ARTICLE TITLE: An Update on Larynx Cancer

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1. Describe the epidemiology and pathogenesis of laryngeal cancer.
2. Summarize current recommendations for surgery, radiation therapy, and supportive care for patients with laryngeal cancer.

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An Update on Larynx Cancer

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Abstract: Laryngeal cancer remains one of the most common tumors of the respiratory tract. Fortunately, significant advancements have been made over the past decade in the treatment of laryngeal cancer. Although surgery has been the historical mainstay for localized disease and still is an integral part of treatment, nonsurgical options like radiation and systemic therapy have emerged as viable options. In addition, in the metastatic setting, novel agents are showing promise for this patient population. The care for patients with laryngeal cancer continues to evolve and truly requires a multidisciplinary team-based approach. Unique morbidities, such as loss of natural voice, respiration, and airway protection during swallowing, are observed with this disease and require special consideration.

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Practical Implications for Continuing Education

> Larynx cancer occurs more commonly in men than women. Additionally, racial disparities exist with African-Americans presenting at a younger age and having a higher incidence and mortality as compared to Caucasians.

> Clinicians and their staff should understand the challenges and limitations they may face in the diagnosis and management of this disease. Common presenting symptoms that should prompt further workup for laryngeal cancer include hoarseness, dysphonia, dyspnea, and swallowing dysfunction.

> Practitioners need to rely on a multidisciplinary team approach in treating larynx cancer. The multidisciplinary team includes among others, head and neck surgeons, radiation oncologists, medical oncologists, head and neck radiologists, nutritionists, as well as speech therapists.

Introduction

Epidemiology and Pathogenesis

In 2016, an estimated 13,430 new cases of laryngeal cancer will be diagnosed, with approximately 3620 patients dying from the disease.1 Laryngeal cancer occurs more commonly in men than in women (5.8 cases per 100,000 vs 1.2 per 100,000, respectively).2 In addition, there are racial disparities observed in laryngeal cancer, with African Americans presenting at a younger age and having a higher incidence and mortality compared with Caucasians.3-5 Approximately 60% of patients present with advanced (stage III or IV) disease at diagnosis.6 Unfortunately, laryngeal cancer is one of a few oncologic diseases in which the 5-year survival rate has decreased over the past 40 years, from 66% to 63%, although the overall incidence is declining.1 This highlights the need for further research and innovation in the field. Several risk factors have been implicated in the pathogenesis of laryngeal cancer. The most significant of these are tobacco and alcohol consumption. Tobacco use has been shown to have a linear association with the development of laryngeal cancer, with a risk for smokers that is 10 to 15 times higher than the risk for nonsmokers, and the heaviest smokers have as much as a 30 times greater risk.7,8
Research has also demonstrated a linear relationship between the amount of alcohol consumed and the risk of laryngeal cancer.\(^9\) In a study that examined the role of alcohol and tobacco in laryngeal cancer, the multivariate odds ratio was 2.46 for nonsmoking heavy drinkers (defined as >8 drinks per day) and 9.38 for nondrinking smokers.\(^1\)\(^0\) It has also been shown that alcohol and tobacco have a multiplicative effect on the risk of laryngeal cancer.\(^1\)\(^0\) Exposure to several other environmental factors is thought to potentially increase the risk of squamous cell carcinoma (SCC) of the larynx, such as asbestos, polycyclic aromatic hydrocarbons, and textile dust.\(^1\)\(^1\),\(^1\)\(^2\) Dietary factors have also been noted, with red meat increasing the risk of laryngeal cancer, while a diet varied in fruit and vegetables potentially has a protective effect.\(^1\)\(^3\),\(^1\)\(^4\) In addition, the role that both gastroesophageal and laryngopharyngeal reflux play in the disease process is still controversial and under investigation.\(^1\)\(^5\),\(^1\)\(^6\)

Although the human papillomavirus (HPV) is a proven driver of the majority cancers of the oropharynx, it was initially thought that HPV did not play a role in laryngeal cancer. However, new research is emerging that demonstrates the presence of HPV and/or the surrogate marker p16 (cyclin-dependent kinase inhibitor 2A/multiple tumor suppressor 1) in a minority of laryngeal tumors, although the biologic and prognostic relevance of this finding is unclear. It is estimated that the prevalence of HPV ranges from 20% to 30% in laryngeal cancer; however, this percentage varies widely between studies and depends on the detection method used.\(^1\)\(^7\),\(^1\)\(^8\) More work is needed to determine the clinical relevance of HPV/p16-positive status in laryngeal cancer, as this remains controversial.\(^1\)\(^9\)–\(^2\)\(^1\)

### Presentation and Initial Workup

Given the unique physiological function of the larynx, there are several common presenting symptoms that should prompt further workup for laryngeal cancer, such as hoarseness, dysphonia, dyspnea, and swallowing dysfunction. The initial evaluation needs to include a detailed history and physical examination to assess clinical risk factors and symptom severity. This is typically accompanied by a flexible nasopharyngoscopy to observe the larynx and mucosal surfaces. However, this procedure is not always adequate, and often direct laryngoscopy with biopsy under anesthesia in the operating room is necessary. Once the diagnosis is made, detailed clinical imaging is required. Common imaging techniques include computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scan. The superiority of CT versus MRI for laryngeal cancer is debatable, with CT typically demonstrating a higher specificity for identifying thyroid cartilage invasion compared with MRI but lower sensitivity.\(^2\)\(^2\) However, recent improvements in and standardization of MRI interpretation have improved the reliability of this imaging modality.\(^2\)\(^3\) Clinically, many patients eventually undergo both imaging modalities to most effectively stage the malignancy and develop an appropriate treatment plan. PET scan imaging has also demonstrated a utility in initial staging as well as detection of metastatic disease. In a retrospective study, the use of PET/CT altered the treatment plan in 38 of 123 included patients (30.9%) with laryngeal cancer.\(^2\)\(^4\) Evaluations by an experienced speech pathologist and a dietician are crucial to make recommendations regarding swallowing function and appropriate nutritional care during treatment. Finally, pretreatment dental evaluation is also recommended for patients who will undergo radiation (XRT), given the risk of dental infection, damage, and treatment-induced osteoradionecrosis.\(^2\)\(^5\)

### Anatomy of the Larynx

Definitive anatomic description of the larynx is beyond the scope of this article. However, it is vital to understand basic laryngeal anatomy to critically evaluate patients who may or may not be candidates for organ-preservation approaches.

### Laryngeal Subsites

The larynx is divided into 3 subsites partially based on embryologic development. The supraglottis extends from the tip of the epiglottis to an artificial horizontal plane extending bilaterally across the apex of the laryngeal vestibule. The glottis extends from this plane to approximately 1 cm below the true vocal folds. The subglottis extends from this horizontal plane to the end of the cricoid cartilage. The supraglottis is made up of 5 separate subsites, including the suprahypopharyngeal epiglottis, infrapharyngeal epiglottis, false vocal folds, arytenoids, and aryepiglottic folds. The glottis includes the true vocal folds themselves, and the space between them known as the rima glottis. The true vocal folds themselves are made up of a layer of stratified squamous epithelium overlying the lamina propria, a gel-filled space that is comprised of a superficial, middle, and deep layer. The vocal ligament is made up of the middle and deep layers, while the superficial layer is the gel layer. This allows for free vibration of the vocal fold epithelium.

### Laryngeal Structure

The larynx is made up of the thyroid, arytenoid, and cricoid cartilages. The cricoid is a complete ring and provides support for the functional portion of the larynx. The thyroid cartilage is the primary cartilage of the larynx. It sits above the cricoid anteriorly and is connected via the cricothyroid joint and the cricothyroid membrane. The arytenoid cartilage is posterior to the thyroid cartilage and sits on the “signet” portion of the cricoid ring. This forms the cricoarytenoid joint. The arytenoid cartilage has 2 primary
attachment points for the musculature of the larynx: the vocal and muscular processes. The vocal process is where the thyroarytenoid and vocalis muscles attach to the thyroid cartilage as well as the vocal ligament. These structures make up the true vocal cords. The epiglottis is attached to the thyroid cartilage through a ligament that inserts at the superior aspect of the thyroid cartilage at the petiole. Understanding the basic cartilaginous structure of the larynx allows for a better understanding of how tumor can spread through the larynx, how the function of the larynx might be affected by treatment, and the anatomic differences between early and advanced-stage cancers. There are multiple connective tissue barriers within the larynx. The conus elasticus, which passes between the vocal ligament and cricoid cartilage, provides a barrier of spread between the glottis and subglottis. The quadrangular membrane, which extends from the edge of the vocal ligament to the epiglottis and arytenoid cartilages superiorly and posteriorly, respectively, provides a barrier to spread from the supraglottis to the glottis. Beitler et al described a periventricular membrane made up of a central and peripheral component. The peripheral component is contiguous with the conus elasticus and quadrangular membrane. These membranes form a barrier of spread from paraglottic tumors.

**Potential Spaces of the Larynx**

The cartilaginous structure of the larynx allows for 3 primary “spaces” intrinsic to the laryngeal structures. The preepiglottic space lies between the epiglottis posteriorly and the thyroid cartilage and thyrohyoid membrane anteriorly. It is a primarily fat-filled cavity, commonly invaded by advanced-stage supraglottic tumors. Tumors occupying this space are immediately upstaged to at least T3 tumors. The paraglottic space is a similar fat-filled space that sits lateral to the true vocal cords between the thyroid cartilage. This space is commonly invaded by advanced-stage glottic tumors; and tumors found here, like the pre-epiglottic space, are upstaged to T3.

**Pathways of Spread**

Cancer of the larynx tends to be contained within the primary structures of the larynx. However, there are several pathways of spread to allow for extrinsic tumor spread without thyroid cartilage invasion. Chen et al looked at 103 laryngectomy specimens and noted that only 44% of T4 tumors had cartilage penetration resulting in extrinsic laryngeal spread. The thyroarytenoid gap, which is the space between the arytenoid and thyroid cartilage, can allow for extrinsic laryngeal spread of tumor in a posterior lateral direction. Tumors in the pre-epiglottic space can hypothetically invade through Broyle’s ligament, where the true vocal cords are suspended to the cartilage, with little or no cartilaginous erosion. This is thought to be related to a weakness in the perichondrium at the insertion point of these ligaments. Otherwise, the tumor can spread through the cricothyroid or thyrohyoid membranes. Finally, the tumors can spread directly through the cartilage of the larynx. Regardless of the path of spread, extrinsic tumor extension upstages the patient to T4 status.

**Basic Laryngeal Function**

The 3 primary functions of the larynx are breathing through the rima glottis, vibration to allow for speech, and protection of the airway during swallowing. It is important to understand how the anatomy of the larynx contributes to these functions, especially as most organ-preservation strategies are aimed at preserving or potentially restoring laryngeal function. The site of the tumor can affect both the presenting symptoms and the stage at diagnosis. Tumors of the glottis often affect the voice at earlier stages. Tumors of the supraglottis can grow relatively unimpeded for extended periods of time before becoming symptomatic, and the patient often presents with shortness of breath or voice change. Tumors of the subglottis often will present with airway obstruction at an earlier stage because of the narrow nature of the subglottis. Speech and breathing can be simultaneously affected by tumors that affect the vocal folds themselves. However, early stage tumors of the vocal fold epithelium, absent invasion into the superficial lamina propria, can be identified by a maintained vibratory wave. The vibratory wave is when the true vocal fold epithelium, which lies over a “gel” layer (the superficial lamina propria), is able to freely vibrate when the true vocal folds are adducted. Tumors that invade directly into the thyroarytenoid muscle and involve the paraglottic space often present as an immobile vocal fold, resulting in upstaging to T3. However, these tumors have a much better prognosis for vocal restoration with nonsurgical means than tumors that invade the cricoarytenoid joint, which are more likely to represent persistent vocal dysfunction secondary to scarring. A complete description of swallowing is beyond the scope of this review; it should suffice to state that it is a complex process involving all aspects of laryngeal function. To create an adequate swallow, a concerted movement involving laryngeal elevation, tongue base protrusion of the epiglottis, and closure of the rima glottis is critical. Inadequate function in any of these areas can result in persistent swallowing dysfunction after therapy. Moreover, inability to restore or preserve function during treatment in any of these areas can lead to persistent swallowing dysfunction after treatment. Tumors that invade either the glottis or the subglottis can severely affect a patient’s swallow related to inability to close the glottis at the level of the epiglottis or the vocal cords. Figure 1A to 1C depicts the appearance of representative laryngeal cancers on examination.
Principles of Surgery

Principles of oncologic surgery in the larynx have evolved significantly as our understanding has grown of the roles played by embryology and anatomy in tumor spread. Patients with early stage tumors have benefited from the success of organ preservation-based surgical approaches. Single-institution studies have supported the finding that laryngeal cancer is amenable to conservative surgical approaches based on appropriate patient selection. Total laryngectomy, which had historically fallen out of favor as primary therapy with the advent of chemoradiation (CRT) for advanced tumors, continues to play an important role in salvage therapy. Furthermore, burgeoning epidemiological evidence and recent single-institution studies support the role of total laryngectomy as primary therapy for advanced T-classification tumors.

Early Stage Tumors

Transoral laser microscopic (TLM) surgery has become the mainstay of surgical treatment for early stage glottis and supraglottic tumors (Tis, T1a, T1b, T2). Multiple authors have noted that overall survival (OS) after TLM surgery is equivalent to that after XRT alone, and the local control rate is approximately 80% to 100%, depending on the study. This is on a par with the local control rate in patients who undergo radiotherapy (XRT). However, TLM surgery confers the distinct advantage of keeping all options open for the treatment of possible recurrences. Successful conservation surgery for early stage tumor relies on two basic principles:

1. Preservation of the cricoid cartilage is necessary for maintaining integrity of the airway. Failure to preserve the cricoid cartilage will result in narrowing of the subglottic airway and can result in subsequent tracheostomy dependence.

2. To create a safe airway, a single cricoarytenoid complex must be preserved. The cricoarytenoid complex is made up of a single arypegion, an intact cricoid, and the full complement of muscles and innervation (recurrent laryngeal nerve) to maintain function.

Failure to observe these principles will result in a non-functional airway. Furthermore, patients who are unable to protect their airway can develop aspiration pneumonia, increasing morbidity and mortality. Patient selection also plays an important role in conservation laryngeal surgery. One of the significant advantages of TLM surgery is that it often reserves XRT as a second option before proceeding to total laryngectomy for patients who recur after initial surgery. Pathologic evaluation of laryngeal specimens has resulted in a deeper understanding of adequate margins. The use of TLM surgery has demonstrated that 2-mm surgical margins are appropriate and allow for the endoscopic excision of tumors in multiple areas of the larynx. The European Laryngological Society has proposed a staging system for endoscopic cordectomy associated with tumor location. Tumors of the anterior commissure represent a continued challenge for TLM techniques, with significant difficulty in achieving 2-mm clear margins at this location while at the same time preserving enough contralateral vocal cord to maintain adequate voicing. Furthermore, there is an associated weakening of the periosteum at the insertion of Broyles ligament, suggesting a mechanism for the higher rate of recurrence of tumors involving the anterior commissure. Anterior commissure tumors have classically been treated with XRT. Patients with T1b tumors, however, classically have worse outcomes after XRT than patients with other early stage tumors.

Open Conservation Laryngeal Procedures

Open conservation procedures, such as supraglottic laryngectomy or supracricoid laryngectomy, follow the same principles as endoscopic procedures in terms of preserving cricoid cartilage anatomy as well as a single cricoarytenoid unit. With the advances in TLM-related techniques, there is limited indication for open supraglottic procedures, particularly open supraglottic laryngectomy. Because of the higher cost and morbidity of these procedures, many surgeons have evolved toward endoscopic techniques. In contrast, however, for appropriate patients who want to avoid XRT, supracricoid laryngectomy offers a surgical approach.

FIGURE 1. Representative Laryngeal Cancers Observed on Examination. (A) Normal larynx. (B) T1 larynx. (C) T2 larynx.
alternative to endoscopic techniques for addressing glottis tumors. Survival outcomes and locoregional control after supracricoid laryngectomy are similar to those after XRT for early stage tumors. In one of the largest series to date, local control rates of 100% were achieved for nonradiated patients with T2 tumors. Contraindications are both tumor related and patient related. Patients who have tumors that extend to the subglottis, involve a fixed cricoarytenoid complex, have posterior commissure involvement, or have through-and-through cartilage involvement are not candidates for supracricoid laryngectomy. At the same time, patients who have significant pulmonary compromise, extensive comorbidity, or are at high risk for aspiration are poor candidates for open conservation procedures. These patients should be treated with total laryngectomy. Voice outcomes after open conservation procedures are regarded as equivalent to those after XRT. Data suggest that patients who undergo endoscopic resection of tumors involving the true vocal cords can expect voice recovery similar to that of patients who undergo nonsurgical therapy. A small, albeit more recent, longitudinal study by Mendelsohn et al demonstrated an initial decrease in vocal quality, which typically returned to presurgical levels.

In summary, although supracricoid laryngectomy and XRT are accepted standards of care, TLM procedures have gained wide acceptance as a standard of care for early stage laryngeal tumors.

Surgical Treatment of Advanced-Stage Laryngeal Cancer

Up until the early 1990s, total laryngectomy had historically been the mainstay of advanced-stage laryngeal cancer. The Department of Veterans Affairs (VA) laryngeal study published in 1990 changed the paradigm to focus on nonsurgical organ preservation using induction chemotherapy protocols. This was further refined by Radiation Therapy Oncology Group (RTOG) study 91-11, published in 2003, which compared concurrent chemotherapy versus induction versus XRT alone. However, by that point, the use of chemotherapy concurrently or as induction therapy had gained widespread use versus total laryngectomy. It is important to note that the key chemotherapy studies excluded subsets of patients with advanced-stage laryngeal cancer, particularly T4 disease, suggesting that these cancers may be treated with surgery. Over the past 20 years, there has been a decrease in survival for patients with laryngeal cancer. Since then, several single-institution studies have suggested improved survival for patients who undergo total laryngectomy for advanced-stage laryngeal cancer. One such study examined 2-year and 5-year survival in patients with T3 and T4a tumors who underwent total laryngectomy and demonstrated a distinct survival benefit for total laryngectomy versus CRT. Further studies using the National Cancer Database also concluded that there was a statistically significant survival benefit for patients with T4a and stage IV laryngeal cancer who underwent total laryngectomy. Currently, treatment planning for patients with advanced laryngeal disease depends on multiple variables. Because of the lack of level I evidence for nonsurgical organ preservation, protocols should be applied with caution to patients with T4 disease. Because of the extremely complicated nature of these patients, it is critical that an experienced multidisciplinary group manage them. The International Head and Neck Scientific Group published an editorial stating that, for patients with T4 tumors of the larynx, except in selected individuals, total laryngectomy may be the only option. Speech pathologists play an important role in determining which patients would do better based on their preoperative functions. Patients with significant structural or functional defects of the larynx, typically T4 tumors, should be given significant consideration for upfront surgical treatment. A subset of patients with T3 disease likely falls into this cohort as well, but strategies to identify them have been few and far between. Several institutions have undertaken chemoselection protocols and have independently published results. However, there has been no multicenter trial looking at chemoselection as a viable, widespread treatment paradigm.

In summary, although larynx preservation ought to be considered for locally advanced T3 and T4 disease, patients who have evidence of functional defects to the larynx, especially in the setting of T4 disease, need to be considered for laryngectomy.

Surgical Treatment of the Lymph Node-Negative Neck for Primary Tumors of the Larynx

Treatment of the neck depends on the subsite of the primary tumor. Patients who have positive lymph node (N+) status require definitive treatment, whether by comprehensive neck dissection or definitive CRT. Patients who have negative lymph node (N0) status may benefit from elective neck dissection for staging and treatment purposes. Generally speaking, the cutoff for elective treatment of the neck is a risk of occult metastasis greater than 20%. For supraglottic cancer, elective treatment of the neck should be undertaken for T2 or greater disease. However, for patients with glottic disease, the risk of occult metastasis does not exceed 20% until tumors are stage T3 or greater. Furthermore, the neck represents a bilateral nodal basin for supraglottic tumors, whereas glottic and subglottic tumors can be treated unilaterally.

In summary, a thorough understanding of the larynx and associated nodal basins is critical for patients undergoing
treatment for laryngeal cancer and dictates the need for surgical treatment of the neck.

Principles of Radiation
Radiation plays an integral role in the management of head and neck cancer. The larynx subsite of head and neck cancers is no different, because XRT continues to be an important part of curative-intent therapy, used either definitively for organ preservation or adjuvantly in the postoperative setting. The specifics of XRT of the larynx depend foremost on the subsite of the larynx in which the cancer arises. As mentioned previously, the larynx is typically subdivided into the supraglottic, glottic, and subglottic components. The subglottic location is rarely a primary site of laryngeal SCC. When it is involved by carcinoma, it is usually via secondary extension of a primary glottic or supraglottic cancer. Therefore, the discussion will focus exclusively on the supraglottic and glottic regions. In addition, there remain significant anatomic differences between the supraglottic and glottic sites that lead to widely variable treatments. These differences relate to the degree of lymphatic drainage. The glottis has poor lymphatic drainage; therefore, early tumor stage disease rarely presents with nodal metastases. Conversely, the supraglottic larynx has a more abundant lymph node basin, and even cancers with limited local extent may present with clinically apparent cervical adenopathy or may be at risk of harboring subclinical nodal disease.

Radiation for the Supraglottic Larynx
Both surgery and definitive XRT are acceptable treatment options for early stage (T1–T2N0) supraglottic larynx cancer. There is no prospective evidence comparing these 2 modalities, but there is abundant information retrospectively evaluating each treatment. These studies provide the basis for establishing the role of XRT and surgery in the definitive treatment of localized disease. Retrospective studies have found various characteristics that can help identify certain groups of patients who would benefit most from either surgical or XRT management. A choice of definitive treatment with XRT is typically based on the stage of the primary lesion (T1, T2, and select T3 lesions because of pre-epiglottic space involvement without vocal cord fixation), performance status (usually poor), and institutional preference. The outcomes of definitive treatment with XRT alone are encouraging. The local control rate after definitive XRT ranged from 73% to 100% for T1 tumors and from 60% to 89% for T2 tumors.49,50 Patients who experienced local failure could then be salvaged with surgery. The treatment of early supraglottic laryngeal cancer involves treatment of the gross primary disease while also covering elective lymph nodes in the bilateral neck from levels II through IV. The gross primary disease is delineated on the CT simulation and necessitates higher doses than elective coverage of the nodal neck volumes. Intensity-modulated XRT (IMRT) and now volumetric arc therapy (VMAT) are generally favored over the traditional 3-dimensional (3D) or even more antiquated 2D techniques. IMRT is useful because of the ability to spare radiation dose to normal tissues, particularly the parotid glands, when covering the level II lymph nodes in radiation treatment volumes. In a randomized trial, IMRT reduced the rates of grade 2 and higher xerostomia compared with 3D conformal radiation techniques, from 74% to 38% at 1-year posttreatment, in patients with head and neck cancer.51 Standard radiation treatment volumes for early stage supraglottic laryngeal cancer include treating the areas of gross tumor to a dose of 70 Gray (Gy) in daily 2-Gy fractions. The bilateral neck lymph node volumes, levels II through IV, will receive a lower dose, typically in the 50-Gy range, for the treatment of possible microscopic, subclinical disease. For more advanced laryngeal cancer beyond the T1–T2N0 population, data support the possibility of preserving laryngeal function, and these data are discussed in detail below. In addition to organ preservation with CRT, TLM surgery is also an evolving technique for patients with stage III and IV glottis and supraglottic laryngeal cancers. Hinni et al reported on patients with stage III and IV larynx cancer treated with TLM surgery from 1997 to 2004. Local control at 2 years was 82%, and overall survival was 75%.52 Further details of TLM surgery are discussed elsewhere in this review (see Principals of Surgery, above). Treatment of the supraglottic larynx with XRT can be completed using a variety of techniques. Older 3D conformal techniques are still appropriate; but, like early stage disease, the introduction of IMRT and VMAT shifted the preferred treatment.
to these newer modalities. The planning for XRT takes place on a CT scan from the apex of the head through the middle of the thoracic cavity. If possible, contrast with the scan is preferred to provide additional anatomical delineation of both normal (particularly blood vessels) and pathologic structures. Setup for simulation remains a critical part of radiation treatment (Fig. 2). Reproducibility of the patient’s position will determine accurate treatment of the target and avoidance of organs at risk. The specifics of radiation dose vary by institution, but general principles remain the same. The primary disease within the larynx and any involved lymph nodes are treated to 70 Gy in 2-Gy daily fractions. Involved lymph node levels and other high-risk areas are treated to an intermediate dose of 60 Gy. Finally, a lower risk volume generally consists of the lymph node-negative neck, if applicable, and is treated to 50 Gy (Fig. 3). With the IMRT technique, radiation fractionation can be given sequentially, delivering the lower dose portion followed by the high-dose boost volume for the last 1 or 2 weeks. This is given in 2 or 3 distinct IMRT plans, with doses typically at 2 Gy per day. Another commonly used fractionation method for IMRT is simultaneous integrated boost, which uses dose painting and applies the same number of fractions to each dose volume at a variable dose per fraction. With simultaneous integrated boost, the primary tumor and involved lymph nodes will typically receive 70 Gy at 2 Gy per day, and the low-risk to intermediate-risk sites (regions of suspected subclinical spread) will receive between 54 and 63 Gy (in 1.6–1.8 Gy per fraction). For patients who are not candidates for, or refuse, concurrent CRT or definitive surgery, XRT alone is a viable option. For these special cases, there is evidence showing benefit for altering the fractionation scheme from the standard 66 to 70 Gy delivered in 1.8 to 2.0 Gy per fraction.\(^{53}\) Hyperfractionated XRT is defined as the delivery of a greater total dose of radiation over the same time interval, usually 7 weeks. The toxicity of such a treatment is partially mitigated by twice daily treatments of from 1.1 to 1.2 Gy per fraction. Accelerated XRT is delivery at the same dose in a shorter time interval, usually over a 5-week or 6-week period. A meta-analysis composed mostly of patients with stage III or IV SCC of the head and neck (SCCHN) showed the benefits of hyperfractionation and accelerated XRT over conventional treatment.\(^{53}\) That analysis included a total of 6515 patients, of whom 74% had stage III/IV disease and 34% had primary cancers of the larynx. Hyperfractionated therapy had an absolute improvement rate of 8% in 5-year OS compared with conventionally fractionated XRT. In addition, locoregional control was improved with altered fractionation schemes. As expected, the rate of distant metastatic failure was not different between the XRT treatment arms. In brief, altered fractionation schemes of XRT, and specifically hyperfractionation, can be delivered for definitive therapy in patients who are not able to undergo surgery or chemotherapy.

In summary, the treatment of early stage supraglottic laryngeal cancer involves treatment of the gross primary disease and covering elective level II through IV lymph nodes in the bilateral neck. Laryngeal preservation can be attempted in more advanced disease, and altered fractionation is an option for patients who are not candidates for concurrent therapy.

**Radiation for Glottic Larynx**

Early stage glottic cancer can be treated effectively using either single-modality surgery or XRT, with good outcomes reported for both. Unfortunately, there is no prospective evidence to compare modalities. As mentioned above, treatment for these early stage glottic primaries can focus on the primary tumor while sparing the adjacent lymph node volumes given the rarity with which these cancers spread through adjacent lymphatics.\(^{54}\) The generally agreed upon preferred treatment method for early stage glottic cancer, defined as T1 or T2N0, is definitive XRT delivered via opposed lateral fields. Treatment planning begins with standard immobilization techniques. A
thermoplastic mask is used to reproduce the planning set-up. During the planning CT scan, it is critical to hyperextend the neck as much as possible while also making efforts to lower the shoulders. These 2 positioning changes expose the larynx and reduce dose delivery through the shoulders or oral cavity. The well-established field size for a T1N0 glottic cancer is a 5-cm × 5-cm open square. The field superiorly covers the thyroid cartilage and inferiorly includes the cricoid cartilage. The anterior edge of the vertebral body serves as the posterior border, while, anteriorly the field will have about a 1-cm flash. T2N0 glottic carcinomas are treated similarly with the exception of using a 6-cm × 6-cm field to extend coverage inferiorly to the first tracheal ring. Because of the contour of the neck, a simple opposed lateral field design may result in under dosing of the anterior commissure of the glottis. The anterior commissure is a common area for local recurrence after definitive XRT, especially if this area does not receive adequate dose. Therefore, using a wedge to augment the dose or skin bolus along the anterior edge of the neck allows adequate dosing to the thinner anterior neck. There is strong prospective evidence regarding the optimal XRT regimen for early stage glottic cancer. A prospective trial randomized patients with T1N0 SCC to receive 2.25 Gy per fraction versus 2 Gy per fraction to approximately equivalent biologic doses. The results showed an improved local control rate of 92% at 10 years for the higher dose per fraction versus 77% for the lower dose. By using the regimen with the greater dose per fraction, the accepted total dose for T1 lesions is 63 Gy. The lower 2 Gy per fraction regimen can be used, but the neck needs to be treated to >66 Gy. Again, when analyzing coverage of a T1 lesion, it is critical to pay special attention to coverage of the anterior commissure. Tumor involvement of the anterior commissure is associated with worse local control for T1 tumors. The RTOG 95-12 trial provides prospective evidence of good outcomes for T2 glottic lesions. That trial compared a twice-a-day fractionation regimen versus daily treatment. There was no statistical benefit of the twice-daily dosing, but there was a trend toward improved local control (local control rate at 5 years, 78% vs 70% for daily treatment; \(P = .14\)), a disease-free survival (DFS) benefit (49% vs 40%, respectively; \(P = .13\)), and an OS benefit (72% vs 63%, respectively; \(P = .29\)). Other retrospective data showed that there was a local control detriment from treatment fractions \(\leq 2\) Gy per fraction compared with >2 Gy per fraction or twice-daily dose schemes. The standard dosage for a T2 lesion is 65.25 Gy delivered in 2.25 Gy per fraction if using a daily scheme. This dose regimen is further supported by retrospective evidence that showed improved local control for T2 lesions when treated with fraction sizes \(\geq 2.25\) Gy and total doses >65 Gy. In evaluating definitive XRT T2 lesions, it is important to pay special attention to any subglottic extension of the primary, as this is associated with worse local control. The treatment of more advanced cancers, including T3, T4, and lymph node-positive disease, necessitates XRT concurrently with chemotherapy. The basics of XRT for advanced glottic cancers are similar to those for advanced supraglottic laryngeal cancer, as discussed above (Fig. 4).

In summary, a higher dose per fraction results in improved local control, and special attention is needed to anterior commissure coverage in T1 and T2 tumors.

**Postoperative Therapy**

Radiation also plays a central role in adjuvant therapy after surgery. The RTOG 95-01 and European Organization for Research and Treatment of Cancer 22931 studies were 2 prospective, randomized controlled trials that compared postoperative XRT versus CRT with a variety of pathologic risk factors for SCCHN, including SCC of the larynx. In a combined analysis of these 2 studies, OS and DFS were improved with the addition of chemotherapy in the presence of positive margins and extracapsular nodal extension. There was also a significant local regional control benefit. Postoperative XRT is generally delivered without chemotherapy in the presence of perineural invasion, lymphovascular invasion, close margins (<1 mm), thyroid cartilage invasion, >1 cm of subglottic extension, extension of the primary tumor into the soft tissues of the neck, T4 disease with bone invasion, and multiple positive cervical lymph nodes. Delivery of XRT in the postoperative setting can be done with 3D techniques; but, as seen with definitive XRT, IMRT and VMAT techniques are increasingly

**FIGURE 4.** Isodose Curves (Regions of Uniform Dose Intensity) for a T3N0 Glottic Cancer. This patient had involvement of the anterior commissure, and a 0.5-cm bolus over the anterior neck was required for the planning target volume to receive the full dose.
preferred. The postoperative bed and high-risk areas for relapse are treated to a total dose of 60 to 66 Gy in 2 Gy per fraction for negative or microscopically positive margins. Any gross disease is boosted to a dose of 70 Gy. The presence of a tracheostomy presents a unique postoperative scenario. This structure is usually limited to 50 Gy. Exceptions to this rule are for significant subglottic extension of the primary tumor, placement of an emergent tracheostomy, level VI extranodal extension, and close or positive margins in the vicinity of the tracheostomy. For these patients, the tracheostomy is boosted to 60 to 66 Gy.

In summary, patients with high-risk postoperative features, including positive margins or extranodal extension, will benefit from adding chemotherapy to XRT.

**The Management of Locally Advanced Disease**

**Supportive Care**

Supportive care during and after treatment of laryngeal cancer is crucial to the successful management of this patient population. The treatment of laryngeal cancer involves a multidisciplinary team effort, including medical, radiation, and surgical oncologists, but also dieticians, speech and swallow experts, radiologists, and social services. A high psychiatric morbidity has been associated with laryngeal cancer, making careful monitoring and evaluation important for a successful treatment. As detailed above, the treatment of laryngeal cancer carries the unique morbidity of loss of natural speech, and patients should be aware of this. If a laryngectomy was performed, then a voice prosthesis provides a valuable tool for patients. However, even for patients undergoing laryngeal preservation, XRT is known to cause voice injury; therefore, post-treatment evaluation and voice training should be considered for patients undergoing XRT.

Similarly, if a tracheostomy is placed, then patients should be instructed in proper maintenance. The maintenance of hydration and nutrition is of crucial importance, and the patient’s weight should be monitored regularly. The placement and use of a nutritional intervention, such as a percutaneous endoscopic gastrostomy tube, should be done in conjunction with an experienced dietician.

**Laryngeal Preservation**

The treatment of locally advanced laryngeal cancer requires a multimodality team approach given the complicated anatomy and significant morbidity of a total laryngectomy. The psychosocial effects of losing the ability of voice is of great consequence for patients and plays a large role in a patient’s treatment decisions regarding their cancer. In addition to loss of voice, other potential quality-of-life concerns for patients after surgical resection include issues with swallowing and permanent tracheostomy. The significant consequences of surgery led to several clinical trials with a relatively unique endpoint for oncology: organ preservation. The landmark initial trial was the VA Larynx Cancer Study Group (VALCSG) trial. The study was a prospective, randomized, phase 3 clinical trial designed to compare induction chemotherapy followed by XRT versus total laryngectomy followed by postoperative XRT for stage III and IV laryngeal cancer. There were 332 patients enrolled. In the chemotherapy arm, patients received 2 cycles of cisplatin and 5-fluorouracil (5-FU) and were subsequently assessed for response. If a response was observed, then patients went on to receive one more dose of chemotherapy followed by definitive XRT, otherwise they proceeded to undergo total laryngectomy. Responses were observed in 85% of patients after 2 cycles of chemotherapy, including 31% complete responses. In terms of outcomes, 2-year OS rates did not differ between the groups and was estimated at 68% for both arms (95% CI, 60%-76%; P = .9846). Importantly, 66% of patients who received chemotherapy were able to preserve their larynx, which translated to large quality-of-life gains for this patient population. This VALCSG study also demonstrated the feasibility of a cisplatin-based chemotherapy approach with the goal of laryngeal preservation without a sacrifice in survival. These results were confirmed in the European Organization for Research and Treatment of Cancer laryngeal preservation trial, which had a design to that of the VALCSG study. Two hundred patients were enrolled and randomized to either upfront surgery with postoperative XRT or induction cisplatin and 5-FU followed by definitive XRT for responders. The study was designed as an equivalence study, and no significant differences between the arms were observed in terms of local or regional recurrence or OS. Fewer distant recurrences were observed in the chemotherapy arm (25% vs 36%, respectively; P = .041). The study reinforced the finding that induction chemotherapy is of clinical value for selected patients with laryngeal cancer. One critique of these studies has been that systemic therapy could have been potentially unnecessary and that these studies were in fact comparing XRT with laryngectomy. The RTOG 91-11 study examined this question. That trial randomized 547 patients to receive either the VA induction regimen followed by XRT, or XRT alone, or concurrent cisplatin and XRT. Patients with stage III or IV SCC of the glottic or supraglottic larynx were included. With a median follow-up of 10.8 years, concurrent cisplatin with XRT produced improved laryngectomy-free rates (81%) versus either induction regimens (67.5%; P = .005) or XRT alone (63.8%; P < .001). However, OS did not significantly differ between the treatment groups, as salvage surgery was an option at recurrence. This has led to the adoption of concurrent chemotherapy with cisplatin and
XRT as the standard of care. We note that patients with bulky T4 masses, defined as a tumor penetrating through the thyroid cartilage or invading ≥1 cm into the base of the tongue, were excluded from that study, and total laryngectomy remains the standard of care for these patients.\(^41,67\) Despite the sound support for larynx preservation with locally advanced head and neck cancers, recent population outcome studies have reported a trend of decreased survival specifically in patients with laryngeal cancer.\(^42\) There is debate regarding the reason for the recent detrimental trend in outcomes for this specific site within SCCHN. One theory postulates that patients in regular practice who are selected for CRT have quite dissimilar characteristics from the patients enrolled on studies. RTOG 91-11 and the VA larynx trial consisted of patients with generally good performance status and younger age. Select T4 lesions were also included on study, but there are ambiguities in the definition of “low-volume” disease that was used for enrollment.\(^68\) There is debate regarding the reason for the recent detrimental trend in outcomes for this specific site within SCCHN. One theory postulates that patients in regular practice who are selected for CRT have quite dissimilar characteristics from the patients enrolled on studies. RTOG 91-11 and the VA larynx trial consisted of patients with generally good performance status and younger age. Select T4 lesions were also included on study, but there are ambiguities in the definition of “low-volume” disease that was used for enrollment.\(^68\) On 10-year follow-up of RTOG 91-11, patients who had received concurrent treatment had a higher rate of long-term mortality unrelated to disease.\(^69\) The significant benefit of larynx preservation and locoregional control for the surviving patients persisted, however. A potential explanation for this finding is the late toxicities from concurrent treatment. A secondary analysis of concurrent CRT trials, including RTOG 91-11, 97-03, and 99-14, examined late toxicity.\(^70\) In cancer-free survivors, the rate of late toxicities reached 43%. The most common grade 3 and 4 late toxicities were related to swallowing and larynx dysfunction. Predictors of late toxicity included increasing age, increasing T-classification, and laryngeal or hypopharyngeal location of the primary tumor. These factors could potentially account for the equivocal survival benefit observed in the long-term follow-up of patients on RTOG 91-11. With improvements in supportive care, it is hoped that late toxicities may be better controlled and long-term survival preserved in more recent trials. In addition, Bonner et al, in a retrospective analysis of a prospective trial, demonstrated a trend of improved larynx preservation with the addition of cetuximab to XRT versus XRT alone. This is an intriguing finding that could potentially lead to decreased toxicities compared with those reported with cisplatin; however, this finding needs to be validated in a prospective setting, such as RTOG 1016, before it becomes a standard of care.\(^71,72\)

### Table 1. Trials of Larynx Preservation

| Trial         | Name                           | Phase | Study Arm               | Rate (Time Point) | DFS          | OS            | Laryngeal Preservation |
|---------------|--------------------------------|-------|-------------------------|-------------------|--------------|---------------|-----------------------|
| VA Larynx Study | 3                               | CF ×3 then RT | NR | 68% (2 y) | 66% (2 y) |
| RTOG 91-11    | 3                               | CF ×3 then RT | 20.4% (10 y) | 39% (10 y) | 67.5% (10 y) |
| EORTC         | 3                               | CF ×3 then RT | RT + C | 21.6% | 28% | 81.7% |
| TREMPLIN      | 2                               | ICT ×3 then RT + C | 91.7% (18 mo) | 75% (3 y) | 95% (3 mo) |

Abbreviations: C, cisplatin; CET, cetuximab; CF, cisplatin and 5-fluorouracil; DFS, disease-free survival; EORTC, European Organization for Research and Treatment of Cancer; ICT, docetaxel, cisplatin, and 5-fluorouracil; NA, not applicable; NR, not reported; OS, overall survival; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; SX, surgery; TREMPLIN, induction chemotherapy followed by either chemoradiotherapy or bioresection for larynx preservation; VALCSG, the US Department of Veterans Affairs Laryngeal Cancer Study Group.

The Role of Induction Versus Concurrent Therapy

The studies discussed above helped define the role of surgery, chemotherapy, and XRT for laryngeal cancer. However, the sequencing of chemotherapy has led to controversies over the past few decades regarding the role of induction chemotherapy. Induction therapy became
As chemotheraphy began to demonstrate significant response rates, with the goal of increasing disease control and survival. Early clinical data had shown the ability of neoadjuvant chemotherapy to provide robust tumor responses and a potential decrease in the rate of distant failure. However, data on induction versus concurrent chemotheraphy specifically for laryngeal cancer had to be derived from broader head and neck studies, given the difficulty of accruing to these trials. As RTOG 91-11 helped define cisplatin as the current systemic agent of choice for concurrent therapy, several studies helped defined an optimul induction regimen. The most instrumental of these were the TAX 323 and TAX 324 phase 3 randomized trials. TAX 323 enrolled 358 patients with stage III or IV unresectable SCC of the oral cavity, oropharynx, hypopharynx, or larynx. Patients were randomized to receive induction therapy with cisplatin plus 5-FU (PF) (cisplatin 75 mg/m^2 on day 1 and 5-FU 750 mg/m^2 daily, continuous infusion on days 1-5), as the control arm, or the same regimen plus docetaxel (TPF) (75 mg/m^2 on day 1). Both regimens were given every 3 weeks for 4 cycles. Patients with laryngeal cancer represented 7% of the overall population. Patients who did not progress on treatment went on to receive XRT. The progression-free survival (PFS) (hazard ratio [HR], 0.72; P = .007) and OS (HR, 0.73; P = .02) outcomes favored the TPF arm. The TAX 324 study also randomized patients to receive induction PF versus TPF. All nonprogressing patients went on to receive concurrent XRT with single-agent carboplatin with an option for surgery afterward. As opposed to TAX 323, approximately 17% of the patients enrolled on TAX 324 had laryngeal cancer. Both PFS (HR, 0.71; P = .004) and OS (HR, 0.70; P = .006) improved with TPF. A subset analysis of TAX 324 examining the laryngeal and hypopharyngeal cancers confirmed the PFS and OS benefit as well as improved laryngeal preservation with TPF. Although these studies, among others, demonstrated that induction therapy is a feasible and effective treatment modality, significant controversy remains over whether it provides any benefit over the standard concurrent CRT approach. Nonetheless, chemotherapy in general has been shown to be integral in the treatment of locally advanced head and neck cancer. The results of multiple studies examining this role are best summarized in a careful and in-depth individual patient meta-analysis completed by Pignon et al and updated in 2009. For that report, 87 studies between 1965 and 2000 that included 16,485 patients were analyzed. Overall, the investigators showed that chemotherapy improved survival for patients treated with local modalities (surgery and/or XRT), with an HR for death of 0.88 (P < .0001). The absolute benefit for chemotherapy on survival at 5 years was 4.5%. Interestingly, a subanalysis on induction versus concurrent therapy revealed improved local-regional control, PFS, and OS for the concomitant treatment arm but not for induction. It is worth noting, however, that there did seem to be a more significant beneficial effect on distant metastasis in the induction cohort. A follow-up study examined this data set with respect to primary tumor site, and 3216 patients with laryngeal cancer were included. Importantly, concurrent chemotherapy had an HR for death of 0.80 versus locoregional treatment alone compared with induction (HR, 1.00) or adjuvant chemotherapy (HR, 1.05; P = .05). Two recent studies have attempted to directly compare induction and concurrent therapy in SCCHN. Neither of those trials was able to reach the planned accrual numbers, highlighting the logistical difficulties faced in the conduct of these studies. The first is PARADIGM, a phase 3 randomized clinical trial comparing TPF induction followed by concurrent CRT versus concurrent CRT alone for patients with locally advanced, unresectable head and neck cancer. One hundred forty-five patients were enrolled, with laryngeal cancer representing approximately 17% of the population. While a nonsignificant improvement in PFS in patients with nonoropharyngeal cancers was reported, overall the study demonstrated no difference in PFS or OS for the addition of induction chemotherapy. However, toxicity was higher with induction therapy, with 52 serious adverse events versus 22 in the CRT arm. Given the high risk of recurrence in patients with advanced SCCHN and the potential benefits of induction therapy, the DeCIDE trial (docetaxel-based CRT with or without induction chemotherapy to decrease events in head and neck cancer) was designed to include only patients with N2 and N3 SCCHN. Much like the PARADIGM trial, the study examined CRT versus CRT plus induction TPF. The concurrent chemotherapy used in DeCIDE was a less frequently used regimen, consisting of docetaxel, fluorouracil, and hydroxyurea. Overall, of a planned 400-patient enrollment, 285 patients were included (approximately 14% had laryngeal cancer). In summary, no statistically significant benefit was seen in response rates, PFS, patterns of failure, or OS, but the incidence of grade 3 and 4 toxicity was higher in the induction treatment arm (47% vs 28%; P = .002). In addition to cytotoxic therapy, the anti-epithelial growth factor receptor (anti-EGFR) monoclonal antibody cetuximab is approved for SCCHN, in both the locally advanced and metastatic setting. Bonner et al demonstrated the effectiveness of cetuximab with XRT for locally advanced SCCHN. Patients were randomized to receive either cetuximab (400 mg/m^2 loading dose, then 250 mg/m^2 weekly during radiation) or XRT alone. The study found that adding cetuximab to treatment improved local control (24.4 vs 14.9 months; P = .005) and OS (49.0 vs 29.3 months; P = .006). However, this effect...
was significantly more pronounced for oropharyngeal cancer than for laryngeal cancer in a subset analysis. There is currently no evidence to support that concurrent cetuximab is superior to concurrent platinum-based therapy. The TREMPLIN (CRT vs bioradiotherapy for larynx preservation) randomized phase 2 study of patients with locally advanced laryngeal cancer who responded after induction TPF compared concurrent triweekly cisplatin versus cetuximab plus XRT with the primary endpoint of laryngeal preservation at 3 months. While there was greater local failure with cetuximab (13.3% vs 21.4%, respectively), necessitating salvage surgery, there were no significant differences in overall disease control or survival. A takeaway from this trial was that treatment delivery for either arm was difficult after induction therapy. A recent Italian study also examined cetuximab versus cisplatin concurrent with XRT for locally advanced SCCHN. Unfortunately, the trial was closed early based on slow accrual, making it difficult to draw conclusions. Nonetheless, efficacy was not significantly different between the arms. Unexpectedly, the rate of serious adverse events was higher in the cetuximab arm (19% vs 3%; P = .044). Finally, there is no role for adding cetuximab to cisplatin in concurrent therapy, because the results of RTOG 0522 demonstrated no efficacy advantage to this combination approach, but the cetuximab and cisplatin arm had a higher rate of toxicity and more dose interruptions than the cisplatin alone arm.

In summary, it has been demonstrated that chemotherapy plays an integral role in the treatment of locally advanced laryngeal cancer. Although induction chemotherapy is feasible, there is currently a lack of clear data favoring one approach over another. Platinum-based, concurrent therapy remains the standard of care regimen for laryngeal preservation, at least in the United States.

Triweekly cisplatin 100 mg/m² remains the most widely used regimen in laryngeal cancer. However, weekly cisplatin is more commonly being used in an attempt to maintain efficacy while decreasing toxicity. These 2 approaches, however, have not been compared in a randomized phase 3 trial. Additionally, although lacking phase 3 evidence, adding a taxane to a platinum backbone can be considered. Finally, as discussed above, cetuximab with XRT is an efficacious treatment for patients with locally advanced SCCHN who are not candidates for platinum-based therapy. For a carefully selected population, laryngeal preservation with concurrent CRT is a viable treatment option. This decision should be made within a multidisciplinary approach.

Salvage Surgery

For patients who fail nonsurgical organ-preservation techniques, salvage surgery often represents the only viable option for cure. Although studies have demonstrated some success with conservation techniques, more commonly, total laryngectomy is the mainstay of salvage. Significant challenges surround salvage attempts for laryngeal cancer. Basic tumor physiology post-CRT suggests an environment less likely to be successfully treated with surgical techniques. Failures of CRT often are associated with disease that has been controlled centrally but failed at the borders of the tumor. Other tumors fail because of physiology in the central portion of the tumor, with central necrosis providing a place for tumor sequestration. Concomitant with the publication of RTOG 91-11 was the publication of the salvage laryngectomy data. Of the 129 patients who underwent salvage surgery, initial local control rates were 74% in the arms that received chemotherapy and 90% in the RT alone arm. The 2-year OS rates were from 69% for patients who received induction chemotherapy, 71% in the concurrent chemotherapy group, and 76% in the RT alone group. In a separate study of patients who underwent salvage laryngectomy for recurrent disease, predictors of positive outcomes were related to the initial disease-free interval exceeding 5 years. Patients who recur at <2 years were more likely to die of their disease after salvage laryngectomy. A second study demonstrated 5-year disease-specific survival rates of 70% and 55%, for early and advanced-stage cancers, respectively. Historically, most patients undergoing total laryngectomy for salvage have also undergone bilateral or unilateral elective neck dissection for N0 disease. There is controversy over whether or not standard elective neck dissection is warranted. Basheeth et al evaluated 94 patients who underwent laryngectomy for salvage after failed nonsurgical therapy and noted an occult metastasis rate of around 8%. Hilly et al published a decision analysis model suggesting that, with cure rates for salvage surgery <82%, standard neck dissection is not warranted in N0 salvage cases, because OS and DFS would not be affected. However, in a follow-up study, a beneficial effect was noted for patients with locally advanced recurrence (rT3-rT4), as opposed to those with limited recurrence (rT1-rT2). Amit et al noted an 18% risk of recurrence in the central/lateral neck among 51 patients and concluded that there was a beneficial effect from elective neck dissection. Koss et al noted an overall 28% rate of occult metastasis of with supraglottic cancer. Clearly, controversy persists, and large-volume, multi-institutional trials need to examine the nodal involvement rate in clinical N0 necks for patients undergoing salvage surgery. It would seem that, based on the aforementioned findings, an elective neck dissection would be prudent at least for some locally advanced tumors. Rates of complications tend to be high after salvage surgery. Poor vascular supply has been implicated in a high rate of wound complications. One of
the most common and devastating complications is the development of a pharyngocutaneous fistula. RTOG 91-11 reported a pharyngocutaneous fistula rate as high as 30% in the CRT arm, which was statistically higher than that in the XRT only arm.\(^8^7\) Fistula formation can result in a significant delay in oral intake, extended hospital stay, and increased cost to the patient. For patients undergoing salvage laryngectomy, it is important to consider postoperative swallowing function. Hutcheson et al looked at a series of patients undergoing total laryngectomy for nononcolgic reasons after CRT and noted that functional outcomes were enhanced for patients with severe laryngopharyngeal dysfunction.\(^8^5\) Often, patients will require pharyngeal reconstruction after total laryngectomy. Conceptually, when the pharynx is involved, reconstitution of the connection between the base of tongue and cervical esophagus is of primary importance. This can be accomplished in several ways. For patients who have significant concerns regarding tissue health, in whom there is enough pharynx to close on itself, an overlay graft can be used. This includes the pectoralis myofascial muscle flap (PMMF) as an overlay to reinforce the primary closure. For patients with partial pharyngectomy defects, the pectoralis flap can be raised with an associated skin paddle (a pectoralis major costomyocutaneous flap [PMCF]) to help maintain the patency of the pharynx. Free-tissue interpositional grafts can also be used. Several studies have demonstrated a significant benefit for patients who undergo PMMF overlay grafting after salvage laryngectomy.\(^9^6-1^0^0\) The Microvascular Committee of the American Head and Neck Society published a multi-institutional, retrospective study comparing primary closure with pectoralis muscle overlay and interpositional free tissue and noted both a significant decrease in the fistula rate for PMMF as well as a decrease in fistula duration for free tissue.\(^1^0^1\) However, because of the more reliable nature of the vascular supply, free tissue may confer advantages over PMCF.\(^1^0^2\) As a result, microvascular reconstruction is becoming the preferred method of surgical fistula prevention in most high-volume institutions, although PMCF reconstruction remains a viable option in cases where microvascular techniques are not available or contraindicated. For patients with circumferential defects (ie, the entirety of the pharynx with cervical esophagus remaining above the thoracic inlet), microvascular free-tissue transfer plays a vital role. This can take the form of either a free jejunal graft or a tubed radial forearm or anterolateral thigh free flap.\(^1^0^3-1^0^6\) There are advantages and disadvantages of each reconstructive option. Patients undergoing free jejunal graft will require a laparotomy and primary small intestine anastomosis. While this can be done using minimally invasive techniques, it requires surgeons who are experienced with the procedure as well as up to 3 teams to perform the operation.\(^1^0^7\) Other disadvantages of the jejunum graft include lack of neovascularization and the continued production of mucus. Advantages of the jejunum relate to its mucosal lining and the fact that there are only 2 mucosal anastomoses. Tubed fascia cutaneous flaps (radial forearm free flap and anterolateral thigh free flap) offer a compelling alternative. They do not require a third team to harvest, neovascularize in the pharynx, and authors report good voice outcomes.\(^1^0^8,1^0^9\) Disadvantages are the need for a third anastomotic line and the lack of mucosal lining. For patients whose disease extends below the thoracic inlet, free-tissue transfer is not an option. These patients typically require a gastric pull-up procedure, wherein the stomach is released in the abdomen and mobilized to the base of tongue. This procedure has very high morbidity and mortality rates and should only be used in rare circumstances. Colonic interposition is an alternative technique for patients who are not candidates for gastric pull-up.

In summary, salvage laryngectomy is the surgery of choice for persistent disease after an attempt at laryngeal preservation. Lymph node dissection is of questionable value in this setting, pharyngeal reconstruction is often needed after salvage laryngectomy, and the proper method of reconstruction needs to be individualized.

**Voice Rehabilitation**

Voice rehabilitation is critical for patients undergoing total laryngectomy. A speech pathology team experienced in multiple methods of voice restoration is a key component of any multidisciplinary team treating laryngeal cancer. Patients should undergo comprehensive prelaryngectomy counseling, including discussion of various voice restoration strategies. Vocal rehabilitation for patients who undergo total laryngectomy has advanced significantly over the past 20 years. Today, tracheoesophageal prosthesis (TEP) is considered the best option for voice rehabilitation. Studies have suggested that TEP speech is superior to both esophageal and electrolarynx speech.\(^1^1^0,1^1^1\) This one-way valve reroutes air through the neopharynx, allowing for vibration, creating speech. TEP can be placed at the time of the initial laryngectomy (primary TEP placement) or after the patient has healed or completed their XRT (secondary TEP placement). However, TEP is not without risks and should be placed only after extensive evaluation of the patient by the speech pathology team. There are multiple issues that affect healthy TEP maintenance. Complications related to TEP placement can include chronic aspiration, chronic leakage, obstruction, and granulation tissue.\(^1^1^2\) Significant consideration should be given to avoiding TEP in patients who have undergone reirradiation, as the tissues are not usually able to tolerate an indwelling prosthesis. In patients who are not candidates for TEP, esophageal speech and the
electrolarynx remain viable alternatives. Every effort should be made to rehabilitate the patient’s communication, because the lack of speech can become mentally and socially isolating for the patient.112

In summary, vocal rehabilitation has advanced over the past 20 years. Today, TEP is considered the best option, with limitations that include possible aspiration, leakage, and obstruction. Esophageal speech and an electrolarynx are possible alternatives.

Larynx Reirradiation
The management of local recurrence of laryngeal cancer after XRT, either postoperatively or definitively, is an active area of investigation. Local relapse of disease after XRT is defined as new gross disease within the prior radiation treatment volume. Outcomes after local recurrence, especially for patients who are not deemed surgical candidates, remain poor. Prospective studies have evaluated standard fractionation schedules delivered concomitantly with chemotherapy to treat local recurrences. RTOG 96-10 and 99-11 both evaluated reirradiation delivered with different chemotherapy regimens.113,114 Outcomes continued to be subpar, with median survivals of 8.5 and 12.1 month, respectively. These outcomes appeared to be marginally better than those achieved by salvage with chemotherapy alone (6-9 month median survival) but come at the expense of high incidences of early and late grade 3 or greater toxicity. With the introduction of stereotactic body XRT (SBRT), both retrospective and prospective studies have evaluated the safety and efficacy of this new treatment in the reirradiation setting.115,116 SBRT involves the delivery of greater doses of radiation over 5 or fewer fractions. SBRT offers unique advantages over traditional fractionated schedules, including shorter treatment times and reduced treatment toxicity. For patients with notoriously short survival after treatment, both of these features may improve quality of life. A recent prospective study examined SBRT delivery concurrently with cetuximab.115 Median survival was 10 months, and grade 3 or greater toxicity was limited to 6%. The relatively well tolerated treatment, combined with a short duration of therapy, fares favorably compared with the longer and more toxic definitive XRT courses. Given the early benefits observed with SBRT, there is currently a study under development within RTOG examining reirradiation in combination with immunotherapy.

In summary, both reirradiation and salvage laryngectomy represent viable options for cure upon recurrence of laryngeal cancer. These decisions should be made at a multidisciplinary conference with all SCCHN specialties represented.

Metastatic Disease
Given the limited number of cases, the treatment of metastatic laryngeal cancer has not specifically been studied alone in randomized clinical trials. Thus, the treatment of the disease is adapted from the broader trials of metastatic SCCHN. The primary treatment of metastatic SCCHN is cytotoxic therapy. Decades ago, the primary systemic agents used in this population were methotrexate and bleomycin.117 However, randomized phase 3 studies were published demonstrating the superiority of single-agent cisplatin compared with both methotrexate and bleomycin.118,119 Subsequently, a series of studies examined the combination of cisplatin and other drugs, such as cisplatin and 5-FU (Cis–5-FU). An important study by Jacobs et al compared this combination versus either agent by itself and found statistically significant increases in response rates for the combination (Cis–5-FU, 32%) versus either cisplatin (17%) or 5-FU (13%; P = .035) alone. However, this did not translate into an OS benefit.120 Nonetheless, a platinum-based combination approach became the basic standard of care for the treatment of metastatic SCCHN. Subsequently, taxanes were also found to be effective in treating advanced SCCHN.121 A head-to-head comparison of Cis–5-FU versus cisplatin-paclitaxel was undertaken in the ECOG trial E1395. Two hundred eighteen patients with metastatic SCCHN were randomized to either arm, and OS was the primary endpoint. Laryngeal cancer represented approximately 25% of the study population. No differences were observed in either the response rate or OS. Cis–5-FU had higher levels of hematological and gastrointestinal toxicity.122 Those trials demonstrate that platinum-based chemotherapy, whether combined with 5-FU or a taxane, is a viable treatment option for metastatic laryngeal cancer. Currently, only one targeted agent is approved for the treatment of head and neck cancer: cetuximab. On the basis of promising efficacy in early phase trials in refractory disease,123 the landmark phase 3 EXTREME study (cetuximab in first-line treatment of recurrent or metastatic head and neck cancer) was undertaken, randomizing patients to the standard Cis–5-FU regimen with and without cetuximab in the first-line setting. The trial demonstrated that the addition of cetuximab increased OS, which was the primary endpoint, by approximately 3 months (7.4 months for chemotherapy alone vs 10.1 months with the addition of cetuximab; P = .04). While a subgroup analysis of laryngeal cancer (about 25% of patients) did not demonstrate this benefit of adding cetuximab, the numbers were small, and it is difficult to draw any conclusions based on primary site.124 In conclusion, for fit patients in whom response is paramount, the EXTREME regimen can be considered the standard of care. However, the treatment is associated with significant toxicity, and each patient should be
evaluated carefully before starting the chemotherapy regimen. Additional targeted therapies are under investigation. The E1305 ECOG trial is a multiarm, randomized phase 3 trial examining the role of bevacizumab in metastatic SCCHN. E1305 has 8 treatment cohorts: cisplatin-docetaxel, carboplatin-docetaxel, cis-5-FU, carboplatin-5-FU, and the same regimens with bevacizumab. The primary outcome is OS. Accrual has completed for the study, and data will be analyzed soon. Although the data are still early, immunotherapy, specifically anti-programmed death 1 (anti–PD-1) and programmed death ligand 1 (PD-L1) monoclonal antibodies, have shown great clinical promise in the metastatic setting for patients with SCCHN. By unmasking the tumors from immune surveillance, the patient’s immune system can target the neoplasm for destruction. This approach has already proved effective in melanoma, nonsmall cell lung cancer, and other cancers, and the US Food and Drug Administration has approved these agents. The results of the phase 1B trial with the anti–PD1 antibody pembrolizumab have recently been reported. Patients with PD-L1–positive SCCHN that was either recurrent or metastatic were enrolled, and the drug was well tolerated overall. A response rate of 18% was reported in this heavily pretreated population, with a median PFS of 2 months and a median OS of 13 months. Pembrolizumab has recently been approved by the US Food and Drug Administration for platinum-refractory, metastatic SCCHN. In the recently presented CheckMate 141 study, nivolumab improved survival versus investigators choice for patients with metastatic SCCHN who progressed after platinum-based chemotherapy (OS, 7.5 months for nivolumab vs 5.1 months for investigator’s choice; HR, 0.70; \( P = .01 \)). These drugs hold promise for the metastatic setting, and clinical trials are needed to examine whether these agents could potentially play a role in locally advanced laryngeal cancer and organ preservation as a less toxic alternative to chemotherapy. Research into novel targeted agents holds promise for the treatment of laryngeal cancer. The Cancer Genome Atlas Research Program (TCGA) performed detailed genomic analysis of 279 SCCHN tumors. The results demonstrated multiple potential therapeutic targets, including tyrosine kinase receptors (such as epidermal growth factor receptor \( [EGFR] \), fibroblast growth factor receptor 1 \( [FGFR1] \), and Erb-B2 receptor tyrosine kinase 2 \( [ERBB2] \)), oncogenes (cyclin-D1 \( [CCND1] \), Harvey rat sarcoma viral oncogene homolog \( [HRAS] \)), tumor suppressor genes (tumor protein 53 \( [TP53] \), neurofibromin 1 \( [NF1] \), and the phosphoinositide 3-kinase pathway. Trials targeting these and other pathways are currently ongoing. In addition, research has been done to investigate resistance mechanisms to active treatment, and receptor tyrosine–protein kinase erb-B3 (HER3) signaling has been implicated in cetuximab resistance. Finally, a unique situation in metastatic SCCHN is the treatment of oligometastatic disease, specifically, metachronous pulmonary metastases. Rather than treating this as incurable metastatic disease, in clinical practice, patients with isolated lung metastases often undergo pulmonary metastectomy. The evidence for this approach is limited to retrospective data, but these studies have produced compelling 5-year survival data. A systematic review and meta-analysis was recently published reviewing the literature regarding resection of oligometastatic pulmonary disease. A 5-year survival rate of 29.1% after pulmonary metastectomy was observed in the 11 included studies that reported long-term outcomes. Patients with nonoral SCC had better OS. In practice, any patient with SCCHN, including those with laryngeal cancer, who develops isolated lung metastasis should be evaluated in a multidisciplinary clinic and considered for resection. In summary, platinum-based chemotherapy remains the standard of care for first-line metastatic laryngeal cancer treatment. For a selected population, the EXTREME regimen is a proven regimen. Recently, immunotherapy has been approved in patients who progress on platinum-based therapy and is currently being investigated in the first-line setting.

Conclusions
The care for patients diagnosed with larynx cancer has improved significantly over the last several decades. While larynx cancer shares similarities with other SCCHNs, the unique anatomy involved requires a specialized approach, such as using organ preservation as a primary endpoint for clinical trials. In addition, there are unique survivorship issues related to definitive treatment of larynx cancer. Dysphonia is one of the most common and significantly impacts quality of life. Voice rehabilitation has been shown to improve function post-treatment and should be recommended for all patients with laryngeal cancer. Furthermore, the development of new treatment options, such as immunotherapy, holds great promise for this patient population. Given the complexity of treating larynx cancer, all patients should have a comprehensive evaluation and treatment plan in a multidisciplinary setting. Further research is needed to better understand and target this disease.

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