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

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KEYWORDS

• Squamous cell carcinoma • Larynx • Intensity-modulated radiation therapy

KEY POINTS

- Laryngeal carcinoma is a devastating malignancy that severely affects patients' quality of life, with compromise of ability to talk, breathe, and swallow.
- Accurate tumor staging is imperative, because treatment plans focus on laryngeal conservation therapy whenever possible.
- Although the mucosal extent of tumor and vocal cord mobility is best assessed with endoscopic evaluation, cross-sectional imaging is essential for accurate T-staging, because only cross-sectional imaging can assess the submucosal extent of the tumor, cartilage invasion, and extralaryngeal spread.
- This article reviews topics crucial for interpreting imaging studies of patients with laryngeal squamous cell carcinoma.

Laryngeal carcinoma is a devastating malignancy that severely affects patients' quality of life, with compromise of ability to talk, breathe, and swallow. Accurate tumor staging is imperative, because treatment plans focus on laryngeal conservation therapy, whenever possible. Although the mucosal extent of tumor and vocal cord mobility is best assessed with endoscopic evaluation, cross-sectional imaging is essential for accurate T-staging, because only cross-sectional imaging can assess the submucosal extent of the tumor, cartilage invasion, and extralaryngeal spread. This article reviews topics crucial for interpreting imaging studies of patients with laryngeal squamous cell carcinoma (SCC).

EPIDEMIOLOGY OF LARYNGEAL SCC

The incidence of laryngeal SCC ranges from 0.3 to 9.8 per 100,000 people annually and represents approximately 1% to 2% of all adult malignancies. Men are affected 3 times more frequently than women, and incidence increases with advancing age, with the median age at diagnosis of 65 years, from 2004 to 2008.[1]

The patient population is similar to that affected by lung cancer, with a strong association with smoking and alcohol use in up to 95% of patients, and reported increased incidence in patients of low socioeconomic status.[2] Other potential risk factors for laryngeal carcinoma include passive tobacco smoke exposure, occupational exposure to chemical irritants, chronic irritation caused by reflux, and possibly viral exposure (see later). Nonsmokers with laryngeal SCC are uncommon but tend to be older and the primary subsite is more often glottis, compared with smokers with SCC.[3]

Laryngeal neoplasms are associated with human papillovirus (HPV) infection, particularly

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with benign laryngeal papillomatosis, most often associated with the low-risk HPV subtypes, HPV 6 and 11. Patients with laryngeal papillomatosis have an approximately 2% risk of developing laryngeal malignancy, particularly if the patient is diagnosed as an adult.[4] The association of HPV infection with the development of SCC has not been well established, and this contrasts with oropharyngeal cancers, in which the clinical significance of and association with the development of SCC and HPV infection have been well documented. There is a broad range of prevalence of HPV infection in laryngeal carcinoma in the literature, present in up to 25% of patients on meta-analysis, with malignancy most commonly associated with the high-risk subtypes 16 and 18. However, the clinical significance and implication of these infections are unclear at this time and require further investigation.[5]

ANATOMY AND BOUNDARIES OF THE LARYNX

The larynx is a mucosa-lined tube that is responsible for phonation and airway protection. The laryngeal structural framework is composed of the thyroid, cricoid, and arytenoid cartilages; ligaments connecting the cartilaginous framework; and a series of 7 separate paired intrinsic laryngeal muscles, surrounded by fat-containing spaces and lined internally by squamous epithelial mucosa.

The superior border of the larynx is the free edge of the epiglottis, dividing it from the oropharynx, and the inferior extent is to the lower border of the cricoid cartilage. Posteriorly, the larynx is separated from the hypopharynx by the aryepiglottic (AE) folds. The larynx is divided into supraglottic, glottic, and infraglottic (or subglottic) components (**Fig. 1**A).

The supraglottic larynx extends from the tip of the epiglottis (lingual and laryngeal surfaces) and AE folds superiorly to the apex of the laryngeal ventricle (see **Fig. 1**B, C). The supraglottic larynx can be subdivided into suprahyoid and infrahyoid regions, divided by the hyoid bone, and the suprahyoid epiglottis contains the free edge of the epiglottis. The petiole of the epiglottis is another term for the base of the infrahyoid epiglottis, at its attachment with the thyroid cartilage (overlying the thyroepiglottic ligament) (**Fig. 2**A). The subsites of the supraglottic larynx, therefore, include the epiglottis (suprahyoid and infrahyoid components), the AE folds, the arytenoids, and the false vocal cords.[6] The AE folds sweep down laterally from the epiglottis and extend to the arytenoid cartilages, and contain 2 small prominences,

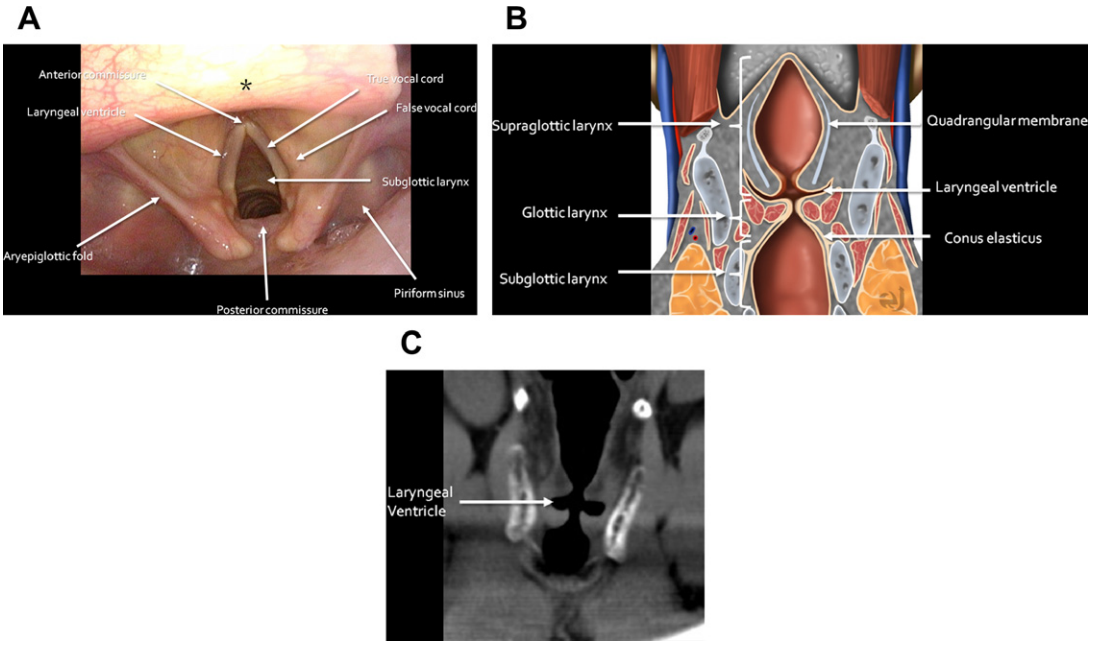

Fig. 1. Normal larynx anatomy. (*A*) Endoscopic view of normal larynx. Asterisk denotes the epiglottis. Note the relationship of the larynx to the hypopharynx (piriform sinus). (*B*) Coronal illustration of the larynx, showing the division into supraglottic, glottic, and subglottic larynx. (*C*) Coronal CE-CT scan dividing the larynx into supraglottic, glottic, and subglottic larynx. Division between supraglottic and glottic larynx is at the apex of the lateral ventricle. Glottic larynx is the extent of the true vocal cords (1 cm anteriorly, and 5 mm posteriorly). (*Courtesy of* Eric Jablonowski.)

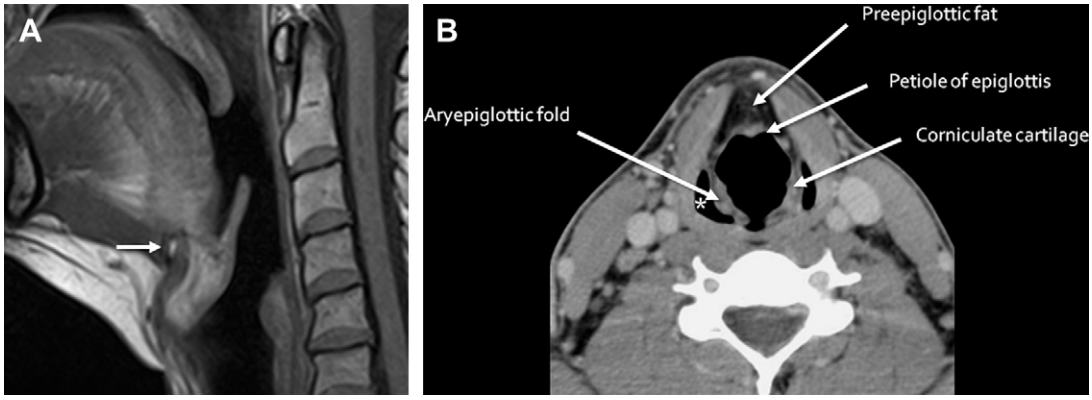

Fig. 2. Supraglottic larynx. (*A*) Mid-sagittal T1-weighted image of a normal supraglottic larynx. The hyoid bone (*arrow*) divides the epiglottis into a suprahyoid and infrahyoid portion. (*B*) Axial CE-CT through the levels of the AE folds, as they extend toward the arytenoid cartilage (not shown). The AE folds separate the larynx from the hypopharynx (piriform sinuses). The small protruberances along the medial AE folds overlie the corniculate cartilage.

which denote the location of the cuneiform and corniculate cartilages. The corniculate cartilage may be seen on imaging perched on top of the arytenoid cartilage; however, the cuneiform cartilage is often too small to resolve (see Fig. 2B).[7] The lateral aspect of the AE folds forms the medial wall of the piriform sinus, actually part of the hypopharynx. On axial cross-sectional imaging, the false vocal cords are at the level of the adjacent paraglottic fat (Fig. 3A). The interarytenoid space forms the posterior border of the larynx, dividing it from the hypopharynx.

The glottic larynx is composed of the true vocal folds, extending from the apex of the lateral ventricle (the inferior boundary of the supraglottic larynx and the superior margin of the true vocal fold) to the inferior margin of the true vocal folds (the beginning of the subglottic larynx). The glottis should be an area 1 cm in height, extending caudal to the plane of the mid ventricle (see Fig. 1B, C). The subsites of the glottic larynx include the anterior and posterior commissures and the right and left true vocal cords.

Histologically, the vocal fold has a surface of stratified squamous epithelium, and beneath the epithelium is the lamina propria, formed of 3 layers. The most superficial layer, Reinke space, can be crucial for transoral laser resections. Beneath Reinke space are the intermediate and deep layers of the lamina propria, which make up the vocal ligament. The true vocal cord is made up of the epithelial layer, Reinke space, the vocal ligament (a thin fibrous band medially within the free margin of the vocal fold, extending the full length of the cord from the vocal process of the arytenoid cartilage to the anterior commissure), and the thyroarytenoid muscle, which also forms the vocalis muscle medially. The anterior commissure is the site of attachment of the vocal ligaments to the thyroid cartilage, via Broyles ligament. The area of anterior attachment is devoid of perichondrium and relatively vulnerable to early cartilaginous invasion.[7] The posterior commissure is the posterior space between the vocal cords, at the vocal process of each arytenoid cartilage.

On axial cross-sectional imaging, the true vocal cord level is identified by the lack of adjacent submucosal fat and the presence of all 3 cartilages (thyroid, cricoid, and vocal process of the arytenoid cartilages) in 1 cross-sectional image (see Fig. 3B).

The subglottic larynx extends from the inferior margin of the true vocal cord (approximately 1 cm below the laryngeal ventricle anteriorly), through the inferior border of the cricoid cartilage (see Fig. 1B, C). On axial cross-sectional imaging, the immediate subglottic mucosa is usually smooth, thin, and symmetric, without any significant soft tissue between the cricoid cartilage and the air column (see Fig. 2C). Any abnormal soft tissue in the subglottic lumen should raise the possibility of tumor extension. Subglottic tumor is difficult to assess endoscopically and is important for the radiologist to detect, because it will impact treatment planning and prognosis.

The preepiglottic space is a pyramid-shaped (in the sagittal plane) or C-shaped (in the axial plane), fat-containing, potential space anterior to the epiglottis, extending superiorly to the hyoid bone. It is bordered posteriorly by the infrahyoid epiglottis and anteriorly by the thyrohyoid membrane and anterior and superior lamina of the thyroid cartilage. Cranially, the preepiglottic space is bounded by the hyoepiglottic ligament and

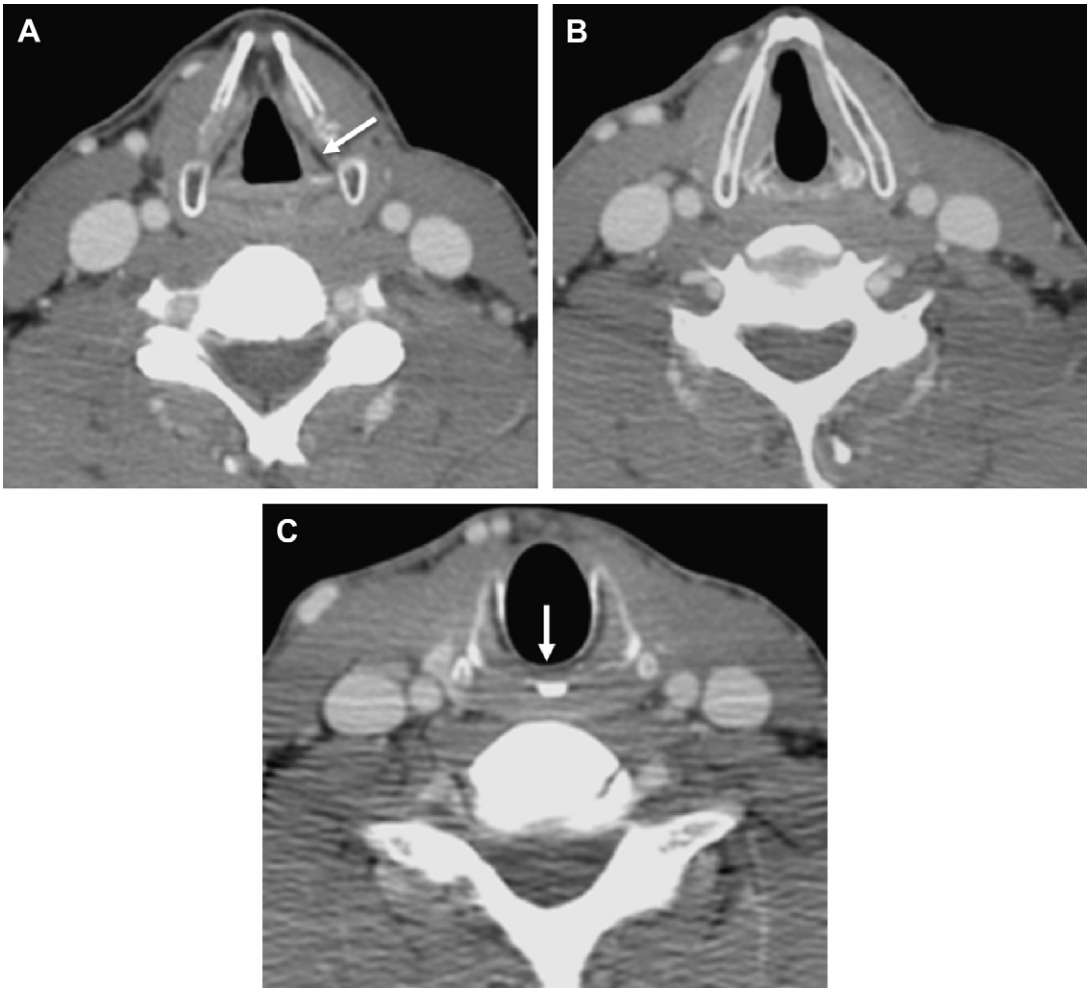

Fig. 3. Axial larynx anatomy. (*A*) Normal axial CE-CT of the larynx at the level of the false vocal cords. Note the paraglottic fat (*arrow*). (*B*) Normal axial CE-CT of the larynx at the level of the true vocal cords. Despite slight volume averaging through the laryngeal ventricle on the right, one can appreciate the linearity of the TVCs, the absence of paraglottic fat, and can see all 3 cartilages on one axial image. (*C*) Normal axial CE-CT of the larynx at the level of the subglottic larynx. Note the normal absence of endoluminal soft tissue at the level of the cricoid cartilage (*arrow*).

caudally by the petiole of the epiglottis. Inferiorly and laterally, the preepiglottic space is contiguous with the paraglottic space. Both spaces are important potential paths of submucosal tumor spread from both laryngeal and oropharyngeal tumors and cannot be identified on clinical examination, and involvement by tumor will upstage the lesion. Although this space can easily be seen in the axial plane, the preepiglottic space is best evaluated in the sagittal plane, on both reformatted contrast-enhanced computed tomography (CE-CT) and sagittal T1-weighted magnetic resonance (MR) imaging (**Fig. 4**).

The paraglottic space is a paired, fat-filled potential space, between the mucosa and laryngeal cartilage framework, and is contiguous superiorly with the preepiglottic space. The paraglottic space is mostly fat containing at the level of the supraglottis, surrounding the laryngeal ventricle, and contains the thyroarytenoid (or vocalis) muscle at the level of the glottis, with a thin sliver of fat laterally deep to the thyroid cartilage. The paraglottic space can be seen in the axial plane but is seen better in the coronal plane on both CT reformations and MR imaging (**Fig. 5**).

Two thin fibrous structures, the quadrangular membrane and the conus elasticus, are not resolved on imaging but dictate the pattern of tumor spread (see **Fig. 1**B). The medial border of the paraglottic space is formed by the quadrangular membrane, a thin fibrous structure just beneath the mucosa of the supraglottic larynx, which gives

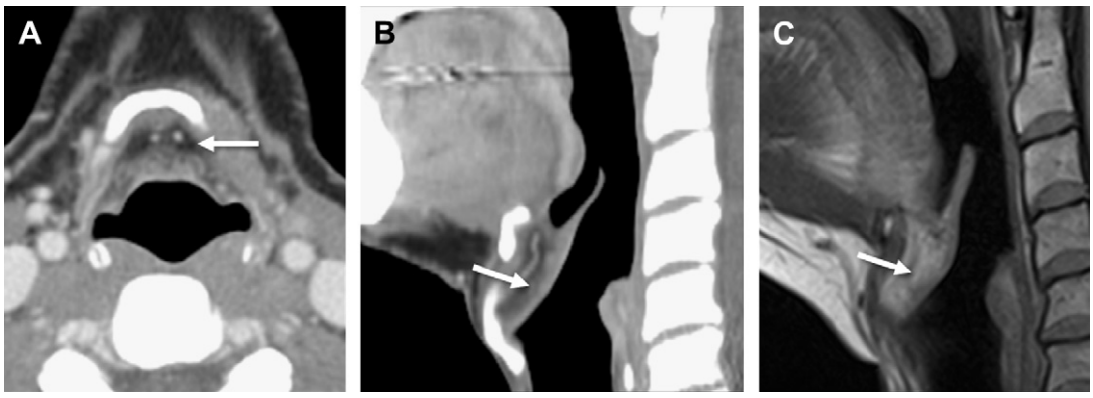

Fig. 4. Preepiglottic space. Axial CE-CT (*A*), sagittal CE-CT (*B*), and sagittal T1-weighted MR imaging (*C*) demonstrating the fatty preepiglottic space (*arrow*) that normally contains vascular structures and lymphatics.

support to the AE fold, and the conus elasticus inferiorly at the glottis and sublottic level, a thicker fibrous layer that extends inferiorly from the vocal ligament of the true cord and attaches along the upper inner margin of the cricoid cartilage, which becomes the cricothyroid membrane anteriorly.[7]

The thyroid cartilage is a triangular shield-shaped cartilage made of paired edges called the thyroid ala, which may or may not be fused anteriorly. It is connected to the hyoid bone by the thyrohyoid membrane, through which the paired external laryngeal arteries and nerves pierce laterally to provide sensation to the supraglottic larynx for airway protection. The cricoid cartilage is a round, ring-shaped cartilage inferior to the thyroid cartilage, separated from the thyroid cartilage by the cricothyroid membrane. The cricoid is the only complete cartilaginous ring in the airway, is much thicker posteriorly, and provides the foundation for the larynx. The paired arytenoid cartilages are triangular in shape and articulate with the cricoid cartilage via the cricoarytenoid joint, a synovial joint. The vocal process of the arytenoid attaches to the true vocal cord, and its mobility is necessary for phonation.[7]

The thyroid, cricoid, and arytenoid cartilages are made of varying amounts of ossified and nonossified hyaline cartilage. Ossified cartilage appears similar to bone on CT, with a peripheral hyperdense

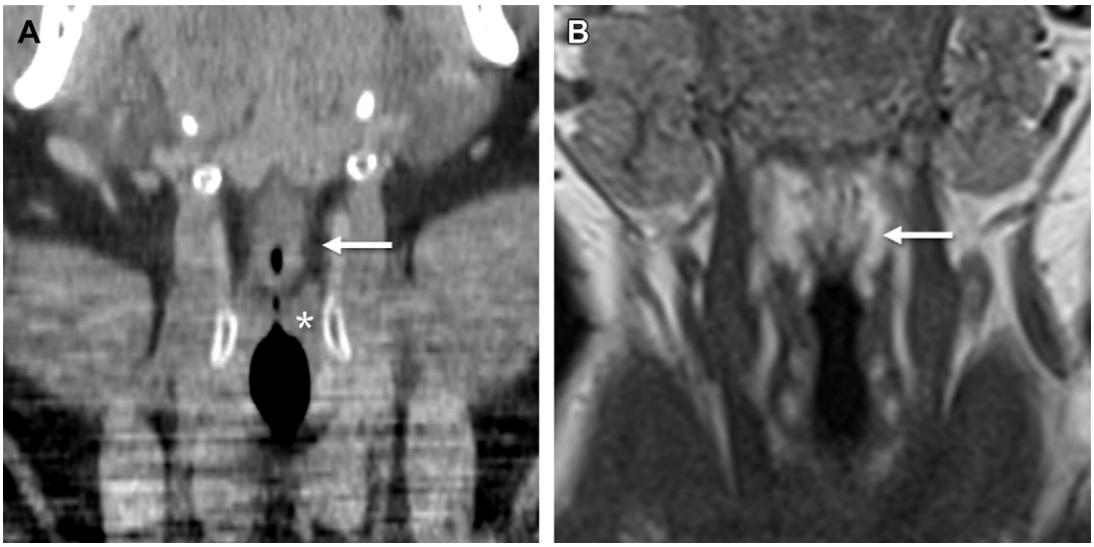

Fig. 5. Paraglottic space. Coronal CE-CT (*A*) and T1-weighted (*B*) images demonstrating the fat containing paraglottic space at the level of the supraglottic larynx, wrapping around the lateral aspect of the thyroarytenoid muscle at the true vocal cord (*asterisk*).

cortex and central hypodense medullary cavity, whereas nonossified bone has an appearance of soft tissue. On MR imaging, ossified cartilage is hypointense peripherally on all sequences (similar to cortical bone), with the medullary cavity similar to fat on all sequences. Conversely, nonossified hyaline cartilage appears intermediate to low signal on both T1- and T2-weighted sequences. On MR imaging, there should be no postcontrast enhancement within the medullary cavity of either ossified or nonossifed cartilage. The trend is toward increased cartilage ossification with advancing age; however, these findings are extremely variable and irregular, often making determination of laryngeal cartilage erosion or penetration by adjacent tumor difficult, particularly on CT (**Fig. 6**). The epiglottis and vocal process of the arytenoid are composed of yellow fibrocartilage and do not ossify.[8]

LYMPHATIC DRAINAGE

There is often significant and bilateral supraglottic lymphatic drainage to the high jugular nodes (levels II and III).[9] Rarely, supraglottic neoplasms can involve submandibular and retropharyngeal nodes. The subglottic larynx initially may also drain in a cephalad direction, and a characteristic lymph node draining the subglottic region is the node anterior to the cricothyroid membrane, the delphian node (**Fig. 7**). However, the low subglottic lymphatics drain to the paratracheal and pretracheal lymph nodes (level VI). There is almost no lymphatic drainage of the submucosa of the true vocal cord, but once tumor infiltrates the preepiglottic or paraglottic spaces, there is a higher likelihood of nodal disease.[7,10]

American Joint Commission on Cancer Staging and Changes from the 6th Edition to the 7th Edition

Clinically, tumors are staged by the tumor-nodes-metastasis (TNM) staging system, a classification system developed by the American Joint Committee on Cancer and used to define treatment and quantify prognosis for patients. The committee periodically updates the staging system, taking into account changes in clinical practice, and the new 7th edition has been in effect since January 1, 2010. Although staging is done primarily via laryngoscopy, imaging is important in staging the deep extent of tumor and nodal and distant disease. Refer to **Table 1** for the most recent TNM staging for laryngeal SCC (**Table 1**).[6]

The primary change in staging of laryngeal carcinoma is the division of T4 lesions into T4a (resectable lesions, with cartilage penetration and/or extralaryngeal spread of tumor) and T4b (unresectable lesions, invading prevertebral space, encasing carotid artery, or invading the mediastinum), leading to development of stage IVA (any T4a primary or any N2 nodal disease), stage IVB (any T4b), and stage IVC (any M1). Additionally, there has been clarification of cartilage involvement and T4 disease. Prior staging systems were vague with regard to cartilage involvement, because patients with *any* cartilage involvement were potentially overstaged as T4 and underwent laryngectomy. With the current staging system, tumors involving only the inner cortex of thyroid

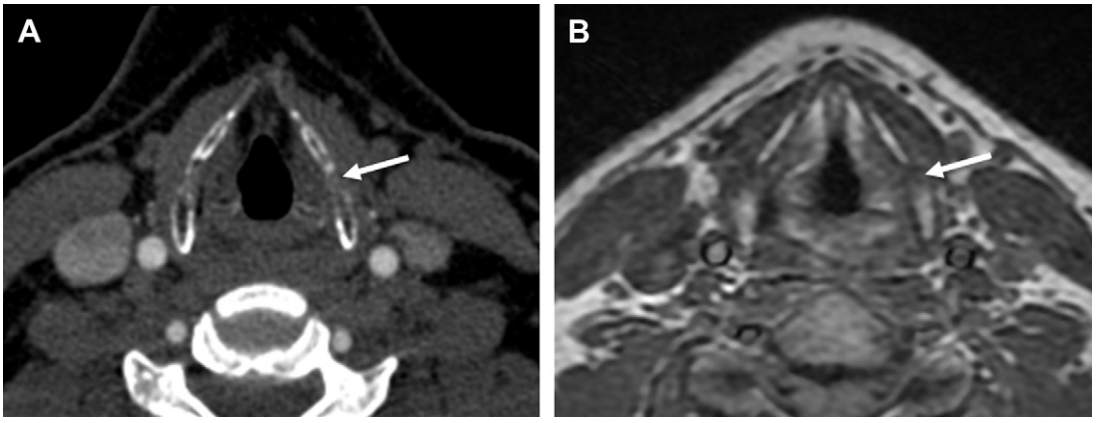

Fig. 6. Thyroid cartilage. Heterogeneous ossification of normal thyroid cartilage on axial CE-CT (*A*) and axial T1-weighted MR imaging (*B*). Note the hypodense fatty marrow (T1 hyperintense), with surrounding hyperdense cortical sclerosis and the intermediate soft tissue density and intensity cartilage. The anterior thyroid ala are often not well ossified.

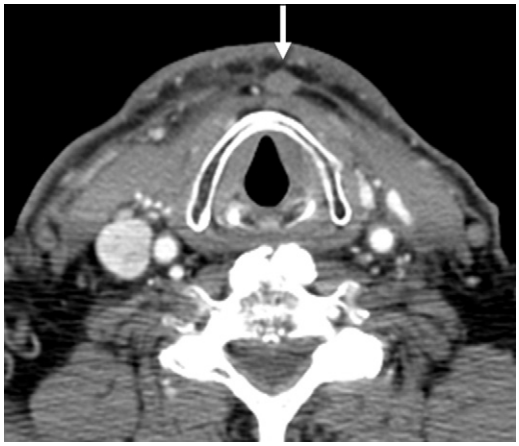

Fig. 7. Delphian lymph node. Axial CE-CT scan demonstrating a small pathologic delphian (prelaryngeal) lymph node, anterior to the cricoid cartilage, which was hypermetabolic on the concordant PET examination (not shown). Note the posttreatment changes from prior radiation therapy in the neck.

cartilage (previously termed "minor cartilage erosion") are classified as T3, but through-and-through cartilage penetration (both inner and outer cortex involvement) and/or extralaryngeal tumor spread are classified as T4a.[1]

TREATMENT TRENDS

The major focus in the management of laryngeal cancer is voice retention. This is precluded when the larynx is functionless or there is aspiration despite working with a speech pathologist. Classic voice preservation operations are the open supraglottic laryngectomy (reserved for those patients with only supraglottic involvement) and the vertical hemilaryngectomy (reserved for patients with lesions predominantly involving one true vocal cord). However, in the past 10 years, there has been a significant decline in the use of open surgery, primarily because of the development of transoral endoscopic laser microsurgery, improvements in radiation therapy, and new combined modality chemotherapy and radiation therapy regimens. Oncologic results, both local control and survival results, are similar to more conventional open surgeries, however, with less morbidity and, overall, improved postoperative function and laryngeal preservation rates. In general, open surgery is now primarily reserved for those patients with persistent or recurrent disease post therapy or for those patients with bulky extralaryngeal extension or cartilage invasion on initial presentation.[11] Specific treatment trends are further discussed with regard to the laryngeal site of involvement.

Site-Specific Evaluation with Imaging

General considerations/pitfalls

The larynx is one of the most difficult organs to image, because the structures are small, it is subject to motion from respiration and swallowing, and early mucosal lesions are difficult to resolve on imaging. Performing thin section images through the larynx (both CT and MR imaging), making every effort to suspend swallowing, and angling the gantry through the plane of the larynx can help with these limitations. Additionally, on CE-CT, delayed imaging after contrast may help improve mucosal enhancement to aid in delineating the extent of tumor.

One of the greatest pitfalls in staging any head and neck cancer is either overstaging or understaging tumors. In the larynx, overstaging may result in unnecessary laryngectomy; however, understaging can result in local treatment failure after radiation (**Table 2**). A study in 2008 demonstrated a false diagnosis rate for detecting the extent of supraglottic laryngeal cancers, and up to 25% of the time, the tumor was overstaged by imaging.[12,13] Becoming familiar with the American Joint Committee on Cancer staging system for the different subsites and the common patterns of spread of laryngeal cancer and pitfalls associated with staging will help the radiologist to avoid these mistakes.

Supraglottic SCC

Because they are initially clinically occult, supraglottic tumors often present later than glottic tumors and are often large. As with other early laryngeal lesions, the T1 and T2 lesions are often best staged with endoscopy. However, imaging is critical for showing the cranial, caudal, and deep extension of supraglottic SCC. Patterns of extension can be anticipated by knowing common pathways of spread.

Small tumors involving the free edge of the epiglottis may be treated with endoscopic surgery, with conservation of a portion of the supraglottic larynx. However, the radiologist must assess the full extent of the tumor and detect submucosal extension. Superior extension with involvement of the vallecula or base of tongue is extremely important to note, because it will upstage to T2 and will likely alter management. Tumor may reach the base of tongue, and even the extrinsic tongue muscles via extension through the preepiglottic space (**Fig. 8**). Spread anteriorly along the glossoepiglottic fold, which overlies the hyoepiglottic ligament, results in extension to the vallecula and base of tongue.

Tumors can extend from the suprahyoid epiglottis laterally along the pharyngoepiglottic fold

Table 1
American Joint Committee on Cancer 7 larynx staging

	Primary Tumor (T)
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
	Supraglottis
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (eg, mucosa of base of tongue, vallecula, medial wall of pyriformsinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
T4a	Moderately advanced local disease. Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
	Glottis
T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3	Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space, and/or inner cortex of the thyroid cartilage
T4a	Moderately advanced local disease. Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
	Subglottis
T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation
T4a	Moderately advanced local disease. Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
	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

From Edge S, Byrd D, Compton C, et al. American Joint Committee on Cancer. AJCC cancer staging manual, 7th edition. New York: Springer-Verlag; 2010; with permission.

Table 2
Pitfalls in staging of larynx cancers

Pitfall	Advice
Understaging of a T2 supraglottic tumor as a T1 from failure to recognize BOT extension.	Carefully evaluate the BOT and vallecula on sagittal images.
Understaging from failure to recognize paraglottic space involvement	Look for replacement of the fat just above and lateral to the thyroarytenoid muscle on axial and coronal images
Overstaging of cartilage invasion on CT	Recognize that there is considerable variability and asymmetry in cartilage ossification on CT. Consider MR imaging for further evaluation.
Overstaging of cartilage invasion and extralaryngeal extension on MR imaging	Look for areas isointense in signal to the tumor on T1-, T2-, and fat-suppressed T2-weighted images. Reactive edema will be T2 hyperintense to tumor.
Failure to recognize extralaryngeal tumor extension without laryngeal penetration	Carefully evaluate the thyroid notch, thyrohyoid membrane, and thyroaretenoid gaps. Consider MR imaging for further evaluation.
Understaging of nodal metastasis by PET-CT	Use intravenous CE-CT along with the PET to evaluate for small abnormal lymph nodes that may be below the resolution of PET or have low FDG uptake as a result of necrosis.

to reach the lateral pharyngeal wall. If there is greater than 2 cm of involvement of the base of tongue, the patient may no longer be a candidate for a supraglottic laryngectomy.[7] Additionally, a patient with any advanced laryngeal tumor (T3 or T4) with greater than 1 cm of extension to the base of tongue may not be considered a candidate for laryngeal conservation therapy,[14] and in the event that the patient is undergoing a total laryngectomy, tumor at the base of tongue will require a more extensive resection, possibly a glossectomy, and reconstruction of the neopharynx.

Both suprahyoid and infrahyoid supraglottic tumors are at risk for involvement of the preepiglottic space, because the epiglottis is a poor barrier to tumor spread. Submucosal involvement of the preepiglottic space by tumor cannot be assessed clinically and involvement will upstage a tumor to T3 status. Preepiglottic space spread is associated with a worse prognosis after radiation and an increased risk of nodal metastasis. Although not precluding a supraglottic laryngectomy, involvement of the preepiglottic space may alter the surgical approach, because the surgeon would likely also apply treatment to the neck. Infiltration of the fat within the preepiglottic space is easy to detect on both CT and T1-weighted MR imaging, in both the axial and sagittal plane, with a reported sensitivity of 100% (**Fig. 9**).[15]

Supraglottic laryngeal tumors that involved the AE folds or false cords may extend inferiorly to cross the laryngeal ventricle, becoming "transglottic" tumors. The inferior margin of tumor extension is the most critical for the surgeon considering a voice-conserving partial supraglottic laryngectomy, because tumor cannot involve the ventricle, more than 1 arytenoid, the interarytenoid region, or the anterior commissure. Additionally, glottic tumors can spread cranially, crossing the ventricle, to become a transglottic tumor, which precludes vertical hemilaryngectomy.[7] Therefore, the radiologist staging a primary laryngeal malignancy must closely evaluate the status of the laryngeal ventricle, with coronal images often aiding in determining tumor relationship to the laryngeal ventricle (**Fig. 10**).

If tumor at the ventricle obstructs outflow of the saccule, a small appendage of the anterior aspect of the laryngeal ventricle, it can cause an air-filled laryngocele or saccular cyst, a laryngocele filled with retained secretions. Laryngoceles have been reported to be associated with laryngeal cancer from 5% to 29% of the time.[16] When a laryngocele is present on imaging, the region of the laryngeal ventricle must be carefully evaluated (**Fig. 11**).

Paraglottic space involvement will also upstage tumors to T3, and because of involvement of the thyroarytenoid muscle are often associated with vocal cord paresis or paralysis. Tumor infiltration of the paraglottic space carries a lower response to radiation therapy alone for local control. In fact, a study by Murakami and colleagues[17] in 2005 described deep paraglottic space invasion with the "adjacent sign," a broad interface with the thyroid cartilage, with or without minor inner

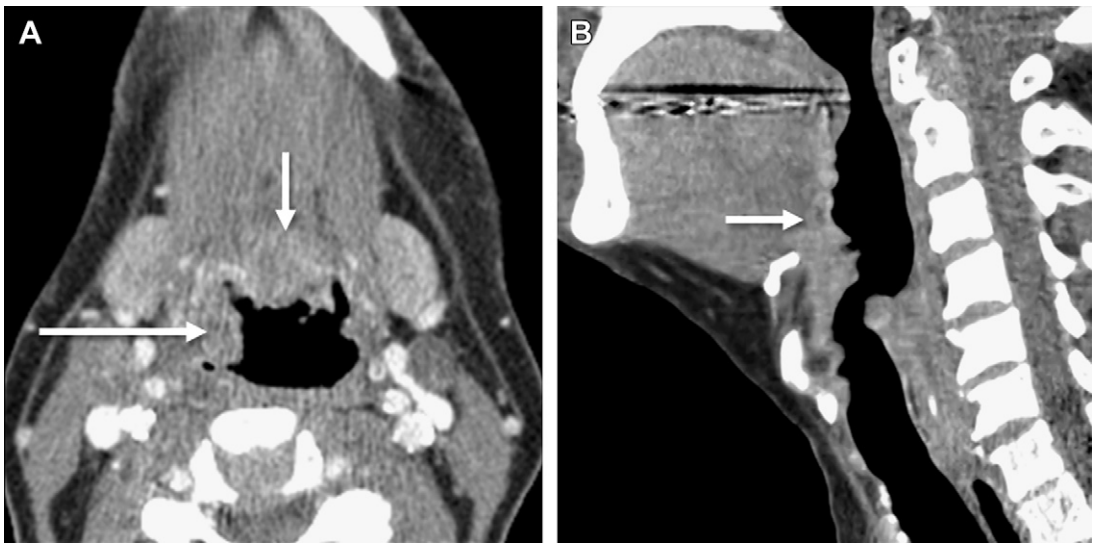

Fig. 8. Supraglottic tumor involving base of tongue. Axial (*A*) and sagittal (*B*) CE-CT scans of a large supraglottic tumor involving the epiglottis and preepiglottic space and extending to involve the right lateral oropharyngeal wall (*long arrow*) and base of tongue (*short arrow*).

cortex erosion, as an independent prognostic factor, heralding lower rates of local control and overall survival rates. Similar to preepiglottic space involvement, tumors in the paraglottic space have a greater risk of transglottic spread and increased risk of cervical nodal metastasis.[10] Axial and coronal imaging demonstrating tumor within the fat just above and lateral to the thyroarytenoid muscle is the characteristic appearance of paraglottic tumor (see **Fig. 10**).

Epiglottic midline tumors may easily extend along the laryngeal surface of the epiglottis to involve the anterior commissure. Involvement of the anterior commissure is frequently associated with early cartilage invasion as a result of extension along Broyle ligament, as well as extralaryngeal spread through the thyrohyoid and cricothyroid membranes. Previously, this was thought to be the overwhelming pattern of extralaryngeal spread, but recent analysis suggests that transthyroid cartilage spread occurs in only 44% of cases with extralaryngeal tumor.[2] Patterns of extralaryngeal spread will be discussed later. Once a tumor extends to the anterior commissure, the

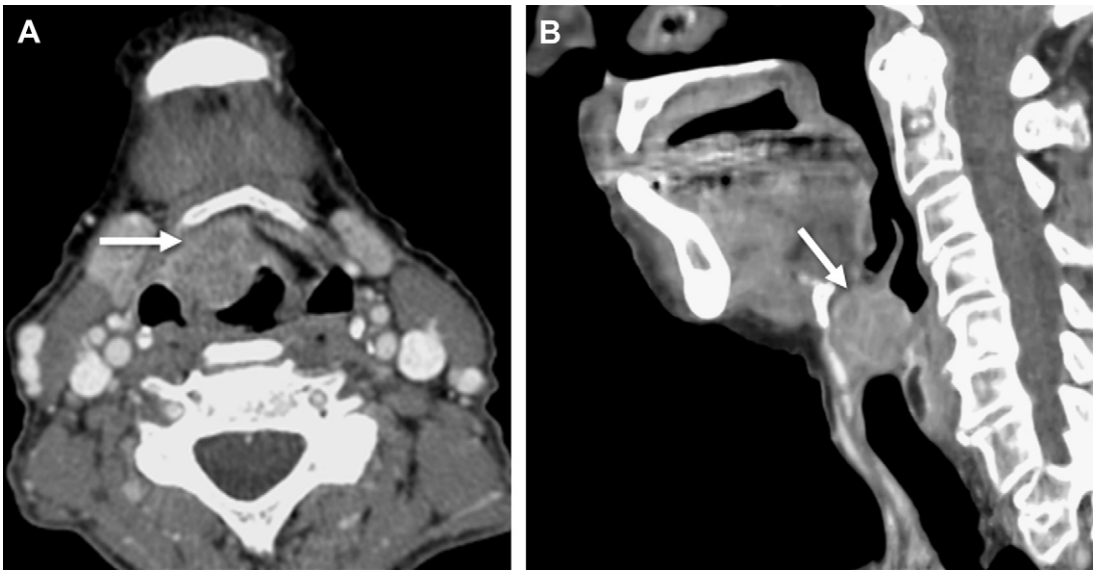

Fig. 9. Axial (*A*) and sagittal (*B*) CE-CT scans of a T3 supraglottic tumor originating in the infrahyoid epiglottis, extending along the right AE fold, with invasion of the right preepiglottic space (*arrow*).

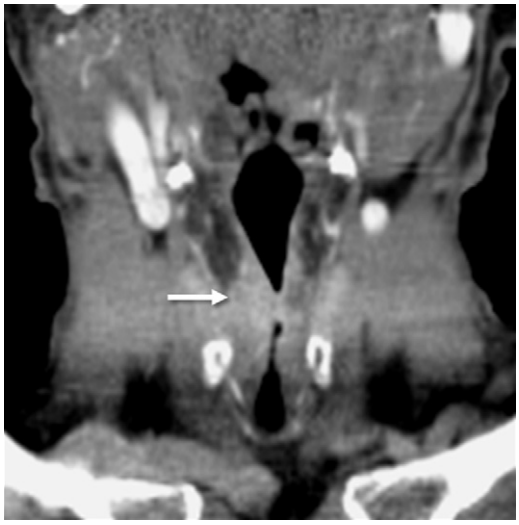

Fig. 10. Coronal CE-CT scan showing a transglottic tumor spanning the right laryngeal ventricle, involving the right false and true vocal cords, and extending into the right paraglottic space (*arrow*).

patient is no longer a candidate for supraglottic laryngectomy, because a 2- to 3-mm separation between tumor and the anterior commissure is necessary to perform that voice-sparing surgery.[7] Axial CT scans through the larynx should be in the plane of the true vocal folds to optimize visualization of these regions (**Fig. 12**).

Subglottic extension is often much better seen on imaging than via laryngoscopy. As described previously, any soft tissue within the airway at the level of the cricoid cartilage should be concerning for subglottic tumor. The conus elasticus, a thick membrane extending from the free edge of the true vocal cord to the upper margin of the cricoid cartilage, acts as a relative barrier to subglottic extension of tumor, with tumor diverted laterally and anteriorly through the cricothyroid membrane. However, once tumor violates this membrane and extends into the subglottic larynx (at the level of the cricoid ring), there is increased risk for cricoid cartilage erosion.[18] The extent of subglottic disease from the level of the true vocal cords is best assessed in the coronal plane, recalling that the subglottis begins at a level approximately 1 cm below the level of the ventricle, anteriorly (**Fig. 13**).

Cartilage invasion

Detecting cartilage invasion is perhaps the greatest pitfall in laryngeal cancer imaging, and for that reason, much of the conventional radiologic literature discussing laryngeal cancer staging focuses on cartilage invasion. Cartilage invasion by tumor upstages the lesion to at least T3, if not T4a, depending on whether there is full penetration through both the inner and outer cortices. The conventional teaching is that invasion of the cartilage is generally associated with a lower response rate to radiation therapy, with a higher risk of recurrence, and a higher risk of radiation-associated chondronecrosis, which can ultimately lead to a nonfunctional larynx. Thus, historically, patients with only minor cartilage invasion previously underwent laryngectomy. The larynx preservation consensus panel in 2009 recommended that patients with cartilage penetration or

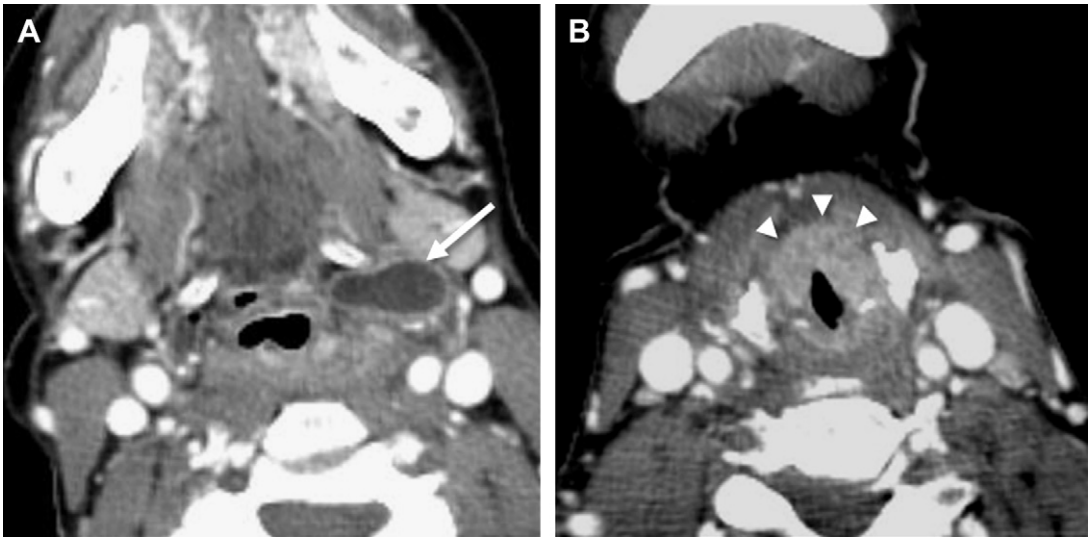

Fig. 11. Axial CE-CT scans showing a left-sided external laryngocele (saccular cyst) (*arrow* in *A*) associated with bilateral true vocal cord and anterior commissure tumor, with transglottic tumor extension (*arrowheads* in *B*).

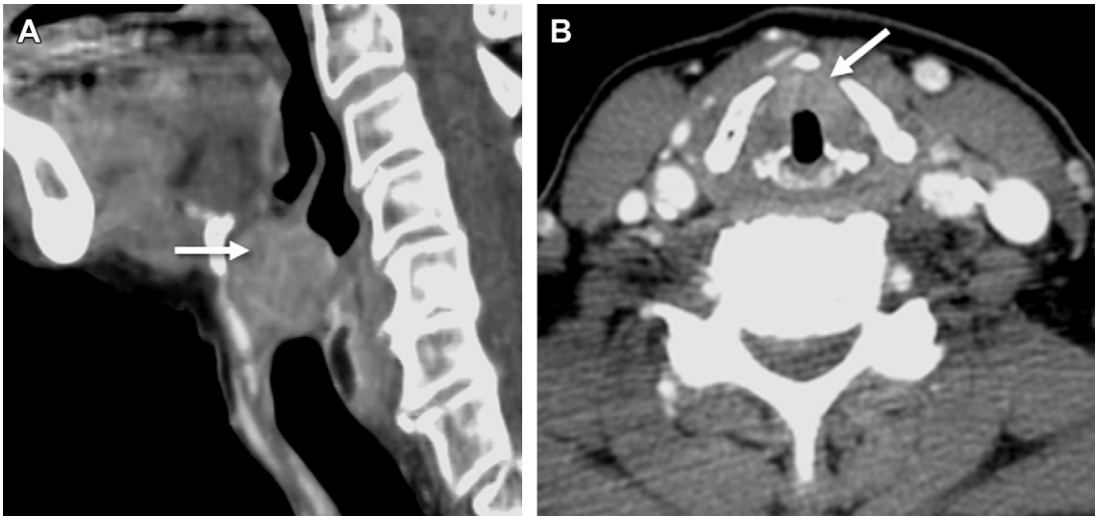

Fig. 12. Sagittal (*A*) and axial (*B*) CE-CT scans showing a supraglottic tumor involving the preepiglottic space (*arrow* in *A*) and extending inferiorly to involve the anterior commissure (*arrow* in *B*).

transcartilaginous extralaryngeal spread of tumor are not candidates for larynx preservation and therefore require initial surgical laryngectomy.[19] In turn, in the absence of frank cartilage penetration or bulky extralaryngeal tumor, laryngeal conservation therapies should be initial treatment. Although still important for staging purposes, and in the assessment of patients who may be a candidate for partial laryngeal resections or laser surgery, the imaging focus should be on determining extralaryngeal extension and frank cartilage penetration because laryngeal conservation may hinge on those findings.

Another reason that emphasis has been placed on cartilage invasion in the radiology literature is that it is very difficult to assess. There is extensive variability in the degree of cartilage ossification, and focal areas of apparent "erosion" of the cartilage on CT may merely be areas of asymmetric nonossified cartilage. Reactive changes (ie, edema) may occur within adjacent cartilage, without intramedullary tumor invasion, which can cause

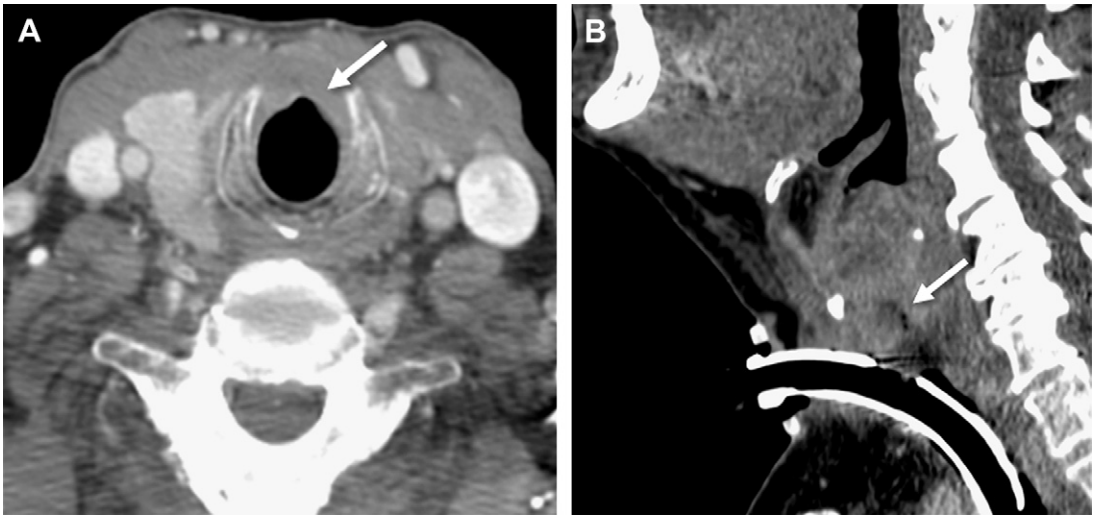

Fig. 13. Subglottic extension of tumor. (*A*) Axial CE-CT scan shows anterior subglottic extension of a glottic tumor. Note the soft tissue anteriorly at the level of the cricoid cartilage (*arrow*). (*B*) Sagittal CE-CT scan of another patient demonstrates a large transglottic SCC with extralaryngeal spread and subglottic extension to the level of a tracheostomy tube (*arrow*). Placement of a tracheostomy tube through tumor increases the risk of parastomal recurrence after laryngectomy.

both sclerosis on CT and T2 hyperintensity on MR imaging. Both CT and MR imaging have limitations in assessment of laryngeal cartilage, with a study from 1995 demonstrating that CT overall seemingly underestimated neoplastic cartilage invasion and MR imaging overestimated cartilage invasion.[20]

CT findings that have been associated with possible cartilage involvement include sclerosis, erosion (focal osteolysis), lysis (more extensive osteolysis), and extralaryngeal tumor extension (cartilage penetration). *Cartilage sclerosis*, initially thought to be a sensitive sign for cartilaginous tumoral involvement, has been found to have a low specificity (40% in the thyroid cartilage, increasing to 76% and 79% in the cricoids and arytenoid cartilages) as a result of the high likelihood of reactive edema and inflammatory change within the adjacent cartilages.[21] Therefore, sclerosis can be caused by tumor adjacent to, but not frankly invading, cartilage.[7] Focal *erosion or lysis* of the adjacent cartilage does increase specificity up to 93%; however, detection of subtle or early erosion is difficult, particularly in the setting of incomplete ossification of cartilage, and focal erosion of the inner cortex still would not upstage from a T3 primary tumor. The most specific finding of cartilage involvement on CT is adjacent *extralaryngeal tumor* extension, with up to 95% specificity (**Fig. 14**).[21] However, CT is only 49% sensitive for the detection of extralaryngeal spread, and in up to 40% of cases, extralaryngeal spread of tumor can be seen in the absence of frank cartilage penetration.[13]

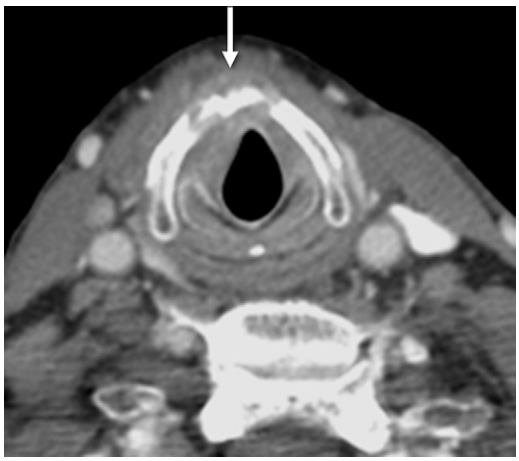

Fig. 14. Axial CE-CT demonstrating sclerosis and lysis of cartilage, with frank cartilage penetration and transcartilaginous extralaryngeal extension. Tumor on the other side of cartilage (*arrow*) is the most specific sign of cartilage involvement.

MR imaging has been reported to be more sensitive for pretreatment determination of laryngeal cartilage involvement. Initial studies demonstrated that peritumoral inflammation and reactive changes causing T2 hyperintensity within the cartilage led to overstaging. However, recent reassessment of imaging criteria for cartilaginous involvement by Becker and colleagues[22] in 2008 demonstrated significantly increased accuracy when describing cartilage involvement based on soft tissue within the cartilage being similar in signal, on both T1- and T2-weighted images, and enhancement to the adjacent tumor (**Fig. 15**). Fat-suppressed T2-weighted images are important to help differentiate tumor from the adjacent fat-containing medullary space. Edema has generally been thought to be higher in signal intensity on the T2-weighted images than the adjacent tumor, whereas frank tumor involvement should be similar in signal to the adjacent tumor on T2-weighted imaging (**Fig. 16**). Additionally, gadolinium-enhanced images through the larynx should be obtained with fat suppression, and any abnormal enhancing soft tissue within the medullary space, similar in signal and enhancement to the tumor, should be considered tumor extension. In summary, current MR criteria for cartilage invasion is that soft tissue in the cartilage should be isointense to the laryngeal component of the tumor on T1, T2, and contrast-enhanced sequences.

Extralaryngeal tumor spread

There are multiple potential pathways for extralaryngeal tumor spread, either through or around laryngeal cartilage (**Fig. 17**).[23] One is direct extension, termed *penetration*, of tumor through the thyroid cartilage into the strap musculature and soft tissues of the anterior and lateral neck (**Fig. 18**). However, tumor can also extend through and widen the thyroid notch between the unfused thyroid ala, without frank cartilage involvement.[23] Tumor can extend into the extralaryngeal anterior soft tissues through the thyrohyoid membrane or through the lateral defects in the thyrohyoid membrane, along the course of the external laryngeal nerve and artery (**Fig. 19**). Superior extension can occur into the base of tongue and oropharynx, along the pharyngoepiglottic or glossoepiglottic fold, or via the preepiglottic space (see **Fig. 8**). Posteriorly, tumor can extend through the arytenoid cartilage or extend from the paraglottic space through the thyroarytenoid gap into the hypopharynx (**Fig. 20**) and then even erode through the pharyngeal constrictors into the soft tissues of the neck. Laterally, tumor can creep over the AE fold into the piriform sinus, and posteriorly, tumor can extend from the interarytenoid space

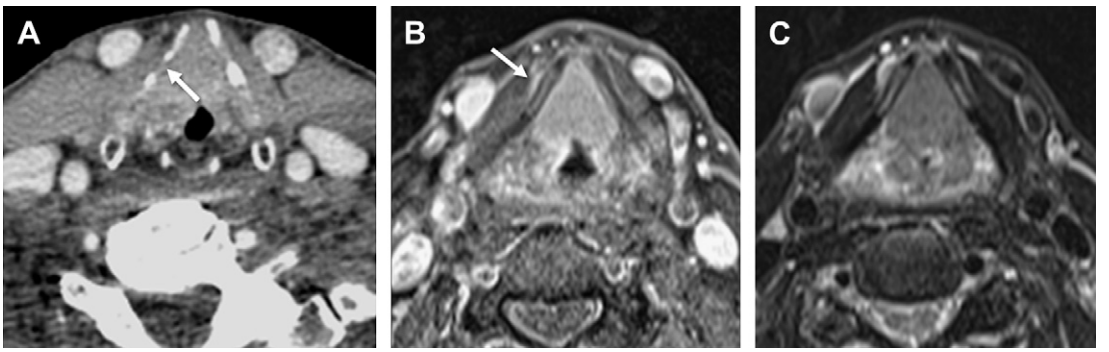

Fig. 15. (*A*) Axial CE-CT scan demonstrating large tumor with a broad interface with the thyroid cartilage, with adjacent heterogeneous ossification of the thryroid cartilage (*arrow*). (*B*) Axial fat-saturated postcontrast T1-weighted image shows enhancing tumor extending through the right thyroid ala into the adjacent strap muscles (*arrow*). (*C*) Axial fat-saturated T2-weighted image shows soft tissue T2 isointense to tumor.

and posterior commissure into the post cricoid hypopharynx and, from there, extend into the proximal cervical esophagus. Finally, as described earlier, tumors can extend inferiorly from the subglottic region through the conus elasticus, through the cricothyroid membrane into the soft tissues of the neck (including the thyroid gland), with or without cricoid or tracheal cartilage erosion, and from there extend inferiorly into the proximal cervical trachea (**Fig. 21**B).[23]

Initially, extralaryngeal tumor was thought to be only transcartilage. In 2011, Chen and colleagues[23] demonstrated that only a minority of pathologically proven extralaryngeal tumor occurred via thyroid cartilage penetration (44% of cases), usually glottic or supraglottic tumors. Additionally, that same study demonstrated that CT may have questionable accuracy when assessing extralaryngeal spread, with only 49% sensitivity and 81% positive predictive value. Tumors may bulge the membranes, without frank invasion of extralaryngeal soft tissues, and there is little discussion in the literature as to whether these are technically T3 versus T4a tumors. In the authors' opinion, they should be staged as T3 (**Fig. 22**). MR imaging may have increased utility but may overestimate extralaryngeal spread.

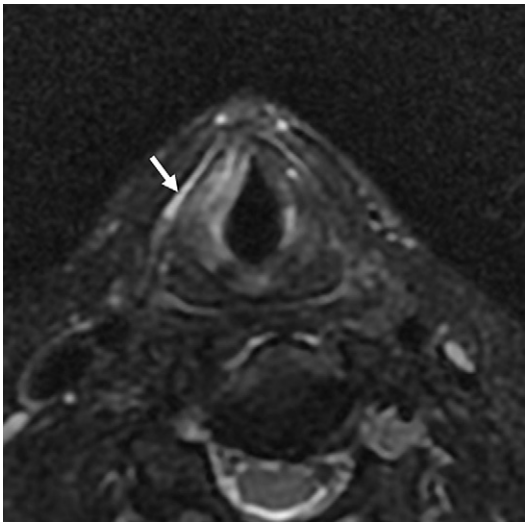

Fig. 16. Axial fat-saturated T2-weighted image showing T2 hyperintense tumor in the right paraglottic space; however the T2 signal in the adjacent thyroid cartilage is hyperintense to the tumor, suggesting reactive edema instead of cartilage invasion.

With the current American Joint Committee on Cancer, 7th edition, all tumors with extralaryngeal spread are staged as T4a. This is a heterogeneous group, and tumors that extend through potential spaces (the thyrohyoid membrane, thyroartyenoid gap, etc) may behave differently than those that penetrate through the cartilage, with the latter being more aggressive and potentially more likely to fail nonsurgical therapy. Chen and colleagues[23] have suggested that this may lead to further subdivision of the T4a category in the future.

With the exception of the patient being a poor surgical candidate or having distant metastatic disease, the only true instances of unresectability are stage T4b tumors that either involve the prevertebral space, encase the carotid artery, or invade the mediastinum.[24] Prevertebral space involvement is most often seen when laryngeal tumors involve the hypopharynx, can be difficult to determine on imaging, and is better assessed surgically. If there is preservation of the retropharyngeal fat plane on T1-weighted MR images between the tumor and prevertebral musculature, there is likely no prevertebral space fixation.[25] However, obliteration of the fat plane does not reliably predict prevertebral tumor extension, and the

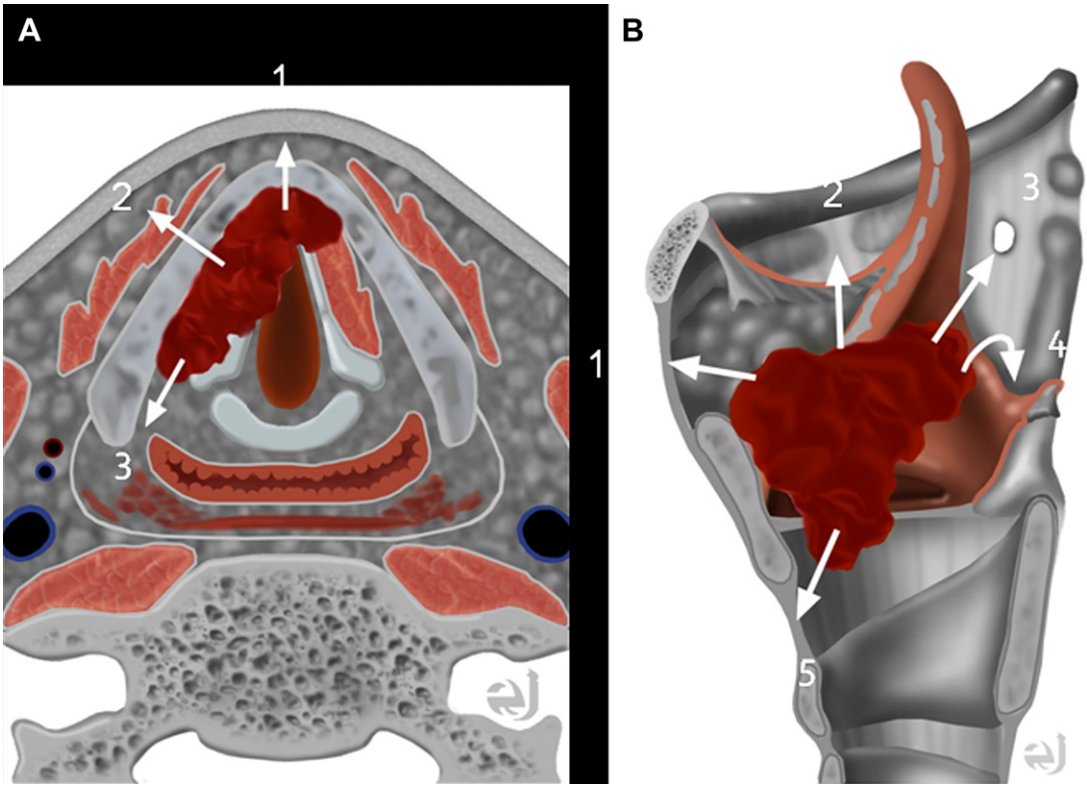

Fig. 17. Extralaryngeal spread of tumor. (*A*) Axial illustration of some of the potential paths of extralaryngeal spread of a glottic tumor. (1) Anteriorly through thyroid notch. (2) Transcartilaginous through the thyroid cartilage. (3) Posteriorly through the thyroartenoid space. (*B*) Sagittal illustration of a large transglottic tumor with some of the potential paths of extralaryngeal spread. (1) Anteriorly through the preepiglottic fat and through the thyrohyoid membrane. (2) Superiorly into the vallecula and base of tongue. (3) Laterally through potential defects in the thyrohyoid membrane. (4) Posteriorly into the hypopharynx. (5) Inferiorly through the cricothyroid membrane. (*Courtesy of* Eric Jablonowski.)

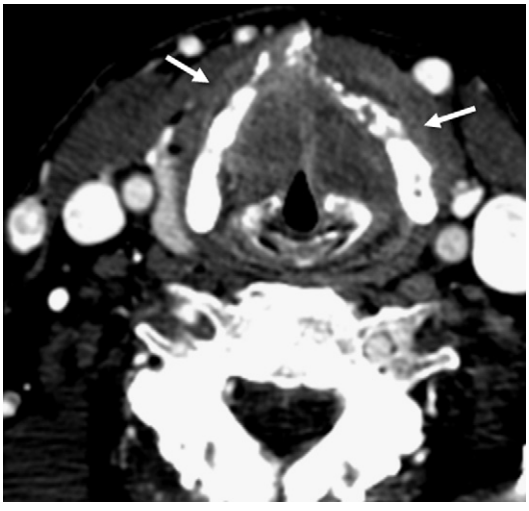

Fig. 18. Bulky laryngeal mass at the level of the true vocal cords with bilateral thyroid cartilage penetration and transcartilaginous extralaryngeal spread of tumor. Not the sclerosis and the frank lysis and obvious tumor outside the margin of the cartilage into the strap musculature bilaterally (*arrows*).

most accurate method of determining prevertebral involvement remains intraoperative assessment.[26] Preoperative determination of carotid arterial encasement is based on imaging findings. Greater than 270° of carotid artery encasement is a reliable predictor for tumor invasion of the adventitia, predicting unresectability reportedly 100% of the time. Contact less than 180° has a low likelihood of tumor invasion, and tumors with contact between 180 and 270° have an intermediate likelihood of fixation (**Fig. 23**).[27] Mediastinal invasion includes laryngeal or hypopharyngeal tumors with extension into the cervical trachea and esophagus below the sternal notch and infiltration of mediastinal fat or involvement of the supra-aortic vessels.[24]

Nodal metastasis

Supraglottic primary laryngeal tumors, or those with preepiglottic or paraglottic space involvement, have a higher propensity for nodal metastasis, particularly to levels II through IV (**Fig. 24**). Purely glottic tumors rarely have nodal metastasis,

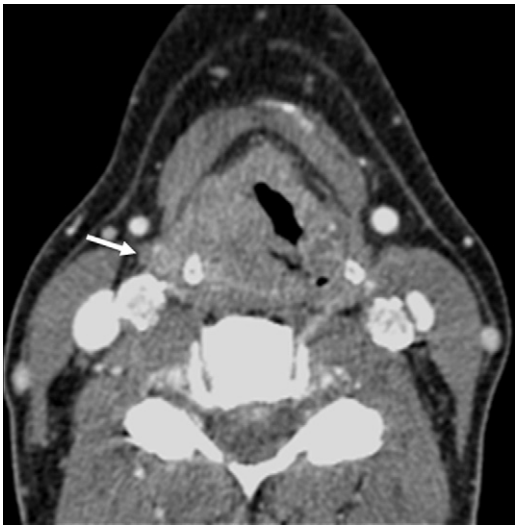

Fig. 19. Axial CE-CT scan through the level of the preepiglottic space and thyrohyoid membrane (note hyoid bone anteriorly and superior aspect of thyroid cartilage posteriorly). Circumferential supraglottic tumor, more bulky on the right, with extralaryngeal spread from the preepiglottic and paraglottic space laterally through the right thyrohyoid membrane into the soft tissues of the neck (*arrow*).

unless transglottic with paraglottic space involvement. Subglottic tumors may involve the delphian nodes but most frequently involve level VI (paratracheal) lymph nodes, cephalad to the innominate artery within the anterior superior mediastinum. Paratracheal lymph node involvement places the patient at a higher risk for mediastinal nodal and distant metastasis.[28,29]

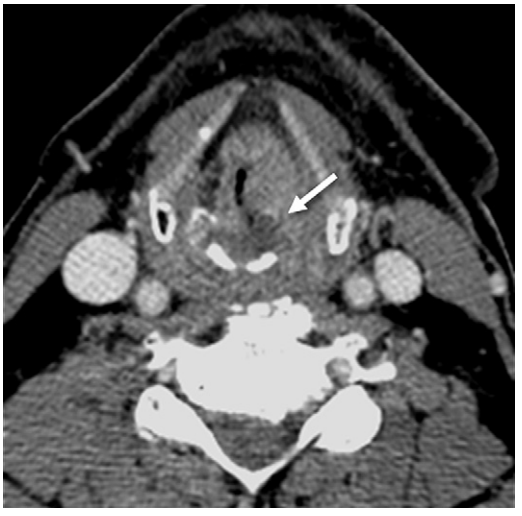

Fig. 20. Axial CE-CT scan of a laryngeal tumor involving the left true vocal cord, extending across the anterior commissure to the right, and extending posteriorly to widen the left thyroarytenoid space, into the left piriform sinus and hypopharynx. Note the lysis of the left arytenoid cartilage, suspicious for involvement (*arrow*), and sclerosis of the left thyroid ala and cricoid cartilage (nonspecific).

Metastatic adenopathy is associated with a much worse prognosis and with lower survival rates, which is reflected in the staging of any tumor with nodal disease as automatically stage III or higher. N2 disease is automatically stage IVA.[6] A single positive lymph node in laryngeal cancer reportedly decreases survival by 50% and bilateral adenopathy decreases the survival by an additional 25%. Imaging is important in detection of cervical metastasis, particularly with small or deep cervical lymph nodes. CT findings suggestive of nodal metastasis are similar to those used in other head and neck primary site SCCs. Extracapsular extension (including conglomerate lymphadenopathy) and contralateral nodal disease are negative prognostic indicators and may alter treatment regimens. Positron-emission tomography (PET)-CT has been shown to have an increased sensitivity, specificity, and accuracy in the detection of nodal metastasis compared with CT alone, particularly in patients with more advanced T stage tumors. The exceptions are completely necrotic nodes or subcentimeter nodes.[30]

Distant metastasis

Laryngeal SCC is associated with a 10% to 20% risk of distant metastases.[14] Unfortunately, the risk of second primary malignancy in the first 5 years[31] is also high. Lung cancer may develop in up to 10% of patients. Sites of distant metastatic disease include mediastinal lymph nodes, lung (most frequent site of metastasis), bones, liver, skin (ie, dermal metastasis), or brain. Extranodal extension or contralateral or paratracheal lymph node involvement increases the risk for mediastinal nodal and distant metastasis (M1 disease) and is an indication for screening with chest CT or PET-CT.[28]

Trends in Management Affecting Staging of Supraglottic Cancer

Treatment options for early supraglottic laryngeal cancer include surgery or definitive radiation. External radiation therapy alone for supraglottic laryngeal cancer has a long and successful track record. Advantages include the lower risk of aspiration and the ability to address both necks without neck dissection. For patients with smaller supraglottic larynx cancers (ie, tumor volumes <6 mL), local control is 83% to 89%.[32,33]

After the Veterans Administration larynx trial proved that nonsurgical therapy produces survival

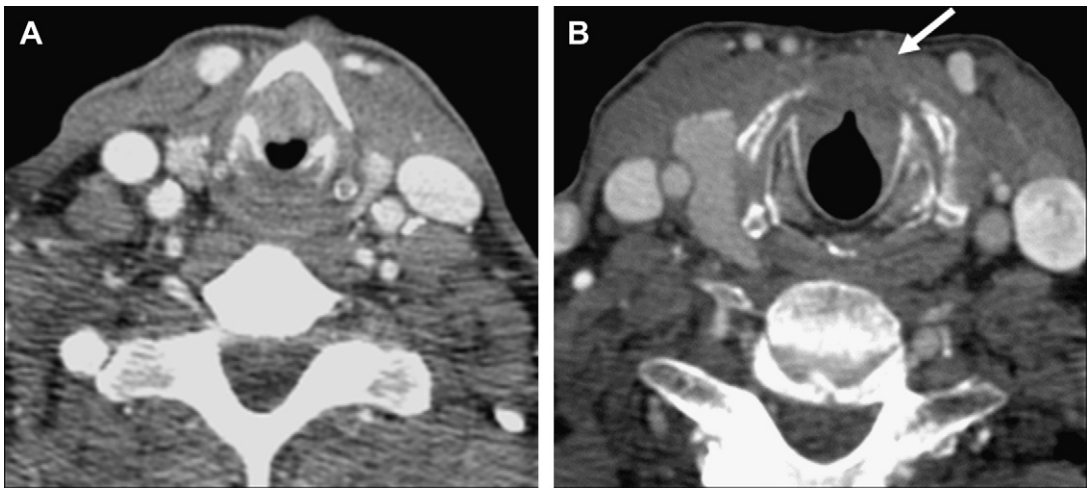

Fig. 21. (*A*) Axial CE-CT scan showing bulky subglottic primary tumor with nonspecific sclerosis of the adjacent thyroid and cricoid cartilages. (*B*) Axial CE-CT of another patient demonstrating subglottic tumor with extralaryngeal extension anteriorly (*arrow*) through the cricothyroid membrane.

rates equivalent to those for surgery plus adjuvant radiation,[34] advanced laryngeal cancer (T3 or higher) not invading more than 1 cm of the base of tongue and without extralaryngeal spread is treated with concurrent chemoradiation.[14] Two-year local control rate with concurrent chemoradiation is 78%.

For patients with adequate pulmonary reserve, the traditional surgery for early supraglottic cancer has been supraglottic laryngectomy. The traditional inferior border of the resection is the apex of the ventricles; however, one arytenoid can also be included in the resection.[35] Bilateral adenopathy justifies either bilateral neck dissection or bilateral external radiation (while sparing the primary anastomosis in most cases). Additional conservational external surgeries, rarely performed, include the near total laryngectomy (resecting hemilarynx, including ipsilateral cricoid

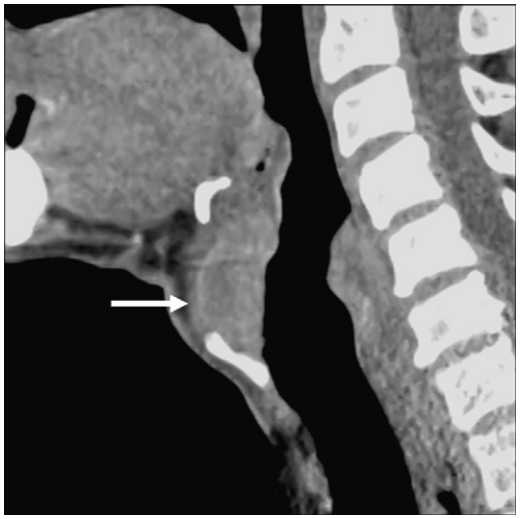

Fig. 22. Sagittal CE-CT scan showing a large supraglottic mass bulging the thyrohyoid membrane (*arrow*), without definite extralaryngeal tumor.

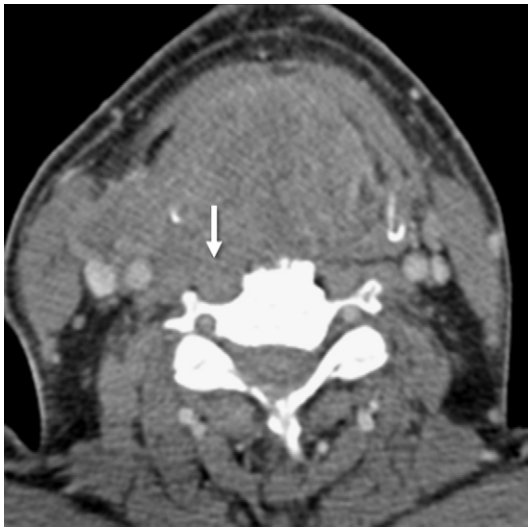

Fig. 23. Axial CE-CT scan of large laryngeal/hypopharyngeal tumor obliterating the airway, with transcartilaginous extralaryngeal spread of tumor into the soft tissues of the neck on the right. There is probable nodal disease within the carotid space on the right, resulting in at least 180° of encasement of the right common carotid artery, and obliteration of the prevertebral fat planes on the right (*arrow*). Findings are concerning for a T4b unresectable laryngeal tumor. MR imaging may be beneficial in this scenario.

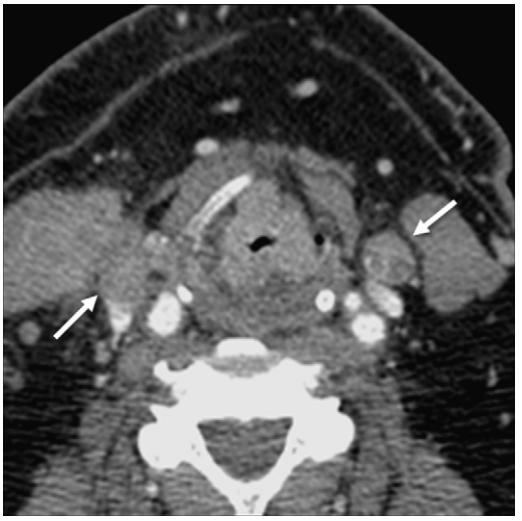

Fig. 24. Axial CE-CT scan through the level of the false cords shows a large circumferential supraglottic tumor with bilateral necrotic level III nodal metastasis (*arrows*), well circumscribed on the left, and with extracapsular extension of disease on the right into the sternocleidomastoid muscle and internal jugular vein.

cartilage) or the supracricoid partial laryngectomy (resecting anterior supraglottic larynx and anterior true vocal cords with or without 1 arytenoid, for supraglottic tumors extending to involve the anterior true vocal cords).

Transoral laser surgery for T1 or T2 supraglottic cancer is very successful in experienced hands if a complete resection can be achieved.[36] One of the limitations of laser surgery is difficult exposure, particularly tumors with anterior commissure involvement. Steiner's series also makes the point that with neck dissection, 5-year survival was 72.9% versus 58.6% without neck dissection (N = 141).[33]

The newest development in treating supraglottic cancer is transoral robotic surgery. Whether the limitations in exposure described with laser surgery are overcome with transoral robotic surgery has yet to be determined.[37]

T4 disease (regardless of nodal status) is usually treated with laryngectomy, appropriate neck management, and postoperative radiation. Adjuvant chemoradiation is administered if there are positive margins or extracapsular nodal extension.[38]

Glottic SCC

Staging/patterns of spread/pitfalls in staging The key points when staging a glottic primary tumor include arytenoid or thyroid cartilage involvement, transglottic (cranial) or subglottic (caudal) extension, paraglottic and preepiglottic extension, and anterior or posterior commissure tumor. Some of these patterns of spread have been described earlier for supraglottic primary malignancies.

Glottic tumors have a propensity to present at an earlier stage, with very small lesions, because they produce hoarseness or airway compromise. Small but symptomatic tumors may be very difficult to detect on imaging and are much better assessed on laryngoscopy. T1 tumors include those confined to the vocal cord(s) (T1a vs T1b). A tumor is T2 if there is transglottic or subglottic extension, even if there is somewhat impaired mobility. Once there is hemilarynx fixation or paraglottic or preepiglottic space invasion, they are T3 and considered advanced, with limited options for laryngeal conservation. Early T1 or even T2 glottic primary tumors will often not undergo imaging, unless there is clinical concern for deep extension, significant transglottic or subglottic spread, or bulky anterior commissure involvement.

Involvement of the anterior commissure is extremely important for the radiologist to appreciate, because these tumors are frequently associated with early cartilage invasion, subglottic extension, and early extralaryngeal extension. T1 and T2 tumors with anterior commissure involvement are more difficult to treat with either surgery or radiation, are often associated with higher recurrence rates, and are often understaged.[39,40] Additionally, if the anterior commissure is crossed and more than the anterior third or half of the contralateral vocal cord is involved, the patient is no longer a candidate for a vertical hemilaryngectomy or extended vertical hemilaryngectomy. Posterior commissure involvement precludes the possibility of a supracricoid partial laryngectomy and may put the patient at risk for hypopharyngeal extension of tumor.[18]

Thus, although extension to the anterior or posterior commissure may not upstage a patient, it is important to detect, because it may affect survival and choice of treatment. If there is air adjacent to the thyroid lamina anteriorly, there is no anterior commissure involvement. However, one should be careful calling any soft tissue in the anterior commissure tumor, because often the phase of respiration or laryngeal edema can cause the vocal cords to oppose, resulting in soft tissue fullness (**Fig. 25**). Axial CT scans through the larynx should be in the plane of the true vocal folds to optimize visualization of the commissures.

Trends in management affecting staging of glottic cancer Early T1 or T2 glottic cancer can be treated with transoral laser excision as long as the anterior commissure is not involved. Anterior commissure involvement increases the risk of local failure for

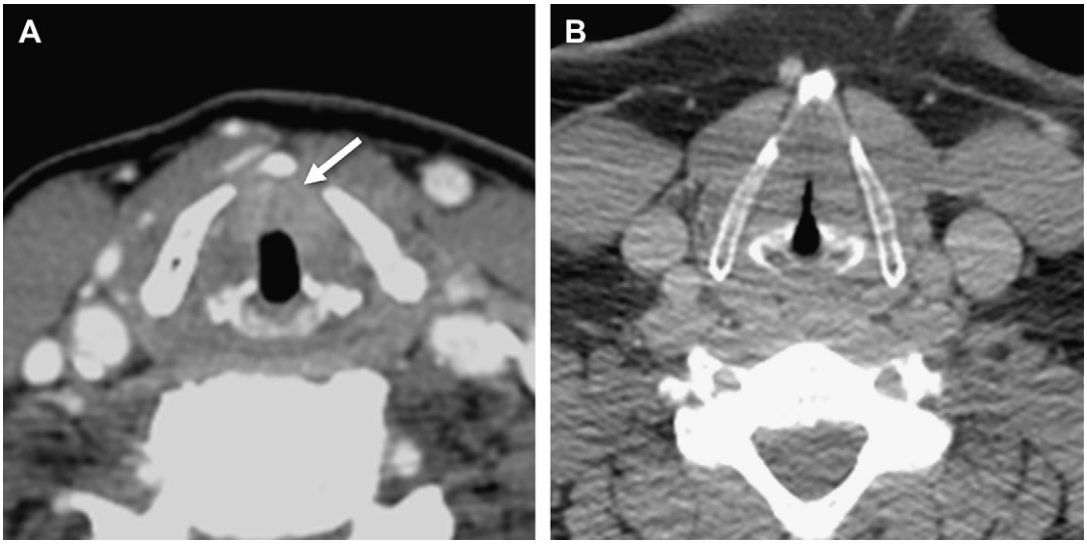

Fig. 25. Pitfall in imaging anterior commissure tumors. (*A*) Axial CE-CT scan demonstrating enhancing tumor thickening the anterior commissure (*arrow*). (*B*) Normal larynx with apparent thickening of the anterior commissure as a result of opposition of the true vocal cords during imaging and limited mucosal enhancement.

transoral laser excision.[41] Generally, the deeper the resection, the worse are the functional results for a surgical approach.[42]

Unilateral disease may be approached with a vertical hemilaryngectomy, but external radiation has a success rate of 90% for T1 glottic disease and of 75% for T2 disease.[43] The disadvantages of radiation include the long course of treatment and the expense. Advantages include superior voice quality for lesions penetrating the lamina propria and the therapeutic effectiveness regardless of anterior commissure location. T1 cancers can be understaged on imaging, especially if subglottic extension is not appreciated, and will result in treatment failure because the radiation fields for T1 and T2 glottic cancer are small.

Advanced glottic cancers (T3 or T4 disease) are treated in a manner similar to advanced supraglottic cancers.

Subglottic SCC

Staging/patterns of spread/pitfalls in staging Primary infraglottic tumors are rare but often present late, because they are relatively asymptomatic until large. Staging depends on the extent of involvement of the true vocal cord, fixation of the hemilarynx, whether there is invasion of the cricoid or thyroid cartilage, or extralaryngeal spread below the cricoid cartilage into the cervical trachea (see **Fig. 21**).

Trends in management affecting staging of subglottic cancer Most treatment recommendations are total laryngectomy, partial or total thyroidectomy, and an extensive neck dissection that includes the pretracheal, paratracheal, prelaryngeal nodes in level VI and the more conventional level II, III, and IV neck dissection.[44] Postoperative radiation therapy to the primary site is the rule.

PET–CE-CT in staging laryngeal cancer Non-intravenous CE-PET or -PET-CT in the initial T staging of laryngeal cancer is difficult, because resolution is limited. Any vocal cord mobility during the approximately 1-hour uptake phase of fludeoxyglucose F 18 (^{18}F FDG) (ie, talking, coughing, even throat clearing) can cause uptake within the larynx in the vocal cords and adjacent laryngeal musculature. With ipsilateral vocal cord palsy, compensatory hypertrophy and overuse of the contralateral cord can cause increased FDG uptake, with a false-positive PET scan on the contralateral side (**Fig. 26**).[45] However, initial PET staging can be useful in patients who undergo radiation therapy because it may serve as a baseline study for comparison posttreatment. Additionally, some studies have shown that the standardized uptake value of a primary tumor may have prognostic value, with an standardized uptake value of greater than 9 heralding a potential higher rate of recurrence and lower overall disease-free survival.[46] However, FDG-PET imaging has been found to be very useful in the detection of nodal disease, with a higher sensitivity and specificity than CE-CT alone, particularly for smaller nodal metastasis. The scanner camera resolution for PET is currently only approximately 7 mm.[47] Therefore, in patients with advanced

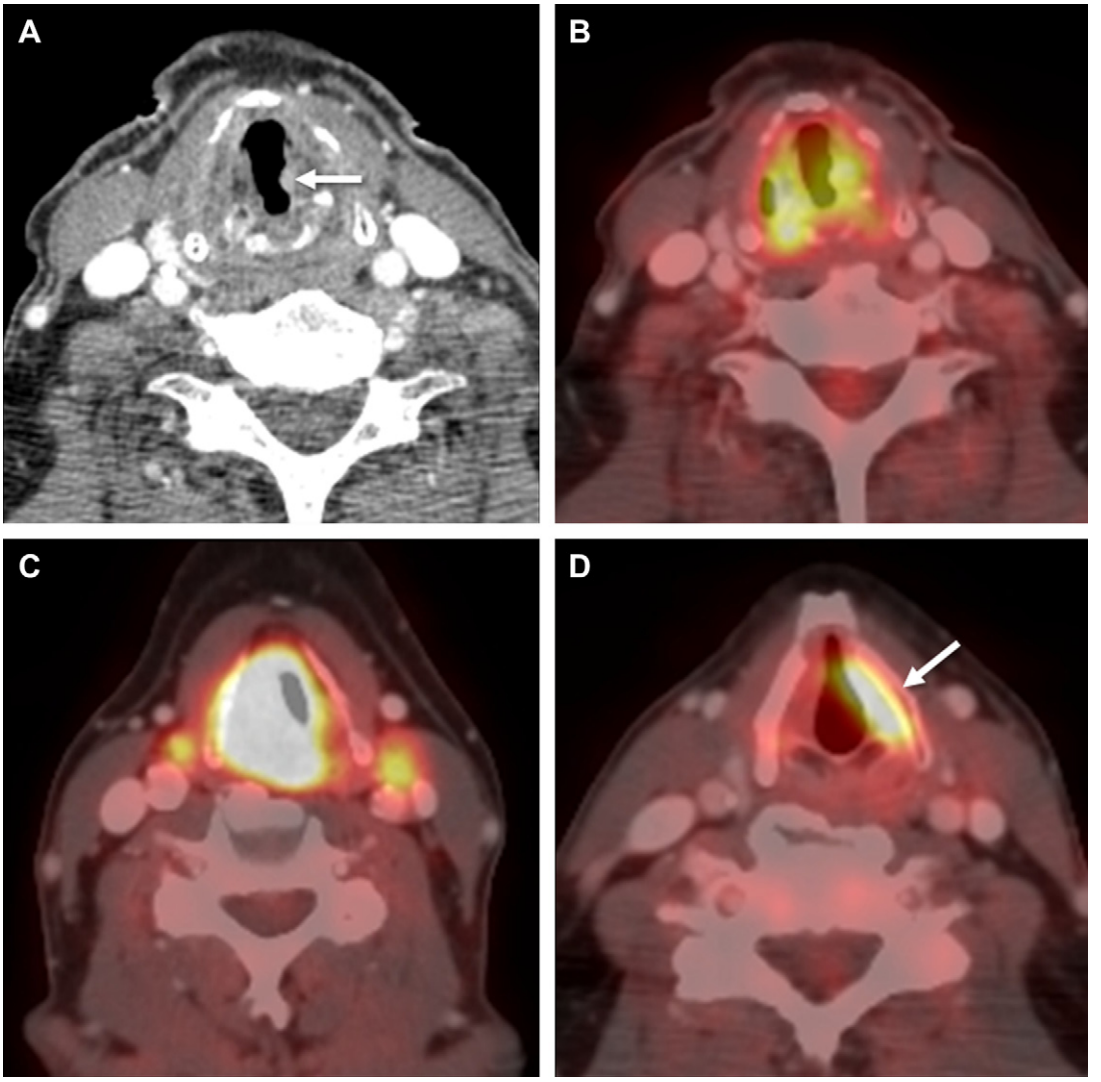

Fig. 26. PET staging pitfall: (*A*) axial CE-CT and (*B*) fused PET–CE-CT scans of a patient with a small polypoid T1 well-differentiated tumor of the posterior third of the left true vocal cord, seen on CT (*arrow*). Note the diffuse laryngeal uptake bilaterally, a false-positive PET result, as a result of phonation during the uptake phase. (*C*) Axial fused PET-CT scans of another patient with a large supraglottic tumor, circumferential, with bilateral nodal metastasis. (*D*) Same patient, more inferiorly. Discontinuous uptake in the contralateral left true vocal cord, without tumor visible on CT or examination as a result of right TVC paralysis, with compensatory hypertrophy and uptake of the contralateral left TVC (*arrow*) as a result of phonation during the uptake phase.

stage primary T3 or T4 tumors, PET should not take the place of a neck dissection if the patient is clinically N0, as the sensitivity for nodal metastasis drops to 50% (from 79%) in patients with a clinically N0 neck.[48] Micrometastases in a T3 or T4 laryngeal tumor are high, and they are beneath the resolution of PET.

PET imaging is critical in detecting both distant disease and synchronous lesions, particularly in patients with more advanced disease on presentation.[30] Overall, PET-CT has been shown to alter TNM staging approximately 15% to 36% of the time.[49] In our practice, the CT is performed with contrast, using diagnostic CT parameters, and is interpreted by an experienced head and neck radiologist. National Comprehensive Cancer Network guidelines from 2011 state to consider PET-CT for advanced (T3 or T4) stage primary tumors.[50]

The authors have adopted the following strategy for initial staging for a T3 or higher laryngeal lesion on examination: The patient undergoes PET–CE-CT, which is interpreted in conjunction by both

a dedicated nuclear medicine physician and a head and neck radiologist, and the images and patient are presented at a multidisciplinary head and neck tumor conference. A consensus regarding the staging is reached, taking into account the findings on endoscopy. If there is concern regarding cartilage invasion or extralaryngeal extension that is not answered on CE-CT and may alter the patient's management, then a dedicated laryngeal protocol MR imaging for problem solving is performed, with thin section T1-weighted, fat-saturated T2-weighted, and postcontrast fat-saturated T1-weighted images through the larynx.

Pitfalls in surveillance and appearance of recurrence Posttreatment follow-up imaging is indicated in patients with clinically suspected residual or recurrent tumor and as routine surveillance in asymptomatic patients with a high risk of recurrence. Local recurrence rates for laryngeal carcinoma range from 15% to 50%, depending on stage of the original tumor.[30] Surveillance imaging is important, particularly in the first 2 to 3 years after therapy, because two-thirds of the local and nodal metastases occur during this period, early detection of recurrence is important as a predictor of survival, and this imaging improves the possibility of performing salvage surgery. However, there is no current evidence-based consensus or guidelines regarding the optimal modality or timing of surveillance imaging. National Comprehensive Cancer Network 2011 guidelines do recommend that some baseline posttreatment imaging be performed at least 6 months posttreatment.[50]

CE-CT has traditionally been the imaging modality of choice to follow patients with head and neck cancer. In general, the literature suggests that CE-CT has good sensitivity and moderate specificity for assessing tumor response to therapy. Recent studies have suggested that FDG–PET–CT may have improved accuracy, particularly within the nodes of the neck.[51–53] One prospective study performed recently on 98 patients showed that PET-CT outperformed CT alone in detecting persistent disease in patients considered high risk for treatment failure but provided little value compared with CE-CT alone for unselected patients with locally advanced disease.[54] Many authors, however, continue to suggest that the combined use of FDG-PET with CE-CT in the posttreatment setting is the most sensitive and specific modality for the detection of recurrent laryngeal carcinoma.[30,47]

CT imaging in the posttreatment setting can be limited because of postradiation edema or postsurgical scarring, fibrosis, flap reconstruction, or streak artifact from surgical clips. Additionally, PET has its own pitfalls in the posttreatment setting. Imaging performed too soon after combined radiation and chemotherapy can elicit false-positive results as a result of postradiation inflammatory changes. Studies and meta-analyses have shown PET-CT to be most accurate at least 2 to 3 months after combined chemotherapy and radiation therapy, and the accuracy increases at 12 weeks or longer.[55] PET-CT has a high (up to 98%) negative predictive value and specificity at this time for excluding residual disease.[53]

Other PET pitfalls in the posttreatment setting include postbiopsy changes and infections, postradiation mucositis, mucosal ulcerations, and pharyngitis, all of which can cause false-positive results. Additionally, radiation-induced chondronecrosis of the laryngeal cartilage can mimic recurrent disease, both on PET imaging and on routine CE-CT. On CT, cartilage necrosis can appear as hypodensity, mixed sclerosis and lysis, with fragmentation of the cartilage, and even air, and these findings can be hypermetabolic on PET imaging. Biopsy, and occasionally laryngectomy, is performed to exclude recurrent disease, particularly if the patient has a nonfunctioning larynx (**Fig. 27**).

After laryngectomy, the most common sites for recurrent tumor are at the margins of the resection, within the neopharynx, or in the parastomal soft tissues (**Fig. 28**). However, postsurgical patients can also have false-positive findings on PET imaging, including uptake around the tracheostomy or laryngectomy site, uptake around a tracheoesophageal speech prosthesis, or uptake around the margins of a neopharyngeal reconstruction.[30]

FUTURE DIRECTIONS/ADVANCED IMAGING

As laryngeal preservation therapies are becoming more prevalent, even in the setting of large-volume T4 disease,[56,57] there is emphasis in the literature on the use of CE-CT, MR, and PET imaging to predict the patient's response to therapy, occasionally in the setting of a cycle of induction chemotherapy.

A technique used frequently by radiation oncologists in treatment planning is measuring gross tumor volume, based on contouring performed around the tumor on a workstation on pretreatment imaging. Based on the subsite, higher gross tumor volume can be one of the strongest independent predictors of outcome and local control. Specific to the larynx, thresholding volumes have been described for supraglottic and T3 glottic carcinomas.[58] Other findings that

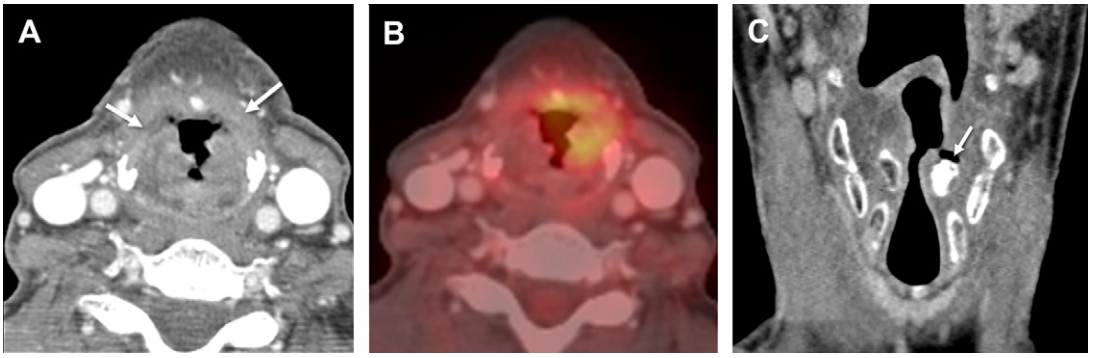

Fig. 27. (*A, B*) Posttreatment PET–CE-CT examination (12 weeks after therapy), demonstrating persistent ulcerated soft tissue within the larynx, extending into the thyroid cartilage bilaterally (*arrows*), with some scattered enhancement and mild FDG uptake. Findings are suspicious for chondronecrosis but may represent persistent tumor. Initial biopsies were negative for tumor; however, patient underwent laryngectomy for nonfunctional larynx, and persistent tumor was noted in the specimen, in addition to areas of chondronecrosis. (*C*) Coronal CE-CT scan of a different patient with persistent pain and ulceration post chemotherapy and radiation demonstrates ulceration extending to a sclerotic and previously infiltrated left arytenoid cartilage (*arrow*). Note sclerosis of the thyroid and cricoid cartilage. Repeat biopsies were negative for persistent tumor. This was thought to be caused by posttreatment chondronecrosis.

predict higher likelihood of local failure include cartilage invasion, hypopharyngeal extension, extralaryngeal tumor, subglottic extension, and preepiglottic and paraglottic space involvement.[58,59]

Tumor or nodal perfusion with CT or MR imaging has been studied, in both a pretreatment and a posttreatment setting (after induction chemotherapy), to help with nodal diagnosis and to help predict response to therapy. For instance, a study by Trojanowska and colleagues[60] in 2011 has shown a statistically significant difference in the blood volume, blood flow, and permeability surface parameters with CT perfusion imaging between benign and malignant lymph nodes. Perfusion imaging (both CT and MR imaging) has also demonstrated that tumors with elevated blood volume and flow and other pharmacokinetic parameters demonstrate a statistically significant improved response to induction chemotherapy.[61–63]

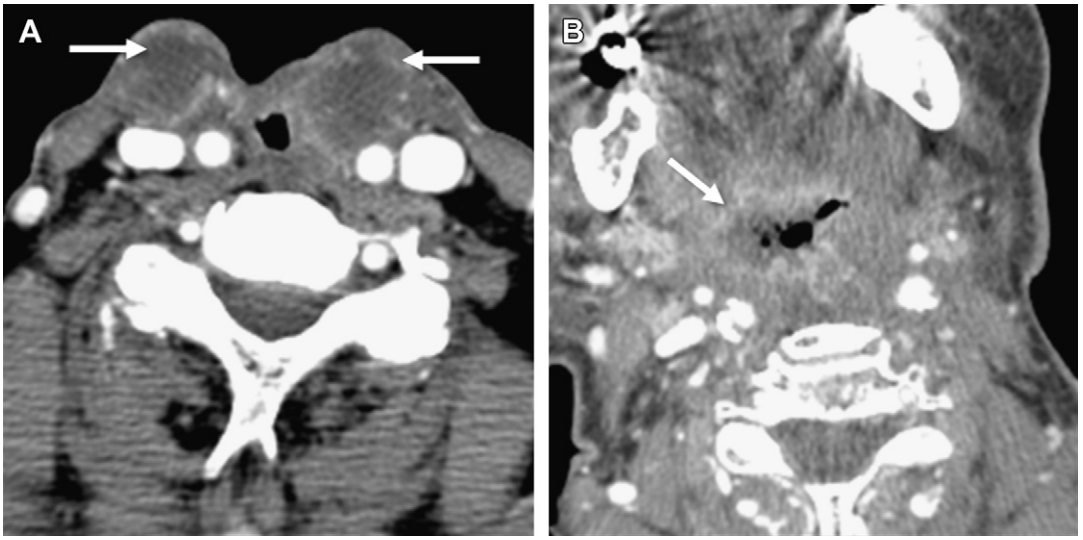

Fig. 28. CE-CT appearance of recurrence post laryngectomy. (*A*) Centrally necrotic masses within the parastomal tissues bilaterally (*arrows*) representing parastomal recurrence. (*B*) Circumferential thick nodular enhancement of the neopharynx at the superior oropharyngeal margin (*arrow*); pathologic examination proved neopharyngeal recurrence.

In addition to improved techniques in FDG-PET scanner resolution and improved PET imaging techniques (such as smaller field of view and high-resolution techniques), new PET radiotracers are in development, including anti–epidermal growth factor receptor antibody imaging.[64]

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