LARYNGEAL PRESERVATION

IN ADVANCED (STAGE III/IV)

CARCINOMA OF THE LARYNX

A dissertation submitted to

the Tamilnadu Dr. M.G.R. Medical University, Chennai,

in partial fulfillment of the requirements for the award of

the degree of

DOCTOR OF MEDICINE (M.D.) IN RADIOTHERAPY

March 2010

CERTIFICATE

This is to certify that this dissertation titled, "**LARYNGEAL PRESERVATION IN ADVANCED (STAGE III/IV) CARCINOMA OF THE LARYNX"** is a bonafide record of the work done by Dr. Jose Paul, in the Division of Radiation Oncology, Cancer Institute (W. I. A.), Chennai, during the period of his postgraduate study for the degree of M.D. (Branch IX – Radiotherapy) from 2007-2010 under my direct guidance and supervision.

Date:

Dr. A. Vasanthan
Professor and Chairman

Place:

Division of Radiation Oncology
Cancer Institute (W.I.A.)
Chennai

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INTRODUCTION

Laryngeal cancer is a malignancy associated with significant psychosocial consequences as impairment of laryngeal function from disease and/or its treatment results in gross disturbances in breathing, speech, and swallowing with profound impact on the patient's lifestyle and self esteem. The successful management of laryngeal cancer is dependent as much upon individualizing the plan of management to suit the particular patient and his/her expectations, as on close co-operation among members of a multidisciplinary team.

EPIDEMIOLOGY

World-wide Distribution

The incidence of laryngeal cancer generally ranges from 2.5 to 17.2 per 100,000 per year. The highest incidence of laryngeal carcinoma has been reported from the Basque Country, Spain (20.4) and the lowest incidence for men from Qidong, China (0.1). Other areas of high incidence include Brazil (15.1) and North Thailand (18.4). European countries with a high incidence in males include France (15.6), Poland (11.9), and Italy (10.1). [1]

INDIAN SCENARIO

The globocan-2002 report showed that in India, carcinoma of the larynx constituted 6.1% of all cancers and is the fifth common malignancy in males while it is comparatively rare in

females. As per the Madras Metropolitan Tumour registry, the incidence rates in Chennai are 3.3 per 100,000 males and 0.6 per 100,000 females.

RISK FACTORS

SMOKING

Smoking is the major risk factor for laryngeal cancer. Tobacco smoke contains more than 30 different carcinogenic agents such as polycyclic aromatic hydrocarbons and nitrosamines. A dose-dependent increase in risk of laryngeal cancer has been demonstrated in case-control studies; patients smoking more than 40 cigarettes a day are 13 times more likely to die of laryngeal cancer than non-smokers. [2] Smoking non-filter cigarettes [3] and/or black (air-cured) tobacco [4] has been linked to higher risk due to the higher exposure to carcinogens. The extent of the role of passive or 'second-hand' smoking in cancer of the larynx is not clear. Apart from the aetiological role of tobacco smoking, its importance in prognosis of patients who develop laryngeal cancer is also relevant. It has been shown that patients who survive 3 years or more after treatment of laryngeal cancer and who continue to smoke are seven times more likely to develop a second primary cancer.

ALCOHOL

Epidemiological studies have proved the long-suspected association between chronic alcohol consumption and the risk of laryngeal cancer. While chronic alcohol consumption is an independent dose-dependent risk factor by itself, in conjunction with chronic tobacco use, the risk multiplies several folds. [5] Alcohol is presumed to act as a co-carcinogen and acts both

locally as well as systemically through various mechanisms at different stages during initiation and promotion. Carcinogenesis is also influenced by the malnutrition and depletion of protective vitamins and minerals that accompany chronic alcoholism. [6]

AGE AND SEX DISTRIBUTION

The age group most commonly affected is 50–70 years, women being affected at a younger age than males. The male to female ratio, which used to be heavily biased towards males at 9:1, has come down to approximately 5:1, due to the increasing trend of smoking among females. In the United States, incidence rates continue to rise at 1.6% per year for white females while the corresponding rate in white males has decreased at 0.6% each year; the rates for both black men and women have been on the increase and the male:female ratio in this population has, therefore, not changed significantly. In patients younger than 35 years, however, the incidence in males and females is equal. [7] Another difference among the sexes is that supraglottic carcinoma is more frequent in women; according to one study 64% of laryngeal carcinomas were supraglottic in women against 46% in men. [8]

ANATOMY

The larynx is divided into the supraglottis, glottis, and subglottis. The supraglottis consists of the epiglottis, the false vocal cords, the ventricles, and the aryepiglottic folds, including the arytenoids. The glottis includes the true vocal cords and the anterior commissure. The line of demarcation between the glottis and supraglottis is the apex of the ventricle. The subglottis is located below the vocal cords and is considered to extend from a point 5 mm below the free margin of the vocal cord to the inferior border of the cricoid cartilage.

The supraglottis has a rich capillary lymphatic plexus; the trunks pass through the pre-epiglottic space and the thyro-hyoid membrane and terminate mainly in the level II lymph nodes; a few drain to the level III lymph nodes. There are essentially no capillary lymphatics of the true vocal cords; as a result, lymphatic spread from glottic cancer occurs only if tumour extends to supraglottic or subglottic areas. The subglottis has relatively few capillary lymphatics. The lymphatic trunks pass through the crico-thyroid membrane to the pre-tracheal (Delphian) lymph nodes in the region of the thyroid isthmus. The subglottis also drains posteriorly through the crico-tracheal membrane, with some trunks going to the paratracheal lymph nodes and others continuing to the inferior jugular chain.

PATTERNS OF SPREAD

LOCAL SPREAD

Suprahyoid Epiglottis

Lesions may grow like a mushroom, producing a huge exophytic mass with little tendency to destroy cartilage or spread to adjacent structures. Others may infiltrate and destroy cartilage and eventually amputate the tip. They tend to invade the vallecula, pre-epiglottic space, lateral pharyngeal walls, and the remainder of the supraglottis.

Infrahyoid Epiglottis

Lesions tend to produce irregular tumour nodules with invasion through the porous epiglottic cartilage into the pre-epiglottic space. They grow circumferentially to involve the false cords,

aryepiglottic folds, and, eventually, the medial wall of the pyriform sinus and the pharyngo-epiglottic fold. Invasion of the anterior commissure and cords is usually a late phenomenon, and subglottic extension occurs only in advanced lesions. Lesions that extend onto or below the vocal cords are at a high risk for cartilage invasion, even if the cords are mobile. [9]

False Cord

Early false cord carcinomas usually have the appearance of a submucosal mass and are difficult to delineate accurately. They extend toward the thyroid cartilage and medial wall of the pyriform sinus. Extension to the infrahyoid epiglottis is common. Initial invasion of the vocal cord may occur submucosally and may be difficult to detect. Vocal cord invasion is often associated with thyroid cartilage invasion. Subglottic extension is uncommon.

Aryepiglottic Fold and Arytenoid

Early lesions are usually exophytic. As the lesions advance, they extend to adjacent sites and eventually cause laryngeal fixation due to invasion of the cricoarytenoid muscle and joint. Advanced lesions invade the base of the tongue, pharyngeal wall, and post-cricoid pharynx.

Vocal Cord

The majority of lesions begin on the free margin and upper surface of the vocal cord and are easily visible. When diagnosed, about two-thirds are confined to one cord, usually the anterior two-thirds of the cord. Extension to the anterior commissure is frequent. As the lesion enlarges, it extends to the ventricle, false cord, vocal process of the arytenoids, and

subglottis. Infiltrative lesions invade the vocal ligament and thyroarytenoid muscles, eventually reaching the thyroid cartilage. As cancers reach the cartilage, they tend to grow up or down the paraglottic space rather than invade cartilage. The conus elasticus initially acts as a barrier to subglottic extension. Advanced glottic lesions eventually invade through the thyroid cartilage or thyro-cricoid membrane to enter the neck and/or thyroid gland.

Subglottic Larynx

Subglottic cancers are uncommon. It is difficult to determine whether a tumour started on the undersurface of the vocal cord or in the subglottis with extension to the cord. They involve the cricoid cartilage early, because there is no intervening muscle layer. Cord fixation is common.

LYMPHATIC SPREAD

Supraglottic Carcinoma

Cancers of the supraglottic larynx are significantly more likely to present with cervical nodal metastasis compared to other laryngeal subsites. The incidence of occult metastasis in supraglottic carcinoma ranges from 20% to 50% depending on the T stage of the primary. The overall rate of nodal metastasis is also related to the T stage. The primary echelons of nodal drainage are levels II, III and IV. In the clinically negative neck, micrometastases were found in 37% of patients with levels II and III being the most frequently involved. Occult metastases at levels I and V were found on pathological examination in only 6% and 1% respectively. [10] Within the supraglottis, tumours of the marginal zone, which includes the

suprahyoid epiglottis and the aryepiglottic folds, have a greater propensity to neck metastases compared to those of the infrahyoid epiglottis. The overall (occult and clinical) incidences of lymphatic metastasis in supraglottic carcinoma according to T-stage are T1 5–25%, T2 30–55%, T3–T4 65–80%. [11]

Glottic Carcinoma

The risk of lymphatic metastases from carcinoma of the true vocal cords is relatively lower than that for supraglottic carcinoma. Since most early glottic cancers are treated using radiation therapy, the incidence of occult cervical metastasis has been reported only for surgically treated higher stage primaries, and ranges from 10% for T3 to 29% for T4 tumours. [12] The overall rate of metastasis is less than 5% for T1, 5–10% for T2, 10–20% for T3, and 25–40% for T4 tumours. [13,14] The primary echelons of drainage are levels II, III and IV. As with other laryngeal tumours, isolated involvement of levels I and V is uncommon. Tumours of the vocal cords rarely metastasize bilaterally or into the contralateral neck except in the presence of extensive supra- or subglottic involvement or invasion of the thyroid cartilage. It is generally agreed that involvement of the Delphian node (which occurs in about 10%) is associated with a poor outcome. [15]

Subglottic Carcinoma

The overall incidence of cervical lymphatic metastasis from primary subglottic carcinoma is less than 20%. The incidence of paratracheal node involvement is, however, much higher at 50–65%. [16, 17] Mediastinal nodes may be involved in a high percentage of cases, with reported incidence of 46%. [18]

DISTANT METASTASIS

The lung is the most commonly affected systemic site followed by the mediastinum, bone and liver. About 15% of patients with supraglottic cancers and 3% with glottis cancers will develop distant metastases within 2 years of diagnosis. [19] The development of distant metastases is generally preceded by locoregional failure, but one study has reported that 11% of supraglottic and 7% of glottic carcinomas developed distant metastases in the absence of local failure or neck recurrence. [20]

PATHOLOGY

Nearly all malignant tumours of the larynx arise from the surface epithelium and therefore are squamous cell carcinoma or one of its variants. Carcinoma-in-situ occurs frequently on the vocal cords. Differentiating among dysplasia, carcinoma-in-situ, squamous cell carcinoma with microinvasion, and true invasive carcinoma is difficult. Most vocal cord carcinomas are well- or moderately differentiated. In a few cases, an apparent carcinoma and sarcoma occur together, but most of these are actually a spindle-cell carcinoma. Verrucous carcinoma occurs in 1% to 2% of patients with carcinoma of the vocal cord. The histological diagnosis is difficult and must correlate with gross appearance of the lesion. Small cell neuroendocrine carcinoma is rarely diagnosed in the supraglottic larynx, but it should be recognized because of its biologic potential for rapid growth, early dissemination, and responsiveness to chemotherapy. Minor salivary gland tumours arise from the mucous glands in the supraglottic and subglottic larynx, but they are rare. [21] Even rarer are chemodectoma, carcinoid, soft tissue sarcoma, malignant lymphoma, or plasmacytoma. Benign chondromas and osteochondromas are reported, but their malignant counterparts are rare.

STAGING

Stage of the disease is the most important prognostic factor in any head and neck cancer.

The TNM staging of laryngeal cancers is as follows:

Primary Tumour (T)

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma *in situ*

Supraglottis

T1 Tumour limited to one subsite of supraglottis with normal vocal cord mobility

T2 Tumour invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, or medial wall of pyriform sinus) without fixation of the larynx

T3 Tumour limited to larynx with vocal cord fixation and/or invades any of the following: post-cricoid area, pre-epiglottic tissues, para-glottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex)

T4a Tumour invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)

T4b Tumour invades prevertebral space, encases carotid artery, or invades mediastinal structures

Glottis

T1 Tumour limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility

T1a Tumour limited to one vocal cord

T1b Tumour involves both vocal cords

T2 Tumour extends to supraglottis and/or subglottis, or with impaired vocal cord mobility

T3 Tumour limited to the larynx with vocal cord fixation, and/or invades paraglottic space, and/or minor thyroid cartilage erosion (e.g., inner cortex)

T4a Tumour invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)

T4b Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Subglottis

T1 Tumour limited to the subglottis

T2 Tumour extends to vocal cord(s) with normal or impaired mobility

T3 Tumour limited to larynx with vocal cord fixation

T4a Tumour invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)

T4b Tumour invades prevertebral space, encases carotid artery or mediastinal structures

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension

N2 Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension

N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension

N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension

N3 Metastasis in a lymph node, more than 6 cm in greatest dimension

Distant Metastasis (M)

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

STAGE GROUPING

I	T1 N0 M0
II	T2 N0 M0
III	T3 N0 M0
	T1-3 N1 M0
IVA	T4a N0 M0
	T4a N1 M0
	T1-4a N2 M0
IVB	T4b Any N M0
	Any T N3 M0
IVC	Any T Any N M1 [22]

SYMPTOMS

The common symptoms of laryngeal cancer are hoarseness, sore throat, stridor, dysphagia and odynophagia. Hoarseness is an early symptom of glottic cancer but may be seen later in advanced supraglottic or subglottic tumours signifying spread to the vocal cord, arytenoid or cricoarytenoid joint. Paraglottic spread can occur submucosally from these sites to produce hoarseness without any mucosal irregularity. Sore throat and dysphagia are more commonly associated with supraglottic tumours and odynophagia signifies involvement of the hypopharynx or base of tongue. Referred otalgia generally indicates base of tongue

involvement, but may also be seen in tumours that have extended into the neck through cartilage. Ulceration and bleeding from exophytic tumours may present as haemoptysis. Dyspnoea and stridor occur with bulky supraglottic tumours or in the presence of vocal cord fixation. A neck mass almost always indicates lymphatic metastasis but may result from direct extension of the tumour into the soft tissues of the neck.

PHYSICAL EXAMINATION

A complete physical examination includes an indirect laryngeal mirror examination, fiberoptic endoscopy, palpation of the neck for any neck nodes and for assessment of the spread of the primary tumour. Flexible fiberoptic endoscopes are now used routinely as a complement to the laryngeal mirror examination. The mirror often provides the best view of the posterior pharyngeal wall. The flexible fiberoptic laryngoscope is inserted through the nose and is useful in more difficult cases. Determination of the mobility of the vocal cords frequently requires multiple examinations because the subtle distinctions between mobile, partially fixed, and fixed cords are often challenging, apparently changing from examination to examination. A cord that appeared mobile to the surgeon before direct laryngoscopy may exhibit impaired motion or even fixation after biopsy. Ulceration of the infrahyoid epiglottis or fullness of the vallecula is an indirect sign of pre-epiglottic space invasion. Palpation of diffuse, firm fullness above the thyroid notch with widening of the space between the hyoid and the thyroid cartilages signifies invasion of the pre-epiglottic space. The pre-epiglottic fat space is a low-density area on the CT scan, and changes resulting from tumour invasion are easily seen. Post-cricoid extension may be suspected when the laryngeal click disappears on physical examination. Post-cricoid tumour may cause the thyroid cartilage to protrude anteriorly, producing a fullness of the neck. Invasion of the thyroid cartilage remains a

difficult clinical diagnosis. Localized pain or tenderness to palpation or a small bulge over one ala of the thyroid cartilage is suggestive. Histopathological diagnosis is by means of biopsy done at the time of direct laryngoscopy. The minority of patients who present in stridor may require an emergency tracheostomy followed by a direct laryngoscopy and biopsy.

IMAGING STUDIES

The appearance of the normal laryngeal cartilages can vary considerably, depending on the degree of ossification and the amount of fatty marrow in the ossified medullar space. In children, the CT density of the laryngeal cartilages is similar to soft tissue. The (endochondral) ossification of hyaline cartilage starts early, in the third decade of life. A high degree of variation exists between individuals. [23] The thyroid cartilage shows the greatest variability in ossification; its ossification may also occur in an asymmetrical fashion. The cricoid and arytenoids show less pronounced variability in ossification. The epiglottis and vocal process of the arytenoids are composed of yellow fibrocartilage; this type of cartilage usually does not ossify.

Squamous cell carcinoma, originating from the mucosal lining, is the most common malignant tumour in the larynx. Mucosal abnormalities can be far better evaluated by the clinician than with even sophisticated imaging methods such as CT or MRI. However, these tumours have the tendency to spread submucosally, and this extension into the deep-lying tissue planes may be difficult to evaluate by clinical examination alone. It is recognized that clinical classification of laryngeal cancer is insufficient when compared with pathologic classification. [24] A marked improvement in accuracy is obtained when the results of CT or

MRI are added to the clinical findings [25, 26] Imaging is mainly of benefit in detecting deep soft tissue extension, such as in the pre-epiglottic space, the laryngeal cartilages, and base of tongue. Findings from imaging studies frequently result in an up classification of the disease. Criteria used for tumour involvement are abnormal contrast enhancement, soft tissue thickening, presence of a bulky mass, infiltration of fatty tissue even without distortion of surrounding soft tissue, or a combination of these. Any tissue thickening between the airway and the cricoid arch is considered to represent subglottic tumour. Several studies have compared the CT/MRI findings with the results of whole organ sectioning after total or partial laryngectomy, showing that both techniques are accurate methods to visualize laryngeal pathology. [27] These studies, correlating whole organ sectioning and imaging, have also revealed some pitfalls. Small foci of mucosal tumour may be difficult to detect or may be invisible, and associated inflammatory and edematous changes may cause over-estimation of the tumour extent. Distortion of adjacent normal structures may mimic involvement by tumour. Gross cartilage invasion can be detected with CT. Due to the large variability in the ossification pattern of the laryngeal cartilages, CT often fails to detect early cartilage invasion. Non-ossified hyaline cartilage shows more or less the same density values as tumour on CT images. Demonstration of tumour on the extralaryngeal side of the cartilage is a reliable, but late sign of cartilage invasion. Asymmetrical sclerosis, defined as thickening of the cortical margin and/or increased medullary density, comparing one arytenoids to the other, or one side of the cricoid or thyroid cartilage to the other side, is a sensitive but non-specific finding on CT. [28] Erosion or lysis has been found to be a specific criterion for neoplastic invasion in all cartilages. Other signs, such as cartilaginous blow-out or bowing, a serpiginous contour or obliteration of the medullary space are not very reliable for cartilage invasion. The combination of several diagnostic CT-criteria for neoplastic invasion of the laryngeal cartilages seems to constitute a reasonable compromise: when extralaryngeal

tumours and erosion or lysis in the thyroid, cricoid and arytenoid cartilages was combined with sclerosis in the cricoid and arytenoid (but not the thyroid) cartilages, an overall sensitivity of 82%, an overall specificity of 79% and an overall negative predictive value of 91% was obtained. [29] MRI was recommended to be the best method to determine the status of the cartilages in the presence of a laryngeal tumour. [30] MRI is a more sensitive technique than CT to detect cartilage abnormalities. Areas of cartilage abnormality will result in an increase in signal intensity on T2-weighted images and contrast-enhanced T1-weighted MRI images. However, due to its high sensitivity for intracartilaginous alterations, MRI will yield, in a considerable number of cases, a false positive result, as distinction between true cartilage invasion and reactive inflammation, edema, fibrosis or ectopic red bone marrow is not possible. [31] Peritumoral inflammatory changes without tumour invasion are common coincidental findings in laryngeal cartilages, especially in the thyroid cartilage. Hence the diagnosis of neoplastic invasion of the thyroid cartilage should be made carefully on MRI.

SELECTION OF TREATMENT MODALITY

The goals of treatment include cure with the best functional result and the least risk of a serious complication. Patients may be considered to be in an early group if the chance of cure with larynx preservation is high, a moderately advanced group if the likelihood of local control is 60–70% but the chance of cure remains good, and an advanced group if the chance of cure is moderate and the likelihood of laryngeal preservation is relatively low. The early group may be treated initially by radiation therapy (RT) or, in selected cases, by partial laryngectomy. The moderately advanced group may be treated with either RT with laryngectomy reserved for relapse, or by total laryngectomy with or without adjuvant postoperative RT. The obvious advantage of the former strategy is that there is a fairly good

chance that the larynx will be preserved. Although some patients may be rehabilitated with a tracheo-esophageal puncture after laryngectomy, only about 20% of patients use this device long term and the majority use an electronic larynx. [32] The advanced group is treated with total laryngectomy and neck dissection with or without adjuvant RT or RT and adjuvant chemotherapy. [33] Recent data indicates that induction chemotherapy probably does not improve the likelihood of loco-regional control and survival, whereas concomitant chemotherapy and RT results in an improved possibility of cure compared with RT alone. [33, 34, 35] There is a subset of patients with high volume, unfavourable, advanced cancers who may be cured by chemoradiation but have a useless larynx and permanent tracheostomy and/or gastrostomy. These patients are best treated with a total laryngectomy, neck dissection, and postoperative RT.

GLOTTIC CANCER

Early Vocal Cord Carcinoma

In most centres, RT is the initial treatment prescribed for T1 and T2 lesions, with surgery reserved for salvage after RT failure. [36] The likelihood of lymph node metastases is low, so the RT portals include only the primary site with a margin. [37] Patients are treated with once daily fractions of 2.25 Gy to 63 Gy for T1–T2A cancers and 65.25 Gy for T2B tumours. [38, 39]

Although hemilaryngectomy or cordectomy produces comparable cure rates for selected T1 and T2 vocal cord lesions, RT is generally preferred. [40] Supracricoid laryngectomy is a procedure designed to remove moderate-sized cancers involving the supraglottic and glottic

larynx. [41] The larynx may be removed with preservation of the cricoids and the arytenoid with its neurovascular innervation, and the defect is closed by approximating the base of the tongue to the remaining larynx. The oncologic and functional results of this procedure in selected patients are reported to be excellent. Transoral laser excision also may provide high cure rates for select patients with small, well-defined lesions limited to the mid-third of one true cord. [42] A small subset of transoral laser surgeons successfully uses this technique in moderately advanced cancers. [43] The major advantage of RT compared with partial laryngectomy is better voice quality. Partial laryngectomy finds its major use as salvage surgery in suitable cases after RT failure.

Moderately Advanced Vocal Cord Cancer

Fixed-cord lesions (T3) may be subdivided into relatively favourable or unfavourable lesions. Patients with unfavourable lesions usually have extensive bilateral disease with compromised airway and are considered to be in the advanced group. Patients with favourable T3 lesions have disease confined mostly to one side of the larynx, have a good airway, and are reliable for follow-up. Some degree of supraglottic and subglottic extension usually exists. The extent of disease and tumour volume, in particular, are related to the likelihood of control after RT. [44] The patient with a favourable lesion is treated with RT or a partial laryngectomy. [45, 46] Most patients are not candidates for the latter and are irradiated. Recent data suggest that the likelihood of loco-regional control is better after some altered fractionation schedules compared with conventional once-daily RT. One preferred fractionation schedule is 74.4 Gy in 62 twice-daily fractions. [47, 33] Additionally, concomitant chemotherapy and RT has been shown to improve the likelihood of cure compared with RT alone. [34] The optimal chemotherapy regimen is unclear. The risk of subclinical regional disease is 20–30% so that

the clinically negative neck is electively irradiated. Follow-up examinations are recommended every 4–6 weeks for the first year, every 6–8 weeks for the second year, every 3 months for the third year, every 6 months for the fourth and fifth years, and annually thereafter. Patients with unfavourable lesions are usually not cured with chemoradiation and those who are cured are less likely to have a functional larynx. Thus, the majority of these patients are best treated with a total laryngectomy.

Advanced Vocal Cord Carcinoma

Advanced lesions usually show extensive subglottic and supraglottic extension, bilateral glottic involvement, and invasion of the thyroid, cricoid, or arytenoid cartilage, or frequently all three. [48, 49] The airway is compromised, necessitating a tracheostomy at the time of direct laryngoscopy in ~30% of patients. Clinically positive lymph nodes are found in about 25–30% of patients. The mainstay of treatment is total laryngectomy and neck dissection, with or without adjuvant RT. The indications for postoperative RT include close or positive margins, subglottic extension (>1 cm), cartilage invasion, perineural invasion, endothelial-lined space invasion, extension of the primary tumour into the soft tissues of the neck, multiple positive neck nodes, extracapsular extension, and control of subclinical disease in the opposite neck. [50, 51] Concomitant chemotherapy is given with postoperative RT for patients with positive margins and/or extracapsular extension. The postoperative RT dose is as follows: negative margins 60 Gy in 30 fractions; microscopic positive margins 66 Gy in 33 fractions; and gross residual disease 70 Gy in 35 fractions. The lower neck receives 50 Gy in 25 fractions; the stoma is boosted to 60 Gy with electrons if there is subglottic extension. Intensity-modulated RT may be used to avoid a difficult low neck match. Preoperative RT is

indicated for patients who have fixed neck nodes, have had an emergency tracheostomy through tumour, or have direct extension of tumour involving the skin.

SUPRAGLOTTIC CANCER

Early and Moderately Advanced Supraglottic Lesions

Treatment of the primary lesion for the early group is by RT or supraglottic laryngectomy, with or without adjuvant RT. [52] Approximately 50% of supraglottic laryngectomies performed are followed by postoperative RT because of neck disease and, less often, positive margins. Transoral laser excision is effective in experienced hands for small, selected lesions. [43] Total laryngectomy is rarely indicated as the initial treatment for this group of patients and is reserved for treatment failures. The decision to use RT or supraglottic laryngectomy depends on several factors, including the anatomic extent of the tumour, medical condition of the patient, physician(s) preference, and inclination of the patient and family. Extension of the tumour to the true vocal cord, anterior commissure, vocal cord fixation, and/or thyroid or cricoid cartilage invasion precludes supraglottic laryngectomy. The procedure may be extended to include the base of tongue if one lingual artery is preserved. Supracricoid laryngectomy is an option for lesions involving one or both vocal cords; at least one arytenoid must be preserved. Vocal cord fixation and/or cartilage destruction are relative contraindications to this procedure.

Overall, about 80% of patients are treated initially by RT. Approximately half of the patients whose lesions are technically suitable for a supraglottic laryngectomy are not suitable for medical reasons (e.g., inadequate pulmonary status or other major medical problems).

Analysis of local control by anatomic site within the supraglottic larynx shows no obvious differences in local control by RT for similarly staged lesions. Primary tumour volume based on pre-treatment CT is inversely related to local tumour control after RT. [44] A large, bulky infiltrative lesion is a common reason to select supraglottic laryngectomy, as local control is probably improved compared to treatment with RT alone.

The status of the neck often determines the selection of treatment of the primary lesion. Patients with clinically negative neck nodes have a high risk for occult neck disease and may be treated by RT or supraglottic laryngectomy and bilateral selective neck dissections (levels II–IV). If a patient has an early-stage primary lesion and N2b or N3 neck disease, combined treatment is frequently necessary to control the neck disease. In these cases, the primary lesion is usually treated by RT and concomitant chemotherapy. CT is obtained 4 weeks after RT, and neck dissection is added if the risk of residual cancer in the neck is thought to exceed 5%; otherwise the patient is observed and a CT is repeated in 3 months. [53] If the same patient were treated with supraglottic laryngectomy, neck dissection, and postoperative RT, the portals would unnecessarily include the primary site as well as the neck. If the patient has early, resectable neck disease (N1 or N2a) and surgery is elected for the primary site, postoperative RT is added only because of unexpected findings (e.g., positive margins, multiple positive nodes, extensive perineural invasion, or extracapsular extension). The primary site and neck are treated to 55.8 Gy at 1.8 Gy/fraction; the involved neck is boosted to 60–70 Gy depending on the risk of residual disease.

Advanced Supraglottic Lesions

Although a subset of these patients may be suitable for a supraglottic or supracricoid laryngectomy, total laryngectomy is the main surgical option. Selected advanced lesions, especially those that are mainly exophytic, may be treated by RT and concomitant chemotherapy with total laryngectomy reserved for RT failures. [35] For patients whose primary lesion is to be treated by a total or partial laryngectomy and who have resectable neck disease, surgery is the initial treatment, and postoperative RT is added if needed. If the neck disease is unresectable, preoperative RT is used.

SUBGLOTTIC CANCER

Primary cancers of the subglottic larynx are extremely rare (about 1% of laryngeal cancers) and generally present in an advanced stage. They involve the cricoid cartilage in the early stage because there is no intervening muscle layer. Partial or complete fixation of one or both cords is common. Misdiagnosis or diagnostic delay is frequent. Apart from squamous cancers, other histological types like minor salivary gland tumours, cartilaginous tumours and soft tissue sarcomas may arise in this region. The subglottis is much more frequently invaded by glottic carcinoma, and these should be distinguished from primary subglottic carcinoma. Early lesions are treated with radiation therapy, and advanced lesions are usually managed by total laryngectomy and postoperative radiation therapy.

TECHNIQUES OF RADIATION THERAPY [54]

RT techniques can be broadly stratified into conventional radiotherapy, 3-dimensional conformal radiotherapy (3D CRT) and intensity-modulated radiotherapy (IMRT). Definition

of the target volume and the normal tissues that must be protected is based on data obtained via treatment planning computed tomography (CT) for both the later techniques. 3D CRT employs forward treatment planning and is much like conventional 2-dimensional RT except that the treatment plans are based on CT-defined 3-dimensional anatomy rather than a 2-dimensional radiograph and surface anatomy. It is still essential to check the relationship of the portals with the surface anatomy on the treatment table. In contrast with 3D CRT, inverse treatment planning is used with IMRT, which may yield a more conformal treatment plan, thus reducing the dose to normal tissues and thereby decreasing the likelihood of acute and late toxicity. One of the major disadvantages of IMRT is that, because the dose distribution is more conformal and the dose gradient much sharper, there may be an increased risk of developing a marginal recurrence. Additional disadvantages may include less homogeneous dose distribution, more beam "on-time" leading to increased total body dose due to scatter, increased treatment planning time for the physicists and radiation oncologists, and increased cost. Therefore, there must be a clear potential advantage for proceeding with IMRT in a particular patient. Some of the advantages are reduction in xerostomia, reduction in dysphagia and avoidance of a difficult low neck match.

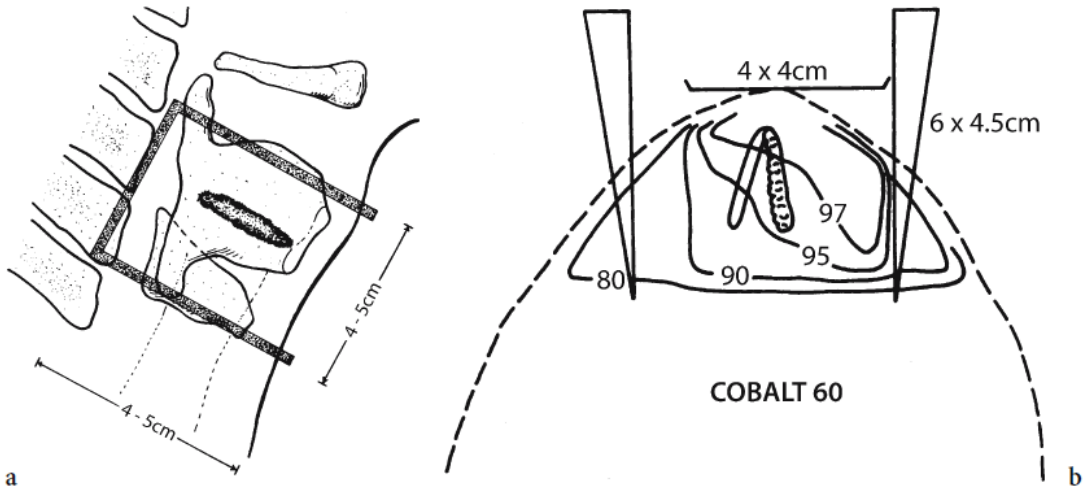
Glottic Larynx

Stage T1–T2

Because the risk of subclinical disease in the cervical lymphatics is remote, the portals are limited to the primary lesion. It is a common practice to treat early vocal cord cancer with a standard field size (5 x 5 cm^2, 6 × 6 cm^2). The patient is treated in the supine position with the neck extended and the head immobilized in an aquaplast mask. The physician at the

treatment machine checks the field each day according to palpable anatomic landmarks. This practice allows the treatment volume to be kept at a minimum, while virtually eliminating the risk of geographic miss. The patient is treated with parallel opposed 6-MV X-ray fields weighted 3:2 to the side of the tumour if it is lateralized. An anterior boost field is usually employed to deliver approximately 5–10% of the total dose to reduce the high dose distribution laterally. ^{60}Co or 4-MV X-ray beams are ideal. The typical borders for a T1 N0 cancer are the middle of the thyroid notch, the bottom of the cricoid cartilage, 1 cm posterior to the thyroid ala, and 1.5 cm anterior to the skin of the anterior neck. The portals may be modified depending on the precise extent of the tumour. The dose fractionation schedule is 63 Gy in 28 once-daily fractions for T1–T2a cancers and 65.25 Gy in 29 fractions for T2b tumours. The prescribed dose is the minimum target dose (MTD). The maximum dose in the irradiated volume is typically less than 103%.

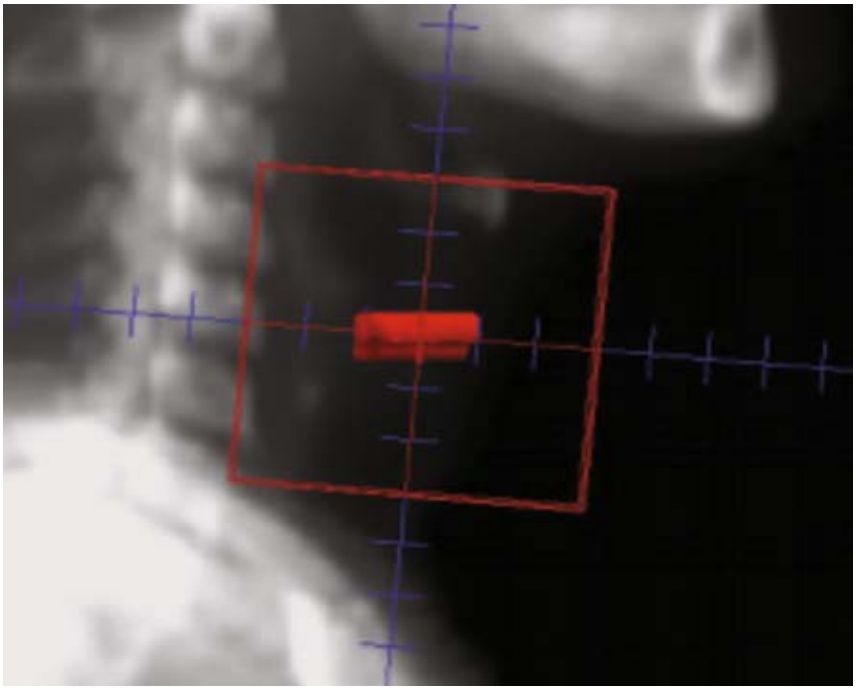
Radiation treatment technique for carcinoma of glottic larynx, stage T1–T2



a For T1 cancer, the superior border of field usually is at mid-thyroid notch (height of notch typically is about 1.0 cm or slightly more in male adults). If ventricle or false vocal cords are minimally involved, top of notch (which corresponds to cephalad portion of thyroid lamina as palpated just off midline) is often selected; more advanced lesions call for greater superior coverage. If only anterior half of vocal cord is involved, posterior border is placed at back of midportion of thyroid lamina. If posterior portion of cord is involved, border is 1.0 cm behind lamina. If anterior face of arytenoid is also involved, posterior border is placed 1.5 cm behind cartilage. If no subglottic extension is detected, inferior border of irradiation portal is at bottom of cricoid arch as palpated at midline. Anteriorly, beam falls off (by 1.5 cm) over patient's skin.

b Three-field technique (two lateral wedge fields and an anterior open field). Lateral fields are differentially weighted to the involved side. Anterior field, which usually measures 4×4 cm^2, is centred approximately 0.5 cm lateral to midline in patients with one cord involved and typically delivers about 5% of total tumour dose (usually on last two treatment days) after treatment from lateral portals is completed. Anterior portal is essentially reduced portal that centres high dose to the tumour. By appropriate field weightings, encompassing the tumour within 95–97% of maximum isodose line is possible.

Simulation film of a 6 × 6 cm^2 field covering the glottis only for treatment of a T1 N0 M0 glottic tumour

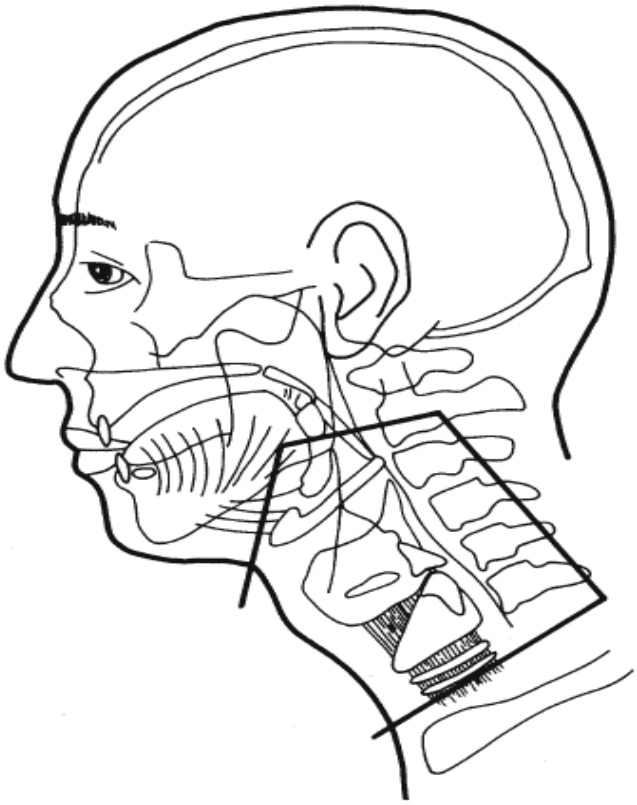


Stage T3–Favorable T4

The initial portals for T3–T4 N0 true vocal cord cancer are as shown in figure. Patients selected for definitive RT have favourable low-volume cancers without significant cartilage destruction. Because of a 20–25% risk of subclinical involvement of the jugulodigastric (level II) or midjugular (level III) lymph nodes, these areas are electively treated with 45.6–50 Gy MTD. A small low-neck portal treats the low jugular (level IV) lymph nodes with a 50-Gy given dose (at Dmax) over a duration of 5 weeks. Primary fields are then reduced, and the treatment is continued to the final tumour dose with fields that are usually slightly larger than for early vocal cord cancer. Most patients receive 74.4 Gy MTD at 1.2 Gy twice a day with a minimum 6-hour interfraction interval. Care must be taken not to underdose tumour that extends anteriorly through the thyrocricoid membrane for patients with favourable T4

tumours who are treated with 6-MV X-rays. Patients with high-volume unfavourable tumours are usually not treated with RT alone or combined with concomitant chemotherapy because of a relatively low probability of cure with a functional larynx.

Radiation treatment technique for carcinoma of glottic larynx, stage T3–T4 N0



Patient is treated in the supine position, and the field is shaped with Lipowitz's metal. Anteriorly, field is allowed to fall off. The entire pre-epiglottic space is included by encompassing the hyoid bone and epiglottis. The superior border (just above angle of mandible) includes jugulodigastric (level II) lymph nodes. Posteriorly, portion of spinal cord must be included within field to ensure adequate coverage of midjugular (level III) lymph nodes; spinal accessory (level V) lymph nodes themselves are at low risk of involvement. Lower border is slanted to facilitate matching with low-neck field and to reduce length of

spinal cord in high-dose field. Inferior border is placed at bottom of cricoid cartilage if patient has no subglottic spread; in presence of subglottic extension, inferior border must be lowered accordingly.

Supraglottic Larynx

RT alone produces high control rates for T1, T2, and low-volume T3 supraglottic cancers. Unfavourable T3 and T4 tumours are often treated with laryngectomy and adjuvant RT; those who receive definitive RT also receive concomitant chemotherapy. The treatment volume is similar, with the exception that the beam generally is not allowed to “fall-off” over the anterior skin surface, except in thin patients, those with very bulky lymphadenopathy that extends anteriorly, or those who have lesions involving the infrahyoid epiglottis near the anterior commissure. Shielding even a few millimeters of the anterior skin, subcutaneous tissues, and lymphatic vessels reduces the likelihood of desquamation (particularly in patients who receive concomitant chemotherapy) and may lessen the risk of serious laryngeal edema. The inferior border of the portal is adjusted according to disease extent. For a false cord or infrahyoid epiglottic cancer, the bottom of the cricoids cartilage is usually chosen. For an epiglottic tip cancer, the lower border may be placed at or above the level of the true cords, depending on the extent and growth pattern (infiltrative versus exophytic) of disease. If the neck is clinically negative and tumour does not extend beyond the larynx, only the level II and level III nodes are treated. If the base of the tongue or pyriform sinus is involved or if neck disease is extensive, the primary portal includes the entire jugular chain, spinal accessory chain (level V) and retropharyngeal nodes. In all situations, the low neck is treated with an anterior en face portal, the size and shape of which vary according to the N-stage and laterality of disease.

Postoperative Irradiation

In this situation, the larynx has been removed. The primary fields are treated through lateral parallel opposed portals to include the anterior and posterior neck from the base of skull to the top of the tracheal stoma. Techniques with either anterior or anterior and posterior portals have the disadvantages of underdosage of lymph nodes at the base of the skull in the region of the mastoid and unnecessary irradiation of a large volume of brain tissue in the posterior cranial fossa. The field is reduced after approximately 45 Gy MTD so that the spinal cord is no longer in the treatment field; the dose to high-risk areas behind the plane of the spinal cord may be boosted with 8- to 10-MV electrons. The low-neck portal includes the stoma. The dose at Dmax in most patients is 50 Gy in 25 fractions. In patients at high risk for recurrence in the low neck (i.e., who have positive level IV nodes), a boost dose is occasionally given through a reduced field. In patients with subglottic extension, the dose to the stoma and peristomal tissues is boosted with electrons, usually 12 MV. The energy selected should be high enough to deliver an adequate dose to the tracheo-esophageal groove (level VI) lymph nodes. Cobalt-60 is the beam of choice because of its build up characteristics. Alternatively, 4-MV or 6-MV X-rays may be employed. A petrolatum gauze bolus is placed on all scars and over drain sites. All scars, suture holes, and drain sites are treated with generous (2–3 cm) margins.

Surgical Methods and Voice Rehabilitation [55]

Stripping of the cord implies transoral removal of the mucosa of the edge of the cord. Cordectomy is an excision of the vocal cord and is usually performed via transoral laser. It is used for well-defined lesions of the midthird of the vocal cord. The major advantages of laser excision are that it requires a day, as opposed to the 5.5 weeks necessary for radiotherapy,

and irradiation may be reserved if the patient develops a second head and neck cancer. Hemilaryngectomy is a partial laryngectomy allowing removal of limited cord lesions with voice preservation. Restrictions include involvement of one cord and up to 5 mm of the opposite cord, partial fixation of one cord, and up to 9 mm of subglottic extension anteriorly and 5 mm posteriorly (to preserve the cricoid cartilage). Extension to the epiglottis, false cord, or interarytenoid area is a contraindication to hemilaryngectomy. One arytenoid may be sacrificed, but the vocal cord must be fixed in the midline to prevent aspiration. The patient must have adequate pulmonary function. More extensive open partial laryngectomies have been described, such as the supracricoid partial laryngectomy.

The last surgical alternative is total laryngectomy with or without a neck dissection. The entire larynx is removed, the pharynx is reconstituted, and a permanent tracheostomy is required. There are several options to accomplish voice rehabilitation after total laryngectomy. Prosthetic devices (e.g., the Singer-Blom valve) have been developed for insertion into a tracheo-esophageal fistula; the prosthesis allows the patient to speak without aspiration. Voice rehabilitation was evaluated in 173 patients who underwent a total laryngectomy and postoperative irradiation at the University of Florida; 118 patients were evaluable 2 to 3 years after treatment and 69 patients were evaluated for 5 years or longer. Methods of voice rehabilitation at 2 to 3 years and 5 years or more after surgery were: tracheo-esophageal speech 27% and 19%; artificial (electric) larynx 50% and 57%; esophageal 1% and 3%; nonvocal 17% and 14%; and no data 5% and 7%, respectively.

RESULTS OF TREATMENT

VOCAL CORD CANCER

Surgical Results

Garcia-Serra et al reviewed 10 series containing 269 patients with carcinoma-in-situ of the vocal cord treated with stripping; the weighted average 5-year local control and ultimate local control rates were 71.9% and 92.4%, respectively. Similarly, 10 series containing 177 patients treated with carbon dioxide laser revealed the following weighted average 5-year local control and ultimate local control rates: 82.5% and 98.1%, respectively. [50]

Thomas et al. reported on 159 patients who underwent an open partial laryngectomy at the Mayo Clinic between 1976 and 1986. Seventeen of 159 patients had in situ lesions; the remaining were T1 invasive carcinomas. Local recurrence developed in 11 patients (7%), and nine eventually required laryngectomy. Ten patients developed recurrent cancer in the neck, and distant metastases were observed in ten patients. [57]

Hemilaryngectomy including the ipsilateral arytenoid was reported by Som for 130 cases of vocal cord carcinoma extending to the vocal process and face of the arytenoid. The cure rate was 74% for 104 patients with T2 lesions and 58% for 26 patients with T3 cancers. [58]

Foote et al. reported on 81 patients who underwent a laryngectomy for T3 cancers at the Mayo Clinic between 1970 and 1981. Seventy-five patients underwent a total laryngectomy and six underwent a near-total laryngectomy; 53 received a neck dissection. No patient

underwent adjuvant radiotherapy or chemotherapy. The 5-year rates of local and regional control, cause-specific survival, and absolute survival were 74%, 74%, and 54%, respectively.

Radiation Therapy Results

Garcia-Serra et al. reviewed 22 series containing 705 patients with carcinoma-in-situ of the vocal cord treated with radiotherapy and observed that the weighted average 5-year local control and ultimate local control rates were 87.4% and 98.4%, respectively.

The results of irradiation for 519 patients with T1 and T2 N0 squamous cell carcinoma of the vocal cord treated by irradiation are as follows: The ultimate local control rates were 98% for T1 lesions and 96% for T2 lesions. The local control rates with larynx preservation rates were 95% for T1 lesions and 82% and 76% for T2A and T2B lesions respectively. The 5-year rates of neck control for 506 patients who received no elective neck treatment for the overall groups and for the subsets of patients who remained continuously disease free at the primary site were: T1, 99% and 100%; T2a, 95% and 97%; and T2b, 87% and 92%, respectively. [38]

The results of definitive radiotherapy for patients with T3 glottic carcinomas are compared to those following surgery in a series of 118 patients treated at the University of Florida. [49] Hinerman et al recently updated the University of Florida experience and reported a 5-year local control rate of 63% for 87 patients with T3 glottic carcinomas. [59] The likelihood of local control after radiotherapy is related to primary tumour volume and cartilage sclerosis. Disease free rates for T4 glottic carcinomas have been reported in the ranges of 40-54% in various series. [60, 61, 62, 63]

Supraglottic Larynx Cancer

The local control and cause specific survival rates after definitive radiotherapy in a series of 274 patients treated between 1964 and 1998 at the University of Florida have been reported as 100% and 100% for stage I, 86% and 93% in stage II, 64% and 81% in stage III, 61% and 50% in stage IVA. The likelihood of local control with a functional larynx is related to tumour volume; those with tumours less than or equal to 6 cc have a more favourable outcome than those with larger primary tumours. [64] Twelve of 274 patients (4%) were reported to have experienced a severe acute or late complications, and two patients (1%) died as a consequence. [59] Lee et al reported on 60 patients who underwent a supraglottic laryngectomy and modified neck dissection at the M. D. Anderson Cancer Centre between 1974 and 1987; 50 of 60 patients (83%) received adjuvant postoperative radiotherapy. Local control was 100% and local and regional control was obtained in 56 of 60 patients (93%). The 5-year disease-free survival rate was 91%. Three of 60 patients (5%) required a completion laryngectomy for intractable expiration. [65] Ambrosch et al reported on 48 patients treated with transoral laser resection for T1 N0 (12 patients) and T2 N0 (36 patients) supraglottic carcinoma. Twenty-six patients underwent a unilateral (11 patients) or bilateral (15 patients) neck dissection. Postoperative radiotherapy was administered to two patients (4%). The 5-year local control rates were 100% for pT1 cancers and 89% for pT2 malignancies. The 5-year recurrence-free survival and overall survival rates were 83% and 76%, respectively. [66]

Results with Induction Chemotherapy followed by Radiation

Decker et al reported on 34 previously untreated patients who received 2 to 3 cycles of cisplatin and fluorouracil: 93% showed an objective clinical response and 63% a complete response. They also pointed out that tumours sensitive to chemotherapy were also sensitive to radiotherapy. The first clinical trial was done by the Department of Veterans Affairs Laryngeal Cancer Study Group (VALSG) on laryngeal cancers and the results marked a turning point in laryngeal cancer treatment. In that trial, 332 patients with laryngeal cancer were randomly divided into 2 groups: one group received complete laryngectomy and the other group underwent 2 cycles of cisplatin and 5-fluorouracil; if they responded well (partial or complete response) they received a third cycle of chemotherapy followed by radiotherapy, and if there was a lack of response, they then underwent a complete laryngectomy. It should be pointed out that 63% of the patients had supraglottic tumours and 57% a fixed hemilarynx. The survival rate was similar in both groups, but two-thirds of the survivors from the chemotherapy group preserved their larynx. [67] A similar trial was done in France with 2 random groups: complete laryngectomy versus 3 cycles of cisplatin and fluorouracil followed by radiotherapy if the clinical response was over 80%, or directly undergoing a complete laryngectomy if the response was lower. In that trial all the tumours were T3 and all had a fixed hemilarynx (only 31% were supraglottic tumours). The 2-year survival rate was significantly better in the surgical group (84% and 69%) but 15 (42%) of the 36 patients from the chemotherapy group did not need surgery. [68]

Results with Concurrent Chemoradiation

The use of chemotherapy and radiotherapy simultaneously is based on the facts that chemotherapy may act as a sensitizer for radiotherapy, while radiotherapy may increase the chemotherapy absorption by the tumour, as well as the spatial co-operation of the two. The MACH-NC meta-analysis findings show that CCR alone increased the 5-year survival rate by 8%, while induction chemotherapy did not improve the survival rate. [35] Forastiere et al assigned patients with laryngeal cancer randomly to 3 groups: induction chemotherapy followed by radiotherapy if there was a response (as with the veterans trial), CCR (cisplatin on days 1, 22, and 43), or just radical radiotherapy. The updated 5 year results in 2006 are as follows: 84% rate of laryngeal preservation in the CCR group, 71% in the induction group (P=.0029) and 66% in the radiotherapy group (P=.0002), with no significant differences among the groups whether for overall survival rates or tumour-free rates. [34] One group from Spain has published results following hyperfractionated radiotherapy and concomitant cisplatin in patients with advanced cancer of the larynx and hypopharynx. There was grade 3-4 mucositis in 68% of the cases. With an average follow-up time of 55 months, the overall 5-year survival rate and the disease-free survival rate were 42% and 39%, respectively. Also, 44% of the patients preserved their larynx. [69] Another group of researchers has presented results of CCR along with 2 cycles of cisplatin and fluorouracil in 127 cases of advanced oral cavity, oropharyngeal, laryngeal, and hypopharyngeal carcinomas. With an average follow up timeframe of 3 years, local control was 89%, without significant differences between locations and an 80% rate of organ preservation. The toxic effects of the treatment were important: 73% of the cases required gastrostomy, 60% lost over 5 kg, and half required additional hospital stays due to a variety of complications. [70]

TREATMENT OF RECURRENCES

Most recurrences appear within 18 months, but late recurrences may appear after 5 years. The latter are likely second primary malignancies. The risk of metastatic disease in lymph nodes increases with local recurrence. [71]

Recurrence after Radiation Therapy

With careful follow-up, recurrence is sometimes detected before the patient notices a return of hoarseness. There is often minimal lymphedema for 1 to 2 months after irradiation, which usually subsides or stabilizes. An increase in edema, particularly if associated with hoarseness or pain, suggests recurrence, even if there is no obvious tumour. Fixation of a previously mobile vocal cord usually implies local recurrence, but the occasional patient has a fixed cord with an otherwise normal-appearing larynx and without evidence of recurrence. It may be difficult to diagnose recurrence if the tumour is submucosal. Generous, deep biopsies are required. If recurrence is strongly suspected, laryngectomy may rarely be advised without biopsy-confirmed evidence of recurrence. Positron emission tomography may be useful to distinguish recurrent tumour from necrosis. Radiation therapy failures may be salvaged by cordectomy, hemilaryngectomy, supracricoid partial laryngectomy, or total laryngectomy. Biller et al reported a 78% salvage rate by hemilaryngectomy for 18 selected patients in whom irradiation failed; total laryngectomy was eventually required in 2 patients. Only two patients died of cancer. These investigators offered guidelines for using hemilaryngectomy: Normal contralateral vocal cord, uninvolved arytenoid, subglottic extension not exceeding 5 mm, and mobile vocal cord. [72] Mendenhall et al reported on 14

patients irradiated for T1 or T2 vocal cord cancers and underwent a hemilaryngectomy after local recurrence and 8 were successfully salvaged. [38]

Recurrence after Surgery

The rate of salvage by irradiation for recurrences or new tumours that appear after initial treatment by hemilaryngectomy is about 50%. Lee et al reported seven successes among 12 patients; one lesion was later controlled by total laryngectomy. [73] Total laryngectomy can be used successfully to treat hemilaryngectomy failures not suitable for radiation therapy. Irradiation can be used occasionally for patients with recurrence in the neck or stoma after total laryngectomy.

Complications of Treatment

Surgical

Repeated stripping of the cord may result in a thickened cord and hoarse voice. Neel et al reported a 26% incidence of nonfatal complications for cordectomy. [74] Immediate postoperative complications included atelectasis and pneumonia, severe subcutaneous emphysema in the neck, bleeding from the tracheotomy site or larynx, wound complications, and airway obstruction requiring tracheostomy. Late complications included removal of granulation tissue by direct laryngoscopy to exclude recurrence, extrusion of cartilage, laryngeal stenosis, and obstructing laryngeal web. The postoperative complications of hemilaryngectomy include aspiration, chondritis, wound slough, inadequate glottic closure, and anterior commissure webs. The postoperative complications of total laryngectomy may

include operative death, haemorrhage, fistula, chondritis, wound slough, carotid rupture, dysphagia, and pharyngeal / esophageal stenosis. The complication rate following supraglottic laryngectomy is about 10%, including fistula formation, aspiration, chondritis, dysphagia, dyspnoea, and carotid rupture. [75]

Radiation Therapy

After irradiation, the quality and volume of the voice tend to diminish at the end of the day. Edema of the larynx is the most common sequel following irradiation for laryngeal cancers. Steroids have been used to reduce edema secondary to radiation effect after recurrence has been ruled out by biopsy. If ulceration and pain occur, antibiotics are used. Soft tissue necrosis leading to chondritis occurs in about 1% of patients. Soft tissue and cartilage necroses mimic recurrence with hoarseness, pain, and edema; a laryngectomy may be recommended in desperation for fear of recurrent cancer, even though biopsies show only necrosis. Mendenhall et al recorded serious complications after definitive radiotherapy in one of 291 patients with T1 true cord cancers and three of 228 with T2 glottic malignancies. [44]

Chemotherapy

Chemotherapy either as part of induction or concurrent regimens is associated with an increased toxicity profile. The commonly used agents are cisplatin, 5-fluorouracil and taxanes (docetaxol and paclitaxel) in various combinations and schedules. The commonly seen toxicities are nausea, vomiting, diarrhoea, myelosuppression, increased rates of mucosits, peripheral neuropathy and allergic reactions. The other toxicities are nephrotoxicity, ototoxicity, fluid retention, cardiac arrhythmias etc.

EVOLVING STRATEGIES

Induction Chemotherapy incorporating Taxanes

Taxanes constitute the newest and one of the most active classes of cytotoxic agents against squamous carcinoma of the head and neck. Both paclitaxel and docetaxel are active as single agents and can be combined with concurrent radiation. Both agents have been evaluated as components of induction chemotherapy. At the University of Chicago, weekly doses of carboplatin and paclitaxel were shown to be well tolerated and highly active.[76] Docetaxel has been evaluated as an induction therapy in combination with 5-FU and cisplatin (TPF) in a number of phase II trials revealing feasibility of administration and encouraging activity. Depending on the number of cycles given as induction therapy, response rates have ranged between 70% and 100%, with complete response rates as high as 50% [77-79]. TAX 323 treated patients with unresectable disease. Single-modality RT to 70 Gy was delivered after induction. Three-year survival was 37% versus 26% (*P*=.02) favouring TPF. TAX 324 compared the same TPF versus PF induction in patients with both resectable and unresectable disease but followed it with radiation and low-dose concurrent carboplatin. [80] The overall 3-year survival rate was 71% versus 30% favouring TPF (*P*=.006), and the 3-year progression-free survival rate was 49% versus 37% (*P*=.004) in favour of TPF. Recent studies have begun to evaluate the effects of induction chemotherapy in the concomitant chemoradiotherapy setting. The rationale for these studies is that concomitant chemoradiotherapy increases survival through better locoregional control, whereas induction chemotherapy increases distant control. The Madrid trial used 3 cycles of concurrent bolus cisplatin (100 mg/m^2) with conventionally fractionated irradiation after either TPF or PF

induction therapy. [81] CR rates favoured TPF 33% versus 14% (*P*=.001). The investigators reported a 2-year survival, 66% versus 61% favouring TPF (*P*=.06).

TARGETED THERAPIES

The success of the phase III randomized study by Bonner et al that showed a significant improvement in survival with the addition of cetuximab to radiotherapy in patients with locally advanced head and neck squamous cell carcinoma (HNSCC) has been hailed as a landmark study for integrating targeted therapy with standard radiation treatment. [82] RTOG 0234 is a recently completed study that examined the feasibility and efficacy of combining cetuximab with different CRT combinations (either concurrent weekly cisplatin or concurrent weekly docetaxel) in high-risk postoperative patients (positive primary site surgical margin and/or involved nodes and/or extracapsular extension). Preliminary toxicity data suggests an acceptable toxicity profile with either cisplatin or docetaxel. [83] Concepts under discussion at the RTOG include phase II trials that would evaluate induction chemotherapy followed by concurrent CRT or cetuximab plus RT. A similar design is being tested by the EORTC using their successful taxane–platinum–5-FU induction platform combined with cetuximab before CRT for locally advanced HNSCC patients. Combining gefitinib with induction chemotherapy before CRT has also been investigated with encouraging early outcomes at 1 year. [84] The experimental arm of the ongoing RTOG trial 0522, “A Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin vs. Concurrent Accelerated Radiation, Cisplatin, and Cetuximab (C225) for Stage III and IV Head and Neck Carcinomas.” This trial will eventually enrol over 700 patients with primary endpoints of survival and locoregional control.

ADVANCES IN RADIOTHERAPY

IMRT has made possible sparing of parotids and has reduced the incidence of xerostomia which has been a long term side effect of head and neck radiation. Another side effect is dysphagia and aspiration. Using current technologies, it is possible to reduce the radiation dose and the volume of critical structures involved in swallowing without compromising the target. Eisbruch et al in 2004 identified the Pharyngeal Constrictors as playing an important role. [85] By decreasing radiation to these structures using IMRT, researchers were able to reduce the incidence of aspiration and swallowing disorders. [86, 87] In a long-term follow-up of these patients, it was noted that dysphagia improved continuously through 2-year follow-up and the rate of grade 2-3 dysphagia was rare (2/107). Notably, pharyngeal transit time has not been lengthened compared with pre-therapy measurements in these patients, representing a potentially important improvement compared with previous data from patients treated with conventional RT.

PET-CT IN TARGET CONTOURING and ADAPTIVE RADIOTHERAPY

FDG-PET appears very promising since it provides smaller, more accurate and reproducible GTVs in comparison with CT or MRI (Daisne et al, 2004). [88] More important, refining the GTV delineation by means of FDG-PET imaging ultimately led to more optimal dose distributions within PTVs and surrounding tissues. (Geets et al) [89, 90] Indeed, the reduction of the primary tumour TVs allowed by such an approach translated into significant decreases of the volumes receiving the highest dose using either 3D-confromal RT [89] or IMRT with helical tomotherapy. [90] The impressive progresses achieved in imaging, dose calculation, and delivery techniques have recently opened avenues for new treatment opportunities such

as adaptive radiation therapy and dose-painting approaches. Adaptive radiation therapy consists of reassessing the tumour volume after a given dose of radiation has been delivered and boosting the residual imaged tumour. Preliminary studies have already demonstrated the feasibility and usefulness of such approaches in pharyngo-laryngeal SCC, and showed significant tumour shrinkages using both anatomical and functional imaging. [90] Selection of small volumes for dose escalation strategies, even more when high dose per fraction is prescribed such as in simultaneous integrated boost IMRT, is mandatory to prevent unacceptable damages of critical structures embedded within the boost volumes. Another appealing approach is the integration of biological information from molecular imaging modalities with the purpose of targeting radiation-resistant regions inside the tumour, such as high clonogen density, proliferation, or hypoxia, hypothesizing that the regionally variable radiosensitivity may require heterogeneous dose distribution to achieve optimal tumour control. This approach, termed “dose painting” by Ling [91], has already been investigated in HNSCC with various tracers (Chao et al, 2001; Lin et al, 2008b; Grosu et al, 2007; Madani et al, 2007; Vanderstraeten et al, 2006). [92-96] If imaging plays a growing role in the target definition in radiotherapy, it should be noted that the macroscopic modalities available will fail to depict subtle tumour extension, and, in particular, the mucosal extent of the disease. As shown by Daisne et al [88], if both CT/MRI and FDG-PET overestimated the GTV in most dimensions, all three imaging modalities failed in accurately assessing the mucosal invasion visualized on the macroscopic specimen. In this context, a careful physical examination, including endoscopy and palpation, still remains the best tool for the appreciation of the mucosal extent of HNSCC.

ORIGIN OF THE PRESENT STUDY

Advanced carcinoma of the larynx has traditionally been treated with total laryngectomy and addition of adjuvant radiation depending on the histopathology. Total laryngectomy is widely recognized as one of the surgical procedures most feared by patients. Of the modalities used for preservation of larynx in advanced carcinoma of larynx, concurrent chemoradiotherapy therapy has been reported to offer a significantly higher chance of larynx preservation than does radiation therapy alone or induction chemotherapy followed by radiation. With the incorporation of salvage total laryngectomy, overall survivals have been reported to be equal to that of an upfront total laryngectomy and adjuvant radiation. For most patients with T3 or T4 disease without tumour invasion through cartilage into soft tissues, a larynx-preservation approach is considered an appropriate, standard treatment option, and concurrent chemoradiotherapy is the most widely applicable approach. [97] This study analyses the treatment methods, results and larynx preservation rates in advanced carcinoma of the larynx in our population.

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AIM OF THE STUDY

The aim of the study was to analyse the treatment methods, outcomes and laryngeal preservation rates achieved in advanced (stage III/IV) squamous cell carcinoma of the larynx.

PATIENTS AND METHODS

One hundred patients registered at the Cancer Institute during the years 2006-2008 with advanced, stage III/IV (as per the AJCC/TNM classification), squamous cell carcinoma of the larynx, who were taken up for treatment with curative intent, were included in this study. Patients who had already undergone treatment and presented with a residue or recurrence, those with distant metastasis, those with histological types other than squamous cell carcinoma as well as those with uncontrolled intercurrent disease (e.g., diabetes, hypertension, thyroid disease) and / or known chronic infection with HIV or viral hepatitis were not taken up for the study.

PRE-TREATMENT WORK UP

- Detailed History
- Complete physical examination and documentation of the TNM staging as per AJCC classification
- Indirect and direct laryngoscopy and biopsy
- Complete haemogram and biochemistry
- Serology (HBsAg, HCV, HIV)
- Chest X-ray and ECG
- Histo-pathological examination
- CT scan of the local part

TREATMENT PROTOCOL

After explaining the nature of the disease, options of treatment and the expected results and obtaining an informed consent the patients were treated by one of the following methods:

- Surgery
- Surgery followed by postoperative radiation
- Concurrent chemoradiation
- Radiation alone.

Surgery was the treatment in 14 patients. Surgery with adjuvant radiation was the modality in 38 patients. 27 patients received concurrent chemoradiation and 21 patients were treated by radiation alone.

Total laryngectomy with addition of neck dissection as and where indicated was the surgical procedure done. Adjuvant radiation was decided after review of histopathological findings. The indications for use of adjuvant radiation were pT4 primary, N2 or N3 nodal disease, perineural invasion, vascular embolism, extracapsular nodal spread and/or positive margins. Concurrent chemo-radiation used radiation concurrently with one of the two following chemotherapy schedules:

Schedule -1

CDDP/5-FU

CDDP 70 mg per m^2 on D1

5-FU 375 mg per m^2 on D1-D3

Cycle was repeated every 3 weeks

Schedule -2

Weekly CDDP

CDDP 40 mg per m^2 on D1 repeated every week to a maximum of 6 cycles

RADIOTHERAPY SCHEDULE

Radiotherapy was given using 6-MV X-rays to deliver a daily tumour dose of 200 cGy/fraction, 5 fractions a week, to a total dose of 60-66 Gy in 6-6½ weeks. Conventional techniques were employed with the help of an X-ray simulator to ensure the accuracy of the fields. The most commonly used field arrangement was two parallel opposing lateral wedged fields. Field reductions and electron boost were used appropriately. Radiation was used as the sole modality in patients who were unsuitable or unwilling for surgery and/or chemotherapy.

FOLLOW UP

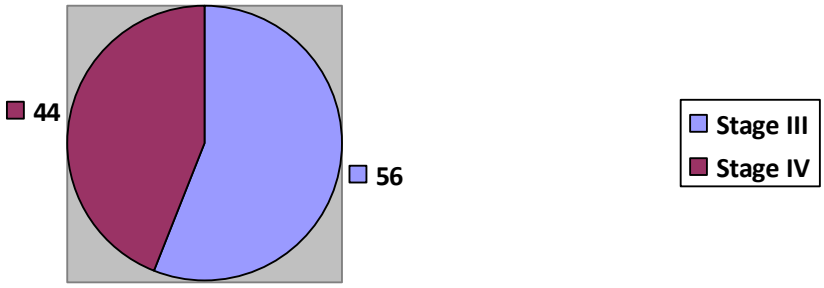
Complete response to therapy was assessed at the first follow-up, at 6 weeks from the completion of treatment, both clinically and endoscopically. Thereafter the patients were

followed up on a monthly basis for the first 6 months, at bi-monthly intervals up to one year and then once every three months up to three years. Patients are followed up once in 6 months for the next two years and annually after five years.

RESULTS

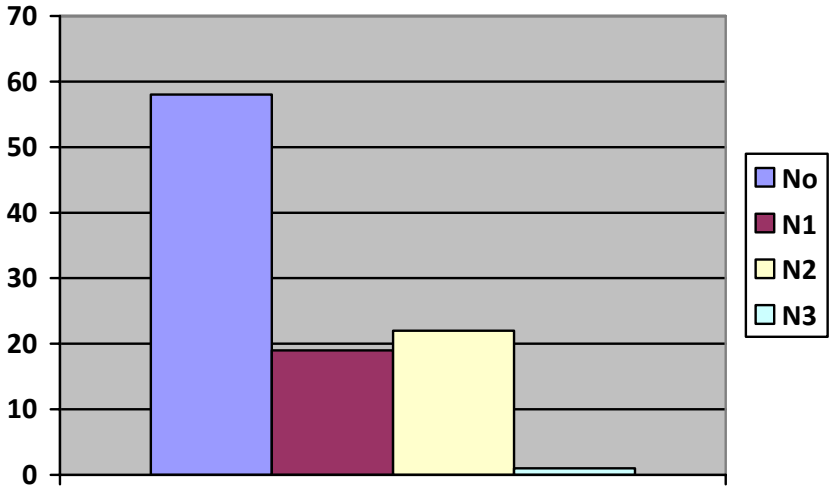
STAGE OF THE DISEASE

There were a total of 100 cases included in this study. On analysis, the stage distribution was as follows: 56 patients had stage III and 44 patients had stage IV disease.



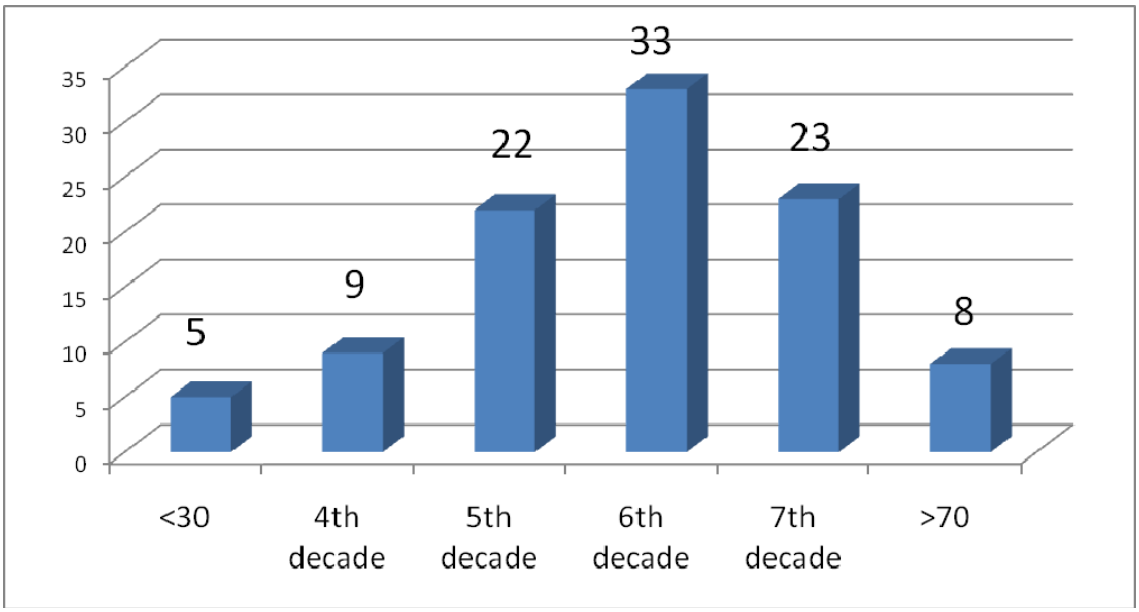
NODAL STAGE

The nodal distribution in the group was: N0 58 cases, N1 19 cases, N2 22 cases and one patient had N3 disease.



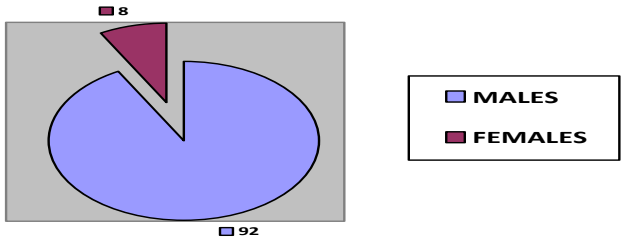
AGE DISTRIBUTION

The age distribution of patients varied between 15 – 83 years and the peak incidence was in the 6th decade.



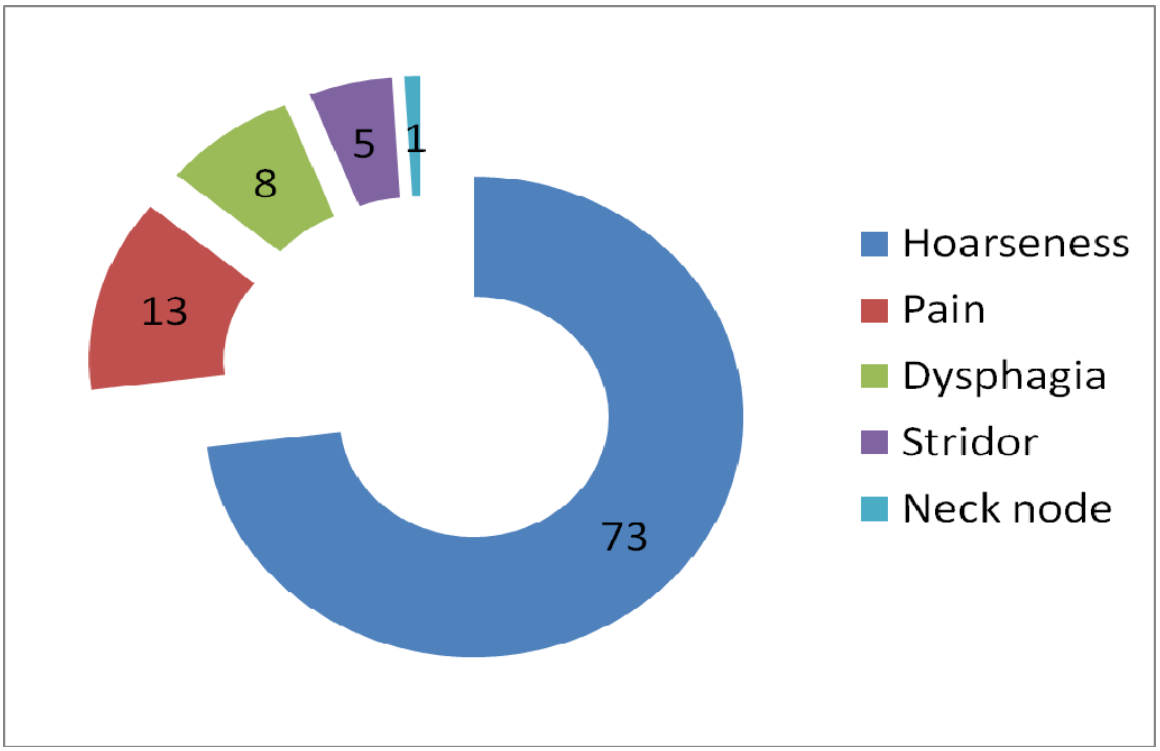
SEX DISTRIBUTION

There were 92 males and 8 females.



SYMPTOMATOLOGY

The predominant symptoms in the patient population included hoarseness which was the predominant symptom seen in 73 patients, pain in 13 patients, dysphagia in 8 patients, stridor in 5 patients, and cervical lymphadenopathy in one patient.



ADDICTION PATTERNS

Smokers constituted 49 of the 100 patients while 31 of the 100 patients in the study were alcoholics.

STAGE CORRELATION

The correlation between the clinico-radiologic pre-operative staging and the pathologic stage for the surgically treated cases were as follows. 5 patients who were pre-operatively staged IV were found to be pathologically stage III. Clinico-radiologic staging in 11 patients was stage III but pathologically they were found to have stage – IV disease . Both stages were the same in 36 patients.

RESPONSE RATES

The results are to be interpreted keeping in mind the fact that the study was not a randomised one. The response rates in the different patient groups are given below.

ANALYSIS ON THE BASIS OF STAGE (III / IV)

COMPLETE RESPONSE RATES

Treatment	Stage – III	Stage – IV
Radiation alone	7/9 (77.8%)	7/12 (58.3%)
Chemoradiation	17/20 (85.0%)	7/7
p-value	ns	0.046

The complete response rates with respect to the type of chemotherapy

Chemotherapy schedule	Complete response	Residue
CDDP/5-FU	20	2
Weekly CDDP	4	1

(p-value ns)

DFS RATES AT ONE YEAR

Clinical Stage-wise

Treatment	Stage – III	Stage – IV
Radiation	7/8* (87.5%)	5/10 (50.0%)
Chemoradiation	16/18* (88.9%)	7/7
Surgery	8/8**	4/6** (66.7%)
Surgery + Radiation	10/15 (66.7%)	15/17 (88.2%)

***** This includes one failure each in the radiation and chemoradiation group which could be salvaged by surgery and both patients are disease free.

** One failure in both stage III and stage IV could be salvaged with radiation.

(p-value for radiation versus chemo-radiation in stage IV was significant (0.025))

(p-value for radiation versus chemo-radiation was not significant in stage III)

The surgically treated cases were analysed as per the pathological stage also and the results are as follows:

Pathological stage-wise

Treatment	Stage - III	Stage - IV
Surgery	11/11*	1/3 (33.3%)
Surgery + Radiation	8/9 (88.9%)	17/23 (73.9%)
p – value	ns	ns

***** This includes two failures salvaged by radiation.

DFS RATES AT TWO YEARS

Clinical Stage-wise

Treatment	Stage - III	Stage - IV
Radiation	3/4 (75.0%)	2/5 (40.0%)
Chemoradiation	7/8 (87.5%)	2/2
Surgery	5/5	3/4 (75.0%)
Surgery + Radiation	8/11 (72.7%)	9/12 (75.0%)

(p-values for radiation versus chemoradiation for stage III and IV diseases not significant)

Pathological Stage-wise

Treatment	Stage - III	Stage - IV
Surgery	8/8	0/1
Surgery + Radiation	6/7 (85.7%)	11/16 (68.8%)
p-value	ns	ns

ANALYSIS ON THE BASIS OF 'T' STAGE (T3 / T4)

The response rates were analysed with respect to the T3 / T4 status also and are as follows**:**

COMPLETE RESPONSE RATES

Treatment	T3	T4
Radiation alone	7/10 (70.0%)	2/3 (66.7%)
Chemoradiation	16/17 (94.1%)	---
p-value	ns	---

DFS RATES AT ONE YEAR

Clincal Stage-wise

Treatment	T3	T4
Radiation	5/7 (71.4%)	2/3 (66.7%)
Chemoradiation	15/16 (93.8%)	---
Surgery	8/8	4/6 (66.7%)
Surgery + Radiation	14/20 (70.0%)	10/11 (90.9%)

(p-value ns for chemoradiation versus radiation)

Pathological stage-wise

Treatment	T3	T4
Surgery	11/11	1/3 (33.3%)
Surgery + Radiation	11/13 (84.6%)	14/18 (77.8%)

(p-value ns)

DFS RATES AT TWO YEARS

Clinical stage-wise

Treatment	T3	T4
Radiation	3/5 (60.0%)	1/1
Chemo-radiation	7/8 (87.5%)	---
Surgery	5/5	3/4 (75.0%)
Surgery + Radiation	11/15 (73.3%)	6/8 (75.0%)

(p-value ns for radiation versus chemo-radiation)

Pathological stage-wise

Treatment	T3	T4
Surgery	8/8	0/1
Surgery + Radiation	9/11 (81.8%)	8/12 (75.0%)

(p-value ns)

LARYNX PRESERVATION RATES

The laryngeal preservation rates achieved were as follows:

Concurrent chemo-radiation – 23/27 (85.2%)

Radiotherapy alone – 13/21 (61.9%)

(p-value (0.06) approaching statistical significance)

DISCUSSION

Laryngeal cancer is one of the most significant malignancies affecting human life because of the significant psychosocial consequences associated with the disease and its treatment. Squamous cell carcinoma is the predominant histological type and approximately 40% of patients will have stage III or IV disease when first evaluated. Most cases of laryngeal cancer are associated with a history of tobacco and/or alcohol use, so the treatment of patients is complicated by medical co-morbidity and the development of second primary cancers. Given the fundamental role the larynx plays in human speech and communication, determining the optimal management of laryngeal cancers must involve consideration of both survival and the functional consequences of a given treatment approach. The potential morbidity of curative treatment is a special consideration when total laryngectomy, either for primary therapy or as salvage treatment, is the recommendation. Total laryngectomy is widely recognized as one of the surgical procedures most feared by patients. Social isolation, job loss, and depression are common sequelae. Pioneering work on patient preferences showed that approximately 25% of healthy individuals interviewed were willing to trade a 20% absolute difference in survival for the opportunity to save their voice. [98] Different voice rehabilitations exist, [99] but many patients are dissatisfied with the results and report associated restrictions in their daily lives. Although the impact of the procedure on voice often receives the greatest attention, the presence of the stoma may adversely affect quality of life as much, if not more. [100] Accordingly, there has been keen interest in the development and refinement of organ preservation therapies, such as radiation therapy alone, the combination of chemotherapy and radiation therapy (concurrent/induction), and function-preserving partial laryngectomy procedures. With all three of these approaches, total laryngectomy is reserved for tumour

recurrence. Concurrent chemoradiotherapy has been reported to offer a significantly higher chance of larynx preservation than does radiation therapy alone or induction chemotherapy followed by radiation. All patients with T1-T2 laryngeal cancer should be treated, at least initially, with intent to preserve the larynx.T1-T2 laryngeal cancer can be treated with radiation or larynx-preservation surgery with similar survival outcomes. Local tumour recurrence after radiation therapy may be amenable to salvage by organ-preservation surgery, but total laryngectomy will be necessary for a substantial proportion of patients, especially those with T2 tumours. Concurrent chemoradiotherapy therapy may be used for larynx preservation for patients with stage II disease. For advanced carcinoma of the larynx , organ-preservation surgery, concurrent chemoradiotherapy, and radiation therapy alone, all with further surgery reserved for salvage, offer potential for larynx preservation. All patients should be evaluated regarding their suitability for a larynx-preservation approach, and they should be informed of these treatment options. No larynx-preservation approach offers a survival advantage compared with total laryngectomy and appropriate adjuvant treatment. A minority of patients with T3-T4 disease will be suitable for specialized organ-preservation procedures, such as a supracricoid partial laryngectomy. The addition of postoperative radiation therapy will compromise anticipated functional outcomes.

Reviewing our data of 100 patients with advanced carcinoma of the larynx, we found that 42% of the patients had clinically positive neck nodes. This is in agreement with data reported in the literature. Lindberg et al reported 55% positive nodes in advanced supraglottic laryngeal malignancies [101] while Mendenhall et al reported 30% incidence in advanced glottic tumours. [38] The age and sex distribution and the addiction patterns also correlated with data in the literature which reports peak incidence in 50-70 years, a pre-dominant male predilection and association with smoking and alcohol. [102] Our study had 78 of the 100

cases in the age 50-70, 92/100 cases being males. With regards to the presenting symptoms the hoarseness was the presenting symptom in 73%, followed by pain, dysphagia, stridor and cervical lymphadenopathy which also correlate well with the reported data. [8] The correlation between pre-operative clinico-radiologic stage was 69% in our study, while the reported rates in the literature vary between 73% and 80%, with studies using MRI having higher accuracy. The most common error reported in the literature was in under-diagnosing a T4 disease which has been the most common error in our study also. [27]

The complete response rates achieved in stage III were 77.8% and 85.0% with radiation and chemoradiation but this improvement did not attain statistical significance. The response rates in stage IV were 58.3% and 100% respectively. The p-value was statistically significant (0.046).

The DFS rates at 1 year in stage III were 87.5% and 88.9% respectively with radiation and chemo-radiation; 100% and 88.9% for surgery alone and surgery with adjuvant RT respectively, when analysed by their pathological stage. In stage IV disease, the rates were 50% and 100% for radiation and chemo-radiation while the rates for surgery alone and surgery with adjuvant RT were 33.3% and 73.9% respectively. Statistical significance was achieved only for radiation versus chemo-radiation in stage IV (p-value-.025).

The DFS rates at 2 years were 75.0%, 87.5%, 100% and 85.7% in stage III with radiation, chemo-radiation, surgery and surgery with adjuvant radiation, respectively. The corresponding rates were 40%, 100%, and 68.8% for radiation, chemo-radiation and surgery with adjuvant radiation in stage IV. None of the values at 2 years attained statistical significance.

The results, when T3 and T4 cases were analysed separately also, showed similar pattern with no statistical significance.

The chemotherapy schedule used did not have any significant impact on the complete response rates.

The larynx preservation rates achieved across the stages were 85% with chemo-radiation and 61% with radiation alone. These results are comparable with data reported in the literature. Forastiere et al, in the RTOG 91-11 trial, reported 88% and 70% larynx preservation rates in the concurrent chemoradiation group and radiation group respectively. [34] The updated 5-year results were reported as 84% and 61%. Lee et al, from MSKCC, reported 89% larynx preservation rates in locoregionally advanced carcinomas of the larynx and hypopharynx and an overall survival of 63% with concurrent chemoradiation. [103] Lambert et al reported 63% and 73% overall and disease-free survival at 3 years in patients treated with concurrent chemoradiation for locoregionally advanced carcinoma of larynx and hypopharynx. [104]

The larynx preservation rates reported are summarised in the following table:

Treatment	**Forastiere et al**	**Lee et al**	**Cancer Institute**
Radiation	70%	---	61%
Chemo-RT	88%	89%	85%

The results from this study show that concurrent chemoradiation is an effective modality of treatment for advanced laryngeal cancer without any detrimental effect on survival while preserving the larynx in our population. Radiation alone can be an option for patients not suitable for chemotherapy but who are extremely motivated for larynx preservation but with lesser results. Randomised trials with larger number of patients are required to confirm the findings.

CONCLUSION

Concurrent chemoradiation offers comparable oncological outcomes for patients with advanced carcinoma of the larynx while preserving their voice and thus offering a better quality of life.

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