Evolution of the management of laryngeal cancer

Eric M. Genden a, Alfio Ferlito b,*, Carl E. Silver c, Adam S. Jacobson a, Jochen A. Werner d, Carlos Suárez e,f, C. René Leemans g, Patrick J. Bradley h, Alessandra Rinaldo b

a Department of Otolaryngology – Head and Neck Surgery, The Mount Sinai Medical Center, New York, NY, USA
b Department of Surgical Sciences, ENT Clinic, University of Udine, Policlinico Universitario, Piazzale S. Maria della Misericordia, I-33100, Udine, Italy
c Department of Surgery, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY, USA
d Department of Otorhinolaryngology – Head and Neck Surgery, Philipp-University Marburg, Marburg, Germany
e Department of Otolaryngology, Hospital Universitario Central de Asturias, Oviedo, Spain
f Instituto Universitario de Oncología del Principado de Asturias, Oviedo, Spain
g Department of Otolaryngology – Head and Neck Surgery, VU University Medical Center, Amsterdam, The Netherlands
h Department of Otorhinolaryngology – Head and Neck Surgery, Queens Medical Centre, Nottingham, UK

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Abstract The treatment of laryngeal cancer has evolved through several phases, starting with wide extirpative surgical resection, and evolving through an era of conservation surgery and, finally, planned treatment using modalities of irradiation, chemotherapy and surgery in various combinations. Attempts to extirpate laryngeal cancer date to the nineteenth century, but only by the mid-twentieth century did advances in anesthesia, blood transfusion and antibiotics, make this surgery safe and reliable. Techniques of partial laryngectomy by external approach developed in the second half of the twentieth century, and endoscopic use of the laser refined the concept and provided a new paradigm for surgical treatment, particularly for early lesions. During most of this era, radiation was employed as an alternative method of treatment, with surgery reserved for salvage of radiation failure. By the last decade of the twentieth century, and to the present time, the value of combined modality therapy, using planned combinations of irradiation, chemotherapy and surgery became the standard of care for advanced laryngeal cancer, permitting maximal laryngeal preservation with the highest attainable cure rates.

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* Corresponding author. Tel.: +39 0432 559302; fax: +39 0432 559339.
E-mail address: a.ferlito@uniud.it (A. Ferlito).

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Introduction

Cancer of the larynx is the most common malignancy of the head and neck. Squamous cell carcinoma represents approximately 85–90% of all the malignant tumors of the larynx. The remaining primary malignancies of the larynx are neuroendocrine, minor salivary gland, cartilaginous and soft tissue tumors. The American Cancer Society estimates that 9510 new cases will be diagnosed and 3740 laryngeal cancer related deaths will occur in the US during 2006.

Our contemporary understanding of laryngeal cancer and our ability to visualize, diagnose, and treat this disease has been the culmination of two centuries of work. A pivotal period in the evolution of understanding laryngeal pathology can be traced back to the 1850s when Manuel Garcia, a singing instructor, developed the technique, now known as indirect laryngoscopy, which permitted visualization of the phonating glottis by reflected light onto a dental mirror. Additionally, during this period Virchow published his historic work on histopathology which recognized the histologic basis of disease and provided a means of precise pathologic diagnosis by the microscopic study of diseased tissue. Nevertheless, at the end of 19th century the diagnosis between syphilis, tuberculosis, and malignant tumors of the larynx was still not clear, either on clinical or histologic examination. Koch did not discover the tubercle bacillus until 1882, and Wassermann introduced his test for syphilis in 1906, so otolaryngologists were obliged to rely solely upon their clinical experience. Often laryngectomy was performed without previous biopsy and pathology museums contain many examples of a wrong clinical diagnosis.

After the introduction of the laryngoscope and revolution in histopathology, the understanding of laryngeal pathology improved rapidly. In 1871, Van Luschka introduced an anatomically accurate description of laryngeal anatomy which set the framework for future laryngeal surgery. Alfred Kirstein introduced the first direct laryngoscope in 1895 that afforded surgeons a direct view of the larynx. This early direct laryngoscope resembled a tongue depressor but allowed for a direct visualization of the laryngopharynx and trachea. It was not the actual instrument, but the concept of direct laryngoscopy that was important, setting the groundwork for future pioneers such as Jackson, Brünings, Mosher and Ingals to make modifications and variations of the laryngoscope establishing modern surgical endoscopy of the upper aero-digestive tract. These advances paved the pathway for the contemporary management of laryngeal cancer.

The evolution of the treatment of laryngeal cancer can be divided into three main eras. The first was focused on curing patients using radical surgical procedures, mainly by total laryngectomy. The second era developed with the goal of voice preservation while using sound oncological principals. The final and current era is of organ sparing protocols utilizing a combination of radiation, chemotherapy, and surgery. Currently, the overall 5-year cure rate for patients with laryngeal cancer is almost 70%.

The era of aggressive surgical extirpation

Laryngofissure

Laryngofissure or thyrotomy is a surgical approach to the interior of the larynx that consists of splitting the thyroid cartilage at or near the midline. The first laryngofissure for the treatment of intrinsic cancer of the larynx was performed on a 51-year-old woman in the United States in 1851 by Gurdon Buck. Remarkably, the patient survived for 15 months post-operatively. In 1867, the American laryngologist Jacob da Silva Solis-Cohen of Philadelphia performed a laryngofissure to resect a cancerous lesion and in 1892 reported the first documented long-term cure of laryngeal cancer by laryngofissure. His patient survived for 20 years without a documented recurrence.

Although the era of surgical removal of malignant tumors of the larynx had begun, piecemeal extirpation was the norm and patients often developed severe intra-operative and post-operative complications. Poor outcomes and less than optimal oncologic procedures led to condemnation by many of the pioneering surgeons of the time. As the limitations of the laryngofissure became apparent and patient selection improved, the laryngofissure procedure slowly came into acceptance in the late 19th and early 20th century for treatment of lesions appropriately confined to the glottis. Improved anesthesia and post-operative care were particularly helpful in reducing the morbidity and mortality experienced by patients.

At the current time, laryngofissure (simple thyrotomy and cordectomy) is rarely employed for treatment of laryngeal cancer. Lesions suitable for this procedure are amenable to cure by transoral excision or radiation therapy, both discussed below. Laryngofissure combined with excision of a portion of the laryngeal framework, and usually requiring some form of reconstruction to rehabilitate the larynx, constitutes "partial laryngectomy," which will also be discussed.

Total laryngectomy

In the early and mid-19th century the idea of complete resection of the larynx for tumor extirpation existed but could not be realized because of the lack of anesthetic agents and the entire armamentarium of airway control, blood transfusion and antibiotics that evolved during the 20th century. Despite the limitations of his era, Theodore Billroth was the first physician to perform a total laryngectomy for laryngeal cancer. His patient was a 36-year-old teacher who developed a subglottic tumor which was extirpated on November 27, 1873 via hemilaryngectomy. The patient later underwent a total laryngectomy on December 31, 1873 because of tumor recurrence. He was discharged home on March 3, 1874, in good health, but eventually expired 7 months after surgery from metastatic disease. This landmark surgery was presented by Billroth's assistant Gussenbauer to the Third Congress of the German Society of Surgeons in April of 1874. The first surgical cure by total laryngectomy was performed by Enrico Bottini of Turin, Italy, in 1875. The patient was diagnosed with a laryngeal...
Eventually, in the mid-20th century, the modern “wide century” to acceptable levels in the early 20th century. Advances in anesthesia and post-operative care, the operation of the larynx that separated the airway from the digestive tract by suturing the trachea directly to the cervical skin, often performing the operation in two stages, thus preventing otherwise inevitable and usually fatal aspiration. With complete separation of the aero-digestive tract and advances in anesthesia and post-operative care, the operative mortality rate dropped from 50% in the late 19th century to acceptable levels in the early 20th century. Eventually, in the mid-20th century, the modern “wide field” total laryngectomy combined with a neck dissection became the treatment of choice for advanced laryngeal cancer.

Surgical voice restoration procedures

Despite its efficacy as an oncologic procedure, complete loss of the larynx, is a devastating event that results in obvious significant diminution of quality of life for many individuals. Few patients were capable of “esophageal speech,” and various “electrolarynx” devices were likewise only intermittently useful. Starting with Billroth and Gusenbauer, surgeons struggled to create devices or devise surgical procedures to permit lung-powered speech by creating connections between the airway and the pharynx that would permit passage of air into the pharynx while preventing aspiration of food and liquid into the airway. After decades of cumbersome devices and complex surgical procedures, the development of modern materials, mainly siliconized rubber, permitted the construction of simple one way valves that could be inserted into a direct surgical shunt between the trachea and pharynx, permitting speech without aspiration. Modern voice restoration procedures, performed either primarily or secondarily, have greatly improved the quality of life after total laryngectomy, although the permanent tracheostoma and various problems related to the shunt still complicate the lives of laryngectomy patients.

The procedure of “near-total” laryngectomy was devised to permit creation of a competent phonyatory shunt from natural tissue without the need for a prosthesis. In suitable cases, the tumor bearing portion of the larynx is removed with adequately safe margins, while a narrow vertical posterolateral strip containing an arytenoid and a small portion of the adjacent vocal cord is preserved in order to create a tubular tracheo-pharyngeal shunt. This allows a lung-powered voice without prosthetic devices. When the dynamic shunt is successfully achieved, patients have a more natural existence than those with prosthetic shunt devices, but the operation has not become widely popular because of its technical difficulty, the possibility of either incompetent or stenotic shunts and the availability of other techniques and modalities to preserve voice while controlling cancer.

The era of conservation laryngeal surgery

Despite the effectiveness of total laryngectomy, it became apparent that in many cases of the earlier stages of laryngeal cancer, removal of the entire larynx was not necessary for cure. The contemporary concept of laryngeal conservation surgery is based upon the known anatomic compartmentalization of the larynx which is defined by connective tissue barriers which resist the spread of tumor from one compartment to another. This understanding of the anatomy of the larynx was elucidated by Tucker and Smith who studied whole organ sections at various stages of fetal development. Additional evidence for the compartmentalization of the larynx was elucidated by Pressman who performed injection studies on the larynx with various radioisotopes and dyes into living as well as cadaver larynges. These studies provided excellent documentation of the anatomic compartments and lymphatic flow within the larynx which was then used to understand the spread of cancer within the larynx and into the regional lymphatic system. The second basis for conservation surgery is that most otherwise healthy patients can adapt to loss of significant portions of the larynx while maintaining the functions of deglutition, breathing and speech. Thus in properly selected cases, portions of the larynx involved with cancer can be removed with narrow resection margins, while maintaining the essential functions of this organ.

Conservation surgery maintains the principles of adequate oncologic surgery. It has been shown that when partial laryngectomies are performed on well selected lesions the long-term survival rates are compatible with that of total laryngectomy for the same lesion. Additionally, the smaller resection margins which are obtained during conservation laryngeal surgeries have been shown to result in similar recurrence rates to procedures that obtain wide margins.

Vertical hemilaryngectomy

Hemilaryngectomies were performed by Billroth and Gluck but they lacked understanding of the oncologic limitations of the procedure, and of the requirements for reconstructing a functional and intact larynx with the tissue remaining after the partial resection. Partial laryngectomy may be performed in the vertical plane, mainly for glottic tumors, or in the horizontal plane, for supraglottic and suitable hypopharyngeal lesions. More recent adaptations have combined these approaches for more extensive neoplasms.
The modern vertical partial laryngectomy evolved in the post-World War II era. A better appreciation of the limitations of hemilaryngectomy, modifications in the amount of soft tissue and cartilage extirpated, and improved methods of reconstruction were responsible for the practical adaptation of this approach. Goodyear\textsuperscript{13} in 1949 reported the use of an obturator to maintain the laryngeal lumen post-operatively, and achieved enough success to inspire further innovation. Figi\textsuperscript{33} employed intralaryngeal skin grafts, Meurman\textsuperscript{34} used external skin flaps and Som\textsuperscript{35} developed a one stage procedure without the use of distant tissues by advancing hypopharyngeal mucosa to resurface the endolaryngeal defect. Further advances for management of anterior commissure, bilateral and subglottic involvement brought vertical partial laryngectomy and conservation laryngeal surgery to its pinnacle in the mid- and late 20th century.

Supraglottic partial laryngectomy

In 1913, Trotter\textsuperscript{36} described resection of tumors of the "epilarynx" via a lateral pharyngotomy approach which was later utilized in South America for resecting tumors of the epiglottis, lateral pharyngeal wall and aryepiglottic folds. Justo M. Alonso of Uruguay, is considered the father of the horizontal partial laryngectomy. Alonso performed the first supraglottic laryngectomy in 1939 which was a major advance in partial laryngeal surgery.\textsuperscript{37,38} Alonso presented his original description of the horizontal supraglottic laryngectomy at the First Pan American Congress of Otolaryngology and Bronchoesophagology.\textsuperscript{39–41} From the 1940s through the 1950s several surgeons, including Alejandro Agra, Jaime del Sel, Ries Centeno, Pietro Caliceti and others described this surgical procedure.\textsuperscript{37} Subsequent modifications and evolution by Ogura,\textsuperscript{42} Ogura et al.,\textsuperscript{43} Ogura and Mallen,\textsuperscript{44} Som\textsuperscript{45} and Bocca et al.\textsuperscript{46} led to oncologically sound procedures with high cure rates and maximum preservation of function. The lateral pharyngotomy approach permitted extension of the procedure to include partial pharyngolaryngectomy for tumors of the aryepiglottic fold, pyriform sinus and posterolateral pharyngeal wall. In its most advanced form, the entire supraglottis as well as the glottis on one side could be resected in cases of supraglottic carcinoma with transglottic extension.\textsuperscript{47} These sophisticated procedures were of value for suitable lesions in selected patients.

Supracricoid laryngectomy

Partial laryngectomy surgery was taken a step further when the supracricoid laryngectomy was introduced.\textsuperscript{48} The concept in this procedure was that a segmental resection of the larynx was performed between the hyoid bone and cricoid cartilage. The larynx is reconstructed by impacting the hyoid bone onto the cricoid cartilage, both of which have been preserved. This procedure maintains the diameter of the airway and produces a functional larynx which is capable of satisfactory deglutition and voicing, as long as one functional arytenoid is preserved. Supracricoid laryngectomy permits resection of glottic and supraglottic tumors with transglottic involvement, which have limited subglottic extension. The procedure has been modified for resection of hypopharyngeal tumors.

While popular in Europe, particularly France, this approach has never achieved widespread popularity in the United States or many other parts of the world — because of its technical difficulties and the availability of other alternatives.

Transoral resection

The first published report of a transoral resection of a glottic carcinoma was by Fraenkel in 1886.\textsuperscript{49} This procedure was performed using rudimentary instruments and the patient eventually required a neck dissection and multiple revision surgeries for tumor recurrence. Although the oncologic soundness of this procedure was unclear, the patient survived for well over 5 years after his original diagnosis and treatment.

The development of endolaryngeal tumor resection stagnated during the early 20th century until 1960 when Scalco et al.\textsuperscript{50} melded direct laryngoscopy with operative microscopy. This innovation enhanced transoral laryngeal surgery because it provided excellent illumination, high-power magnification and a three-dimensional stereoscopic field of vision.

Jako and Kleinassser simultaneously, but separately, developed techniques of microendolaryngoscopy, developing the instruments and methodology and teaching widely about them.\textsuperscript{51} Kleinassser’s textbook proved a milestone in this area.\textsuperscript{52} The carbon dioxide (CO\textsubscript{2}) laser was developed by Polanyi et al.\textsuperscript{53} In 1972, Jako\textsuperscript{54} and Strong and Jako\textsuperscript{55} published their landmark paper in describing their use of the CO\textsubscript{2} laser in combination with microscopic direct laryngoscopy. Since this initial report, the CO\textsubscript{2} laser has been successfully used to address early (T1) laryngeal malignancies with cure rates reported to be equivalent to those of the classic hemilaryngectomy, laryngofissure with cordectomy, and radiation therapy.\textsuperscript{56–58}

Starting in the 1980s, other surgeons, mostly in Europe, began to employ transoral laser resection for more advanced tumors of the glottis, and then for supraglottic cancer, achieving results comparable to those obtained with more conventional treatment. These surgeons, challenged the principle of "en bloc" resection which had been the paradigm for cancer treatment since the time of Halstead, by using the CO\textsubscript{2} laser to cut directly through tumor, subdividing larger lesions into smaller easy to manage pieces. Years of experience with laser surgery of this type have proven that cutting through the tumor with the laser beam does not cause cancer to implant or recur, as long as tumor has been removed completely.

The largest amount of work was done by Wolfgang Steiner, and his associate, Petra Ambrosch, in Göttingen, Germany, who summarized their work in a book written in 2000.\textsuperscript{59} Other European surgeons, particularly in Germany, began to extend the indications for transoral laser surgery to moderately advanced and some advanced glottic and supraglottic tumors, until this modality became the treatment of choice for a majority of these lesions. Others have followed this lead, in the United States and elsewhere, although the indications for laser surgery vary considerably,
and no American surgeons have attempted laser treatment of lesions as advanced as those reported by Steiner and his colleagues.

With microscopic visualization of the tissue, the surgeon may identify the interface between the tumor and normal tissue with considerable accuracy, permitting preservation of normal tissue where possible. The most striking benefit of endoscopic laser surgery is that the functional results, especially after resection of supraglottic carcinomas, are often excellent and generally superior to transcervical surgery.\(^6^0,6^1\) Thus the procedure is more suitable for a wider variety of elderly and debilitated patients than is conventional conservation surgery. It may be used in combination with irradiation, although the results of laser surgery after radiation failure have been less well studied and documented.

The reason for the apparent ability of laser surgery to permit piecemeal removal of tumor, in seeming violation of principles of cancer surgery, remains uncertain. Sapunzhiev et al.\(^6^2\) recently published an animal experimental investigation on the question of intra-operative tumor cell dissemination after piecemeal technique. They employed a very aggressive and rapidly metastasizing animal model for their studies which demonstrated that lymphogenic metastatic spread after laser surgical tumor transection is significantly higher than after en bloc resection. Additional investigations regarding the analysis of those results have been initiated.

At the present time, endoscopic laser surgery has become the mainstay of surgical treatment of early to moderately advanced laryngeal cancer. In many such cases, the therapeutic choice for T1 and T2 glottic cancer as well as T1–3 supraglottic cancer lies between laser excision, or radiation therapy, and finally chemoradiation either alone or in conjunction with salvage surgery.

**The era of combined therapy**

The employment of non-surgical modalities has gone through three phases; radiation alone as an alternative to surgery, neoadjuvant radiation to selected patients who were likely to respond to subsequent therapeutic radiation therapy, and finally chemoradiation either alone or in conjunction with salvage surgery.

**Radiation alone**

Radiation therapy has been employed as an alternative to surgical treatment of laryngeal cancer since at least 1909 when Finzi reported good results with the use of external beam radiation therapy to the larynx.\(^6^3\) Coutard treated patients with tonsillar, laryngeal, and hypopharyngeal cancer at the Curie Foundation in Paris, France, during the 1920s with radiation therapy.\(^6^4,6^5\) In the period from the 1940s through the 1980s, radiation therapy was often employed as an alternative to, and in preference to surgery as the initial treatment of both early and advanced laryngeal cancer.\(^6^5,6^6\) Results of treatment of early laryngeal cancer were, and still are, considered by many surgeons and radiation oncologists to be comparable to those obtained with surgery.\(^6^7,6^8\) While cure rates for irradiation treatment for advanced tumors were not as good as with laryngectomy, surgery was often reserved for attempts to salvage irradiation failures. Results of such salvage surgery were not as good as results of surgery performed as primary treatment, and surgical morbidity was greatly increased.\(^6^9\)

During this era, great debate transpired between advocates of primary irradiation therapy, and surgery for initial treatment of laryngeal cancer. By the late 1980s, many of the radiation oncologists who had witnessed the poor results of early attempts at surgical treatment of head and neck cancer had left the scene. The newer generation of radiation oncologists had an appreciation of the safety and efficacy of modern laryngeal surgery. At the same time, surgeons came to appreciate the value of modern radiation techniques, the efficacy of newly developed chemotherapeutic regimens, and particularly, the advantage achieved by combining these modalities in a planned manner. Surgeons, once convinced that cure was possible with non-surgical treatment and that modern surgical techniques permitted better results with salvage surgery than had been the case in the past, became more sensitive to the desirability of preservation of the larynx, if equivalent results could be obtained with non-surgical treatment. Rather than debate, cooperative treatment planning became the norm.

**Neoadjuvant chemotherapy — the "VA Protocol"**

In 1991, the VA Laryngeal Cancer Study Group published their landmark study in the New England Journal of Medicine which ushered in the era of organ preservation therapy.\(^7^0\) This study effectively demonstrated the efficacy of induction chemotherapy and radiation therapy in the treatment of advanced laryngeal cancer. The premise was based on the observation that patients who had significant response to chemotherapy were likely to respond well to definitive radiation therapy. Patients in the first arm of the study were treated initially by total laryngectomy. Patients in the second arm were treated initially with neoadjuvant, or "induction" chemotherapy followed by radiation therapy. Patients who did not respond to chemotherapy or who failed radiation therapy were treated with total laryngectomy. In this study, approximately two-thirds (64%) of all non-surgically treated patients retained their larynges and their 5-year survival was equivalent to that of patients treated by initial total laryngectomy. The VA study results were later bolstered by the results of the EORTC larynx preservation study for hypopharyngeal primaries in 1996.\(^7^1\)

In 2003, the important phase III study RTOG 91-11 was published in the New England Journal of Medicine.\(^7^2\) Three arms were compared in this study. The first was radiation alone. The second was radiation with cisplatin. The third arm was induction cisplatin and fluorouracil for two cycles. If there was no response, salvage total laryngectomy was performed. If there was a partial or complete response, one additional cycle of cisplatin and fluorouracil was given, followed by definitive radiation therapy. The induction arm of this study showed similar overall survival as patients who underwent total laryngectomy in the VA larynx preservation study. Overall survival was similar for all three arms. Locoregional control was superior in the concurrent...
Chemoradiation

Clearly, the results from the 1991 VA Laryngeal Cancer Study Group and RTOG 91-11 provide evidence that organ preservation treatment is an option for the appropriately selected patient with advanced laryngeal cancer. Contemporary non-surgical approaches to laryngeal cancer are currently exploring treatment intensification such as altered fractionation radiation therapy, concomitant intravenous chemotherapy and radiation therapy, and supradose intraarterial chemotherapy and radiation therapy, as well as combinations of induction chemotherapy and concomitant chemoradiation with surgical salvage. In 2006, one of the more promising protocols was published by Urba et al. from the University of Michigan. In this study they explored the use of induction chemotherapy (cisplatin and fluorouracil) to determine which form of definitive treatment is appropriate, total laryngectomy followed by post-operative radiation or concurrent chemoradiation.

Another area of active exploration is combining various agents with radiation therapy to enhance the efficacy of the radiation treatment. Cetuximab, an EGFR blocking agent, is one of the more promising agents which has been shown to improve local control and overall survival in treatment of squamous cell carcinoma of the head and neck. Interestingly, this agent has the added benefit of being safe to use in patients with renal insufficiency and hearing impairment. The study by Bonner et al., however, included relatively few laryngeal primary cancers and larynx subset analysis was not possible.

Functional results after chemoradiation and larynx preservation

Rieger et al. in a literature review found that the majority of reports suggested that organ preservation techniques have the potential to result in swallowing disorders, often related to dysmotility of the oropharyngeal and laryngeal structures, resulting in temporary or long-term aspiration. Fung et al. reported on voice and swallowing outcomes of an organ-preservation trial for advanced laryngeal cancer. Fifty-six of the original 97 patients were alive and free of disease at the time of the survey. Thirty-seven patients had an intact larynx, while 19 had undergone total laryngectomy. The voice-related quality of life score for patients with intact larynx was 80.3. Nutritional mode consisting of oral intake alone without nutritional supplements was achieved in 88.9% of patients with an intact larynx. Eisbruch et al. found that the structures most often associated with dysphagia and aspiration were the pharyngeal constrictor muscles, and the glottic and supraglottic larynx. They found that moderate sparing of these structures could be achieved by intensity-modulated radiotherapy (IMRT). While this technique may be helpful in paralaryngeal neoplasms, for primary laryngeal cancer these structures often require the highest dosage. Staton et al. evaluated factors predictive of poor functional outcome after chemoradiation for advanced laryngeal cancer and found that patients who presented with a fixed vocal cord stood the highest chance of post-treatment dysphagia and aspiration.

These reports demonstrate that approximately 10% of patients are left with a "functionless larynx", which had been known previously to occur after high dose irradiation of the larynx. A small number of these patients will require laryngectomy in order to permit oral nutrition and prevent aspiration pneumonia.

The place of surgery in current management of laryngeal cancer

Early laryngeal cancer is often managed by surgery, either transoral or with various conservation procedures. Recurrent early stage cancer often requires total laryngectomy, but a minority of cases are suitable for partial laryngeal resection, either by conventional conservation surgery, supracricoid partial laryngectomy or transoral laser surgery. Several authors have concluded that conservation laryngeal surgery is a safe and effective treatment for recurrent localized disease after radiotherapy for early stage glottic cancer. Supracricoid laryngectomy has been employed for salvage of recurrent early and moderately advanced glottic cancer with results equivalent to those obtained by total laryngectomy.

The use of laser surgery for recurrent carcinoma after failed radiation therapy has been less well documented. Steiner et al. reported on 34 patients with early and "advanced" recurrent glottic carcinoma after full-course radiotherapy. Twenty-four (71%) patients were cured with one or more laser procedures. The others had total laryngectomy or palliative treatment. Overall 3- and 5-year disease specific survival was 86%. The authors emphasized the expertise required for management of the more advanced cases.

Total laryngectomy may be used as primary treatment in cases of advanced laryngeal carcinoma, but at the present time, it is more often used as a salvage procedure in facilities with equipment and expertise to treat the majority of patients initially with larynx preservation protocols. Nevertheless, there are situations, either because of patient preference, unreliability or lack of suitability for chemotherapy or irradiation, in which total laryngectomy may be the preferred mode of initial management of advanced laryngeal cancer. Efforts should be made to select patients on an individual basis based on tumor characteristics, other clinical aspects, patient expectations and the expertise and facilities available for treatment by various therapeutic strategies.
protocols produce overall survival equivalent to total laryngectomy, with a significant percentage of patients retaining functional larynges, this "trade off" would seem appropriate.

Actually, reports in the literature vary in their confirmation of these assumptions. Nikolaou et al. observed a 16% recurrence rate after initial total laryngectomy compared to 44% after salvage laryngectomy, with mean follow-up of 68 months. However, other factors such as T stage, supraglottic and transglottic involvement, degree of differentiation and presence of positive cervical nodes influenced the results. Hall et al. after multivariate analysis of patients treated by initial and salvage laryngectomy found no difference in 5-year survival between the two groups. The incidence of pharyngocutaneous fistula did not correlate with previous treatment. The authors concluded that patients whose laryngectomy was performed as a salvage procedure did not have worse outcomes than previously untreated patients.

Other reports have demonstrated that complications, particularly pharyngocutaneous fistula, are higher after salvage laryngectomy than primary laryngectomy. Ganly et al. using multivariate analysis demonstrated that previous chemoradiotherapy was an independent predictor of local wound complications and pharyngocutaneous fistula. Grau et al. found the risk of fistulae significantly increased in postirradiated patients. Multiple logistic regression analysis demonstrated that non-glottic tumor site and advanced initial T stage, as well as the era in which the laryngectomy was performed (actually higher between 1993 and 1997 opposed to 1987 and 1992), were also independent prognostic factors for fistula risk. The latter finding was attributed to the smaller number (hence less experienced surgeons) of laryngectomies performed in the later time period.

**Treatment of the neck**

The management of the neck in laryngeal cancer has evolved along with the procedures employed for treatment of the primary tumor. Prior to the introduction of the modified radical neck dissection, in particular the "type III" (or functional neck dissection), the radical neck dissection represented the primary method for management of neck disease associated with laryngeal cancer. The radical neck dissection, with its associated morbidity and deformity, has been replaced by the functional neck dissection except in cases where there is gross invasion of the structures of the neck. More recently, complete functional neck dissection, has been considered unnecessarily extensive for treatment of the clinically negative neck and therefore the lateral neck dissection, also called SND (II–IV), is now routinely employed for elective and some therapeutic neck dissections. Preliminary multi-institutional prospective and molecular studies support preservation of sublevel IIB and level IV for laryngeal cancer with clinically negative neck and indicate a more selective neck dissection, limited to sublevel IIA and level III, for these patients. In doing so, spinal accessory nerve dysfunction can be minimized, chylous leakage or phrenic paresis may be avoided and operative time can be saved without adversely affecting oncological outcomes.

The indications and necessity for neck dissection following combined chemoradiation has been called into question. While patients with residual disease following planned chemoradiation require a neck dissection, there are a selected group of patients who demonstrate a complete clinical response that may not require this treatment. Identifying the high risk group remains elusive and will likely require a combination of functional imaging, such as positron emission tomography (PET) and molecular markers. The management of the neck in many ways parallels the management of the primary tumor of the larynx. Early management was focused on radical surgical management while contemporary approaches are focused on combined therapy.

**Conclusion**

Treatment of laryngeal tumors was attempted and performed in the 19th century, but physicians were hindered by a lack of knowledge, technologically advanced instruments, and equipment which allowed for accurate examination, diagnosis, mapping, and treatment of these lesions. With the advent of instruments which provide excellent visualization and access to the larynx, the diagnosis and treatment of laryngeal cancer began a steady and rapid advance. From the late 1800s to the mid-1900s treatment of laryngeal cancer was often a large ablative procedure. Around the mid-20th century the era of conservation laryngeal surgery was entered which consisted of a variety of partial laryngectomy procedures which were considered oncologically sound and provided the patient a chance to avoid permanent aphony and stoma dependence. In addition to an improved understanding of the biology of laryngeal cancer, management of the neck and its impact on outcome became increasingly important. In 1991, the VA Laryngeal Cancer study group published their study which ushered in the era of organ preservation protocols which consist of a combination of chemotherapy, radiation therapy, and surgery. Over the last 20 years the larynx sparing treatment strategies have evolved considerably from the original protocol put forth by the VA study. A multitude of strategies are actively being investigated in an attempt to improve overall and disease free survival and decrease morbidity associated with the treatment of laryngeal cancer.

**Conflict of interest statement**


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