INTRODUCTION

While more commonplace in an otolaryngology practice, oropharyngeal cancer is a relatively uncommon occurrence overall. Accounting for fewer than 1% of all newly diagnosed cancers, malignancies in this portion of the upper aerodigestive tract constitute only 10-12% of cancers in the head and neck. Although there is a known association with tobacco and alcohol consumption, there is an increasing role for another etiology related to the human papillomavirus (HPV).

ANATOMY

The oropharynx is comprised of the soft palate, tonsillar fossae, base of tongue, oropharyngeal walls, and the vallecula. The hard palate correlates with the most superior extent while the hyoid defines the most inferior border. The most anterior aspect of the oropharynx is marked by the circumvallate papillae of the tongue and palatoglossus muscle, and the second and third cervical vertebrae mark the most posterior border. Laterally, the oropharynx is housed by the palatine tonsil and palatopharyngeal arch.

Five muscles make up the soft palate; the tensor veli palatini, levator veli palatini, palatoglossus, and palatopharyngeus attach at the palatine aponeurosis to form the anterior soft palate. The uvular muscle attaches to the posterior nasal spine and is the characteristic midline structure associated with the posterior soft palate. A unique feature of the soft palate is the presence of two distinct types of epithelium. Ciliated columnar cells line the nasal surface, but stratified squamous cells are present on the oral surface. Although not as abundant as on the tongue, taste buds can be found on the soft palate but only on the oral surface.

Most of the arterial supply for the soft palate arises from the ascending branch of the facial artery and ascending pharyngeal artery, while the pterygoid plexus facilitates most of the venous drainage. Anteriorly, the lesser palatine nerve arises from the maxillary division of the trigeminal nerve to provide sensation, and the greater petrosal nerve traverses through the
pterygopalatine ganglion without synapsing to provide taste in that area. Sensation from the posterior soft palate is transmitted by branches of the glossopharyngeal nerve. Secretomotor fibers to the anterior soft palate are provided by postganglionic nerves from the pterygopalatine ganglion, while the lesser petrosal nerve synapses in the otic ganglion to provide similar fibers posteriorly.

The palatine tonsil is a structure of mucosa-associated lymphoid tissue that is bounded by the palatoglossus anteriorly and the palatopharyngeus posteriorly. The superior constrictor, styloglossus, and the anterior fibers of the palatopharyngeus abut the tonsil laterally. Most of the arterial supply comes from the external carotid artery and concentrates at the tonsil’s superior and inferior poles. The ascending pharyngeal artery and descending palatine artery provides most of the vascular supply superiorly, while branches from the facial artery (via the tonsillar artery), lingual artery, and the ascending palatine artery constitutes the bulk of the inferior supply. Branches from the maxillary division of the trigeminal nerve and the glossopharyngeal nerve form a tonsillar plexus. The tympanic branch of the glossopharyngeal nerve, otherwise known as Jacobson’s nerve, is responsible for the referred otalgia that results from pathology involving the tonsil.

Going from medial to lateral, the oropharyngeal walls consist of the mucosa, submucosa, pharyngobasilar fascia, the superior and occasionally the middle constrictor musculature, and the buccopharyngeal fascia. Not surprisingly, the pharyngeal walls share a similar vascular supply as the tonsil in the form of branches from the ascending pharyngeal artery and facial artery. Similarly, a pharyngeal plexus is in place that innervates the constrictor muscles and is composed of branches from the glossopharyngeal and vagus nerves.

The posterior third of the oral tongue constitutes the tongue base and is defined as the circumvallate papillae anteriorly, pharyngoepiglottic and glossoepiglottic folds posteriorly, and the lingual tonsils laterally. Most of the sensation and taste in this area is provided by the glossopharyngeal nerve, although the internal laryngeal branch of the vagus nerve does provide some innervation to the vallecula. As with the rest of the oral tongue, the lingual artery is the main arterial supply to the base of tongue.

**EPIDEMIOLOGY**

Squamous cell carcinoma (SCCA) is present in 90% of oropharyngeal malignancies and is commonly affiliated with male individuals in their sixth or seventh decades of life. Tobacco and alcohol play a synergistic role as a significant risk factor in leading to SCCA, but attention has shifted toward a new demographic of affected people. There is an increasing incidence of oropharyngeal SCCA (OP SCCA) in people in their fourth and fifth decades of life with a better performance status and who often do not have a significant tobacco history. Both genders are affected equally, and there has been some association with marijuana use and orogenital sexual practices.

A review of information from the Surveillance, Epidemiology, and End-Results data from 1975 to 2006 reflects this change in cancer demographics. There has been a progressive decrease in the incidence of well-differentiated oral and oropharyngeal carcinomas from 33% down to 16% that is associated with an increase in five-year survival rates by 15.5%. Simultaneously, poorly-differentiated tumors have risen in incidence from 23% to 34% yet with an increase in five-year survival rates by 57% (Mehta 2010).
This change is attributed to the emergence of HPV and its contribution to OP SCCA. While types 16 and 18 have been involved with cancers of the genital tract, type 16 is the main culprit thought to result in 45-70% cases of OP SCCA (Cohen 2011). HPV is thought to exert this effect by integrating his genome into a host cell’s nucleus by expressing E6 and E7 oncoproteins and inactivating the tumor-suppressant p53 and retinoblastoma proteins. Histologically, these types of cancer tend to exhibit poorly differentiated SCCA in a basaloid background. There is a correlation with p16-positivity on immunohistochemical staining, which is highly predictive of lymph node metastasis but without an increase in lymphovascular or perineural invasion.

While investigating different types of radiotherapy regimens, Ang et al had noted over 60% of their patients with OP SCCA presented with stage III or IV disease but demonstrated improved three-year progression-free and overall survival. Although they had concluded that HPV-positivity conveyed a 58% reduction in death, there was a 1% increase in the risk for relapse or death with each pack-year of smoking regardless of HPV status (Ang 2010). Other studies supported this assertion, with a meta-analysis of eight studies between 2000 and 2010 observing that HPV-positive tumors generally respond well to treatment (Ihloff 2010). Even though an affiliation with HPV appeared to connotate a favorable prognosis, an advanced primary lesion was associated with recurrence and death (Sedaghat 2009). At the moment, studies are needed to evaluate the impact that HPV vaccinations exert on OP SCCA.

LYMPHATICS

OP SCCA tends to extend to the lymph nodes located in levels II, III, and IV of the neck, but there is a higher susceptibility for retropharyngeal nodal disease particularly with lesions along the posterior pharyngeal wall or palatine tonsil. While locoregional spread is typically ipsilateral to the side of the primary site of the malignancy, bilateral neck disease can also occur with cancers on the tongue base, soft palate, and posterior pharyngeal wall.

SYMPTOMATOLOGY

Malignancies in this region of the head and neck may present in a myriad of ways, but affected individuals typically complain of pain or sore throat. Dysphagia and odynophagia may also be present, while some patients may report more of a globus sensation. Referred otalgia is facilitated predominantly through Jacobson’s nerve. Some may complain of voice changes or present with hemoptysis, while others may actually be relatively asymptomatic and present merely with a neck mass.

STAGING

The most common system utilized to classify OP SCCA is with the staging guidelines as dictated by the American Joint Committee on Cancer (AJCC) that describes the size of the primary tumor (T), the degree of nodal involvement (N), and if there is the presence of distant metastasis (M). These individual guidelines are presented in figures 1, 2, and 3 below.
Oropharyngeal Cancer Staging

- T, tumor
  - Tx: primary site cannot be evaluated
  - T0: no evidence of carcinoma
  - Tis: carcinoma in-situ
  - T1: tumor ≤ 2cm in greatest dimension
  - T2: tumor 2-4cm in greatest dimension
  - T3: tumor > 4cm in greatest dimension
  - T4
    - T4a: invades larynx, deep/extrinsic tongue muscles, medial pterygoid, hard palate, or mandible
    - T4b: invades lateral pterygoid, pterygoid plates, lateral nasopharynx, skull base, or carotid

Figure 1. AJCC T Classification

- N, node
  - Nx: lymph nodes cannot be evaluated
  - N0: no evidence of nodal metastasis
  - N1: single node involved, ≤ 3cm
  - N2
    - N2a: single node involved, 3-6cm
    - N2b: multiple nodes involved unilaterally, ≤ 6cm
    - N2c: bilateral nodal involvement, ≤ 6cm
  - N3: nodal involvement > 6cm

Figure 2. AJCC N Classification
The individual T, N, and M classifications can then be combined to give a generalized staging system as outlined in Table 1 below.

**Table 1. Oropharyngeal Cancer Staging**

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Distant metastasis automatically places an individual as Stage IVC regardless of the T or N status.

**TREATMENT**

Surgery and radiotherapy (XRT) have traditionally been the mainstays of treatment, although chemotherapy (CTX) has established itself as an equally effective modality, especially when combined with radiotherapy (CXRT). Such a shift in the treatment paradigm is motivated by organ preservation strategies with good local and regional control rates using CXRT. A meta-analysis of 87 randomized trials between 1965 and 2000 revealed improved disease-free and overall survival when CTX is administered concurrently compared to adjuvant or neoadjuvant
delivery to all head and neck SCCA, reaching statistical significance in tumors of the oropharynx and larynx (Blanchard 2011).

Typically, a single-modality treatment strategy is acceptable for small primary lesions such as those classified as T1 or T2 or for low neck disease as present with N0 or N1. A combined approach, such as CXRT or surgery with adjuvant XRT, is warranted for a higher tumor burden that comes with an advanced T or N classification. In regards to OP SCCA, retropharyngeal lymph nodes should be addressed and both sides of the neck need to be treated with midline tumors. Such an aggressive approach to the cervical nodal basins is undertaken due to the presence of occult lymph node metastasis in up to 35% of clinically negative necks (Vartanian 2003).

Indication for postoperative XRT depends on the presence of concerning histological findings upon excision of the primary malignancy or from the neck dissection contents. Close or positive surgical margins, perineural or vascular invasion, or an advanced T classification would warrant adjuvant therapy. In a clinically negative or N1 neck, postoperative XRT is employed with the presence of two or more positive lymph nodes or positive nodes in multiple sites, perineural or vascular invasion, or extracapsular spread. XRT is typically implemented with clinically N2 or N3 disease. While distinctly different in the order treatment is rendered, XRT with surgery as a salvage effort appears to afford a five-year locoregional control and overall survival of 60-76% and 43-52% in OP SCCA, respectively (Fein 1996, Parsons 2002).

CHEMOTHERAPY

The benefit to adding CTX with adjuvant XRT has been demonstrated in a number of clinical trials. An investigation from the European Organization for Research and Treatment of Cancer compared conventional adjuvant XRT with adjuvant CXRT using cisplatin in patients with stage III or IV head and neck SCCA between 1994 and 2000 and noticed a significant five-year improvement in progression-free and overall survival with the CXRT group. The risk for locoregional relapse was also lower with CXRT, but there was no difference in the occurrence of distant metastases or second primary tumors. Of note, the incidence of grade 3 toxicities or higher was noticeably higher in patients receiving CXRT. Of note, although this study involved SCCA from all regions of the upper aerodigestive tract, there were more individuals with oropharyngeal primaries (Bernier 2004).

A similar study echoed similar conclusions with a multi-institutional trial involving the Radiation Therapy Oncology Group, Eastern European Cooperative Oncology Group, and the Southwest Oncology Group. Reviewing a similar demographic of people with stage III or IV head and neck SCCA between 1995 and 2000, with more of them presenting with oropharyngeal tumors, they had noticed improved two-year locoregional control and disease-free survival in those who received adjuvant CXRT with cisplatin compared to those given adjuvant XRT alone. While there was no difference in the occurrence of distant metastasis, the overall survival between the two groups was also not found to be significantly different, which contrasted with the findings from Bernier et al. Not surprisingly, there were more grade 3 or higher toxicities in the CXRT group, although four patients reportedly died during the study period (Cooper 2004).

BRACHYTHERAPY

XRT for OP SCCA is typically delivered with some form of external beam radiation. There has been some investigation to the role of brachytherapy in treating these malignancies. In
a retrospective review of patients treated with base of tongue SCCA, interstitial brachytherapy was delivered to the primary tumor after having first undergone CXRT with salvage neck dissections. While the T classification was observed to correlate with locoregional control and disease-specific and overall survival, three-year control and survival results were promising with a low complication rate associated with mucositis, nausea, and vomiting (Cano 2009).

**SURGERY**

Any surgical endeavor to excise oropharyngeal tumors utilizes either a transoral, transpharyngeal, or transmandibular approach. Small, superficial, or exophytic lesions of the soft palate, anterior tonsillar pillar, or posterior pharyngeal wall may be removed with a transoral approach provided that there is enough access to ensure a 1-2cm margin of normal tissue around the surgical specimen.

The benefit to a transoral approach is the relative rapidity by which to conduct this compared to other techniques. Furthermore, performing surgery through the oral cavity generally results in decreased morbidity and may even afford the possibility of avoiding adjuvant therapy in appropriately selected patients, often resulting in improved functional outcomes. This is hindered with poor visualization depending on trismus, mandibular height, and dentition. Other approaches should be implemented when such occasions arise.

**Transpharyngeal Approaches**

A mandibular lingual release entails making an incision along the floor of mouth and delivering the tongue into the neck. The exposure from this technique is ideal for base of tongue lesions and does not require a lip split or mandibulotomy. There is less access laterally to the parapharyngeal space, however, and the process of delivering the tongue places the lingual artery and nerve and hypoglossal nerve at risk for injury.

Entering the pharynx at the level of the vallecula is the key feature of performing a suprahyoid pharyngotomy. While this may also afford access to the tongue base, it also allows access to small tumors along the pharyngeal walls and simultaneously preserving the lingual and hypoglossal neurovascular structures. Some of the main disadvantages of this technique is the potential of obtaining inadequate superior margins with larger tumors or unintentionally cutting into the neoplasm if it resides within the vallecula or on the inferior aspect of the tongue base.

By placing the incision of a suprahyoid pharyngotomy laterally, a lateral pharyngotomy allows the pharynx to be entered posterior to the thyroid cartilage ala with retraction of the hypoglossal and superior laryngeal nerves. The exposure of small base of tongue and pharyngeal wall tumors is comparable to a suprahyoid pharyngotomy, but the entire posterior pharyngeal wall, contralateral pharyngeal wall, and entire tongue base can be visualized with this approach. Similar to the suprahyoid pharyngotomy, there is the risk of limited superior margins although this can be addressed by extending the incision medially to encompass the vallecula or performing a lateral mandibulotomy. In addition, there is the potential for hypoglossal or superior laryngeal nerve injury with retraction.

**Transmandibular Approaches**

Otherwise known as a Trotter Procedure, the midline labiomandibular glossotomy incorporates incising the lip, gingiva, mandible, and tongue at the midline to facilitate access to midline neoplasms along the posterior pharynx or tongue base that may be too inferior for a
transoral approach. Although this spares the hypoglossal nerves and lingual arteries, there is minimal exposure of the parapharyngeal spaces.

A mandibular swing provides a wider view of the entire oropharynx and even allows the possibility of conducting an en bloc resection with a lymphadenectomy. This approach also requires a lip split, incising the gingiva and floor of mouth, and performing a mandibulotomy, but it also entails dissecting out critical neurovascular structures including the carotid and lingual arteries and the lingual and hypoglossal nerves. While this provides the opportunity for an extensive surgical endeavor, such an undertaking places a great deal of anatomy at risk for unintentional injury and usually results in a defect that warrants microvascular free flap reconstruction. This technique is precluded with any mandibular involvement, which would necessitate at least a partial mandibulectomy. The resulting composite resection would address any bony cortical invasion but lead to significant functional and cosmetic deficits.

Transoral Lateral Oropharyngectomy

First described in 1951 by Huet as a salvage procedure in a patient with recurrent tonsillar SCCA, surgically excising the lateral oropharynx transorally has reemerged as a viable primary treatment modality for conservative resection in selected cases of tonsillar SCCA. Patients with trismus or present with poor transoral exposure would not be suitable candidates for this approach. Tonsillar neoplasms fixated to the lateral oropharyngeal wall are not ideally excised using this technique. Similarly, this type of surgery is precluded if there is invasion of the mandible, nasopharynx, glossopharyngeal fold, pharyngoepiglottic fold, base of tongue, vallecula, or pyriform sinus (Holsinger 2005).

While the exact steps need to be tailored to the individual, the general steps incorporate incising the raphe between the superior constrictor and the buccinator muscles. The tonsil is retracted medially to allow dissection in the submuscular plane toward the prevertebral fascia. This dissection occurs along the buccopharyngeal fascia, which separates the constrictors from the retrostyloid parapharyngeal space. Knowledge of the anatomical relationships in this area is crucial as the internal carotid artery is medial to the fascia, superficial to the prevertebral musculature and fascia but should be covered with fat globules to indicate its presence, while the internal maxillary artery is located laterally. The primary objective with this surgery is to achieve complete resection with adequate margins, and the anterior and posterior tonsillar arches, a portion of the soft palate, styloglossus, and stylopharyngeus will usually be incised during this process. Consequently, posterior pharyngeal flaps may be created to help prevent postoperative rhinolalia. Obturators are used to reconstruct larger defects.

As a treatment modality alone, this transoral approach appears capable of achieving satisfactory surgical results. In a two-center retrospective review from 1996 through 2008, Grant et al observed a five-year local control and locoregional control rate of 90-94% and 74-82%, respectively, in patients who underwent transoral laser microsurgical (TLM) excision of OP SCCA who either did not warrant or refused adjuvant XRT. Despite such positive findings, the overall survival rate for those who refused XRT was significantly lower than those who did not require such adjuvant treatment (Grant 2009).

The addition of adjuvant therapy to TLM has been evaluated in other investigations. Moore et al studied 102 patients with tonsillar SCCA treated primarily with TLM and neck dissections (ND), with over 80% having stage III or IV disease and half of that due to advanced neck disease. This was followed with adjuvant XRT or CXRT if there were concerning findings
on histological analysis. These patients demonstrated a five-year disease-free and overall survival rate of 94% and 85%, respectively. The rate of permanent tracheostomy and gastrostomy tube status was acceptably low at 1% and 4%, respectively, with 86% of patients successfully resuming a normal diet. Six individuals experienced an orocutaneous fistula, but they all eventually healed. Of particular note, however, is the exclusion of patients with T4 disease (Moore 2009).

A similar study was conducted on those with base of tongue SCCA, where 20 patients from 1996 through 2005 were treated at a single institution with TLM and ND and adjuvant XRT or CXRT based on histological analysis of the surgical specimen. Virtually all of them presented with T1 or T2 lesions but exhibited stage III or IV disease due to significant nodal disease, and they demonstrated a favorable five-year overall survival rate of 83%. No permanent tracheostomies were needed, and three experienced an orocutaneous fistula which eventually healed. Two patients were gastrostomy tube dependent, while 75% were able to return a normal diet (Henstrom 2009).

While additional studies may be needed to further elucidate, HPV status appears to not affect the survival and control rates in patients with OP SCCA excised with a transoral approach as based on the findings from Cohen et al. While these procedures employed robotic-assisted surgery, neck dissections and adjuvant therapy were performed with similar indications as the aforementioned trials. In a single-center retrospective series looking into 50 individuals with stage III or IV disease between 2005 and 2007, no significant difference in local and locoregional control rates nor the incidence of distant recurrences were appreciated at two years. Similarly, disease-free and overall survival rates were comparable to each other (Cohen 2011).

CONCLUSION

OP SCCA is often treated with a multimodality approach, and it is becoming increasingly apparent that two distinct processes are occurring that can lead to this malignancy. Carcinogen exposure from tobacco and alcohol is clearly one etiology that is shared with SCCA from other areas in the head and neck region, but the genomic instability introduced by HPV warrants further research. The impact that HPV exerts on the prognosis of individuals with OP SCCA is formidable, and there is growing evidence that transoral surgery provides a viable alternative to conventional therapies that can offer favorable outcomes in appropriately selected patients.
REFERENCES


