

An Update on Larynx Cancer

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DOI: <https://doi.org/10.5281/zenodo.8369372>

Published Date: 22-September-2023

Abstract: The exact causes of larynx cancer are not fully understood, but certain risk factors have been identified. • **Tobacco use:** Smoking, as well as smokeless tobacco use, increases the risk of developing larynx cancer. • **Alcohol consumption:** Excessive and long-term alcohol consumption is associated with an increased risk of larynx cancer. The risk is even higher for individuals who both smoke and drink alcohol. **Human papillomavirus (HPV) infection:** Certain strains of HPV, primarily HPV type 16, have been linked to an increased risk of larynx cancer. Common signs and symptoms of larynx cancer may include:

- Hoarseness or voice changes that persist for more than two weeks.
- Persistent sore throat or pain in the throat.
- Ear pain. The diagnosis of larynx cancer involves a thorough examination by a healthcare professional, including a physical examination of the throat and neck. Additional tests such as imaging studies (e.g., CT scan, MRI) and a biopsy may be performed to confirm the diagnosis and determine the stage of cancer. Treatment options for larynx cancer depend on various factors including the stage and location of the cancer, as well as the overall health of the patient. Treatment modalities may include surgery, radiation therapy, chemotherapy, targeted therapy, or a combination of these approaches. It's important for individuals experiencing any persistent symptoms related to the larynx or voice changes to consult with a healthcare professional for a proper evaluation and diagnosis.

Keywords: larynx cancer, smokeless tobacco, HPV infection.

1. 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 pre- sent 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.

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.

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 subglottic extends from this horizontal plane to the end of the cricoid cartilage. The supraglottic is made up of 5 separate subsites, including the suprahyoid epiglottis, infrahyoid 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.

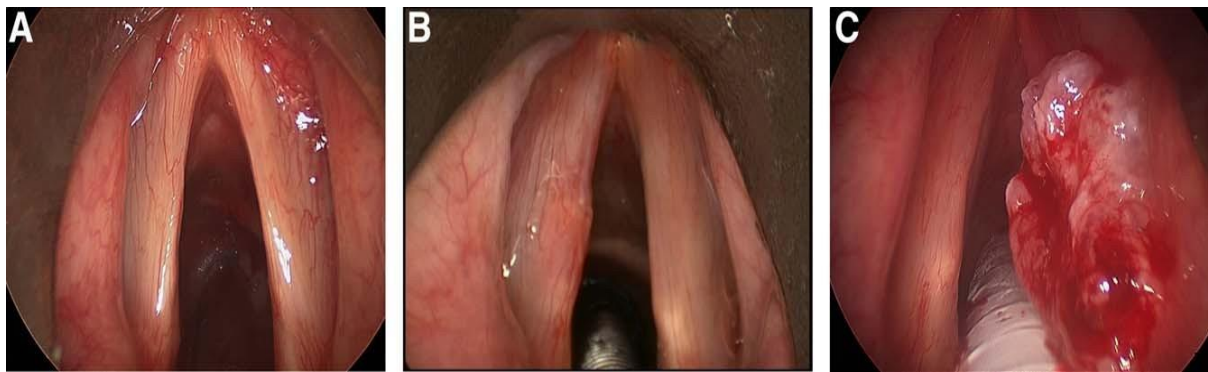


FIGURE 1. Representative Laryngeal Cancers Observed on Examination. (A) Normal larynx. (B) T1 larynx. (C) T2 larynx.

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. 29 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. 30 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 principles³⁰

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 arytenoid, 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 nonfunctional 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.

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.



FIGURE 2. Typical Treatment Setup for a Patient With Locally Advanced Supraglottic Larynx Cancer. A thermoplastic head/neck/shoulder mask is used to immobilize the patient and aids in creating a reproducible treatment setup for a 7-week course of radiotherapy.

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.

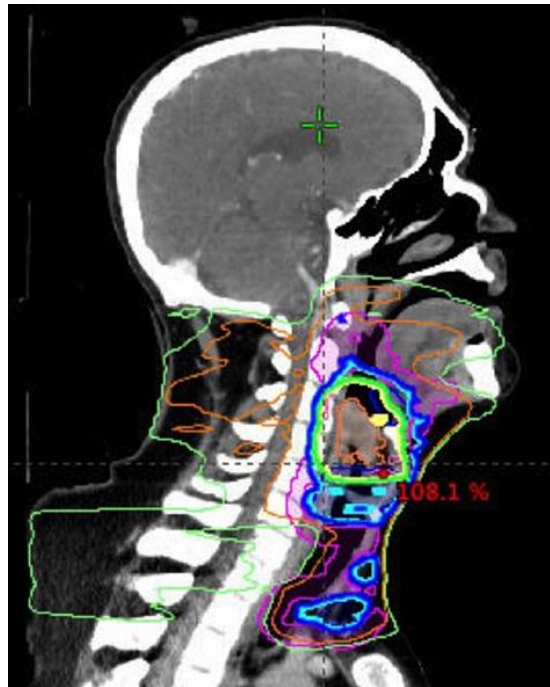


FIGURE 3. Sagittal Image of Treatment Volumes for a T3N2c Squamous Cell Carcinoma of the Supraglottic Larynx. The tissue encompassed by the yellow line is receiving 100% of the prescription dose (70 grays). This patient was unable to receive chemotherapy because of medical comorbidities and was treated with accelerated radiation in 6 fractions per week.

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

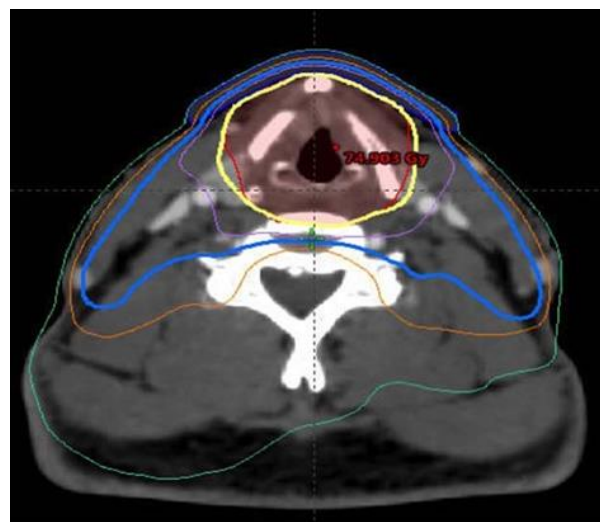


FIGURE 4. Isodose Curves (Regions of Uniform Dose Intensity) for a T3N0 Glottic Cancer. This patient had involvement of the anterior commissure, and a 0.5-cm bolus over the anterior neck was required for the plan-ning target volume to receive the full dose.

Standard radiation treatment volumes for early stage supra- glottic 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.

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 dietitians, 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. 60 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. 61 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 patients weight should be monitored regularly. 62 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 patients treatment decisions regarding their cancer. 63,64 In addition to loss of voice, other potential quality-of-life concerns for patients after surgical resection include issues with swallowing and permanent tracheostomy. 65

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 cis- platin 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 5 . 9846. Importantly, 66 of patients who received chemotherapy were able to preserve their larynx,40 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 5 . 041. 66 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.

TABLE 1. Trials of Larynx Preservation

TRIAL	NAME	PHASE	STUDY ARM	DFS	RATE (TIME POINT)	LARYNGEAL PRESERVATION
VALCSG 1991 ⁴⁰	VA Larynx Cancer Study	3	CF 33 then RT	NR	68% (2 y)	66% (2 y)
Forastiere 2013 ⁶⁷	RTOG 91-11	3	SX then RT	NR	68%	NA
			CF 33 then RT	20.4% (10 y)	39% (10 y)	67.5% (10 y)
			RT 1 C	21.6%	28%	81.7%
Lefebvre 1996 ⁶⁶	EORTC	3	RT	14.8%	32%	63.8%
			CF 33 then RT	32% (5 y)	30% (5 y)	35% (5 y)
Lefebvre 2013 ⁷³	TREMP LIN	2	SX then RT	27%	35%	NA
			ICT 33 then RT 1 C	91.7% (18 mo)	75% (3 y)	95% (3 mo)
			ICT 33 then RT ICET	85.7%	73%	93%

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; TREMPIN, induction chemotherapy followed by either chemoradiotherapy or biotherapy for larynx preservation; VALCSG, the US Department of Veterans Affairs Laryngeal Cancer Study Group.

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. 86 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 69 for patients who received induction chemotherapy, 71 in the concurrent chemotherapy group, and 76 in the RT alone group. 87 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 recurred at 2 years were more likely to die of their disease after salvage laryngectomy. 88 A second study demonstrated 5-year disease-specific survival rates of 70 and 55, for early and advanced-stage cancers, respectively. 89 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.

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. 110,111 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.

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 Cis5-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 Cis5-FU, 32 versus either cisplatin 17 or 5-FU 13 P 5 . 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 Cis5-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. Cis5-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.

2. CONCLUSIONS

The care of patients diagnosed with laryngeal cancer has improved significantly in recent decades. Although laryngeal cancer has similarities with other SCCHNs, the unique anatomy involved requires a specialized approach, such as using organ preservation as a primary endpoint in clinical trials. In addition, there are special survival issues involved in the definitive treatment of laryngeal cancer. Dysphonia is one of the most common and has a significant impact on quality of life. Voice Rehabilitation has been shown to improve function after treatment and should be recommended for all patients with laryngeal cancer.^{132,136,137} Additionally, the development of new treatment options, such as immunotherapy, holds great promise for this patient population. Due to the complexity of laryngeal cancer treatment, all patients require comprehensive evaluation and treatment planning in a multidisciplinary setting. Further research is needed to better understand and target this disease.

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