

ROLE OF ORGAN PRESERVATION IN CARCINOMA LARYNX

Abstract

This chapter explores the role of organ preservation in the context of carcinoma larynx, focusing on both early and locally advanced stages of laryngeal cancer. Laryngeal cancer, a significant malignancy in the head and neck region, presents various challenges in diagnosis and management. The chapter provides insights into the etiology, clinical presentation, and diagnostic workup of laryngeal cancer, emphasizing the importance of accurate assessment through physical examinations and radiographic studies. The primary modalities for treating laryngeal cancer—radiation therapy, surgery, chemotherapy, targeted therapy, radiosensitizers, and immunotherapy—are comprehensively discussed, highlighting their specific applications and potential synergies.

The chapter delves into the evolving landscape of organ preservation strategies, particularly in early-stage disease, where the emphasis is on achieving a cure while optimizing functional outcomes. Various treatment options, including radical radiotherapy, transoral laser surgery, and function-preserving open partial laryngectomy, are explored. The debate surrounding the relative merits of these approaches is discussed in the context of efficacy and functional results for early glottis cancer.

In the context of locally advanced disease, a historical shift in treatment paradigms is explored, with the introduction of induction chemotherapy followed by chemoradiotherapy as an alternative to total laryngectomy. The pivotal findings of the Veteran Affairs trial and its impact on the organ preservation strategy for locally

Authors

Vishwadeep Mishra

Assistant Professor
Department of Radiation Oncology
Rohilkhand Medical College and Hospital
Bareilly, Uttar Pradesh, India.

Sudeep Bisht

Assistant Professor
Department of Radiation Oncology
Rohilkhand Medical College and Hospital
Bareilly, Uttar Pradesh, India.

advanced laryngeal cancer are highlighted.

The conclusion emphasizes the transformative impact of organ preservation strategies on the treatment paradigm for laryngeal cancer. Advances such as transoral laser surgery, radiotherapy, and novel approaches like induction chemotherapy have reshaped therapeutic landscapes, offering comparable survival outcomes to traditional surgical approaches. The chapter underscores the importance of tailoring treatment plans based on individual patient factors, tumour characteristics, and preferences to optimize functional outcomes and overall quality of life.

I. INTRODUCTION

Laryngeal cancer accounted for approximately 0.8% of the total cancer incidence in 2010¹ and emerged as one of the prevalent malignancies affecting the head and neck region². In the same year, the United States documented approximately 12,720 new cases of laryngeal cancer, affecting 10,110 men and 2,610 women. The mortality rate attributed to laryngeal cancer in 2010 was estimated to be around 3,740³.

An analysis of US data spanning from 1992 to 1997 at the time of diagnosis revealed that about 51% of laryngeal cancer cases were localized, 29% had progressed regionally, and 15% had developed distant metastases⁴.

The larynx is anatomically divided into three primary regions: the supraglottic region, the glottic region, and the subglottic region. The supraglottic larynx comprises the epiglottis, false vocal cords, ventricles, aryepiglottic folds, and arytenoids. The glottis encompasses the true vocal cords and the anterior commissure, while the subglottic region is located beneath the vocal cords⁵.

Drawing from US data spanning from 1973 to 1998, it was observed that at the time of diagnosis, approximately 51% of laryngeal cancer cases were localized, 29% had regional spread, and 15% had disseminated to distant sites⁶.

II. ETIOLOGY

Laryngeal cancer exhibits a strong association with cigarette smoking⁷. The vulnerability to tobacco-related cancers impacting the upper digestive and respiratory tracts diminishes in individuals who have quit smoking for 5 years⁸. It is suggested that this risk approximates that of non-smokers after a decade of abstention. This transitional period is characterized by a notable reduction in risk⁹.

The role of alcohol in the initiation of laryngeal cancer remains unclear and lacks definitive evidence¹⁰. Despite ongoing research, the precise contribution of alcohol to the development of laryngeal cancer has not been conclusively established.¹¹

Furthermore, there are certain indications suggesting a potential link between heavy marijuana smoking and the incidence of laryngeal cancer in young patients¹². However, additional research is necessary to establish a clearer understanding of this association¹³.

III. CLINICAL PRESENTATION

Carcinoma originating from the true vocal cords gives rise to early-stage hoarseness. Advanced lesions manifest with symptoms such as a sore throat, ear discomfort, localized pain in the thyroid cartilage, and obstructed airflow¹⁴. Hoarseness does not emerge as a prominent indication of supraglottic larynx cancer until the lesion reaches an extensive stage. Initial symptoms often involve mild pain upon swallowing, akin to a sore throat, and some patients may experience a sensation of a "throat lump."¹⁵ Pain is referred to the ear through the vagus nerve and Arnold's auricular nerve. A discernible neck mass could be an initial

indicator of supraglottic cancer. Subsequent symptoms in the later stages encompass weight loss, malodorous breath, dysphagia, and aspiration.¹⁶

IV. INVESTIGATIONS

1. Physical Examination

- Flexible fiberoptic endoscopes are commonly employed as a valuable complement to the laryngeal mirror examination, enhancing diagnostic capabilities.¹⁷
- The mirror technique frequently provides an optimal view of the posterior pharyngeal wall, aiding in comprehensive assessment.¹⁸
- In complex cases, the utilization of flexible fiberoptic laryngoscopy through nasal insertion proves advantageous.¹⁹
- Assessing vocal cord mobility often necessitates multiple examinations due to intricate distinctions between mobile, partially fixed, and fixed cords. These challenges in differentiation may lead to varying observations between examinations.²⁰
- Indirect signs of pre-epiglottic space invasion may include ulceration of the infrahyoid epiglottis or vallecula fullness. Palpation of diffuse fullness above the thyroid notch and an expanded space between hyoid and thyroid cartilages indicates pre-epiglottic space invasion.²¹
- Changes in the pre-epiglottic fat space, as observed on CT scans, provide insight into alterations resulting from tumor invasion.²²
- Suspicion of postcricoid extension arises when the laryngeal click becomes imperceptible during physical examination. A postcricoid tumor may induce anterior thyroid cartilage protrusion and neck fullness.²³
- Diagnosing thyroid cartilage invasion remains challenging. Localized pain, tenderness upon palpation, and a slight bulge over one thyroid cartilage ala serve as suggestive indicators.²⁴

V. RADIOGRAPHIC STUDIES

Contrast-enhanced CT scanning stands as the preferred method for comprehensive laryngeal examination.²⁵ It is recommended that the CT scan be conducted prior to biopsy to prevent potential confusion between biopsy-induced abnormalities and tumor-related findings. CT is favored over magnetic resonance (MR) imaging due to the prolonged scanning duration of MR that leads to motion artifacts.²⁶ Thin CT slices, ranging from 1 to 2 millimeters in thickness, are acquired at intervals of 1 to 2 millimeters across the larynx, and 3-millimeter intervals for the remainder of the study. The utilization of finer sections (1 to 2 millimeters in the laryngeal region) aids in producing high-quality multiplanar reconstructions. The gantry is strategically positioned to ensure scan slices align parallel to

the plane of the true vocal cords. A complete neck CT scan is also essential to identify non-palpable lymph nodes exhibiting positive characteristics. Notably, in cases of laryngeal cancer with advanced neck disease, positive retropharyngeal nodes may be detected at the time of diagnosis.²⁷ while retropharyngeal adenopathy often evades detection through physical examination, it is typically discernible on CT scans.

Contrast enhancement is instrumental in delineating blood vessels and the thyroid gland. Tumor visibility is often augmented, likely due to associated reactive inflammatory changes. In tandem with CT, MR imaging may be employed to capture subtle exolaryngeal spread or early cartilage deterioration. The precise utility of MR in detecting early cartilage deterioration remains a matter of conjecture. Sagittal MR imaging could be valuable for early detection of base of tongue invasion.

Diagnostic Work up for Carcinoma of The Larynx	
General	History Physical examination Indirect laryngoscopy Direct laryngoscopy Biopsies
Radiographic studies	Chest x-ray films Computed tomography with contrast enhancement (before biopsy) Magnetic resonance imaging (selected cases)

1. Management: There are different types of treatment for patients with laryngeal cancer. Three types of standard treatment are used:

- Radiation therapy
- Surgery
- Chemotherapy

New Types of Treatment are being tested In Clinical Trials.

- Targeted therapy
- Radio sensitizers
- Immunotherapy

2. Three Types of Standard Treatment are Used:

- **Radiation Therapy:** Radiation therapy is a cancer treatment modality that harnesses the power of high-energy x-rays or other forms of radiation to eliminate cancerous cells or inhibit their growth. This therapeutic approach encompasses two distinct methodologies:
 - External radiation therapy entails employing an external machine to direct radiation beams towards the cancer site.²⁸
 - Internal radiation therapy involves utilizing sealed needles, seeds, wires, or catheters containing radioactive substances that are inserted directly into or adjacent to the cancerous tissue.²⁹

The administration of radiation therapy varies based on the cancer type and stage under consideration. In the context of laryngeal cancer, external radiation therapy is the preferred mode of treatment.³⁰

Patients who have ceased smoking prior to commencing treatment may experience enhanced efficacy from radiation therapy. Notably, external radiation targeting the thyroid or the pituitary gland could potentially impact the thyroid gland's functionality. To ensure proper thyroid gland function, a pre- and post-therapy blood test may be conducted to assess thyroid hormone levels.³¹

3. Surgery: Surgical intervention, involving the removal of cancer through operative procedures, is a prevalent approach for addressing all stages of laryngeal cancer. The subsequent surgical methods are employed:

- **Corpectomy:** Surgical removal of solely the vocal cords.³²
- **Supraglottic laryngectomy:** Excision of the supraglottis exclusively.³³
- **Hemilaryngectomy:** Elimination of half of the larynx (voice box), preserving vocal function.³⁴
- **Partial laryngectomy:** Extraction of a portion of the larynx (voice box) while retaining speech capabilities.³⁵
- **Total laryngectomy:** Full excision of the entire larynx, accompanied by the creation of a neck hole to facilitate breathing, known as a tracheostomy.³⁶
- **Thyroidectomy:** The partial or complete removal of the thyroid gland.³⁷
- **Laser surgery:** An innovative surgical technique utilizing a focused laser beam to achieve precise, bloodless incisions in tissues or to eliminate surface lesions, such as laryngeal tumors.³⁸

Following the surgical removal of visible cancer, certain patients may receive postoperative chemotherapy or radiation therapy to eliminate residual cancer cells. Termed adjuvant therapy, this treatment mitigates the risk of cancer recurrence.³⁹⁻⁴⁰

4. Chemotherapy: Chemotherapy serves as a therapeutic regimen designed to impede the proliferation of cancer cells, achieved through the use of medications that either induce cell death or halt cell division.⁴¹ Administered orally, intravenously, or through injection into muscles, these drugs enter the bloodstream, thereby reaching cancer cells dispersed throughout the body (systemic chemotherapy).⁴² Conversely, when chemotherapy is specifically introduced into the cerebrospinal fluid, an organ, or a confined body cavity such as the abdomen, its impact primarily targets cancer cells residing in those localized areas (regional chemotherapy). The mode of chemotherapy delivery is contingent upon the specific type and stage of cancer under treatment.⁴³

5. Targeted Therapy: Targeted therapy emerges as a specialized treatment approach utilizing precise drugs or substances to selectively combat particular cancer cells. This therapeutic strategy generally inflicts less harm on normal cells in comparison to chemotherapy or radiation therapy.⁴⁴

Among the innovative targeted therapy options being explored for laryngeal cancer treatment, monoclonal antibodies stand out. Monoclonal antibody therapy entails

leveraging laboratory-generated antibodies derived from a singular type of immune system cell. These antibodies exhibit the ability to recognize specific substances present on cancer cells or normal substances within the blood or tissues, which might contribute to the proliferation of cancer cells. Upon binding to these substances, the antibodies undertake various actions, including the elimination of cancer cells, inhibition of their growth, or prevention of their metastasis. The administration of monoclonal antibodies involves infusion, either as standalone treatment or as carriers of drugs, toxins, or radioactive materials directly targeted at cancer cells.⁴⁵

One notable example in the realm of laryngeal cancer treatment is cetuximab, a monoclonal antibody. Cetuximab operates by binding to a protein situated on the surface of cancer cells, thereby obstructing their growth and division.⁴⁶

- 6. Radio Sensitizers:** Radiosensitizers are pharmacological agents designed to heighten the susceptibility of tumor cells to the effects of radiation therapy. The synergy created by combining radiation therapy with radiosensitizers can potentially lead to the destruction of a greater number of tumor cells.⁴⁷⁻⁴⁸
- 7. Immunotherapy:** Immunotherapy operates through various mechanisms, including immune checkpoint inhibitors, therapeutic vaccines, and adoptive T cell therapies, all of which contribute to boosting the immune response against cancer cells. As the understanding of the complex interactions between tumors and the immune system deepens, researchers have explored immunotherapeutic interventions to potentially enhance the efficacy of conventional treatments and address challenges posed by advanced or recurrent laryngeal carcinomas.⁴⁹

Recent studies have demonstrated encouraging results, highlighting the potential of immunotherapy in promoting durable responses and prolonged survival rates in certain cases of laryngeal carcinoma. Immunotherapy's capacity to target specific tumor antigens and stimulate the immune system's vigilance against cancer cells offers a novel approach to complement existing treatment modalities.⁵⁰⁻⁵¹

As ongoing research continues to uncover the intricacies of immunotherapy's role in laryngeal carcinoma, it is essential to emphasize the need for tailored treatment strategies that consider individual patient profiles. While immunotherapy holds substantial promise, its integration into clinical practice necessitates a comprehensive assessment of patient factors, tumor characteristics, and treatment goals.⁵²

VI. ORGAN PRESERVATION IN EARLY STAGE DISEASE

1. Treatment options for laryngeal cancer encompass radical radiotherapy (RT), transoral laser surgery (TLS), and function-preserving open partial laryngectomy.⁵³ The selection of treatment is contingent upon various factors, including the extent of disease involving the supraglottis and subglottis, anterior commissure participation, patient preferences, vocational considerations, voice quality, performance status, patient compliance, comorbidities, physician expertise, treatment expenses, and medical bias. All therapeutic modalities exhibit commendable tumor control. A study conducted by the University of

Florida established that rates of local control, voice preservation, and overall survival are comparable across patients treated with RT, TLS, and open partial laryngectomy.

2. The primary objective of treating early glottic cancer is to achieve a cure while optimizing functional outcomes. Presently, radical RT and TLS constitute the established frontline treatments for early glottic cancer.⁵⁴ Given that both modalities yield exceptional and comparable cure rates, an enduring debate revolves around the relative merits of each approach concerning efficacy and functional results in the context of treating early glottic cancer.
3. In conclusion, both RT and conservation laryngeal surgery confer equivalent local control and functional outcomes. The practice of employing narrow margins followed by postoperative RT is not deemed a viable treatment strategy.
4. For patients prioritizing organ preservation, a single-modality treatment approach should be pursued whenever possible. The amalgamation of surgery and radiation therapy should be cautiously considered, as the combination may compromise functional outcomes. Single-modality treatment has demonstrated efficacy for limited-stage disease.

VII. ORGAN PRESERVATION IN LOCALLY ADVANCED DISEASE

About 25 years ago, the conventional approach to managing locally advanced laryngeal cancer involved total laryngectomy coupled with traditional postoperative radiotherapy (RT).⁵⁵ A transformative shift occurred in 1991 with the introduction of induction chemotherapy as a component of larynx-preserving treatment. This pivotal change was marked by the publication of the Veteran Affairs (VA) trial⁵⁶, which determined that patients with cartilage destruction were not suitable candidates for the organ preservation strategy. This groundbreaking trial established the viability of induction chemotherapy followed by RT as an alternative to laryngectomy for managing locally advanced laryngeal cancer.

VIII. CONCLUSION

Organ preservation strategies in early and locally advanced laryngeal cancer have transformed the treatment paradigm by offering patients effective oncologic control while maintaining vital organ function. Transoral laser surgery, radiotherapy, and novel approaches such as induction chemotherapy followed by chemoradiotherapy have reshaped the therapeutic landscape, demonstrating comparable survival outcomes to traditional surgical approaches. These advancements underscore the importance of tailoring treatment plans based on patient factors, tumor characteristics, and individual preferences to optimize functional outcomes and overall quality of life.

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