

Advanced Laryngeal Carcinoma: Surgical and Non-surgical Management Options

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In this article advanced laryngeal carcinoma is defined as clinical stage III and clinical stage IV malignant tumors arising from the laryngeal epithelium. This advanced stage depends on tumor size, presence of neck disease, or both (Box 1) [1].

A further elaboration of the definition would include the term “anaplastic or undifferentiated” in the overall description. According to one study, these tumors account for 46.03% of all squamous cell cancers that occur in the larynx [2] and therefore 0.46% of all malignancies in humans [3].

Classification

Classification is fundamental for the understanding of epidemiology, for therapeutic decision-making, and for preemptive prognosis. Although Broder’s grading [4] is still mentioned in histopathologic reports, the TNM classification [1] as accepted by the International Union against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) in 1978 is more pertinent and therefore is widely followed. TNM staging considers anatomic distribution and T-staging together with nodal status and presence or absence of distant metastasis.

The larynx is divided into three regions for studying anatomic distribution of laryngeal carcinoma: supraglottic, glottic, and subglottic. The glottic region extends from the floor of the ventricles to the undersurface of

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Box 1. Staging of advanced laryngeal tumors according to the American Joint Committee on Cancer Staging [1]

Stage III tumors

T1, N1, M0

T2, N1, M0

T3 N0 M0

T3, N1, M0

Stage IV tumors

Stage 4 A

T4 N0 M0

T4, N1, M0

Any T, N2, M0

Stage 4 B

Any T, N3, M0

Stage 4 C

Any T, Any N, M1

the true vocal folds. The supraglottic and subglottic regions lie above and below the glottis, respectively. The supraglottic region is further divided into an upper epilarynx and a lower supraglottis. The epilarynx is comprised of the suprahyoid epiglottis, the right and left arytenoids, and the two aryepiglottic folds. The supraglottis consists of the infrahyoid epiglottis, the laryngeal ventricles, and the two false vocal cords. The distribution of laryngeal carcinoma among these subsites is 76% in the glottic area, 19% in the supraglottic area, and 5% in the subglottic region. The most common site for carcinoma to develop is the vocal cords (73%) [3]. The aryepiglottic folds and false vocal cords follow suit with 7% and 5%, respectively. The anterior commissure is involved in 2% of cases and is perhaps the most dangerous area in which cancer occurs, followed by the subglottic area. At the anterior commissure a thin fibrous tendon connects a very thin laryngeal submucosa directly with the thyroid cartilage. The intervening tissue barrier consisting of Reinke's membrane and the conus elasticus is missing. As a result even a T1 neoplasm involving this area can frequently invade the cartilaginous laryngeal frame in the midline [5] and become a T4 tumor. The subglottic area is not easily visible to the examining eye. Also, subglottic tumors present late, usually after the vocal cords are involved, and metastasize to rather inaccessible mediastinal lymph glands.

In 1954 the UICC began trying to formalize a TNM-based classification of malignant tumors, including those that affect the larynx. Not until 1978 was a consensus developed with the AJCC, and a classification of laryngeal cancers was finalized. This classification has since been updated [1]. The main denominators in this classification are the letters *T*, which stands for

tumor size, N , which denotes regional lymph node secondary tumors, and M , which indicates tumor metastasis to distant areas below the clavicle or above the skull base. Further details of the classification can be found in the American Joint Committee on Cancer *Staging Manual* (sixth edition) [1].

Treatment

During the last 10 years, there has been a complete reconsideration of the options for treating advanced laryngeal cancer. At one time the only options considered were radiotherapy or surgery [6]. Surgery was considered efficient but mutilating [7]. Billroth of Vienna did the first total laryngectomy for cancer in 1873, but the operation was not widely adopted until the next century because it was mutilating and fraught with complications [8]. Undoubtedly it gave efficient local site control, but it resulted in the loss of laryngeal functions and airway integrity [9]. Radiotherapy preserved the larynx, but it required mutilating laryngeal surgery for salvage. Later came the era of surgery in combination with postoperative radiotherapy. Often concurrent or induction chemotherapy was added to this regimen to improve the results [10]. This approach gave most patients a longer disease-free survival, but the loss of laryngeal functions still remained. As a result a new paradigm was developed in which organ preservation replaced all other considerations. To preserve function, surgical techniques aimed at conserving functionally important tissues were developed. These new operations, usually in combination with radiotherapy or chemotherapy, could obtain the desired oncologic and functional outcomes in terms of speech, swallowing, respiration, and airway integrity [12]. At the same time organ-preserving chemotherapy and radiotherapy protocols were created.

The present scenario is therefore encouraging. Palliative treatment is given to the approximately 11% of patients who initially present with distant metastases. For the remaining 89%, a large spectrum of new techniques [11] offers disease clearance, functional preservation, and, in combination with radiotherapy and chemotherapy, longer disease-free survival. The standard surgical treatment as practiced today consists of induction chemotherapy followed by conservation surgery and postoperative radiotherapy.

Palliation

Palliation aims at suppressing the cancer and its symptoms without any real intent to cure. It is indicated for terminal cases and for patients who refuse other forms of treatment. In advanced laryngeal cancer, palliation consists of

1. Pharmacologic treatment of pain. In advanced laryngeal cancer, some patients complain of pain. This pain is usually referred to the ipsilateral ear but may also be felt elsewhere in the head and neck. In most patients

therapeutic doses of narcotics or nonsteroidal anti-inflammatory drugs given either by mouth or parenterally are effective. Sometimes, a supplement of some sedative drug (eg, diazepam) may also be required. Rarely, pain relief requires more intense measures such as removal of larynx, removal of nodal metastases in the neck, radiotherapy, and chemotherapy.

2. Tracheostomy. Tracheostomy is indicated to obviate dyspnea, which may be distressing in some cases. Another reason for tracheostomy is pulmonary toilet. With a massive growth in the larynx, the patient may not be able to cough and therefore needs assistance to clear secretions.
3. Radiotherapy. Radiotherapy for palliation is time honored. It is given locally, focusing on the area of symptoms. Doses are given in smaller fractions and shorter courses unless they are tolerated well.
4. Chemotherapy. Chemotherapy is also used for palliation. Usually a combination of chemotherapeutic agents (eg, cisplatin plus 5-fluorouracil or methotrexate plus bleomycin) is used. The expected outcomes include regression of lesions and relief of symptoms. Significant side effects may occur.

Curative treatment

Organ preservation is the mainstay of modern curative treatment. It encompasses all modalities and options that satisfy this principle and preserve laryngeal functions. As outlined in **Box 2**, these techniques include radiotherapy, chemotherapy, and surgical approaches that have been refined during the last decade or so.

Vertical partial laryngeal resections are performed through a laryngofissure. Epiglottectomy and supraglottic partial laryngectomy (SGPL) are done through an anterior pharyngotomy. More recently this type of conservation surgery has also been performed through transoral laser surgery [12]. Supracricoid partial laryngectomy (SCPL) entails resection of the thyroid cartilage, pre-epiglottic space, paraglottic space, and one of the two arytenoids. The epiglottis may or may not be resected. The hyoid bone, cricoid cartilage, and the remaining arytenoid are preserved. A crico-hyoidopexy or crico-hyoidoepiglottopexy is used for closure of the larynx.

Indications for a SCPL are [21]

1. Selected T1 supraglottic tumors involving the infrahyoid epiglottis or ventricle
2. Selected T2 transglottic and supraglottic tumors
3. Selected T3 transglottic and supraglottic tumors with true vocal cord fixation or limited pre-epiglottic space invasion, without arytenoid involvement
4. Selected T4 transglottic and supraglottic tumors with limited invasion of the thyroid ala without extension through the outer perichondrium

Box 2. Curative treatment for laryngeal carcinoma

1. Vertical partial resection
 - Corpectomy
 - Frontal partial laryngectomy
 - Lateral partial laryngectomy
 - Frontolateral partial laryngectomy
2. Horizontal partial resection
 - Epiglottectomy
 - Supraglottic partial laryngectomy
3. More extensive partial resection
 - Supracricoid partial laryngectomy
 - Near-total laryngectomy

Contraindications for SCPL are [21]

1. Arytenoid cartilage fixation. Because of cricoarytenoid joint fixation, the cricoid cartilage cannot be spared.
2. Infraglottic extension of tumor more than 10 mm anteriorly or 5 mm posterolaterally
3. Extensive invasion of the pre-epiglottic space
4. Tumor extending to the hyoid bone superiorly or the cricoid cartilage inferiorly. Reconstruction will be almost impossible if these structures are removed.
5. Extralaryngeal tumor spread

Total laryngectomy in conjunction with procedures such as tracheoesophageal puncture is now restricted to T4 lesions not amenable to SCPL, to radiation failures, and to salvage after failed conservation surgery. Radiotherapy is no longer a primary modality in the treatment of laryngeal cancer except for T1a and T1b lesions of glottic area and for a well-differentiated carcinoma situated in the middle of a mobile vocal cord (T1a). The same is true for chemotherapy. These two modalities are now used in conjunction with surgery and for palliation purposes in cases with distant metastases (M1). Whereas chemotherapy sensitizes the tissues to the action of radiotherapy, postoperative radiotherapy improves the prognosis in cases treated with surgery.

Options for surgical treatment of advanced laryngeal tumors in cases other than those with distant metastases (M1) are summarized here.

Supraglottic carcinoma

T3 N0 disease

In treating T3 N0 disease, there is a choice between SGPL and SCPL. Cases with extension into pre-epiglottic space or involvement of the anterior

commissure, the glottis, and the hypopharynx are treated with SCPL, provided at least one arytenoid cartilage is disease free with clear margins. All other cases are dealt with SGCL. In both groups induction chemotherapy and postoperative radiotherapy are given to improve results.

T4 N0 disease

T4 N0 cases may be treated with SCPL (see indications listed previously) that gives efficient disease clearance along with preservation of laryngeal functions and integrity of airway. If both arytenoids are involved or the cricoid cartilage is infiltrated, SCPL is contraindicated. In that case total laryngectomy with some speech reconstruction procedure is undertaken. In both groups induction chemotherapy and postoperative radiotherapy are given to improve results.

Glottic carcinoma

T3 N0 disease

T3 N0 cases are treated with frontolateral partial laryngectomy, which is also called "hemilaryngectomy." When the paraglottic space, anterior commissure, and thyroid cartilage are involved, SCPL is performed. If there is any contraindication to SCPL or if salvage surgery for recurrence needs to be performed, total laryngectomy with some speech reconstruction procedure is performed. In all groups induction chemotherapy and postoperative radiotherapy are given to improve results.

T4 N0 disease

The treatment for T4 N0 cases is the same as for the T4 N0 supraglottic carcinoma, that is, SCPL. If there is any contraindication to this procedure, total laryngectomy is done along with tracheoesophageal puncture or some other speech reconstruction procedure. In both groups induction chemotherapy and postoperative radiotherapy are given to improve results.

Subglottic carcinoma

Subglottic tumors are not easily visible on laryngoscopy. Also, they present late and metastasize to mediastinal lymph glands that are not palpable on routine clinical examination. Furthermore, the subglottis abuts the cricoid cartilage, which therefore is involved in many cases. Therefore SCPL is contraindicated in such patients. Induction chemotherapy followed by total laryngectomy and postoperative radiotherapy is the treatment of choice. Because of the possibility of mediastinal spread, postoperative radiation should cover both the lower neck and mediastinum [13,14].

Induction chemotherapy before surgery has been suggested because of the presence of an intact blood supply, a more responsive cell mass, the elimination of micrometastases, and possibility of tumor regression. Because of synergism, various drug combinations (eg, cisplatin plus 5-fluorouracil or

methotrexate plus bleomycin) are preferred over single agents. The drugs administered should have the least toxicity with demonstrable response against the cancer. Furthermore, results are better if cancer chemotherapeutics are given in short spurts (eg, for 24–36 hours) and intermittent courses (eg, 3–4 weeks) [15].

Management of neck disease

The risk of occult metastasis is approximately 40% from the supraglottis (which can be bilateral) and 24% from the glottis [22]. According to the clinical guidelines of the American Head and Neck Society [23], in the presence of a N0 neck (no demonstrable secondary tumors in the neck), both the ipsilateral and the contralateral neck need to be addressed either through a selective neck dissection (level II, III, IV) or by elective neck irradiation, especially in supraglottic cancer. N1 disease may be managed by an ipsilateral selective neck dissection. More aggressive neck dissection may be performed depending on the location of the lymph node. N2-N3 disease generally requires a comprehensive modified radical neck dissection or a radical neck dissection. For supraglottic cancer, bilateral neck treatment is important because of the high likelihood for metastasis in the contralateral neck. Obviously, bilateral neck dissection will be performed for midline lesions. The final decision to treat the neck depends upon the patient's preference, on input from medical and radiation oncology and the head and neck surgeon, and on the modality used to treat the primary cancer.

Nonsurgical management

Nonsurgical approaches to larynx preservation include radiation alone, neoadjuvant chemotherapy with radiation for responders, or concurrent chemotherapy and radiation therapy [24,25]. These management approaches have been used in response to a shift in paradigm to avoid a total laryngectomy whenever possible. Many patients choose to forgo the chance of cure through a total laryngectomy in return for the superior quality of life afforded by an intact airway and useable voice.

The Veterans Affairs (VA) Laryngeal Cancer Study Group published its results in 1991 [26]. This study randomly assigned 332 patients with stage III or stage IV laryngeal cancer to receive induction chemotherapy with two cycles of cisplatin-fluorouracil followed either by a third cycle and then radiation therapy (in responders) or by total laryngectomy and postoperative radiation (in nonresponders). Patients in the chemoradiation group were treated with salvage laryngectomy when there was a less than 50% reduction in tumor size, posttreatment persistence of tumor, or tumor recurrence. In the chemotherapy group 36% of the patients who did not respond to the chemotherapy were referred for total laryngectomy and postoperative radiation therapy. The estimated 2-year survival in this study

was 68% for both the surgery and chemoradiation arms. The larynx was preserved in 64% of patients in the chemoradiation group, and 64% of patients in this group were alive and free of disease at 2 years. Hence, the authors concluded that a positive response to induction chemotherapy may be used as an indication to proceed with radiation therapy instead of surgery. Critics of this study noted that this study did not prove the survival benefit of chemotherapy because there was no arm for treatment by radiation therapy alone [27]. Furthermore neoadjuvant chemotherapy has little proven value except as a radiosensitizer [24].

Follow-up studies to the VA laryngeal study group assessed the functionality of patients treated in the chemoradiation group. This group had better objective speech, and only two patients required a tracheostomy [28,29]. After a 10-year follow-up, however, there was no difference in self-reported assessment of speech and swallowing between the two groups [30]. Other studies have demonstrated significant swallowing dysfunction after chemoradiation [28].

In 2001 Forastiere et al [31] presented preliminary results of the three-arm trial conducted by the National Cancer Institute Cooperative Trials Head and Neck Intergroup (R91-11). In this trial, 547 patients were randomly assigned to one of three arms: induction chemotherapy and radiotherapy (A), concomitant chemoradiotherapy (B), or radiation therapy alone (C). There was no difference in survival in the three groups at 2 years. Laryngectomy-free survival was longer in arm B (66%) than in arm A (58%) or arm C (52%).

In another study [32], 80 patients with stage III and IV laryngeal cancer were assigned to receive either radiation therapy alone or neoadjuvant chemotherapy followed by radiation therapy. The 5-year survival was similar in the two groups (24% for radiation therapy alone versus 31% for combined group). The laryngeal preservation rate was also similar at 62% for the former group and 63% for the latter group. Hence, it was concluded that radiation therapy without neoadjuvant chemotherapy is a viable alternative to treatment of advanced laryngeal carcinoma.

Organ-preservation protocols should be avoided in patients with major pre-epiglottic and paraglottic spread, cartilage destruction, massive subglottic disease, and major soft tissue extension. In such situations consideration should be given to total laryngectomy with postoperative radiation therapy for the best oncologic result [24]. Furthermore organ preservation does not equate with organ function, and patients who have undergone nonsurgical management do have swallowing and vocal quality problems [24,27].

There are several disadvantages to treating patients with nonsurgical chemotherapy and radiation therapy protocols. These disadvantages include the risk of major mucosal necrosis or chondronecrosis in case endolaryngeal biopsies need to be performed for surveillance. Moreover, surgical salvage after tumor persistence or recurrence requires a total laryngectomy and can

be complex. The complication rate ranges from 33% to 61% according to some studies [33,34].

Prognosis

With 73% of carcinomas occurring on the vocal cords, the larynx is perhaps the best place to have a malignancy. The vocal cords are functionally active most of the time and hence the slightest suspicion of functional aberration is detected early. Moreover, they do not have a rich lymphatic network, so the rate of neck metastasis from the glottis is low. Besides, a continuous sheet of connective tissue, Reinke's membrane, surrounds the larynx. The net result of these special attributes is early diagnosis and late spread of cancers occurring here. Therefore prognosis of these tumors is good. A number of controlled clinical trials performed at different centers have demonstrated positive treatment results even in advanced cases. Thus in supraglottic carcinomas recurring after radiotherapy and treated with SGPL, the 5-year survival rate is 70% [7]. Similarly, failures and more advanced T4 supraglottic tumors treated by SCPL or by total laryngectomy when SCPL is contraindicated also have a reasonable prognosis. Radiotherapy failures in T1 and T2 glottic tumors treated with hemilaryngectomy have a 3-year survival rate of 60% [16]. The 5-year survival rate for failures and more extensive T3 and T4 glottic tumors treated with total laryngectomy is 47% [17]. Subglottic cases treated with radical surgery and postoperative radiotherapy have a similar prognosis. Hill and Price [18] reported a 7-year survival rate of 63% in 65 cases of advanced laryngeal cancer that they treated with two cycles of induction chemotherapy followed by surgery and postoperative radiotherapy. Kisch et al [19] reported a 5-year survival rate of 79% in 85 cases of advanced head and neck cancer that they treated with three courses of cisplatin in combination with 5-fluorouracil at monthly intervals followed by surgery and postoperative radiotherapy. Jacob et al [20] treated 462 cases of advanced, recurrent, and metastatic disease (48% of which had metastatic disease) with induction chemotherapy using cisplatin plus bleomycin followed by surgery and postoperative radiotherapy. The major response rate at the end of 2 years was 37%. In summary, when advanced laryngeal cancer is treated with surgery and radiation, the 5-year survival ranges from 54% to 91%. When chemoradiation is used as the primary modality, the 2-year survival ranges from 52% to 81%.

Summary

There is a plethora of management techniques for advanced laryngeal cancer. The decision to proceed with surgical or nonsurgical management needs to be made according to the patient's wishes and quality-of-life goals

and with input from the medical oncologists, radiation oncologists, and head and neck surgeons. The much-discussed total laryngectomy of the past is now relegated to T4 cases with extensions into neighboring areas and for salvage in recurrent cases. For cases with distant metastases (M1) palliation is the only treatment the physician can offer. Partial laryngectomy techniques are gaining popularity again, but large, randomized trials to compare the voice quality and oncologic control still need to be performed. Chemoradiation therapy protocols have allowed nonsurgical management, but their judicious use is advocated because surgical salvage for failures is both complicated and morbid. Organ preservation does not equate with preservation of organ function. Therefore surgery should not be abandoned or considered as the last option in patients with advanced laryngeal cancer but should remain as a primary therapy in these patients.

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