Consensuses, Controversies, and Future Directions in Treatment Deintensification for Human Papillomavirus-Associated Oropharyngeal Cancer

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Abstract

The most common cancer caused by human papillomavirus (HPV) infection in the United States is oropharyngeal cancer (OPC), and its incidence has been rising since the turn of the century. Due to substantial longterm morbidities with chemoradiation and the favorable prognosis of HPV-positive (HPV+) OPC, identifying the optimal deintensification strategy for this group has been a keystone of academic head-and-neck surgery, radiation oncology, and medical oncology for over the past decade. However, the first generation of randomized chemotherapy deintensification trials failed to change the standard of care, triggering concern over the feasibility of de-escalation. National database studies estimate that up to one-third of patients receive non-standard de-escalated treatments, which have subspecialty-specific nuances. A synthesis of the multidisciplinary deintensification data and current treatment standards is important for the oncology community to reinforce best practices and ensure optimal patient outcomes. In this review, the authors present a summary and comparison of prospective HPV+ OPC de-escalation trials. Chemotherapy attenuation compromises outcomes without reducing toxicity. Limited data comparing transoral robotic surgery (TORS) to radiation raise concern over toxicity and outcomes with TORS. There is promising data to support de-escalating adjuvant therapy after TORS, but consensus on treatment indications is needed. Encouraging radiation deintensification strategies have been reported (upfront dose-reduction and induction chemotherapy-based patient selection), but level one evidence is years away. Ultimately, stage and HPV status may be insufficient to guide de-escalation. The future of deintensification may lie in incorporating intra-treatment response assessments to harness the powers of personalized medicine and integrate real-time surveillance.

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Introduction

The most common cancer caused by human papillomavirus (HPV) infection in the United States is oropharyngeal cancer (OPC), and its incidence has been rising since the turn of the century[1,2] Even further, OPC incidence is projected to rise until the mid-2030s despite the availability of an HPV vaccine.[3] In 2019, only 54% of adolescents and 21% of young adults were up-to-date with their HPV vaccines, and studies have reported drastic (up to 77%) declines in vaccine uptake in 2020 due to the Coronavirus Disease 2019 pandemic and vaccine hesitancy.[3] Although increasing prevalence of oropharyngeal HPV infection has been implicated in the rising incidence of pathogenesis of the disease, increases in OPC survival have fortunately also been attributed to an increasing proportion of OPC cases resulting from HPV infection and a decline in OPC attributable to other causes such as tobacco.[1]

Regardless of HPV status, ample level one evidence established definitive concurrent cisplatin-based chemoradiotherapy (CRT) to 70Gy as one standard of care for locally advanced oropharyngeal cancer (OPC).[4–10] Altered fractionation radiotherapy (AFRT), the addition of cetuximab, and induction chemotherapy failed to improve outcomes.[4,5,6,11,12] Although 70Gy CRT cures the majority of patients treated, treatment comes at the cost of significant longterm toxicities. Unfortunately, up to 25% of ten-year survivors develop pharyngeal/laryngeal toxicity and 47% develop oral cavity toxicity.[13] Pooled analysis of RTOG trials demonstrated that up to 43% of CRT patients experienced severe late toxicities including gastrostomy tube dependence, infection, fistula, or death.[14]

HPV-associated (HPV+) OPC has such a favorable prognosis that investigators have sought to deintensify treatment to reduce longterm morbidities in patients who are likely to live many years beyond their diagnoses. Recursive partitioning analysis (RPA) of RTOG 0129 defined "low-risk" as any HPV+ OPC with ≤ 10 pack-year smoking history (PYSH) or N0-N2a disease with >10 PYSH, and "intermediate-risk" as any HPV+ OPC with N2B-3 disease and >10 PYSH.[4] Some deintensification trials included only low-risk while others also included intermediate-risk patients, highlighting discord even among experts on the most appropriate candidates for de-escalation.

However, enthusiasm for deintensification was tempered by apprehension of its viability when the first randomized controlled trials (RCTs) of chemotherapy attenuation and omission demonstrated the importance of standard of care (SOC) cisplatin to outcomes in HPV+ OPC.[15–17] A recent meta-analysis of prospective and retrospective studies reported inferior overall survival (OS), progression-free survival (PFS), locoregional control (LRC), and distant metastasis-free survival (DMFS) with treatment deintensification in HPV+ OPC compared to SOC therapy.[18] Ultimately, the American Society of Clinical Oncology (ASCO) issued a clinical provision that treatment de-escalation for HPV+ OPC "is a hypothesis that requires appropriate testing" and that "current treatment recommendations have not changed.[19] Despite the failure of chemotherapy deintensification, the drive to decrease toxicity continues through other strategies: de-escalation through transoral robotic surgery (TORS) or deintensification of radiation therapy (RT).

A National Cancer Database (NCDB) registry analysis from 2010–2013 revealed that one-third of postoperative T1-T2 HPV+ OPC patients with intermediate-risk factors (2–4 involved nodes, lymphovascular invasion (LVI), or microscopic extracapsular extension (ECE)) received de-escalated adjuvant RT.[20] Given that 85% of cancer patients are treated in the community but only 3% enroll on clinical trials, the vast majority of those de-escalated presumably were treated off clinical trial.[21] The preponderance of deintensification trials and divergence in treatments administered despite no change in the SOC warrant an analysis of the data. Given subspecialty-specific nuances to de-escalation, interdisciplinary knowledge is ever more critical for these cancers which require multidisciplinary care. The aim of this review is to provide a synthesis of prospective deintensification trials (chemotherapy, surgery, and radiation), summarize current treatment standards, and explore consensuses and controversies in the management of HPV+ OPC to help reinforce best practices and ensure optimal patient outcomes.

Chemotherapy Deintensification Approaches

Cisplatin Attenuation

Considering its significant acute and chronic toxicities (nephrotoxicity, nausea/vomiting, ototoxicity, neuropathy), cisplatin attenuation was the first deintensification approach attempted. Table 1 illustrates eligibility criteria, treatment details, and outcomes from various chemotherapy attenuation and omission clinical trials. Given validated efficacy in head and neck cancer (HNC), the epidermal growth factor receptor (EGFR) inhibitor cetuximab became a promising alternative to cisplatin given seemingly less severe toxicities in the skin, gastrointestinal tract, and oropharyngeal mucosa.[22] Another EGFR inhibitor (panitumumab) had failed to replace cisplatin in American Joint Committee on Cancer 7th Edition (AJCC7) Stage III/IV HNC.[23,24] However, subset analysis from a randomized trial confirmed LRC, PFS, and OS benefits with cetuximab over RT alone in HPV+ OPC, warranting further comparison of cetuximab against cisplatin in this subset of patients.[25] RTOG 1016 and De-ESCALaTE were the first chemotherapy deintensification RCTs, and both reported inferior outcomes with cetuximab with no improvements in acute or late severe toxicity (Table 1).[15,16] In RTOG 1016, cisplatin conferred superior LRC, PFS, and OS.[15] De-ESCALaTE showed significantly inferior LRC, DMFS, and OS, along with triple the recurrences (18% vs. 6%), with cetuximab.[16] Ironically, attenuation of chemotherapy was not profoundly less toxic; although the mean number of grade 3–4 acute adverse events per patient was lower with cetuximab (2.35 cetuximab vs. 3.19 cisplatin, p<0.0001), the proportion of patients experiencing any grade 3–4 toxicity was similar in both groups (77.4% cetuximab vs. 81.7% cisplatin, p=0.16). While these trials did not change the SOC, they established high standards for modern 2-year PFS in HPV+ OPC (~85–94%) which appear favorable compared to historical RTOG studies (~80–87%).[26]

Not only should cetuximab not replace SOC bolus high-dose (HD) cisplatin (100 mg/m^2 q3weeks x3 cycles) in HPV+ OPC, it should not replace low-dose (LD) cisplatin (30–40 mg/m^2 weekly) either. ARTSCAN III randomized HNC patients (~75% HPV+ OPC) to LD cisplatin versus cetuximab; three-year locoregional failure (LRF) was 23% with cetuximab versus 9% with LD cisplatin, and with similar toxicity.[27] Subgroup analysis of HPV+ OPC

patients in a phase two trial showed trends for inferior local control (LC) and OS with cetuximab versus LD cisplatin.[28] Finally, TROG12.01 randomized patients with HPV+ OPC to cetuximab versus LD cisplatin (40 mg/m^2), and 3-year PFS was inferior with cetuximab (93% vs. 80%, p=0.015) without less toxicity (Table 1).[29]

The potential synergism of immunotherapy in this immunosuppressive virus-associated cancer was hypothesis-generating and instigated much investigation. Survival advantages with immunotherapy in recurrent/metastatic disease piqued interest in its utilization in the definitive setting.[30,31] REACH (GORTEC 2017–01) is a randomized trial comparing concurrent avelumab, cetuximab, and radiation followed by twelve months of adjuvant avelumab versus two SOC therapies (against HD cisplatin for cisplatin-eligible, and against weekly cetuximab for cisplatin-ineligible) in locally advanced HNC; results from the safety phase of the trial showed that the addition of avelumab was tolerable with no difference in grade ≥ IV across groups (12% avelumab/cetuximab, 14% HD cisplatin, and 10% cetuximab).[32] The PembroRAD study randomized cisplatin-ineligible HNC patients to cetuximab-RT versus the anti-PD1 pembrolizumab with RT; pembrolizumab-RT did not improve cancer outcomes but appeared to have less acute grade ≥ 3 toxicity (74% vs 92%, p=0.006).[33] Table 1 illustrates three HPV+ OPC-specific immunotherapy trials which will assess durvalumab followed by adjuvant durvalumab or tremelimumab/durvalumab (with SOC 70Gy RT), nivolumab (HN005, which will also de-escalate RT to 60Gy), and ipilimumab and nivolumab (which will also de-escalate RT to 50–66Gy).[34] While there is a need to discover appropriate upfront uses of immunotherapy, there is cause for caution as well. JAVELIN Head and Neck 100 uncovered a possible antagonistic effect of concurrent immune checkpoint inhibition with definitive CRT.[35] Corroborating this, a randomized phase two study comparing concurrent versus sequential pembrolizumab with CRT in HNC showed numerically higher 2-year PFS with sequential administration (78% versus 89%) and recommended sequential pembrolizumab as the preferred regimen to compare with SOC CRT in HNC in a phase three trial.[36] While not powered for subgroup analysis, HPV+ HNC patients on JAVELIN did not benefit from immunotherapy. Furthermore, a systematic review and meta-analysis of HNC immunotherapy trials found no significant difference in response when results were stratified by HPV status.[37] At this time, there is no data to support that HPV status influences the decision to use immunotherapy, highlighting the need to identify biomarkers to predict response.

Cisplatin Omission

Even further than attenuation are attempts at chemotherapy omission. A multicenter phase two trial from Osaka treated HPV+ OPC with intensity-modulated RT (IMRT) alone, reporting 94% 2-year PFS (Table 1).[38] HN002 (Table 1) was a phase two randomized trial which hypothesized that modestly reduced CRT (60Gy IMRT with LD cisplatin) and AFRT (60Gy/5 weeks IMRT alone) would both achieve 2-year PFS ≥ 85%.[17] Two-year PFS without cisplatin did not meet the threshold to support omission. While there were more acute grade 3–4 toxicities with cisplatin, late grade 3–4 toxicities were comparable at ~20%. Given that HN002 randomized over 300 patients and included more favorable patients than the Osaka trial (n=39), the best available data clearly refute the omission of chemotherapy.

Given canonical studies, the supremacy of CRT in HPV+ OPC is not surprising. The Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH) reported absolute 5-year LC and OS benefits of 9% and 7%, respectively, with concomitant chemotherapy.[39,40] Subsite analysis from the MACH showed the greatest survival benefit in early-stage OPC (p=0.02): Stage I/II (hazard ratio (HR) 0.75, n=362), Stage III (HR 1.01, n=1606), and Stage IV (HR 0.83, n=3679).[41] However, the effect of stage did not retain significance on multivariate analysis. Furthermore, AFRT does not compensate for the absence of chemotherapy; the Meta-Analysis of Radiotherapy in Carcinomas of Head and Neck (MARCH) showed a 5.8% 5-year OS benefit with chemotherapy plus conventional RT over AFRT alone in non-metastatic HNC.[42] Given that these landmark analyses included trials when HPV prevalence was lower and before HPV testing was routine, there was a conception that the benefits of chemotherapy may not extend to low-risk HPV+ OPC. However, the first randomized deintensification trials firmly concluded that chemotherapy improves outcomes—even in HPV+ OPC.

Optimal Cisplatin Administration

Not only does cisplatin remain SOC with RT, but HD bolus remains its standard administration. In the postoperative adjuvant setting, there are conflicting data on the supremacy of HD cisplatin. An RCT from India of mostly postoperative HNC patients showed inferior LRC with LD cisplatin (30 mg/m^2) versus HD cisplatin, with trends towards inferior PFS and OS.[43] An RCT from Japan of exclusively postoperative HNC patients showed noninferiority with LD cisplatin (40 mg/m^2) versus HD cisplatin, although the HR noninferiority margin was set high at 1.32.[44] As a current standard for postoperative HPV+ OPC with high-risk features, ECOG E3311 administered adjuvant radiation therapy with LD cisplatin (40 mg/m^2 weekly) and reported a favorable 2-year PFS of 90.7% [90% confidence interval (CI) 86.2–95.4].[45] Taken together, although HD cisplatin is SOC in the postoperative HNC setting, LD cisplatin at 40 mg/m^2 weekly is defensible while adjuvant LD cisplatin at 30 mg/m^2 weekly is not. However, in the definitive setting, HD cisplatin remains the SOC. A small retrospective study of CRT in specifically HPV+ OPC found more local and distant failures with LD (40 mg/m^2 weekly) versus HD cisplatin (2-year PFS 75% vs. 96%, p=0.04), although OS was similar.[46] ConCERT was a randomized noninferiority trial of HD versus LD (40 mg/m^2 weekly) cisplatin for definitive CRT in OPC (87% HPV-negative), laryngeal cancer, hypopharyngeal cancer, and oral cavity cancer; 2-year LRC with LD cisplatin was within the 10% non-inferiority margin, but only about 20 patients in the trial had HPV+ OPC.[47] Although not limited to HPV+ OPC, NRG-HN009 will randomize definitive CRT HNC patients to LD (40 mg/m^2) versus SOC HD cisplatin. Until published, HD cisplatin remains the SOC for definitive CRT patients.

Summary

In summary, three RCTs (De-ESCALaTE, RTOG 1016, TROG 12.01) confirmed PFS benefits, two RCTs (De-ESCALaTE, RTOG 1016) confirmed OS benefits, two RCTs (De-ESCALaTE, TROG 12.01) confirmed DMFS benefits, and two RCTs (De-ESCALaTE, RTOG 1016) confirmed LRC benefits with cisplatin over cetuximab. Cisplatin omission also compromises outcomes (HN002), and bolus HD cisplatin remains its standard administration with definitive CRT in HPV+ OPC. The failure of chemotherapy

deintensification prompted international cooperative groups to caution against deviation from the SOC and advocate that "harm minimization techniques should also be evaluated as an alternative to de-escalation."[48] It is important to highlight that modern deintensification trials report about half the late toxicities (~20%) with SOC CRT compared to historical RTOG trials (~40%).[14,15,17] This may be in part due to better supportive care and the utilization of IMRT technology which has level one evidence to support toxicity improvements over conventional RT.[49] The optimization of treatment delivery and harm minimization are important practices to sustain and enhance.

Surgical Deintensification Approaches Through Transoral Surgery (TORS)

TORS to Replace Definitive Radiation

Weighted average results from 51 series from North American academic institutions showed similar disease control and survival outcomes but higher severe or fatal complications with open transmandibular or transcervical surgery versus definitive RT for OPC.[50] A meta-analysis of HPV+ OPC showed no difference with RT versus surgery for the combined endpoint of death, recurrence, or progression.[51] However, the advent of TORS raised the question if the balance might now favor minimally invasive surgical intervention. In 2016, a comprehensive review of small-volume primary OPC showed no high-quality evidence comparing TORS to RT.[52] But TORS utilization rapidly expanded and only five years later by 2021, a systematic review and meta-analysis of HPV+ OPC treatments concluded that TORS was associated with worse performance on certain measures of patient-reported swallow and overall function compared to CRT; additionally, there was a trend favoring CRT for gastrostomy tube dependence at 24–36 months (10.5% TORS vs. 3.3% CRT with cisplatin, p=0.06).[53]

Table 2 shows eligibility criteria, treatment details, and outcomes from various TORS trials. ORATOR compared quality-of-life (QOL) in patients randomized to SOC 70Gy RT (with chemotherapy for AJCC7 N1-N2 disease) versus TORS + neck dissection (ND) with pathology-directed adjuvant therapy (SOC 60Gy RT ± chemotherapy).[54] There was no difference in outcomes (3-year PFS: 96.3% RT vs. 93.3% TORS, p=0.32; 3-year OS: 96.3% RT vs. 90.0% TORS, p=0.58) and longitudinal assessment demonstrated superior, but not clinically meaningful, dysphagia with RT over time.[55] Post hoc subgroup analysis with longterm follow-up from the ORATOR trial revealed that the statistically significant and clinically meaningful superiority of dysphagia with RT was driven entirely by base of tongue tumors, with no difference in dysphagia between modalities for tonsil cancers.[56] TORS patients had more pain, trismus, and bleeding, while RT patients had more mild ototoxicity, xerostomia, and mild neutropenia. ORATOR2 randomized only p16-positive (p16+) HPV+ OPC patients to de-escalated RT (60Gy ± LD cisplatin) versus TORS + ND ± de-escalated 50Gy postoperative RT (PORT); the trial explicitly attempted to avoid trimodality therapy.[57] The trial closed early to accrual due to two deaths in the TORS arm: cervical spine osteomyelitis and oropharyngeal hemorrhage (despite trial-mandated external carotid artery ligation). At median follow-up of 17 months, all four PFS events had occurred in the TORS arm; 2-year PFS was inferior with TORS (83.5% TORS vs. 100% RT), but statistics could not be reported as survival data was immature due to early closer

for unforeseen excess grade 5 toxicity events in the TORS arm.[57] Of note, both definitive and adjuvant RT doses were de-escalated on ORATOR2. The Comparativeness Effectiveness Trial (Table 2) will attempt to provide further clarity regarding safety and efficacy with TORS compared to RT, using SOC definitive and adjuvant doses. And, other studies will address the role of TORS versus RT in resectable HNC, but are not limited to HPV+ OPC: the EORTC "Best Of" trial (NCT02984410) will randomize T1–2N0–1 OPC of any HPV status or supraglottic larynx cancer or T1N0 hypopharynx cancer to TORS versus SOC 66–70Gy RT and the QoLATI trial (NCT04124198) will randomize T1–2N0–1 OPC (any HPV status) to accelerated RT ± chemotherapy versus TORS with staging ND prior to planned TORS for clinically node-positive patients. Critical to these, and any, surgical de-escalation strategy is careful patient selection, complete staging workup, and implementation at a high-volume center with robotic surgery expertise.

TORS to Attenuate Adjuvant Therapies

Another approach de-escalates adjuvant therapy after TORS. Eastern Cooperative Oncology Group (ECOG) E3311 (Table 3) randomized resected HPV+ OPC with intermediate-risk factors (close margin <3 mm, perineural invasion (PNI), LVI, 2–4 involved lymph nodes (LN), or <=1 mm ECE) to reduced-dose (50Gy) versus standard-dose (60Gy) PORT.[45] Patients with ECE >1 mm, positive margins, or pN2 disease (5 LNs) were not de-escalated and received SOC 60–66 Gy PORT with LD cisplatin (40 mg/m^2). TORS with reduced-dose 50Gy PORT retained outstanding 94.9% 2-year PFS, raising the question if TORS + reduced-dose PORT may obviate chemotherapy and should be compared against SOC 70Gy CRT in a phase III trial. It is important to note that although 2-year PFS with 50Gy PORT was comparable to SOC 60Gy PORT (96.0%), there was no difference in patient-reported outcomes, raising the question if modest dose-reduction meaningfully improves toxicity. Figure 1a illustrates radiation dosimetry with SOC 60Gy (pink 6000 line) PORT to the neck. Figure 1b illustrates radiation dosimetry with reduced-dose 50Gy PORT to the neck (magenta 5000 line). With IMRT, medium/high 40–45Gy dose spillover (teal 4000 line, blue 4500 line) to central swallowing structures like the esophagus (pink) can be effectively minimized without significant differences between 50Gy and 60Gy dose prescriptions.Although E3311 was not a comparison of TORS versus RT as both ORATOR trials were, there was only one grade 5 hemorrhage among 495 TORS patients on E3311, providing proof of concept that TORS can be incorporated into de-escalation protocols when supported by a comprehensive credentialing process.

The Mayo Clinic MC1273 trial (Table 3) enrolled p16+ OPC patients with negative margins after surgery and <10 PYSH to even greater reductions in de-escalated adjuvant RT (DART).[58,59] Intermediate-risk patients (T3, any LN>3 cm, 2 LNs, LVI, or PNI) received DART to 30Gy CRT bidaily (BID) with docetaxel, while high-risk ECE patients received 36Gy CRT BID with docetaxel. Two-year LRC and PFS were 96.2% and 91.1%, with no grade 3 toxicity within two years of treatment. Of note, 8 of 59 (14%) of N2 patients experienced progression, half of which were distant and raised questions about adequate radiosensitization and distant protection with docetaxel. Accelerated BID radiation is known to increase late toxicity, so these results warranted a toxicity comparison of lower total dose BID versus standard doses conventionally fractionated.[60] Accordingly, 30–36Gy

DART BID with docetaxel was compared against SOC 60Gy PORT with LD cisplatin (40 mg/m^2) in the DART-HPV/MC1675 RCT (Table 3). Two-year PFS with DART 30–36Gy BID with docetaxel was 86.5% [95% CI 80.2–93.3] versus 95.1% [95% CI 88.8–100.0] with SOC. However, the DART arm experienced significantly smaller percentage that required feeding tubes (1.6% versus 27.4%, p>0.0001) and fewer grade 3 toxicities at three months (1.6% versus 7.1%, p=0.058).[61] Again, progression was predominantly observed in patients with American Joint Committee on Cancer 8th edition (AJCC8) pN2 (>4 LNs) disease and ECE treated with DART, who experienced 42.9% 2-year PFS (versus 100% with SOC); conclusions in pN2 patients without ECE cannot be drawn as only two such patients were enrolled. A pre-planned pooled analysis of MC1273 and MC1675 reported 2-year PFS of 91.1% [95% (CI), 87.2%–95.3%]; this was both non-inferior to the target 92.3% PFS for HN005 (p = 0.29) and also higher than the HN005 acceptable PFS threshold of 86.9% (p=0.043).[62] The ECE-positive cohort did not achieve the target 92.3% or acceptable 86.9% PFS thresholds (85.2% and 78.6%, respectively), which was driven by failures in N2/ECE-positive patients.[62] A true noninferiority trial is estimated to require upwards of 4,000 patients to achieve a 1% noninferiority margin (more than all the TORS performed annually across all US academic centers), so these pooled results may be the best that can reasonably be achieved to address the question of DART after TORS. Ultimately, 30Gy DART with docetaxel appeared to meet target PFS thresholds with notable toxicity benefits in well-selected patients with intermediate-risk factors (those without ECE and with negative margins); 36Gy DART with docetaxel did not meet acceptable PFS thresholds in high-risk patients with ECE. Of note, postoperative patients with 1 mm ECE and negative margins were treated favorably with 50Gy without chemotherapy on E3311. So the question remains whether 50Gy PORT would meet the target and lower boundaries of acceptable 2-year PFS in a RCT, and whether modestly-reduced 50Gy PORT or DART with 30Gy BID with docetaxel is the optimal postoperative de-escalation regimen with intermediate-risk factors.

Based on E3311, MC1273, and MC1675, 2-year PFS estimates with DART doses ranging from 30Gy BID with docetaxel to 50Gy PORT alone range between ~86–95% for patients with postoperative intermediate-risk factors.[45,59,61] It is important to note that adjuvant therapy indications varied widely between trials. On E3311, PORT was administered for LVI, PNI, <3mm margin, ECE 1mm, or 2–4 LNs; chemotherapy was added for 5 LNs, ECE >1 mm or positive margin. On MC1273/MC1675 both PORT and chemotherapy were administered for >1 LN, LN >3 cm, T3, any ECE, LVI or PNI. Table 3 shows four additional ongoing trials (SIRS, University of Pittsburgh, MiNT, PATHOS) exploring PORT doses ranging from 42–56Gy. A unique PORT deintensification strategy was volume reduction studied on AVOID (Table 3), which harnessed a negative 2 mm margin after TORS (no PNI or LVI) to omit primary site PORT; this strategy has profound implications as primary site mucosal axis RT causes the bulk of toxicity (mucositis, stomatitis, dysphagia, xerostomia). SOC 60–66Gy PORT was administered to the at-risk neck and 2-year local recurrence-free survival was 97.9%.[63]

Positive margins and ECE have been longstanding high-risk pathology indications for adjuvant chemotherapy with PORT.[64] Despite only these two universal indications for adjuvant CRT, in practice a majority of surgical patients receive adjuvant CRT due to limitations in current preoperative staging methods and discrepancies in postoperative

therapy indications. An NCDB study on surgery versus CRT for cT1–2N1–2B OPC showed no difference in OS but 59% of surgical patients received adjuvant CRT, illustrating that many seeking surgical deintensification end up escalated to trimodality therapy.[65] One limitation of this study is that all surgical patients (including those undergoing non-definitive operations like simple palatine tonsillectomy for diagnostic workup of unknown primary cancers) were included, suggesting rampant adjuvant CRT rates with surgery. Another NCDB series focused on a cleaner subset of HPV+ OPC patients who had TORS (excluding open simple palatine tonsillectomy), reported 33% adjuvant CRT rates.[66] As a standard, on ORATOR and E3311, adjuvant chemotherapy was administered to only 24% and 31% of TORS patients respectively. Of note, they had different chemotherapy indications (ORATOR for any ECE or positive margins and E3311 for >1 mm ECE, positive margins, or   5 LNs).[45,54] The prognostic value of ECE in HPV+ OPC has been questioned, with some retrospective data suggesting no survival benefit for chemotherapy with PORT for HPV+ OPC.[67,68] However, a multi-institutional retrospective study of HPV+ OPC patients who refused standard adjuvant therapy after TORS reported a 52% 3-year relapse rate in patients with high-risk pathologic features, highlighting the risk conferred by ECE.[69] Future trials like PATHOS, ADEPT, and ADAPT (Table 3) will assess if ECE and positive margins remain indications for adjuvant chemotherapy in resected HPV+ OPC.

Finally, the utilization of TORS to improve primary site identification for HPV+ unknown primary cancers (UPC) is an emerging, powerful application for TORS to facilitate treatment deintensification. The FIND trial incorporated TORS to reduce radiation volumes in HPV+ UPCs; the pharynx was omitted from the radiation fields if primary tumors were excised with   3 mm margins or if no primary tumor was found. Half of patients qualified for omission of pharynx radiation, and 2-year LRC and DFS were 100% and 95%, respectively.[70] The favorable disease control results highlight the promise of TORS as a diagnostic and potentially therapeutic tool that may facilitate substantial treatment de-escalation in HPV+ UPC.

Neoadjuvant therapy before TORS

Neoadjuvant immunotherapy is nascent, with current trends typically favoring its use in the very locally advanced setting. NECTORS (Table 2) administered induction cisplatin/ docetaxel before TORS in AJCC7 T1–4 N0–2c HPV+ OPC and reported 94% 3-year cancer-specific survival (CSS).[71,72] One phase IB/II trial will administer neoadjuvant stereotactic body RT and immunotherapy prior to TORS for AJCC7 T0–3 N0-N2B HPV+ OPC (NCT03618134). In AJCC7 T1–2 non-bulky N2A-2B HPV+ OPC, OPTIMA II (Table 2) administered induction carboplatin/nab-paclitaxel/nivolumab, and reported 66.7% pathological complete response at TORS among nine low-risk patients with   50% tumor reduction after induction.[73,74]

Summary

In the definitive setting, one phase II randomized trial (ORATOR) reported no difference in PFS or OS and no clinically meaningful difference in toxicity with TORS + SOC PORT versus definitive RT, while another phase II randomized trial (ORATOR2) comparing TORS + de-escalated PORT versus de-escalated definitive RT closed early due to excessive

grade 5 toxicities in the TORS arm. In the adjuvant setting for intermediate-risk patients, a phase II trial reported the feasibility of PORT dose to 50Gy without chemotherapy (E3311). A preplanned pooled analysis of phase II (MC1273) and III (MC1675) trials reported decreased toxicity with 30–36Gy BID DART plus docetaxel versus SOC PORT, but de-escalation in high-risk ECE patients did not meet acceptable PFS thresholds. There is considerable variability in adjuvant RT and chemotherapy criteria, and robotic surgery expertise is of paramount importance in strategies incorporating TORS as a part of the treatment paradigm.

Radiation Therapy Deintensification Approaches

Reduction of Elective Radiation Doses and Volumes

Radiation deintensification (volume and/or dose) is a promising approach with ample literature. Adaptive RT, modifying volumes to account for weight loss or tumor shrinkage, is already common clinical practice. Subclinical/elective radiation doses and volumes have also evolved and decreased. The Infield trial reduced elective nodal irradiation (ENI) volumes to involved and adjacent levels only and decreased subclinical radiation doses from a standard of ~44–63Gy to 40Gy in oropharyngeal and laryngeal cancers.[75] RAVD (Table 4) was a trial of induction chemotherapy in locally advanced HNC; those with 50% shrinkage on CT or MRI received no ENI and >90% of locoregional failures (LRF) developed within high-dose RT volumes.[76] Specific to HPV+ OPC, a phase II trial from Montreal (Table 4) achieved 100% LRC with 43.2Gy ENI and contralateral retropharyngeal and level IV LN omission in CRT patients.[77] OPTIMA was an induction chemotherapy trial in HPV+ OPC which limited prophylactic lymph node RT to only the first echelon of uninvolved nodes in all patients, and reduced ENI dose to 30Gy for favorable responders in the de-escalated CRT arm.[78,79] Two trials, SAVER and EVADER, are currently investigating ENI volume reductions (Table 4). At Memorial Sloan Kettering, both subclinical dose (to 30Gy) and ENI volume (omission of levels IB and V) are reduced off clinical trial in all HPV+ OPC receiving cisplatin.[80,81] Figure 2 illustrates radiation dosimetry with ENI to 56Gy with omission of level IB LNs (right) versus inclusion (left); there is a dramatic difference in anterior oral cavity dose spillover with level IB omission. Thus, elective radiation dose and volume reduction are harm-mitigation strategies which have already been implemented.

Reduction of Definitive Radiation: Upfront Modest Dose Reduction

Radiation dose reduction to gross disease has been investigated in multiple phase II trials with two main strategies: upfront (empirically based on stage and PYSH) or selective (based on response to induction therapy). Four phase II trials (Table 5) have reported success with upfront modest dose reductions in p16+ OPC based on stage (AJCC7 T1-T3,N0-N2) and 10 PYSH. HN002 reported 90.5% 2-year PFS with LD cisplatin (40 mg/m^2) and 60Gy IMRT.[17] UNC/UF treated similar patients to 60Gy IMRT, reserving LD cisplatin (30 mg/m^2) for T3 or N2 disease, and reported 86% 2-year PFS.[82,83] LCCC1612 administered 60Gy IMRT or proton therapy with LD cisplatin and reported 92–93% 1-year PFS.[84] PacCIS randomized AJCC7 Stage III/IV HNC patients to SOC 70Gy with cisplatin/5FU or reduced-dose 63Gy with cisplatin/paclitaxel and reported no difference in outcomes, but <15% of patients had p16+ OPC.[85] Although all four trials showed that modest radiation dose

reduction may be acceptable with chemotherapy, none used SOC HD cisplatin. Ultimately, results from HN005 (Table 5) will elucidate whether 60Gy is non-inferior to SOC 70Gy with SOC HD cisplatin in both arms. Based on HN002 and UNC/UF, 2-year PFS outcomes approach 90% with LD cisplatin and upfront modest RT dose reduction to 60Gy.

Reduction of Definitive Radiation: Induction Chemotherapy-Based Patient Selection

Five phase II trials (Table 6) administered induction chemotherapy to select the most favorable patients: early responders. None excluded T4, N3, or smokers, and only one used the SOC induction regimen of docetaxel/cisplatin/fluorouracil. Radiation was attenuated for those with complete response (CR) or partial response (PR) to induction. In ECOG E1308, responders to induction cisplatin/paclitaxel/cetuximab received 54Gy with cetuximab; cohort 2-year PFS of 80% fell short of the target (85%), but was 96% for the AJCC7 T1-T3 N1-N2B and <10 PYSH subset.[86] The University of California multi-institutional trial administered induction carboplatin/paclitaxel followed by paclitaxel with 54Gy if CR/PR or 60Gy RT if <PR/no response); it reported 92% 2-year PFS (three of four failures were in 60Gy patients with minimal response to induction, one failure in a 54Gy patient with PR).[87] On OPTIMA, low-risk and high-risk patients received induction carboplatin/nab-paclitaxel followed by both response- and risk-adjusted therapy ranging from 50Gy RT alone or 45Gy CRT in responders, to 75Gy CRT in non-responders; 2-year PFS was 94.5% for the entire cohort.[78–79] OPTIMA II added immunotherapy to the induction regimen, and early results reported 96.3% 2-year PFS in low-risk patients with 50% tumor shrinkage; 2-year PFS fell to 85.8% in low-risk patients with 30 but <50% response or high-risk patients with 50% response, although median follow-up was less than two years.[73–74] The Quarterback Trial administered induction docetaxel/cisplatin/fluorouracil and randomized responders by HPV-genotype to carboplatin with SOC 70Gy versus 56Gy; 2-year PFS with 56Gy was 84.4% [95% CI 66.5–93.2] with all recurrences occurring in high-risk patients with T4, N2c, ECE, or non-HPV16 disease.[88–89] Overall, two-year PFS appears to approximate 90% with induction chemotherapy and reduced-dose RT in patients with good response to induction therapy without high-risk features.

Summary

Induction-based dose-reduction seems to achieve favorable outcomes, but critics question whether the toxicity of neoadjuvant chemotherapy followed by reduced-dose CRT truly constitutes deintensification. Incidence of grade 3+ mucositis was 63% with definitive CRT on TROG 12.01 compared to 56% and 63% with induction plus 54Gy or 45Gy CRT on E1308 and OPTIMA, respectively.[29,78,86] In contrast, grade 3 mucosal toxicities occurred in 34% with upfront dose reduction to 60Gy CRT on the UNC/UF trial.[82] However, induction offers advantages of incorporating *in vivo* tumor behavior into the algorithm and extends eligibility to a broader spectrum of more advanced-stage HPV+ OPC patients typically excluded from other trials. Upfront dose-reduction could be considered with smaller volume disease, but induction with response-guided reduced-dose CRT could be considered for more advanced HPV+ OPC.

Despite abundant data from phase II studies showing 2-year PFS on the order of 85–95% and OS over 90% with modest RT dose reductions from 45–60Gy, it is important to note that

there is yet no level one evidence.[17,78,82–84,86–88] ASCO issued a statement that de-escalated RT should only be administered on protocol.[15] Nevertheless, two NCDB analyses revealed that ~15% of HPV+ OPC patients received de-escalated RT doses <66Gy, with the vast majority presumably treated off of protocol and without the associated extensive eligibility workup, multidisciplinary discussion, and close surveillance typical of clinical trials.[90–91]

Controversies in Deintensification

Small-volume primary T1–2N1 HPV+ OPC

Four historical RCTs which included small-volume AJCC7 T1–2N1 OPC patients showed LRC, DMFS, PFS, and CSS benefits with concurrent cisplatin over RT alone.[92–96] Because AJCC7 T1–2N1 OPC comprised only a minority of patients and the studies preceded the discovery of the prognostic relevance of HPV in OPC, the utility of these data was limited and chemotherapy use for AJCC7 T1–2N1 HPV+ OPC has been inconsistent--even amongst experts. Current National Comprehensive Cancer Network Guidelines favor TORS with risk-adapted adjuvant therapy or RT alone for these patients; CRT is assigned a category 2b recommendation. In contrast, United Kingdom National Multidisciplinary Guidelines recommend CRT for T1N1 OPC.[97] While there is no level one evidence in HPV+ OPC, there is strong level one evidence that chemotherapy improves DMFS, PFS, and OS versus RT alone in EBV-associated T1–2N1 nasopharyngeal cancer.[98] According to four different medical, surgical, and radiation professional societies, the SOC for AJCC7 T1-T2N1 HPV+ OPC includes the option of CRT after careful consideration (Table 7).[99–102]

AJCC7 Stage III OPC (T1–2N1, T3N0–1) encompassed a heterogeneous population with various treatment options and consequently wide practice patterns. Although guidelines reveal discrepancies amongst experts on chemotherapy in the small-volume AJCC7 T1–2N1 subset, in practice most received CRT. An NCDB analysis showed that 70% (2379 of 3399 patients) of T1–2N1 OPC received CRT, with no evidence that patients with HPV+ versus HPV-negative (HPV-) OPC benefitted differentially from chemotherapy.[103] With AJCC8, N1 expanded to include any ipsilateral LNs <6 cm and ≤4 LNs (formerly AJCC7 N1–2B). Despite downgrading of T1–2N1 from Stage III in AJCC7 to Stage I in AJCC8, contemporary data still suggest a benefit with chemotherapy. An NCDB study of HPV+ OPC confirmed a survival detriment with RT alone compared to CRT in AJCC8 Stage I patients (HR 1.798, 95% CI 1.064–3.039, P=0.029).[104] And among all AJCC7 T1–2N1 HNC in the NCDB, subset analysis actually showed the greatest survival benefit with CRT in OPC (HR 0.74, 95% CI 0.65–0.85, P <0.001).[103]

The majority of recent randomized deintensification trials administered CRT as SOC for AJCC7 T1–2N1 HPV+ OPC (Table 8), and all retained CRT as the SOC. Subset analysis from De-ESCALaTE revealed that even AJCC8 stage I/II HPV+ OPC (n=276) had a 5% 2-year OS advantage with cisplatin over cetuximab (98.4% versus 93.2%, p=0.043).[16] On HN002, two of ten T1N1 patients treated with RT alone experienced LRF.[17] The International Collaboration on Oropharyngeal Cancer Network for Staging found no difference in 5-year OS between AJCC7 N0, N1-N2A, and N2B HPV+ OPC patients: 80% (95% CI 73–87) versus 87% (95% CI 83–90) versus 83% (95% CI 80–86), respectively.[105]

This reflects shortcomings of nodal staging to stratify risk, with N1 HPV+ OPC patients having comparable prognosis to N2 patients (for whom chemotherapy is the consensus).

Although limited, the available evidence suggests that omitting or de-escalating chemotherapy from RT in AJCC7 T1–2N1 HPV+ OPC results in inferior outcomes. The next generation of randomized deintensification trials (like HN005) administers HD cisplatin with RT as their SOC. There are differing opinions among experts, but the randomized trials which included these patients consistently showed superior outcomes when HD cisplatin was administered with RT. Ultimately, since distant metastasis is their predominant mode of failure, chemotherapy should be considered in eligible AJCC7 T1–2N1 patients.

Bulky, very locally advanced T4 or N3 HPV+ OPC

The inclusion of very advanced (T4 or N3) patients in deintensification studies was variable (Table 8). Subset analysis of T4 or N3 patients from De-ESCALaTE showed dismal 2-year OS with cetuximab versus cisplatin (67.1% vs. 93.3%, p=0.03).[16] E1308 and Quarterback did not meet the target 92% 2-year PFS thresholds, largely due to poor outcomes in T4 patients.[86,88] Given these patients' propensity for DM and LRF, many trials escalate treatment in this cohort (e.g. KEYCHAIN, NCT03383094, is randomizing T4 or N3 HPV+ OPC patients to SOC 70Gy CRT with or without concurrent/adjuvant pembrolizumab). Considering their poor prognosis with cetuximab and their inclusion in treatment escalation trials, caution should be exercised before considering these patients for deintensification.

Smokers

Smoking was a defining factor in the original RTOG RPA and is believed to negate some of the prognostic benefits of HPV positivity.[4,106] However, there is dissonance on the impact of smoking and it was ultimately not included into the AJCC8 staging system. Subset analysis of MARCH patients with known p16 and smoking status from four RCTs showed that p16+ former/current smokers had significantly worse PFS (HR 0.49, 95% CI 0.33–0.75) and an 18,7% 5-year OS detriment compared to never smokers.[107] In contrast, a more contemporary multi-institutional RPA demonstrated that only current smokers experienced 2-year PFS below 91%, and any PYSH former smokers experienced 2-year PFS over 91%.[108] Another RPA projected that AJCC7 T1–2N0–1 HPV+ OPC with 20 PYSH would fall into RPA-I with 89% 5-year OS, while the same patient with >20 PYSH would fall into RPA-II with 64% 5-year OS.[109] In contrast, a nomogram based off RTOG 0129, RTOG 0522, and RTOG 9003 estimates that an AJCC7 T1–2N0–1 p16+ OPC nonsmoker or smoker should achieve 5-year OS of ~88% or 87% respectively.[110] Ultimately, smoking is an eligibility factor for some trials and not others (Table 8). E3311 patients were stratified by PYSH, and >10 versus 10 PYSH smoking did not affect PFS on subsequent analysis.[45] Even more recent analysis of outcomes on E3311 showed no significant PFS or OS differences when comparing current versus former smokers.[111] Thus, the 10 PYSH rule may not apply to all early-stage HPV+ OPC, and former smokers can likely be included on deintensification trials but treatment should be stratified by smoking history when feasible.

Lessons Learned from Modern Deintensification Trials

HPV disrupts staging and inspires evolution in treatment paradigms, but is it enough to guide de-escalation?

It is widely accepted that HPV+ OPC constitutes a distinct clinical entity with more favorable biology and treatment responsiveness than their HPV-counterparts.[112–113] Multiple meta-analyses have reported a 28–66% reduced risk of death in HPV+ OPC.[107,114–116] Six RCTs with post-hoc stratification of HPV status (RTOG 0129, RTOG 0522, TROG 02.02, TAX 324, RTOG 9003, PET-NECK) showed improved OS (HR 0.49) and disease-free survival (DFS) (HR 0.41) in HPV+ OPC cohorts.[117–118] However, it is important to note that not all HPV+ OPCs are equally favorable, outcomes are heterogeneous, and de-escalation may thus compromise outcomes for some patients. Genotypic heterogeneity has been identified, with The Cancer Genome Atlas and Quarterback Trial corroborating inferior outcomes with non-HPV16 sutypes.[88,119] However, most trials do not mandate HPV subtyping and positivity on p16 immunohistochemistry is considered an adequate surrogate for HPV+ disease (although p16 immunohistochemistry does not discriminate between HPV16 and non-HPV16 subtypes). P53 mutations are enriched in recurrent/metastatic HPV+ OPC and PIK3CA mutation may be a biomarker of more aggressive disease.[120–121] Additionally, there is a 2.6-fold greater risk of death in black versus non-Hispanic white patients after adjustment for HPV status.[122] These findings underscore risk variations not captured by P16 status alone.

Given limitations of the staging system to discriminate risk, stage-based empirical deintensification efforts seem susceptible to failure. As cautionary tale, RTOG 0022 was a trial of accelerated IMRT (66 Gy over 6 weeks) without chemotherapy for the earliest stage AJCC7 T1–2N0–1 OPC patients (unknown HPV status): 2-year LRF was 9% and 2-year DFS was only 82.0%.[123] While 2-year LRF rates of 9% without chemotherapy may seem reasonable at first glance, long-term follow-up of higher stage T1–2N1–2B or T3N0–2B p16+ OPC patients from RTOG 0129 reported 13.5% 8-year LRF with CRT—a metric that would not likely be achieved with 9% LRF sustained in the first two years after RT alone.[5] Additionally, 82% DFS in the first two post-treatment years does not meet the currently accepted 92% threshold. Ultimately, there was no difference in 5-year PFS between AJCC8 Stage I and II patients treated with CRT on RTOG 0129 and RTOG 0522, suggesting that Stage I patients do not have a substantially superior prognosis warranting less therapy.[26]

Finally, the importance of long-term follow-up cannot be overemphasized. A meta-analysis of HPV+ tonsil cancer showed superior PFS to HPV-disease in the first three years that was not sustained at years four or five.[124] The surgical literature estimates 88.7% 5-year CSS for T1–2N0–1 OPC after surgery ± adjuvant RT or CRT.[125] However, when considering deintensification, given the morbidity of salvage, PFS is a critical consideration in addition to CSS. A retrospective study defined the ideal deintensification candidate as a T1–3N0–2C HPV+ OPC patient with 95% 3-year LRC and 93% 3-year DMFS.[126] A viable deintensification approach must achieve excellent outcomes and maintain them on longer follow-up before it can change practice.

Re-examining the Radiation Dose-Response Relationship in HPV+ OPC

Seminal radiation dose-response curves for tumor control probability (TCP) were modeled at the turn of the century, and tonsil cancer curves were observed to be shallow due to underlying tumor heterogeneity. Doses of 55–75Gy achieved LRC rates ranging from ~60–85% for T2 tumors to ~35–70% for T3 tumors (Figure 3a); after accounting for treatment time and stage and assuming LC of 40–80%, each 1Gy increase of dose was estimated to improve TCP by 1.75%.[127] This translated into an effort to escalate dose to maximize outcomes. Of note, these radiobiology models were built upon data from patients treated with RT alone, predating concurrent chemotherapy and the discovery of HPV as a prognostic factor in OPC.

We performed an exploratory analysis to reassess the dose-response relationship in AJCC7 Stage III-IV HPV+ OPC treated with modern definitive CRT. Dose-response relationships between radiation dose and LRC and PFS were analyzed with the Spearman rank correlation test (an ideally suited non-parametric test that does not assume a linear relationship and makes the least assumptions on the data). It yields a p-value (significant at <0.05) and correlation coefficient rho (ranging from −1 to +1). Robustness was performed by using Grubbs's test to remove outliers at a level of $p<0.05$ (two-tailed); no outliers were identified. When plotting TCP for HPV+ OPC patients treated with CRT on modern trials (colored dots), we found no correlation between RT dose and LRC (Spearman's rho=0.009, p=0.978, Figure 3a). We also found no correlation between RT dose and PFS (Spearman's rho=−0.357, p=0.254, Figure 3b). Several notable trends were observed. First, the absolute TCP was much higher than historical rates, approximating 85–100% LRC with 45–70Gy CRT. Second, TCP in the 54–70Gy range appears flat and shallower than the original model (black lines, Figure 3a), suggesting even less of a response to dose-escalation.[127] Finally, the TCP appears to be left-shifted, with high cure rates at lower doses and raising the question: how low can we reduce RT dose in the setting of CRT and still maintain excellent outcomes in HPV+ OPC?

THE FUTURE OF DE-ESCALATION: Intratreatment Response Assessments to Guide Treatment Deintensification

Although most HPV+ OPCs have favorable prognoses, distant metastasis is the predominant mode of failure and often occurs later and sometimes with a more disseminated pattern.[126,128] While p53 mutational status is being used to guide RT de-escalation (NCT03077243, Table 9), no dominant predictive biomarker has been firmly established. However, technological advances in liquid biopsy and imaging allow us to monitor disease responses much earlier--even during treatment. Thus, until we have discovered a better biomarker, currently available tools can be utilized to assess response, personalize treatment, and perhaps even change course if needed.

Circulating tumor HPV DNA

Circulating tumor HPV DNA (ctHPVDNA) holds promise to assess treatment response and early recurrence.[129] A prospective clinical trial of CRT in HPV+ OPC found that post-treatment ctHPVDNA positivity had a 100% negative predictive value, and two

consecutively positive values had a 94% positive predictive value with median 3.9 month lead-time from ctHPVDNA positivity to biopsy-proven recurrence.[130] Of note, approximately 10–20% of patients had undetectable baseline ctHPVDNA and higher pretreatment levels were not associated with prognosis, so the use of liquid biopsy to assess intratreatment response or prescribe treatment is promising but still in need of further study. The ReACT Study (Table 9) will use ctHPVDNA levels to guide RT dose de-escalation in low-risk HPV+ OPC. Memorial Sloan Kettering (Table 9) will use ctHPVDNA to select patients for adjuvant therapy omission in postoperative low/intermediate-risk HPV+ OPC.

Radiomics and Functional Imaging

Another approach harnesses radiomics, using intratreatment imaging to identify early responders. A study from NYU showed that low-risk OPC with 43% nodal decrease on cone-beam computed tomography (CT) by treatment day 20 had superior 2-year LRC.[131] Consequently, NCT03215719 (Table 9) will use interval scan at four weeks to identify responders and adaptively de-escalate to 60Gy in those with >40% nodal shrinkage. NCT03656133 will investigate if the individual patient proliferation saturation index (a mathematical model incorporating pre-treatment CT) can select RT fractionation to increase rapid response (32% volume reduction at 4 weeks) in p16+ AJCC8 T1–3N0–1 OPC. In addition to CT changes, decreased uptake on ^{18}FDG-PET as early as one to two weeks into treatment (at ~10Gy or 20Gy) has also been found to predict PFS and OS in HPV+ OPC.[132–133] NCT03416153 (Table 9) will use pre- and mid-treatment PET to selectively de-escalate patients to 54Gy CRT. Incorporating intratreatment volumetric or functional assessments to guide deintensification offers the advantage of not subjecting patients to extra therapy (i.e. induction chemotherapy), but modest 10–16Gy reductions in RT dose may be insufficient to translate into improved toxicity and QOL compared to SOC therapy. For example, radiation dose goals to swallowing structures were similar with SOC 70Gy on RTOG 1016 versus modest reductions to 54Gy and 60Gy on the CCRO022 and HN002 deintensification trials: oral cavity (mean <30Gy), esophagus (mean <30Gy), and uninvolved pharynx (<1/3 over 50Gy).[15,17,87] More dramatic prescription dose reductions are likely necessary to achieve meaningful dosimetric and clinical toxicity advantages.

There is both preclinical and clinical data to support the consideration of more drastic dose de-escalation. A model using pre- and early-treatment (week four) CT tumor volume dynamics to estimate personalized RT doses was applied to a cohort of HNC patients from Moffitt and MD Anderson Cancer Centers; the in silico trial of dynamics-adapted dose personalization estimated that 77% of patients treated with SOC 66–70Gy were overdosed by an average of 39Gy.[134] Even further beyond this mathematical model predicting that a majority of patients may only need ~30Gy was the most drastic dose de-escalation trial to date which delivered 30Gy to the majority of patients: the 30 ROC trial from Memorial Sloan Kettering. Hypoxic tumors are known to be treatment-resistant and have poor prognosis.[135] The 30 ROC trial utilized functional PET imaging to select more favorable hypoxia-negative patients for drastic RT dose reduction to 30Gy (a 60% reduction from SOC 70Gy). In the pilot trial, nineteen p16+ OPC patients had upfront primary site resection and planned ND 4 months post-CRT; 15 patients had no hypoxia on baseline or early interval ^{18}F-FMISO-PET and were de-escalated to 30Gy CRT.[136] On planned post-30Gy CRT ND,

11 of 15 patients had pathological CR and 2-year LRC and PFS among de-escalated patients was 100% and 92.9%, respectively. Diffusion-weighted MR changes correlated with pathological CR, but tumor volume and ctHPVDNA changes did not. The follow-up Phase II trial enrolled 158 patients with primary site resection but no planned ND after 30Gy CRT; one-year LRC and PFS were 94%, with all 8 nodal recurrences successfully salvaged with surgery.[137] Without induction chemotherapy and by incorporating functional imaging, about 80% of patients received drastically de-escalated therapy. The next cohort of patients on 30 ROC will proceed with hypoxia-guided definitive CRT de-escalation to 30Gy without any surgery at all. The incorporation of early interval, intra-treatment response assessments has the potential to revolutionize the de-escalation paradigm.

Genomics

Given lack of consensus on who and how to de-escalate patients, there is a need to identify novel therapeutic targets and pathways implicated in disease pathogenesis, response, and progression. If the ultimate goal of deintensification is toxicity mitigation, there is still much room to improve the therapeutic ratio by identifying biomarkers of radiosensitivity and perhaps reducing dose in these patients first.[138] Moffitt Cancer Center combined a gene-expression-based radiosensitivity index with the linear quadratic model to generate an algorithm to predict radiation response.[139] The genomic-adjusted radiation dose (GARD) score was significantly associated with time to first recurrence and OS, with a higher score predicting a greater therapeutic effect of RT.[140] Interestingly, total radiation dose was not associated with recurrence or OS, suggesting that inherent tumor biology supersedes the radiation dose-response. Perhaps one of the most impactful uses of the GARD score would be to identify patients for whom radiation de-escalation (or escalation) should be considered. Accordingly, the Moffitt group is developing a trial of genomically-guided dose prescription for HPV+ OPC.[141] In the 30 ROC trial, whole-genome sequencing identified a DNA repair defect predictive of response that was confirmed on an independent cohort from the MC1273 de-escalation study.[136] Moving forward, the combination of biology-driven patient selection and confirmatory intra-treatment assessments seems ideal to personalize therapy and most safely guide de-escalation.

CONCLUSIONS

Although the favorable prognosis of HPV+ OPC changed the staging system, the first-generation of randomized de-escalation trials failed to justify a change in its management. HD cisplatin with RT remains the de facto SOC in HPV+ OPC (RTOG 1016, De-ESCALaTE). For primary management, TORS has more grade 5 toxicity compared to definitive RT (ORATOR2) and appears to have inferior PFS as well (ORATOR2). However, there is promising data that PORT may be de-escalated to 50Gy (E3311) in patients with intermediate-risk features. An RCT (MC1675) compared 30–36Gy BID DART plus docetaxel versus SOC 60Gy PORT (2-year PFS 86.5% versus 95.1%). However, a preplanned pooled analysis (MC1273, MC1675) reported outcomes above accepted PFS thresholds in patients with intermediate-risk features (negative margins, no ECE). Moving forward, an RCT will assess PORT de-escalation to 50Gy with intermediate-risk postoperative factors and establish consensus on chemotherapy guidelines with high-risk

pathology (PATHOS). The data to date suggest that radiation dose may empirically be modestly reduced to 60Gy with concurrent cisplatin in non-bulky HPV+ OPC (HN002, UNC/UF), but level one evidence is years away (HN005). Induction chemotherapy to select early responders may permit RT dose reductions to 45–56Gy (OPTIMA, CCRO-022, E1308, Quarterback) in more advanced HPV+ OPC. However, the utilization of intratreatment assessments may allow de-escalation without induction chemotherapy. Even more drastic RT dose de-escalation with biology-driven tumor characterization via functional hypoxia imaging appears feasible (30 ROC). Although the SOC has not yet changed, there is justifiable optimism that with careful selection criteria, intratreatment response assessments, and sufficient longterm follow-up, one (or more) feasible de-escalation strategies will be established. Table 10 summarizes these findings.

As we await the next generation of deintensification trials, it is important to evaluate lessons learned and clinical gaps identified. Small volume AJCC7 T1–2N1 HPV+ OPC is a cohort whose risk may have been underestimated and is thus at danger for undertreatment. De-ESCALaTE reported inferior outcomes with cetuximab and HN002 confirmed that chemotherapy omission is inappropriate. Although RT alone is recommended by some guidelines, it does not reflect the practice amongst many cooperative groups and experts conducting trials who administer cisplatin with RT as their SOC (HN005,ORATOR2). On the opposite end of the spectrum, some deintensification trials included locally advanced T4 and N3 HPV+ OPC patients. Historically, patients with bulky disease have been considered for treatment escalation (often induction chemotherapy), so it seems that practice trends against deintensification in this group. Finally, risk quantification based on smoking history/ status is in need of further refinement; although those with >10PYSH (and especially current smokers) were considered high-risk, contemporary trials in HPV+ OPC fail to show an impact on PFS and smoking ultimately did not impact staging.

The optimal de-escalation approach remains unknown. While many clinical trials have reported promising results, it should be explicitly noted that the only strategy (chemotherapy attenuation) formally compared against the SOC in RCTs failed. There are ongoing deintensification trials evaluating the efficacy and toxicity of other strategies including radiation dose reduction or TORS to de-escalate adjuvant therapy. However, the adoption of multiple deintensification approaches simultaneously may confound our ability to understand which treatment(s) can be decreased, or potentially, omitted. There is already level two evidence to support various promising de-escalation strategies, but conducting multiple randomized phase three trials powered to confirm non-inferiority of each feasible deintensification method against the SOC is unfortunately not practicable. This raises the question: what level of evidence is required to change clinical practice? In principle, level one evidence would be necessary for de-escalation to become the standard of care. In practice, national registry data demonstrates that clinical management has already changed for some despite the absence of level one evidence; although no radiation deintensification strategy has been proven noninferior to the SOC, one-third of HPV+ OPC patients had received reduced postoperative and ~15% had received reduced definitive RT doses before 2015 (years prior to the publication of recent de-escalation studies).[20,90,91] Given the limitations of national registry data, it is not possible to know whether these reduced doses were due to physician recommendation, patient request, toxicity, or non-compliance.

However, it is important to point out that 69% of patients would not risk a potential 0–5% drop in survival to de-escalate treatment.[142] Alternatively stated, 31% of patients might be willing to risk a potential 0–5% drop in survival to deintensify their therapy. Of note, on the RTOG 1016, De-ESCALaTE, TROG 12.01, and MC1675 phase III trials, PFS decrements ranged from 8.6–13% in the de-escalated compared to the SOC arms.[15,16,29,61] But as practitioners who will be challenged with caring for patients who are ineligible or do not provide informed consent for SOC therapy, how can we navigate which de-escalation strategies are most suitable for clinical practice? Given that a number of potentially viable deintensification approaches have been reported, informed decision-making would rely on patient-specific factors (eligibility for TORS, systemic agents, or radiation), multidisciplinary consensus (all published deintensification trials were multidisciplinary efforts), resources (infrastructure, supplies, clinician expertise), patient preferences, and the data (how well the patient fits the trial eligibility criteria for the deintensification method being employed, multi-institutional studies may have less center-specific biases or be potentially more broadly applicable).

Ultimately, with the discovery of novel biomarkers and the development of new systemic therapies, future trials will eventually redefine and elevate the SOC. In the interim, as deintensification efforts continue, clinical trials and even clinical practice may benefit from utilizing currently available pre-, intra-, and early post-treatment parameters (ctHPVDNA, functional imaging) to better select, monitor, and personalize therapy for patients.

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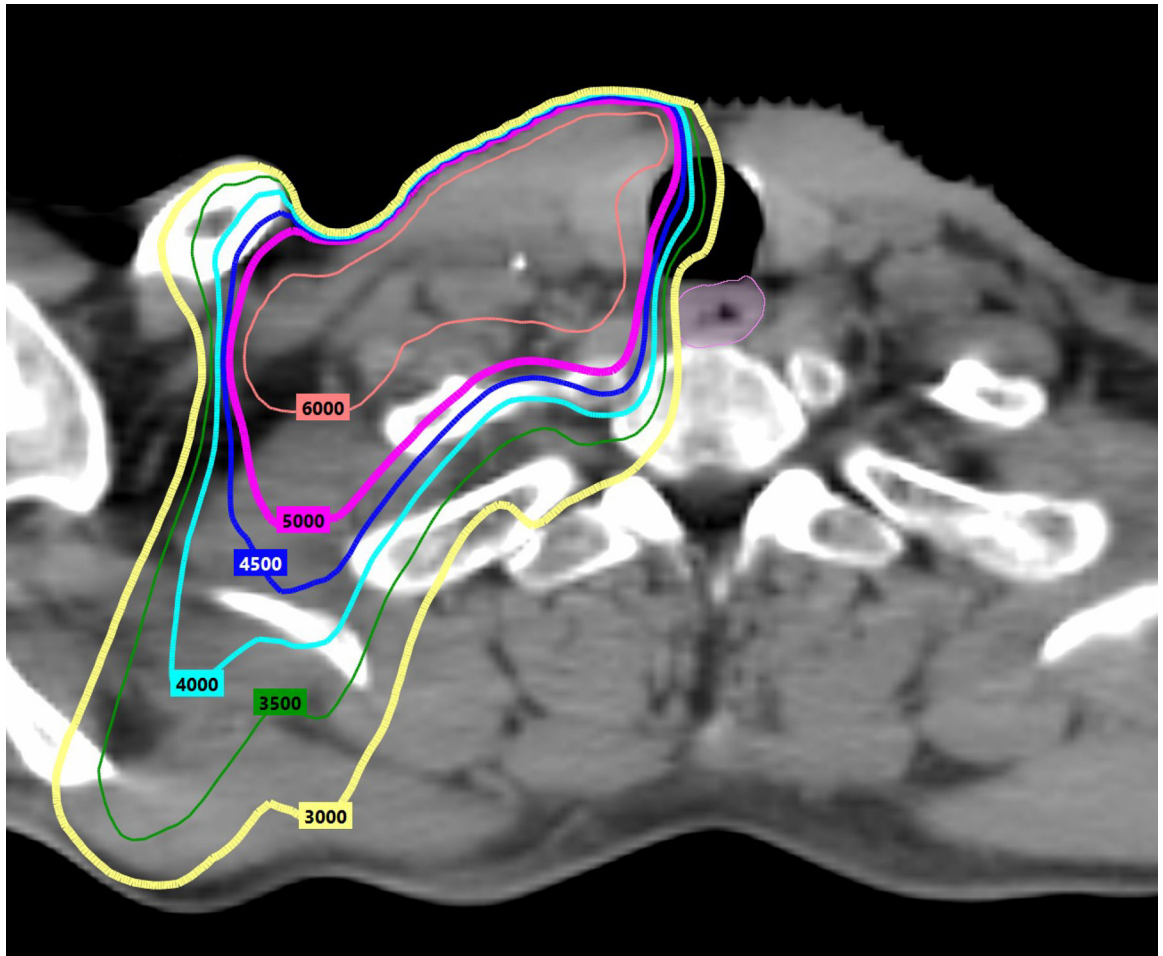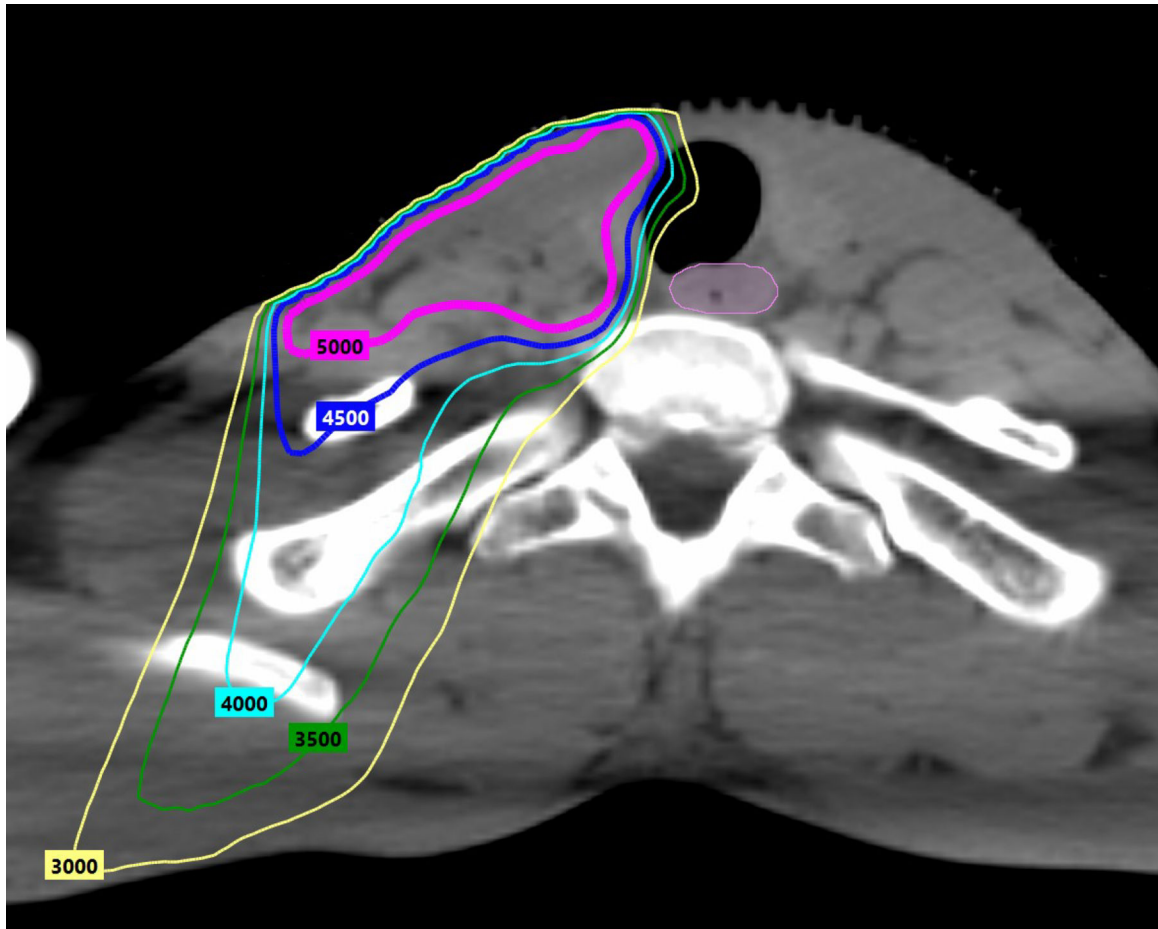
Figure 1.

Radiation dosimetry with standard versus reduced PORT doses. Figure 1a illustrates radiation dosimetry with SOC 60Gy (pink 6000 line) PORT to the neck. Figure 1b illustrates radiation dosimetry with reduced-dose 50Gy PORT to the neck (magenta 5000 line). IMRT can limit medium/high dose scatter to central swallowing structures like the esophagus (pink). There is no notable difference in medium/high dose spillover of 45Gy (blue 4500 line) or 40Gy (teal 4000 line) between 60Gy and 50Gy dose prescriptions.
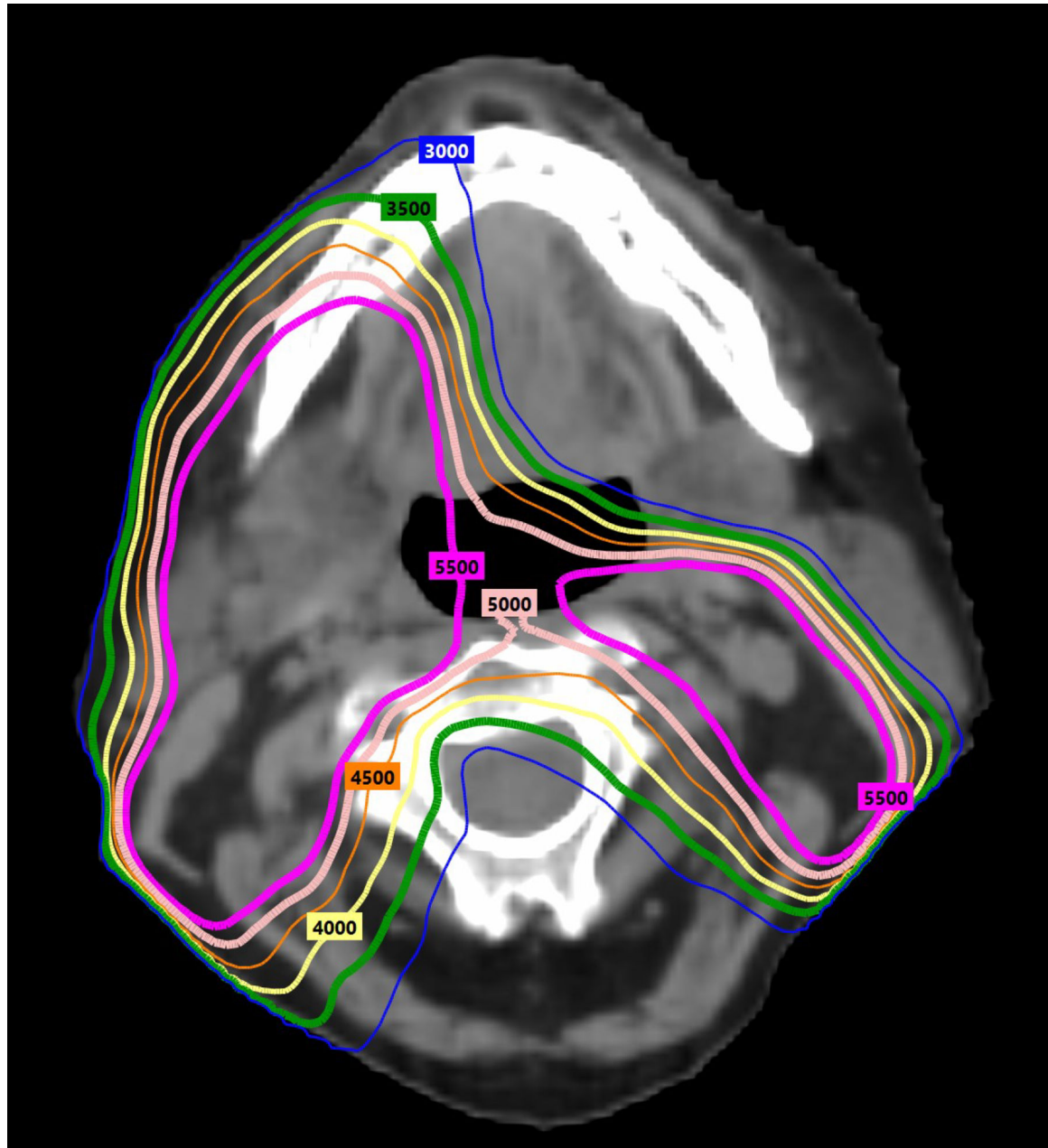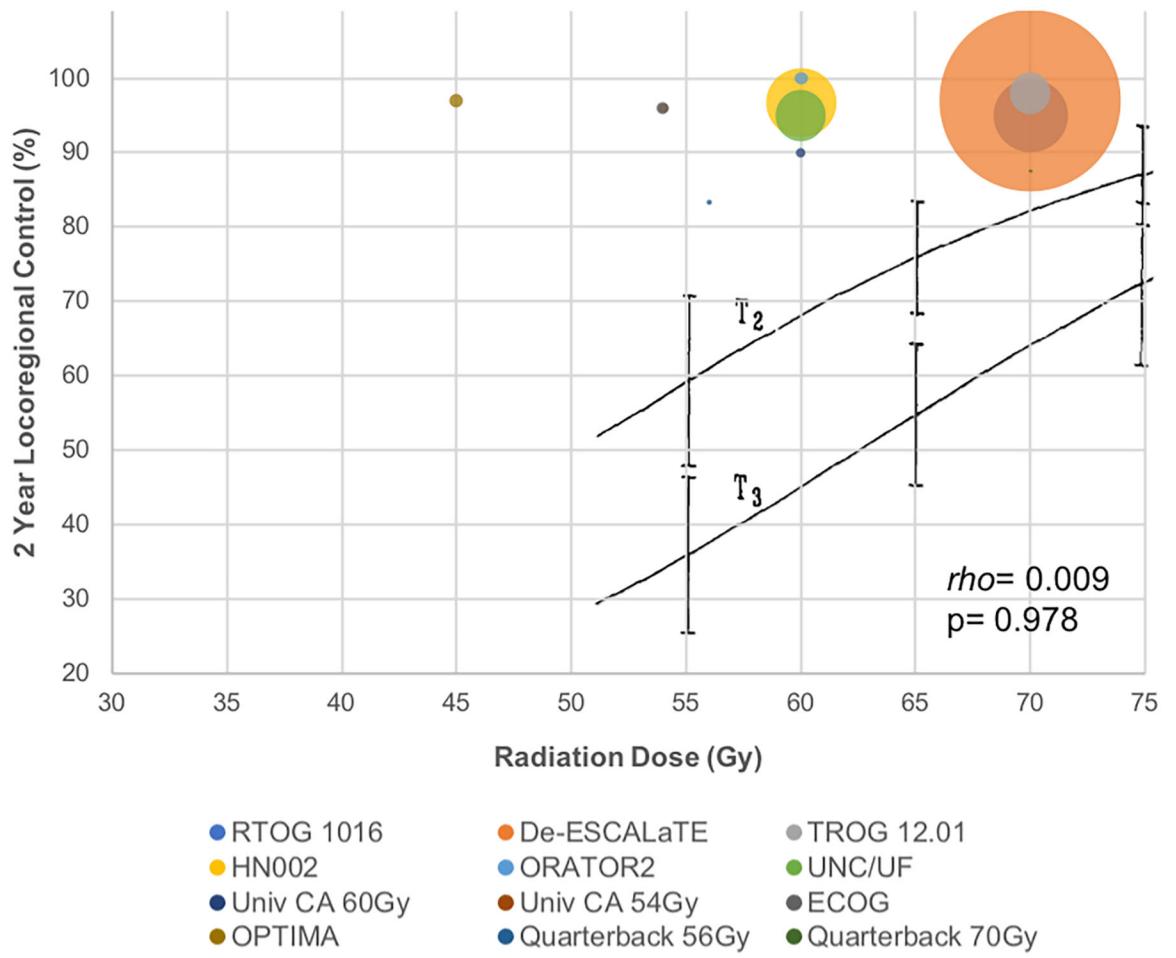
Figure 2.
Radiation dosimetry with nodal irradiation to 56Gy (magenta 5600 line) with inclusion of level IB LNs (left) versus omission (right). There is a drastic difference in anterior oral cavity dose spillover with level IB omission.
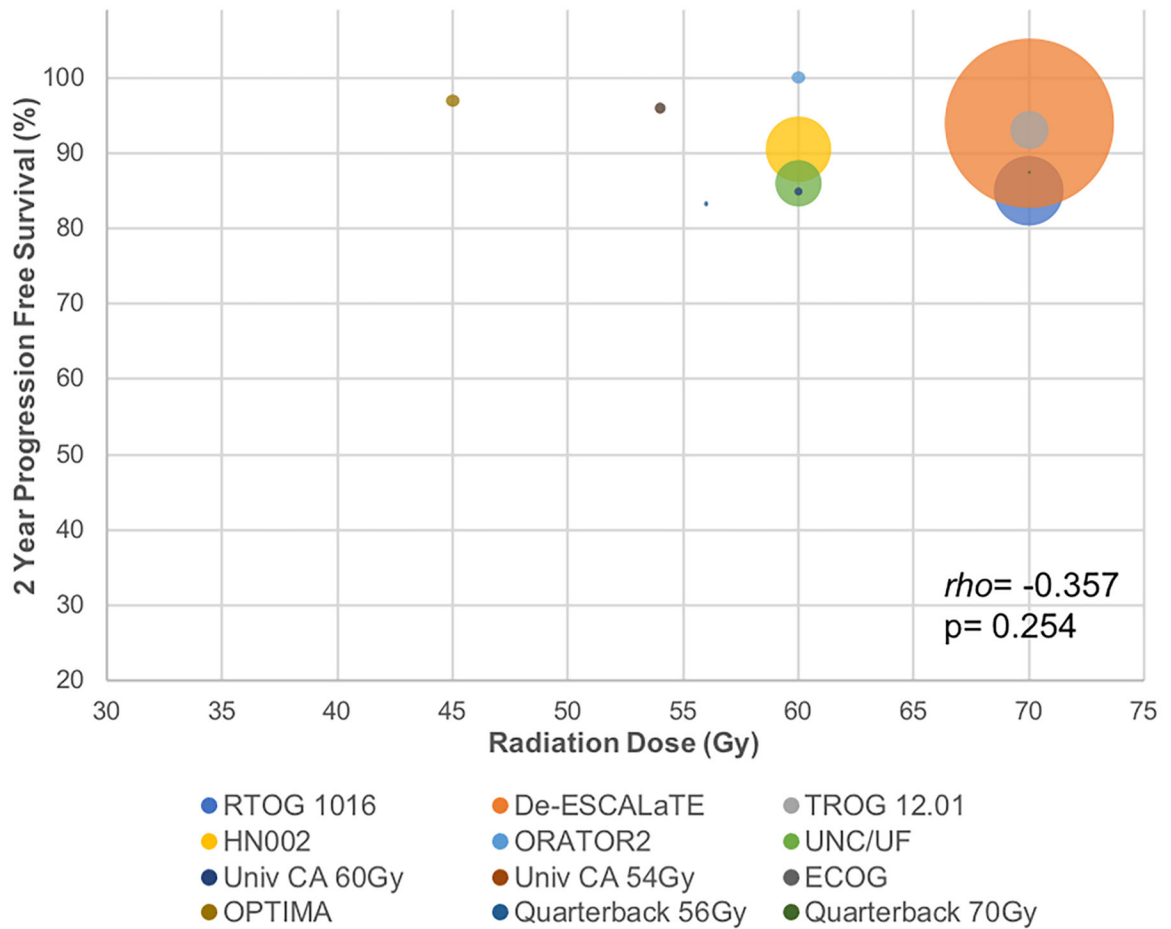
Figure 3.

Tumor control probability (TCP) dose-response curves with definitive chemoradiation in HPV+ OPC.

(**A**) Bubble plot of LRC rates from modern chemoradiation trials (colored circles) shows no relationship between radiation dose and LRC (rho= 0.009, p= 0.978). Superimposed seminal T2 and T3 tonsil cancer TCP curves with radiation (black lines) modeled at the turn of the century[117] (predating concurrent chemotherapy use) show shallow LRC improvements when increasing radiation doses from 55–75Gy.

(**B**) Bubble plot of PFS rates from modern chemoradiation trials show no relationship between radiation dose and PFS (rho= −0.357, p= 0.254).

Table 1.

Chemotherapy Deintensification Trials

Study	Treatment Arms	Outcomes	Toxicities
		Chemotherapy Attenuation	
De-ESCALaTE [16]	**SOC def RT 70Gy** (IMRT, 5 fxs/wk) with:	2 yr PFS (p=0.0007): 94.0% vs. 83.9%, HR 3.4 [1.6–7.2]	Similar overall acute grade 3–5 toxicity: 87.6% vs. 87.9%
(Phase III)	**HD cis 100 mg/m²× 3c** (n=166)	2 yr LRF (p=0.0026): 3% vs. 12%	Similar overall late grade 3–5 toxicity: 29.5% vs. 22.4%
p16+ OPC.	VS.	2 yr DM (p=0.0092): 3% vs. 9%	
AJCC7 T1N1-T4N3, T3-T4N0.	**cetux wkly** (n=168)	2 yr OS (p=0.01): 97.5% vs. 89.4%, HR 5.0 [1.7–14.7]	
If >10 PYSH: N0-N2a.	Median FU = 25.9 months	2 yr OS AJCC8 I/II (p=0.043): 98.4% vs. 93.2%, HR 4.3 [0.9–19.8]	
RTOG 1016 [15]	**SOC def AFRT 70Gy** (IMRT, 6 fxs/wk) with:	5 yr PFS (p=0.0002): 78.4% vs. 67.3%, HR 1.7 [1.3–2.3]	Similar overall acute grade 3–4 toxicity: 81.7% vs. 77.4%
(Phase III)	**HD cis 100 mg/m²× 2c** (n=406)	5 yr LRF (p=0.0005): 9.9% vs. 17.3%, HR 2.1 [1.4–3.1]	Similar overall late grade 3–4 toxicity: 20.4% vs. 16.5%
p16+ OPC.	VS.	5 yr DM (p=0.09): 8.6% vs. 11.7%, HR 1.5 [0.9–2.4]	
AJCC7 T1N2a-T4N3, T3-T4N0-N3.	**cetux wkly** (n=399)	5 yr OS (p=0.0163): 84.6% vs. 77.9%, HR 1.4 [upper CI 2.1]	
Any PYSH.	Median FU = 4.5 years	5 yr OS AJCC8 I (p=NS): 92.4% vs. 85.9%	
TROG 12.01 [29]	**SOC def RT 70Gy** (IMRT, 5 fxs/wk) with:	3 yr PFS (p=0.015): 93% vs. 80%, HR 3.0 [1.2–7.7]	No difference in primary endpoint of symptom severity.
(Phase III)	**LD cis 40 mg/m²× 7c** (n=92)	3 yr LRF (p=0.11): 2% vs. 8%, HR 3.4 [0.7–16.6]	Similar acute Grade 3 dysphagia: 50% vs. 46%
p16+ OPC.	VS.	3 yr DM (p=0.018): 3% vs. 12%, HR 4.1 [1.2–14.9]	Similar acute Grade 3 oral mucositis: 63% vs. 72%
AJCC7 T3N0-N2c, T1-T2 N2a-N2c;	**wkly cetux** (n=90)	3 yr OS (p=0.32): 98% vs. 96%, HR 2.3 [0.4–12.7]	No difference in enteral feeding: 61% vs. 58%
excluded N2b-N2c if >10 PYSH.	Median FU = 4.1 years	AJCC8 I subset : 13 events, 121 pts, HR ~2.5	
		Immunotherapy	
NCT03410615 /*CCTG HN.9* [34]	**SOC def CRT (70Gy + HD cis 100 mg/m2 × 3c)**	Ongoing, not reported	Ongoing, not reported
(Phase II, randomized)	VS.		
p16+ OPC.	**durva + RT** + (adj durva or tremelimumab+durva)		
AJCC7 T1–3 N2 (any PYSH);			
if 10PYSH: T1–2N1 or T3N0–1.			
NRG-HN005	**SOC def CRT (70Gy+HD cis × 2c)**	Ongoing, not reported	Ongoing, not reported

Study	Treatment Arms	Outcomes	Toxicities
(Phase II/III) p16+ OPC. AJCC7 T1–2 N1–2B, T3 N0–2B. <10 PYSH.	VS. **Reduced dose def CRT (60Gy+HD cis × 2c)** VS. **Reduced dose def RT + IO (60Gy+nivolumab)**		
MDACC / NCT03799445 (Phase II) p16+OPC. AJCC7 T1N2A-2CM0, T2N1–2CM0	**Reduced def RT (50–66 Gy) with:** **Anti-CTLA4 (ipilimumab) +** **Anti-PD-1 (nivolumab)**	Ongoing, not reported	Ongoing, not reported
Chemotherapy Omission			
NRG-HN002 [17] (Phase II, randomized) p16+ OPC. AJCC7 T1–2 N1–2b, T3 N0–2b. <10 PYSH.	**Reduced dose def CRT** **(60Gy IMRT + LD cis 40 mg/m² × 6c, n=157):** VS. **AFRT alone (60Gy/5 wks IMRT, n=149):** 19.9% Unilateral RT. 80.1% Bilateral RT. Median FU = 2.6 years	Null hypothesis 2 yr PFS 85%: - CRT 90.5% [84.5–94.7], p=0.0350, rejecting null hypothesis - AFRT 87.6% [81.1–92.5], p=NS, failing to reject null hypothesis 2 yr LRF (p=0.02): 3.3% vs. 9.5%, HR 2.56 [1.11–5.88] 2 yr DM (p=0.58): 4.0% vs. 2.1%, HR 0.70 [0.20–2.50] 2 yr OS (p=0.93): 96.7% vs. 97.3%, HR 1.05 [0.34–3.23]	Higher acute toxicity with CRT. Acute Grade 3–4 (p<0.001): 79.6% vs. 52.4% Late Grade 3–4 toxicity similar (p=NS): 21.3% vs. 18.1%
Osaka Multicenter [38] (Phase II) p16+ and HPV+ OPC. AJCC7 Stage III/IV. T1N1, T4, and N3 excluded. Any PYSH.	**SOC def RT (IMRT, n=39).** **70Gy/35 fxs or 70.4Gy/32fxs.** **No chemo.** Median FU = 51 months	2/3 yr PFS: 94% [81–99] / 89% [74–96] 2/3 yr OS: 100% / 97% [84–99] 2yr cumulative incidence of DM: 5% [1–15]	Acute grade 3 mucositis: 26% Acute grade 3 dysphagia: 18% No late grade 3 toxicity.

AFRT= altered fractionation radiation therapy, AJCC7=American Joint Committee on Cancer 7th Edition, AJCC8=American Joint Committee on Cancer 8th Edition, c=cycles, cetux=cetuximab, cis=cisplatin, CRT=chemoradiation therapy, def=definitive, DM=distant metastasis, durva=durvalumab, FU=follow-up, fxs= fractions, Gy=gray, HD=high-dose, HR=hazard ratio, IMRT=intensity-modulated radiation therapy, LD=low-dose, LRF= locoregional failure, NS=not significant, OPC= oropharyngeal cancer, OS=overall survival, PFS=progression-free survival, PYSH=pack-year smoking history, RT=radiation therapy, SOC=standard of care, wk=week, wkly=weekly, yr=year.

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Table 2.

Surgical Trials: TORS to Replace Definitive RT

Study	Treatment Arms	Outcomes	Toxicities
ORATOR [54–56]	**SOC def RT 70Gy ± chemo** (n=34)	For p16+ subset (88% of pts in both arms):	RT patients had superior (but not clinically meaningful)
(Phase II, randomized)	- Chemo for N1–2 (n=23, 68%), HD cis preferred.	3 yr PFS: 96.3% [76.5–99.5] vs. 93.3% [75.9–98.3], p=0.32	swallowing-related QOL (p=0.049).
Resectable OPC.	vs.	3 yr OS: 96.3% [76.5–99.5] vs. 90.0% [72.1–96.7], p=0.58	RT pts had more dry mouth over time (p=0.0491).
AJCC7 T1-T2 (4 cm),	**TORS+ND ± SOC 60Gy PORT ± chemo** (n=34)		TORS patients used more nutritional supplements at 3 yrs (p=0.015).
N0-N2, any PYSH.	- PORT for: <2 mm margin, 1 LN, +LVI, T3		
	Median FU = 45 months		
ORATOR2 [57]	Stratified by PYSH, then 1:1 randomization:	2 yr PFS: 100% [100–100] vs. 83.5% [60.8–93.7]	1 yr mean MDADI scores (P = 0.85):
(Phase II, randomized)	**Reduced def RT 60Gy ± chemo** (n=30)	2 yr OS: 100% [100–100] vs. 89.1% [69.6–96.4]	RT: 85.7 ± 15.6 vs. TORS: 84.7 ± 14.5
p16+ or HPV+ OPC.	- LD cis (40 mg/m²) for LN+ (n=21, 72%)	p-values not reported for OS and PFS comparisons.	
AJCC8 T1-T2 (4 cm),	vs.	Trial was reported with immature survival outcomes.	N=1 in each arm required a peg, none at 1 year.
N0-N2, any PYSH.	**TORS + ND ± Reduced PORT 50–60Gy** (n=31)	Trial closed to accrual in November 2020 due two treatment-	
	- 60Gy: +margin or +ECE	related deaths from complications in the TORS arm.	Grade 2–5 toxicities: RT 67% vs. TORS+ND 71%
	- 50Gy: <3mm margin, >1 LN, LN > 3cm, LVI, T3	All 4 PFS events occurred in TORS arm (1 bleed, 1 cervical	-significantly more anorexia and dysgeusia in the RT arm
	Median FU = 17 months	osteomyelitis, 1 myocardial infarction, 1 local recurrence).	
Comparativeness Effectiveness Trial/	TORS + ND +/– 56–66Gy adj CRT	Ongoing, not reported	Ongoing, not reported
NCT03691441. (Phase IV)	vs.		
p16+ OPC resectable by TORS.	SOC def CRT 70–72Gy		
AJCC7 T1N2a-c, T2N1–2c, T3N0–2c.	HD cis preferred.		
NECTORS [71–72]	Experimental (n=55):	5 yr PFS (p=0.03):	Peg-dependence 12 months post-treatment (p < 0.0001):
(Phase II)	NAC (cis 75 mg/m² + doce) → TORS + selective ND	- NAC + S: 96.1% [90.8–100]	0% NAC+TORS vs. 24.5% CRT
p16+ OPC.		- CRT historical cohort: 67.6% [50.7–84.5]	Severe Grade 3+ events:

Study	Treatment Arms	Outcomes	Toxicities
AJCC7 T1–4N0–2c.	CRT historical cohort (n=145): HD cis + IMRT. Median FU 20.4 months.	Pathologic CR rates: 72% primary and 57% nodal. Only 2 of 55 TORS pts received adj CRT.	12.7% NAC+TORS vs. 24.6% CRT
OPTIMA II[73-74] (Phase II) p16+ and HPV+ OPC. LR: T1-T2 non-bulky tonsil or well-lateralized BOT ≤3 cm, non-bulky N2A-2B with ≤2 non-lower neck LNs measuring ≤5 cm. HR: T4, N2C-3, >20 PYSH, or non-HPV16 subtype.	**NAC carbo/nab-pacl/nivolumab x3c** → RECIST response: De-escalated treatment administered in 84.9%. LR with ≥50% reduction: - **TORS+selective ND** (n=9) - **Reduced dose def RT 50Gy**(n=28): did not qualify for/refused TORS	Among 9 TORS patients, 66.7% had pCR.	1 patient died during NAC.

adj=adjuvant, AJCC7=American Joint Committee on Cancer 7th Edition, AJCC8=American Joint Committee on Cancer 8th Edition, chemo=chemotherapy, cis=cisplatin, CRT=chemoradiation therapy, def=definitive, ECE=extracapsular extension, FU=follow-up, Gy=gray, HD=high-dose, IMRT=intensity-modulated radiation therapy, LD=low-dose, LN=lymph node, LVI=lymphovascular invasion, NAC=neoadjuvant chemotherapy, ND=neck dissection, NS=not significant, OPC= oropharyngeal cancer, OS=overall survival, +=positive, peg=percutaneous endoscopic gastrostomy, PORT=postoperative radiation therapy, PFS=progression-free survival, PYSH=pack-year smoking history, RT=radiation therapy, SOC=standard of care, TORS=transoral robotic surgery, wkly=weekly, wks=weeks, yr=year.

Table 3.

Surgical Deintensification Trials: TORS to Deintensify Adjuvant Therapy

Study	Treatment Arms	Outcomes	Toxicities
ECOG-ACRIN E3311 [45]	**TORS+ND → risk-adapted adj therapy:**	2 yr PFS OBS: 96.9% [90%CI 91.9–100] VS.	Grade 3 toxicity:
(Phase II)		50Gy: 94.9% [90%CI 91.3–98.6]	OBS 17%
Resected HPV+ OPC.	**LR** (T1–2N0–1, 3mm margin, no ECE/PNI/LVI) → **OBS** (n=38)	60Gy: 96.0% [90%CI 92.8–99.3] VS.	50Gy: 15%
AJCC7 T1–2N1–2b with RFs:	**IR → SOC PORT 60Gy** (n=108) *vs.* **Reduced PORT 50Gy** (n=100)	60–66Gy CRT: 90.7% [90%CI 86.2–95.4]	60Gy: 24%
IR: close margin <3 mm, PNI, LVI, LN>3 cm,	**HR → SOC adj CRT 60–66Gy + LD cis 40 mg/m²wkly** (n=113)	2 yr OS OBS: 100% VS.	60–66Gy CRT: 61%
2–4 LNs, or 1 mm ECE		50Gy: 99.0% [90%CI 9.3–100] VS.	
HR: +margin, ECE >1mm, 5 LNs	Median FU = 35 months	60Gy: 98.1% [90%CI 95.9–100] VS. 60–66Gy CRT: 96.3% [90%CI 93.3–99.3]	PROs did not differ between 50Gy and 60Gy PORT.
Mayo MC1273 [58–59]	All had surgery + ND with margin neg resection. 95% TORS.	2 yr PFS: 91.1% overall, 97.2% IR, 86.0% HR	1 patient required a peg.
(Phase II)	**DART + wkly doce for all.**	2 yr LRC: 96.2% overall, 100.0% IR, 93.0% HR	0% grade 3 or worse toxicity 2 yrs after treatment.
p16+ OPC resected with neg margins AND 1 RF:	**IR** (n=37) → **30Gy** (1.5Gy BID)	2 yr OS: 98.7% overall, 100.0% IR, 97.7% HR	
IR: T3, N2, PNI, LVI	**HR** (n=43) → **36Gy** (1.5Gy BID/1.8Gy BID SIB)	2 yr DMFS: 94.9%	
HR: ECE			
AJCC7 Stage III/IV, 10 PYSH.	Median FU = 35.7 months	21% of HR ECE pts recurred (5 of 9 distant)	
DART-HPV/MC1675 [61–62]	**IR:**	2 yr PFS: 86.5% DART vs. 95.1% SOC	Grade 3 toxicity at 3 months (p=0.058):
(Phase III)	**DART 30Gy + wkly doce** (n=53)	2 yr LRRFS: 95.5% DART vs. 97.9% SOC	1.6% DART vs. 7.1% SOC
p16+ OPC resectable by TORS.	VS.	2 yr OS: 96.1% DART vs. 97.0% SOC	
Neg margins (2 excisions to clear a margin edge)	**SOC 60Gy + LD cis 40 mg/m²wkly** (n=26)	If pN2 and +ECE:	Pegs (p<0.0001):
AND at least one risk factor:		- 2 yr LRC 77.0% DART vs. 100% SOC	1.6% DART vs. 27.4% SOC
IR: T3, N2, PNI, LVI	**HR:**	- 2 yr DMFS 59.4% DART vs. 100% SOC	
HR: ECE	**DART 36Gy + wkly doce** (n=77)	- 2 yr PFS 42.9% DART vs. 100% SOC	

Study	Treatment Arms	Outcomes	Toxicities
AJCC7 Stage III/IV, 10 PYSH.	VS. **SOC 60Gy + LD cis 40 mg/m²·wkly** (n=38)	If pN0–1 and +ECE: - 2 yr LRC 95.8% DART vs. 100% SOC - 2 yr DMFS 96.4% DART vs. 95.8% SOC - 2 yr PFS 89.6% DART vs. 95.8% SOC ***MC1273/MC1675 pooled analysis, 2 yr PFS:*** ECE+: 85.2% [78.6%–92.5%] ECE+/pN1: 92.5% [86.9%–98.5%] ECE+/pN2: 54.5% [36.4%–81.7%] No ECE: 97.7% [94.6%–100.0%] No ECE/pN0–1: 97.5% [94.7%–100.0%] No ECE/pN2: 100.0%	
***SIRS Sinai Robotic Surgery Trial*/ NCT02072148** (Parallel Assignment) p16+ and HR HPV subtype (16/18/33/35,etc) OPC. AJCC7 T1–2N0–2b. IR: <1 mm margin tonsil, <1 mm margin tongue, LVI, PNI, <3 LNs, 1 mm ECE HR: 3 +LNs, >1 mm ECE, contralateral or supraclavicular LNs	TORS, and then based on pathology (n=200): - **LR** (>1 mm margin for tonsil, >3 mm margin for tongue, no LVI, no PNI, <3 +LNs, no ECE, no matted/level IV/level V LNs): **OBS** - **IR: 50Gy Reduced PORT** - **HR: 50Gy Reduced PORT + LD cis 40 mg/m²·wkly** - **HR incomplete resection** (+margins, >1 mm ECE, matted LNs): **56Gy Reduced PORT + LD cis 40 mg/m²·wkly**	Ongoing, not reported	Ongoing, not reported
***Univ of Pittsburgh*/NCT03715946** (Phase II) p16+ OPC resected by TORS. T0–3 with at least 1 IR factor. <10PYSH: >N2b (>5 LNs), >1 mm ECE, +margin >10PYSH: N2, > 1 mm ECE, +margin	**Reduced PORT (45 or 50Gy)** + immunotherapy (concurrent+adj nivolumab)	Ongoing, not reported	Ongoing, not reported
***Minimalist Trial(MINT)*/ NCT03621696** (Phase II) p16+ or HPV+ OPC, resectable by TORS. AJCC8 I-III.	**LR** (neg margin, no T4, no N3): **42Gy Reduced PORT** **IR** (+margin or ECE): **42Gy Reduced PORT + HD cis x1c** **HR** (T4 or N3): **SOC 60Gy adj PORT + HD cis x3c**	Ongoing, not reported	Ongoing, not reported

Study	Treatment Arms	Outcomes	Toxicities
PATHOS / NCT02215265 (Phase III) p16+ and HPV+ OPC. AJCC7 T1–3 N0–2B.	**TORS → risk-adapted adj therapy:** T3, N2a or N2b, +PNI, +LVI, 1–5 mm margin: **SOC 60Gy PORT vs. 50Gy Reduced PORT** +ECE or +margin: **SOC 60Gy PORT ± cis (HD or LD)** No risk factors: **OBS**	Ongoing, not reported	Ongoing, not reported
AVOID [63] (Phase II) HPV+ OPC resected by TORS, **pT1–2N1–3, neg margin (≥ 2 mm), no PNI, no LVI.**	**Omission of PORT to resected primary site (n=60).** SOC 60–66Gy PORT to at-risk neck. Chemo for ECE. - LD cis 40 mg/m2 wkly (n=9); HD cis (n=2); cetux (n=2) Median FU= 2.4 years	2 yr PFS: 92.1% [80.2–97.0]. 2 yr LRC: 97.9% [86.1–99.7] 2 yr RRFS: 97.9% [86.3–99.7] 2 yr DMFS: 96.2% [85.5–99.0] Only 1 of 60 pts recurred at the omitted primary site	No pegs during RT. - 2 pegs (3.3%) due to surgery for recurrence with soft tissue necrosis, both at 3 months after RT. Both pegs subsequently removed.
ADEPT / NCT01687413 (Phase III) p16+ OPC. AJCC7 T1–4a N1–3. TORS + ND with neg margin and must have +ECE.	**Omission of adjuvant chemo in +ECE patients:** **SOC PORT (60Gy) VS. CRT (60Gy + LD cis 40 mg/m²wkly)**	Trial terminated due to poor accrual	Trial terminated due to slow accrual
ADAPT/ NCT03875716 (Phase II) p16+ or HPV+ OPC, resectable by TORS. AJCC8 cT0-2N0–1, ≤20PYSH. IR: >2 LNs, <15 LNs dissected, +Level IB/IV/V LN, ≤1 mm ECE, close margins, or +contralateral LN. HR: >1 mm ECE or microscopic +margin.	**Omission of adjuvant chemo in +ECE or +margin patients:** LR (pT0–2N0–1, neg margin, no ECE, 2 LNs in Level II/III, 15 LNs dissected): OBS IR: 46Gy **Reduced PORT** HR: 60Gy **SOC PORT**, but no SOC chemo	Ongoing, not reported	Ongoing, not reported

PORT=postoperative radiation therapy, PRO=patient-reported outcome, PYSH=pack-year smoking history, RF=risk factor, RRFS=regional relapse free survival, RT=radiation therapy, SIB=simultaneous integrated boost, SOC=standard of care, TORS=transoral robotic surgery, wkly=weekly, wks=weeks, yr=year.

Table 4.

Radiation Deintensification Trials: Elective Radiation Dose or Volume Reduction

Study	Treatment Arms	Outcomes	Toxicities
RAVD [76] (Phase I/II) AJCC7 IVA-IVB HNSCC. Oral cavity, OPC, Larynx, Hypopharynx, Unknown Primary cancers all included.	**IND cis/pacl/cetux x2c ± everolimus (n=89) →** GR 50% shrinkage (n=37) → **No ENI. 75Gy to gross disease (BID every other wk).** NR <50% shrinkage (n=52) → **45Gy ENI (to next LN station) + 75Gy to gross disease.** Mean FU = 24 months	HPV+ OPC (n=59): 2yr PFS (p=0.10): 93.1% GR vs. 74.0% NR 2yr OS: 92.1% GR vs. 95.2% NR >90% of LRFs developed in the highest risk/dose RT volume.	Acute pegs (p=0.040): 50.0% GR vs. 73.5% NR Peg dependence at 6 months (p = 0.005): 5.7% GR vs. 32.6% NR
Montreal [77] (Phase II) p16+ OPC AJCC7 III/IV T1–4N0–2b and N3 with primary not extending beyond midline and ipsilateral nodes only; smokers permitted.	IMRT + concurrent carbo/5FU (n=29). SOC def CRT 70Gy to HR volume, 59.4Gy IR volume **Reduced ENI dose: 43.2 Gy/24 fxs** **Reduced ENI volume: no contralateral RP or level IV LNs.** Median FU = 44 months	2 yr PFS : not reported 2 yr LRC: 100% 2 yr OS: 100%	Acute grade 3 mucositis: 52% All patient-reported QOL outcomes (except dry mouth) returned to baseline within 10 months of treatment end.
EVADER / NCT03822897 (Phase II) HPV+ OPC. AJCC8 T1–3 N0–1.	SOC def RT 70Gy SOC def CRT 70Gy + HD cis x3c **ENI volumes reduced.**	Ongoing, not reported	Ongoing, not reported
SAVER / NCT04609280 (Phase II) p16+ OPC. AJCC8 T1–4 and N0, N1, or N3.	**ENI volumes reduced. Omission of contralateral LNs.** **Treat only ipsilateral level II and III LN levels.** If PORT: 54 Gy SOC If def RT: 69.96Gy SOC	Ongoing, not reported	Ongoing, not reported

5FU=5-fluorouracil, AFRT= altered fractionation radiation therapy, AJCC7=American Joint Committee on Cancer 7th Edition, AJCC8=American Joint Committee on Cancer 8th Edition, BID=bidaily, c=cycle, carbo=carboplatin, cetux=cetuximab, cis=cisplatin, CRT=chemoradiation therapy, def=definitive, ENI=elective nodal irradiation, FU=follow-up, fxs= fractions, GR=good response, Gy=gray, HD=high-dose, HNSCC=head and neck squamous cell carcinoma, IMRT=intensity-modulated radiation therapy, IND=induction, LN=lymph node, LRF= locoregional failure, NR=no response, OPC= oropharyngeal cancer, OS=overall survival, pacl=paclitaxel, PFS=progression-free survival, PORT=postoperative radiation therapy, QOL=quality of life, RP=retropharyngeal, RT=radiation therapy, SOC=standard of care, yr=year.

Table 5.

Radiation Deintensification Trials: Upfront Radiation Dose Reduction

Study	Treatment Arms	Outcomes	Toxicities
NRG-HN002 [17] (Phase II, randomized) p16+ OPC. AJCC7 T1–2 N1–2b, T3 N0–2b. <10 PYSH.	**Reduced dose def CRT** (60Gy IMRT + LD cis 40 mg/m²× 6c, n=157): VS. **AFRT alone (60Gy/5 wks IMRT**, n=149): 19.9% Unilateral RT. 80.1% Bilateral RT. Median FU = 2.6 years	Null hypothesis 2 yr PFS ≥ 85%: - CRT 90.5% [84.5–94.7], p=0.0350, rejecting null hypothesis - AFRT 87.6% [81.1–92.5], p=NS, failing to reject null hypothesis 2 yr LRF (p=0.02): 3.3% vs. 9.5%, HR 2.56 [1.11–5.88] 2 yr DM (p=0.58): 4.0% vs. 2.1%, HR 0.70 [0.20–2.50] 2 yr OS (p=0.93): 96.7% vs. 97.3%, HR 1.05 [0.34–3.23]	Higher acute toxicity with CRT. Acute Grade 3–4 (p<0.001): 79.6% vs. 52.4%. Late Grade 3–4 toxicit (p=NS): 21.3% vs. 18.1%
UNC/UF [82-83] (Phase II) p16+ OPC. AJCC7 T0–3 N0–2C and ≤10 PYSH or > 5 yrs smoking abstinence.	**Reduced def CRT for all (n=114):** **60Gy RT + LD cis 30 mg/m²wkly** No chemo for T0-T2 N0–1. Median FU = 31.8 months	2 yr PFS: 86% [77.5–91.3] 2 yr LRC: 95% [88.6–97.9] 2 yr DMFS: 91% [83.9–95.4] 2 yr OS: 95% [89.3–98.1] - 4 local failures, half in T2N0–1 treated without chemo.	Acute Grade 3 toxicity: - 2% xerostomia - 34% mucositis - 21% dysphagia - 38/113 (33%) patients required peg
LCCC1612 [84] (Phase II). p16+ OPC. AJCC7 T0–3 N0–2C and ≤10 PYSH or > 5 yrs smoking abstinence. If ≤10 PYSH: only wild-type p53 eligible.	**Reduced def CRT for all** **60Gy RT + LD cis 30 mg/m²wkly** **IMPT** (n=25) vs. **IMRT** (n=46) No chemo for T0–2 N0–1. Median FU = not reported	1 yr PFS was comparable: 92% IMPT, 93% IMRT	More short-term pegs with IMRT: 8% vs. 39% IMPT patients had better patient-report QOL and swallowing symptom scores than IMRT.
PacCIS [85] (Phase III) AJCC7 Stg III/IV HNC.	**SOC def CRT 70.6Gy + cis/5FU** (n= 105 total; 19 p16+ OPC) VS. **Reduced def CRT 63Gy + cis/pacl** (n= 111 total; 13 p16+ OPC) Median FU = 3.7 yrs	p16+ OPC subset analysis: 3yr PFS (p=0.653): 83.9% SOC VS. 84.6% 63Gy 3yr OS (p=0.76): 83.5% SOC VS. 92.3% 63Gy	Grade 3 acute dysphagia: 77.1% SOC, 81.1% 63Gy Grade 3 acute functional mucositis: 64.2% SOC, 59.4% 63Gy
NRG-HN005 (Phase II/III)	**SOC def CRT (70Gy+HD cis × 2c)** VS.	Ongoing, not reported	Ongoing, not reported

Study	Treatment Arms	Outcomes	Toxicities
p16+ OPC.	**Reduced def CRT (60Gy+HD cis × 2c)**		
AJCC7 T1–2 N1–2B, T3 N0–2B.	VS.		
<10 PYSH.	**Reduced dose def RT + IO (60Gy+nivolumab)**		
PROTEcT / NCT04104945	**Reduced def CRT 60Gy + chemo**	Ongoing, not reported	Ongoing, not reported
p16+ OPC.	Chemo options: HD cis, LD cis 40 mg/m^2, cetux		
AJCC8 T1–3 N1–2.	Omission of IB from ENI volume.		

5FU=5-fluorouracil, AFRT= altered fractionation radiation therapy, AJCC7=American Joint Committee on Cancer 7th Edition, AJCC8=American Joint Committee on Cancer 8th Edition, c=cycle, cetux=cetuximab, chemo=chemotherapy, cis=cisplatin, CRT=chemoradiation therapy, def=definitive, DM=distant metastasis, DMFS=distant-metastasis free survival, FU=follow-up, fxs= fractions, Gy=gray, HD=high-dose, HNC=head and neck cancer, HR=hazard ratio, IMRT=intensity-modulated radiation therapy, IMPT=intensity-modulated proton therapy, IO=immunotherapy, LD=low-dose, LRF= locoregional failure, NS=not significant, OPC= oropharyngeal cancer, OS=overall survival, peg=percutaneous endoscopic gastrostomy, PFS=progression-free survival, PYSH=pack-year smoking history, QOL=quality of life, RT=radiation therapy, SOC=standard of care, wk=week, wkly=weekly, yr=year.

Table 6.

Radiation Deintensification Trials: Induction Chemotherapy to Select Patients from Radiation Dose Reduction

Study	Treatment Arms	Outcomes	Toxicities
ECOG 1308[86]	**IND cis/pacl/cetux** (n=80).	2 yr PFS : 81% [69–89] 54Gy, 67% [38–85] SOC	Acute Grade 3 toxicity:
(Phase II)	Response to IND (n=51) → **Reduced dose def CRT 54Gy + cetux**	2 yr OS : 93% [83–97] 54Gy, 87% [56–96] SOC	- Mucositis : 30% 54Gy, 47% SOC
p16+ and/or HPV+ OPC.			- Dysphagia : 15% 54Gy, 29% SOC
AJCC7 III, IVA, IVB.	No response to IND (n=15) → **SOC CRT 69.3Gy**	2 yr PFS, 54Gy in T1–3,N1-N2b,<10 PYSH: 96% [76–99]	At 12 months:
T4 included, N3 allowed but none enrolled. Smokers permitted.		Primary site clinical CR to IND (n=51)	- Difficulty swallowing solids: 40% 54Gy, 89% SOC
	Median FU = 35.4 months	CR/PR/SD (n=62)	- Impaired nutrition: 10% 54Gy, 44% SOC
University of CA CCRO-022[87]	**IND carbo/pacl** (n=45).	2 yr PFS: 92% [77–97]	Acute Grade 3 toxicities in 39%:
(Phase II)	CR/PR (n=24) → **Reduced dose def CRT (54Gy + pacl)**	2 yr LRC: 95% [80–99]	9% mucositis, 9% dysphagia
p16+ OPC.	<PR/no response (n=20) → **Reduced dose def CRT (60Gy + pacl)**	2 yr OS: 98% [85–100]	3 pegs before and 3 pegs during RT
AJCC7 Stage III or IV. T4 and N3 enrolled.			
Smokers permitted.	Median FU = 2.5 years	3 of 4 failures in 60Gy with minimal response to IND	
OPTIMA[78–79]	**IND carbo/nab-pacl**→	2 yr PFS: 95% overall, 95% LR, 94% HR	Acute Grade 3 mucositis:
(Phase II)	-LR 50% response (n=30):	2 yr LRC: 98% overall, 100% LR, 97% HR	30% 50Gy RT, 63% 45Gy CRT, 91% 75Gy CRT
p16+ OPC. AJCC7	**Reduced dose def RT 50Gy**	2 yr DMFS: 100% overall, 100% LR, 100% HR	Peg tubes: 3% RT50, 33% CRT45, 80% CRT75
T1–4 N2–3 and T3–4 N0–3. Smokers permitted.	-LR 30–50% response, HR 50% response (n=45):	2 yr OS: 98% overall, 100% LR, 97% HR	
LR (n=44): T3, N2B, and 10 PYSH	**Reduced dose def CRT 45Gy BID + pacl/5FU/HU** (n=15)		
HR (n=46): T4, N2C, or >10 PYSH)	BID on days 1–5, 15–19, 29–33 (over 6 wks)	3 recurrences within 2 yrs: 2 in 45Gy CRT, 1 in 50Gy RT	
Note: prophylactic LN RT was limited to only	- All others **75Gy BID + pacl/5FU/HU** (n=15)		
the first echelon of uninvolved LNs	BID on days 1–5,15–19,29–33,43–47,57–61 (over 10 wks)		
	Median FU = 4.2 years		
OPTIMA II[73–74]	**IND carbo/nab-pacl/nivolumab x3c** → RECIST response:	2yr PFS 90.4%[79.3–95.7]:	Peg tubes:
(Phase II)	De-escalated treatment administered in 84.9%.	50Gy RT: 96.3%	50Gy RT 7.1%

Study	Treatment Arms	Outcomes	Toxicities
p16+ and HPV+ OPC.	LR with ≤50% reduction:	45–50Gy CRT: 85.8%	45–50Gy CRT 44.1%
LR:	- **TORS-selective ND** (n=9)	70–75Gy CRT: 100%	70–75Gy CRT 75.0%
T1-T2 non-bulky tonsil or well-lateralized BOT ≤3 cm,	- **Reduced dose def RT 50Gy**(n=28): did not qualify for/ refused TORS	2yr OS 93.3%[82.4–97.5]:	Grade 4 toxicity:
non-bulky N2A-2B with ≤2 non-lower neck LNs measuring ≤5 cm.	LR <50% but ≥30% reduction, HR with ≤50% reduction:	50Gy RT: 96.0%	50Gy RT 7.1%
HR:	- **Reduced dose def CRT** (n=34): **50Gy+HD cis x2c or 45Gy+THFXx3c**	45–50Gy CRT: 91.9%	45–50Gy CRT 8.8%
T4, N2C-3, >20 PYSH, or non-HPV16 subtype.	LR <30% reduction, HR <50% reduction:	70–75Gy CRT: 100%	70–75Gy CRT 10.0%
	- **SOC def CRT** (n=10): **70Gy+HD cis x3c or 75Gy+TFHX x5c**	–3 local failures, 0 distant failures	1 patient died during IND.
	Adjuvant nivolumab x6 months in all.	- among 9 TORS patients, 66.7% had pCR.	
	Median FU = 23.1 months		
Quarterback[88–89]	**IND doce/cis/5FU x3c** (n=20).	Initial results:	After enrolling first 4/12 patients in 56Gy arm, due to
(Phase III)	If response → randomized 1:2 to	2 yr PFS (p=0.85): 87·5% SOC vs. 83·3% 56Gy	higher than expected mucositis and 2 pegs, protocol
p16+ and HPV+ OPC. HPV subtype assessed.	**SOC def CRT 70Gy** (n=8) or **Reduced dosed def CRT 56Gy** (n=12)	- 1 LRF in SOC, 2 LRF in 56Gy	was amended. Remaining 8/12 paties in 56Gy arm
AJCC7 Stage III/IV.	CRT=RT+carbo	- PFS hazard ratio: 1·46 [0·13–16·12]	received carbo only.
T4 and N3 enrolled.	Phase 2b update, IND doce/cis/5FU x3c and responders (n=20):	Including phase 2b update (n= 32 patients 56Gy):	- 6 pegs in total: 4 (33%) 56Gy, 2 (25%) 70Gy
T1N1 permitted, none enrolled.	**Reduced dose def CRT 56Gy + carbo**	- 2yr PFS: 84.4% [66.5–93.2]	- no therapy-related mortality
Smokers permitted.	- 3yr LRC 85% was considered non-inferior to SOC CRT	- 2yr LRC: 87.4% [69.8–95.1]	- Phase 2b trial toxicity to be reported
	- 3yr PFS 80% was considered acceptable	- 2yr OS: 90.6% [73.7–96.9]	
		72% had poor risk factors (ECE, T4, N2c, Non-HPV16)	
	Median FU = 50 months	- All 5 recurrences occurred within 1 yr	
		- All 5 recurrences had ≥1 poor risk factors	

OS=overall survival, pacl=paclitaxel, pCR=pathological complete response, peg=percutaneous endoscopic gastrostomy, PFS=progression-free survival, PR=partial response, PYSH=pack-year smoking history, RT=radiation therapy, SD=stable disease, SOC=standard of care, THFX=paclitaxel,5FU,HU, TORS=transoral robotic surgery, wk=week, wkly=weekly, yr=year.

Table 7.

Society guidelines for chemoradiation in the management of T1-T2 N1 oropharyngeal cancer.

ASTRO Clinical Practice guideline [99]	"After a careful discussion of patient preferences and the limited evidence supporting its use, concurrent systemic therapy may be delivered to patients with T1-T2 N1 OPSCC receiving definitive RT who are considered at particularly significant risk for locoregional recurrence. (Conditional, LQE, 100%)"
	"However, certain patients with T1–2 N1 OPSCC who are considered at particularly significant risk for locoregional recurrence may receive concurrent systemic therapy, because the absolute benefit of combined modality therapy may justify its toxicities in this population."
ACR Appropriateness Criteria [100]	"Patients with T1–2 N1–2aM0 disease can receive radiation, chemoradiation, or transoral surgery with neck dissection and appropriate adjuvant therapy."
AHNS guidelines [101]	"Nevertheless, treatment strategies remain the same despite HPV status. Further research is necessary to determine the safety and efficacy of altering the management for patients with HPV-positive HNSCC with respect to the new staging."
ASCO guidelines [102]	"Concurrent systemic therapy may be delivered to patients with T1-T2 N1 OPSCC receiving definitive radiotherapy who are considered at particularly significant risk for locoregional recurrence, after a careful discussion of patient preferences and the limited evidence supporting its use (Recommendation strength: conditional, Quality of evidence: low)."

Table 8.

Eligibility for Chemoradiation Deintensification Trials

	T1-2N1 Included	T4 or N3 included	Smokers included
RTOG 1016 [15]		☑	☑
De-ESCALaTE [16]	☑	☑	Only N0-N2a if >10PYSH
TROG 12.01 [29]	☑		Only N0-N2a if >10PYSH
HN002 [17]	☑		Only <10PYSH
ORATOR2 [57]	☑		☑
UNC/UF [82–83]			<10PYSH or >5 yrs abstinence from smoking
ECOG 1308 [86]	☑	☑	☑
OPTIMA [78–79]	☑	☑	☑
Univ of CA [87]	☑	☑	☑
Quarterback [88–89]	☑	☑	☑
MSK 30 ROC [137]	☑		☑
HN005	☑		Only <10 PYSH

PYSH= pack-year smoking history

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Table 9.

Personalized Radiation Deintensification Trials

Study	Treatment Arms	Outcomes	Toxicities
MSKCC 30 ROC[136-137] / NCT03323463	Baseline FMISO-PET scan prior to CRT start.	Pilot Study (n=15 de-escalated patients):	0 grade 3 RT-related toxicities on the pilot trial.
(Phase II).	If first FMISO-PET +hypoxia, second FMISO-PET performed 2 wks after CRT start.	−2 yr LRC 100%	Acute grade 3 toxicity on the Phase II trial:
p16+ OPC.		−2 yr PFS 92.9%	
AJCC7 T1–2 N1–2C. Any PYSH.	**Hypoxia-neg: 30Gy CRT (with HD cis)**	−2 yr OS 92.9%	- 2 diarrhea, 2 syncope, 1 vasovagal, 1 dysphagia
Pilot Study:	- n=19 Pilot trial (15 de-escalated)	−11 of 15 pathological CR.	- No grade 3 mucositis, 0 pegs.
- primary site resection before CRT	- n=158 Phase II trial (128 de-escalated)	Phase II (whole cohort):	
- planned ND at 4 months post-CRT.		−1 yr LRC 94%	
Phase II FU:	**Hypoxia+: 70Gy CRT (with HD cis)**	−1 yr DMFS 100%	
- primary site resection before CRT	Median FU = 34 months (pilot study)	−1 yr PFS 94%	
- no planned ND at 4 months post-CRT.	Median FU = 12 months (Phase II).	−1 yr OS 100%	
		- No 30Gy patients failed in the primary site	
		- 8 patients with LN recurrences, all successfully salvaged with surgery.	
UNC+UF / NCT03077243	>10 PYSH AND p53 wild-type, Or 10 PYSH:	Ongoing, not reported	Ongoing, not reported
(Phase II)	**Deintensified def CRT (60Gy + LD cis 30–40 mg/m²wkly)**		
p16+ and/or HPV+ OPC.	p53 mutant: SOC CRT 70Gy + LD cis 30–40 mg/m² wkly		
AJCC7 T0-3 N0-2C.	- ctHPVDNA will be prospectively assessed and correlated with outcomes.		
The ReACT Study/ NCT04900623	NavDX **ctHPVDNA** test (detects HPV16) at baseline, 4 wks and end of treatment.	Ongoing, not reported	Ongoing, not reported
(Phase II)	**LR: 5–6 wks reduced dose def RT ± chemo**		
p16+ and HPV+ OPC.	**HR: 7–8 wks SOC def RT ± chemo**		
AJCC8 Stage I, II, or III.	Chemo: HD cis, LD cis, or carbo/pacl.		
MSKCC / NCT05307939	Must have preoperative NavDX **ctHPVDNA** >50 copies/mL.	Ongoing, not reported	Ongoing, not reported
(Phase II)	Check NavDX ctHPVDNA levels (Frag/mL) postoperatively and every 3–6 months		
HPV-16 OPC or unknown primary	to select patients for active surveillance (OBS) or SOC adjuvant therapy		
cancer with no residual disease on	LR: <5 (OBS), 5–7 (repeat NavDX), >7 (SOC adjuvant therapy)		

Study	Treatment Arms	Outcomes	Toxicities
postoperative imaging. T1N1-T4N3. No positive margin or ECE.	IR: <5 (OBS), 5 (SOC adjuvant therapy)		
Univ of Michigan / NCT03416153 (Phase II) p16+ or HPV+ OPC. AJCC8 Stage I or II.	Pre- and mid-treatment PET scans to select patients for de-escalation. **Deintensified def CRT (54Gy + carbo/pacl)**	Ongoing, not reported	Ongoing, not reported
NYU / NCT03215719 (Phase II) p16+ OPC. AJCC7 T1–3 N1–2B.	**Interval CT scan at 4 wks** to select responders. >40% LN shrinkage → **reduced dose def RT (60Gy + cis)**	Ongoing, not reported	Ongoing, not reported

AJCC7=American Joint Committee on Cancer 7th Edition, AJCC8=American Joint Committee on Cancer 8th Edition, carbo=carboplatin, chemo=chemotherapy, cis=cisplatin, CRT=chemoradiation therapy, ctHPVDNA=circulating tumor HPV DNA, def=definitive, DM=distant metastasis, FU=follow-up, Gy=gray, HD=high-dose, HPV=human papillomavirus, HR=high-risk, IR= intermediate-risk, LD=low-dose, LN=lymph node, LR=low-risk, LRC= locoregional control, OBS=observation, OPC= oropharyngeal cancer, OS=overall survival, +=positive, pacl=paclitaxel, PET=positron emission tomography, PFS=progression-free survival, PYSH=pack-year smoking history, RT=radiation therapy, SOC=standard of care, wkly=weekly, wks=weeks, yr=year.

Table 10.

Summary of Deintensification Trials

De-Escalation Strategy	Relevant Trials	Results
Definitive CRT (SOC=HD cisplatin)		
Attenuation with cetuximab	*RTOG 1016*[15]	Cetuximab is inferior to HD cisplatin
	De-ESCALaTE[16]	Cetuximab is inferior to HD cisplatin
	TROG 12.01[29]	Cetuximab is inferior to LD cisplatin
Omission of cisplatin	*HN002*[17]	Cisplatin cannot be omitted from Definitive RT
Attenuation with LD cisplatin	*HN009 (not exclusive to HPV+ OPC)*	Trial ongoing
Surgery (SOC=Open/Transmandibular/Transcervical Resection + ND)		
TORS + ND ± adj RT VS. Def RT ± chemo	*ORATOR*[54–56]	TORS does not have less toxicity than def RT
	ORATOR2[57]	TORS has inferior PFS and more grade 5 toxicity than def RT
Adjuvant Radiation Therapy (SOC= 60Gy PORT)		
TORS + ND + De-escalated Adj Therapy	*ECOG 3311*[45]	50Gy PORT appears feasible with postoperative IR factors
	MC1273[58–59], *MC1675*[61–62]	30Gy BID PORT + chemo is comparable to SOC with postoperative IR factors
	PATHOS	RCT ongoing (50Gy PORT vs. SOC for IR factors; SOC ± chemo for HR factors)
Definitive Radiation Therapy (SOC=70Gy)		
De-escalate Def RT Dose	*ECOG E1308*[86], *OPTIMA*[78–79], *Univ of CA*[87], *Quarterback*[88–89]	NAC with deintensification to 45–60Gy in responders with bulky HPV+ OPC is feasible
	HN002[17], *UNC/UF*[82–83]	Upfront de-escalation to 60Gy CRT appears feasible in non-bulky HPV+ OPC
	30ROC[137]	Selective de-escalation to 30Gy CRT appears feasible in hypoxia-negative patients
	HN005	RCT ongoing (SOC 70Gy CRT vs. upfront de-escalation to 60Gy CRT)

adj=adjuvant, chemo=chemotherapy, CRT=chemoradiation therapy, def=definitive, HD=high-dose, HPV=human papillomavirus, HR=high-risk, IR=intermediate-risk, LD=low-dose, NAC=neoadjuvant chemotherapy, ND=neck dissection, OBS=observation, OPC=oropharyngeal cancer, +=positive, PFS=progression-free survival, PORT=postoperative radiation therapy, RCT=randomized control trial, RT=radiation therapy, SOC=standard of care, TORS=transoral robotic surgery