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INVITED REVIEW

The Role for Surgical Management of HPV-Related Oropharyngeal Carcinoma

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Abstract Human papillomavirus (HPV)-associated oropharyngeal carcinoma has become the predominate cause of oropharyngeal carcinoma in the United States and Europe. Management of this disease is controversial. Traditional open surgical techniques gave way to concurrent chemoradiotherapy following several American and European organ-preservation trials suggesting that both modalities were equally efficacious. More recently, minimally invasive surgical techniques have gained popularity. These techniques provide an opportunity to achieve a complete surgical resection without the treatment-related morbidity associated with open surgery. Proponents of this technique contend that transoral surgical techniques provide a means to analyze the tumor tissue, prognosticate, and personally direct therapy. Skeptics suggest that HPV-associated oropharyngeal carcinoma responds well to chemoradiotherapy and that surgery may not provide a treatment advantage. Both approaches provide a unique perspective and both are currently being studied under trial.

Keywords Human papillomavirus · Robot · Surgery · Minimally invasive

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Introduction

While rates of laryngeal, oral, and hypopharyngeal squamous cell carcinoma have been decreasing, the incidence of oropharyngeal squamous cell carcinoma (OPSCC) has been rising [1, 2]. Commensurate with this change, there has also been a change in the patient demographic from a population of older patients with a strong history of tobacco and alcohol use to a younger population of patients with a limited history of tobacco and alcohol use. In spite of the increasing incidence of OPSCC, overall survival has been improving. Until recently, these trends were poorly understood. However evidence suggests that the increased incidence, changing demographics, and improved survival characteristic of OPSCC may be associated with HPV infection [1]. Minimally-invasive surgical techniques provide an opportunity to perform a complete surgical resection, obtain tissue for prognostication, and establish a personalized approach to therapy based on tumor tissue markers. The aim of this manuscript was to review that advantages and limitations of transoral surgery for the management of HPV-associated oropharyngeal carcinoma.

HPV and Carcinogenesis

Experimental work related to HPV-associated carcinogenesis in the oropharynx is in its infancy. Most of what we know draws from the science of cervical carcinogenesis [3]. Cervical and anal squamous cell carcinoma typically develop at sites of squamous metaplasia such as the transformation zone of the cervix where the external squamous cell lined epithelium meets internal columnar-lined epithelium [4]. In the oropharynx, HPV appears to preferentially, although not exclusively, target the highly specialized reticulated epithelium that lines tonsil crypts. It is within the depths of the tonsil crypts that the carcinogenesis is initiated.

Zur Hausen's work [3, 5] was initially focused on cervical lesions; however, the concepts that he defined seem to hold true for oropharyngeal disease. As early as 1975, Newell et al. reported a 5–6-fold increased risk of oral cancer in women with cervical cancer [6]. Later, Syrjänen et al. [7] identified HPV antigens in premalignant oropharyngeal lesions, suggesting the role of HPV in the development of carcinoma and soon thereafter Löning et al. [8] established the relationship between specific HPV types and OPSCCs. More recently, Weinberger, Psyrri, and Gillison have confirmed the causal relationship between HPV and OPSCC [9–11].

These reports justified the observation of many clinicians that the number of tobacco-related OPSCC has declined and a younger population of non-smokers has become more prevalent. These reports have also prompted investigators to reevaluate previously reported survival data for OPSCC. Most investigators have identified that patients with OPSCC can be stratified into two groups. One group responds exceptionally well to therapy while another group seems recalcitrant to therapy. It is only recently that re-analysis of the data confirms that the former group is commonly HPV-positive while the latter group is commonly HPV-negative [12].

While some have suggested that the observed survival advantage in HPV-positive patients may be a result of multimodality chemoradiotherapy, these trends have not been observed in other sites such as laryngeal, hypopharyngeal or oral cavity cancers. It is clear that HPV–related carcinoma of the oropharynx responds to treatment significantly better than HPV-negative disease, irrespective of the treatment regimen. The survival benefit conferred by HPV status is thought to extend from the molecular differences encountered between virally-induced and carcinogen-induced cancers. While smoking and alcohol abuse are known to mutate p53 and other intrinsic tumor suppressor genes, HPV-positive tumors maintain wild-type protein sequences. Consequently, when stressed by treatment modalities such as chemotherapy and radiation, HPV-positive tumor cells are more able to undergo controlled cell death and immune system surveillance.

Treatment Options for HPV-Associated OPSCC

The emergence of HPV-associated disease in the younger population has prompted some to ask "is it time to change our treatment paradigm" [13]? De-intensification trials have gained popularity as the population of HPV-positive non-smokers with OPSCC increases. The goals of de-intensification are to achieve acceptable cure rates with minimal long-term morbidity. This is particularly important to the HPV population because the population is generally young and therefore at risk for a lifetime of compromised quality of life as a result of the chronic toxicities related to chemoradiotherapy. The drive to reduce treatment-related morbidity yet achieve oncological cure has resulted in the introduction of both non-surgical and surgical de-intensification trials.

Non-Surgical Options for Treatment of OPSCC

There are no trials to date demonstrating the efficacy of non-surgical de-intensification; however, there are several trials underway. The Radiation Therapy Oncology Group (RTOG) is currently conducting a phase III randomized control trial (1016) in which patients with advanced OPSCC (excluding T1, 2 and N0, 1 tumors) are randomized to two arms. The first arm consists of accelerated intensity-modulated radiation therapy (IMRT) (70 Gy in 6 weeks) with cisplatin (100 mg/m^2 on day 1, 22). The second arm consists of the same radiation schedule followed by weekly cetuximab (starting one week prior to radiotherapy). Critics suggest that this trial fails to significantly reduce the dose of radiotherapy and will continue to result in chronic toxicities including xerostomia, dysphagia, chronic pain, pharyngoesophageal stenosis, and osteoradionecrosis. The European Cooperation Oncology Group (ECOG) has initiated a phase II study (1,308) to investigate deintensification for Stage III/IV resectable HPV-positive OPSCCs. Patients enrolled in the study will receive three cycles of induction chemotherapy followed by chemoradiotherapy. The induction arm consists of weekly paclitaxel (90 mg/m^2) and cetuximab (250 mg/m^2) and cisplatin every third week (75 mg/m^2). Patients with a complete response will get dose-reduced IMRT (54 Gy/27 fractions) with weekly cetuximab, while those with less than a complete response will receive 69.3 Gy in 33 fractions with weekly cetuximab (250 mg/m^2). Although it has been suggested that these trials are aimed at reducing toxicity, very few of the trials offer a significant reduction in radiation dose, the most significant contributor to treatment toxicity.

Surgical Options for Treatment of OPSCC

Minimally-invasive approaches to the oropharynx have gained favor by obviating the need for a mandibulotomy and reducing the morbidity profile of extensive surgery. Advances in minimally invasive techniques have resulted in a reevaluation of the role of surgical therapy in the management of OPSCC. Early reports by Laccourreye et al. [14] demonstrated the role for transoral surgery after reporting excellent outcomes with lateral pharyngectomy for tonsillar cancer. They reported a 5-year local control rate of 89.0 % for T1 cancers and 81.7 % for T2 cancers using this technique. Steiner expanded the role of transoral resection and popularized transoral laser microsurgery (TLM) for oncologic resection of upper aerodigestive tumors [15]. Steiner's work was subsequently supported by other authors including investigators at Washington University and The Mayo Clinic [16, 17]. Haughey et al. [18] published a prospective multicenter study of 204 patients with stage III and IV tonsil and tongue base cancer treated primarily with TLM. At a mean follow-up 49 months, 79.4 % of patients were alive. The 3-year overall survival, disease-specific survival, and disease-free survival were 86, 88, and 82 %, respectively, and the local and regional control rates were 97 and 87 %. This work supports the earlier work done by Laccourreye et al. and suggests that transoral surgery provides a treatment advantage for the management of oropharyngeal carcinoma.

More recently, transoral robotic surgery (TORS) was introduced and is fast becoming a popular approach for the management of OPSCC. Initially introduced by the group at the University of Pennsylvania for radical tonsillectomy [19], this technique has demonstrated great promise for the management of OPSCC. The robot provides several unique advantages unrealized by conventional transoral techniques. The robotic approach allows for surgical manipulation of the oropharyngeal tissue and multiple points of articulation for the surgical instrumentation. This, in turn, allows for more degrees of freedom during the resection and provides excellent access to the complex and often cavernous anatomy of the upper aerodigestive tract. A human arm, for example, has 7 *df*, 3 at the wrist, 1 at the elbow, and 3 at the shoulder. Using an endoscope, a human arm is limited to 4 *df*. The robot, however, allows for a full 7 *df* [20]. Other advantages include the "master–slave interface" of the robot. This translates the surgeon's hand movements to scaled down movements of the robotic arms while filtering tremors. This feature provides more accurate dissection of complex anatomy. The 3-dimensional high-definition image at the surgeon's console provides excellent visualization. The visualization is also improved over conventional transoral techniques by the use of angled scopes that help the surgeon navigate around corners. These technical advantages allow for meticulous dissection and extirpation of tumors of the oropharynx that previously required an open surgical approach.

Since the initial reports on feasibility of TORS, a number of small surgical trials have demonstrated excellent outcomes. Genden et al. at The Mount Sinai Medical Center reviewed an early institutional experience reporting their experience with robotic management of tonsil, tongue base, and supraglottic carcinoma. In this series, patients did not require prophylactic gastrostomy tubes, and the median time to oral diet was 1.4 days after surgery. Patients were discharged on average 1.7 days after surgery [21] Subsequent reports by this group comparing robotic resection with stage-matched patients treated with concurrent chemoradiotherapy demonstrate that the robotically-treated patients enjoy an improved swallowing profile and oral diet [22].

Moore et al. [23] at The Mayo Clinic reported a prospective series of 45 patients with T1–T4 squamous cell carcinoma of the base of tongue or tonsillar fossae who were all treated with TORS. They found that TORS was safe and feasible and reported that all of the 45 TORS procedures performed were resected with negative margins. Moore et al. described the morbidity and outcomes associated with TORS. Tracheostomy was performed on 14 patients, the majority of which were decannulated prior to discharge; the remaining were decannulated during or after completion of adjuvant therapy. In this series, 88.9 % were able to resume an oral diet within four weeks of surgery. While 17.8 % of patients required a PEG tube, all patients eventually had their feeding tube removed. The need for a PEG tube was associated with larger tumor size and tumor location at the base of tongue. In this series, adjuvant radiotherapy dose was reduced because all margins were negative.

Weinstein et al. at The University of Pennsylvania [24] reported their outcomes with TORS citing an average follow-up of 26 months. In this study, there were 47 patients with oropharynx cancer staged III and IV. All tumors were successfully excised and final pathology evaluation revealed only 1 with a positive margin (2.1 %) as defined by tumor cells at the inked margin. Using the treatment regimen of primary TORS and staged neck dissection with adjuvant chemoradiation as indicated, results showed that local, regional, and distant disease control were achieved in 46/47 (97.9 %), 45/47 (95.7 %), and 43/47 (91.5 %) of patients, respectively, at a mean follow-up of 26 months (range 18 to 44 months). Actuarial overall survival rates at 1 and 2 years for the cohort were 95.7 % (45/47) and 81.8 % (27/33), respectively, and disease-specific survival at 1 and 2 years were 97.8 % (45/46) and 90.0 % (27/30). For patients without extracapsular nodal extension, disease-specific survival at 1 and 2 years was 100 % (27/27) and 100 % (15/15), respectively. For patients with extracapsular nodal spread, disease-specific survival at 1 and 2 years was 94.7 % (18/19) and 80.0 % (12/15), respectively.

The oncologic outcomes from TORS surgery for oropharyngeal cancer (OPC) are slowly emerging, and early outcomes seem promising [24–27]. In the studies to date, local failure rates vary between 0 and 3 %, with median follow-up rates ranging from 18 to 24 months [24–27].

Regional recurrence rates in the same studies varied between 2 and 8 %, while distant disease was identified in 1–9 % of patients. The 18-month overall survival was 90 % in one study, and the 2-year overall survival was 82 and 80.6 % between two other studies. Cohen et al. stratified survival by HPV status and there was no difference, with an overall survival of 81 % in the HPV-positive group and 80 % in the HPV-negative group [26]. Similarly, the 2-year disease-specific survival rates were 90 and 92.6 %. Meanwhile, the 18-month recurrence-free survival rates were 78 % (for both groups) while the 2-year rates were 79 and 86.3 %, respectively. These early figures compared favorably to existing reports of OPC treated with chemoradiotherapy [24–27] yet the functional outcomes associated with transoral approaches are significantly better than chemoradiotherapy.

Functional Outcomes and Quality of Life

Proponents of transoral surgery for oropharynx cancer contend that it offers improved functional outcomes when compared to non-surgical treatment with radiation therapy with or without chemotherapy. Many of the functional limitations incurred by chemoradiotherapy are related to toxicities. A recent retrospective analysis of three RTOG trials suggested that the rate of severe late toxicities in patients receiving chemoradiotherapy is 43 % for all comers, and 35 % for patients with OPC [28]. This group defined late toxicities as grade 3 or 4 pharyngeal and laryngeal toxicity, feeding tube dependence at 2 or more years from treatment, and/or treatment-related death. Another prospective study of 104 patients (72 of whom had OPCs) suggested that approximately half of patients experience hematologic toxicities, while 26.4 % are feeding tube-dependent at one year, and 13.8 % were tracheotomy-dependent (70). In patients undergoing transoral surgery, surgical removal of tumors can provide staging information that may obviate the need for toxic adjuvant treatments.

Several studies report favorable swallowing outcomes using TLM and TORS for resection of head and neck cancers. Rich et al. [29] performed a retrospective analysis and longitudinal descriptive study of 118 patients to evaluate swallowing outcomes on patients treated with TLM for AJCC stage III-IV OPC at Washington University. Patients tolerated TLM well with 82 % enjoying good swallowing at 1 month after surgery. During adjuvant therapy, swallowing scores dropped; however, at 1 and 2 years after TLM, 89 and 88 % of patients had good swallowing function, respectively, and 93 % of patients with T1–T3 enjoyed good swallowing at 2 years. T4 base of tongue disease was associated with persistently poor swallowing function in multivariate analyses, with 40 % having good swallowing at 2 years. They concluded that treatment of advanced stage OPSCC with TLM, with or without adjuvant therapy, resulted in excellent swallowing outcomes for patients with either tonsil or base of tongue resections.

Several TORS studies have demonstrated similar outcomes. Genden et al. reported outcomes following TORS in 20 patients and found that patients tolerated an oral diet at a mean 1.4 days after surgery without any patients requiring gastrostomy tubes [21, 30]. Iseli et al. [31] performed TORS on 54 patients, and 83 % of their patients were tolerating a diet within 14 days, 17 % required a feeding tube at 12 months follow-up, and 5.6 % of patients demonstrated signs or symptoms of aspiration. Moore et al. performed TORS on 45 patients, and 82 % of patients were tolerating an oral diet by the first post-operative visit. Seventeen percent of patients required a feeding tube, but none required assistance with feeding at 1-year follow-up [23]. Hurtuk et al. [32] also described an early return to oral diet with all 54 patients in their study tolerating oral diet on the day of surgery. They reported 20 % of their patients requiring feeding tubes mainly for adjuvant therapy. In these studies, tracheostomy rates varied from 0 to 31 % of patients requiring temporary tracheostomy tubes. However, the majority of these patients were decannulated within two weeks and no patients required tracheotomy tubes at 1-year follow-up.

Patient-reported quality of life may be the next most important outcome, second only to survival. In many instances, patients are willing to trade-off a *longer* life for a better *quality* of life. Treatment for cancer often entails some negative effects on quality of life during the treatment period that may improve over time. Leonhardt et al. prospectively administered the Performance Status Scale (PSS), a disease-specific questionnaire, and the SF-8, a generic questionnaire, to 34 patients with TORS surgery and followed these patients for a year [33]. They observed that the swallowing, and eating and diet domains in the PSS suffered and experienced significant decreases that returned to normal at the 1-year time point. The speech domain, however, was significantly reduced at both the 6-month and the 1-year time-points. They also noted that patients who had TORS with chemoradiation had significantly lower swallowing scores compared to those without. Genden et al. performed a case–control study to compare quality of life for patients undergoing TORS compared to those undergoing primary chemoradiotherapy [25]. In the swallowing and eating and diet domains, TORS patients had significantly better scores immediately post-treatment (72 vs. 43, $p = 0.008$; and 43 vs. 25, $p = 0.01$). While TORS patients had a return to baseline in all domains at 12 months, patients who had chemoradiotherapy did not have a return to baseline in the diet domain.

Advantages and Limitations of the Trans Oral Surgical Technique

Studies suggest that robotic surgery has a more favorable learning curve than traditional transoral laser microsurgery and open surgery [34]. Studies demonstrate that trainees were able to acquire skills in the non-dominant hand more readily using the robot than without [34]. Another study demonstrated reduced task times and abbreviated instrument path lengths in trainees performing the same skills on the robot compared to laparoscopically [35]. Overall, these advantages serve to reduce both physiologic and cognitive stress levels in operators.

Although many benefits have been delineated, several limitations exist with robotic surgery. The cost of a robotic system is well in excess of a million dollars. Maintenance costs and the cost of disposable instruments with limited lifespan can be prohibitive in many institutions or health care climates. Another limitation of robotic surgery is the lack of tactile feedback. This is of particular importance for removal of tumors in TORS surgery. One study, however, suggests that experienced surgeons develop visual cues to overcome this limitation [36]. The girth of the robot and the articulating arms also poses a challenge, particularly for TORS surgery. Large articulating arms can make working in a tight space challenging. Proper positioning of the robot at 30°–45° to the head of the bed as well as positioning of the remote center bands to prevent interference of the arms with adjacent tissues can help overcome these challenges.

Conclusion

In conclusion, the ability to achieve transoral resection of OPSCC with minimal morbidity may provide an opportunity to reduce the doses of adjuvant therapy and thereby reduce treatment morbidity. The pathological information gained by surgical resection can help to personalize therapy. While high-risk features such as lymphovascular invasion and extracapsular extension may mandate adjuvant therapy, these features can only be appreciated if the tissue is available for analysis. Transoral surgery provides the tissue for analysis. Additionally, extirpation of the carcinoma may confer a treatment advantage.

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