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A B S T R A C T

Human papilloma virus (HPV) is a well-established causative factor in a subset of squamous cell carcinomas of the head and neck (HNSCC). Although HPV can be detected in various anatomical subsites, HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) is the most common HPV-related malignancy of the head and neck, and its worldwide incidence is constantly rising. Patients with OPSCC are generally younger, have less co-morbidities and generally have better prognosis due to different biological mechanisms of carcinogenesis. These facts have generated hypotheses on potential treatment modifications, aiming to minimize treatment-related toxicities without compromising therapy efficacy. Numerous randomized clinical trials have been designed to verify this strategy and increasingly real-world evidence data from retrospective, observational studies is becoming available. Until now, the data do not support any modification in contemporary treatment protocols. In this narrative review, we outline recent data provided by both randomized controlled trials and real-world evidence of HPV-positive OPSCC in terms of clinical value. We critically analyze the potential value and drawbacks of the available data and highlight future research directions.

This article was written by members and invitees of the International Head and Neck Scientific Group. (www.IHNSG.com)

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Introduction

It was almost four decades ago after Syrjänen et al. [1] defined human papillomavirus (HPV) as a potential risk factor for the development of head and neck squamous cell carcinoma (HNSCC). Since then, it has become evident that HPV plays a key role in head and neck oncology. The presence of certain (high-risk) types of HPV, that are biologically active, has an impact on epidemiology, prevention, diagnosis, staging workup, prognosis, and will likely impact treatment strategies in the future. Table 1.Table 2.

Oncogenic types of HPV constitute a well-established causative factor in a subset of HNSCC. It is now the predominant epidemiologic risk factor in the development of squamous cell carcinoma of the oropharynx (OPSCC) in multiple geographical regions, particularly in the USA and Northern and Western Europe [2]. In those regions, HPV-positive OPSCC well outnumbers HPV-negative cases [3–5]. The presence of HPV in other anatomical subsites has also been noted. The role of HPV infection in the development and progression of laryngeal malignancies has been investigated but has not been definitively established. According to the literature, HPV DNA can be detected in 3.5–24% of laryngeal tumors with some major regional differences noted [2,6]. However, the true rate of HPV-associated laryngeal carcinoma is estimated at<5 % when based on both p16 immunohistochemistry and HPV-DNA testing [6]. Unlike in OPSCC, the significant association between HPV and more favorable survival rates has not determined to date [7–8] and P16 (INK4A) immunostaining is highly variable and should not be used as indicator for HPV presence in larynx cancer [8–9].

Interestingly, however, while the oral cavity is a predilection site for productive HPV infections the figures in HPV attribution in oral squamous cell carcinoma are variable but relatively low ranging between 2.2 and 4.4% [2,10–11]. A recently published study by Nauta et al. [10] on a large series of oral cancer patients (N = 1069) clearly indicated no difference in survival between HPV-positive and HPV-negative tumors suggesting that determining HPV status in oral cancer patients is irrelevant thus far.

The mechanism of carcinogenesis is proved to be significantly different in HPV-positive versus -negative carcinomas. The number of genetic and epigenetic changes in HPV-positive disease is significantly lower [12]. Viral oncoproteins altering the function of the major regulatory pathways of the cell cycle are responsible for the alternative carcinogenesis in HPV-positive tumors [13]. There is also a major difference in the patients' profile. In general, the typical patient with HNSCC is male, over age 60 and usually has a history of tobacco smoking and alcohol abuse and has a relatively low socioeconomic status [14–15]. Patients with HPV-positive disease are younger, have few comorbidities and tend to have more lifetime sexual partners [15]. Carcinogenesis is not directly linked to traditional risk factors such as smoking or alcohol abuse, although those are not uncommon also in HPV-positive OPSCC patients [16]. Since the early 2000 s and the milestone paper of Gillison et al., it became evident, that regardless of treatment strategy, HPV-positive OPSCC is characterized by a significantly better outcome [17]. Ang et al. [18]proposed the first recursive partitioning model where the HPV status along with TNM staging and smoking status constituted the most important prognostic factors. Based on these prognostic factors, three different risk categories were created: low, intermediate, and high-risk. In the low-risk category including nonsmokers with HPV-positive disease, the 3-year overall survival (OS) was as high as 93%. This excellent prognosis after standard curative regimens for locally advanced disease led to a current research focus on treatment de-escalation. Moreover, in HPV-positive OPSCC, extranodal extension (ENE), a well-established adverse pathological feature traditionally implicating adjuvant chemoradiation, may not have as clear a prognostic impact, although the available literature is somewhat inconclusive in this matter [19–20]. This is an important issue to clarify as overtreatment is possible if ENE determines multimodality adjuvant treatment in this population.

Therefore, the critical question arises: "Can present treatment strategies associated with high morbidity be replaced by de-escalated protocols that reduce radiation dose and/or modify systemic therapies and maintain high survival rates?" This trend in clinical trial designs is clearly noticeable in recent years. However, the conclusions of these trials were not as had been keenly anticipated.

The aim of this narrative review is to present the most relevant recent evidence on the actual impact of HPV in the outcome of OPSCC patients as well as on potential treatment strategies for the future. We also aim to critically review the value of recent data from randomized clinical trials (RCT) and from Real-World Evidence (RWE) observational studies.

Table 1
Recent Real-World Evidence Studies.

Study	Total no OPSCC cases	No HPV + OPSCC	Design	Outcomes and measures
[57]	1873(NCDB)	1367	TORS vs. Non-surgical approach	3 OS
[58]	4473 stage I OPSCC (NCDB)	4473	RT vs.CRT	OS
[59]	22,676 (NCDB) stage III/IV (6872 HPV status known)	2711	Surgery+/-RT, RT vs.CRT	OS
(ref 60)	9745 T1-2 OPSCC (NCDB) (4071 HPV status known)	3057	Robotic vs.non-robotic surgery	OS
[62]	263 OPSCC stage III/IV	263	RT vs.CRT	OS

Treatment de-escalation strategies

The fact that a subset of HPV-positive OPSCC may be associated with a more favorable prognosis than HPV-negative tumors triggered the question about possible modifications of standard treatment protocols. The younger age of patients, longer life expectancy, and quality of life became crucial issues supporting the investigation of possible de-escalation strategies which potentially could reduce morbidity related to treatment-related toxicities without compromising survival outcomes.Table 2Table 1

Radiation therapy combined with other systemic agents instead of cisplatin

In 2010 Ang et al. published a seminal paper, demonstrating that among the RTOG 0129 cohort [18] HPV-positive HNSCC patients have more favorable outcomes than the HPV-negative HNSCC patients (overall 3-year survival rate of 82.4% versus 57.1%.) Since then, constant initiatives to design novel de-escalating strategies followed. Most of these studies are focused on decreasing radiation-induced acute and late toxicities. Several strategies have been adopted to achieve this goal: (1) an outright reduction of radiotherapy (RT) dose, (2) a dose reduction based on response to induction chemotherapy and (3) a replacement of cisplatin, the gold standard in concurrent chemoradiation, by a potentially less toxic systemic agent, such as cetuximab.

In 2006 the well-known, level 1 evidence study by Bonner et al. comparing radiotherapy alone to radiotherapy plus cetuximab was published. The authors concluded that toxicity from concurrent RT and cetuximab appeared to be less than that from concurrent cisplatin-based chemoradiation based on historical comparison and was less toxic than cisplatin but at the same time concurrent RT and cetuximab was very effective, particularly in the treatment of OPSCC [21]. These findings were supplemented 5 years later with promising information, that concurrent cetuximab and radiotherapy significantly improved the 5-year overall survival with 9.2% compared to radiotherapy alone [22]. Based on this and the previous study by Ang [18], the RTOG designed a non-inferiority trial to compare the overall survival of patients with

Table 2
Randomised clinical trials for HPV positive OPSCC treatment de-escalation.

Study	Participants	Design	Primary endpoint
RTOG 1016	987 HPV-positive, T1-T2, N2a-N3 M0 or T3-T4, N0-N3 M0	RT + cisplatin vs. RT + cetuximab	OS
De-ESCaLate HPV	348 HPV-positive low-risk oropharyngeal cancer (non-smokers or lifetime smokers with a smoking history of < 10 pack-years)	RT + cisplatin vs. RT + cetuximab	Overall severe and acute late toxicity
ECOG ACRIN 3311	"intermediate- risk" (clear/close margins, 2–4 + nodes, or ENE ≤ 1 mm), p16 + OPSCC	TORS + 60GyRT vs.TORS + 50GyRT	2 year PFS
TROG 12.01	186 low and intermediate-risk HPV positive OPSCC	RT + cisplatin vs. RT + cetuximab	treatment symptom severity, from baseline to 13 weeks post completion of treatment
NRG HN002	p16-positive, T1-T2 N1-N2b M0 or T3 N0-N2b M0 OPSCC (AJCC 7th edition), with a ≤ 10 pack-year smoking history	reduced dose IMRT 60 Gy with concurrent weekly cisplatin (40 mg/m2) or IMRT 60 Gy alone	2-year PFS
PATHOS *(ongoing)*	T1-3 N0-N2b (TNM7) HPV positive OPSCC	Intermediate and high-risk based on pathology Intermediate risk group: 60 Gy/30 fractions/6 weeks vs.50 Gy 25 fractions/ 5 weeks High-risk group: 60 Gy/ 30 fractions/ 6 weeks + Cisplatin (either high dose or weekly permissible) and the test arm of RT alone, 60 Gy/30 fractions/ 6 weeks.	OS MDADI

HPV-positive OPSCC treated with radiotherapy plus cetuximab with that of patients receiving radiotherapy plus high-dose cisplatin (RTOG 1016) [23]. The hypothesis was that cetuximab would not compromise overall survival, but would reduce acute and late toxicities. A total of 987 HPV-positive, T1-T2, N2a-N3 M0 or T3-T4, N0-N3 M0 (AJCC 7th Edition) OPSCC patients from 82 centers in the US and Canada were enrolled.

Out of the 849 randomized patients, ultimately 399 were assigned to the cetuximab arm, and 406 to the cisplatin arm. Cetuximab and cisplatin were administered per protocol in 85% and 88%, respectively, and at least 95% of the planned 70 Gy dose was delivered to 95% of patients in both cetuximab and cisplatin groups. Radiotherapy plus cetuximab did not meet the criterion for non-inferiority, and overall survival (OS) was worse in the cetuximab arm versus the cisplatin arm (5-yr OS 77.9% versus 84.6%, p = 0.0163). This was driven by a significantly worse progression-free survival (PFS) in the cetuximab arm (5-y PFS 67.3% vs 78.4% with cisplatin, p = 0.0002). The risk of locoregional failure with cetuximab was more than twice that in the cisplatin group (5-y recurrence rates 17.3% vs 9.9%), with no difference in the rate of distant metastases.

The study led Gillison et al [23] to the following conclusions. Firstly, high-dose cisplatin remains the standard of care in platinum-eligible low and high-risk patients. Secondly, current promising phase II de-intensification protocols must be validated in non-inferiority trials with a control group of patients treated with concurrent 70 Gy radiotherapy and high dose cisplatin.

The group from the UK of Mehanna et al. investigated the use of cetuximab as a substitute for cisplatin in an open-label randomized controlled phase 3 trial (De-ESCALaTE trial) [24], but used a different primary endpoint. They focused on the question of the superiority of cetuximab in terms of overall severe acute and late toxicity. A total of 348 patients were enrolled and 334 were randomized. After randomization, 168 and 166 received cetuximab and cisplatin, respectively. The study revealed no difference in severe toxicities (4.8%) between the two arms. Moreover, quality of life assessment using the same measuring instrument showed no difference at 1 year. In line with RTOG 1016, the De-ESCALaTE HPV trial also revealed that the 2-year OS was worse with cetuximab than cisplatin (89.4% vs 97.5%, p = 0.0012), which was due to significantly higher locoregional relapse rates when patients were treated with cetuximab.

The Swedish ARTSCAN III RCT compared oncological outcomes and treatment toxicities between RT with concomitant weekly cisplatin versus concomitant weekly cetuximab in patients with locoregionally advanced HNSCC, of which 76% were p16 positive OPSCC. They also reported inferior OS with cetuximab with no reduced treatment toxicity. [25]

The final RCT on this topic was recently completed from Australia (TROG 12.01) [26]. They randomised 189 low to intermediate risk HPV OPC patients (patients with T4, N3 or N2b/c if > 10 pack year smoking history were ineligible) to 70 Gy in 2 Gy fractions with either cetuximab or weekly cisplatin (40 mg/m^2). The primary endpoint of this study was treatment symptom severity, as assessed by the MD Anderson Symptom Inventory HN symptom severity scale, from baseline to 13 weeks post completion of treatment. This study contains the most comprehensive completed patient reports outcomes (PROs) but found no difference in the symptom severity between the 2 groups. As in the other 2 studies, the oncological outcomes for the cetuximab group were inferior: 80% (95 % CI,70%-87%) 3 year FFS compared to 93% (95 %CI, 86%-97%) for the cisplatin arm, p = 0.015.

These RCTs confirm that radiotherapy and concurrent cisplatin remains the standard of care in HPV-positive OPSCC. The de-escalation strategy of substituting a reportedly less toxic systemic therapy (cetuximab) for cisplatin to reduce toxicity without negatively impacting survival revealed a negative impact on treatment efficacy in terms of locoregional control and overall survival, without any advantage in reducing treatment toxicities [23–24].

Three-weekly high-dose vs. Weekly low-dose cisplatin

Three-weekly high-dose cisplatin (100 mg/m2) is still considered the standard systemic regimen given concurrently with postoperative or definitive radiotherapy in locally advanced squamous cell carcinoma of the head and neck [27–28]. The high rates of severe acute and late toxicities with high dose cisplatin means there is a lot of clinical interest in the potential to safely substitute weekly cisplatin. As attractive as this seems, the data to date is inconclusive. The only RCT published to date is the one from Tata Memorial, India which randomised 300 patients to either weekly cisplatin (30 mg/m2) or high dose cisplatin. Ninety percent were post-operative oral cavity patients who smoked. They found significant poorer oncological outcomes in the weekly cisplatin arm: 59% versus 73% 2-year locoregional control. This study has been criticised because of the relative low dose of the weekly cisplatin (usually 40 mg/m2) [29]. A Japanese study [30], published only in abstract form to date, randomised 261 patients to weekly cisplatin (40 mg/m2) versus high dose cisplatin. The 3-year OS was 72% in the weekly cisplatin arm versus 59% in the high dose arm. The rate of hearing loss requiring hearing aids (G3) was 3% versus 8%. This study was for all

subsites and the abstract contained no data on p16 status. Hence what is really needed is a RCT of weekly versus high dose cisplatin in HPV OPC. Such a study would be clinically very useful but difficult to fund.

We do have the prospective data from the TROG 12.01 study which showed a 3 year PFS of 93% in low-risk group HPV OPC (i.e., excluding T4 and/or N3 and/or N2b-c if smoking history > 10 pack years) patients treated with weekly cisplatin. This is further evidence in support of weekly cisplatin in low risk HPV OPC patients, but to date we have insufficient evidence for an overall definitive conclusion. [31].

Radiation dose de-escalation

The urge for optimising the quality of life(QOL) for low-risk HPV positive OPSCC patients led to a study utilising a reduction in radiation treatment dose. Whether reduced-dose radiation produces disease control and QOL equivalent to standard chemoradiation is not proven.

Yom et al. [32]. reported the results of NRG HN002, a phase II RCT that was designed to potentially choose a suitable treatment de-escalation arm for their prospective phase II or III RCT, NRG HN005. Patients who qualified for this study were diagnosed with p16-positive, T1-T2 N1-N2b M0 or T3 N0-N2b M0 OPSCC (AJCC 7th edition), with a ≤ 10 pack-year smoking history. Eligible patients were randomly assigned to reduced dose IMRT 60 Gy with concurrent weekly cisplatin (40 mg/m2) or IMRT 60 Gy alone, delivered over a moderately accelerated 5-week schedule (six treatments per week). To be considered as a future arm for NRG HN005, the winning arm had to achieve goals of 2-year PFS rate superior to a historical control rate of 85% and a one-year mean composite score ≥ 60 on the MDADI. On final analysis, the IMRT plus cisplatin arm met both goals, with a 2-year PFS of 90.5% and a 1-year MDADI mean score of 85.30, while the moderately accelerated IMRT arm did not, with a 2-year PFS of 87.6% and a 1-year MDADI mean score of 81.76.

NTG HN005 study plans to randomise 711 HPV OPSCC patients to compare 70 Gy over 6 weeks with high dose cisplatin days 1 and 22, with 60 Gy over 6 weeks with high dose cisplatin days 1 and 22 or 60 Gy over 5 weeks with nivolumab. The question arises then, while waiting for the results of NRG HN005 should we continue to treat the patients with the full dose IMRT and cisplatin? As Chundury and Kim pointed out in their comment article to the NRG HN002, previously published phase III de-escalation RCTs serve as a stark reminder that promising single-institution or phase II results often do not measure up when actually compared with standard of care in phase III RCTs [33].Therefore potential off-protocol treatment deintensification should be strongly discouraged.

Transoral surgery followed by risk-adjusted adjuvant therapy

Over the last decades, the management of OPSCC has mostly relied on radiotherapy-based treatment strategies. Although surgical approaches might have quite comparable outcomes to radiotherapy, traditional surgical techniques frequently requiring mandibulotomies and large incisions have been associated with significantly higher morbidity and mortality rates and poor quality of life [34–37]. In recent years, novel transoral surgical techniques including transoral robotic surgery (TORS) and transoral laser microsurgery (TLM) have become an alternative for nonsurgical approaches [38–39]. Meanwhile, implementation of intensity-modulated radiotherapy (IMRT) has also significantly improved patient outcomes by reducing late treatment toxicities [40–41]. This trend is particularly evident in HPV-positive OPSCC [42].

Excellent treatment outcomes, younger age of patients, and long-life expectancy after treatment opened the discussion about possible avoidance of acute and long-term side effects of radiotherapy or chemoradiation including swallowing dysfunction, mucositis, xerostomia, fibrosis, osteoradionecrosis, neutropenia, neurotoxicity, and hearing loss [43]. Currently, surgical or non-surgical treatment plan selection is made mainly based on the institutional experience and/or patient preferences, since there is no level 1 evidence to support the superiority of one approach over the other. In the USA most of the patients with early low-risk disease receive surgical treatment, but in most European institutions primary RT remains the dominant management strategy [44]. In 2015, Yeh et al. [45] in a systematic review of the literature identifying 44 papers comparing the outcome in OPSCC patients treated with intensity-modulated radiotherapy (IMRT) with or without chemotherapy versus patients treated with TORS. Only 6 studies compared the outcome in HPV-positive versus HPV-negative groups, and all found significantly better survival in the HPV-positive group. The conclusions of the uncontrolled reports, mainly institutional case series, included in the analysis pointed out the need for further investigations, preferably by RCT's. Survival outcomes seemed to be comparable, functional outcomes in favor of TORS, but that could be related to selection bias in the included patient populations. It is noteworthy that RCTs were not included. Most of the patients also required some form of adjuvant treatment and only in selected patients was TORS was the only treatment modality. Nichols et al. [46], reported the first-ever Phase 2 RCT comparing the functional outcome of radiotherapy (with or without concomitant chemotherapy) versus TORS and neck dissection (with risk-stratified management afterward) for the treatment of T1 or T2, N0-2 OPSCC (ORATOR trial). The primary endpoint of this study was MD Anderson Dysphagia Inventory (MDADI) score after 1 year. It was 86.9, SD 11.4, in the radiotherapy group that was significantly better than the 80.1, SD 13, score in the TORS with neck dissection group. This trend remained unchanged over time. Other endpoints including the percentage of patients on a total oral diet with no restriction were also in favor of radiotherapy. There were no significant differences in both of overall survival and progression-free survival. The incidence of treatment-related toxicity grade 2 or higher was similar between the two treatment strategies. Nevertheless, one needs to note, that while all primary tumors were limited to T1 and T2, patients with N2 nodal disease were eligible and present in 50% of enrolled patients. Hence it is not surprising that 70% of the TORS patients required PORT and 25% required adjuvant chemoradiotherapy. Ultimate bi- or tri-modality treatment can hardly be seen as an overall de-escalation patient treatment strategy. Of concern, all patients, as per protocol, underwent a tracheostomy, which has a negative effect on swallowing, and is not standard practice for the majority of TORS surgeons. Grégoire and Nicolai, in their comment to the ORATOR study [47], also pointed out several other issues that might have affected the quality-of-life assessment in the surgical arm, such as quite large (5 mm) surgical margins and the relatively short observation time for MDADI score assessment.

In another study, Chen et al. [48] compared functional outcomes and quality of life between 31 patients who underwent TORS or TLM versus 31 matched control patients treated by chemoradiotherapy for oropharyngeal cancer. Only swallowing function had better rates in the surgical group (91.5 vs 72.1, p = 0.01). There were no significant differences in other functional domains of the University of Washington Quality of Life instrument. Most of the patients (74%) treated with transoral surgery (TOS) reported swallowing "as well as ever". The same was achieved by just 32% of the patients who were treated with chemoradiation.

Until recently, there were no studies investigating the feasibility of de-escalation of adjuvant therapy in surgically treated HPV OPSCC patients [23–24]. The first of such studies is the Phase 2 ECOG-ACRIN 3311 study, published recently in Abstract form [48]. ECOG-ACRIN 3311 examines reduced postoperative therapy in patients with intermediate-risk (clear/close margins, 2–4 + nodes, or ENE ≤ 1 mm) p16 + oropharynx cancer patients undergoing primary transoral surgical management. The authors report the primary endpoint of 2-year progression-free survival (PFS) for patients randomized to 50 Gy versus 60 Gy without chemotherapy to be 95.0% (90% CI = 91.4%, 98.6%) and 95.9% (90% CI = 92.6%, 99.3%) respectively, with no significant benefit for the group treated with 60 Gy. These early results look very promising and will likely form the investigative arm of a RCT

comparing arm B with current standard of care in adjuvant therapy.

The second study in this area is the appropriateness of de-intensifying adjuvant therapies in HPV OPSCC. PATHOS [49], a phase II/III RCT of risk-stratified, reduced intensity adjuvant treatment in patients who have undergone transoral surgery.

Patients with T1-3 N0-N2b (TNM7) HPV positive OPSCC undergo TOS and neck dissection before being stratified into risk groups according to pathological findings. Randomization takes place within the intermediate (T3/N2, perineural invasion, vascular invasion) and high-risk (involved < 1 mm margins and/or ECS) groups. Patients in the intermediate group are randomized between the control arm of 60 Gy in 30 fractions over 6 weeks and the test arm of 50 Gy in 25 fractions over 5 weeks. Patients in the high-risk group are randomized between a control arm of 60 Gy in 30 fractions over 6 weeks with concurrent Cisplatin (either high dose or weekly permissible) and the test arm of RT alone, 60 Gy in 30 fractions over 6 weeks. There is an option to boost high-risk sub-volumes to 66 Gy in 30 over 6 weeks in high-risk patients. The co-primary end points are patient-reported swallowing function (MDADI) 12 months after treatment and overall survival. This study has not yet completed accrual.

It is very appropriate to be studying new treatment paradigms for adjuvant therapy in surgically treated HPV OPSCC patients as the current standard adjuvant criteria were developed with studies performed on all HNSCC subsites, including the poor prognosis sites of oral cavity and hypopharynx, and prior to any knowledge of the excellent prognosis of the HPV OPSCC subsite. The results of these studies will hopefully allow us to be able to avoid the current clinical situation whereby these good prognosis surgical patients end up with a total treatment package longer and more intense than standard definitive chemoradiotherapy.

The EORTC 1420 "Best of" [50] trial is an ongoing open-label phase III prospective randomized trial assessing the "best of" surgery compared to the "best of" RT initially in patients with T1-2 N0 OPSCC. The main objective of the study is to assess and compare swallowing function (MDADI) over the first year after randomization between TOS and IMRT. This trial has been slowly accruing since 2016, demonstrating the difficulty of randomization between surgical and non-surgical arms.

Real-World evidence

For the last decade, the debate on de-escalation strategies reflects the pendulum swinging from enthusiasm for de-escalation to more conservative conclusions that the protocols we presently use should not be changed. At the end of the day, the potential quality of life benefits may compromise oncological outcomes. After the initial attractive possibility to identify a low-risk group following the criteria of Ang et al., several clinical studies revealed that none of the experimental strategies brought a real breakthrough in the management of HPV-positive OPSCC. It has also become clear that RCTs comparing surgical versus non-surgical approaches are difficult to accrue patients to, and in more advanced disease are complicated by the frequently high rate of addition of adjuvant therapy, so comparisons can only be between "treatment packages" rather than surgical or non-surgical treatment. The results of these trials to date lead to the conclusion that we must not yet alter our treatment strategies, but the design of further trials is ongoing [51].

The increasing incidence of HPV-positive OPSCC worldwide in recent years has resulted in a growing body of "real world" retrospective data (RWE) which should not be ignored. Table 1The important question is, can we extract clinically useful information from casual analyses of real-world, non-randomized data. The RCTs are designed to define how a drug, device, or treatment protocol performs under well-defined, controlled conditions. The inclusion and exclusion criteria are well defined for the research participants [52]. Therefore, RCTs imply definite limitations and restrictions. As they usually refer to very tightly controlled, homogenous populations, the results may not necessarily properly reflect the given treatment outcomes in less controlled, broader populations. For example, the study groups for numerous trials are composed of patients from the low-risk category according to criteria by Ang et al. [18]. Rietbergen et al. proposed [53] and then validated [54] a recursive partitioning model which could also work not only on selected RTOG 0129 patients from the study by Ang et al. but also on the unselected Western-European cohort of patients. The authors revealed, that apart from HPV status, comorbidities defined by ACE-27 score constituted a significant prognostic marker for both HPV-positive and HPV-negative OPSCC. Moreover, that model may be more suitable for heavy smoking populations from various geographical locations.

By definition, RWE delivers information gathered through observations of routine clinical practice from multiple sources that can be linked together to provide meaningful patterns. RWE is typically based on patients and their clinicians choosing treatments according to the patients' clinical characteristics and preferences—not the needs of a researcher to maintain consistency in recruitment or treatments [52]. The RWE studies may be subject to design flaws, including unrecognized bias (due to unequal distribution of confounding factors), incomplete datasets, classification errors, and record linkage errors [55].

Anglemyer and the Cochrane Methodology Review Group [56] published an overview of methodological reviews comparing the outcomes of observational studies with RCTs and addressing this question. Their key objective was to assess the impact of the study design (including RCTs versus observational study design) on the estimated effect measures. The primary quantitative analysis including 14 reviews, showed that the pooled ratio of odds ratios comparing effects from RCTs with effects from observational studies was 1.08 (95% confidence interval (CI) 0.96 to 1.22). Of the 14 reviews included in this analysis, 11 (79%) found no significant difference between observational studies and RCTs. Recently, robust observational studies were published trying to compare the outcomes of different approaches for HPV-positive OPSCC. Mahmoud et al. [57] in the population-based study of patients from the National Cancer Database evaluated 3-year overall survival by treatment strategy, TORS vs. non-surgical approach, independently in HPV-related and HPV-nonrelated OPSCC. Of 1873 patients, 73% were HPV-positive and 30% were treated with TORS. Comparing TORS and primary radiotherapy - treated HPV-positive OPSCC following propensity-matching did not reveal a significant difference in 3-year survival (95% versus 91% (P = 0.116). In the HPV-negative cohort, TORS was associated with superior survival; 84% versus 66% (P = 0.01). A deeper analysis of the patient characteristics indicates that in fact, individuals in the surgical arm in the HPV- negative cohort received double or triple modality treatment so they represent an escalated arm which potentially could explain the better outcome. Another robust population-based analysis [58] (n = 4473) of AJCC eight edition clinical stage I OPSCC queried from the National Cancer Database compared overall survival of patients treated with radiotherapy alone and patients receiving concurrent chemoradiotherapy (CRT). On multivariable analysis, CRT was associated with more favorable overall survival than radiotherapy alone, hazard ratio (HR), 0.782; 95% CI, 0.645–0.948 [P = 0.012]. Chemotherapy had a positive impact on survival particularly for patients with lymph node-positive stage I disease (stage III-IVA according to the AJCC seventh edition: HR, 0.682; 95% CI, 0.557–0.835 [P < 0.001]), but not for patients with N0 disease (stage I-II according to the AJCC seventh edition: HR, 1.646; 95% CI, 1.011–2.681 [P = 0.05]). Similar results were noted among propensity score-matched cohorts.

Kamran et al. [59] analyzed 22,676 cases registered in the National Cancer Database (NCDB) treated by primary surgery or primary radiation-based treatment for locally advanced oropharyngeal carcinoma. The 3-year OS rates were 85.4% among the 8,555 patients who underwent surgery and adjuvant RT or CRT and 72.6% in the group of 14,121 patients submitted to chemoradiotherapy. Multivariate analysis adjusted for age, gender, race, insurance status, median income, percentage with no high-school degree, Charlson-Deyo score, clinical T and N classes, tumor grade, facility type, treatment at more than one facility and human papillomavirus status, showed that patients who underwent surgery with adjuvant RT or CRT radiotherapy or chemoradiotherapy

had a reduced hazard of death (HR 0.79; 95% CI 0.69–0.91). However, in that study HPV status was missing in 70.6% of patients. The 3-year survival rates after surgery with adjuvant RT or C-RT and surgery alone for HPV-positive patients were 92.2% and 86.1%, P < 0.0001, and for HPV-negative patients were 79.9% and 64.7%, P < 0.0001, respectively.

More recently, also using the NCDB, Nguyen et al. [60] analyzed the results of 9,745 patients with T1 and T2 OPSCC who underwent TORS (2,694 cases) or nonrobotic surgery as definitive treatment. The rates of positive margins were lower in the TORS group (13% vs. 20%, p < 0.001) and they also were less frequently referred for postoperative adjuvant chemoradiation (29% vs 36%, p < 0.001). Among 4,071 patients with known HPV status, TORS was associated with improved overall survival compared to non-robotic surgery in multivariate Cox proportional hazard regression (HR 0.74; 95% CI 0.61–0.90, p = 0.02). This study strongly suggests that TORS was associated with improved surgical outcomes and survival compared to non-robotic surgery in patients with early-stage OPSCC.

De Almeida et al. [61] performed an economic evaluation comparing TORS and chemoradiotherapy for the treatment of early-stage oropharyngeal carcinoma. TORS demonstrated a cost saving of $1,366 and an increase of 0.25 quality adjusted lifer years (QALYs) per case in comparison to chemoradiotherapy. However, in two-way sensitivity analysis, with increasing use of adjuvant therapy for TORS patients and decreasing use of concurrent chemotherapy in patients submitted to radiotherapy, TORS was decreasingly cost-effective. They conclude that TORS is only cost-effective for treatment of selected patients with early stage OPSCC with minimal risk of the indication of adjuvant treatment.

The real-world data is frequently biased by the indications used to assign a certain treatment. Patients with comorbidities are generally treated less intensely, so both the less intense treatment and/or the comorbidities themselves may impact on patient survival, causing a problem to discern specifically the treatment-related effect. Lately, novel statistical methods aim to adjust for that problem. A recently published study by Nauta et al. [62] on a retrospective cohort of 263 advanced stage OPSCC patients from 5 European centers, treated with RT alone or cisplatin-based CRT based on standard clinical indications, apply causal inference to adjust for treatment assignment, thereby simulating a randomized setting. In this study, average treatment effect of concurrent cisplatin on OS probability was estimated using Bayesian Additive Regression Trees (BART) and Bayesian logistic regression. As a result, significantly better survival probabilities were found for HPV-positive OPSCC treated with CRT compared to RT alone (3-year OS probability 0.961 versus 0.798, p = 0.008). This very novel approach indicates the added value of conducting causal retrospective analyses with adjustment for confounding factors. Firstly, to study upfront whether a newly planned RCT is supported by a causal analysis of available retrospective data, and secondly, to evaluate the generalizability of RCT results to a real-world patient population.

At this point, it is crucial to stress that as the number of robust and comprehensive RWE studies become increasingly available, they in themselves must not lead to any form of treatment de-intensification. RWE and even phase II RCTs can deliver promising data that is hypothesis generating for ultimate validation in phase III RCTs. The importance of not modifying treatment prematurely is demonstrated by RTOG 1016, De-Escalate and TROG 12.01 HPV trials which all reported inferior outcomes with the de-intensified treatment arm. Adelstein et al. [63] in ASCO provisional clinical opinion, concludes that whilst the prognostic ability of the 8th edition of AJCC staging edition is considered to be strong and reflective of the current outcomes of treatment for HPV-positive OPSCC “careful study and the analysis of well-designed clinical trials” are mandatory prior to altering current standard practice in this group of patients.

Conclusions

In the present era, there is no doubt that constant search for optimal de-escalation strategies in treatment of low risk, HPV-positive OPSCC will continue. The design of the further clinical trials most likely will be focused on defining the role and form of adjuvant treatment rather than assessing superiority of surgical to non-surgical approaches.

The question remains about how to select proper patient populations for future de-escalation protocols. It is possible, that depending just on the criteria of RTOG 0129 may be simply not sufficient. Implementation of new prognostic factors, including highly advanced molecular diagnostics could be crucial in selecting more defined cohorts of low-risk patients as potential target for de-escalation. Moreover, it has been proven that some presently used risk factors such as smoking may significantly vary in affecting treatment outcomes in different patient populations around the world. The use of more specific surveillance using for example HPV DNA load in the blood of OPSCC patients facilitating earlier initiation of salvage therapy, may increase capacity for safer de-escalation. In respect to the design of further RCT, the information we obtained from RWE cannot be ignored. Obviously, RWE does not provide level 1 evidence and unlike randomized clinical trials, its utility in the decision-making process and the treatment modifications recommended by multidisciplinary teams is limited. A too enthusiastic attitude to this data may lead to pragmatic approximations and potentially dangerous under- or over-treatment. However, one should keep in mind, that in the absence of evidence from RCT, RWE retrospective data constitute an important supplement to our knowledge. Data from non-selected real-world patient populations may indicate future directions for new trials.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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