG-HNOO2	2014	2019	Against de-escalation	Cisplatin+IMRT (60 Gy/30#/6 weeks) *vs.* IMRT (60 Gy/30#/5 weeks)
ORATOR2	2018	2020	For RT	Reduced dose RT+/-cisplatin *vs.* TORS+neck dissection+/-reduced dose RT

low dose IMRT group showed complete response to ICT. OS and PFS rate was found to be significantly better in the Cetuximab+low dose IMRT group compared to the Cetuximab+SFX IMRT group (OS 96% *vs.* 94%; PFS 96% *vs.* 80%). Early toxicity was lower for the Cetuximab+low dose IMRT group compared to the Cetuximab-SFX IMRT group with a significantly lower rate of dysphagia to liquids (40% *vs.* 89%) and lower rate of malnutrition (10% *vs.* 44%) [22].

RTOG 0129 a multicentre, randomized, phase 3 completed trials (USA, 2010) compared Cisplatin+SFX RT with Cisplatin+accelerated fractionation with concomitant boost (AFX-C RT 72 Gy). It highlighted the prognostic implication of HPV-positive in OPSCC and stratification of risk groups based on findings and HPV status on prognosis with 3 yr OS of 82.4% *vs.* 57% with risk reduction of death by 58%. However, no significant difference was seen in 3 yr OS between Cisplatin+AFX-C RT and Cisplatin+SFX RT (70% *vs.* 64.3%), albeit with 10% reduction of death rate amongst Cisplatin-AFX-C group [25].

Further report in 2014 updated the RTOG 0129 findings highlighting significant 8 yr OS [23], PFS in HPV-positive OPSCC patients receiving Cisplatin+AFX-C RT compared to Cisplatin+SFX RT. LRF was significantly reduced in HPV-positive group receiving Cisplatin+AFX-C RT. But no significant difference in toxicity was seen between the two groups.

63.8% of participants had HPV-positive OPSCC. No significant difference was found in OS or late toxicity between the groups. The HPV-positive OPSCC participants were noted to have significantly better outcomes compared to HPV-negative OPSCC (8 yr OS 70.9% *vs.* 30.2%). 8 yr PFS was significantly better and 8 year LRF was lower in the HPV-positive OPSCC compared to HPV-negative OPSCC (8 yr PFS 64% *vs.* 23.3%; 8 yr LRF 19.5% *vs.* 52.4%). Of note tobacco smoking was found to partially negate the HPV benefit [23].

TORPEdO a multicentre, RCT, phase 3 in process trial (UK) started recruitment in January 2020 and is comparing concurrent chemotherapy + Intensity Modulated Proton beam Therapy (IMPT) with concurrent chemotherapy + IMRT for locally advanced OPSCC [24].

Radiotherapy: RT Alone. Without Chemotherapy

Single modality treatment with RT alone has been suggested as a de-escalation strategy for HPV-positive OPSCC.

NRG-HN002 a multicentre, randomized, phase 2 completed trial (USA, 2019) compared concurrent Cisplatin+IMRT (60 Gy/30#/6 weeks) with IMRT (60 Gy/30#/5 weeks) alone in patients with loco-regionally advanced OPSCC with a pack year history of less than 10 years. The 2 yr PFS was found to be better in the concurrent Cisplatin+RT group compared to RT alone (2 year PFS 90.5% *vs.* 87.6%). Two year LRF rate was lower in the concurrent Cisplatin+RT group compared to RT alone (LRF 3.3% *vs.* 9.5%) [26].

RTOG 9003 a multicentre, randomized, phase 3 completed trials (USA, 2010) compared four different RT strategies as a de-escalation strategy for HPV positive OPSCC. They compared SFX (70 Gy/35#/7 weeks) with hyper fractionation radiotherapy (hyper-FX RT) (81.6 Gy/68# twice daily/7 weeks), AFX with split (AFX-S) (67.2 Gy/42#/6 weeks with 2 weeks rest after 38.4 Gy) and AFX-C (72 Gy/42#/6 weeks). 39% of patients had HPV positive OPSCC and tended to have better out-comes with significantly higher 5 yr OS rates in the HPV positive OPSCC group compared to traditional OPSCC (5 yr OS 49% *vs.* 19.6%). The hyper-FX RT group was the only group with showed improved Locoregional Control (LRC) and OS without increasing late toxicity at 5 year follow up [27].

Surgery: Minimally Invasive Surgery

Use of minimally invasive surgical techniques for HPV-positive OPSCC is another proposed de-escalation strategy [4,20,28]. Patients with early stage T1/2 N0 tumors can be treated with single modality treatment with either surgery or RT alone. One of the main benefits of surgery over RT is the fact that it can provide information regarding the staging of the tumor which can then be used to guide adjuvant treatment with CT or RT and de-escalation with dose reduction. Adverse pathological features such as extra-capsular spread are significant in HPV-negative OPSCC but have less relevance in HPV-positive OPSCC [29,30].

Open surgical resection with free flap reconstruction is associated with high rates of morbidity and is therefore a less favored surgical option. More recently, new surgical techniques have been developed; including, Trans Oral Robotic Surgery (TORS) which is minimally invasive and now being considered for both patients with T1/2 N0 tumors and also for locally advanced T3 tumors. TORS has many benefits including easier access, better vision, tremor reduction and 3D infield optics allowing for better evaluation of margins. However, there are some limitations with the use of minimally invasive surgical techniques. For instance, TORS is not widely available in all centers due to the significant associated cost, limiting availability and access. Other minimally invasive surgeries such as trans-oral laser microsurgery are more widely available in most centers and are a good alternative. Previous concerns' regarding the initial line of sight has been largely resolved through the use of fiber optic delivery systems.

A number of published and ongoing trials are investigating such minimally invasive surgical techniques including MOSES, ORATOR and EORTC 1420-HNCG-ROG [31-33].

MOSES a prospective descriptive observational cohort study (UK) started recruitment in November 2019 and is expected to be completed in November 2021 comparing different surgical techniques including robotic surgery, laser surgery and endoscopic surgery [31].

ORATOR a multicentre, randomized, phase 2 completed trial (Australia, Canada, 2019) compared TORS+neck dissection+adjuvant CRT (based on pathology) (60 Gy/30#) with concurrent CRT SFX if nodal involvement (N1-2). 88% of patients recruited to the trial were HPV p16 positive and were equally split between the two arms. Quality of life at 1 year was slightly better with regards to lower rates of dysphagia in the RT group compared to TORS but not to a clinically significant level [32].

The ORATOR2 trial, a multicentre, randomized, phase 2 trial led on from this to compare reduced dose RT ± Cisplatin (60 Gy/30#) with TORS plus neck dissection ± adjuvant reduced dose RT for intermediate risk for patients with T1-2, N0-2, M0 HPV-positive disease. Unfortunately, due to unacceptable grade 5 toxicity reported in the surgery arm this trial had to be stopped early in November 2020 prior to completion. Two deaths including an oropharyngeal bleed and cervical spine osteomyelitis were reported in the surgical group secondary to treatment. Initial outcomes in the RT group compared to TORS were promising including 36-month OS (100% *vs.* 89.1%) and 36-month PFS (100% *vs.* 83.5%). MDADI score was slightly better in the RT group (85.7 ± 15.6 *vs.* 84.7 ± 14.5 at 1 year, p=0.85)

with no patients requiring a feeding tube a 1 year [34].

EORTC 1420-HNCG-ROG a multicentre, randomized, phase 3 in process trial (UK, Europe) started recruitment in November 2017 and has an estimated completion date of January 2028 and is comparing trans oral surgery with selective neck dissection with IMRT with boost (66-70 Gy/33-35#). In the surgical group close margins of <1 mm are re-resected and adjuvant treatment with RT alone or concurrent CRT is offered based on pathology [33].

Surgery: Surgery followed by De-escalated RT

Another de-escalation strategy proposed for HPV-positive OPSCC is surgery followed by adjuvant low dose RT.

PATHOS a multicentre, RCT, phase 2/3 completed trial (UK) started recruitment in October 2015 with expected completion in April 2027 and is investigating post operative adjuvant low dose RT in patients with HPV-positive OPSCC. Following transoral laser microsurgery participants are split into low, medium or high risk groups, based on histology. The low risk group does not receive any further treatment. The medium risk group receives standard FX RT or low dose RT. The high risk group receives concurrent Cisplatin-RT or standard FX RT alone. The estimated completion date of this trial is the October 31st, 2022 [35].

ECOG 3311 a multicentre, randomized, phase 2 completed (USA, 2020) investigated post-operative adjuvant low dose RT in patients with HPV p16 positive OPSCC. Following transoral resection plus neck dissection, patients with pT1-2 N0-1 OPSCC were observed, patients with clear or close margins (≤ 1 mm), ECS, PNI/LVI or 2 to 4 metastatic lymph nodes will receive IMRT with either 50 Gy or 60 Gy and patients with positive margins, 5 or more metastatic lymph nodes or 1 mm ECS received Cisplatin-IMRT. 2 yr PFS was found to be better in the IMRT groups compared to observation or Cisplatin+IMRT (2 yr PFS 95% *vs.* 93.9% *vs.* 90.5%). Based on the outcomes of this a future, randomized phase 3 trial will be designed [36].

Combination of De-escalation Strategies

Compare (UK) started recruitment in July 2015, is expected to be completed in January 2023 and has five different treatment arms including Cisplatin+IMRT (70 Gy/35#) *vs.* ICT (Cisplatin+5-Fluorouracil)+docetaxel then Cisplatin+IMRT (70 Gy/35#) *vs.* Cisplatin-dose escalated IMRT (64 Gy/25#) *vs.* surgery then Cisplatin+IMRT (70 Gy/35#) *vs.* Durvalumab+Cisplatin+IMRT (70 Gy/35#) then Durvalumab [37].

Most of the ongoing trials look at overall survival, event free survival as primary outcome measures. Adverse events including toxicity (acute/late), quality of life, swallow, cost effect of treatment, surgical complications are secondary outcomes.

Conclusion

The results of several clinical trials are awaited; however, the available results are not promising for de-escalation in HPV-positive OPSCC. ECOG 1308 has shown de-escalation with ICT followed by cetuximab-low dose RT to be superior. NRG-HN002 found low dose Cisplatin-RT superior to AXF. De-escalate and RTOG 1016 both found Cetuximab-RT to be inferior to Cisplatin-RT with significantly worse outcomes and no significant difference in severe toxicity. ECOG 3311 supports reducing the dose of RT after surgery. Further validation through randomized control trials is needed prior to widespread changes in practice.

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