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HEAD AND NECK CANCERS (EY HANNA, SECTION EDITOR)

Present and Future of De-intensification Strategies in the Treatment of Oropharyngeal Carcinoma

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Abstract

Purpose of Review The treatment of patients with squamous cell carcinoma of the oropharynx (OPSCC) remains controversial. HPV positivity is widely accepted as a favorable prognostic factor, and HPV+ OPSCC is considered a distinct pathological entity with dedicated NCCN guidelines and may deserve a more personalized therapeutic strategy. The possibility to reduce surgical invasiveness and acute and late toxicity of radiotherapy/chemotherapy has led to the new concept of de-escalation treatment strategies. In particular, several de-intensified approaches have been investigated with the aim to give patients less toxic treatments, while maintaining comparable results in terms of disease's control and survival. The aim of the present review is to systematically illustrate the current status of research in de-intensification surgical and non-surgical strategies in the treatment of the OPSCC.

Recent Findings We categorized all completed and on-going trials on the basis of the specific de-escalated treatment protocol. Several de-intensified approaches have been investigated with the aim to give patients less toxic treatments, while maintaining comparable results in terms of disease's control and survival.

Summary Considering the conflicting results reported so far by preliminary studies, it is necessary to wait for the final results of the on-going trials to better clarify which is the best de-intensified strategy and which patients would really benefit from it.

Keywords Oropharyngeal cancer · Deintensification · Oropharynx · Head and neck carcinoma · TORS

Introduction

The treatment of patients with squamous cell carcinoma of the oropharynx (OPSCC) remains controversial since no randomized trials have adequately addressed the question of whether surgery, radiation therapy (RT), or combined treatment is the most effective [1]. Open surgical approaches, often requiring a lip mandibular split, have been proposed in the past with an important postoperative morbidity and long-term sequelae [2, 3]. The introduction of RT treatment regimens has led to a more conservative management able to partially preserve the anatomical structures and to ameliorate the long-term function [4, 5].

In the absence of prospective randomized studies, the most comprehensive data comparing open surgery with non-surgical approaches on OPSCC comes in 2002 [1]. The rates of local control (LC), local-regional control (LRC), 5-year overall survival (OS), and 5-year cause-specific survival (CSS) were similar for patients who underwent surgery ± RT or RT ± neck dissection, whereas functional results and complications favored the use of RT ± chemotherapy (CT).

Based on this evidence, between the 1900s and 2010, traditional surgical approaches to the oropharynx were gradually substituted by radiation and chemo-radiation regimens, and

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nowadays, oncologic and functional benefits of non-surgical approaches are well established. This trend was later reinforced by the introduction of the intensity-modulated radiation therapy (IMRT) [6].

The introduction of trans-oral robotic surgery (TORS) in 2009 dramatically changed the history of oropharyngeal carcinoma treatment pushing again surgery as a valid alternative in selected cases [7–10]. The possibility to reduce surgical invasiveness allows to achieve a radical treatment with excellent functional results [11, 12]. Although no randomized comparisons are now available, oncological and functional results appear overlapping from the analysis of gross data coming from the literature on TORS and IMRT [13].

As a consequence, from 2009, we can observe a significant increase in the proportion of all surgical procedures performed as primary treatment for oropharyngeal SCC and especially in T1–2 tumors. In parallel, in the first 2000, it became clear that HPV positivity represents a positive prognostic impact for OPSCC [14, 15]. In general, the prognosis for HPV-positive oropharyngeal cancer patients is better than that for patients with HPV-negative tumors, regardless of nodal status, age, stage, tumor differentiation, or gender [16, 17]. Several studies have shown OS rates of 80–95% at 2–3 years for the HPV-positive patients compared to 57–62% for the HPV-negative subgroup of oropharyngeal tumors [14, 18]. Nowadays, HPV+ OPSCC is considered by NCCN a distinct pathological entity with dedicated guidelines and TNM staging [19].

The evidence of the excellent OS of HPV+ OPSCC pushed the dispute between TORS and IMRT into a new battlefield. Radiation oncologists and surgeons hypothesize that a less aggressive cancer could be efficiently treated with a less aggressive treatment: de-escalation was born.

The aim of the present review of the literature is to illustrate the current status of research in de-intensification surgical and non-surgical strategies in the treatment of the OPSCC.

Radiotherapy/Chemoradiotherapy-Based De-intensification Trials

There are currently three non-surgical strategies for de-intensification of HPV-associated OPSCC treatment. Approaches include reduction of RT dosage, the use of systemic agents with a milder pattern of toxicity, and complete removal of CT. These appear to be attractive strategies with potential benefits regarding lower treatment-related side-effects and/or long-term morbidity. Several studies have been conducted to investigate these treatment options (Table 1). Furthermore, various on-going trials have been designed in order to better clarify the role of RT/systemic therapy-based de-intensification strategies (Table 2).

Reduced Radiotherapy

When looking at de-escalation through reduced RT dose, we have to focus on the ECOG1308 and the Quarterback trials. In ECOG1308 [20•] (NCT01084083), an open-label, non-randomized phase II trial completed in January 2015, patients with stage III/IV (HPV+ or HPV−) received induction chemotherapy (IC) followed by cetuximab and either normal or low-dose RT. Patients were classified into two groups according to their response to IC that included cisplatin, paclitaxel, and cetuximab. Patients with complete clinical response at the primary tumor site underwent additional treatment with cetuximab and lower dose IMRT (54 Gy in 27 fractions) while patients with evidence of less than complete clinical response received cetuximab and standard dose RT (69.3 Gy in 33 fractions). The majority of patients (70%, $n = 56$) demonstrated complete clinical response to IC, and at a median follow-up of 35.4 months, the progression-free survival (PFS) was 80% ($n = 51$) and the OS was 94% ($n = 51$). Significant decrease in adverse effects was also evident in terms of difficulty swallowing solids (40% vs 89%; $P = .011$) or impaired nutrition (10% v 44%; $P = .025$). These results appear promising but, as noted by Deschuymer et al. [21], it is worth mentioning that various patients experienced grade 3 or higher toxicity during IC, raising the question if reduction of RT-related toxicity outweighs the added toxicity of IC.

The Quarterback trial [22••] (NCT01706939) is a phase III randomized trial studying a treatment strategy of IC (3 cycles of docetaxel, cisplatin, and 5-fluorouracil) followed by either 56 Gy or 70 Gy concomitant to carboplatin. This study included 24 patients with HPV+ oropharynx, unknown primary or nasopharynx cancer. After evaluation, 20 patients (16 HPV 16+ and 4 high-risk variants, 14 with high-risk features: T4, N2c, or N3) were randomized into two groups: 8 patients received standard dose of 70 Gy and 12 patients received reduced dose of 56 Gy. The 3-year PFS and the OS rates for standard dose and reduced dose RT were 87.5% vs 83.3% (log-rank test $p = 0.85$), respectively. All three reported failures were local or regional within 4 months after completion of treatment, and two were in the randomized patients with high-risk variants (50%).

Although these results support the de-escalation strategy based on reduction of RT doses, the small sample size and the various disease etiologies raise some concerns. Many on-going and future studies have the aim of providing data able to clarify with a high level of evidence these promising results.

At this time, there are two phase II trials (NCT03215719 [23], NCT01088802 [24]) currently looking at reduced IMRT with standard CT, with 54 and 60 participants respectively. Moreover, the PROTEcT trial [25] (NCT04104945) aims to reduce elective RT treatment volumes, but with an aim of enrollment of 32 participants. With a significantly larger sample size, the DELPHI trial [26] (NCT03396718) aims to

Table 1 Completed radiotherapy-based trials

Trial	Start year	Status	Type	Characteristics	Population	Primary outcomes
Reduced radiotherapy						
NCT01084083 (ECOG1308)	2010	Completed	Single-arm (phase II)	IC (cisplatin, paclitaxel and cetuximab) + IMRT (54 or 69.3 Gy)	HPV+ and/ or p16+; stages III–IV	PFS, OS, RR
NCT01088802 (Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins)	2010	Active, not recruiting	Single-arm (phase II)	Cisplatin/carboplatin + IMRT (63 Gy/50.75 Gy)	HPV+; T1-T3 N0-N3b (AJCC 7th Edition)	Late toxicity, QoL, adverse events
NCT01706939 (The Quarterback trial)	2012	Active, not recruiting	Randomized phase III	Carboplatin + RT (56 Gy) vs. carboplatin + RT (70 Gy)	HPV+ and/ or p16+; stages III–IV	PFS, OS, LRC, acute toxicity, failure biomarkers
Less toxic chemotherapy treatment						
NCT01302834 (RTOG 1016)	2011	Active, not recruiting	Randomized phase III	Cisplatin + RT (70 Gy) vs. cetuximab + RT (70 Gy)	p16+; T1–2, N2a-N3 or T3–4, any N (AJCC 7th Edition)	OS, PFS, LRC, QoL, acute and late adverse events, swallowing function
NCT01663259 (University of Michigan Rogel Cancer Center)	2011	Completed	Single-arm (phase II)	Cetuximab + RT (70 Gy/50–60 Gy)	HPV+ or p16+; stages III–IV (excluding N3 or T4)	Recurrence rate, adverse events
NCT01874171 (De-ESCALaTE)	2012	Active, not recruiting	Randomized phase III	Cisplatin + RT (70 Gy) vs. cetuximab + RT (70 Gy)	HPV+; T3N0-T4N0 and T1N1-T4N3	Toxicity profile, QoL, OS, swallowing function, cost-effectiveness, recurrence rate
NCT01855451 (TROG 12.01)	2013	Active, not recruiting	Randomized phase III	Cisplatin + RT (70 Gy) vs. cetuximab + RT (70 Gy)	HPV+ and p16+; stage III (excluding T1–2N1) or stage IV (excluding T4, N3, and distant metastasis)	Symptom severity, QoL, OS, PFS, swallowing function, toxicity profile, cost-effectiveness, biomarkers
Removal of chemotherapy						
NCT02254278 (NRG HN002)	2014	Active, not recruiting	Randomized phase II	Cisplatin + IMRT (60 Gy) vs. IMRT (60 Gy)	p16+; T1-T2, N1-N2b or T3, N0-N2b (AJCC 7th Edition)	Swallowing function, PFS, LRC, OS, distant metastasis, HPV DNA analysis, toxicity profile

Abbreviations: *IC* induction chemotherapy, *IMRT* intensity-modulated radiation therapy, *RT* radiotherapy, *PFS* progression-free survival, *OS* overall survival, *RR* response rate, *QoL* quality of life, *LRC* local-regional control

Table 2 On-going radiotherapy based trials

Trial	Start year	Status	Type	Characteristics	Population	Primary outcomes
Reduced radiotherapy						
NCT03215719 (NYU Langone Health)	2017	Recruiting	Single-arm (phase II)	Cisplatinum + IMRT (standard vs dose-deescalated)	HPV+ and p16+; T1-T2, N1-N2b or T3 N1-N2b (AJCC 7th Edition)	PFS
NCT03323463 (Memorial Sloan Kettering Cancer Center)	2017	Recruiting	Single-arm (phase II)	Cisplatin or carboplatin or 5fluorouracil + RT (30 Gy)	HPV+; Hypoxia-; T1-T2 N1-N2c (AJCC 7th Edition)	Treatment effectiveness
NCT03396718 (DELPHI)	2018	Recruiting	Multi-level (phase I)	Level 1: HPV+ CRT (59.4 Gy/54 Gy); Level 2: HPV+ CRT (55 Gy/48.8 Gy); Comparator: HPV− CRT (66 Gy/60 Gy); Comparator: HPV+ CRT (66 Gy/60 Gy)	HPV+ or –; pT3-pT4 N1-N3b R0-R1	LRC, OS toxicity profile, QoL
NCT04104945 (PROTEcT)	2019	Not yet recruiting	Single-arm, prospective cohort	Cisplatin or cetuximab + RT (60 Gy/54 Gy)	p16+; T1-T3 N1-N2 (AJCC 8th Edition)	QoL, toxicity profile, OS, PFS, LRC, swallowing function
Less toxic chemotherapy treatment						
NCT04106362 (Jonsson Comprehensive Cancer Center)	2019	Not yet recruiting	Randomized phase II	Cisplatin + RT vs. cisplatin + cetuximab + RT	HPV+ and KRAS variant; stages III–IV (T3-T4 or N2-N3) (AJCC 8th Edition)	OS, LRC, toxicity profile
Removal of chemotherapy						
NCT03822897 (EVADER)	2019	Recruiting	Single-arm phase II	Cisplatin + RT vs. cisplatin + cetuximab + RT	HPV+; T1–3 N0–1 M0 (AJCC 8th Edition)	EFS, OS, LRC, distant metastasis

Abbreviations: *IMRT* intensity-modulated radiation therapy, *RT* radiotherapy, *CRT* chemoradiotherapy, *PFS* progression-free survival, *LRC* local-regional control, *OS* overall survival, *QoL* quality of life, *EFS* event-free survival

include 384 participants and is comparing two levels of de-escalated RT with concurrent standard CT. Finally, an additional phase II non-inferiority study [27] (NCT03323463) is recruiting 150 participants receiving standard CT, with a greater reduction of RT dose down to 30 Gy delivered over 3 weeks. Interestingly, this study is specific for patients affected by HPV+ but hypoxia-negative tumors.

Less Toxic Chemotherapy Treatment

As it pertains to de-escalation with the use of less toxic CT agents, the discussion includes the De-ESCALATE, RTOG1016, and the TROG12.01 trials. The De-ESCALATE [28••] (NCT01874171) trial started in 2012 involving 334 patients with the aim of studying the proposed equal efficacy with lower toxicity of cetuximab/RT compared to the current standard of care cisplatin/RT in HPV+ low-risk patients with oropharyngeal cancer. Patients were randomized and received RT with 70 Gy in 35 fractions concomitant to intravenous (IV) cisplatin or IV cetuximab. Results from this trial revealed no significant differences between the cisplatin group and the cetuximab group in terms of grade 3 to 5 toxicity and overall-grade toxicity (mean number of events per patient: 4.8 vs 4.8, $p = 0.98$; and 29.2 vs 30.1, $p = 0.49$). However, significant difference was seen between the cisplatin arm and the cetuximab arm in 2-year OS rates (97.5% vs 89.4%; $p = 0.001$) and 2-year local recurrence (6.0% vs 16.1%; $p = 0.0007$). Although there were a higher number of serious adverse events in the Cisplatin group, these results confirm the superiority of the current standard of care with Cisplatin for fit patients. In addition, as noted by Jones et al. [29], cisplatin provided more quality-adjusted life years (QALYs) and was less costly when compared to cetuximab.

RTOG 1016 [30••] (NCT01302834), a phase III non-inferiority trial with 987 participants, tested the efficacy of treatment with RT and cisplatin or cetuximab similarly to the De-ESCALATE trial. Patients were stratified by T stage (T1–2 vs T 3–4), N stage (N0–2a vs N2b-3), Zubrod performance status (0 vs 1), and smoking history (≤ 10 pack-years vs > 10 pack-years) and were then randomized into two groups. The first group underwent IMRT twice daily since day 4 for 6 weeks as well as high-dose cisplatin. The second group began with cetuximab over 2 h for 1 week, then cetuximab over 1 h once weekly for a total of 7 weeks along with IMRT (analogous to group 1). In accordance with the De-ESCALTE trial, at median follow-up of 4.5 years, RT with cetuximab failed to meet the noninferiority criteria for OS (HR 1.45, 95% upper CI 1.94; $p = 0.5056$ for noninferiority; $p =$ 00163). In particular, estimated 5-year OS for cetuximab was 77.9% (95% CI 73.4–82.5) vs 84.6% (95% CI 80.6–88.6) for cisplatin. Moreover, toxicity profiles were similar in both groups (acute moderate-to-severe toxicity 77.4%, 95% CI 73.0–81.5 vs 81.7%, 95% CI 77.5–85.3; $p = 0.1586$; and late moderate-to-severe toxicity 16.5%, 95% CI 12.9–20.7 vs 20.4%, 95% CI 16.4–24.8; $p = 0.1904$). Although both trials support the conclusion that RT plus cisplatin remain the standard of care in HPV+ oropharyngeal cancer, it is important to note some differences such as the different study sample, the different inclusion criteria (De-ESCALATE only included "low-risk" patients), other the different RT regimen.

On the other hand, a phase II trial conducted by the University of Michigan Rogel Cancer Center [31] (NCT01663259) revealed excellent disease control with the combination of cetuximab with RT, despite a more significant acute toxicity profile compared to the standard treatment cisplatin and RT. This study included 43 participants, who received 70 Gy in 35 fractions to the primary tumor and 50–60 Gy to subclinical target volumes, delivered over 7 weeks. Thirty-eight patients were assessed at a mean follow-up of 20.2 months, and only 1 patient experienced disease recurrence and subsequently died.

The TROG 12.01 trial [32] (NCT01855451), with an estimated completion in June 2020, may also provide additional information on this matter. This is a randomized trial with 189 participants that again compares the treatment-related side effects between standard dose RT associated with cisplatin or cetuximab. Of note, all of the participants are characterized with low-risk HPV OPSCC. These patients were randomized into two groups. Group 1 receives RT (70 Gy in 35 fractions, 5 days a week over 7 weeks) with weekly cetuximab (400 mg/m2 loading dose IV prior to radiation, followed by weekly 250 mg/m2 for the duration of the RT), while group 2 receives RT (70 Gy in 35 fractions, 5 days a week over 7 weeks) with weekly cisplatin (40 mg/m^2 IV for the duration of the RT). Primary outcome measures symptom severity at 20 weeks.

Finally, a randomized phase II trial [10] (NCT04106362) comparing RT with concurrent cisplatin with or without the addition of cetuximab is studying specifically patients with KRAS-variant HPV+ OPSCC. It will include 70 patients and may shine a light to more personalized treatment of patients with KRAS-variant.

Removal of Chemotherapy

Lastly, the discussion turns to completely remove CT, maintaining exclusively lower-dose RT.

NRG HN002 [33] (NCT02254278) is an on-going, randomized phase II trial studying a strategy to treat patients with locoregionally advanced OPSCC with reduced-dose IMRT with or without cisplatin. Given the purpose of reducing the risk of important sequelae, primarily as it regards swallow function, without compromising survival, this study aims to obtain a 2-year PFS rate of at least 85% without severe swallowing toxicity (e.g., long-term feeding tubes) at 1 year [18]. A total of 295 patients with p16+ (cT1–2, cN1–2b, or cT3, N0–2b), non-smoking-associated OPSCC will be

randomized into two groups. In the first group, patients will undergo IMRT (total dose of 60 Gy) delivered 5 days per week and intravenous cisplatin weekly for a total of 6 weeks. On the other hand, the second group will undergo only IMRT with the same dose regimen. This trial, which is estimated to be completed in 2024, promises to yield crucial data in order to continue optimizing treatment strategies.

HN10 [34] (NCT03822897) is a phase II single-arm trial (beginning in February 2019) of elective volume adjusted de-escalation RT (EVADER) in patients with low-risk HPV-related oropharyngeal cancer. The investigators' purpose is to discover whether RT to some drainage areas can be safely omitted to reduce side-effects without increasing recurrence rates. There are two treatment options including RT delivered in 35 fractions, 5 days per week, for 7 weeks, with a total dose of 70 Gy/56 Gy with concomitant cisplatin versus exclusive RT. The study is expected to enroll 100 participants and to be completed by December 2024 with a primary outcome looking at event-free survival at 5 years.

Surgical Based De-escalation

In recent years, there has been renewed interest in primary surgical treatment for OPSCC. Historical open approaches have been substituted with the advent of minimally invasive techniques, such as transoral laser microsurgery (TLM) or transoral robotic surgery (TORS) [35, 36]. To note, decision about necessity of adjuvant therapy is mostly based on the presence of high-risk factors. For example, Kim et al. [37] treated patients with perineural invasion (PNI), lymphovascular invasion (LVI), or multiple metastatic lymph nodes with adjuvant RT alone, while postoperative concurrent RT/CT was given to patients with positive margins or extranodal extension. However, these criteria have been established in studies that included squamous cancers from multiple head and neck anatomical subsites and did not evaluate HPV status (EORTC 22931/RTOG 9501) [38, 39].

Given that patients suffering from HPV-associated OPSCC are mostly young, healthy, and no-smoker and can be expected to survive longer, strategies to de-intensify treatment appear to be attractive and demanded [40]. At this time, only few trials drawn to confirm this hypothesis have been completed (Table 3), while others are currently on-going (Table 4).

Induction Chemotherapy

IC could be used also as a neoadjuvant therapy before OPSCC transoral surgical treatment, other than in the classic setting of CRT [41]. Weiss et al. [42] (2018) published a phase 2 trial (NCT01412229) (including 39 patients) of neoadjuvant CT and transoral endoscopic surgery with risk-adapted adjuvant therapy in patients with head and neck cancer. Patients received treatment with weekly carboplatin plus paclitaxel and daily lapatinib for 6 weeks followed by transoral surgery. Patients with N0-N1 without adverse features did not receive further treatments. Histopathologic assessment revealing margins < 5 mm, extracapsular extension, N2a of N2b lymph node status, perineural invasion, or lymphovascular space invasion resulted in adjuvant ipsilateral neck RT concurrent with weekly cisplatin. Pathology with N2c/N3 lymph node status or positive margins resulted in bilateral neck radiation with bolus cisplatin. Optimistic data showed thirty (76.9%) patients who did not receive adjuvant RT. No patient has recurred or died at a median follow-up of 2.4 years. Moreover, the excellent functional results were obtained, with speech, swallowing, weight, and performance status adequately preserved.

A phase II study provided by Robert Siegel at George Washington University assessed the role of new taxane-based CT (such as docetaxel) along with platinum drugs (cisplatin and carboplatin) in a high-dose neoadjuvant setting, coupled with novel minimally invasive transoral surgery. In this single-arm clinical trial (NCT02760667), started in 2016, Siegel et al. [43] proposed cisplatinum and docetaxel at a dose of 75 mg/m^2 every week for a maximum of 3 cycles during the induction phase for previously untreated moderately advanced OPSCC. If subjects were unable to tolerate cisplatin, carboplatin was administered. Twenty stage III or IVA patients were treated, and tumor shrinkage was evaluated after each cycle. In particular, patients underwent TORS and neck dissection(s) if the primary tumor was > 80% smaller. Primary outcome measures, presented in the ASCO 2018 annual meeting, at mean follow-up of 33 months, 18/20 patients were alive and without evidence of recurrence. Secondary outcomes (PFS, OS and QOL) are expected for June 2020. Early and promising results reported by this trial indicate IC followed by TORS as a possible new paradigm in definitive treatment of OPSCC, significantly improving the functional outcome and avoiding the permanent sequelae and adverse effect of radiation therapy [44].

Surgery plus Reduction Adjuvant Radiotherapy

Standard RT dose for the adjuvant treatment of OPSCC is 66–60 Gy, and to date, no trial has demonstrated the feasibility of radiation dose de-intensification. On the other hand, multiple studies have shown 50–60 Gy to be a critical dose range concerning the risk of long-term dysphagia when delivered to the pharyngeal musculature. In this setting, a potential reduction of the adjuvant radiation dose in order to limit late radiation toxicity, maintaining oncological outcomes, have been explored for HPV-related OPSCC patients.

The Eastern Cooperative Oncology Group (ECOG) 3311 trial [45] (NCT01898494), a phase II study, aim to response to this question. Primary outcomes (define proportions of

Table 3 Completed surgery based trials

Trial	Start year	Status	Type	Characteristics	Population	Primary outcomes
Surgery plus reduction adjuvant radiotherapy						
NCT01898494 (ECOG3311)	2013	Active, not recruiting	Risk-stratified RCT phase II	Low risk: TORS; Intermediate risk: a) TORS +50 Gy, b) TORS +60 Gy; High risk: TORS + CRT	T1–2 N1–2b (7th Ed. AJCC)	PFS, accrual rate, risk distribution
Induction chemotherapy						
NCT02760667 (Siegel et al.)	2015	Active, not recruiting	Single-arm (phase II)	IC (cisplatin/carboplatin and docetaxel) + TORS	HPV+/HPV−; Stage III + IVa (7th Ed. AJCC)	OS, PFS, QoL, toxicity
NCT01412229 (Weiss et al.)	2018	Active, not recruiting	Single-arm (phase II)	IC (carboplatin, cetuximab, Nab-paclitaxel) + TORS ± CRT	HPV+/HPV−; Unresectable T N2b or greater	OS, PFS, RR, QoL, toxicity

Abbreviations: *RCT* Randomized controlled trial, *TORS* Trans-oral Robotic Surgery, *CRT* Chemoradiotherapy, *IC* Induction Chemotherapy, *PFS* Progression-free Survival, *OS* Overall Survival, *QoL* Quality of Life, *RR* Response Rate

patients alive and progression free at 24 months) will be available in February 2020. On the other hand, the secondary outcomes will stress incidence of adverse events, OS, swallowing, and voice function. Sixty-two surgeons from 50 centers in North America are credentialed for enrolment in this trial. All patients, 511 participants at date, are stage III or IVA and underwent TORS and neck dissection. Subsequent adjuvant management was based on the pathological findings and risk stratification (low, intermediate, or high). Low-risk patients (T1–2 N0–1, with clean margins and without ENE or perineural or lymphovascular invasion) were treated with surgery alone (group A). High-risk patients (positive surgical margin, ENE or five or more metastatic lymph node) received standard radiation IMRT with concurrent weekly cisplatin (group D). Patients who fell into the intermediate-risk category (clear or close margins (< 2 mm), 2–4 lymph nodes involved, perineural or lymphovascular invasion, minimal ENE < 1 mm) were randomly assigned in two subgroups: (B) TORS and low-dose IMRT 50 Gy in 25 fractions and (C) TORS and standard dose IMRT 60 Gy in 30 fractions. The primary objective of this study is to demonstrate that upfront surgery can permit reduced dose with the same oncologic efficacy and less radiobiological effect.

At the same time, the Lawson Health Research Institute group in ORATOR 2 clinical trial [46] (NCT03210103) (expected to end in 2028) compares outcomes in HPV-related oropharyngeal cancer tumors treated with a primary RT versus a primary surgical approach followed by low-dose RT. At date, they enrolled 140 participants (T1–2 N0–2), randomized, and assigned to two arms: (1) primary RT 60 Gy ± CT for patients with multiple lymph nodes or single > 3 cm and (2) transoral surgery and neck dissection ± adjuvant RT 50 Gy if required for adverse features. The goal of this trial is to compare both oncologic and functional outcomes (overall survival, quality of life, dysphagia, and speech intelligibility) in HPV-related OPSCC, providing a high-level evidence able to guide the treatment selection.

Surgery plus Reduced Adjuvant Chemoradiotherapy

Another possible approach to the de-intensification of postoperative adjuvant therapy is to reduce adjuvant CT dose.

One of the objectives of already cited ECOG 3311 [45] is to distinguish between different types of extracapsular extension (ECE) and its consequences in p16+ patients. In this study, ECE was distinguished as absent, present but minimal (tumor extends ≤ 1 mm beyond lymph node capsule), or present with extensive infiltration (tumor extend > 1 mm beyond the lymph node capsule). These subcategories might change the standard use of adjuvant CT. In the most recent NCCN guidelines [19], there is no difference between small or gross extranodal extension, while both are considered as an adverse feature and treated with systemic therapy. In the ECOG

Table 4 On-going surgery-based trials

Trial	Start year	Status	Type	Characteristics	Population	Primary Outcomes
Surgery plus reduction adjuvant chemoradiotherapy						
NCT02072148 (SIRS TRIAL)	2014	Recruiting	Non-randomized	Low risk: TORS; Intermediate risk: TORS +50 Gy; High risk: a) TORS + CT (cisplatin) RT (50 Gy), b) TORS + CT (cisplatin) RT (56 Gy)	HPV+; T1-T3 N0-N2b	DFS, LRC
NCT02215265 (PATHOS)	2015	Recruiting	Risk-stratified RCT Phase II-III	Low risk: TORS; Intermediate risk: a) TORS +50 Gy, b) TORS +60 Gy; High risk: a) TORS + CRT, b) TORS + RT	HPV+; T1-T3 N0-N2b (7th Ed. AJCC)	OS, swallowing function
Surgery plus reduction adjuvant radiotherapy						
NCT03210103 (ORATOR2)	2018	Recruiting	Randomized Phase II	RT ± CT vs. TORS ± RT (50Gy)	HPV+; T1–2 N0–1-2	OS, QoL, PFS, toxicity profile

Abbreviations: *RCT* randomized controlled trial, *TORS* trans-oral robotic surgery, *CT* chemotherapy, RT radiotherapy, *CRT* chemoradiotherapy, *DFS* disease-free survival, *LRC* local-regional control, *OS* overall survival, *QoL* quality of life, *PFS* progression-free survival

cohort, patients with minimal ECE are included in the intermediate-risk group, thus receiving only radiation therapy without concurrent cisplatin. The rationale for this categorization is based upon the unclear prognostic value of ENE in OPSCC that does not seem to be a reliable prognostic factor in p16 positive oropharynx tumors [47].

Similar clinical trials are recruiting patients at stage III or IVA in Europe to explore the potential of less intensive adjuvant treatment after surgery. PATHOS [48] (Post-Operative Adjuvant Treatment for HPV-Positive Tumours) is a phase II/III randomized controlled trial (NCT02215265) that is testing reduced intensity adjuvant treatment in patient undergoing transoral surgery for HPV-positive OPSCC. The study started in the UK in 2015 and transitioned in phase III in 2018. PATHOS aims to establish whether de-intensification of adjuvant treatment will confer improved swallowing outcomes, maintaining high rates of cure. Following transoral surgery, patient with T1–3 N0-N2b were allocated into study groups based on histological findings: (A) patients in the low-risk pathology group (no adverse features) will receive no adjuvant treatment, as in common practice; (B) patient in the intermediate-risk pathology group (T1–3, N2a or N2b, perineural or vascular invasion, close margins) will be randomized to receive standard dose postoperative RT (control group) or de-escalation RT; and (C) patients in the high-risk pathology group (positive margins with negative marginal biopsies and/or ECS) will be randomized to receive postoperative chemoradiotherapy, as in standard practice (control group), or RT alone.

The SIRS TRIAL [49] (NCT02072148) is another ongoing non-randomized study conducted in order to assess the de-intensified adjuvant CRT. All patients underwent TORS and are then randomized in four different groups based on several prognostic factors (complete resection, ECS, number and location of positive nodes, PNI, LFI). In case of no adverse prognostic features (low risk group), the adjuvant therapy is omitted, while in the intermediate group a postoperative reduced dose RT (50 Gy) is administered. High-risk patients are otherwise treated with concurrent CRT and are randomized in two different groups based on adjuvant RT dose (50 Gy plus Cisplatin or 56 Gy plus Cisplatin). The study is expected to enroll a total of 200 patients with an estimated completion date on October 2020.

Surgery plus Radiotherapy—Omission Chemotherapy

Use of CT in addition to RT has been standardized in case of adverse factors such as positive surgical resection margins and/or presence of ECS. On the other hand, acute and late toxicity related to adjuvant treatment has been largely demonstrated with worse functional outcomes in the long-term period [50].

Moreover, given that the benefit of adjuvant CT in case of ECS has not been fully elucidated, particularly in HPV-related OPSCC, the already cited PATHOS [48] trial will randomize the group of "high-risk" patients (those with involved < 1 mm margins and/or ECS) between a control arm of POCRT (60 Gy in 30 fractions over 6 weeks with concurrent cisplatin) and the test arm of PORT alone (60 Gy in 30 fractions over 6 weeks). The co-primary endpoints are patient-reported swallowing function 12 months after treatment and overall survival. Secondary outputs include loco-regional control and quality of life [51].

An et al. [52] published a paper reporting data from the National Cancer Database (NCDB) about 371 patients with high-risk HPV OPSCC who received adjuvant treatment after primary surgery. In particular, ENE-positive patients were selected, and a comparison was performed between adjuvant concurrent CRT ($n = 305$, 82.2%) or RT alone ($n = 66$, 17.8%). No significant difference was found for the 3-year OS (CRT 89.3% vs RT 89.6%).

Finally, the phase 3 ADEPT trial [53] (NCT01687413) started in 2013 with the aim to assess the omission of CT in the adjuvant setting, according to the primary outcomes of DFS and LRC. Patients (p16+) were randomized in two different groups treated with IMRT (60 Gy in 30 fractions) alone or IMRT (60 Gy in 30 fractions) plus CT (six doses of weekly Cisplatin). Although the study completion date was expected in October 2019, the trial prematurely terminated with only 41 patients enrolled due to the slow accrual and funding issues.

Summary

Nowadays HPV-associated OPSCC can be considered a distinct entity from HPV-negative disease, characterized by different diffusion pattern in the population and different prognosis. Considering the better outcome compared to HPV-negative patients, HPV-positive OPSCC may deserve a more personalized therapeutic strategy in order to reduce late sequelae induced by surgery, radiotherapy, and systemic therapies. Several de-intensified approaches have been investigated with the aim to give patients less toxic treatments, while maintaining comparable results in terms of disease's control and survival. Considering the conflicting results reported so far by preliminary studies, it is necessary to wait for the final results of the on-going trials to better clarify which is the best de-intensified strategy and which patients would really benefit from it.

Compliance with Ethical Standards

Conflict of Interest Armando De Virgilio, Andrea Costantino, Giuseppe Mercante, Gerardo Petruzzi, Daniela Sebastiani, Ciro Franzese, Marta Scorsetti, Raul Pellini, Luca Malvezzi, and Giuseppe Spriano declare that they have no conflict of interest.

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- • Of importance
- •• Of major importance

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