Oropharyngeal cancer: current understanding and management

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Current Opinion in Otolaryngology & Head and Neck Surgery 2009, 17:88–94

Purpose of review

The goals of this article are: to briefly review oropharyngeal anatomy; to provide a review of the epidemiology of oropharyngeal cancer in the Western Hemisphere; to review the literature on the association of human papilloma virus with oropharyngeal cancer; to review the recent literature on evolving diagnostic techniques for oropharyngeal cancer; and to summarize accepted management strategies for oropharyngeal cancer by subsite.

Recent findings

The incidence of oropharyngeal cancer may be increasing among younger age groups in the Western Hemisphere, and this may be related to an increased association with human papillomavirus 16. The implications of this viral association with regard to outcomes and management strategies remain under investigation. Screening with toluidine blue, autofluorescence, or both may be useful adjuncts to physical examination and panendoscopy in assessing potentially invasive or dysplastic lesions of the oropharynx. These techniques remain under study. MRI and PET scan are proving to be useful techniques for assessing local extension, regional metastases, and recurrences of squamous cell carcinoma (SCC) of the oropharynx in selected cases. However, serial computed tomography scanning remains the imaging modality of choice in the United States. Early SCCs of the oropharynx (T1–2), in general, may be managed effectively with either surgery or primary irradiation, though, with either technique, clinicians must have a management plan for the neck. Advanced SCCs of the oropharynx (T3–4, nodally aggressive, or both) require multimodal approaches consisting of either surgery along with adjuvant irradiation or concurrent chemoradiation along with salvage surgery (as necessary).

Summary

Management of SCC of the oropharynx is in a period of transition because of evolving changes in our understanding of the oncogenic process; evolving diagnostic techniques; and evolving combinations of therapies, both surgical and nonsurgical. For the time being, we propose using local subsite and disease stage to guide therapeutic decision-making.

Keywords

concurrent chemoradiation therapy, human papilloma virus, neck dissection, oropharynx, squamous cell carcinoma

Curr Opin Otolaryngol Head Neck Surg 17:88–94

1068-9508

Introduction

The epidemiology, diagnosis, and treatment of oropharyngeal cancers are in a state of transition. New models of oncogenesis are under investigation. New imaging and screening methodologies are making early diagnoses more common, and new treatment modalities – and combinations thereof – are proving to have roles in the management of these cases. However, the clinical challenges for both patient and provider remain essentially unchanged. Although there has been improved loco-regional control of patients afflicted with upper aerodigestive tract malignancies, this has not translated into improved overall survival.

Clinically relevant oropharyngeal anatomy

The oropharynx is bounded proximally by the posterior edge of the hard palate and distally by the valleculae and hyoid bone. The muscular pharyngeal wall defines the posterior/posterolateral limits of the oropharynx, and the circumvallate papillae and palatoglossal muscle mark

 DOI:10.1097/MOO.0b013e32832984c0

the anterior borders. The lateral walls of the oropharynx are composed of the tonsils and tonsillar fossae. For the purposes of management of oropharyngeal tumors, the oropharynx should be understood to consist of four subsites: the posterior pharyngeal wall, the soft palate, the tonsillar complex (i.e. tonsil, tonsillar fossa, and pillars), and the base of the tongue [1]. There are two clinically important potential spaces surrounding the oropharynx: posteriorly, there is potential for tumor invasion into the retropharyngeal space (behind the pharyngeal constrictors). Laterally, the parapharyngeal space – an inverted pyramid lateral to the pharyngeal constrictors between the base of skull and the hyoid cornu – contains the pterygoid muscles, branches of the trigeminal nerve, and the internal maxillary vasculature. Both of these spaces have treatment implications. Extension of disease to the retropharyngeal space increases the likelihood of contralateral regional metastatic involvement of the neck [2]. The potential for regional recurrence of soft-palate carcinoma into the parapharyngeal space mandates that the area be considered for adjuvant radiation therapy in cancers staged T2 or higher [3].

Histopathology of oropharyngeal tumors

Although minor salivary tumors (adenomas/adenocarcinomas), primary lymphoid tumors, undifferentiated tumors, various sarcomas, and 'mixed cellularity' neoplasms also present primarily in the oropharynx, the vast majority of primary oropharyngeal tumors are squamous cell carcinomas (SCCs) [1]. Therefore, unless otherwise specified, the remainder of this article refers to the diagnosis and management of invasive oropharyngeal squamous cell neoplasms. Histologic subtypes of head and neck SCCs, their nomenclature, and their clinical implications have been the subjects of debate for decades. Although a review of that literature lies outside the scope of this article, a few key points deserve emphasis. Although the basaloid and other nonkeratinzing subtypes of oropharyngeal SCCs have previously been thought to be more aggressive than other subtypes, recent literature suggests that many of these tumors (at least in the United States) are associated with human papilloma virus (HPV) infection and potentially more amenable to curative treatment. (The emerging link between HPV and oropharyngeal SCCs is further discussed in the next section.) [4]. In retrospective analyses across all anatomic subsites, approximately 60% of oropharyngeal SCCs have been found to be moderately differentiated, 20% well differentiated, and 20% poorly differentiated [1]. Genomics and proteomics are likely to alter the ways in which we subclassify many cancers, including SCCs of the head and neck, as increasingly specific molecular markers and patterns of gene expression are identified.

Epidemiology and oncogenesis of oropharyngeal squamous cell carcinoma

In the United States, approximately 5000 new cases of oropharyngeal cancer are diagnosed annually, of which 85–90% are SCCs [2]. The incidence of oropharygeal SCC is closely correlated with tobacco use and excess alcohol use. Alcohol abuse appears not only to be an independent risk factor for oropharyngeal SCC but also seems to potentiate the carcinogenic potential of tobacco smoke in the oropharynx. Moreover, the carcinogenic effects of both alcohol and tobacco smoke on the oropharynx appear to function in dose-dependent manners. Although SCC of the oropharynx is diagnosed predominantly in people over the age of 45 years, Western European and American studies suggest an increasing incidence of the disease in people less than 45 years of age, over the past 20–30 years [5•].

The role of HPV in the oncogenesis of oropharyngeal SCC is the subject of a rapidly emerging literature. A number of studies have shown an increased relative risk (RR) for oropharyngeal SCC in people with HPV seropositivity, oral HPV infection, or both. This increased risk appears to be higher in younger populations, although different patterns of sexual behaviors may partially account for this trend. In some case–control cohorts, this RR appeared to be increased more than 10-fold. For reasons not yet understood, most HPV-associated oropharyngeal SCCs originate in the tonsil. Although HPV-18 and HPV-16 are associated with genital cancers, the vast majority (84%) of HPV-associated head and neck cancers are associated with HPV-16 only. As mentioned previously, several authors have suggested that HPV-associated oropharyngeal cancers may be less aggressive than those not associated with the virus; specifically, HPV association tends to confer much better survival rates. The biologic/molecular reasons for these clinical observations have not been clearly elucidated. Important work remains in progress on the molecular pathways of HPV oncogenesis in head and neck cancer; the role of HPV vaccination in the prevention of head and neck cancer; and the combined oncogenic effects of HPV with tobacco, alcohol, or both [4,5•,6–12].

The roles of diet and nutritional status in the development of oropharyngeal carcinoma are also still debatable. Two points, however, are worth noting. A diet high in fruits and vegetables appears to confer a protective effect (from oral cancers) on people who drink, smoke, or both. Malnutrition, as determined by low BMI, may contribute to the risk of oral cancers [5•].

The role of inheritable predispositions to cancer in the development of oropharyngeal carcinoma is difficult to study for several reasons. Family members tend to have

similar exposures to carcinogens (e.g. alcoholism is familial), which confound the data. Oral cancers are rarely associated with known cancer syndromes. Nevertheless, two important points should be highlighted. Individuals with Fanconi anemia have a 500–700-fold increase in the risk of head and neck SCC, the majority of which are HPV associated. A family history positive for head and neck SCC confers a 2–4-fold increase in the risk of developing head and neck SCC across all anatomic sites, including the oropharynx. This RR increases greatly in people with a positive family history who use alcohol and/or tobacco [5•].

Further, subsite-specific epidemiologic details about SCC of the oropharynx are provided in each of the sections on specific subsites below.

Evaluation and staging of oral pharyngeal tumors

The first step in evaluating a potential oropharyngeal tumor is a comprehensive history and physical examination. Typically, this is followed by panendoscopy with biopsies of suspicious areas. Particularly important points to elicit in taking a history include the presence/absence of trismus, dysphagia, odynophagia, altered tongue mobility, otalgia, or all. On physical examination and endoscopy, size and gross characteristics (e.g. ulceration) of lesions, as well as anatomic subsite(s), should be carefully documented. A detailed examination of the lymph node bearing regions of the neck is crucial for accurate staging. Attention should also be paid to the supra and infraclavicular fossae [2,13•].

Several recent articles have reviewed the roles of screening and various screening modalities in the diagnosis of oral cancers. Unfortunately, none of these articles separates oropharyngeal lesions from oral cavity lesions. Moreover, although toluidine blue and autofluorescence appear to be useful in the early diagnosis of malignant and premalignant lesions, no consensus has been reached on the applications of these techniques. Still, there are several crucial lessons to be garnered from this literature. Annual detailed physical examinations of the oral cavity, oropharynx, and neck should be performed by primary care providers on patients at high risk for the development of oral cancers, including smokers, heavy drinkers, and patients with a prior history of head and neck cancer. A number of oral premalignant lesions have been identified, including leukoplakia, erythroplakia, mixed red and white lesions, lichen planus, and verrucous lesions. The potential for malignant transformation of these lesions appears to correlate with the degree of dysplasia exhibited. Topical application of toluidine blue appears to assist in the identification of oral premalignant lesions, in the delineation of the borders of malignant and dysplastic lesions, and in predicting the malignant potential of various oral mucosal lesions (on the basis of degree of dye retention) [13•,14].

The roles of advanced imaging technologies in the diagnosis and staging of oropharyngeal cancer are under investigation. Most cancer centers in the United States use computed tomography (CT) scans (ideally with intravenous contrast) of the head, neck, and chest to evaluate local extent of disease, regional spread, and the development of metastases, respectively. CT is also the mainstay imaging modality for assessment of response to therapy and regional disease recurrence. The addition of PET to CT scanning appears to enhance the detection of both primary tumors and cervical metastases; however, there are presently no definitive data to say that this screening modality has any more efficacy than CT alone. The one exception to this statement may be in the screening of patients with regional metastaic disease of unknown primary origin. In this setting, in a patient who has not been recently surgically manipulated, PET scan may be of benefit in locating the primary tumor site. PET scan alone appears to have comparable sensitivity and specificity to either CT or MRI in the detection of metastases of head and neck SCCs, though these data are not specific to oropharyngeal primaries [15,16•].

MRI is increasingly being used in both the staging of oropharyngeal cancers and in surveillance for recurrence. In terms of staging, MRI provides superior soft-tissue contrast, superior resolution of bone marrow involvement, and superior resolution of perineural spread versus CT scanning. MRI also overcomes the 'beam-hardening artifact' often caused by dental amalgams on CT scans. Disadvantages of MRI include prolonged time of data acquisition versus CT, which can be particularly unpleasant/risky for patients who have difficulty controlling oral, upper airway secretions, or both; greater susceptibility to motion artifact than CT scans; and considerably higher cost than CT scans [17,18].

Discussion of oropharyngeal carcinomas by subsite

Posterior pharyngeal wall

Tumors that originate in the posterior pharyngeal wall are rare. Because these tumors tend to remain asymptomatic until they gain considerable bulk, they are often (50–75%) diagnosed at late stages. Given the proximity of these tumors to the anatomic midline, posterior wall tumors frequently metastasize to lymph nodes bilaterally. Lateral extension is uncommon, but these tumors often invade the retropharyngeal and prevertebral spaces. CT may be useful to assess invasion of vertebral bodies, and MRI may help define intraspinal extension [17]. Small, node-negative posterior pharyngeal wall tumors appear to

be best managed with definitive radiotherapy. In larger or regionally metastatic posterior pharyngeal wall carcinomas, multimodality therapy, including chemoradiation with or without neck dissection, primary or salvage surgery, or both, is recommended [1,19].

Tongue base

SCC of the tongue base tends to be locally, regionally, and systemically aggressive. In contrast to lesions of other oropharyngeal subsites, base of tongue tumors are often poorly differentiated, up to 60% in one series. Even T1 and T2 lesions typically present with at least one cervical metastasis, and up to 20% of patients present with bilateral nodal disease. Thirty to fifty percent of patients with uncontrolled locoregional SCC of the base of tongue will progress to the development of distant metastases [2].

The most common presenting symptom of tongue base carcinomas is persistent sore throat. Because visualization of the tongue base is difficult, and because submucosal spread of these lesions is common, digital palpation of the tongue base can be crucial to a timely diagnosis [2].

MRI is proving to be a useful tool in the analysis of size and local spread of tongue base carcinomas. Often these tumors will enhance with the addition of gadolinium on T1-weighted images, and MRI more clearly delineates deep muscular invasion than does CT [17,18].

Institutional preferences in the treatment of tongue base cancers are reflected in the literature as selection bias. Surgery alone and radiotherapy alone appear to achieve equal and satisfactory rates of local control of T1 and T2 tumors of the tongue base. Although patient preferences, underlying health status, and other individual factors should guide treatment decisions, most institutions prefer to use primary external beam radiotherapy for these lesions. Brachytherapy, which was previously a popular therapeutic modality for tumors of the tongue base, has now been replaced in many institutions by intensity modulated radiation therapy. Cervical lymph node bearing regions are included in the irradiated fields, and the role of planned interval neck dissection remains controversial [1].

Small sample size and selection bias make the data on management of advanced (T3 and T4) tumors of the tongue base difficult to interpret. Many such tumors are deemed 'unresectable' and therefore referred for irradiation. Also, in one study [20], 58% of lesions initially classified as T3 were downstaged following surgical resection, again confounding the data. Based more on institutional biases than clear data, two multimodal therapeutic approaches have become popular in the United States for advanced tongue base tumors: initial chemoradiation followed by salvage surgery as necessary and radical resection followed by adjuvant irradiation. Justification of the former approach is that chemosensitization seems to improve the local control rate of radiation alone, allowing a subset of patients to avoid the morbidities and long-term quality of life issues associated with radical resection. Justification of the latter approach is that adjuvant radiation appears to improve locoregional control over resection alone [1].

Although the factors governing individual tumors' responses to radiotherapy remain the subjects of important ongoing research, tumors of the tongue base may be unique in that their gross morphology seems predictive of outcomes. In one study [21] of T3 and T4 lesions, patients with exophytic tumors showed a 5-year local control rate of 84% and survival rate of 67%, whereas patients with ulceroinfiltrative tumors demonstrated a 58% local control rate and a 33% survival rate at 5 years.

Soft palate

Soft-palate carcinomas are also relatively uncommon but tend to be diagnosed at early stages, because the soft palate is the most amenable oropharyngeal subsite to direct visual inspection and manual palpation. Nevertheless, most soft-palate carcinomas are asymptomatic until the time of diagnosis, and – given a propensity for submucosal growth – this can often mean deceptively large primary lesions [1].

Extent of tumor spread in soft-palate carcinomas is clinically important. The overall 5-year survival rate for patients presenting with unilateral lesions is 70.8%, but this falls to 51% for patients with tumors that cross the midline or with bilateral lesions. Approximately 25% of patients treated for a soft-palate tumor will present with a second primary tumor, most commonly on the floor of the mouth. Because there are no lateral or medial barriers to the spread of soft-palate tumors, they often extend to the tonsillar complex, cross the midline, or both [1]. T1-weighted coronal MRI images may be particularly helpful in assessing this extension. Although ipsilateral nodal spread is most often seen, bilateral nodal metastases are not uncommon, reaching 50% in some series of T3 and T4 lesions [17].

Prognoses of soft-palate carcinomas are directly related to the presence/extent of nodal disease, which – in turn – is related to T stage. Although only 20% of T1 and T2 lesions are regionally metastatic at the time of presentation, 60–70% of T3 and T4 lesions present with nodal metastases. T1 and T2 soft-palate carcinomas have demonstrated equal rates of local control when treated primarily with either surgery or radiation therapy, 91–100% for T1 lesions and 70–75% for T2 lesions. Either primary surgical resection or radiation therapy is an

acceptable treatment for early (T1/T2) soft-palate cancers. The potential advantage of primary radiation therapy to early soft-palate cancers is the inclusion of the parapharyngeal space and regional nodal basins at primary treatment. By contrast, T3 and T4 soft-palate tumors appear to be best approached by multimodal therapy, involving chemoradiation and surgery. We and others presently recommend surgical resection followed by concurrent chemoradiation therapy in advanced soft-palate cancer [1,3].

The critical issues in the surgical management of soft-palate carcinomas are three-fold and interrelated: adequacy of margins, given the tendency for submucosal spread; functional outcomes after creation of a palatal defect; and options for prosthetics, surgical reconstruction, or both. Laser resection, oral prostheses, and microvascular free flaps are becoming increasingly important in designing approaches to these complex challenges [1,2,16•].

Tonsillar complex

Seventy to eighty percent of oropharyngeal SCCs originate in the tonsillar complex. Although these tumors are often asymptomatic initially, the majority of patients report odynophagia, dysphagia, or both. Late symptoms include otalgia, bleeding, decreased tongue mobility, and trismus (usually due to invasion of the pterygoid plate) [2].

Although the American Joint Committee on Cancer staging system for oropharyngeal tumors bases T stage on size, the extent of local spread appears to be the more important prognosticator. In several studies, tumors with multiple subsite involvement have demonstrated significantly worse responses to radiotherapy and higher rates of recurrence than have tumors of equal T stage confined to the tonsillar complex [1].

Clinically positive nodal metastases are common at the time of diagnosis of tonsillar SCCs, ranging from 66 to 76% of patients, across multiple series. As compared with palatal and posterior pharyngeal wall tumors, these metastases tend to be confined to the ipsilateral jugulodigastric nodes. Contralateral nodal disease has been reported in up to 22% of cases involving the posterior pillar and true tonsil versus up to 6% of those confined to the anterior pillar [1,2,17].

Management of tonsillar complex tumors is based on clinical stage, individual patient factors (comorbidities and preferences), and institutional biases. Early disease (stage I/II) has consistently proven amenable to single modality therapy, either surgery or irradiation. The two modalities demonstrate comparable outcomes in terms of both locoregional control and 5-year survival. Given these equivalent results, primary radiation therapy has become the treatment of choice for early tonsillar complex carcinomas in the United States, for several reasons: it carries less short-term morbidity and mortality, many patients prefer the anticipated functional and cosmetic results, it reserves the surgical option for salvage, and it treats occult nodal disease. The role of salvage surgery after radiation for early tonsillar carcinomas is well established. Several authors have demonstrated that salvage surgery improves the overall rate of 5-year survival in both T1 and T2 tumors [1,22].

As with tumors in other oropharyngeal subsites, multimodality therapy has become the standard of care for advanced tumors of the tonsillar complex, for several reasons. Foremost, a number of authors have demonstrated that radiotherapy alone provides inadequate rates of local control in T3 and T4 lesions. Second, although surgery alone provides a better chance of local control than does radiation alone in stage III/IV tonsillar complex disease, the rate of locoregional recurrence remains unacceptable, even when surgery achieves negative margins. Finally, a number of meta-analyses have demonstrated significantly lower rates of local recurrence when multimodal approaches are used, as compared with either surgery alone or radiation therapy alone [1,22].

Several practical and philosophical questions remain unanswered, with regard to the ideal order and aggressiveness of multimodal therapy for advanced tonsillar carcinomas. What is the role of induction chemotherapy? Is chemoradiation best given first, followed by salvage surgery as necessary? Is resection followed by adjuvant chemoradiation more efficacious? These questions become complicated because the morbidity associated with surgical approaches to large tumors is significant, because mean survival after 'salvage surgery' (in irradiated patients) is less than 2 years in some series (which calls 'salvageability' itself into question), because new irradiation techniques and chemotherapeutic agents appear to improve results and decrease side effects, and because primary 'surgical failures' appear to be more manageable than do 'radiation failures.' Resection followed by chemoradiation would appear the more conventional first-line therapy, closely followed by concurrent chemoradiation therapy (CCRT) with surgery for salvage, until more light is shed on the aforementioned questions [1,22].

Special topics in oropharyngeal cancer

Management of the neck

Management of regional nodal disease associated with oropharyngeal SCC is based on two factors: the presence/extent of nodal disease and the choice of treatment for the primary disease.

Across all subsites and T stages, 15–30% of patients initially staged as N0 will eventually present with regional nodal metastases, so called 'occult' metastases. Therefore, all patients with oropharyngeal SCC should be considered candidates for some form of regional nodal therapy. A number of studies have demonstrated that the incidence of subsequent nodal disease in patients with N0 disease can be decreased equally effectively with either regional radiotherapy or elective neck dissection. For this reason, the 'staging neck dissection' has become obsolete. Unless there is a specific contraindication or patient objection to doing so, the node-bearing regions of the neck are typically included in the planned radiation field of N0 tumors managed with primary radiation therapy, reserving surgical options for radiation failures. Conversely, in N0 patients to be managed with surgery alone, elective ipsilateral or contralateral neck dissection – depending on subsite and extent of local spread – is often performed, reserving radiation for recurrences. In N0 patients with locally aggressive (T3/T4) tumors in whom multimodal therapy is planned, management of the neck is individually tailored and often mirrors management of the primary tumor, either by chemoradiation with surgical salvage or surgical resection followed by adjuvant irradiation [1,23].

Treatment of clinically positive (N+) neck disease related to oropharyngeal SCC also depends on the chosen therapeutic pathway for the primary disease, though there are a few special considerations. In patients with bulky nodal disease who undergo primary radiotherapy, including neck irradiation, interval neck dissection should be considered as it may confer a survival advantage. In patients who undergo primary surgical resection with neck dissection, adjuvant neck irradiation should be given in the presence of extracapsular spread [1,23].

Mandibular invasion

The management of mandibular invasion of oral SCC has recently been reviewed. Although none of the relevant literature discriminates between primary disease of the oral cavity and oropharynx, a few points should be emphasized. Cortical bone invasion portends a worse response to radiation therapy, which should be taken into account when planning management strategies for individual tumors. A combination of advanced imaging techniques [CT scan, Dentascan (GE Healthcare Company, Chiltern, Buckinghamshire, UK), MRI, or all] with pre and intraoperative clinical assessment (which may include periosteal stripping) seems to be the best strategy for determining the presence and extent of mandibular invasion. Soft-tissue factors appear to be more important than the extent of bony invasion in the prognoses of head and neck SCCs. There is a role for marginal mandibulectomy in the surgical management of tumors abutting the bone or involving the bone without erosion. Patients with gross bone erosion or medullary invasion appear to be best managed with segmental mandibulectomy [24].

Conclusion

Although advanced screening and imaging techniques may allow earlier detection and more accurate staging of SCC of the oropharynx, there is no consensus yet as to their applications.

HPV appears to be an important causative agent of oropharyngeal SCC in the Western Hemisphere, but the clinical implications of this causation remain under investigation.

On the basis of our review of the recent literature and our own published and clinical data, we recommend the following paradigms for the management of oropharyngeal SCC. All medically able patients with a biopsy-proven base of tongue cancer will receive CCRT to their primary disease and neck. Neck dissection is reserved for those patients with initial N2 disease or greater, those patients with detectable disease after completion of therapy regardless of initial nodal (N) presentation, or both. Patients with posterior pharyngeal wall cancer will also be offered CCRT as a primary treatment modality, reserving surgery for salvage therapy. Early soft-palate cancer (T1/T2) will be offered surgical resection of the primary site. Patients with endophytic T2 lesions will, in addition, be offered adjuvant radiation therapy encompassing the primary site, the parapharyngeal space and the neck.

Tonsillar fossa cancer presents a clinical treatment dilemma, as there are neither prospective randomized trials nor site-specific retrospective analyses that clearly indicate a superior approach to this locally and regionally aggressive disease. Our patients are offered as equal first-line therapy choices CCRT with surgery for salvage or primary surgical resection with adjuvant CCRT.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 133).

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