Imaging in laryngeal cancers

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Abstract

Imaging plays an important complementary role to clinical examination and endoscopic biopsy in the evaluation of laryngeal cancers. A vast majority of these cancers are squamous cell carcinomas (SCC). Cross-sectional imaging with contrast-enhanced computed tomography (CT) and magnetic resonance (MR) imaging allows excellent depiction of the intricate anatomy of the larynx and the characteristic patterns of submucosal tumor extension. CT, MRI and more recently PET-CT, also provide vital information about the status of cervical nodal disease, systemic metastases and any synchronous malignancies. Additionally, certain imaging-based parameters like tumor volume and cartilaginous abnormalities have been used to predict the success of primary radiotherapy or surgery in these patients. Integration of radiological findings with endoscopic evaluation greatly improves the pretherapeutic staging accuracy of laryngeal cancers, and significantly impacts the choice of management strategies in these patients. Imaging studies also help in the post-therapeutic surveillance and follow-up of patients with laryngeal cancers. In this article, we review the currently used laryngeal imaging techniques and protocols, the key anatomic structures relevant to tumor spread and the characteristic patterns of submucosal extension and invasion of laryngeal cancer. The role of CT, MRI and PET-CT in the evaluation of patients with laryngeal SCC and the impact of imaging findings on prognosis and clinical management is also discussed.

Key words: CT; imaging; laryngeal cancer; MRI; post-treatment; staging

Introduction

Cancers of the larynx constitute about 25% of all head and neck malignancies. They commonly present in adults between 50 and 70 years and show a strong male predominance.¹ Over 90% of these cancers are squamous cell carcinomas (SCC). Tobacco smoking and alcohol consumption are important risk factors for laryngeal SCC.¹,² Patients with laryngeal SCC have a higher risk for synchronous malignancies arising from the lung and upper aerodigestive tract.³

Majority of these SCCs are readily identified at endoscopy. Integration of endoscopic findings with cross-sectional imaging to assess the submucosal and loco-regional extent of the SCC improves the T staging accuracy and influences the treatment decisions in these patients. Imaging also provides information about the nodal disease, systemic metastases, any synchronous tumors and recurrent disease.⁴

This article reviews the standard imaging protocols to evaluate the larynx and the key anatomical structures relevant to tumor spread, and illustrates the characteristic patterns of submucosal spread of this SCC. The influence of imaging findings on prognosis and choice of treatment options in these patients is also described.

Imaging Protocols

CT

Evaluation of laryngeal SCC requires a contrast CT study of the neck. Excellent images of the neck are obtained using a multidetector CT (MDCT) following the injection of an iodinated contrast agent (total dose 35-40 g). The contrast may be hand injected or an automated power injector may be used, in which case sufficient delay should elapse before scan acquisition begins. The patient lies in supine position, breathing quietly and is asked to refrain from coughing or swallowing. Axial scanning is performed from the skull base to the aortic arch with the acquisition plane parallel to...
the plane of hyoid bone, to obtain scans parallel to the true vocal cords. The raw axial image dataset is reconstructed with a section thickness of as little as 0.75 mm to obtain high quality sagittal and coronal reformatted images. A 512 × 512 matrix is used with a small field of view (FOV) between 16 and 20 cm. All images are reviewed in soft tissue and bone windows. An additional examination for better assessment of the tumor in laryngeal ventricle, anterior commissure and aryepiglottic folds may be done with e-phonation.[5,6]

MRI
A high field MRI scanner using a dedicated neck coil is preferred. A combination of multiplanar noncontrast T1-weighted, T2-weighted and T2-weighted fat saturation images with postcontrast T1 fat-suppressed images are routinely used. It is important to take the T1 and T2 sections at the same levels. A section thickness of 4 mm is preferred with an interslice gap of 0-1 mm. The entire examination takes about 30 minutes, and the patient is asked to refrain from coughing and swallowing during the acquisition.

The choice of imaging modality is subject to the availability of the CT or MR scanner and the expertise in interpretation of the scans, as also the ability of the patient to tolerate an MR examination. In most institutions, CT is the preferred imaging method for evaluating laryngeal SCC and MRI is used as a complementary problem-solving tool when CT does not provide all the information prior to therapy.[7]

Key Anatomical Features of the Larynx

A clear understanding of the laryngeal anatomy is fundamental to the interpretation of CT and MRI scans of patients with laryngeal SCC. A detailed review of the anatomy[8] is beyond the scope of this article. A few key anatomical features are discussed below[8,9] [Figures 1-4].

Laryngeal cartilages
The larynx extends from the tip of epiglottis to the inferior margin of the cricoid cartilage. The epiglottis, thyroid, cricoid and the paired arytenoid cartilages are the four principal laryngeal cartilages [Figure 1].

The epiglottis is the superiormost, midline leaf-shaped cartilage. It has a free margin and a fixed portion (stem). The hyoepiglottic ligament attaches the free epiglottic margin to the hyoid bone and the thyroepiglottic ligament attaches the epiglottic stem to the inner surface of the thyroid cartilage at a caudal level. The free margin of the epiglottis is closely related to the base of tongue – the median glosso-epiglottic fold runs over the thyroepiglottic ligament and projects above the level of the hyoid. Hence, on serial axial CT or MR images of the neck, the free epiglottic margin appears before the hyoid is visualised. The thyroid cartilage has two laminae fused anteriorly,
and enlarged posteriorly, to form the superior and inferior cornua. The superior cornua provide attachment to the thyrohyoid ligament and the inferior cornua articulate medially with the sides of the cricoid at the cricothyroid joint. The cricoid is the inferiormost ring-shaped laryngeal cartilage and the foundation of the larynx. The paired arytenoid cartilages sit along the upper margin of the cricoid lamina, forming the cricoarytenoid joints. The vertical height of the arytenoid spans the laryngeal ventricle. The apex of the arytenoid attaches the vestibular ligament and corresponds to the level of the false cords. The base of the arytenoids projects the vocal processes anteriorly, that attach the vocal ligament running along the inner margin of true vocal cords.

The imaging appearance of these cartilages depends on whether or not they are ossified. The epiglottis and the vocal process of arytenoids are fibrocartilages that do not ossify. Nonossified cartilages have soft tissue attenuation on CT and intermediate signal intensity on T1-weighted (T1W) and T2-weighted (T2W) images. The thyroid, cricoid and arytenoid are hyaline cartilages that show progressive ossification with age. On CT, the ossified cartilages have hyperattenuating inner and outer margins with low attenuation of the medullary cavity. On MRI, the ossified cortical margins are of low signal and the fat-filled medullary cavity is of high signal on T1W and T2W images.
Laryngeal Ventricular Complex (LVC)

This is the key component in organizing the larynx into the supraglottis, glottis and subglottis [Table 1]. It comprises the false cords, true cords and intervening laryngeal ventricle.

The LVC is best identified on coronal images [Figure 4]; the ventricle itself is seen as a small air-filled outpouching between the false and true cords. On axial images, the superior margin of the LVC is defined by a section through the apex of the arytenoids, the false cords and the fat-filled paraglottic spaces deep to the false cords [Figure 2E]. The inferior margin is defined by a section through the true cords with the thyroarytenoid muscle and the cricoarytenoid joint [Figure 2F].
however, axial images also provide good delineation of the same [Figure 2C-E].

**Tumor Origin and Characteristic Patterns of Spread (T staging)**

Clinical examination followed by endoscopy is always the first step in T staging of laryngeal SCC. CT and MRI are performed to define the submucosal extent and deeper margins of the tumor. Small and superficial mucosal tumors may not be appreciated at CT or MRI and hence, it is mandatory that an endoscopy is done prior to any imaging study. Integration of cross-sectional imaging with endoscopy findings significantly improves the accuracy of T staging. Zbaren, et al. reported the accuracy of clinical T staging alone for laryngeal SCC to be 57.5%, but as high as 80% when combined with contrast-enhanced CT.[11]

The TNM classification laid down by the American Joint Commission on Cancer (AJCC) is universally accepted for staging laryngeal cancer[10] [Table 2]. This classification incorporates all information available prior to treatment, including the clinical examination, endoscopy, endoscopic biopsy and cross-sectional imaging. The guidelines rely heavily on the use of cross-sectional imaging for the T staging; however, no recommendation is made regarding the preference of one technique over the other.

The general radiological criteria used for tumor involvement include asymmetric soft tissue prominence or thickening, abnormal contrast enhancement, a bulky mass, obliteration of the normal fat planes and spaces, or a combination of these.[11]

**Supraglottic SCC**

Approximately 30% of all laryngeal cancers arise in the supraglottis. They often present in advanced stages, because symptoms (hoarseness, due to vocal cord
II and III) is a frequent finding in these patients. The overall 5-year survival rate is 75%.[12]

Supraglottic SCC may arise in the anterior compartment (epiglottis) or the postero-lateral compartment (aryepiglottic fold and false cords).

a. Epiglottic SCC

These are anterior midline cancers that primarily invade...
Figure 5A: Supraglottic mass arising from the epiglottis. Sagittal line diagram shows the pathways of spread (thick black arrows) of epiglottic mass (red colour)

Figure 5B: Supraglottic mass arising from the epiglottis. Axial line diagram shows the pathways of spread (thick black arrows) of epiglottic mass (red colour)

into the PES [Figures 5 and 6]. While the SCCs arising from the mobile portion of the epiglottis may spread from the PES further into the base of tongue and laterally into the PGS, those arising from the stem often invade the low PES and via the anterior commissure, reach the glottis or subglottis [Figure 5]. The primary sign of PES invasion at imaging is replacement of the normal fat by abnormal enhancing soft tissue [Figures 6, 7, 9, 18A and 19B]. The sensitivity of CT and MRI to detect invasion of the PES is 100% and the corresponding specificities are 93% and 84-90%.[9,13]

b. Aryepiglottic fold (AE fold) SCC

These cancers present as exophytic or infiltrative masses. They expand the AE fold and spread into the PGS. They may spread further anteriorly into the PES or posteriorly to invade the piriform sinus [Figures 8 and 9].

c. False cord SCC

These are lateral masses with a strong predilection for submucosal spread into the PGS [Figures 10 and 11]. More extensive tumor may destroy the thyroid cartilage and spread transglottically into the glottis and subglottis. Tumor spread to the PGS on CT or MRI is seen as replacement of the normal paraglottic fat by the enhancing tumor tissue [Figures 11 and 18A]. Both CT and MRI have a high sensitivity of about 95% to detect paraglottic tumor spread, the specificity, however, ranges between 50 and 75% as peritumoral inflammation may mimic tumor resulting in false positive assessments.[7,9]

Glottic SCC

Glottic SCCs represent about 65% of all laryngeal cancers. Hoarseness of voice due to vocal cord involvement is the primary presenting symptom in these patients. Metastatic nodal disease is rare in glottic carcinomas due to the sparse lymphatic drainage of the glottis. The 5-year survival rate for T1 glottic cancers is 90% and falls to 25% for T4 cancers.[12]

Glottic SCCs commonly arise from the anterior half of the vocal cord and spread into the anterior commissure. Anterior commissural disease is seen on CT or MRI as soft tissue thickening of more than 1-2 mm. The accuracy of CT in predicting anterior commissure involvement is about 75%.[14]

From the anterior commissure, the tumor may spread further anteriorly into the contralateral cord and the thyroid cartilage or posteriorly into the posterior commissure,
Figure 6: Supraglottic SCC – epiglottis. Axial contrast CT image shows a lobulated enhancing epiglottic mass filling the preepiglottic space (black asterisk).

Figure 7: Supraglottic SCC – epiglottis. Axial contrast CT image in another patient shows the epiglottic mass (arrowheads) filling the right vallecula (white asterisk). Enlarged necrotic deep cervical node level II on the right side (elbow arrow).

Figure 8: Supraglottic mass arising from the aryepiglottic fold. Line diagram shows a section through the aryepiglottic fold in the axial plane. The mass in the false cord is seen in red with pathways of spread in black curved arrows.

Figure 9: Supraglottic SCC – aryepiglottic fold. A right aryepiglottic fold mass (thin white arrows) is seen invading into preepiglottic (white asterisk) and right paraglottic space (black asterisk) and narrowing the right piriform sinus (curved white arrow). Note sclerosis of thyroid lamina (thin black arrow) with extralaryngeal tumor (white curved elbow arrows).

The tumor may spread superiorly to access the PES and the PGS, or inferiorly to reach the subglottis. Subglottic spread below the anterior commissure is seen as an irregular thickening of the cricothyroid membrane. Tumor may gain access into the extralaryngeal tissues through the cricothyroid membrane [Figure 14].

Subglottic SCC
These cancers are rare, accounting for only 5% of all laryngeal cancers, clinically silent and present late in the course of the disease and have a poor prognosis with a 5-year survival rate of 40%.[12] Lymph node metastases are common and affect the pre and paratracheal nodes. Hence, the neck CT should be extended to include the superior mediastinum in patients with primary subglottic cancer.

Subglottic cancer is diagnosed if any tissue thickening is noted between the airway and the cricoids ring [Figure 15]. Due to their late presentation, invasion of the cricoids
Transglottic SCC
Laryngeal SCC encroaching on both, the glottis and supraglottis, with or without subglottic component and when the site of origin is unclear, is termed as transglottic tumor [Figure 17A, B]. This tumor spread is frequently through the PGS and is readily identified on CT or MR imaging [Figure 18]. Transglottic carcinoma is frequently accompanied by metastatic lymphadenopathy. Coronal images are particularly helpful in assessing transglottic extension of tumor [Figure 18D].

Influence of T-Staging on Treatment Options
The treatment options for patients with laryngeal SCC
include primary radiation, surgery, chemotherapy and combinations of these. Surgical treatments include endoscopic laser resections, partial laryngectomies and total laryngectomy.

Important parameters for T-staging that influence the management in patients with laryngeal cancer include presence of tumor in the laryngeal submucosal spaces, spread across the commissures, cartilage invasion, transglottic, deep subglottic and extralaryngeal extension. These are clinical blindspots and can be assessed on imaging studies alone.

Tumor in the laryngeal submucosal spaces is associated with an increased incidence of nodal metastases and a high risk of recurrence following radiation therapy. Bulky disease in the PES and PGS, transglottic and deep subglottic extension are negative indicators for primary radiotherapy and partial laryngectomy procedures.\textsuperscript{[4,7]} It is of prime importance to ascertain the inferior margin of a supraglottic mass. Only
if the tumor is restricted to the supraglottis and does not involve the laryngeal ventricle or the arytenoids, is a partial laryngectomy indicated [Figures 19A, B]. Extension of glottis carcinoma across the anterior commissure to involve greater than 1/3 of the contralateral vocal cord contraindicates a vertical hemilaryngectomy. Disease in the interarytenoid region and the posterior commissure precludes supracricoid laryngectomy.\[6,7\] Presence of significant cartilage invasion on CT or MRI is also associated with a higher risk of tumor recurrence, increased risk of late complications and is predictive of poor response to radiation therapy.\[7\] Isolated sclerosis of arytenoids cartilage at CT does not affect the radiation outcomes in patients with laryngeal carcinoma.\[16\] Cricoid cartilage invasion always requires a total laryngectomy.

**T-staging Parameters Used for Prognosis of the Disease Process**

**Cartilage invasion**

MRI has a high sensitivity (89%-95%) but lower specificity (74%-84%) as compared to CT for the detection of cartilage invasion. The negative predictive value of MRI to exclude cartilage invasion is also very high, at around 94%-96%.\[17,18\]

Presence of tumor invasion can be readily identified on the T1-weighted images if the cartilage is ossified [Figure 20A]. Tumor is seen as abnormal soft tissue intensity within the bright signal of the medullary fat of the cartilage. High intracartilaginous signal on fat-suppressed T2 weighted and cartilaginous enhancement on postcontrast fat-suppressed T1-weighted sequences have been the accepted criteria for positive identification of neoplastic cartilaginous invasion [Figures 20B and 21]. However, peritumoral inflammation may mimic neoplastic invasion if these criteria are used, especially in the thyroid cartilage, thereby leading to false positive assessments. Recently, Becker, et al,\[19\] reported that in assessing neoplastic infiltration of laryngeal cartilage at MR imaging, the T2-weighted and gadolinium-enhanced T1-weighted signal intensity should be compared with the signal intensity of the adjacent tumor on the corresponding sequences. If the cartilage displays higher signal intensity than tumor, a diagnosis of peritumoral inflammation within the cartilage is suggested; if, however, the cartilage displays a similar signal intensity to tumor, neoplastic cartilage invasion is suggested [Figures 20B and 21].\[18\]

The CT criteria for reporting cartilage invasion include sclerosis, erosion, lysis and the presence of extralaryngeal tumor [Figures 22A, B].\[19,20\] While sclerosis has a high sensitivity (83%) to detect intracartilaginous disease, it has a specificity that varies from one cartilage to another, being lowest in the thyroid cartilage (40%) and higher in the cricoid and arytenoid cartilages (76% and 79% respectively).\[17-19\] Erosion or lysis and extralaryngeal tumor are highly specific criteria (86%-95%) for neoplastic cartilage disease; however, their sensitivity ranges between 64% and 72% and 44%, respectively, as they occur very late in the course of the disease.\[18\] By applying a combination of all the above criteria, the overall sensitivity of CT is as high as 91% with a negative predictive value of 95%.
Pretreatment tumor volume
An increasing volume of the primary tumor correlates with an increasing rate of local failure. Supraglottic cancers with pretreatment CT volume of ≤6 ml and glottic cancers with volumes <3.5 ml have shown better control rates (83% and 85%, respectively), as compared to supraglottic cancers > 6 ml and glottic cancers >3.5 ml (46% and 22%, respectively).[21,22] Abnormal signal intensity of laryngeal cartilages at MRI correlates with poor prognosis after radiation therapy if the tumor volume >5 ml, but not if it is <5 ml.[23] Mukherji, et al. have found that the local surgical control rate for supraglottic tumors with volumes <16 ml was 98% compared with 40% for tumors with volumes >16 ml.[24,25]

Nodal Disease (N Staging)
A minimum axial diameter more than 10mm, round or spherical shape, a necrotic node of any size and a node with indistinct spiculated margins (suggesting extranodal disease spread) are the generally accepted radiological criteria to diagnose malignant nodes at CT and MRI.[26,27] The sensitivity and specificity of CT to detect nodal disease using these criteria are 90% and 75% respectively. The overall accuracy of PET-CT in identifying nodal disease is higher than that of CT alone, by almost 20%.[28] However, PET-CT is not useful to exclude the presence of metastases in the clinically N0 neck. This is because 40% of metastatic lymph nodes are <7 mm in diameter and PET-CT is not useful in evaluating small subcentimeter nodes.[29] Standardized uptake values (SUV) of FDG uptake by the nodes has been used by some authors to identify nodal metastases,[30] however, to date, no universally accepted SUV threshold has been determined to differentiate benign from malignant nodal disease. Currently, ultrasonography (USG) with USG-guided fine needle aspiration cytology (FNAC) is the most accurate method for evaluating metastatic disease in subcentimeter size nodes.[31] Nodal staging is the most
Figure 17C: Transglottic mass. Coronal line diagram shows the spread of transglottic cancer in the paraglottic space

Figure 18A: Large transglottic SCC. Axial contrast CT image shows mass in the supraglottis invading the preepiglottic (black asterisk) and right paraglottic space (white asterisk). Extralaryngeal tumor (white arrows) is seen along outer aspect of right thyroid lamina abutting right carotid artery (black arrow)

Figure 18B: Large transglottic SCC. Axial CT image shows tumor in right true cord, anterior commissure (curved black elbow arrow) and anterior left true cord (thick black arrow). Widened thyroarytenoid gap (curved black arrow), extralaryngeal tumor (thin white arrows) abutting right carotid artery (black arrow)

Figure 18C: Large transglottic SCC. Axial contrast CT image shows subglottic extension with extralaryngeal tumor (thin white arrows) while a bilateral nodal involvement indicates a 75% reduction. Additionally, extranodal spread increases the risk of treatment failure and increases the risk of recurrence by a factor of 10 and reduces the survival by 50%.[30,32]

**Systemic Metastases (M staging)**

The single most frequent site for distant metastases in laryngeal SCC is the lung, followed by bones and the abdomen. Systemic metastases are encountered in patients with advanced stage laryngeal SCC and upstage the disease from M0 to M1. While a chest radiograph may suffice in patients with early cancer, a contrast CT of the chest or whole body PET-CT is recommended in patients with advanced...
laryngeal SCC. Presence of systemic metastases upstages the disease to M1 and precludes curative attempts by surgery.

**Post-Treatment Evaluation**

Post-treatment follow-up is critical in detecting the response to treatment and also for assessment of early recurrent disease. Surveillance is especially crucial in the first 2-3 years because two-thirds of local recurrence and nodal metastases occur in this period.

A baseline pretreatment FDG PET CT has been recommended...
to use for comparison at subsequent post-treatment follow-up in patients with laryngeal SCC. A decreased FDG activity in the early phase of combined chemoradiation is associated with greater tumor response, survival and local control.\cite{29} A pretreatment SUV less than 9 in the primary tumor has been found to be predictive of a lower rate of local recurrence and improved disease free survival compared with a primary tumor SUV of 9 or more.\cite{30}

While endoscopy remains the preferred method to diagnose mucosal recurrences, imaging contributes to the detection of deep recurrence. Surgery for laryngeal cancer results in significant anatomic distortion making the diagnosis of recurrence extremely difficult. Recurrence following surgery is generally reported on CT, when focal areas of nodularity or soft tissue are noted in the surgical bed. These typically occur at the cut margins of the surgery where the tumor was previously located. Radiation for laryngeal SCC is followed by significant edema, thickening and abnormal enhancement in the laryngeal tissues. The normal fat in the PES and the PGS has a stippled appearance. The epiglottis, aryepiglottic folds and the arytenoids are swollen. Fragmentation, sclerosis and lysis of the cartilages may

Figure 19B: Aryepiglottic fold SCC confined to supraglottis. Axial contrast CT image at the level of the false cord shows no tumor. Tumor confined to supraglottic larynx precluded the need for a total laryngectomy.

Figure 20A: Cartilage invasion on MRI. T1 axial image shows a large mass destroying left thyroid lamina with extralaryngeal spread encasing left carotid artery (curved arrow). See the normal ossified right thyroid lamina (thick arrow).

Figure 20B: Cartilage invasion on MRI. T2 axial image shows the large mass with cartilage destruction. The intracartilage signal is similar to the adjacent mass (thin arrow).

Figure 21: Cartilage invasion on MRI. Contrast fat-suppressed T1 image shows a large laryngohypopharyngeal mass invading preepiglottic (black asterisk), right paraglottic space (white asterisk) and right piriform sinus (thick arrow). Intracartilaginous enhancement is seen of similar intensity as tumor with thin rim of extralaryngeal tumor (thin arrow).
be seen suggesting the onset of chondronecrosis. While the knowledge of post-treatment larynx on CT and MRI scans helps in the interpretation of CT and MRI scans in these patients, PET-CT has superior diagnostic accuracy in detecting tumor recurrence [Figures 23A, B]. The best results are obtained when PET-CT is performed 2-3 months after the completion of treatment. Successful radiation therapy leads to a substantial reduction of tumor volume within 4 months and treatment failure must be suspected if 50% or more of the tumor mass is still visible after this period.

**Other Laryngeal Cancers**

While SCC is the commonest laryngeal cancer, the less common laryngeal cancers include the chondrosarcoma, lymphoma and the paraganglioma. These are usually submucosal and may not be seen at endoscopy except for a subtle bulge or asymmetry. The role of imaging in such tumors is to detect or confirm the presence of a submucosal mass, to define the deeper margins and to guide the endoscopist to the most appropriate site for biopsy.
Conclusions

CT and MRI play a significant complementary role to clinical endoscopy in pretherapeutic staging of laryngeal SCC. Determination of the precise extent of cancer spread within the larynx (T staging) is the single most critical factor guiding treatment decisions in patients with localized laryngeal cancer. Additionally, imaging studies are routinely used to assess associated nodal disease (N staging) and systemic metastases (M staging), presence of synchronous cancers and also post-therapeutic tumor recurrence in these patients. A clear understanding of the standard imaging techniques and protocols for imaging the larynx, and familiarity with the key anatomical features and characteristic patterns of tumor spread within the different regions of the larynx, are fundamental to the interpretation of CT and MRI scans of these patients.

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