Pitfalls in the Staging of Cancer of the Oropharyngeal Squamous Cell Carcinoma

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KEYWORDS

- Oropharyngeal squamous cell carcinoma • Oropharynx • Human papilloma virus
- Transoral robotic surgery

KEY POINTS

- Oropharyngeal squamous cell carcinoma (OPSCC) has a dichotomous nature with 1 subset of the disease associated with tobacco and alcohol use and the other having proven association with human papilloma virus infection.
- Imaging plays an important role in the staging and surveillance of OPSCC.
- A detailed knowledge of the anatomy and pitfalls is critical.
- This article reviews the detailed anatomy of the oropharynx and epidemiology of OPSCC, along with its staging, patterns of spread, and treatment.

Anatomic extent of disease is central to determining stage and prognosis, and optimizing treatment planning for head and neck squamous cell carcinoma (HNSCC). The anatomic boundaries of the oropharynx (OP) are the soft palate superiorly, hyoid bone, and vallecula inferiorly, and circumvellate papilla anteriorly. The OP communicates with the nasopharynx superiorly and the hypopharynx and supraglottic larynx inferiorly, and is continuous with the oral cavity anteriorly. The palatoglossus muscle forms the anterior tonsillar pillar, and the palatopharyngeus muscle forms the posterior tonsillar pillar. The OP has 4 subsites:

- Base of tongue including pharyngoepiglottic and glossoepiglottic folds
- Palatine tonsils including tonsillar fossa and anterior and posterior tonsillar pillars
- Ventral soft palate including the uvula
- Posterior and lateral pharyngeal walls at the oropharyngeal level[1]

Contents of the OP include mucosa, lingual and palatine tonsillar lymphoid tissue, minor salivary tissue, constrictor muscles, and fascia. The overwhelming tumor pathology is squamous cell carcinoma (SCC), arising from the mucosal surface. As the OP contents include lymphoid tissue and minor salivary glands, lymphoma and nonsquamous cell tumors of salivary origin can occur.[2]

In understanding spread of disease from the OP, it is helpful to remember the fascial boundaries subtending the OP, to recall the relationship of the pharyngeal constrictor muscles with the pterygomandibular raphe and the deep cervical fascia, and to be aware of the adjacent spaces and structures. In staging of OP lesions, extension of malignancy to the larynx (but not the lingual surface of the epiglottis), oral cavity, masticator space, nasopharynx, and skull base or tumors with internal carotid artery encasement upstage the disease, regardless of tumor size.[3] Note that mucosal extension to the lingual surface of the epiglottis does not constitute invasion of the larynx.

The OP is bounded deeply by the middle layer of deep cervical fascia (buccopharyngeal fascia), which is deep to the middle and superior

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constrictor muscles. The superficial (mucosal) surface of the OP is not bounded by fascia. To attach to the skull base, the superior constrictor muscle attaches to the pharyngobasilar fascia. The buccopharyngeal fascia is deep to the pharyngobasilar fascia. Tumors can potentially spread along the muscle and fascial routes from the OP to the skull base.

The middle pharyngeal constrictor muscle is connected with the buccinator muscle via the pterygomandibular raphe, which extends from the posterior mylohyoid line of the mandible to the hamulus of the medial pterygoid plate. This connection provides a potential route of tumor spread between the OP and the OC, between the OP and the central skull base (sphenoid bone), and between the OP and the pterygoid muscles in the masticator space (Figs. 1–3).

EPIDEMIOLOGY

SCC accounts for 95% of neoplasms arising in the OP, and OP cancers represent over 50% of all head and neck cancers in the United States. Annually, 5000 OP cancers are newly diagnosed.[4–7] The proportion of HNSCC arising in the OP increased from 18% in 1973 to 32% in 2005.[8] Minor salivary tumors (adenomas/adenocarcinomas), lymphoid lesions (including lymphoma), undifferentiated malignancy, and sarcomas make up the balance of the tumors arising in the OP.[9] While overall incidence of other HNSCCs has been declining since the 1980s, the incidence of OP SCC has been stable or increasing. Decline in smoking is the reason for the decline in overall numbers of HNSCC, while human papilloma virus (HPV)-associated malignancy explains the increase in otopharyngeal squamous cell carcinoma (OPSCC), particularly in younger patients.[7]

OPSCCs occur most frequently in men over the age of 40. Tumors are often insidious, growing in an infiltrative pattern, clinically silent until reaching a large size. The base of the tongue lacks pain fibers, and tumors in this location are often asymptomatic until quite large.[10] Symptoms vary from site to site, but most commonly patients complain of throat discomfort. Small lesions can present as painless ulcerations. When the lesions are larger, the local extent is greater, and/or metastatic adenopathy is present, patients may complain of difficulty swallowing, ear pain, trismus, or neck mass from metastatic adenopathy.[6,11]

Alcohol abuse and tobacco use, in a dose-dependent fashion, together and independently, are associated with increased incidence of OPSCC. Alcohol abuse has been found to potentiate the cancerous effects of tobacco exposure in the OP.[12,13] In fact, it has been reported that synergistic action between alcohol and tobacco could increase relative risk of HNSCC by as much as 30-fold.[14] Other factors implicated in the development of OPSCC include: history of SCC of the head and neck in a first-degree relative, history of cancer in a sibling, history of oral papillomas, poor oral hygiene, regular marijuana use, heavy tobacco use (20 pack–years or more), or history of heavy alcohol use (15 drinks or more per week for 15 years or more).[13] Other risk factors identified for development of OPSCC are: a diet poor in fruits and vegetables,[15] drinking mate, a brewed herb,[16] and chewing betel quid.[17]

In developed countries, OPSCC makes up 15% to 30% of head and neck cancers. In the past 25 years, the incidence of OPSCC has increased in the United States, Scandinavia, Canada, Netherlands, and Scotland in spite of stability or decline in overall HNSCC incidence.[5,18] Three percent to 9% of OPSCC in these countries occurs in patients denying a history of tobacco/alcohol exposure, especially in young patients (10% to 30% non-smokers and nondrinkers).[5] HPV exposure and infection are responsible for the rise in OPSCC in western countries. Of the HPV-associated HNSCC, over 90% of cases arise in the OP and most commonly in the palatine tonsil, followed distantly by the lingual tonsil/base of tongue. HPV-negative tumors, on the other hand, are found in all subsites of the OP.[18] HPV-associated tumors represent a separate subset of OPSCC with unique epidemiology, etiology and biologic characteristics, and prognosis.

HPV is an epithelliotropic DNA virus that primarily infects transitional epithelium that is found in the upper aerodigestive tract and anogenital regions. Over 120 different HPV types have been identified, but the subtypes implicated in OPSCC include HPV-16, 18, 31, 33, and 35, with HPV-16 identified in approximately 90% of HPV-positive tumors. The malignant potential of the HPV infection lies in the expression of viral oncoproteins E6 and E7; which, in turn, are able to inactivate 2 human tumor-suppressor proteins, p53 and pRb.[18]

HPV is predominately a sexually transmitted disease, and infection is an independent risk factor for development of OPSCC. Its association with the development of cervical cancer and other anogenital malignancies is well known. People with HPV-16 oral infection are at a 15-fold higher risk for OPSCC and a 50-fold increased risk for HPV-positive HNSCC.[8] As reported in the New England Journal of Medicine in 2007, lifetime number of vaginal sex partners of 26 or more was associated with development of OPSCC; so too was a lifetime number of oral-sex partners of 6 or more (with
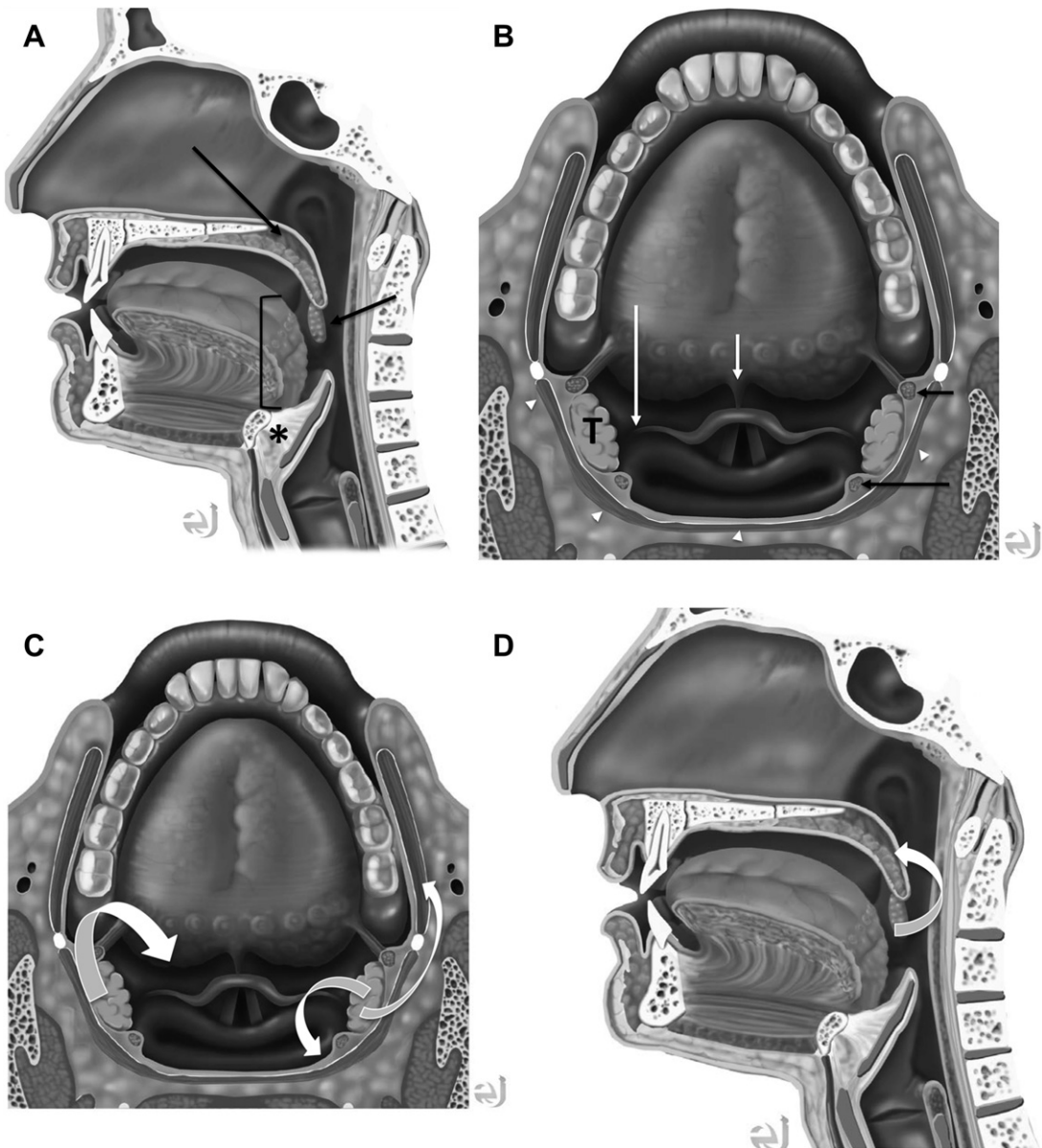
Fig. 1. (*A*) Upper aerodigestive tract. Soft palate (*long arrow*). Palatine tonsil (*short arrow*). Posterior one-third of the tongue (*brackets*). Pre-epiglottic fat (*asterisk*). (*B*) Superior view of oropharynx. Pharyngeal constrictor muscles (superior and upper fibers of middle) (*arrowheads*). Pharyngoepiglottic folds (*long white arrow*) and glossoepiglottic (*midline*) fold (*short white arrow*). Palatoglossus (*anterior*) (*short black arrow*) and palatopharyngeal (*posterior*) (*long black arrow*) muscles forming the anterior and posterior tonsillar pillars. Palatine tonsil (T). (*C*) Superior view of oropharynx. Pattern of tumor spread from the tonsillar fossa (*arrow*). (*D*) Midline sagittal. Pattern of tumor spread from the tonsillar fossa (*arrow*). (*Courtesy of* Eric Jablonowski.)

a 9-fold increase in relative risk). Synergy between tobacco and alcohol abuse/use and HPV infection with increased odds of OPSCC was not found.[13,19]

HPV-positive OPSCC patients have been found to have significantly better outcomes as compared to HPV-negative patients, with a 28% lower risk of death than the HPV-negative patients.[8,20,21] Also, nonsmoking patients with HPV- positive tumors

have better disease-specific survival rates as compared with smokers with HPV-positive tumors.[22] Black patients with head and neck cancer live significantly shorter periods after treatment than white patients, at least in part due to the fact that the black population in the United States has dramatically lower rates of HPV infection than Caucasian population. HPV status directly
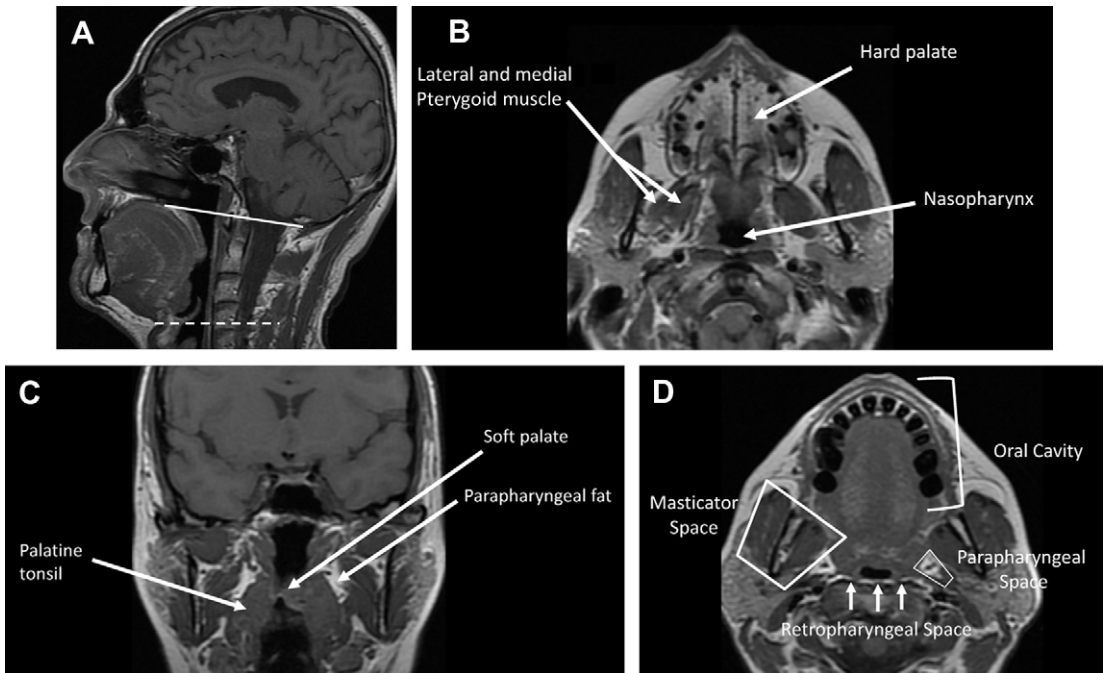
Fig. 2. Normal anatomy. (*A*) Boundaries of the oropharynx. Superiorly, the solid line at the level of the palate and inferiorly, the dashed line at the level of the hyoid bone and vallecula. (*B*) Axial T1-weighted image at level of hard palate and nasopharynx. (*C*) Coronal T1-weighted image. Nasopharynx and oropharynx. (*D*) Spaces adjacent to the oropharynx.

correlates with the significant survival disparities between the 2 patient groups.[23,24] When survival is compared between black and white HPV-negative patients, survival is similar.[23]

HPV-positive tonsillar cancers have been shown to have a lower number of chromosomal alterations as compared to HPV-negative OPSCC.[25,26] HPV-associated OPSCCs are more likely to be undifferentiated and have basaloid histology and more frequent nodal metastasis.[27] HPV-negative tumors, in contrast, have keratinized rather than nonkeratinized histology. Improved overall and disease-free survival after surgery, radiation therapy, and chemotherapy have been reported in HPV-positive OPSCC.[28–32]

AMERICAN JOINT COMMITTEE ON CANCER STAGING

Appropriate staging of cancer at the time of presentation is important, as stage predicts survival rate and guides management. Prognosis and treatment are directly linked to cancer stage (based largely on anatomic factors) as well as other nonanatomically based patient or tumor-specific factors such as overall health, age, sex, race, and the tumor type or biology of malignancy. Evidence-based treatment paradigms are defined by reported outcomes relative to stage and treatment received. Interdisciplinary and inter-institutional reporting of results needs to be reproducible, clear, consistent, and comparable. With accurate staging, careful follow-up, and multidisciplinary input, treatment outcomes can be compared and related back to stage at presentation.

With the American Joint Committee on Cancer (AJCC) 7 staging of OP cancer, as with all head and neck cancers, staging is primarily based upon anatomic information (**Tables 1** and **2**). For OP, the AJCC 7 has only one change as compared to AJCC 6. The T4 lesions have been divided into T4a and T4b categories. T4a lesions are moderately advanced local disease, and T4b lesions are very advanced local disease. In association with the new stratification of T4 lesions, stage IV has been subdivided into stage IVA (moderately advanced local/regional disease), stage IVB (very advanced local/regional disease), and stage IVC (distant metastatic disease). For head and neck cancers, in general, the terms resectable and unresectable are replaced with moderately advanced and very advanced in the current staging manual. Extracapsular spread (ECS) of nodal disease is specifically denoted as ECS + (present) or ECS – (absent).[3]

The importance of a thorough physical examination and clinical assessment of the primary lesion
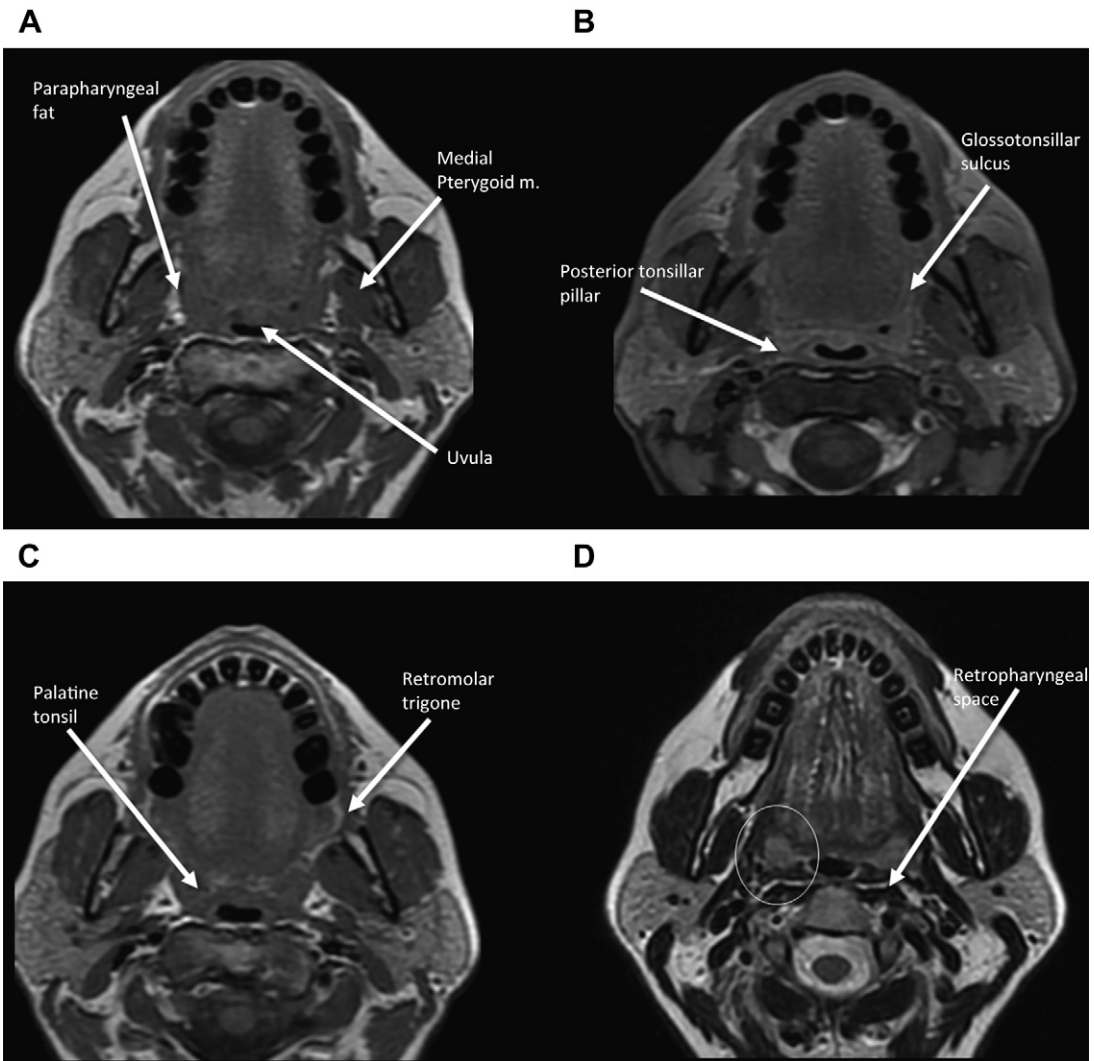
Fig. 3. Normal anatomy. (*A*) Axial T1-weighted image. (*B*) Axial fat-saturated T1-weighted image. Note enhancement of the tonsil. (*C*) Axial T1-weighted image. (*D*) Axial T2-weighted image. Note the hyperintensity of the palatine tonsil (*circle*).

cannot be overemphasized. Cross-sectional and metabolic imaging is complementary, and can further define the T, N, and M status of the patient. In AJCC 7, general rules for tumor node metastases (TNM) staging after include

> Microscopic confirmation of malignancy is needed.
> When uncertainty exists with assignation of T, N, or M status, the lower category should be assigned.
> Separate staging and independent reporting of synchronous primary tumors is necessary.

The guidelines also state that the clinical (pretreatment) stage assigned prior to institution of therapy (surgery, radiation, chemotherapy, or a combination thereof) is not changed on the basis of new information obtained at the time of pathologic examination.[3]

The T portion of the TNM staging classification defines the malignancy by size or contiguous extension. T designation in the OP is mainly size-based for tumors confined to the OP and includes T1: a tumor 2 cm or less in size, T2: a tumor 2 to 4 cm in size (**Fig. 4**), and T3: a tumor larger than 4 cm in size or with extension to the lingual surface of the epiglottis. T4 tumors have extension into adjacent structures. Moderately advanced local disease, T4a, is defined as tumor invasion of larynx (**Fig. 5**), extrinsic tongue muscles (**Fig. 6**), medial pterygoid muscle, hard palate, or mandible. T4b
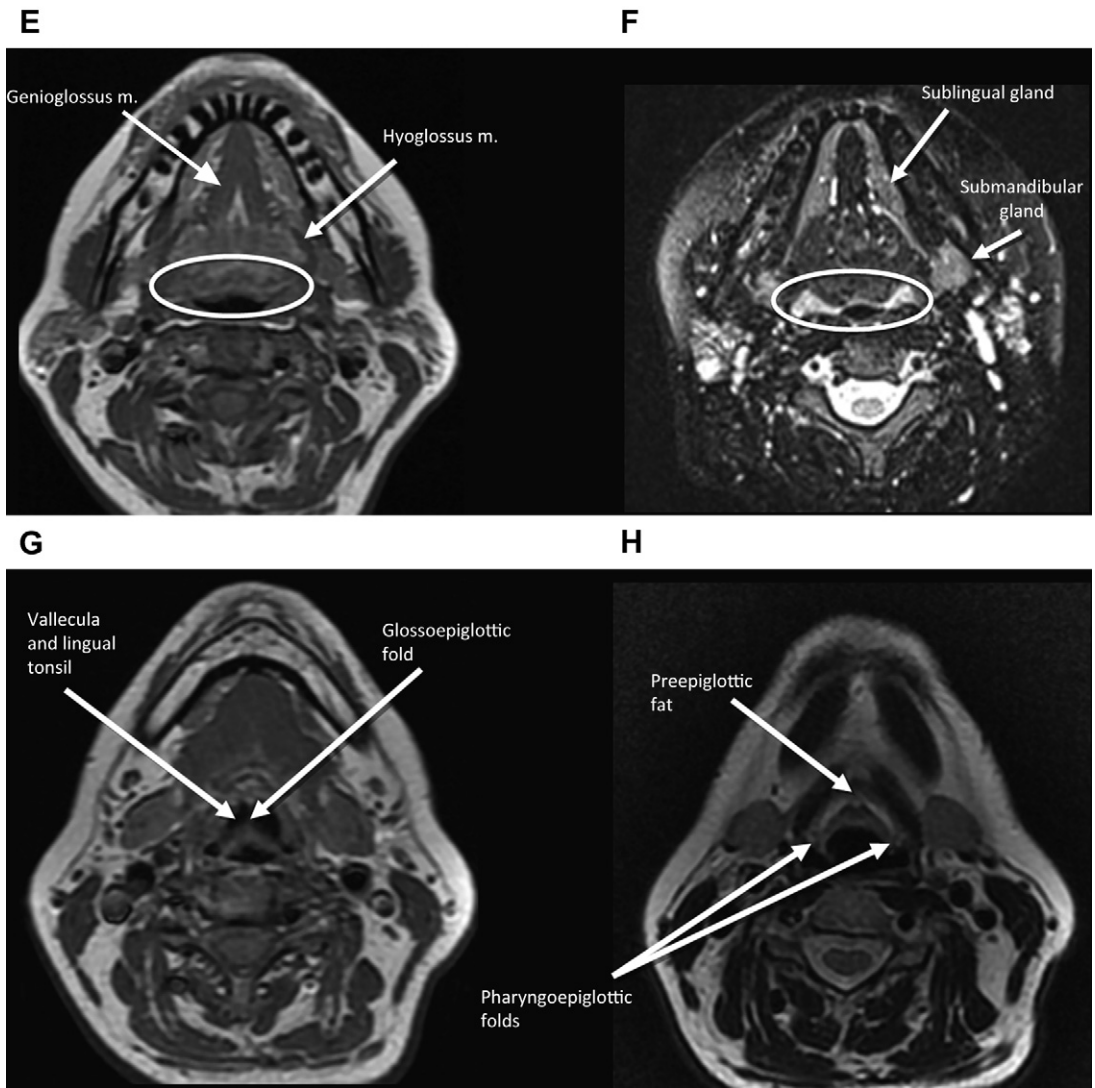
Fig. 3. (*E*) Axial T1-weighted image with 2 of the extrinsic tongue muscles identified. Circled structures are the lingual tonsils. (*F*) Axial fat-saturated T2-weighted image shows lingual tissue (*circled*) is normally T2 hyperintense. (*G*) Axial T1-weighted image. Inferior oropharynx landmarks. (*H*) Axial T2-weighted image. Inferior oropharynx landmarks.

classification is used with very advanced local disease when tumor encases the internal carotid artery (ICA), invades the lateral pterygoid muscle or pterygoid plates, or extends into the lateral nasopharynx or skull base (**Fig. 7**).

The N component addresses the status of the regional lymph nodes. The OP and hypopharynx have identical nodal classification. Nx refers to situations where the lymph nodes cannot be assessed. N0 is the absence of regional lymph node metastasis. N1, N2, N3 describes increasing number or extent of regional lymph node involvement. Further description of nodal staging can be found in the article by Amit Saindane, entitled Imaging and Staging of Lymph Node Metastases

in this issue. Lymph node status is of great prognostic significance. The more distant the spread in the lymphatic system, the worse the prognosis. Similarly, the presence of ECS worsens the prognosis. ECS is characterized by marginal irregularity and matting of nodes on imaging studies and by the adherence of nodes to adjacent structures on physical examination and imaging (**Fig. 8**). With OPSCC, the key nodal stations are levels II and III. Levels IA and IB are less commonly involved.[3]

At the time this manuscript was written, the American College of Radiology (ACR) did not have appropriateness criteria for generally accepted standards for diagnostic (imaging) evaluation to aid in staging of the OP cancers. Appropriateness

Table 1
AJCC 7th edition oropharynx staging

	Primary Tumor (T)
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 3 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension or extension to the lingual surface of the epiglottis
T4a	Moderately advanced local disease Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible[a]
T4b	Very advanced local disease Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery
	Regional Lymph Nodes (N)
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension
	Distant Metastasis (M)
M0	No distant metastasis
M1	Distant metastasis

[a] Mucosal extension to lingual surface of epiglottis from primary tumors of the base of tongue and vallecula does not constitute invasion of larynx.

From Edge S, Byrd D, Compton C, et al. AJCC Cancer staging manual, 7th edition. Chicago: Springer; 2010. p. 41–56; with permission.

Table 2
Final tumor stage using the AJCC staging system for oropharyngeal carcinoma, 7th edition

Group	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

From Edge S, Byrd D, Compton C, et al. AJCC Cancer Staging Manual, 7th edition. Chicago: Springer; 2010. p. 41–56; with permission.

criteria do exist for the work-up of neck mass/aden-opathy.[33] Variant scenarios include the adult presenting with a nonpulsatile solitary neck mass, the adult presenting with multiple neck masses, and the adult with a history of treatment for cancer presenting with a neck mass. In the first 2 cases,


Fig. 4. T2 primary oropharyngeal cancer (*circle*) affecting right lateral soft palate, right anterior tonsillar pillar and right posterior tonsillar pillar. The parapharyngeal fat is normal (*arrow*).

Fig. 5. T4a primary tumor with invasion of the larynx. Tumor (*short arrow*) fills the pre-epiglottic fat and abuts the lingual surface of the epiglottis at the level of the hyoid bone and extends into the pyriform sinus on the right (*long arrow*). N3 necrotic nodal conglomerate measured over 6 cm (*circle*).

contrast-enhanced computed tomography (CECT) or magnetic resonance imaging (MRI) without and with contrast is recommended. In the post-treatment case, CECT of the neck with positron emission tomography (PET) are considered complementary. MRI without and with contrast is an alternative to computed tomography (CT).[33]
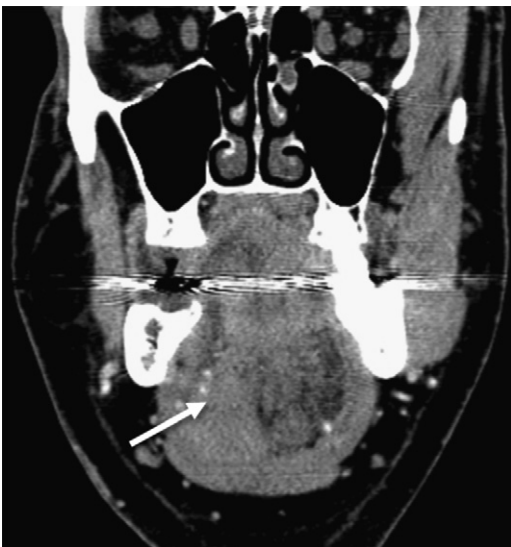
Fig. 6. T4a disease with invasion of the extrinsic tongue muscles. Tumor (*arrow*) surrounds the lingual artery and invades the genioglossus–geniohyoid complex on the right.

Guidelines are available at the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology site with recommendations for work-up of OP cancer. Work-up should begin with complete history and physical examination to include mirror and fiberoptic examination (as clinically indicated). The tumor should be biopsied, and immunohistochemical staining for p16 is recommended. Chest imaging and CT with contrast and/or MRI with contrast of the primary and of the neck are the next step. PET-CT for stage III to IV disease is recommended, but PET-CT should not replace anatomic imaging. PET-CT is not designed to assess the primary tumor, but rather to assess node status and identify distant metastasis. The patient should complete consultations for oral surgery, nutrition, speech, and swallowing for evaluation/therapy and audiogram as indicated. Examination under anesthesia with endoscopy may be performed prior to treatment to confirm extent of disease.[34] Both the NCCN and ACR have guidelines for therapeutic intervention in OP cancer. The ACR criteria apply to resectable OPSCC.[34,35]

## TRENDS IN TREATMENT AFFECTING STAGING

The OP has intricate anatomy, rich lymphatic drainage, and provides critical function central to optimal quality of life. Approximately 60% of patients present with stage III to IV disease.[7] At least 70% of patients have ipsilateral cervical nodal metastases, and 30% or less have bilateral cervical nodal metastases.[1]

The treatment approach for OPSCC is typically multidisciplinary, with the goal to maximize cure potential while minimizing toxicity and preserving functionality. The NCCN and ACR Guidelines separate treatment paradigms on basis of TNM clinical stage. The ACR guidelines further categorize patients by HPV status, smoking history, and age.[34,35] Key to correctly placing the patient in a treatment regimen is accurate staging, pathologic findings (including HPV status), and patient condition.

Treatment options for OPSCC include surgical and nonsurgical regimens. With the more aggressive, but successful, nonsurgical treatments, the risk of swallowing difficulty, salivary gland dysfunction, and other quality-of-life issues exists. Surgical approaches have cosmetic and functional implications. In light of the distinctly different biologic behavior of HPV-positive OPSCC, treatment de-intensification in select patients is considered.[35]

Chemotherapy, radiation therapy, brachytherapy, transoral laser microsurgery, transoral robotic surgery (TORS), open surgery, and bioradiotherapy are current treatment options.[36] TORS and transoral
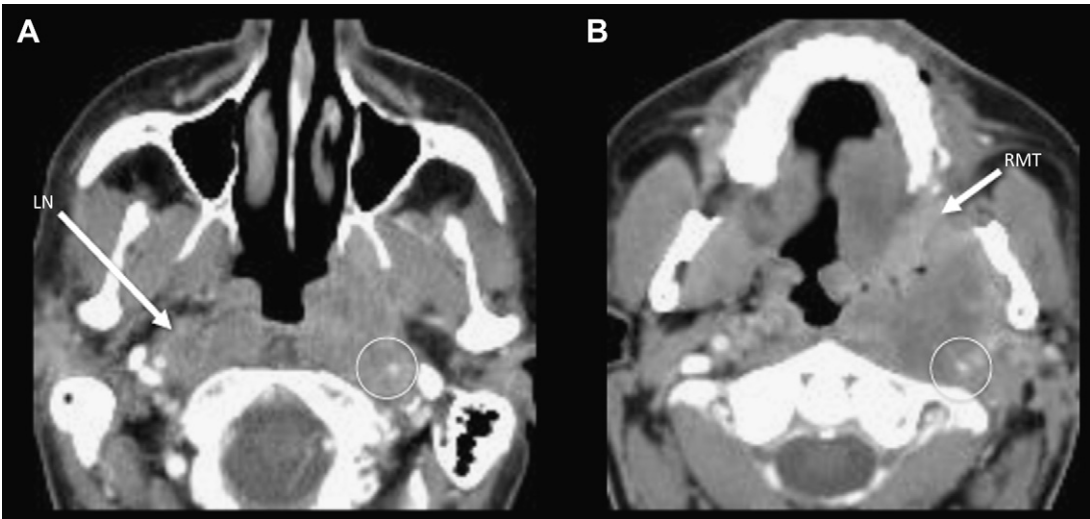
Fig. 7. (*A*, *B*), T4b tumor extends to encircle and narrow the left internal carotid artery (*circle*) and into left nasopharynx and adjacent prevertebral muscles. Tumor invades the left medial pterygoid muscle and extends into the left retromolar trigone (RMT) (*short arrow*) and soft palate. A right (contralateral) retropharyngeal node is partly necrotic (LN) (*long arrow*).

laser microsurgery offer the benefits of surgical excision of primary tumor without the morbidity of traditional open surgery. Also, patients treated to cure (with de-escalation of adjuvant therapy) avoid some of the toxicities of traditional radiation and chemotherapy. This minimally invasive approach to local control, used in T1 and T2 tumors, is associated with improved quality of life (avoiding permanent feeding tube or tracheostomy tube and preserving swallowing and speech function) (**Fig. 9**). However, bulky or locally invasive cancers, and cancers located in the inferior OP are not typically suited to TORS.[37]

Early stage (I-II) OPSCC can be handled with definitive radiotherapy; surgical excision of the primary and neck dissection as needed; or for T2, N1 patients, chemotherapy and radiation. Pathologic features such as positive margins, ECS, perineural invasion, or vascular embolism discovered at surgery could necessitate further

Fig. 8. Extracapsular spread of disease and right level 2A/B nodal conglomerate (*arrows*). Nodal disease is inseparable from the sternocleidomastoid muscle, effaces the right jugular vein (J), and displaces the internal and external carotid artery (*circle*) medially. In the floor of mouth, oropharynx primary surrounds the lingual artery (L) and invades the extrinsic tongue muscles. Primary tumor fills the right vallecula and crosses midline posteriorly at base of tongue.

Fig. 9. 2.0 cm mass (*arrow*) centered in the left tonsil. The lesion is localized and somewhat exophytic. Patient underwent TORS procedure with negative margins.

treatment with radiation, chemotherapy, and radiation or re-excision (in the setting of positive margins). For the patients receiving radiation and chemotherapy or definitive radiation who show evidence of persistent disease, salvage surgery is recommended.

More advanced cancers (T3–4a, N0–1; or any T, N2-3) can be managed with concurrent systemic therapy/radiation therapy with cisplatin as the preferred method according to 2011 NCCN guidelines. Surgery of the primary and neck dissection is another provided option. Induction chemotherapy followed by radiation and concurrent chemotherapy and radiation are third and fourth possibilities. In the surgical patients, if ECS and/or positive margins are found at pathologic assessment, additional therapy with chemotherapy and radiation therapy is recommended. NCCN states that the best management of any cancer patient is in a clinical trial and encourages participation in clinical trials.

In cases of newly diagnosed (M0), T4B, any N, or unresectable nodal disease, the NCCN guidelines suggest enrollment in an appropriate clinical trial or treatment arm, and those paradigms include chemotherapy and radiation therapy, alone or in combination.[34]

Ideally, imaging together with clinical findings will define tumor margins, determine lymph node status, and assess for distant disease. Local disease extent that would preclude curative therapy at surgery such as invasion of the lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base, or ICA encasement needs to be established. Imaging findings of ECS, level IV or V disease, or contralateral nodal disease impact treatment.

The evidence-based treatment models reported in the NCCN and ACR guidelines depend upon accurate and consistent definition of primary tumor size and extent, presence and character of nodal disease, and more recently, the HPV status of the patient. The ACR guidelines describe 3 recognized prognostic groups of OPSCC and their fundamentally different treatment objectives. HPV-positive tumors in patients without a smoking history are found to have the most favorable prognosis with mature disease-free survival rates of 80% or higher. The group with intermediate risk is HPV-positive tumors in patients with a smoking history. Disease-free survival in this group is between 55% and 65%. The third group, with worst prognosis, is made up of patients with HPV-negative OPSCC; survival is 50% or less. Clearly establishing HPV status of the tumor is of great clinical and outcome importance.[35] OPSCC is considered a curable cancer, and the

therapeutic options expand with greater understanding of disease biology and as new treatment techniques emerge.[7]

PATTERN OF SPREAD

Local tumor extension occurs in a predictable fashion. Tumors with multiple subsite involvement have a worse response to therapy and higher rates of recurrence as compared with similar T lesions without extension outside the tonsillar fossa.[12] Lymphatic drainage shows slight variation between the different sites, but is predictable.

Tonsillar Pillars

The anterior tonsillar pillar and tonsil are the most common locations for primary tumors of the OP.[1,6] Cancers arising at the anterior tonsillar pillar can spread along the palatoglossus muscle superiorly to the lateral soft palate. The tumor may spread to the masticator space (pterygoid muscles), nasopharynx, and the skull base (pterygoid plates and sphenoid bone or along palatine muscles). Once a tumor is in the pterygoid musculature, pain and trismus are present. Inferior extension along the palatoglossus muscle course results in tumor at the base of tongue. If the tumor spreads laterally and anteriorly, it can travel along the pharyngeal constrictor muscles and pterygomandibular raphe to the oral cavity at the retromolar trigone and into the buccinator muscle.[1,6,12,38–40] Lymphatic drainage from the anterior tonsillar pillar is to levels I, II, and III. Forty-five percent of patients have positive nodes at presentation. Higher T lesions are more likely to have positive nodes. Contralateral nodal involvement is found in 5% of lesions.[6,38]

The posterior tonsillar pillar is the mucosa over the palatopharyngeus muscle. Tumor can spread to the soft palate, posterior thyroid cartilage, middle constrictor muscle (and from there, along the pterygomandibular raphe to the oral cavity), posterior pharyngeal wall and pharyngoepiglottic fold to the top of the pyriform sinus.[6,12,38–40] Lymphatic drainage from the posterior tonsillar pillar is to level II. Once a tumor reaches the posterior oropharyngeal wall, level V and retropharyngeal nodal stations are in the drainage pathway.[6,38]

Tonsillar Fossa

Cancers of the tonsillar fossa are often clinically silent and may present as a neck mass from malignant adenopathy. From the tonsillar fossa, a tumor can spread directly into the parapharyngeal space and from there to the carotid space, into the masticator space, and into the mandible. Additionally a tumor can spread along the anterior and

posterior tonsillar pillars with routes of extension as discussed previously.[6,12,38–40]

Lymphatic drainage from the tonsillar fossa is to levels I–IV. Parotid lymph nodes and level V nodes can rarely be affected. Tonsillar primaries have between a 71% and 89% chance of having nodal metastasis with increasing likelihood of nodal disease with increasing T designation. Contralateral nodal disease is found in up to 22% of patients. Tumors with tongue base or soft palate extension have an increased chance of contralateral nodal disease.[6,38]

Soft Palate

Soft palate tumors are typically found on the ventral surface and are generally small at time of diagnosis. Patients complain of odynophagia. These tumors are often well differentiated and have the best prognosis of the oropharyngeal cancers. Local extension can occur anteriorly onto the hard palate; laterally into palatine muscles and the parapharyngeal space, and from there to skull base and nasopharynx; and inferiorly onto the tonsillar pillars. Additionally, perineural extension of disease can occur along the palatine nerves and retrograde to pterygopalatine fossa and cavernous sinus along V2.[6,12,38–40] Lymphatic drainage from the soft palate is to levels II and III as well as the retropharyngeal nodes. Twenty percent to 45% of patients with soft palate primary SCC will present with positive lymph nodes.[6,38]

Base of Tongue

Base of tongue cancers are difficult to diagnosis with imaging when small, and mucosal lesions are best assessed with direct inspection. Of the subsites in the OP, the base of tongue is associated with the highest rate of regional (nodal) disease.[41] These tumors are more aggressive and as such, the advanced stage cancers have a poor overall survival of approximately 20%.[6] Tumors arising in this location spread anteriorly into root of tongue and extrinsic tongue muscles, and into the sublingual space and neurovascular bundle of the oral cavity. Caudal extension is into the vallecula and potentially the pre-epiglottic fat. If the pre-epiglottic fat is invaded, surgical management includes a supraglottic laryngectomy. Lateral extension is potentially into the lateral wall, pterygomandibular raphe, and mandible. More posteriorly, a tumor can invade the parapharyngeal fat and from there, the carotid space. Tumors can extend superiorly along the tonsillar pillars.[6,12,38–40]

Lymphatic drainage of the base of tongue is complicated by cross-drainage. At presentation,

20% to 30% of patients have bilateral nodal disease.[41] Nodal drainage is to levels II to IV. Occasionally level V disease is also found. If the cancer invades the floor of mouth, level I malignant nodes can be seen. As at the other sites, presence of cervical nodal disease decreases survival by more than 50%. At presentation, 70% of T1 lesions have nodal disease, while 84% of T4 lesions do.[6,38]

Posterior Pharyngeal Wall

The last subsite of the OP is the posterior pharyngeal wall. The patient may complain of dysphagia and odynophagia. Tumors here are often large at the time of diagnosis and can spread superiorly to the nasopharynx, laterally into the parapharyngeal space, inferiorly into the hypopharynx, and anteriorly into the tonsil. If the tumor has deep extension, it invades the prevertebral musculature (longus colli and capitus). Recognition of prevertebral muscle invasion is important, as this finding renders the patient unresectable. However, unresectability should be determined at surgery, as imaging is limited in detecting prevertebral muscle invasion. Many of these tumors extend past midline.[6,12,38–40] Lymphatic drainage of the posterior pharyngeal wall includes bilateral jugular chain lymph nodes and the retropharyngeal lymph nodes (**Fig. 10**).[6,38]

PITFALLS IN STAGING

Difficulties encountered in staging of OPSCC are not unique to this location. CECT with adequate mucosal enhancement is a widely used staging tool. Unfortunately, streak artifact from dental amalgam and metal surgical hardware can limit evaluation of the adjacent structures. (**Fig. 11**). Postcontrast fat-saturation MRI is particularly useful in the assessment of the primary lesions and in the search for perineural tumor extension (**Fig. 12**).[12] Motion artifacts are more likely with MRI than with CT given the time it takes to acquire the images. PET-CT can be useful in identifying the primary lesion and malignant adenopathy, but has limitations when evaluation of the skull base, cranial nerves, or small lesions (<1 cm) is necessary.

Mucosal and smaller lesions are best assessed clinically. Lesions arising in areas of lymphoid tissue can be obscured by the normal enhancement/fluorodeoxyglucose (FDG) uptake of the lingual and palatine tonsils. Normal asymmetry in lymphoid tissue further makes staging smaller tumors difficult. The importance of knowing the clinical examination findings while reviewing
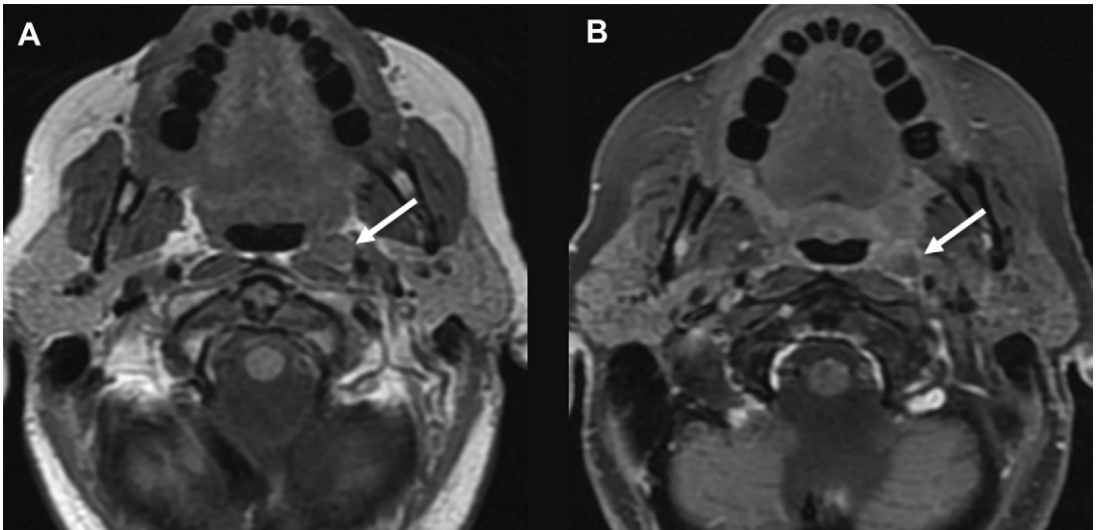
Fig. 10. Metastatic retropharyngeal lymph node (*arrows*) on axial T1-weighted (*A*) and axial fat-saturated post-contrast T1-weighted images (*B*).

imaging studies cannot be overemphasized. (**Fig. 13**).

The overall size/volume of the tumor needs to be measured. When tumors are discrete and exophytic in nature, this is more easily accomplished. However, tumors of the OP are more commonly infiltrative, invasive, and extend along muscle and fascial planes, thus making accurate size determination difficult. Base of tongue cancers can be particularly problematic, as dense

interdigitation of muscle without intervening fat to define the tissue planes can obscure lesion margins.[41]

Extension of tumor into the larynx (pre-epiglottic fat), root of tongue, masticator space, skull base, nasopharynx, and carotid space can change the staging to T4 regardless of lesion size. Clues of deep invasion can be found in the clinical note. Trismus suggests pterygomaxillary space extension, and trismus often complicates the clinical
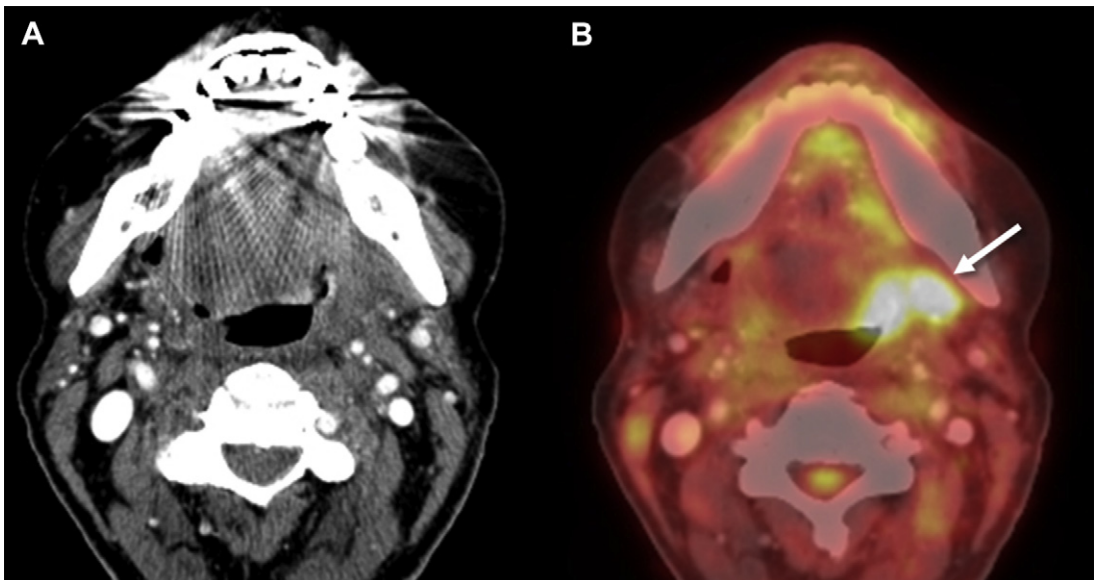
Fig. 11. (*A*) CT with significant dental amalgam artifact. The oropharyngeal primary is partly obscured. (*B*) PET-CT image performed concurrently demonstrating abnormal FDG uptake at the site of recurrent oropharyngeal tumor (*arrow*).
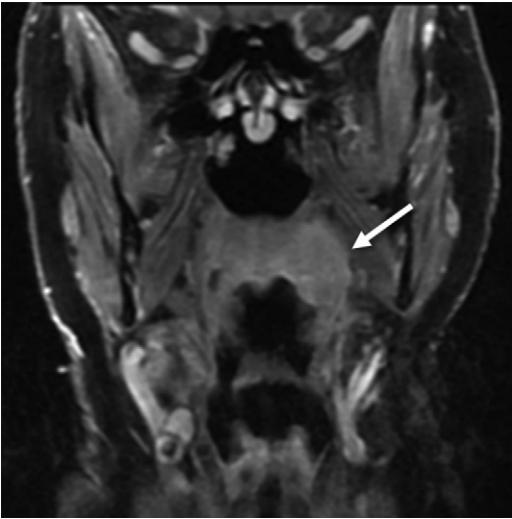
Fig. 12. Coronal fat-saturated postcontrast T1-weighted image of a soft palate and anterior tonsillar pillar primary tumor with extension into pharyngeal constrictor muscles and parapharyngeal fat (*arrow*).

assessment of the primary lesion. The physical examination should also test for intact cranial nerves, especially 5, 7, 9, 10, and 12. Decreased mobility of the tongue suggests deep tongue muscle invasion.[6] Tumor extension into the masticator space and retromolar trigone region can be overlooked and on CT be obscured by streak artifact from dental amalgam, particularly when re-angled views (15° off parallel line to hard palate) are not obtained. MRI is less susceptible to dental amalgam artifacts and often provides superior soft tissue assessment.

Attempts should be made to determine whether the tumor crosses midline, as midline extension increases the likelihood of bilateral/contralateral nodal involvement. At the base of tongue, cross-midline extension changes the surgical plan, as the contralateral neurovascular bundle is at risk.

Because osseous invasion upstages the patients to T4, the mandible, maxilla and pterygoid plates must be carefully evaluated. On CT, cortical and medullary extension can often be appreciated by erosive changes, periosteal reactions, lucency centrally, and/or pathologic fractures (**Fig. 14**). MRI can be used to assess medullary cavity and cartilage. Caution should be exercised, however, as not all marrow signal changes result from infiltrating tumor. Marrow signal changes consisting of low signal on T1 and relative hyperintensity on fat saturation T2 images can be seen with fibrosis from radiation, osteoradionecrosis, and non-neoplastic reactive changes related to dental disease.[41] Regardless, bony invasion can change the surgical plan and needs to be prospectively determined.

With cross-sectional imaging, structures parallel to the plane of the image acquisition are more difficult to appreciate. For example, in the assessment of the soft palate, coronal and sagittal images are often superior to axial images. Reconstruction of thin-slice axial CT image data into the coronal and sagittal planes can accomplish this multiplanar approach. The inherent multiplanar nature of MRI with its superior soft tissue contrast lends itself well to soft palate staging and evaluation of the structures abutting the skull base.

MRI is superior to CT in the assessment for perineural spread (PNS). Clues on CT to perineural extension of tumor include loss of fat in the neural foramen (eg, mandibular foramen, foramen ovale, pterygopalatine fossa), widening of the osseous canals through which the nerves travel, and denervation changes in muscle. Affected nerves are enlarged and enhanced on MRI. Findings of tumor extension along cranial nerves almost always change treatment and prognosis.[41]

Identification of tumor extension into adjacent structures that would render the patient nonoperative should be made. Posterior pharyngeal wall tumor extending into the prevertebral space is one such finding. With imaging, invasion of the prevertebral muscles can sometimes be difficult to determine. Muscular enhancement can occur with direct extent as well as with inflammation. Broad interface of tumor with the prevertebral structures does not necessarily mean invasion of the prevertebral structures, as the deep and middle layers of deep cervical fascia may still be intact. Loss of the normal fat density/signal in the retropharyngeal space is particularly concerning.[38,42,43] If normal fat signal of the retropharyngeal space is preserved, there is probably no invasion of prevertebral muscles. Contiguous aggressive changes in the vertebral body confirm perivertebral space invasion. Tumor encasing the carotid artery (270° or greater) is another example of tumor extension into adjacent spaces, rendering the patient nonsurgical.

Overall, approximately 65% of OPSCC patients present with metastatic lymphadenopathy. Lesions of the base of tongue are the most likely to present with malignant lymph nodes (**Fig. 15**).[41] Accepted imaging criteria for metastatic adenopathy is reviewed in the article on nodal disease by Amit Saindane in this issue. Any node with irregular borders as seen in extracapsular disease extension or with necrosis is considered pathologic. ECS is associated with a 3.5-fold increase in the local recurrence rate.[44]

Lack of recognition of skip and contralateral nodal metastases and/or pathologic retropharyngeal lymph nodes provides other potential staging
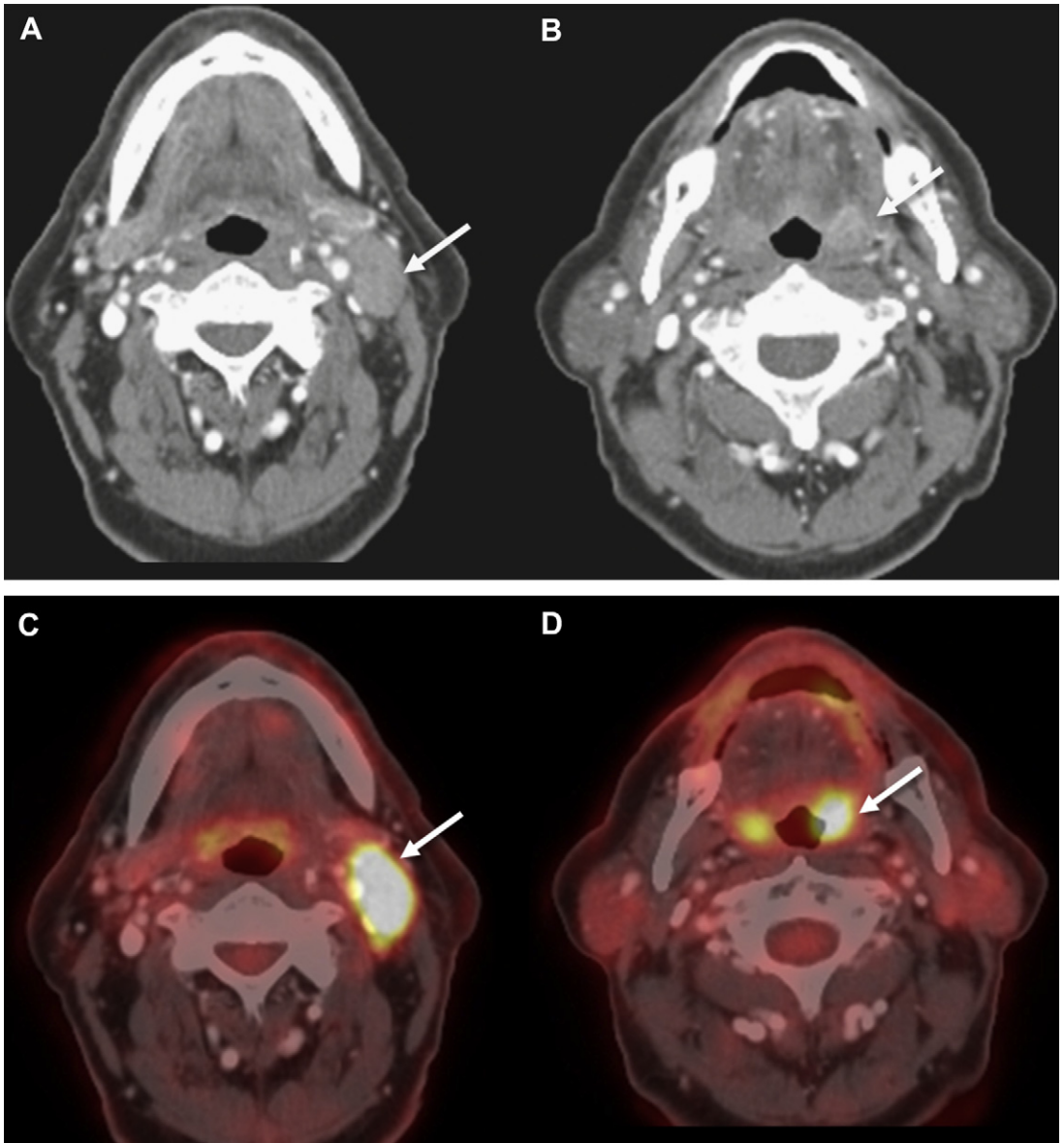
Fig. 13. (*A*) CE-CT neck performed for palpable left neck mass (*arrow*) of level IIA adenopathy. (*B*) Palatine tonsillar tissue is mildly asymmetric on the left (*arrow*). This finding corresponded to physical examination abnormality and metabolic activity on PET-CT. (*C*) PET-CT image showing metastatic lymphadenopathy (*arrow*). (*D*) PET-CT image showing the left palatine tonsil primary (*arrow*) with asymmetric FDG uptake.

pitfalls. Fifteen percent to 30% of patients initially staged as N0 will be proven to have regional nodal metastases. In light of that fact, treatment of the neck with either nodal dissection or radiation therapy is part of the therapeutic paradigm.[12] PET alone may miss cystic nodal metastasis and necrotic lymph nodes, reinforcing the need for anatomic imaging as well as PET (**Fig. 16**). At the author's institution, diagnostic quality CECT is performed in conjunction with the PET, and nuclear medicine physicians and the head and neck radiologists perform consensus interpretation.

As with all HNSCCs, synchronous and second primary tumors can occur (**Fig. 17**). The risk of developing a second primary tumor in patients with tumors of the upper aerodigestive tract has been estimated to be 3% to 7% per year.[45,46] The radiologist must be vigilant in the imaging assessment and critically examine the images to prevent missing the second lesion.

Fig. 14. Axial CT bone windows showing oropharyngeal T4b primary lesion has eroded the pterygoid plates and posterior wall of the maxillary sinus on the left (*circle*).

PITFALLS IN SURVEILLANCE

For a patient with OPSCC, surveillance is lifelong but is especially important in the first 2 years following treatment, when locoregional failure is most likely.[47,48] Patients may have local or regional (neck) failure with persistent or recurrent disease following definitive treatment or even present with distant metastases during follow-up. The development of a second primary is a risk in patients with either HPV-positive tumors or HPV-negative tumors.[45]

In HPV-negative tumors, the second primary lesions are more likely in the upper and lower aerodigestive tract and bladder with a rate of 15% to 30%. This risk can be cut in half by abstaining from alcohol and tobacco products.[49,50] HPV-positive tumors have a lower risk of second primary at 5% to 10%. In addition to sites of second primary in the upper aerodigestive tract and bladder, these patients are at risk for SCC of the anogenital regions.[50]

Surveillance imaging of the neck following definitive treatment for OPSCC can be done with CECT, MRI without and with contrast, PET-CECT, ultrasound, or a combination thereof. The NCCN guidelines stress the importance of regular history and physical examinations with attention to signs or symptoms of recurrent, progressive or metastatic disease and for the development of a second primary lesion. Assessment for locoregional failure on physical examination as well as with imaging is complicated by post-treatment changes in the neck and loss of the normal tissue planes following surgery and radiation treatment, scar and fibrotic tissue, sterile/treated disease residua, and loss of symmetry (**Fig. 18**).

The assessment of any muscle flap and tissues adjacent to the flap can be complex, with fluctuation in flap appearance over time. In the acute postoperative setting, confounding tissue and muscle edema can cause false-positive imaging findings with MRI and PET-CECT. Following chemotherapy and radiation therapy, false-negative findings can be found on PET-CECT when imaged early (1 month vs 4 months following therapy).[51] Therefore, it is recommended that post-treatment MRI and/or PET-CECT be performed at least 3 months following radiation therapy.

False-positive PET-CECT can occur from fasciculation in myocutaneous flaps, fibrosis at the surgical site, aspiration or fungal pneumonia, and normal activity in Waldeyer ring, muscle, mucosa, and salivary tissue. False-negative PET-CECT may occur when there are necrotic or cystic lymph nodes or when the lesion is small, beneath the resolution of the PET. Radiation damage

Fig. 15. Primary base of tongue squamous cell carcinoma (*arrow*) with ipsilateral lymphadenopathy (*circle*) on (*A*) Axial T1-weighted MRI. (*B*) CE-CT. (*C*) PET-CT.
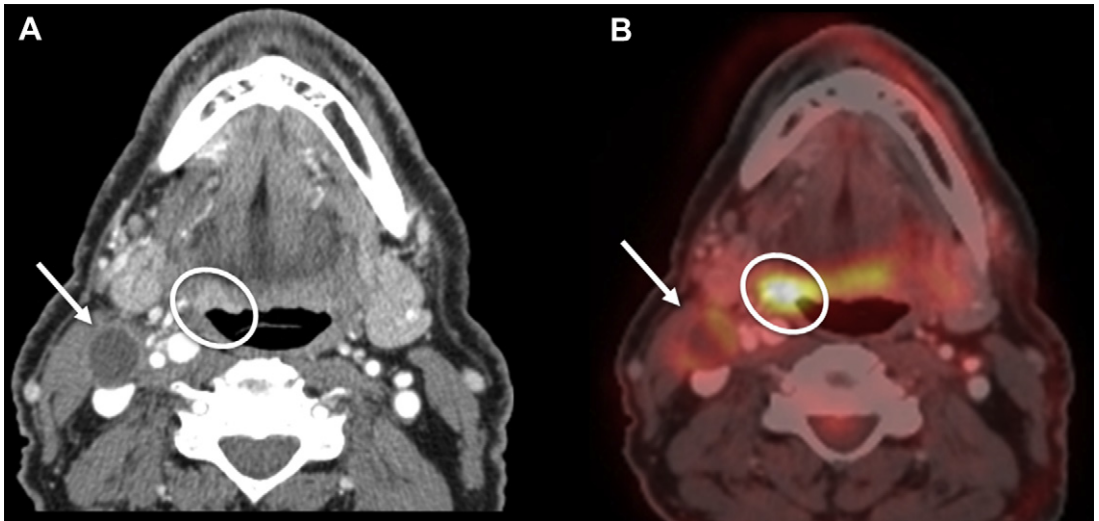
Fig. 16. Cystic lymph nodes (*arrow*) can be a source of false negative PET-CT findings. Contrast enhanced neck CT (*A*) Performed with the PET-CT (*B*) For staging of a base of tongue primary cancer (*circle*).

decreases background physiologic uptake to the affected side, creating asymmetric uptake. Infection and inflammation can cause otherwise normal lymph nodes to show increased FDG avidity, potentially the result of upregulation of glycolysis.[51]

Recurrences can be as subtle as progressive thickening and enhancement in the tumor bed or as obvious as a new mass. After neck surgery, lymphatic drainage will shift to the contralateral side and therefore the lymph node stations in both the ipsilateral and contralateral sides of the neck relative to the site of primary tumor warrant equally close scrutiny. Tumor recurrence/implant

can be recognized by nodular enhancement in the flap, skin, or musculature.

PET-CECT has shown promise in assessment of the post-treatment population. Sensitivity of FDG PET-CECT for detection of residual or recurrent cancer is between 84% and 100% when the scan is obtained more than 12 weeks following the end of therapy. The specificity of this test is 61% to 93%. PET-CT has been shown to be superior in detection of regional or distant disease as compared to local recurrence. PET-CT has a high negative predictive value after treatment for head and neck cancer, especially in assessment of the
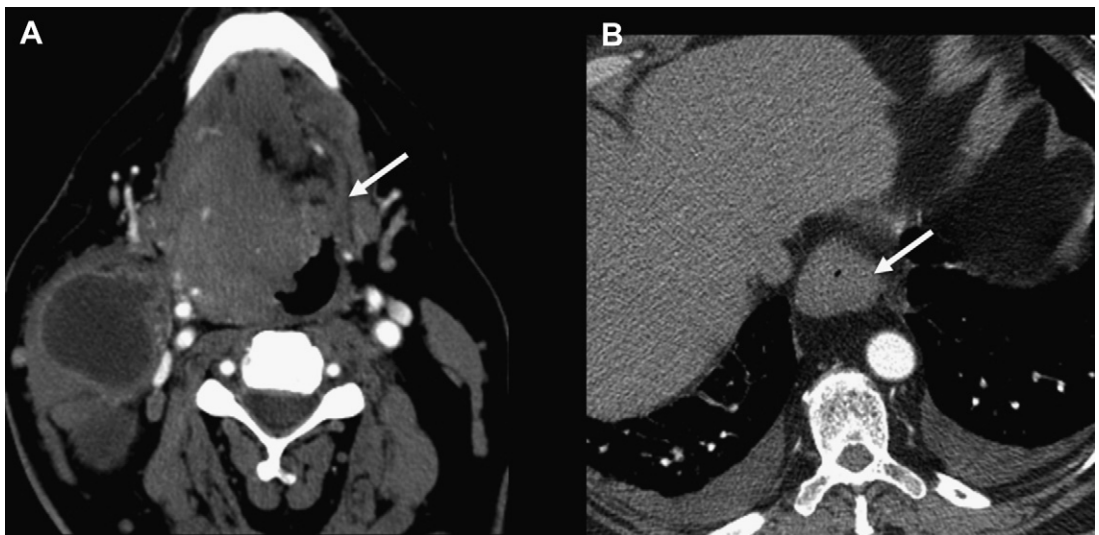
Fig. 17. (*A*) T4a oropharyngeal cancer with N3 nodal disease. Normal hyoglossus muscle on left (*arrow*). (*B*) Staging chest CT noted abnormal distal esophagus (*arrow*). This mass is a biopsy-proven adenocarcinoma, the patient's second primary cancer.
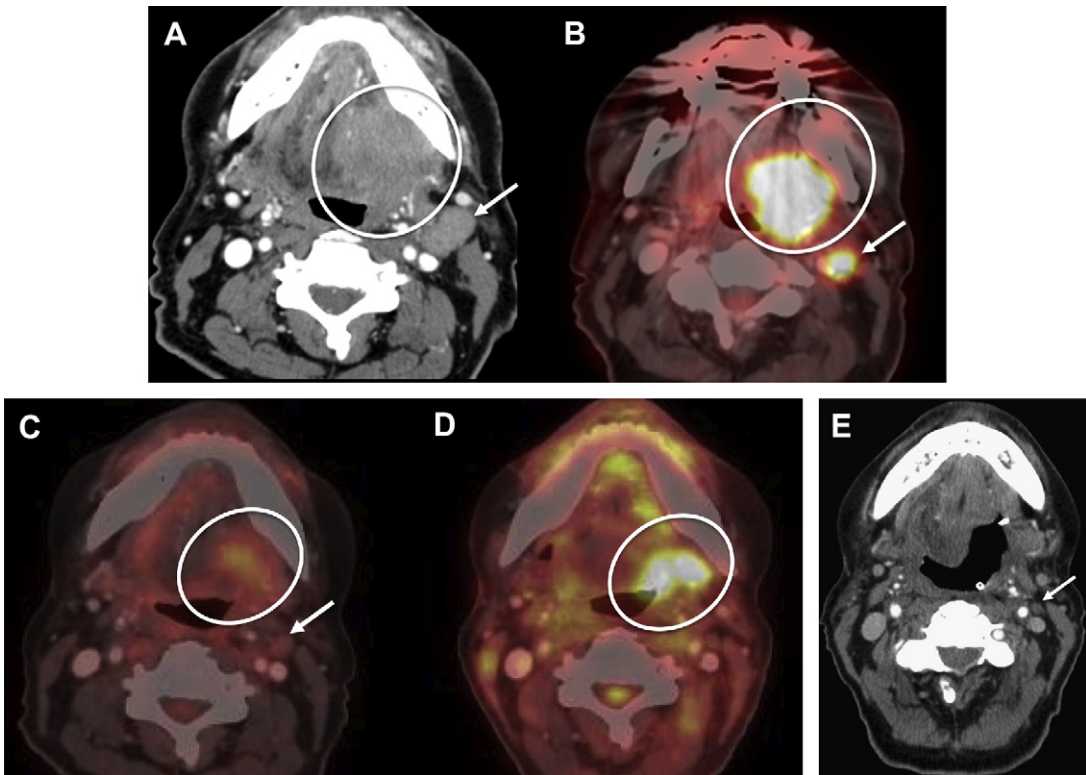
Fig. 18. (*A*, *B*). Presentation CE-CT (*A*) and PET-CT (*B*) of a T4 oropharynx cancer. Tumor invades sublingual space and adjacent musculature (*circle*). Left level IIA malignant adenopathy (*arrow*). (*C*) PET-CT obtained 3 months following combined modality therapy with significant interval decrease in activity in the tumor bed (*circle*). The previously hot IIA lymph node no longer shows FDG avidity (*arrow*). (*D*) Subsequent surveillance scan with new activity of recurrent disease 1 year following diagnosis (*circle*). (*E*) Postoperative baseline scan following TORS to the site of recurrent tumor. Note the IIA lymph node is now normal in size and appearance (*arrow*).

lymph nodes. It is still debated whether a negative PET-CECT can be used to defer a planned neck dissection. If findings are indeterminate on PET-CECT, ultrasound-guided fine needle aspiration (UG-FNA) could be performed. For evaluation of distant disease, PET-CT is preferred.[51]

While standardized imaging follow-up regimens are not yet supported by evidence-based data, recommendations are available in the NCCN literature. In summary, these guidelines suggest post-treatment baseline imaging of the primary tumor bed (and neck if treated) within 6 months for patients with T3 to T4 or N2 to N3 disease and by re-imaging as indicated based on signs or symptoms concerning for recurrence. Imaging is not routinely recommended in asymptomatic patients.[34]

In patients who have undergone multimodality treatment regimen of surgery, radiation and chemotherapy, the NCCN Guidelines suggest clinical assessment at 4 to 8 weeks. If there are signs or symptoms of persistent or progressive disease, CECT or MRI is recommended. PET is listed as optional. In patients with no clinical signs of disease, PET-CT with anatomic assessment is recommended at a minimum of 12 weeks after treatment. If PET-CT is not available, the guidelines recommend CE-CT or MRI. Close clinical follow-up is encouraged with scheduled history and physical examimnations every 1 to 3 months in the first year, every 2 to 4 months in the second year, every 4 to 6 months in the third to fifth years, and every 6 to 12 months thereafter.[34]

It is not yet proven whether surveillance imaging leads to earlier detection of treatment failure and whether earlier detection actually improves outcome and survival. Salvage treatment success does appear to be better in local and regional recurrences as compared to distant recurrences.[48]

SUMMARY

The face of OPSCC is changing. It has a dichotomous nature, with 1 subset of the disease associated with tobacco and alcohol use and the other having proven association with HPV infection. Imaging plays an important role in the staging and

Table 3
Pitfalls in staging of oropharyngeal carcinoma

Pitfall	Advice
Streak artifact on CE-CT degrades axial images	Obtain additional reangled images (15° off parallel line to hard palate)
Inability to see small mucosal primary lesion	Recognize limitations of all imaging techniques for evaluation of mucosal lesions, and realize that the clinical examination is complementary
Under-recognition of extension of a tonsillar primary to the soft palate on axial CE-CT	Reconstruct the thin CT image data into the coronal and sagittal planes to better evaluate the soft palate
Understaging of the primary site by failure to recognize skull base involvement on CE-CT	Carefully evaluate the ptergyoid plates for erosion on bone windows; consider MRI for further evaluation
Understaging of lymphadenopathy by not recognizing retropharyngeal metastatic lymph nodes	Evaluate the retropharyngeal nodes ipsilateral and contralateral to the primary, particularly if the primary crosses midline

surveillance of OPSCC, and a detailed knowledge of the anatomy and pitfalls is critical (**Table 3**).

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