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REVIEW

Advanced oropharyngeal squamous cell carcinoma: Pathogenesis, treatment, and novel therapeutic approaches

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Abstract

Oropharyngeal cancer accounts for approximately 2.8% of newly cancer cases. Although classically a tobacco related disease, most cases today are related to infection with human papilloma virus (HPV) and present with locally advanced tumors. HPV related tumors have been recognized as a molecularly distinct entity with higher response rates to therapy, lower rates of relapse, and improved overall survival. Treatment of oropharyngeal cancer entails a multi-disciplinary approach with concomitant chemoradiation. The role of induction chemotherapy in locally advanced tumors continues to be controversial however large studies have demonstrated no difference in survival or time to treatment failure. Surgical approaches may be employed with low volume oropharyngeal cancers and with development new endoscopic tools, more tumors are able to be resected *via* an endoscopic approach. Given advances in the understanding of HPV related oropharyngeal cancer, ongoing research is looking at ways to minimize toxicities *via* de-intensification of therapy. Unfortunately, some patients develop recurrent or metastatic disease. Novel therapeutics are currently being investigated for this patient population including immunotherapeutics. This review discusses the current understanding of the pathogenesis of oropharyngeal cancer and treatment. We also discuss emerging areas of research as it pertains to de-intensification as well novel therapeutics for the management of metastatic disease.

Key words: Oropharyngeal cancer; Human papilloma virus; Transoral robotic surgery; Immunotherapy; Metastatic head and neck squamous cell carcinoma

Core tip: Treatment of oropharyngeal cancer entails a

multi-disciplinary approach with concomitant chemoradiation. Given advances in the understanding of human papilloma virus related oropharyngeal cancer, ongoing research is looking at ways to minimize toxicities *via* de-intensification of therapy. Unfortunately, some patients develop recurrent or metastatic disease. This review discusses the current understanding of the pathogenesis of oropharyngeal cancer and treatment. We also discuss emerging areas of research as it pertains to de-intensification as well novel therapeutics for the management of metastatic disease.

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INTRODUCTION

Oropharyngeal cancer accounts for approximately 2.8% of newly diagnosed cancer cases and, in 2015, will result in 8650 estimated deaths[1]. Today, most cases are related to human papilloma virus (HPV) infections and many are curable with definitive combinations of surgery and radiation or chemoradiotherapy. Hence, HPV is a prognostic biomarker, but not yet predictive. As the field of clinical research continues to advance, methods for de-intensifying treatment for such patients are becoming more important. Here, we will review the epidemiology of oropharyngeal cancer as well as treatment strategies and areas of developing research for those afflicted with this disease.

EPIDEMIOLOGY, PATHOGENESIS, AND RISK STRATIFICATION

Classically, use of tobacco products has been the leading factor for development of oropharyngeal cancer, although this has been shifting with changes in societal trends in tobacco usage[2-4]. This increased risk pertains to use of cigarettes, cigars, and pipes and increases with the number of years an individual has smoked[5]. Smoking cessation resulted in a normalization of risk in casual smokers after approximately 15 years[6,7]. Additionally, tobacco usage during definitive therapy for head and neck cancer is associated with an increased rate of disease progression and death, particularly in those whose cancers are not related to HPV or are p16 negative[8]. Similarly, alcohol intake increases the risk of head and neck cancers in a dose dependent manner[7,9-11].

HPV, most notably genotype 16, has been identified as an increasing causative factor for oropharyngeal cancer and is chiefly seen in patients with minimal tobacco and alcohol use. This is especially important since the pathogenesis, presentation, and prognosis differ in HPV(+) *vs* HPV(-) oropharyngeal carcinomas. The molecular carcinogenesis of HPV associated oropharyngeal cancer has been explored in detail and is separate from that seen in HPV(-) cancer and relates to loss of cell cycle checkpoints[12,13]. In a subset of patients with chronic HPV infections, the viral oncoproteins E6 and E7 bind p53 and pRb/p21, respectively. The resultant effect is that E6 binding causes p53 degradation whereas E7 binding to pRb and p21 leads to an activation of transcription factors. These transcription factors cause malignant cells to progress into the G1 cell cycle phase which is unopposed due to the loss of p53. The latency from time of primary infection to development of malignancy is approximately 15-20 years. Over the last 20 years there has been an steady rise in the number of newly diagnosed HPV(+) oropharyngeal cancers, increasing from 16.3% to 71.7%, accompanied by a corresponding 50% decline in the incidence HPV(-) oropharyngeal carcinomas[3,14-16].

Clinically, HPV+ cancers are more likely to present in younger patients and involve the base of the tongue or tonsils[3,17,18]. Additionally, patients with HPV+ oropharyngeal cancers are much more likely to respond to therapy, have lower rates of disease relapse, and enjoy improved overall survivals. Furthermore, such tumors are less likely to develop second malignancies compared to matched HPV(-) patients[3,14-16,19]. Based on these studies, a model for risk stratification has been generated based on HPV status, smoking history, tumor stage, and nodal involvement. A classification of low, intermediate, or high risk disease has been generated, predicting 3 year overall survivals of 93%, 70.8%, and 46.2%, respectively[15]. Interestingly, a single center study analyzing survival and TNM staging in oropharyngeal cancers found that survival based on TNM status did not correlate with survival in those patients with HPV(+) disease, but it did correlate with survival in those with HPV(-) disease. A retrospective, multivariate analysis of the HPV+ patients, however, was able to generate an accurate prognostic model by including tumor stage, smoking status, and age by recursive partitioning analysis (RPA). Thus, the authors propose an RPA-based staging system in HPV-related oropharynx cancers, whereby stage Ⅰ cancers would be classified by T1-3, N0-N2b tumors, stage Ⅱ by T1-3, N2c, and stage III by T4 or N3 disease[20].

TREATMENT STRATEGIES

Surgical approaches

Surgical approaches are currently one of the primary modalities in the treatment of low volume oropharyngeal cancers. Early stage squamous cell carcinomas of the oropharynx can be managed with either surgery or radiation therapy. Given the significant acute and long term side effects of radiation therapy, minimally invasive surgical approaches [including transoral robotic surgery (TORS) and transoral laser microsurgery (TLM)] have

been increasingly employed for the management of early stage tumors. This increased utilization has been further driven by development of new endoscopic tools including the da Vinci Robot, enabling better visualization and surgical manipulation in the oropharynx. These technologies have allowed tumors only previously resectable *via* external and highly morbid approaches (mandibular split and pharyngotomy approaches) to now be treatable *via* the transoral route with significantly less morbidity. One report of TLM demonstrated the promise of this modality in patients with early stage oropharyngeal cancer (T1-4a, N0). In this study, sixty-nine patients in two centers underwent TLM and neck dissection, of which no patients were treated with adjuvant radiation. Excellent patient outcomes were reported, including a five year overall survival of 86%. Similarly, locoregional recurrences were quite low, with a 90% locoregional control rate in patients with T1 disease, and a 94% control rate in patients with T2 disease[21].

Although treatments with TORS and TLM are increasingly becoming employed in early stage oropharyngeal carcinomas, the bulk of the evidence supporting their use stems from the surgical management of patients with locally advanced (stage Ⅲ/Ⅳ) disease. The utilization of TORS was first reported in 2005[22], and since then has been described in numerous publications as an effective treatment for oropharyngeal cancers[23-25]. In one large case series of patients with locally advanced oropharyngeal cancers (T2-4a, N0-2c), treatment with TORS and selective neck dissections resulted in excellent outcomes, notably with a 98% 1-year disease specific survival. Regarding the need for further multimodality therapy, only 39% required radiation and 39% received chemoradiation. Based on these results, the use of TORS accompanied by selective neck dissection may be a method to de-intensify therapy, sparing patients from the toxic effects of adjuvant chemotherapy, and in some select cases, adjuvant radiation as well[26]. Further matched retrospective patient studies, directly comparing TORS to chemoradiation, have demonstrated that patients treated with TORS have less acute toxicities and a higher rate of recovery to baseline swallowing function at 12 mo[27]. Although these studies support the use of transoral surgery in select patient populations for both early and locally advanced, low volume oropharyngeal cancers, further multi-center, randomized studies comparing transoral surgery-based approaches to definitive chemoradiotherapy are needed in order to establish the role of primary surgery in standard of care practice.

Chemoradiotherapy

The management of locoregionally advanced oropharyngeal cancer (stage Ⅲ-ⅣB) is complex and emphasizes the need for a multidisciplinary approach as treatment for each patient is individualized based on the clinical setting. Currently, the treatment of locally advanced disease focuses around definitive chemoradiotherapy.

Organ preservation with chemoradiation has been studied exhaustively over the last 20 years. The relative benefit of concomitant chemotherapy and radiation has been established through numerous trials; however, the MACH-NC meta-analysis, which combined 93 randomized trials and more than 17000 patients, offers the most comprehensive perspective to date. In this study, concomitant chemotherapy and radiation was found to offer a significant improvement in 5-year overall survival compared to radiation therapy alone (33.7% *vs* 27.2%, absolute difference of 6.5% ± 1%). In an exploratory multivariate analysis, the observed effect of chemotherapy on improved survival decreased as a function of age; in the group of patients 70 and older, no improvement in survival was observed[28]. A similar analysis, presented at the 2015 American Society of Clinical Oncology (ASCO) annual meeting in Chicago, also noted lower survival rates in patients 70 years or older collectively from three previously published Radiation Thoracic Oncology Group (RTOG) studies[29]. A subsequent analysis, based on tumor site, also noted improvement of the 5-year overall survival rate in patients with oropharyngeal cancers, whereby the absolute benefit in 5-year overall survival was 8.1%[30].

A number of chemotherapeutic agents have been utilized as radiation sensitizers during concomitant therapy. However, the most commonly used regimens include high-dose cisplatin (100 mg/m^2 every 21 d for two or three doses), weekly cisplatin (30-40 mg/m^2), weekly carboplatin (AUC = 2) plus paclitaxel (45 mg/m^2), and weekly cetuximab. Landmark studies defining non-surgical approaches established high-dose bolus cisplatin as the original, standard concomitant agent[31-33]. Given the proven efficacy of bolus cisplatin, several phase Ⅱ studies and retrospective case series have sought to establish if weekly cisplatin is an effective and well-tolerated alternative[34,35]. Sharma *et al*[34] demonstrated that the addition of weekly cisplatin (40 mg/m^2) to radiotherapy improved overall survival when compared to radiation alone, though 40% of patients experienced Grade 3 or 4 toxicities in the concomitant arm as compared to 20% treated with radiation alone. Similarly, 29% of patients receiving cisplatin required treatment interruptions, compared to 9% in the radiation alone arm[34]. One meta-analysis found that increased cumulative cisplatin dose, regardless of schedule (bolus *vs* weekly), was associated with improvement in survival[36]. To date, there still are still no prospective, randomized published trials comparing weekly cisplatin and radiation with bolus cisplatin and radiation. Several retrospective reviews presented as abstracts suggest that survival may not be compromised with weekly platinum *vs* high-dose platinum-radiation regimens. Furthermore, patients with low risk disease (*i.e.*, p16+, low tumor volume, < 10 pack smoking histories) will inherently enjoy longer survival times regardless of the chemoradiotherapy regimen administered. Patients with poor prognosis tumors (T4, N2c, N3 tumors, > 10 pack year smoking histories), on the other hand, may benefit from high-dose cisplatin combined with radiation[37].

Given the persistent toxicities with weekly cisplatin and issues with renal failure, carboplatin has been explored alone or in combination with 5-fluorouracil or paclitaxel for use with radiation therapy[38,39]. In a pilot study of 60 patients, the combination of carboplatin and paclitaxel given concomitantly with radiation was well tolerated. Eighty-two percent of patients achieved a complete response and the 2 year overall survival rate was 62%. Fifty nine of the patients completed treatment, with the most common grade 3 toxicities being mucositis, dysphagia, leukopenia, and skin desquamation[38]. In another multicenter phase Ⅲ study, weekly carboplatin and 5-flurouracil given with radiation was compared to radiation alone in patients with locally advanced oropharyngeal carcinomas. Although this study demonstrated increased rates of grade 3 or 4 toxicities in patients receiving chemoradiation *vs* radiation alone (71% *vs* 29%), the three year overall survival rates favoring the chemoradiotherapy arm were impressive (51% *vs* 31%)[39].

Randomized, prospective studies comparing weekly platinum regimens to high-dose cisplatin with radiation have yet to be conducted. Investigators at the University of Michigan compared their institutional studies, utilizing weekly carboplatin and paclitaxel with intense modulated radiation therapy (IMRT) and bolus cisplatin with IMRT, in stage Ⅲ/Ⅳ oropharyngeal cancer patients *via* a matched, paired, retrospective analysis. This evaluation demonstrated that patients treated with high dose cisplatin had higher numbers of grade 3 or 4 toxicities (54% *vs* 40%). After accounting for HPV status, there was no significant difference noted in overall or progression-free survival between the two treatment arms[40].

The anti-EGFR monoclonal IgG1 antibody Cetuximab has been established as an effective agent for use with radiation therapy. In a large Phase Ⅲ trial, the median overall survival and 5-year overall survivals were both significantly improved with the addition of Cetuximab to radiation therapy over radiotherapy alone (49 mo *vs* 29.3 mo and 45.6% *vs* 36.4%, respectively). Of note, on exploratory multivariate analysis it was noted that the greatest benefit was seen in patients with oropharyngeal cancers but a benefit was not seen in those > 65 years old. In addition, it was noted that the development of a prominent acneiform rash (grade 2 or greater) was associated with a significantly improved overall survival[41,42]. Analysis of the effect of cetuximab on overall survival based on pre-treatment characteristics demonstrated that the addition was most beneficial in non-elderly men with oropharyngeal tumors, grade 1-3 tumors, node positive (N1-3), with good performance status[42]. A biomarker analysis evaluating outcomes related to HPV status was recently conducted on this study, and the results were presented at the 2014 ASCO annual meeting in Chicago. This investigation demonstrated improvement in OS with the addition of cetuximab to radiation in both HPV+ *vs* HPV- tumors, though a greater degree of improvement was seen in those tumors which were p16+. This study was exploratory in nature and not powered to make definitive conclusions; however, it does confirm that HPV is a prognostic biomarker, not yet predictive[43].

Given the improvement in clinical outcomes seen with cetuximab, several large trials have sought to answer whether the addition of anti-EGFR monoclonal antibodies (cetuximab or panitumumab) to conventional platinum based chemoradiation results in clinical improvement. Each of these studies has failed to demonstrate improvement in clinical outcomes with the addition of EGFR inhibition[44,45]. One of these studies did demonstrate that although EGFR expression did not distinguish outcome in patients treated with cetuximab, patients with p16 positive oropharyngeal carcinomas had a better 3 year progression free survival (72.8% *vs* 49.2%) and overall survival (85% *vs* 60.1%)[44]. Unplanned post-hoc analysis of RTOG 0522 (reviewing the role of cisplatin based chemoradiotherapy plus cetuximab) demonstrated that patients with high baseline metabolic tumor volumes on PET/CT had an inferior response to chemoradiotherapy in terms of progression-free survival and locoregional control. Interestingly, this remained an independent prognostic factor on multivariate analysis even after factoring for T stage[46].

Based on the evidence of efficacy with the use of Cetuximab as a radio-sensitizing agent, the question has arisen regarding the comparative efficacy *vs* a platinum based regimen. A published single center retrospective study was recently published describing the outcomes of patients with locally advanced head and neck squamous cell carcinoma treated with concurrent chemoradiation stratified by chemotherapeutic agent. It was noted that patients treated with platinum based chemotherapy had significantly superior relapse free and overall survival compared to those treated with cetuximab monotherapy or in combination with chemotherapy[47]. One meta-analysis including 15 trials and 1808 patients which was presented in a preliminary form demonstrates that studies to date support a greater improvement in both locoregional recurrence and overall survival with the use of cisplatin. However, this study had significant heterogeneity and did not account for p16 status[48]. Other studies comparing panitumumab and radiation with cisplatin and radiation have also failed to demonstrate the improvements of this fully human monoclonal antibody against EGFR to the standard of care[49,50]. Ongoing studies are still seeking to answer this question in select populations, including RTOG 1016.

The role of induction chemotherapy in oropharyngeal cancer has been debated extensively and there continues to be some controversy regarding its role. In general, the use of induction chemotherapy has been intended to decrease the rate of distant metastases, to cause rapid cytoreduction, to offer high doses of chemotherapy to tumor prior to disruption of vasculature by radiation, and to decrease tissue volume requiring

exposure to radiation[51]. Three large, randomized phase Ⅲ studies have been performed to date evaluating the role of induction *vs* concurrent chemoradiation, all of which demonstrated no difference in survival or time to treatment failure[52-54]. In the recently published DeCIDE trial, evaluating induction chemotherapy primarily in oropharyngeal cancer, enrollment was difficult and the study was closed after enrollment of 285 of the planned 400 patients. Although overall survival was no different between the arms at three years, one should note that (albeit not statistically significant) the difference in the rate of distant failure was 10% in the induction chemotherapy group *vs* 19% in the concurrent chemoradiation group. HPV status was available for only 49 patients and on subgroup analysis is was noted that there was no statistically significant difference in overall survival between HPV(+) and HPV(-) patients[54]. Early results of a phase Ⅲ trial from Italy, comparing induction chemotherapy followed by definitive chemoradiotherapy *vs* concomitant chemoradiation with cetuximab *vs* cisplatin and 5-flourouracil (5-FU) *via* 2 × 2 factorial design, were presented at the 2014 ASCO annual meeting in Chicago. This trial had a primary endpoint of 3 year overall survival between the induction *vs* no induction groups. Preliminary results demonstrated a statistically significant improvement with induction chemotherapy in both median progression-free (29.7 mo *vs* 18.5 mo, $P = 0.12$) and overall survival (57.6 mo *vs* 45.7 mo, $P = 0.03$). On unplanned subgroup analysis, these improvements were not seen in patients with oropharyngeal cancers. Additionally, when compared with similar previously published trials as historical controls[41,44,54], both progression-free survival and overall survival appear to be lower across the board, for which the etiology is unclear. Reporting of HPV status amongst the treatment groups is pending and will be important in fully interpreting the results of this study[55].

Investigators at the University of Michigan have studied the use of induction chemotherapy as a means of chemoselection, whereby patients with oropharyngeal cancers who had a response to one cycle of induction chemotherapy were treated with definitive chemoradiation, whereas those patients without evidence of response proceeded to salvage surgery. In this study, induction therapy failed to successfully select patients for surgical salvage, but a subgroup analysis demonstrated that higher HPV titers were associated with a significant reduction in tumor burden following the administration of a single cycle of chemotherapy, demonstrating the robust response of p16 positive oropharyngeal tumors to cytotoxic agents[56]. In the companion paper published with this article, correlative analysis noted that EGFR expression was inversely associated with response to chemoselection as well as patient outcomes including disease specific survival and overall survival. Moreover, when biomarkers were combined low EGFR and high p16 expression were associated with a good response to chemoselection however the combination of high EGFR expression, low p53 expression, and high Bcl-xL expression was associate with a poor response to chemoselection and overall survival[57].

DE-INTENSIFICATION OF THERAPY

Although chemoradiotherapy has improved survival outcomes in patients with loco-regionally advanced oropharyngeal cancers, this has come at the expense of both acute and late treatment related toxicities. These toxicities substantially impair patients' quality of life, potentially for the remainder of their lives, and include long-term swallowing dysfunction as a result of radiation. HPV+ oropharyngeal cancer is now being increasingly recognized as a biologically distinct malignancy with a distinct disease course and response to therapy. Moreover, HPV+ tumors have higher response rates to multimodality therapies, lower rates of disease relapse, and improved overall survivals compared with HPV- tumors. In an attempt to mitigate acute and late toxicities, an area of research looking to define patients with low risk oropharyngeal cancer who may be candidates for de-intensification of therapy is actively underway. Proposed methods of de-intensification include decreasing doses of radiation (so called de-escalation) or switching from cisplatin based radio-sensitization to targeted therapy with cetuximab.

To date, few published trials provide insight into this matter, and hopefully with the maturity of several ongoing prospective trials, there will be a body of literature as to guide the field. One retrospective study sought to define the pattern of recurrence in HPV + low risk patients (< 10 pack-year smoking and T1-T3 disease) based on treatment with radiation alone *vs* concomitant chemoradiation. It was shown that low risk patients, those with N0-N2a nodal involvement, had no difference in disease control rates with the introduction of chemo-sensitization as compared to those receiving only radiotherapy[58]. Given the retrospective nature of this study and the fact that the majority of patients not receiving chemotherapy were those with advanced age or restricting medical co-morbidities, it is difficult to draw definitive conclusions. However, this research certainly supports the consideration for de-escalation of therapy in a subset of low risk patients. Currently, RTOG 1333 is assessing such an approach with the primary endpoint of 2 year progression free survival. In this study low, risk patients (HPV+ with a ⩽ 10 pack-year smoking history) with oropharyngeal cancer are being randomized to either radiation (60 Gy, 2.0 Gy/fraction in 6 wk) with concurrent weekly cisplatin (40 mg/m^2 × 6 doses) or radiation alone (60 Gy of radiation, 2.0 Gy/fraction over 5 wk)[59]. As a chief aim of de-escalation is improving treatment related toxicities, one of the main secondary endpoints being followed in this trial includes quality life, most notably swallowing function. ECOG 3311 is an ongoing risk stratified randomized phase Ⅱ

study evaluating an approach of TORS followed by a risk adapted approach in patients with HPV(+) stage Ⅲ/Ⅳ oropharyngeal carcinoma. In this study, based on post-operative findings low risk patients will be observed, intermediate risk patients will be treated with radiation alone, and high risk patients will be treated with chemoradiation.

ECOG 1308 is a prospective, phase Ⅱ study that also examined the role of de-escalation. In this trial, patients were treated with 3 cycles of induction chemotherapy, and if they were found to have a complete response, they were treated with weekly cetuximab and low dose intensity IMRT (54 Gy/27 fractions). If, on the other hand, patients had less than complete response, they received weekly cetuximab with full dose IMRT (68.3 Gy/33 fractions). Preliminary analyses demonstrated that patients with complete responses, treated with low dose IMRT, had an improved 2 years progression free and overall survival compared to those patients in the standard-dose IMRT arm. Additional insights from the analysis of the patient cohort receiving low dose radiotherapy demonstrate that progression-free survival and overall survival were better in patients with a ⩽ 10 pack-year smoking histories and low volume (< T4, T1-N2b) disease. This favorable risk cohort had a significantly improved 2 year progression-free survival compared to other enrolled patients (96% *vs* 64%)[60]. Although this data yields valuable insights into the potential for reducing intensity of treatment for a select population of oropharyngeal cancer patients, a larger, multi-center phase Ⅲ is needed study to verify the results of this de-escalation trial, comparing this concept to standard cisplatin and radiotherapy.

Finally, RTOG 1016 is an ongoing non-inferiority phase Ⅲ trial that is seeking to identify the role of substituting Cetuximab for high dose bolus Cisplatin (100 mg/m^2 q 21 d × 2 doses) in combination with accelerated IMRT. This protocol exclusively enrolled 1000 patients with p16+ locoregionally advanced oropharyngeal cancer (clinical stage T1-2 N2a-N3 or T3-4 any N) with any smoking status. In addition to defining whether the substitution of cisplatin is non-inferior to standard therapy, this study will assess the effect of tobacco exposure and molecular profiles on patient outcomes. This study is now closed to accrual and the results are eagerly awaited.

LOCALLY RECURRENT AND METASTATIC DISEASE

Despite increased understanding of oropharyngeal cancer and advances in treatment of both early stage and loco-regionally advanced disease, a number of patients still develop locally recurrent and metastatic disease. Evidence now supports that HPV(+) oropharyngeal cancer patients who develop progression have a better median overall survival than those cancers which are HPV(-) (2.6 years *vs* 0.8 years). Fakhry *et al*[61] noted a worse survival upon progression in patients with distant metastases or those who initially presented with T4 lesions. Patterns of recurrence are also related to HPV status in oropharyngeal cancers. HPV(+) status markedly reduces the risk for loco-regional recurrence (HR = 0.09, P = 0.03)[62] and in one study was associated with a longer time to distant failure (16.4 mo *vs* 7.2 mo)[63].

The goal of therapy in patients with locally recurrent or metastatic oropharyngeal cancer who are treated with chemotherapy is palliative. As prognosis is poor and effective treatment options are limited, enrollment onto clinical trials offers the best possible care, especially for those who have failed a front-line platinum containing regimens. If trial involvement is not possible, numerous treatment modalities with standard agents may be considered.

Surgical salvage should be entertained in select situations as a treatment for locally recurrent or metastatic oropharyngeal cancer. Recent studies have demonstrated that surgery is an effective treatment option, often improving survival. One large study of 181 patients demonstrated that even when factoring in T/N stage, progression type (distant *vs* locoregional), smoking history, and p16 status to a multivariate analysis, salvage surgery still remained a significant predictor of overall survival (HR = 0.56, P = 0.02)[61]. Another similar retrospective study attempted to gain similar insight; however, this evaluation also considered whether salvage treatment with nonsurgical methods or with surgical methods offered superior overall survival. The investigators found that surgical salvage offered an improvement in overall survival compared to those treated with salvage radiation or chemotherapy. Similar to previous studies, this finding remained significant even on multivariate analysis when p16 status, T/N stage, smoking history, site of disease recurrence, and number of sites with disease recurrence were factored in[64].

If surgical salvage is not an option, there are numerous classes of cytotoxic chemotherapy drugs including platinum agents, taxanes, methotrexate, 5-FU as well as the anti-EGFR targeted therapy, cetuximab, which have proven efficacy in metastatic head and neck cancer. Response rates to chemotherapy range between 10%-30% with single agent regimens and 20%-40% for multi-drug regimens[65-67]. It is important to appreciate that although conventional cytotoxic agents may be combined as doublet therapies (traditionally platinum based), these combinations increase response rates but not overall survival, and they have notable increases in toxicities[66]. There have been no studies showing superiority of one cytotoxic regimen over the other, median overall survivals ranging from 6.6-8.7 mo[65-68]. Incorporation of cetuximab into a 5-FU and platinum containing regimens is associated with an increased objective response rate (36% *vs* 20%), progression free survival (5.6 mo *vs* 3.3 mo), and overall survival (10.1 mo

vs 7.4 mo) relative to platinum-5 FU doublet therapy in patients with metastatic head and neck cancer[69]. Although underpowered to draw conclusions, a post-hoc analysis of p16+ oropharyngeal cancers seemed to have a greater degree of benefit with the incorporation of cetuximab compared to those that were p16-[70].

FUTURE DIRECTIONS

There are currently numerous ongoing trials involving the treatment of oropharyngeal cancer. Among the current research avenues are novel predictive factors for recurrence and the development of immunotherapeutics. Although the prognosis of HPV+ advanced oropharyngeal cancer is impressive with 3 year survival rates of 62%-83%[71,72], there is an increasing rate of distant treatment failure, not accounting for 45% of long term deaths in the population[15,73]. Numerous prognostic factors have been explored as methods to better tailor therapy for those at increased risk, including micro-RNA, advanced T and N classification, and smoking status[58,74,75]. One novel finding, identified as prognostic as well as predictive, is the presence of matted nodes on pre-treatment imaging (CT or PET/CT). Matted nodes are defined as the presence of three lymph nodes abutting one another with loss of the intervening fat plane which is thought to represent radiologic evidence of extracapsular spread. Matted nodes have been identified in 20% of patients presenting with advanced oropharyngeal cancer. In one analysis, patients presenting with matted nodes had a three year disease specific survival of 58% *vs* 97% in those without. This bore out as a predictive marker on a further analysis and on a multivariate analysis whereby the presence of matted nodes remained an independent predictor of poor prognosis even when controlling for age, tumor classification, HPV status, and smoking status[76,77].

There has also been interest in searching for novel biomarkers as to guide patients at risk for reoccurrence. Retrospective analysis of patients with locally advanced HPV+ oropharyngeal cancer has demonstrated that patients who recurred were noted to have a significantly lower rate of E7 antibody clearance[78]. Prospective analyses are needed to determine the utility of E6 and E7 antibody clearance perhaps in combination with plasma HPV DNA levels. Two abstracts presented at the 2015 ASCO annual meeting may also aid in identifying patients at high risk for recurrence. In one study, loss of function tumor suppressor gene mutations appears to decrease the efficacy of treatments for locally advanced squamous cell carcinomas of the head and neck. Activating driver gene mutations, on the other hand, may define poor risk patients, in particular those with HPV(+) oropharyngeal carcinomas[79]. A second study evaluated the implication of persistent HPV-16 DNA detection in oral rinses in patients with p16 positive oropharyngeal carcinomas, treated for locally advanced disease. Data from this evaluation suggests that persistent oral HPV DNA in post-treatment rinses is strongly associated with poorer outcomes[80]. These findings may help to tailor intensification of therapy in high risk populations as to improve patient outcomes.

Immunotherapy [namely Programmed Death-1 (PD-1) inhibition] is currently one of the most exciting and rapidly changing areas of oncology with impressive response rates and improvements in overall survival seen in melanoma and lung cancer[81-83]. PD-1 targeting in head and neck cancer has been of interest as these malignancies [especially HPV(+) tumors] are thought to be quite antigenic[84]. In addition, pathologic samples in both HPV(+) and negative tumors have demonstrated a high frequency of PD-1 and PD-L1 expression, suggestive of a potential role for checkpoint inhibitors[85,86]. Preliminary results of the KEYNOTE-012 study, a phase 1b multisite study evaluating the activity of Pembrolizumab in patients with recurrent or metastatic HNSCC regardless of PD-L1 or HPV status, were reported at the ASCO Annual Meeting in 2015. An overall response rate of 24.8% and stable disease rate of 24.8% was reported with activity observed in both HPV(+) and HPV(-) patients. Although follow up was limited as only preliminary results were available, it was intriguing that the median duration of response was not reached[87]. An accompanying study analyzed this population as to try and identify predictors of response as both HPV and PD-L1 status have been non-discriminatory. It was demonstrated that an inflamed-phenotype gene expression, chiefly interferon gamma, was able to predict 6 mo progression free survival with a 95% negative predictive value and 40% positive predictive value[88]. Similar findings have been reported in melanoma where inflamed-phenotype gene expression signatures appear to predict benefit from pembrolizumab[89]. There are multiple ongoing phase Ⅱ/Ⅲ clinical trials investigating the role for Pembolizumab and Nivolumab in the setting of metastatic disease for head and neck cancer, which include the evaluation of markers to potentially identify responders[87]. Results of these studies will offer new insights and may drastically alter the treatment of metastatic oropharyngeal cancer.

CONCLUSION

The management of oropharyngeal cancer is complex and depends on a multidisciplinary team including otolaryngologists, medical oncologists, and radiation oncologists. Although great strides have been made in the last 20 years in approaches to organ preservation and risk stratification, improvements are needed in delineating the role of treatment de-intensification and development of novel therapeutics for the treatment of metastatic disease. We eagerly await final publications of the data from the recent ASCO annual meetings to further validate the use of several novel agents and treatment approaches.

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