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인유두종바이러스 연관 구인두암의 치료 약화 전략: 보고된 결과를 중심으로 분석

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Treatment Deintensification for Human Papillomavirus-Associated Oropharyngeal Cancer: Focused Review of Published Data

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= Abstract =

Human papillomavirus (HPV) is a causative agent for a subset of oropharyngeal cancer (OPC). The current standard of care (SOC) for locally advanced OPC is 70 Gy definitive radiotherapy (RT) concurrent with cisplatin, which entails significant proportions of acute and late grade 3 or higher toxicities. Accordingly, discovery of favorable prognosis of HPV-related OPC has led to enthusiasm to attenuate subspecialties therapy in multidisciplinary treatment. Diverse deintensification strategies were investigated in multiple phase 2 trials with an assumption that attenuated treatments result in comparable oncologic outcome and less toxicities compared with SOC. Several trials on chemotherapy deintensification revealed that concomitant administration of cisplatin is not to be omitted or substituted for cetuximab without compromising progression-free survival or local control. A transoral robotic surgery (TORS) is investigated as alternative local treatment, but TORS plus SOC or mild deintensified adjuvant RT showed similar toxicities and inferior oncologic outcomes compared with SOC definitive RT or moderately deintensified RT. However, it has been reported that TORS plus deintensified 30-36 Gy adjuvant RT results in excellent outcome and less late toxicity compared with SOC adjuvant RT. Several phase 2 trials reported apparently equivalent progression-free survival and local control and similar adverse effects with moderately deintensified 60 Gy RT compared with SOC 70 Gy RT. Further dose reduction below 60 Gy has been investigated using biology-directed approaches, which use response to induction chemotherapy or metabolic images to triage HPV-positive OPC for deintensified RT. In summary, these trials provide valuable insights for future directions. Available evidence consistently showed that moderately deintensified RT is effective and safe for HPV-positive OPC in both definitive and adjuvant settings. Concurrent cisplatin remains an essential component without which progression-free survival is significantly compromised for advanced HPV-positive OPC. A simple incorporation of TORS to SOC may be detrimental for oncologic outcome without anticipated toxicity reduction. Given the lack of level 1 evidence, it is prudent to curb an unjustified deviation from the current SOC and limit any deintensified strategies to clinical trials and adhere to the current SOC.

Key Words : Human papillomavirus · Oropharyngeal neoplasms · Deintensification · Chemotherapy · Radiotherapy · Transoral robotic surgery

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Introduction

The current standard of care (SOC) for locally advanced oropharyngeal cancer (OPC) is definitive, concurrent, cisplatin-based chemoradiotherapy (CRT) of 70 Gy.[1-3] Any

attempts to deviate from the current SOC have failed to improve oncologic outcomes such as altered radiotherapy fractionation schedules, induction chemotherapy and addition of cetuximab.[4-6] Radical surgery with or without radiotherapy shows similar tumor control for OPC compared with definitive radiotherapy.[7] Postoperative radiotherapy or CRT is indicated for OPC with intermediate and high risk features after surgical excision.[8] Since the favorable prognosis of human papillomavirus (HPV)-related OPC is known, the risk stratification for OPC patients has been well established.[9] Accordingly, enthusiasm has arisen to explore the deintensification of treatment for OPC with favorable to intermediate risk. Various de-intensification strategies spanning surgical techniques, reduced RT doses and omission or replacement of systemic agents have been investigated. However, studies are heterogeneous in criteria for patient eligibility and nuances of de-intensification, which hampers the formation of consensus regarding the optimal de-intensification approach for HPV-positive OPC. A recent meta-analysis reported inferior oncologic outcomes of overall survival (OS), progression-free survival (PFS), locoregional control (LRC) and distant metastasis-free survival with treatment deintensification compared with SOC therapy.[10] The hypothesis that treatment deintensification for p16+ OPC can reduce long-term toxicity without compromising oncologic outcome is a valuable avenue worth thorough investigation, but supporting evidence is not yet solid and the major groups are reluctant to endorse de-escalation approaches over SOC therapy.[11,12] Despite the lack of high-level evidence, deintensification approaches have gained wide acceptance. A report using a National Cancer Database from 2010 to 2013 showed that about 15% of intermediate risk patients with HPV-positive OPC received surgery alone without any adjuvant RT and 4-yr OS of about 91% was no worse than OS for surgery+RT and surgery+CRT groups (p=0.72).[13] Current proliferation of deintensification trials and discrepancy between the endorsed SOC and clinical practice warrants critical appraisal of available evidence. This review aims to summarize recent deintensification trials according to multidisciplinary treatment HPV-positive OPC by highlighting deintensification approaches with the current SOC. This review has explicitly limited the scope to the trials that reported oncologic outcomes with highest relevance to current clinical practice. Ongoing studies and experimental approaches are beyond the scope of this review and well presented in the recent literature.[14]

Chemotherapy Deintensification

CRT with concurrent cisplatin is the current SOC for locally advanced OPC regardless of HPV infection. Compared with RT alone, CRT confers absolute 5-yr OS benefit of 5.3% for patients with OPC.[15] Deintensification approaches range from different cisplatin dosing, alternative agents to omission. Definitive RT combined with cetuximab improves LCR and OS compared with RT alone without increasing toxicity.[16] So far, RTOG 1016 and De-ESCALaTE trials compared cisplatin-based SOC with definitive RT combined with cetuximab in patients with HPV-positive OPC.[17,18] In both trials, the standard arm used 100 mg/m^2 cisplatin ever 3 weeks. Disappointingly, all these trials reported inferior outcome with cetuximab-RT compared with SOC treatment. In RTOG 10106, cisplatin-based RT showed significantly superior LRC, PFS and OS.[17] De-ESCALaTE revealed inferiority of cetuximab-based RT in terms of LRC, MDFS and OS.[18] Both randomized controlled trials confirm that cisplatin-based RT is the current SOC for locally advanced HPV-positive OPC. Although lacking solid evidence, modified dosing of concurrent cisplatin is widely used in clinical practice in anticipation of reduction of RT-related toxicity. Two trials compared cetuximab-RT with RT combined with attenuated cisplatin dosing in HPV-positive OPC.[19,20] ARTSCAN III randomized head and neck cancer patients to either cetuximab-RT or definitive RT combined with weekly 40 mg/m2 cisplatin.[19] Of randomized 291 patients, 85% had OPC, 89% of which were p16-positive. ARSCAN III was prematurely closed after an unplanned interim analysis, and reported 3-yr locoregional failure (LRF) or 23% with cetuximab and 9% with reduced cisplatin (p=0.0036). TROG 12.01 randomized HPV-positive OPC to cetuximab versus 40 mg/m^2 cisplatin combined with SOC definitive 70 Gy RT.[20] TROG trial reported inferior 3-yr PFS with cetuximab compared with cisplatin (80% versus 93%, p=0.015). In both trial, toxicity of cetuximab-RT was no less than reduced dosing of cisplatin. The current evidence refutes unjustified substitution of cetuximab for any dosing schedule of cisplatin in definitive RT for HPV-positive OPC. An analysis of SEER-Medicare da-

tabase reported outcome of 2135 patients (61.2% OPC) who received definitive RT, CRT and cetuximab-RT for head and neck cancer diagnosed over 2005 to 2011.[6] In 1306 patients with OPC (HPV status unknown), 5-yr OS is significantly superior for CRT compared with either RT or cetuximab-RT. Given the increasing incidence of HPV-related OPC since 2000s, the analysis further corroborates the inferiority of cetuximab compared with cisplatin when combined with definitive RT for HPV-positive OPC. Thus, cetuximab-RT should be limited for patients intolerable to cisplatin after careful clinical consideration.

Omission of cisplatin was investigated in HN002 trial.[21] HN002 is a randomized phase 2 trial to compare two non-SOC, deintensified treatments, which complicate its interpretation. The trial randomized patients with HPV-positive OPC to 60 Gy reduced-dose RT combined with attenuated weekly cisplatin versus accelerated 60 Gy RT alone with an assumption that both regimens would achieve a 2-yr PFS of 85% or higher. PFS at 2 years were 90.5% and 87.6% for CRT and RT alone. The outcome rejected the null hypothesis for the CRT group (p=0.04), suggesting dose-reduced RT combined with attenuated cisplatin is justified for direct comparison with the current SOC of full-dose cisplatin-based RT in HPV-positive OPC. However, 2-yr PFS of accelerated RT alone failed to reject the null hypothesis (p=0.23). Although it is not hypothesis-confirming, HN002 suggests that cisplatin omission risks deterioration of oncologic outcome in patients with highly-curable HPV-positive OPC.

Given the available evidence, concomitant cisplatin remains the key element of current SOC definitive RT for locally advanced HPV-positive OPC.

Surgery Deintensification

Oncologic outcomes and OS after primary surgery and definitive RT are similar in patients with OPC in general[7] and HPV-positive OPC.[22] Both approaches are equally endorsed by the NCCN guideline.[12] Transoral robotic surgery (TORS) is minimally invasive intervention compared with more traditional surgical procedures of transmandibular or transcervical approaches. Introduction of TORS for HPV-positive OPC led to limited number of studies to investigate its role as treatment deintensification.

ORATOR is a phase 2, randomized trial to compare the current SOC of 70-Gy definitive RT with TORS plus neck dissection with risk-directed adjuvant therapy.[23] Adjuvant RT is the current SOC 60 Gy with cisplatin for margin-positive or extranodal tumor extension. Sixty-eight patients with resectable T1-2, N0-2 OPC were randomized (88% HPV-positive). Thirty-four patients were randomized to the TORS+ND arm: 10 (29.4%), 16 (47.1%) and 8 (23.5%) received no RT, RT alone and CRT, respectively. Although all procedures in ORATOR are SOC except TORS, the phase 2 trial is not powered to test the difference of two arms. After 45 month follow-up, TORS arm showed significantly worse dysphagia outcome compared with SOC arm.[24] For p16-positive patients, 3-year OS were 96.3% and 93.3% for the SOC and TORS+ND arms. Different toxicity profiles were revealed between two arms: pain, trismus and bleeding are more common in the TORS arm, whereas patients in the SOC arm suffered more mild ototoxicity, xerostomia and mild neutropenia. Subsequent ORATOR2 compared deintensified RT with TORS plus neck dissection with risk-directed deintensified adjuvant RT.[25] ORATOR2 is a phase 2 trial randomizing HPV-positive T1-2N0-2 OPC to deintensified 60-Gy definitive RT with risk-directed weekly cisplatin versus TORS +/- deintensified adjuvant RT. Patients with extranodal extension (ENE) or positive margin received 60-Gy adjuvant RT without concurrent cisplatin, and those with intermediate risk factors underwent deintensified 50-Gy adjuvant RT alone. Overall, 61 patients were randomized (30 to the RT arm, 31 to the TORS and neck dissection).[26] Twenty-one patients (70%) received concurrent cisplatin in the RT arm and 21 patients (68%) received adjuvant RT. The trial design excluded trimodality therapy. ORATOR2 closed early to accrual because of two deaths in the TORS arm. At a median follow-up of 17 months, 2-yr PFS was apparently inferior with TORS (83.5% TORS vs. 100% RT), but immature data prevent any statistical conclusion on PFS and OS. Grade 2 to 5 toxicity occurred in 67% and 71T in the RT and TORS plus neck dissection arms, respectively. Given the lack of phase 3 trial, a meta-analysis reported higher gastrostomy dependence for TOR compared with cisplatin-based CRT at 24-36 months (10.5% versus 3.3%, p=0.06).[27] Available evidence suggests that the TORS-based approach may be a feasible, effective and safe alternative to the current SOC of 70-Gy

RT in carefully selected HPV-positive OPC patients. However, TORS with risk-adapted adjuvant RT may be no less toxic than SOC in terms of dysphagia.

RT Deintensification

Deintensification of RT can be explored on various avenues such as upfront dose reduction, response-directed dose reduction, reduced prophylactic dose and modified target volume in both definitive and adjuvant RT. Several trials addressed various approaches of RT deintensification, but interpretation of these data is hampered by heterogeneous patient selection, lack of direct phase 3 comparison with the current SOC and deintensification of more than a single RT parameter (eg. both volume and doses). The current SOC 70-Gy definitive RT is associated with a high risk of grade 3 or higher acute and late toxicity.[1,2] As RT toxicity is a function of prescribed doses, reduced radiation dose is seemingly a most rational approach for low risk HPV-positive OPC. So far, 4 deintensification trials reported the outcome of reduced-dose RT for HPV-positive OPC. HN002 is a phase 2 trial randomizing T1-2N1-2b or T3N0-N2b HPV-positive OPC to two deintensified regimens: 60 Gy RT over 6 weeks with weekly cisplatin versus accelerated 60 Gy RT over 5 week without cisplatin.[21] The trial accrued T1-2N1-2b or T3N0-N2b with 10 pack-years of smoking or less. HN002 reported 2-yr PFS of 90.5% with deintensified 60 Gy RT with weekly cisplatin. This metric rejected the null hypothesis of 2-yr PFS of 85% or less and justified the regimen worthy of comparison with the SOC 70 Gy RT with cisplatin. Despite radiation dose reduction, it is notable that both acute and late grade 3-4 adverse effects were common (79.6% and 21.3%). Other single-arm phase 2 trials reported similar excellent PFS and OS using deintensified 60 Gy RT with reduced weekly 30 mg/m^2 cisplatin only reserved for T3 or N2 disease.[28,29] LCCC1612 (ClinicalTrials.gov identifier NCT03077243) is a prospect trial of deintensified 60 Gy intensity-modulated proton therapy with reduced weekly cisplatin 30 mg/m^2 for HPV-positive T0-3N0-2M0 OPC.[30] Cisplatin was administered only for T3 or, N2. Oncologic outcome and toxicity were reported for deintensified proton therapy and randomly selected deintensified 60 Gy photon therapy. Deintensified 60 Gy proton therapy with reduced cisplatin resulted in 1-yr PFS of 92%. Altogether, these four trials showed that deintensified 60 Gy RT may be effective and promising with reduced concurrent cisplatin dosing, but none compared reduced RT regimens directly to the current SOC 70 Gy RT concomitant with full dose of cisplatin 100 mg/m^2. The verdict on the noninferiority of 60 Gy RT is anticipated from an ongoing HN005 (ClinicalTrials.gov Identifier: NCT03952585).

Six trials investigated induction chemotherapy-directed RT deintensification in a phase 2 setting.[31-36] The overall strategy is deintensification of RT components according to response to induction chemotherapy. Trials varies with selection of induction chemotherapy regimens and RT deintensification. In E1308, responders to cisplatin/paclitaxel/cetuximab induction received deintensified 54 Gy RT with cetuximab.[32] CCRO-022 administered induction carboplatin/paclitaxel and 54 Gy with paclitaxel for responders.[31] OPTIMA used 50 Gy RT alone or 45 Gy CRT for responders.[35,36] Quarterback randomized responders to induction to SOC 70 Gy with carboplatin versus 56 Gy by HPV-genotyping.[33,34] Overall, reported 2-yr PFS is apparently in the order of 90% for HPV-positive OPC patients who responded to induction chemotherapy and underwent deintensified RT. It is notable that the oncologic outcomes are seemingly similar across various phase 2 trials despite variability in RT deintensification approaches and patient selection. Given the overall futility of induction chemotherapy for head and neck cancer,[37] the efficacy of induction-directed strategy needs be investigated in properly designed phase trials and corroborated by level 1 evidence. 30 ROC trial boldly attempted to reduce RT dose to 30 Gy based on hypoxia change after 2 weeks of RT.[38]

Other avenues of response-directed RT deintensification are radiomics and tumor metabolism. 30 ROC trial harnessed probably the most drastic RT deintensification approach.[38,39] The trial used hypoxia imaging positron emission tomography (PET) to select favorable, hypoxia-negative HPV-positive patients for striking 30 Gy RT compared with 70 Gy SOC. In the pilot study phase, 19 patients with T1-2N1-2b p16-positive OPC underwent primary site resection and CRT with neck dissection planned 4 months after CRT. Fifteen patients who showed no hypoxia on baseline or repeat (2 weeks into CRT) 18-F-fluoromisonidazole PET completed CRT at 30 Gy over 3 weeks. Planned neck dissection showed pathologic complete response in 11 out

15 patients (73.3%) with 2-yr LRC and PFS were 100% and 92.9%, respectively.[39] Subsequent phase 2 trial enrolled 158 patients who underwent primary site resection but no elective neck dissection at all.[38] Based on PET-identified hypoxia, 128 patients were de-escalated to 30 Gy and chemotherapy (86% cisplatin). 1-year LRC, DMFS and OS were 94%, 100%, and 100%, respectively. Among the 30Gy de-escalated patients, none failed in the primary site. 8 patients had recurrent nodal disease underwent successful salvage surgery. 30 ROC showed that hypoxia-directed deintensification is feasible and effective. Future investigation is surely warranted into functional imaging-aided deintensification.

The current SOC adjuvant RT is 60 Gy concomitant cisplatin.[40] ORATOR and ORATOR2 phase 2 randomized trials, though not hypothesis-confirming, provide valuable insights on deintensification of adjuvant RT. ORATOR showed that TORS-directed SOC 60 Gy adjuvant RT failed to provide clinically meaningful amelioration of dysphagia compared with the SOC 70 Gy definitive RT.[23,26] Following ORATOR2 reported apparently inferior 2-yr PFS and similar toxicity profiles and dysphagia for TORS plus risk-adapted 50 to 60 Gy deintensified adjuvant RT compared with deintensified 60 Gy definitive RT.[26] ECOG E3311 randomized patients who had TORS-resected, HPV-positive OPC with intermediate-risk factors (close margins <3 mm, perineural invasion], lymphovascular invasion, 2-4 involved lymph nodes, or ≤1 mm ENE) to receive deintensified 50 Gy versus SOC 60 Gy adjuvant RT.[41] No chemotherapy was administered for both arms. Both arms showed excellent 2-yr PFS of 94.9% and 96.0%, respectively. Unlike ORATOR2, E3311 eliminated chemotherapy from deintensified 50 Gy adjuvant RT. MC1273 and MC1675 evaluated the efficacy of 30 to 36 Gy adjuvant RT in TORS-resected, HPV-positive OPC with negative resection margin.[42-45] MC1273 is a single-arm phase 2 trial with 2 cohorts.[42] Patients with intermediate risks received 30 Gy twice-daily RT with weekly 15 mg/m^2 docetaxel. Patient with ENE received the same treatment with a simultaneous integrated boost to areas of ENE. Long-term results showed that 5-yr LRC of 100% and 84.1% for both cohorts.[43] Given the favorable outcomes, subsequent MC1675 is a phase 3 trial randomizing margin-negative, HPV-positive OPC after TORS to deintensified 30-36 Gy RT with docetaxel from MC1273 versus the SOC 60 Gy RT with risk-directed weekly 40 mg/m2 cisplatin.[45] Two-yr PFS were 86.5% versus 95.1% for 30-36 Gy RT and 60 Gy RT, respectively. Significantly less patients required feeding tubes (1.6% versus 27.4 %, p<0.0001). A preplanned pooled analysis of MC1273 and MC1675 reported 2-yr PFS of 91.1% (95% CI, 87.2%-95.3%), which is noninferior to the target PFS (92.3%, p=0.29) and higher than the acceptable PFS threshold (89.6%, p=0.043) for HN005.[44] Data from E3311, MC1273 and MC1675, deintensified adjuvant RT apparently results in 2-yr PFS in the order of 90%.[41,43,45] However, one should note different indications for concurrent adjuvant chemotherapy among trials. Despite promising outcomes from phase 2 trials, a paucity of level 1 evidence and heterogeneous adjuvant regiments still warrant well-designed future trials for optimal deintensification of adjuvant RT.

Summary

Since the favorable prognosis of HPV-positive OPC was known, the initial enthusiasm for treatment deintensification suffered dampened apprehension on finding the superiority of current SOC in trials like RTOG 1016, De-ESCALaTE, TROG 12.01, HN002, ORATOR, ORATOR2.[17,18,20,21,24,26] Despite the lack of level 1 evidence, several trials suggest that modest dose reduction of 60 Gy definitive RT is feasible and provides short-term PFS comparable to the SOC 70 Gy RT with cisplatin.[21,28,29] Several trials showed induction chemotherapy-guided deintensification of RT is feasible. 30 ROC, MC1273 and MC1675 are trials that used the most drastic reduction of radiation doses for definitive and adjuvant RT and reported promising PFS rates.[38,43,45] These trials reduced radiation doses down to the order of 30 Gy delivered over 2 weeks for selected HPV-positive OPC. The literature is abundant to support dose-response relationship between radiation dose to swallowing structures and treatment-related dysphagia. Thus, a drastic dose reduction of these trials clearly warrants further investigation. 30 ROC unequivocally showed a power and feasibility of biology-directed treatment deintensification.[38,39] Given a multitude of trials ongoing with heterogeneous eligibility and deintensification strategies, critical appraisal and consensus building is a huge challenges for multidisciplinary teams to navigate the optimal management of HPV-positive OPC.

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