Clinical and Imaging Assessment, Staging and Decision Making in Laryngeal Cancers

Rakesh Badhe

Assistant Professor, Department of Surgery, Grant Medical College and Sir JJ Group of Hospitals, Mumbai, Maharashtra, India

Correspondence: Rakesh Badhe, Assistant Professor, Department of Surgery, Grant Medical College and Sir JJ Group of Hospitals, 407, B-Wing, Sheetal Apartments, Behind Sheetal Cinema, LBS Marg, Kurla (W), Mumbai-400070, Maharashtra, India

Abstract
Cancer of the larynx has numerous implications—respiration, swallowing and speech, besides disability, vocational, recreational, etc. There are numerous treatment options which have been proven to be effective with randomized controlled trials and meta-analysis. Often, the choice of modality offered to the patient is tailored to the patient's requirements as regard to his/her domestic, vocational and recreational environment. Although we may have a plethora of options for patients belonging to each stage of the disease, there are certain guidelines which must be adhered to in order to prevent any compromise of oncological safety. This article focuses on the planning of the treatment options based on various assessment modalities.

Keywords: Larynx, cancer, treatment.

INTRODUCTION
The larynx is the most complex of the mucosal lined structures of the upper aerodigestive tract. Its important roles in speech, swallowing, and airway protection make the treatment considerations of cancers of this structure varied and controversial. The larynx is bordered by the oropharynx superiorly, the trachea inferiorly, and the hypopharynx laterally and posteriorly. The larynx is comprised of a cartilaginous frame work, and is subdivided vertically by the vocal cords into the supraglottic, glottic, and subglottic subsites. The supraglottic larynx includes the epiglottis, which has both lingual and laryngeal surfaces, the false vocal cords, the arytenoids cartilages, and the aryepiglottic folds. Anterior to the supraglottis is the pre-epiglottis space. This is a complex space with a rich lymphatic network that contributes to the early and bilateral spread of tumors that arise from supraglottic structures to upper, middle, and lower jugular chain lymph nodes.1

The glottic larynx describes the true vocal cords, and where they come together anteriorly at the anterior commissure, as well as where they meet the mobile laryngeal cartilages at the posterior commissure. The glottic larynx extends from the ventricle to 1 cm below the level of the true cords. The vocal cords are lined with stratified squamous epithelia, which contrasts with the pseudo stratified ciliated respiratory mucosa lining the remainder of the larynx. Glottic laryngeal cancers tend to metastasize unilaterally and spread regionally less commonly than supraglottic tumors do. Between the thyroid cartilage and the vocal cord lies the paraglottic space, which is continuous with the pre-epiglottis space. This serves as a pathway for submucosal spread of tumors from the glottis to the supraglottis, or vice versa, which is known as transglottic spread. The subglottic larynx starts 1 cm below the vocal folds and continues to the inferior aspect of the cricoid cartilage. While it is rare for tumors to arise initially in the subglottis, tumors arising in the supraglottic or glottic larynx commonly spread in a “transglottic” fashion to involve the subglottic larynx. Subglottic tumors tend to metastasize to paratracheal (Level VI) as well as middle or lower jugular lymph (Levels III and IV) node groups.1

CLINICAL ASSESSMENT
History Taking2
h/o Main symptoms: Progressive continuous hoarseness. Hoarseness is unremitting and may be fluctuating in very early stage of the disease. Sensation of foreign body in the throat can also occur along with cough and irritation of the throat.
h/o Etiology: H/O tobacco and/or alcohol in any form.
h/o Complications: Pain is a late feature and referred pain to the ear is an ominous sign s/o cartilage invasion. Dyspnoea and stridor indicates obstruction of the airway and usually indicates advanced disease. Rarely patients present with hemoptyis when bleeding occurs from the epiglottis and in late cases symptoms of fetor and/or anorexia may be apparent.
H/o Associated Pathologies: Dysphagia indicates involvement of pharynx and may be a presenting feature of transglottic disease with extension into the pyriform sinus through the paraglottic space.

H/o Treatment Taken: History of any treatment taken for the present disease or in the past for any malignant lesion of the upper aerodigestive tract should be noted.

**Specific Clinical Examination before Definitive Treatment**

All patients require a general ENT examination with particular attention focussed on the examination of the larynx. It is important to examine and assess the mobility of the larynx. Movements of the vocal cords, the arytenoids joints and the whole hemilarynx should be assessed. The mobility of the medial visceral compartment of the neck upon the prevertebral fascia should be assessed along with the presence of laryngeal crepitus. Examination of the neck should be performed for palpable lymphadenopathy and particular attention should be to the first echelon nodal draining areas in levels II, III and IV. In addition, direct extension of tumor should be felt for extending through or posterior to the thyroid cartilage, or in the subglottic area into the thyroid gland.

**ENDOSCOPIC EVALUATION**

- Indirect laryngoscopy/Hopkins telescopy/flexible laryngoscopy: To access cord mobility and the extent of mucosal disease. Any focal abnormality seen should be drawn in the notes.
- Direct laryngoscopy: To define the exact extent of the disease, assess areas not well seen on IDL/Hopkins namely anterior commissure; pyriform fossa and post-cricoid and obtain a biopsy.
- Microlaryngoscopy: For early cord lesions and also to obtain a biopsy.

**RADIOLOGIC INVESTIGATIONS**

- Barium swallow: To map the mucosal extent of disease. Postcricoid involvement well seen.
- Imaging CT/MRI scan: Mandatory before conservative laryngectomy/laryngeal preservation therapy. Gives information regarding:
  1. Extent of disease
  2. Cartilage invasion
  3. Extralaryngeal spread
  4. Para/Pre-epiglottis spaces
  5. Tumor volume
  6. Nodal disease
    - CT scan preferred for cartilage erosion.
    - MRI preferred for soft tissue invasion.

![Fig. 1: Carcinoma of the larynx eroding the thyroid cartilage and of the cord results from neoplastic infiltration or from paralysis of extending into the soft tissue of the neck shown on an axial T section](image1)

![Fig. 2: A gradient-echo FLASH section with gadolinium enhancement showing extension of a laryngeal carcinoma into the base of the tongue](image2)
## AJCC staging of carcinoma of the larynx

<table>
<thead>
<tr>
<th>Site</th>
<th>Subsites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraglottis</td>
<td>Suprahyoid epiglottis</td>
</tr>
<tr>
<td></td>
<td>Infrahyoid epiglottis</td>
</tr>
<tr>
<td></td>
<td>Aryepiglottic folds (laryngeal aspect)</td>
</tr>
<tr>
<td></td>
<td>Arytenoids</td>
</tr>
<tr>
<td></td>
<td>Ventricular bands (false cords)</td>
</tr>
<tr>
<td>Glottis</td>
<td>True vocal cords, including anterior and posterior commissures, including the region 1 cm below the plane of the true vocal folds</td>
</tr>
<tr>
<td>Subglottis</td>
<td>Region extending from 1 cm below the true vocal folds to the cervical trachea</td>
</tr>
</tbody>
</table>

### Primary tumor (T)

<table>
<thead>
<tr>
<th>T-stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed.</td>
</tr>
<tr>
<td>T0</td>
<td>There is no evidence of primary tumor.</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma is in situ</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Supraglottis</th>
<th>T1</th>
<th>Tumor is limited to one subsite of the supraglottis with normal vocal cord mobility.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T2</td>
<td>Tumor invades mucosa of more than one adjacent subsite of the supraglottis or glottis or region outside the supraglottis (e.g. mucosa of base of tongue, vallecula, medial wall of pyriform sinus), without fixation of the larynx.</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>Tumor is limited to the larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (e.g. inner cortex).</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g. trachea, soft tissues of the neck, including deep extrinsic muscle of the tongue, strap muscles, thyroid, or oesophagus).</td>
</tr>
<tr>
<td></td>
<td>T4b</td>
<td>Tumor invades prevertebral space, encases the carotid artery, or invades mediastinal structures.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Glottis</th>
<th>T1</th>
<th>Tumor is limited to the vocal cord(s) (may involve anterior or posterior commissure), with normal mobility.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1a</td>
<td>Tumor is limited to one vocal cord.</td>
</tr>
<tr>
<td></td>
<td>T1b</td>
<td>Tumor involves both vocal cords.</td>
</tr>
</tbody>
</table>

### Neck

<table>
<thead>
<tr>
<th>N-stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Ipsilateral lymph node metastasis ≤ 3 cm</td>
</tr>
<tr>
<td>N2</td>
<td>Lymph node metastasis in a single ipsilateral lymph node &gt; 3 cm and ≤ 6 cm, or in multiple lymph nodes none more than 6 cm (including bilateral nodal metastasis)</td>
</tr>
<tr>
<td>N2A</td>
<td>Lymph node metastasis in single ipsilateral lymph node &gt; 3 cm and ≤ 6 cm</td>
</tr>
<tr>
<td>N2B</td>
<td>Lymph node metastasis in multiple ipsilateral lymph nodes all ≤ 6 cm</td>
</tr>
<tr>
<td>N2C</td>
<td>Lymph node metastasis in bilateral or contralateral lymph nodes all ≤ 6 cm</td>
</tr>
<tr>
<td>N3</td>
<td>Lymph node metastasis &gt; 6 cm</td>
</tr>
</tbody>
</table>

### FACTORS AFFECTING THE CHOICE OF TREATMENT FOR EARLY GLOTTIC CANCERS

#### Tumor factors
- Mobility of vocal cord
- Anterior commissure involvement
• Depth of cord invasion
• Extent of tumor involvement of cord
• Proximity of supraglottic cancer to commissure
• Differentiation of tumor
• Exophytic vs. Endophytic

**Patient Factors**

• Patient wishes
• Medical condition
• Occupation
• Distance from treatment facilities
• Mental status of patient

**Health Care Factors**

• Team approach to treatment
• Skills of surgeon and radiation oncologist
• Modern radiation facilities
• Availability of support services

The following self-explanatory flow diagram shows the management protocols:

**VERTICAL PARTIAL LARYNGECTOMY**

**Advanced Glottic Cancers**

**Stage III – T1-2 N1/T3N0-1**

- Concomitant CT + RT
- Surgery: Vertical Partial Laryngectomy/Near-Total laryngectomy/Total laryngectomy + RT
- Radical radiotherapy in patients with low GC/poor performance status who might not tolerate CT+RT

**Stage IV – T4a N0-1/ T1-4aN2-3**

- Surgery: Near-Total laryngectomy/Total laryngectomy + RT
- Concomitant CT+RT
- Radical radiotherapy in patients with low GC/poor performance status who might not tolerate CT+RT

**NECK NODES**

N0-1 nodes are managed with RT if the primary is treated with RT. If surgery is the primary treatment, modified neck dissection for N1 nodes is recommended.

**Elective Neck Dissection**

Elective treatment of cervical lymph node metastasis is generally recommended when the risk of occult disease is around 15 to 20 percent. Candela and colleagues demonstrated that the nodal groups at risk from laryngeal cancer are at levels II, III and IV. Level I was rarely involved in isolation and level V was never involved alone. This tends to support the removal of levels II, III and IV, the so-called jugular node dissection or lateral neck dissection.

**GLOTTIS**

*Glotis: Aim of treatment: To maximize cure and to preserve voice*
Clinical and Imaging Assessment and Staging of Laryngeal Malignancies

N2-3 nodes need MND/RND with Postoperative chemoradiotherapy. If radiotherapy is the primary treatment, neck dissection follows radiotherapy 4-6 weeks later if residual nodes persist, or electively irrespective of nodal status.

EARLY SUPRAGLOTTIC CANCER

Management depends on nodal disease, pulmonary reserve and exact site and extent of the disease as shown in the following flow diagram.

ADVANCED SUPRAGLOTTIC CANCER

SUPRAGLOTTIS

Surgery is preferred over radiotherapy in cases with
- Large volume disease
- Cartilage erosion

Flow Chart 1

Suprathyroid lesion

- Radical radiotherapy (N₁)
- CTRT (N₁)
- Endoscopic CO₂ laser resection ± interval neck dissection
- SGL with neck node sampling for N₂ and Bil MND for N₁

Infrahypoid lesion

- No pre-epiglottic space invasion
- Radical radiotherapy (N₂)
- CT RT (N₁)
- SGL with neck node sampling for N₂ and Bil MND for N₁

RT = Radiotherapy
CT = Chemotherapy
SGL = Supraglottic laryngectomy

Note: Conservation surgery/Laser preferred in young patient, unwilling to attend 6 weeks of RT.

Figs 4A and B: Diagram demonstrating the extent of resection during supraglottic partial laryngectomy.

Flow Chart 2

Early supraglottic lesion (T₁,₂) with bulky nodal disease (N₂,₃)

- Radiotherapy
  - Concurrent CT + RT
  - Radical radiotherapy

- Surgery

Suprahyoid lesion

- Endoscopic CO₂ laser resection + MND/RND & postoperative RT to primary and neck
  - Good pulmonary reserve
    - SGL with MND/RND + postoperative RT to neck
    - Split therapy: Excision of nodal mass + RT to primary and neck
  - Poor pulmonary reserve
    - Wide field NTL with MND/RND + postoperative RT to neck
    - Split therapy: Excision of nodal mass + RT to primary and neck

Infrahoid lesion

- Endoscopic excision not possible/not available
  - Good pulmonary reserve
    - SGL with MND/RND + postoperative RT to neck
    - Split therapy: Excision of nodal mass + RT to primary and neck
  - Poor pulmonary reserve

Flow Chart 3

Advanced supraglottic lesions T₃, any N

- Radiotherapy
  - Concurrent CT + RT
  - Radical radiotherapy

- Surgery

T₁ due to massive pre-epiglottic space inv.

- Good pulmonary reserve
  - Supraglottic laryngectomy + Bilateral anterolateral (level II, III, IV) neck dissection in NT or MND in N+

- Poor pulmonary reserve
  - Near-total laryngectomy
    - (one mobile cord, at least ½ uninvolved vocal cord, uninvolved interarytenoid and postcricoid)
  - Total laryngectomy

Large volume T₂/T₃
• Bulky nodal disease
• Gross pre epiglottis space involvement
• General condition not permitting concurrent chemoradiotherapy

Management of Neck Nodes
N0
Bilateral neck nodes need to be addressed either with surgery lateral neck dissection (II-IV) or RT.
N1
Bilateral Comprehensive/anterolateral neck dissection (II-IV) + Postoperative RT.
N2-3
Bilateral MND/RND (on side of greater disease) + Postoperative RT.

Small primary (radiocurableT1-2) with large resectable disease (N2-3) may be considered for neck dissection with RT to primary and neck.

SUBGLOTTIS
The treatment of subglottis is same as for the other subsites and depends on the stage. Thus, early stage I and II are treated with single modality radiotherapy, whereas advanced stage III and IV are treated initially by surgery and then followed by radiotherapy.

Indications for Postoperative Radiotherapy

Primary
• Large primary – T3 or T4
• Close or positive margins of excision
• Deep infiltrative tumor
• High grade tumor
• Lymphovascular and perineural invasion

Lymph Nodes
• Bulky nodal disease N2/N3
• Extra nodal extension
• Multiple level involvement.

EVILOUTION OF CHEMORADIOThERAPY AND ORGAN PRESERVATION PROTOCOLS
After the discovery of cisplatin in 1970s, the entire decade of 80s tried for various chemotherapy regimes in Head and neck cancer. The VA study published in 1991 was the first to suggest that chemotherapy (CT) given as Neoadjuvant (NACT) was helpful in making larynx preservation possible without compromising the survival. The following is the study design of the VA trial:

The study confirmed that a treatment strategy involving induction chemotherapy and definitive radiation therapy can be effective in preserving the larynx in a high percentage of patients, without compromising overall survival. The MACH-NC meta analysis proved that there was no significant benefit associated with adjuvant or neoadjuvant chemotherapy. Chemotherapy given concomitantly to radiotherapy gave significant benefits, but heterogeneity of the results prohibits firm conclusions. So, RTOG initiated a study to test this hypothesis and the RTOG91-11 randomized control trial was published in 2003 which proved that in patients with laryngeal cancer, radiotherapy with concurrent administration of cisplatin is superior to induction chemotherapy followed by radiotherapy or radiotherapy alone for laryngeal preservation and loco regional control. Hence, the standard organ preservation protocols in the year 2010 employs concomitant chemoradiotherapy over sequential chemoradiotherapy.

REHABILITATION AND QUALITY OF LIFE ISSUES
Recently, Lazarus retrospectively studied patients being treated with chemotherapy and radiation therapy and found that 40 percent had swallowing difficulties. Clinical evidence of disorders in the pharyngeal phase of swallowing has been demonstrated in patients who have undergone chemotherapy and radiation therapy for tumors of the upper aerodigestive tract. Specifically, reduced laryngeal closure, reduced laryngeal elevation and reduced posterior tongue base movement relative to age-matched controls has been documented.

Certainly, patients who successfully undergo chemo/RT treatments to preserve their larynx have a much improved
quality of life relative to patients requiring total laryngectomy.\textsuperscript{12}

Nevertheless, it should be realized that anatomic preservation does not always result in functional preservation. Very rarely, total laryngectomy is performed in order to restore the ability to swallow when a larynx is incompetent and non functional but clinically free of cancer. When the patients treated in the Veterans Affairs Laryngeal Cancer Study Group were evaluated, an improved long-term quality of life was seen in the cohort who were randomized to chemotherapy and radiation therapy compared to those treated by surgery and radiation therapy.\textsuperscript{11}

Interestingly, this difference was primarily related to freedom from pain, better emotional well-being and lower levels of depression rather than the preservation of the ability to speak.\textsuperscript{12}

Nevertheless, several methods are available to rehabilitate the ability of a patient to communicate following total laryngectomy. Many patients are able to acquire esophageal speech, in which air is swallowed and then used to create a voice. Approximately 2 decades ago a significant advance in the rehabilitation of patients with laryngectomies took place when the tracheoesophageal puncture was developed.\textsuperscript{13}

This is a relatively minor procedure where a fistula is created between the trachea and esophagus. A prosthesis with a one way valve is placed into this fistula, which allows the creation of a lung powered voice. In the motivated patient, this voice can be quite good.

**FUTURE TRENDS**

- Concurrent CT + RT (Cisplatinum based)
- NACT(Taxane based) → Response → CT + RT
- Altered fractionation RT : Hyperfractionated or Accelerated (alone or in combination with CT)
- Molecular targeted therapy(cetuximab) combined with RT or CT or both

The above four competing regimes are at this moment trying to prove each other’s superiority. At this moment based on the available evidence in literature only concurrent CT+RT can be recommended over the other 3 treatment regimes. A dedicated multidisciplinary team (like a tumor board) is strongly recommended in all institutes to test and
prove these new treatment regimens in experimental and clinical settings.

REFERENCES

3. Evidence Based Management Guidelines for Head and Neck Cancer, Volume IV 2005 Published by Tata Memorial Hospital, 2005.
4. Peter D Phelps. chpt. 47, Pharynx and larynx. In David Sutton’s Textbook of Radiology and Imaging