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The interplay of IMRT and transoral surgery in HPV-mediated oropharyngeal cancer: Getting the balance right

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ABSTRACT

Transoral surgery (TOS) and IMRT represent two primary local ablative treatment modalities for oropharyngeal cancer (OPC). The choice of one over the other represents an interplay between the chance of cure vs risk of late sequelae. HPV-mediated (HPV+) OPC patients generally have excellent outcomes, especially in TNM-8 stage I disease. Controversies exist over which treatment has a more favorable toxicity profile and equal efficacy in the management of this population. Non-randomized retrospective data show comparable oncological and functional outcomes between TOS-based vs IMRT-based treatment for this disease. Several de-intensification concepts have been explored in this subset in both primary surgery-based vs primary radiotherapy-based trials. However, no robust mature trial data are available to convincingly guide treatment selection. TOS is often presented as one of the de-intensification options although the majority of series also describe the use of adjuvant treatments which inevitably result in non-negligible toxicities. Patient selection and surgeons' training are paramount. Understanding tumor biology and the prognostic value of traditional 'adverse' features will further guide trial design for refinement of risk tailored approach. In conclusion, comparative data suggests TOS and IMRT are both effective treatment for TNM-8 stage I HPV+ OPC with similar oncological and functional outcomes. TOS as a single modality has potential advantages in mitigating radiation included toxicities. TOS should be avoided in the presence of clinically overt extranodal extension or when negative margins are unlikely to be achieved. TOS is also less ideal for cases with radiological features predicting a high risk of distant metastasis.

Introduction

The oropharynx plays an important role in swallowing, speech and airway protection. Achieving tumor control while retaining organ function is paramount when treating patients with oropharyngeal cancer (OPC). Surgery and radiotherapy (RT) are two established local ablative treatment candidates for head and neck cancer (HNC). The choice of one over the other, as a primary treatment modality, represents an interplay between the chance of cure vs risk of late sequelae. To maximize oncologic outcomes, RT and surgery can also complement each other when necessary. For example, in the primary surgery setting, post-operative RT (PORT) or chemo-radiotherapy (POCRT) could be given for cases with adverse histological features to enhance disease control, while in the primary RT setting (RT alone or chemo-radiotherapy, CRT), surgery can salvage persistent or recurrent disease. However, single modality (definitive RT alone or surgery alone) generally carries a more favorable toxicity profile compared to bi-modality or tri-modality treatment. Identifying a subgroup of patients who are suitable for single modality remains an active research area.

Due to high complication rates and unsatisfactory oncologic and functional outcomes with primary open surgery [1], OPC patients have typically been treated with an organ-preservation approach reserving surgery for salvage of locoregional failure (LRF). Guided by the Meta-analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) [2], the standard organ preservation approaches for OPC are RT alone for 7th edition (TNM-7) stage I-II and CRT for stage III-IV disease. Major treatment guidelines, such as those of the National Comprehensive Cancer Network (NCCN), have adopted these approaches as standard-of-care since year 2000, although such recommendations do not account for the impact of tumor HPV status and the evolution of surgical and RT techniques. It is important to point out that the clinical trials

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included in the MACH-NC were generally conducted in the pre-HPV era where smoking-related HNC predominated and involved traditional RT techniques with less precise target inclusion and sparing of normal tissues than is achievable using contemporary techniques. It is now known that the prognostic value of nodal involvement has reduced in HPV-mediated (HPV+) OPC [3] and most HPV+ OPC with TNM-7 early nodal disease (N0-N2a and minimal smoking N2b) has excellent outcomes with RT alone [4]. As well, IMRT has improved outcome significantly [5]. Whether the recommendations derived from MACH-NC should still be considered as level I evidence in HPV+ OPC treated with contemporary technique has now been challenged and have stimulated the design of new clinical trials. While randomized trial data are emerging, as yet there is no robust level 1 evidence to convincingly change regular clinical practice. This review summarizes current understanding and future direction in management of HPV+ OPC.

Evolving risk tailored approach in HPV+ OPC: Interplay of IMRT and trans-oral surgery

Risk-tailored approaches are emerging as the cornerstone of contemporary management of HPV+ OPC where low risk patients might be treated less intensively while more intensified treatment should be deployed in higher risk patient populations. In the de-intensification frontier, the fundamental questions are who are at 'low-risk', and which approach has the most favorable toxicity profile. The 8th edition UICC/AJCC TNM classification (TNM-8) now classifies T1-T2 tumor without neck disease (N0) or with ipsilateral lymph nodes all under 6 cm (7th edition N1-N2b) as stage I disease, which carries a low mortality risk. Several retrospective series have confirmed excellent outcomes for this patient group regardless of primary modality (surgery or RT) (Table 1). However, since most of the patients in these studies received intensified treatment, it is unclear if the high cure rates could be replicated with less intensified treatment. Although NCCN Guidelines in 2018 [6] now consider HPV-positive and HPV-negative OPC separately, treatment recommendations have not been altered due to lack of high levels of evidence. HPV+ OPC patients often have earlier nodal involvement disproportionate to primary tumor local extension. Since clinically overt lymph node(s) (LNs) [7,8] are present in > 90% HPV+ OPCs, they are typically treated with CRT and high tumor control is achieved in the majority of the these patients. However, many such cancer survivors risk suffering from long-term sequelae. Reduction of the overall treatment toxicity burden without compromising cure is emerging as a critical dimension of the treatment philosophy for these relatively young patients who can expect long-term survival. Various non-surgical and surgical de-intensification strategies are being investigated including substitution of cisplatin by cetuximab, reduction of RT dose or chemotherapy intensity for definitive treatment, response adaptive approach [9], and reduction of PORT/POCRT intensity (Table 2).

In parallel with the emergence of HPV+ OPC, the dynamics between surgery and radiotherapy have also changed due to the evolution of trans-oral surgical (TOS) techniques, including trans-oral robotic surgery and trans-oral laser microsurgery. Comparable to image-guided IMRT which improves precision in targeting and provides substantially superior normal tissue sparing compared to conventional RT, TOS also permits precision in removal of tumor through the mouth; this approach avoids external excision to access the primary tumor thereby reducing normal tissue damage. This represents a renaissance in surgery for T1-T2 OPC, and is often portrayed as a de-intensification strategy compared to traditional CCRT for this subgroup. However, aggregated data from TOS series published in 2014–2018 have also shown the frequent presence of adverse pathological features: extranodal extension (ENE) is present in 33% patients and 13% appear to experience positive final resection margins (even after revision during surgery) (Table 3). In fact, 75% of patients received postoperative radiotherapy (PORT), of whom 40% received postoperative chemoradiotherapy (PORT, 41%). One can reasonably argue that PORT or POCRT generally comprise slightly reduced RT doses (often 60–66 Gy, delivered on an adjuvant basis) compared to primary RT/CRT (70 Gy) which might result in less toxicity. However, RT volumes in the post-operative setting are often larger when addressing the full extent of the post-operative risk regions (surgical bed) following open surgical techniques such as neck dissections, if recognised radiation oncology

Table 1
Overall survival in HPV-positive Oropharyngeal Cancer by the TNM-8 Clinical Stage Classification.

Study	Study Period	Sample Size	Primary Tx	No. of Cases and 5-yr Overall Survival			
				I	II	III	IV (M1)
Study	**Clinical TNM Classification for HPV+ OPC**						
ICON-S (O'Sullivan, 2016) [8]	1998–2011	N = 1907	Sx: 2% RT: 98%	**85%** (n = 962)	**78%** (n = 564)	**53%** (n = 381)	NA
Australia (Porceddu, 2017) [71]	2005–2015	N = 279	Sx: – RT: 100%	**94%** (n = 132)	**82%** (n = 82)	**69%** (n = 65)	NA
US JHH (Malm, 2017) [72]	2005–2015	N = 435	Sx: 38% RT: 62%	**92%** (n = 281)	**87%** (n = 77)	**74%** (n = 72)	**40%** (n = 5)
US NCDB (Husain, 2017) [73]	2010–2012	N = 5626	Sx: 42% RT: 56%	**90% (3-yr)** (n = 3631)	**82%** (n = 1242)	**72%** (n = 753)	NA
US NCDB (Cramer, 2018) [74]	2010–2013	N = 15116	Sx: 44% RT: 54%	**90% (3-yr)** (n = 8895)	**81%** (n = 3012)	**68%** (n = 1847)	**31%** (n = 320)
Germany (Wurdemann, 2017) [75]	2000–2016	N = 150	Sx: 69% RT: 31%	**94%** (n = 79)	**77%** (n = 31)	**64%** (n = 31)	**25%** (n = 9)
US 5 centers (Haughey, 2016) [35]	1985–2015	N = 704	Sx: 100% RT: –	**90%** (NA)	79% (NA)	70% (NA)	NA
Study	**Pathologic TNM Classification for HPV + OPC**						
US 5 centers (Haughey) [35]	1985–2015	N = 704	Sx: 100% RT: –	**90%** (NA)	**84%** (NA)	**48%** (NA)	NA
US NCDB (2010–2014) (Zhan) [34]	2010–2014	N = 3742	Sx: 100%	**92% (4-yr)** (n = 3001)	**81%** (n = 663)	**62%** (n = 78)	
US NCDB (2010–2013) (Cramer) [74]	2010–2013	N = 5527	Sx: 44% RT: 54%	**92% (3-yr)** (n = 4793)	**81%** (n = 522)	**73%** (n = 103)	**31%** (n = 109)

Abbreviation: Tx: treatment; Sx: surgery; RT: radiotherapy; NCDB: National Cancer Data Base; JHH: Johns Hopkins; ICON-S: the International Collaboration on Oropharyngeal cancer Network for Staging; US: United States; yr: year.