Treatment preferences in human papillomavirus-associated oropharyngeal cancer

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The population of survivors with human papillomavirus-associated oropharyngeal squamous cell carcinoma (HPV-OPSCC) is rising. The improved prognosis of this etiologic subset is reflected in new staging guidelines as well as ongoing deintensification trials aiming to preserve excellent survival while decreasing treatment-related toxicities. However, as staging criteria and treatment standards evolve in the era of transoral surgery and deintensification, little is known regarding the needs and treatment preferences of patients with HPV-OPSCC. Herein, the current knowledge regarding treatment preferences and priorities, quality of life and concerns among patients with HPV-OPSCC is reviewed.

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Human papillomavirus (HPV)-associated head and neck squamous cell carcinoma (HNSCC) is a growing subset of HNSCC, with distinct risk factors, etiology and prognosis. The majority of HPV-HNSCCs occur in the oropharynx, where in North America and Northern Europe around 60% of incident cancers are due to HPV [1]. This etiologic subset has dramatically improved prognosis relative to other HNSCCs and HPV-unassociated HNSCCs [2]. On average, HPV-positive oropharyngeal squamous cell carcinoma patients (HPV-OPSCC) are younger at diagnosis, although median age at diagnosis appears to be shifting upward [3]. The improved prognosis coupled with younger age and rising incidence has resulted in a growing population of survivors [4]. In light of increasing prevalence of long-term HPV-OPSCC survivors who are expected to encounter late effects of treatment, clinical trials are underway to evaluate deintensification regimens for a subset with low risk of progression or death (Table 1) [5,6].

The goal of therapeutic 'deintensification' is to reduce treatment-related short- and long-term toxicities, while preserving favorable oncologic outcomes and optimizing survivor quality of life (QoL). Deintensification strategies include reducing the number of treatment modalities, modulating radiation or chemotherapy dose, introducing alternative chemotherapy agents or primary transoral surgery (TOS) [7].

Around 2000, it was recognized that OPSCC patients treated with primary surgery had equivalent oncologic outcomes but a higher rate of life-threatening complications when compared with those treated with radiotherapy [8,9]. Thereafter, chemoradiation became the mainstay of treatment. However, the improvement of transoral approaches in the past decade has reintegrated surgery as an acceptable and safe primary therapeutic strategy both in standard clinical care [10] and clinical trials. The overall and progression-free survival after treatment with primary TOS compared with primary radiation appears to be similar in retrospective studies [11]. As TOS is now an acceptable means of primary therapy, is included in National Comprehensive Cancer Network (NCCN) guidelines [10], and as transoral robotic surgery (TORS) is US FDA-approved, the treatment trend has begun to shift away from chemoradiation and back toward surgery [12,13]. Over the same time period, new radiotherapy techniques have been developed and adopted with the goal of improving functional outcomes. While primary radiotherapy remains the mainstay for patients who are not suitable TOS candidates, there are many patients for whom surgery and radiation

Table 1. Selected deintensification trials for oropharyngeal squamous cell carcinoma.

Identifier	Phase	Treatment	Primary outcome(s)	Selected functional outcome(s)
Surgery vs radiation				
NCT01590355 ORATOR	II	TORS vs radiotherapy ± chemotherapy	QoL	Dysphagia (MDADI, feeding tube rate) QoL (EORTC QLQ C30 and H&N35) Voice (VHI-10)
NCT02984410 EORTC 1420	III	TOS vs IMRT	MDADI	Dysphagia (MDADI)
NCT03210103 ORATOR2	II	TOS vs radiotherapy ± chemotherapy	PFS	Dysphagia (MDADI, feeding tube rate) QoL (EORTC QLQ C30 and H&N35) Voice (VHI-10)
Upfront surgery				
NCT01687413 ADEPT	III	TOS, then IMRT ± cisplatin	DFS, LRC	Function QoL
NCT01898494 ECOG 3311	II	TOS, then risk stratification for adjuvant therapy	PFS	Dysphagia (MBS, PSS-HN, MDADI) QoL (FACT-HN) Voice (VHI-10)
NCT02072148 SIRS	–	TORS, then risk stratification for adjuvant therapy	DFS, LRC	Dysphagia (MDADI) QoL (EORTC QLQ C30, MDAI-HN) Xerostomia (XQ)
NCT02215265 PATHOS	II/III	TOS, then risk stratification for adjuvant therapy	MDADI	Dysphagia (MDADI, water swallow test) QoL (EORTC QLQ C30 and HN35)
Reduced-dose radiation				
NCT01084083 ECOG 1308	II	Induction chemotherapy, then low- vs standard-dose IMRT with cetuximab	PFS	VHNSsv2
Radiotherapy alone				
NCT02254278 NRG 002	II	Low-dose IMRT ± cisplatin	Dysphagia, PFS	Dysphagia (MBS, MDADI, DIGEST)
Alternative chemotherapeutic agent				
NCT01302834 RTOG 1016	III	Radiotherapy with cetuximab vs cisplatin	OS	Dysphagia (feeding tube rate, weight loss) QoL (WSQ, EORTC QLQ-C30 and HN35) Dental (dental status) Hearing (HHIA-S)
NCT01874171 De-ESCALaTE	III	Radiotherapy with cetuximab vs cisplatin	Severe toxicity	Dysphagia (feeding tube rate, MDADI) QoL (EORTC QLQ C30 and HN35)

Details available at www.clinicaltrials.gov.

ADEPT: Postoperative adjuvant therapy deintensification trial for human papillomavirus-related, P16+ oropharynx cancer; De-ESCALaTE: Determination of cetuximab versus cisplatin early and late toxicity events in HPV-positive oropharyngeal squamous cell carcinoma; DFS: Disease-free survival; DIGEST: Dynamic imaging grade of swallowing toxicity; ECOG: Eastern Cooperative Oncology Group; EORTC: European Organization for Research and Treatment of Cancer; EORTC QLQ C30: EORTC quality of life questionnaire core module; EORTC QLQ H&N35: EORTC quality of life questionnaire head and neck module; FACT-HN: Functional assessment of cancer therapy-head & neck; HHIA-S: Hearing handicap inventory for adults; IMRT: Intensity-modulated radiation therapy; LRC: Locoregional control; MBS: Modified barium swallow; MDADI: MD Anderson dysphagia inventory; NRG: National Surgical Adjuvant Breast and Bowel Project, Radiation Therapy Oncology Group and Gynecologic Oncology Group; ORATOR: Early-stage squamous cell carcinoma of the oropharynx: radiotherapy versus transoral robotic surgery; PATHOS: Postoperative adjuvant treatment for HPV-positive tumors; PFS: Progression-free survival; PSS-HN: Performance status scale for head & neck cancer patients; QoL: Quality of life; SIRS: Sinai robotic surgery trial in HPV positive oropharyngeal squamous cell carcinoma; TORS: Transoral robotic surgery; TOS: Transoral surgery; VHI-10: Voice handicap index; VHNSsv2: Vanderbilt head and neck symptom severity survey version 2.0; WSQ: Work status questionnaire; XQ: Xerostomia questionnaire.

are both acceptable therapeutic strategies to start with. The decision between primary radiation and primary surgery on the individual patient level is poorly understood, as is the value of each primary treatment strategy as quantified by patient-reported outcomes.

As treatments evolve, knowledge regarding patient needs and preferences remains lacking. In its 2001 report on high-quality cancer care, the Institute of Medicine Committee on Quality of Health Care in America identified patient-centered care as one of six aims for healthcare improvement, and emphasized that progress should be measured in terms of patient-reported outcomes [14]. There is evidence that a cancer patient's active role in decision-making is correlated with higher QoL [15–17] as well as higher satisfaction with care [18,19]. In an era where OSPCC treatment paradigms are shifting and goals of treatment are evolving, it is increasingly important to explore and incorporate patient preference and experience into decision-making.

Patient perspectives on deintensification

Though the focus of deintensification is on QoL and function, the available literature demonstrates that cure is paramount to patients despite the toxic effects of treatment. HNSCC patients overwhelmingly choose cure as a top priority before and after curative therapy. Following cure, patients ranked living the longest and having no pain as next in importance both at diagnosis and post-treatment [20,21]. A separate study explored deintensification preference in patients with OPSCC after chemoradiation. On a five-point scale, the majority (73%) of patients 'agreed' that less chemotherapy (78% of respondents) or less radiation (20% of respondents) would be desirable should there be no resultant decrease in survival. Interviews were then conducted using a time trade-off (TTO) method to assess at what percentage decrease in quoted 2-year overall survival patients would opt to add chemotherapy to radiation. Notably, the majority switched theoretical treatment preference from radiation to chemoradiation after less than a 5% sacrifice in cure despite advisement of the greater morbidity with chemotherapy. Most patients stated that they thought about survival rate when considering deintensification, followed by physician's advice, personal knowledge and then impact on work or career [22]. Acceptability of significant toxicities in order to preserve seemingly small gains in cure and longevity has also been demonstrated in other cancer sites [23–26].

There are no additional data to our knowledge that describe the relative valuations of cure and potential treatment toxicities for OPSCC patients at diagnosis and post-treatment and in the context of HPV. As the incidence of HPV-OPSCC rises, such data are important in order to give context to results of deintensification trials, inform future clinical trial design and support shared deliberation in the interim.

Patient decision-making in cancer

Although little is known about patient preferences for treatment modality or intensity, treatment patterns shed light on differences in care by patient attributes. Analyses using the National Cancer Database describe an increase in the proportion of surgery as opposed to chemoradiation as management for OPSCC after the FDA approval of TORS in 2009 (30.4%) until 2012 (34.8%), with an increase among early-stage OPSCC from 2004 (56%) to 2013 (82%) [12,13]. Surgical treatment was independently associated with patient age (young), socioeconomic status (high), insurance type (private), residence more than 75 miles from the treating hospital, hospital type (academic), and hospital location (West North Central US) [13]. Travel distance has previously been identified by patients as a barrier to head and neck cancer treatment [27], and a recent study in prostate cancer shows that despite equivalent oncologic outcomes, probability of receiving radiation over surgery decreases the farther the patient lives from the treatment center [28].

Co-morbidities are of prognostic significance in oropharyngeal cancer [29] and predict receipt of less aggressive treatment [30]. It is possible, yet unknown, that frailty predicts favoring a less intense treatment regimen by the physician and the patient. Among patients with cancer, younger patients accept chemotherapy at a lesser quoted benefit than older adults [31]. According to SEER data, OPSCC patients who are older are more likely to receive no treatment [32,33], and less likely to receive combined therapy [33] than their younger counterparts. It is unknown whether the trend toward less treatment by older age is driven by providers or by patients concerned about toxicity of treatment with curative intent, as nuanced analysis is lacking.

Where treatment options are available, preferences are rarely generated by patients alone. Physician and tumor board recommendations often carry heavy weight in decision-making, and these parties are ideally cognizant of patient values during deliberation. In prostate [34] and breast [35] cancer, physician recommendation between equivocal treatment options exerts significant influence on decision-making. Interestingly, access to and order of specialist consultation has additional bearing. Prostate patients who see a radiation oncologist are more likely to choose radiation therapy [36]. Among larynx cancer patients, the specialist first seen (Medical Oncologist, Radiation Oncologist or Surgeon) was considered by patients to be the most involved in and the most important to making the treatment plan [37].

In addition to providers, family members and companions often share the deliberation. For example, prostate cancer patients report that their family members affect their treatment choice [34], and patients were more likely to choose treatment with curative intent over active surveillance after consultation with friends [36]. In OPSCC, however, no such data exist to describe the role of family and companions.

Patient values & treatment choice

Differential value placed on function by individual patients likely contributes to treatment preference. For example, in prostate cancer, among patients who preferred brachytherapy over radical prostatectomy or active surveillance, urinary incontinence was more likely to be considered worse than bowel complaints [38]. In one study, laryngeal cancer survivors' regret regarding initial treatment decision (surgery vs radiotherapy) was measured using a validated survey instrument along with patient values and QoL. Among survivors for whom speech and eating/drinking was especially valued, higher regret correlated with lower voice and swallow-specific QoL domains, respectively [37]. Although similar data are not available in OPSCC, it is possible that the importance patients ascribe to different functions affect treatment choices which may reflect these relative values. For example, those patients for whom any risk of temporary tracheostomy would be unacceptable may favor nonsurgical treatment.

Health-related QoL (HRQoL) affects patient preference as well. A recent discrete choice experiment (DCE), wherein scenarios were presented as paired options with varying life expectancy and severity of toxicity, examined models of therapy preferences among lung and colorectal cancer patients. The study found that those with worse HRQoL tended to favor length of life, whereas a willingness to sacrifice longevity to preserve functionality was observed in those with better HRQoL [39]. This positive correlation between health and perceived severity of loss of health has been reported among general patient populations [40]. Accordingly, the TTO study among OPSCC patients after chemoradiation found that patient-reported severity of treatment-related toxicity predicted a lower percentage trade-off of 2-year overall survival [22]. In other words, patients who had the hardest time with treatment were counterintuitively more likely than those who experienced less side effects to accept more toxic treatment for small gains in survival. In addition, HPV-positive patients, who tend to have less co-morbidities, were found to have a greater pretreatment to post-treatment drop in QoL compared with HPV-negative patients [41], implying that the 'hit' of toxicity is experienced more intensely by high functioning adults despite the greater magnitude of toxicity in frail patients. A working population or those caring for family members in the home, for example, may experience greater insult from speech dysfunction, disfigurement and fatigue than patients whose pretreatment functional status disallows these responsibilities. Nuanced explorations are needed to effectively describe treatment decision-making in the heterogeneous oropharyngeal cancer patient population. Useful investigations will describe how patient values, characteristics and QoL affect TTO and desire for cure relative to loss of function.

QoL & treatment modality

SEER data show that although OPSCC patients have lower HRQoL 13 months after diagnosis compared with non-OPSCC, this difference dissipates by 5 years [42]. While there are demographic differences from non-OPSCC, OPSCC patients tend to report similar distress, fatigue, anxiety, depression, psychological and practical problems. During treatment, changes in these domains are similar among OPSCC and non-OPSCC [43]. In cases where treatment options exist, it is important for both patients and physicians to understand patients' baseline QoL as well as the trajectory that anticipated therapies will yield, most appropriately reflected in patient-reported outcomes. There are limited data on the oncologic and functional outcomes of deintensified and surgical versus nonsurgical regimens to date, although prospective clinical trials exploring such outcomes are underway.

Whereas open surgical techniques negatively impacted patients' functional status in comparison with radiotherapy [8], TOS offers similar oncologic outcomes while carrying lower complication rates, a shorter hospitalization and less frequent and shorter duration of feeding tube placement [44,45]. As an increasingly widespread TOS technique, TORS may present a favorable alternative in comparison to chemoradiotherapy [46–48]. The post-treatment eating ability and diet-related functional status after TORS with or without adjuvant therapy and primary intensity-modulated radiotherapy (IMRT) and chemotherapy has been compared. Function was improved in the surgical group at 2 weeks post-treatment, and returned to baseline by 9 months. In contrast, oral intake and diet domains remained below baseline at 9 and 12 months after completion of primary chemoradiotherapy [49]. In a separate study, improved swallow outcomes were appreciated at 6 and 12 months post-treatment with TORS as compared with chemoradiotherapy [50].

Multiple studies demonstrate that postoperative QoL related to pain, speech and swallow function decreases [51–53], with appreciable recovery by 1 year [54,55]. This recovery is attenuated in those patients that require adjuvant radiation and, to a greater extent, in those that receive adjuvant chemoradiotherapy [52,53,56]. Importantly, one of the main advantages of surgery is pathologic staging, which in one study resulted in changes to clinical stage (upstage or downstage) in 40% of cases [57]. Surgery can provide the opportunity for some patients to avoid long-

term morbidity associated with adjuvant therapy, while others may warrant more treatment based upon pathologic stratification.

Radiation, though carrying the benefit of avoiding acute surgical risks, has challenging late effects [58]. Dysphagia and xerostomia in particular represent the greatest detriment to QoL [59]. However, the advent of IMRT in place of conventional 3D conformational radiotherapy allows for protection of adjacent pharyngeal constrictor muscles [60] and salivary glands [61], while preserving acceptable oncologic outcomes [62]. Indeed, a longitudinal salivary-sparing chemo-IMRT study showed favorable results at a median follow-up of 6.5 years, with HRQoL similar to pretreatment [63]. A randomized trial is underway to evaluate dosimetric sparing of critical swallowing structures with the goal of preventing long-term dysphagia and aspiration [64].

One of the first deintensification trials showed that a complete clinical response to induction chemotherapy may identify patients suitable to receive lower doses of radiation (≤ 54 Gy) with concurrent chemotherapy while maintaining acceptable progression-free survival. Importantly, when compared with standard dose chemoradiation in a clinical trial, significantly fewer patients treated with the deintensified regimen had impaired nutrition or difficulty swallowing solids [65]. Similar functional preservation is anticipated from other deintensification trials.

Overall, pooled QoL scores from 1997 to 2016 show OPSCC survivors who had undergone surgical and nonsurgical management had comparable outcomes [66]. In the midst of changing practice patterns, diversity of measurement tools and lack of high-level data, it is yet unclear how different primary treatments affect QoL in the short or long term.

Defining needs among HPV-associated head & neck cancers

HPV-positive and HPV-negative OPSCC are distinct entities, however, there is a paucity of data relating the unique experiences of patients by HPV tumor status. The available literature suggests patient preferences are similar, although patients with HPV-associated cancer have unique needs.

The only available preference study stratified by HPV tumor status is the TTO analysis wherein interviewers elicit percent sacrifice in survival in exchange for avoiding chemotherapy among patients after chemoradiation. No difference in theoretical sacrifice in 2-year overall survival was found among HPV-positive compared with HPV-negative patients despite dramatically different quoted survival rates by interviewers (95% in HPV-positive compared with 55% in HPV-negative) [22]. The similar preference for aggressive treatment in the face of disparate prognostic forecasts seems to undermine the spirit of deintensification, although additional studies are needed.

The sexually transmitted nature of HPV-positive OPSCC presents unique psychosocial implications, including anxiety regarding diagnosis and concern about transmitting HPV [67] as well as feelings of guilt or responsibility [68]. Distress among these patients is reported to be moderate, with correlation between distress and self-blame [69]. Indeed, significant increases in abstinence from sex follow diagnosis of oral cavity and oropharyngeal cancers [68]. Understanding psychosocial wellbeing is important to defining the decisional needs of this group. Distress may impact a patient's desired decisional role or alter preference for family member involvement, which may necessitate a disclosure of the diagnosis.

Decision quality is necessarily reliant on patient knowledge. The significant knowledge gaps regarding HPV as the main etiologic cause of HPV-OPSCC represent a decisional need, as only 35–52% [67,69] of patients identified it as such. In addition, only half of patients in one study felt that they had the knowledge base to comfortably discuss HPV with their doctor and family [70]. Certainly, there is additional work to be done to ensure patients' knowledge gaps are addressed, most importantly because of the drastic differences in overall and progression-free survival conferred by HPV-positive tumor status.

Conclusion & future perspective

The field has embarked on a migration toward deintensification with the goal of preserving QoL and meeting patient needs for functional preservation, with insufficient evidence as to what QoL and functional needs entail in the targeted patients. It is unclear what degree of decisional conflict patients experience, or what support is needed in order for a patient with OPSCC facing multiple treatment options to make the best personal decision. Furthermore, how patient values and characteristics affect treatment choice need to be better studied in HPV-associated HNSCC.

Preferences should ideally be explored with additional studies utilizing optimized methods. Patient preference in scenarios where improving length of life requires temporary or lasting toxicity is best assessed with either TTO or DCE methods [71]. DCEs, such as those involving lung and colorectal cancer patients mentioned herein [39], present treatment goals (cure, life expectancy) paired with negative attributes of treatment. The likelihood or severity of

goals and toxicity are inversely varied, and the participant is asked to choose between scenarios. DCEs are analyzed with regression, allowing multiple patient characteristics to be included [71]. Both methods are useful tools to assess patient preferences to support health economic, policy and clinical decisions.

Clinical decisions regarding cancer treatment are best informed by preference studies involving cancer patients. Some OPSCC treatment preference studies have been performed with lay adults as subjects. Interestingly, study members overwhelmingly choose primary surgery [72,73], with the cutoff point for switching to primary radiation at a mean 'cure rate' of 15% [73]. Preference analyses in healthy individuals, however, are poorly generalizable to head and neck cancer patients [74,75] and should be interpreted with caution. Studies involving the selected patient group of interest best speak to the decision in question.

Preference data lay the bedrock for shared decision-making. Now integral to health policy [76], shared decision-making is supported by a growing body of literature describing models and strategies for implementation, notably decision aids [77]. Decision aids are evidence-based tools used in the context of consultation to help patients participate in complex decisions, and are especially useful in settings of clinical equipoise. Decision aids designed for breast and prostate cancer treatment, along with other medical diagnoses, have been shown to assist patients in complex decision-making [78] and are attaining validation and evidence for use in consultations regarding treatment for a variety of conditions. Head and neck patients would theoretically derive great benefit from shared decision-making, as these patients experience high rates of emotional distress among cancer patients [79], with anxiety, depression, uncertainty and hopelessness as the most frequently reported psychological problems [80].

In the era of deintensification, there is a need for additional studies delineating patient preferences and concerns in the context of oropharyngeal subsite and HPV tumor status. Importantly, such studies should be performed as TTO or DCE, and designed for the translatability of findings to the discrimination between treatment options among selected patients, in order to support informed deliberation. These findings will lay groundwork for the development of decision aids, enrich consultations and support clinical trial findings and design.

Executive summary

- Deintensification: the field of head and neck oncology has begun a shift toward deintensification for patients with human papillomavirus-associated oropharyngeal cancer with the goal of preserving quality of life (QoL) and meeting patient needs for functional preservation, with little evidence as to what QoL and functional needs entail in the targeted patients.
- Cure versus toxicity: existing data from oropharyngeal cancer and cancers in other anatomic sites suggest patients are willing to endure significant toxicities for small gains in survival, and that treatment decisions are complex and multifactorial.
- Anticipated data: though deintensified regimens may yield better swallowing outcomes according to retrospective data, anticipated clinical trial results will better define QoL, functional and oncologic outcomes for primary surgical and nonsurgical treatment.
- Call for patient preference studies: in light of the emphasis on shared decision-making by the government, health policy organizations and funding entities, further study is warranted regarding oropharyngeal cancer patient preferences. This investigation would best be performed utilizing time trade-off or discrete choice experiment methods.

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