

Update on the endoscopic management of laryngeal cancer

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Purpose of review

This update addressing the endoscopic management of laryngeal cancer presents new data published after January 2003. This new information is interpreted in the context of contemporary management principles established before 2003.

Recent findings

Endoscopic techniques in the management of laryngeal cancer continue to undergo modifications designed to improve oncologic efficacy in a manner that maximally preserves function. The modifications reported over the past two years have included the introduction of new diagnostic techniques, new surgical approaches, new endoscopic equipment, and new management philosophies.

Summary

Endoscopic resection has become a widely accepted and commonly employed management option in the treatment of laryngeal cancer. Advances in outcomes analysis have improved the capacity to objectively compare endoscopic treatment to other options. The prospects for applying these tools to a prospective randomized study are limited. Debate will continue as to the role for endoscopic management of laryngeal cancer.

Keywords

laryngeal cancer, laserendoscopic, glottic, supraglottic

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Introduction

The practice of transoral removal of laryngeal neoplasms predated the development of illuminated endoscopes specifically designed for that purpose. Zeitels credits Horace Green with the first successful direct laryngoscopy used to enact a visually controlled excision of a laryngeal neoplasm [1]. In 1852 Green reported use of a bent tongue spatula with sunlight illumination to remove a ball-valving fibroepithelial polyp obstructing the glottic aperture in a child. Development of indirect mirror-guided approaches to the larynx led to the first report of transoral resection of a laryngeal cancer by Bernhard Fraenkel in 1886. Endoscopes designed specifically to directly expose the larynx were developed by Kirstein in the 1890s [2].

Application of transoral endoscopic management of laryngeal cancer has continued to evolve with the introduction of new technology including use of the microscope to facilitate laryngoscopy in the 1960s. The transoral use of the laser through an endoscope to manage laryngeal cancer as was first reported by Strong and Jako in the early 1970s was another major advance that continues in its development [3].

The background needed to provide the context for interpreting recent advances is presented by listing concepts derived from data published before January 2003. Those reviews included in this section that were published after January 2003 contain no new data.

Nonsurgical treatment

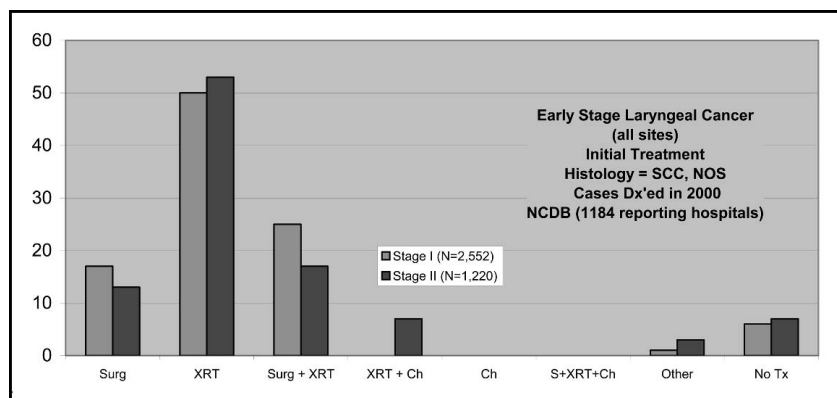
Despite the technical advances that have made endoscopic management more effective, advances in the application of radiotherapy and chemotherapy have gained even more influence resulting in a notable increase in the nonsurgical treatment of laryngeal cancer between the 1980s and 1990s [4].

Technical advances predating January 2003

Endoscopic management of laryngeal cancer has been enhanced by introduction of [5–7]:

Improved laryngoscopes (designed for specific sites of the larynx including use of expanding laryngoscopes)

Figure 1. Radiotherapy alone is the most common initial treatment modality for early (stage I and II) laryngeal SCC in an analysis grouping all sites (supraglottis, glottis, and subglottis) together



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Improved optical equipment (including the now routine use of 30 and 70 degree telescopes as well as contact endoscopes)

Improved microinstrumentation

Improved laser equipment (micromanipulators with “focus-able” spot sizes)

Adjuvant management (supravital staining, subepithelial infusion of vasoconstrictors, photodynamic therapy)

Reconsideration of the former standard of ‘en bloc’ resection advocated by Halstead. Steiner and Ambrosch [8] are among the strongest promoters of the concept that endoscopic laser cuts are safely made directly through the tumor both to initially debulk it and to obtain (through microscopic dissection) the interface between the tumor and normal tissue. The value of this approach has been questioned by others—especially in cases in which this technique results in positive margins requiring subsequent treatment with irradiation [9]. In 1991, Goepfert *et al.* published their opinion that laser surgery before

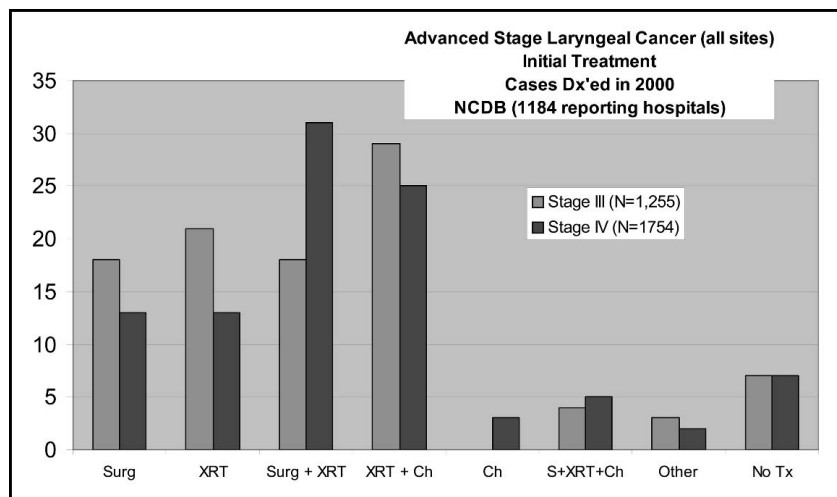
irradiation is an unnecessary dissection that ‘distorts the local anatomy’ and leaves an ‘indeterminable amount of cancer in tissues injured by the procedure’ [10].

Extensions of endoscopic approaches to include open approaches through ‘mini-open’ procedures by concurrent creation of ‘window’ laryngoplasties to remove cartilage segments at risk [11].

Survival

Retrospective analysis comparing treatment with surgery, irradiation, or combined surgery with irradiation is difficult primarily because of the unmeasurable bias in selecting patients for treatment [12]. A systematic search of the literature (published in 2000) for prospective studies addressing this selection bias in the comparison of irradiation versus surgery for early glottic cancer found only three randomized clinical trials (RCTs) [13]. Each of these prospective studies was sufficiently flawed as to render their conclusions suspect.

Figure 2. Radiotherapy combined with chemotherapy is currently the most common initial treatment modality for stage III laryngeal SCC in an analysis grouping all sites (supraglottis, glottis, and subglottis) together



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Problems in classifying treatment type also create difficulty in comparing outcomes following endoscopic surgical excision versus treatment with irradiation 'alone'. It is rare for a patient to receive irradiation without having undergone a prior endoscopic resection. In many cases, the endoscopic excision is only a small biopsy. In other cases the resection may have been designed for cure but found to be inadequate and therefore requiring treatment with irradiation that could be considered either definitive or adjuvant [14].

It is widely considered that management by endoscopic laser surgery for early glottic cancer offers a similar high survival rate comparable to management with irradiation as the initial treatment [15]. Successful salvage treatment for recurrent or persistent disease adds to the overall survival.

Most clinicians also accept that small minimally invasive supraglottic cancers with corresponding minimal chance for the occult metastases are adequately treated with endoscopic laser resection. The value of initial treatment with endoscopic laser resection for all other supraglottic cancers as well as advanced glottic cancers is less well established. Survival statistics following endoscopic treatment of these more advanced cancers is thought to be highly dependent on the following variables:

- Selection of patients based on co-morbidities
- Selection of patients based on extent of tumor
- Surgical technique
- Use of adjuvant therapy (irradiation/chemotherapy)
- Dose and method of administration of adjuvant therapy
- Management of occult or apparent neck metastases

Quality of voice and swallowing

Although reports have indicated that endoscopic management of early glottic cancer may produce vocal results equivalent to that following irradiation [16], most investigators contend that a better voice more reliably follows treatment with radiotherapy [17–21]. The degree of dysphonia following endoscopic resection is dependent on the extent of the tissue resected. Small lesions that do not involve the contact surface of the vocal cord may be resected with minimal or no vocal disability. Larger defects result in less predictable vocal results but may result in near normal voicing if scarring occurs in a favorable manner to permit adequate glottic closure. Radiotherapy does not require removal of adjacent healthy tissue to provide a clear margin about a cancer. It does affect normal tissue by inducing drying effect, fibrosis and occasionally tissue necrosis, all of which may contribute to vocal impairment. Benninger *et al.* [22] offered insight into another variable that may contribute to the poor vocal result that follows 'treatment with irradiation'. These investigators identified that large biopsies performed at the time of diagnostic microlaryngoscopy may

result in greater dysphonia than more conservative biopsies.

The impact of treatment on swallowing is often substantial when the fibrosis induced by irradiation is further compounded by the addition of chemotherapy. A well-recognized and substantial advantage to endoscopic laser supraglottic resection over both open surgical procedures and irradiation is the maximal preservation of laryngeal and pharyngeal sensation and movement. Just as the phonatory results following endoscopic resection of glottic cancer are dependent on the extent of the resection, so is the impact of laser supraglottic resection dependent on the size and location of the tumor tissue resected.

Laryngeal preservation

Although most investigators concur that vocal quality is usually better following treatment of laryngeal cancer with irradiation than with surgery, vigorous debate continues regarding which modality is best in preserving a functional larynx. In 1991 Ton-Van *et al.* [23] evaluated 356 patients with early glottic cancer and identified that a functional larynx was preserved in 92% of those whose first treatment was surgical compared to 81% initially treated with irradiation.

Quality of life

Sophisticated methods to assess vocal quality have been used to promote the value of irradiation as superior to surgery in the management of cancer affecting the vocal cords. Recent studies using global quality of life measure have reported the relative lack of importance many patients place on the measured quality of their voice [24]. A 2-year prospective study by Morton actually reported no global quality of life differences between those laryngeal cancer patients treated with irradiation and those receiving laryngectomy [25].

Publications after January 2003

Multiple publications (by review of the abstract or the full article) published between January 2003 and July 2004 were felt to offer valuable contributions but were not sufficiently novel to warrant discussion. Some of these articles are listed in references [26–33]. The following discussion offers a limited review of selected articles that introduce new concepts, new data, or new techniques.

Nonsurgical treatment

The nonsurgical treatment of laryngeal cancer has increased dramatically over the past 25 years to the point that radiotherapy is the most common initial treatment of laryngeal cancer in the United States as of 2002 [34,35].

Technical advances published after January 2003

Zeitels *et al.* [36] in 2004 described technical advances and surgical innovations they used to perform endoscopic en bloc frontolateral laryngectomy by endoscopy in 15 pa-

tients (9 of whom had failed previous irradiation). These investigators enhance exposure of the anterior commissure by the routine removal of the infra-petiole region and anterior vestibular folds. En bloc resection is further facilitated by infusion of epinephrine and use of electrocautery for hemostasis. Key to the exposure is use of a large triangular (rather than round) laryngoscope suspended to distend the anterior larynx. Despite these innovations, 4 of the 15 patients (27%) developed local recurrences within the brief (mean of 21 months) follow-up period. Among these four patients (all of whom were irradiation failures), two were salvaged with open partial laryngectomy and two eventually required total laryngectomy. These investigators acknowledge the value of piecemeal resection to remove cancer in selected cases but identify the advantage of en bloc resection in maintaining orientation for more accurate margin assessment.

Most investigators concur that endoscopic treatment of cancer should employ the CO₂ laser used as a cutting tool rather than one to vaporize the lesion. The laser affords precision and hemostasis but at the potential cost of obscuring margin assessment if excessive carbonization results from the laser cut. Difficulty in margin assessment may also follow endoscopic laser resection when, unlike Zeitels' technique, piecemeal resection is effected. Shvero *et al.* [37] in 2003 addressed this margin assessment problem in reporting their technique for laser resection for glottic cancer to include a planned second examination under general anesthesia 4 to 8 weeks after the initial laser resection.

Davis *et al.* [38] in 2004 cited Zeitels' technique in their report, which refined the definition of endoscopic vertical partial laryngectomy (EVPL). This technique similarly employs removal of the false cords and thyroepiglottic ligament as an important step needed to adequately expose T1b and T2 glottic cancers. In addition, they identify the value in treating more extensive glottic cancers by extending the exposure to include resection of the aryepiglottic fold and posterior false cord to uncap the posterior paraglottis. As with the technique of Zeitels, dissection was effected in a subperichondrial plane along the thyroid cartilage. This technique was used to treat 26 patients over a 13-year period ending in 2000. Irradiation was employed in all but four T2 lesions. Davis *et al.* contend that the addition of EVPL for T2 glottic cancers is intended to improve upon the local control rates offered by irradiation alone at the expense of inducing moderate vocal impairment [38].

Advances in contact endoscopy for the microscopic study of epithelial cells of the uterine cervix have been transferred to the larynx. In 2003, Arens *et al.* [39] published their development of "Compact Endoscopy" as a combination of autofluorescence and contact endoscopy. This promising tool permits analysis of the laryngeal epithe-

lium stimulated to autofluoresce with blue filtered light. Further refinements were addressed by Arens in a publication in 2004.

Survival following treatment

The recent decrease in the incidence of laryngeal cancer in the United States has been credited to decreased tobacco use. Despite this decrease in the absolute numbers of cases, there is evidence that the survival of patients with laryngeal cancer has also decreased. A recent expansion of the Surveillance, Epidemiology, and End Results (SEER) database program has increased the number of registries to represent approximately 26% of the US population. Data from this registry is available online [40] and has been summarized in a recent journal publication [41]. These sources identified an increase in 5-year survival for 23 of the 24 cancer types reported between the earlier period (1983–1985) and later period (1992–1999). The twenty-fourth cancer type, laryngeal cancer, was the only one that failed to show an increase in survival across these time periods. Five-year survival for patients with laryngeal cancer diminished from 67% (1983–1985) to 65% (1992 to 1999).

A recent presentation provided a more detailed review of the SEER data and showed a worsening 5-year survival for early stage laryngeal carcinoma from 1983 (82.3%) to 1997 (74.3%) [42]. These investigators reported improved 5-year survival (type of analysis not specified) for late stage laryngeal carcinoma from 1974 (22.2%) to 1997 (38.3%).

A review article from the University of Florida [43] carefully evaluated a published series of T1 and T2 glottic cancer patients to come to the following conclusions:

- Local control rates, laryngeal voice preservation, ultimate local control, and survival are comparable for patients treated with transoral laser excision, open partial laryngectomy, and radiotherapy.
- Anterior commissure invasion does not significantly influence local control after irradiation.
- Unfavorable T2 tumor may have better local control rates after open partial laryngectomy than following irradiation.

As a result of the similar favorable outcome between treatment types, these investigators identify that factors other than traditional survival analysis may become more important in choosing a treatment modality. Cost, convenience, and voice quality are factors that have become a larger part of the decision-making process at their institution.

Controversy persists regarding the capacity of radiotherapy to adequately address glottic cancer involving the anterior commissure. In 2001, Maheshwar and

Gaffney reported a 57% recurrence rate among patients with T1 glottic cancer with anterior commissure involvement who were treated with a minimum dose of 63 Gy in 30 fractions (6-week course) between the years 1989 and 1996 [44]. These investigators suggest their poor results may have resulted from the lack of pre-treatment CT imaging, which possibly caused understaging the extent of the disease at the anterior commissure.

Quality of voice and swallowing

Krengli *et al.* [45] in 2004 presented additional support for the premise that voice quality is generally better following treatment with radiotherapy rather than laser cordectomy. Other recent publications [46,47] also support this contention with the proviso that superficial endoscopic resections (type I and II as per the European Laryngological Society Working Committee [48]) may only minimally alter the voice in a manner that may not be discriminated from patients treated with irradiation [49].

Jepsen *et al.* [49a] in 2003 reported the retrospective analysis of voice and swallowing outcomes of 17 patients treated for T2 glottic (5) and T2 supraglottic (12) cancers. Although the numbers were too small to obtain statistical significance, trends toward poorer outcomes were seen for both speech and swallowing when adjuvant irradiation was used. Patients treated for supraglottic cancers tended to report better voice than swallowing outcomes; patients treated for glottic cancers reported better swallowing than voice outcomes.

Bernal-Sprekelsen *et al.* [50] published (2003) a large prospective analysis of swallowing function following endoscopic laser surgery. This analysis of 210 consecutive patients between 1998 and 2002 was performed at a single institution in Spain. T1 glottic cancers were excluded from analysis because laser treatment was not expected to impact negatively on swallowing function. The remainder of the patients with hypopharyngeal and supraglottic cancers of all stages coupled with T2–T4 glottic cancers was evaluated. The treatment philosophy at their institution during that time directed approximately 70% of all patients with laryngeal and hypopharyngeal cancer to receive primary treatment with endoscopic laser resection. All T1 and T2 tumors at these sites were initially treated with transoral resection. Among those cancers in this study, 28% were T3 and T4 tumors that were selected for laser excision based on good intraoperative exposure and “in which the amount of resected tissue or location was not expected to compromise deglutition”. A minimum follow-up period of 5 months was established with multiple variables analyzed. Nasogastric feeding tubes were required in 23% of small tumors (average 2.5 days) and in 63% of locally advanced tumors (average 14 days). A temporary cough was identified with feeding in 28% and pneumonia iden-

tified in 5.7% postoperatively. Tracheotomies “for severe swallowing difficulties” were needed in 3.8% and gastrostomies required in 6.2%. Six tracheotomies and five gastrostomies were considered permanent. These authors identified postoperative radiation had an adverse affect on swallowing function. Age was a variable that did not influence outcome. Through a comparison of their results with those published for external (open) approaches to tumor resection, these investigators endorse their management approach as one that reduces the need for tracheotomies and feeding tubes while likely preserving organs that otherwise would be sacrificed.

Laryngeal preservation

Supraglottic cancer

Davis *et al.* [51] in 2004 reported results from 46 patients treated by endoscopic laser resection and irradiation (in all but 8) for clinically determined T2 supraglottic cancer between the years 1987 and 1999. The follow-up for the 38 patients who completed treatment was from 9 to 156 months (average 66 months) with ultimate survival of 63%. The majority of deaths occurred from intercurrent disease. The purpose of article—to determine whether laser resection is a useful adjuvant to planned primary radiotherapy—distinguishes this article from most others that describe radiotherapy as the adjuvant to be used when surgery alone is expected to have a higher chance of failure. The authors cite a local control rate of 97% as evidence support for their use of endoscopic laser resection to precede definitive irradiation. They cite this figure as 10 to 20% better local control rates than seen with irradiation alone. As with other similar retrospective analyses, selection bias as well as differences in treatment (dose of irradiation, technique of supraglottic resection) makes a comparative interpretation of results with other studies difficult. The investigators identified that the number of cases was too small to assess the value of endoscopic surgery without irradiation as a useful technique. The article is distinguished by a clearly composed description of endoscopic laser technique and by the low complication rate seen despite the average postoperative irradiation dose of 66 Gy.

Glottic cancer

The work of Zeitels and Davis supporting the value of endoscopic resection of cancers affecting the anterior commissure is countered by that of Puxeddu *et al.* [52]. These investigators identified that two of the three patients with anterior commissure involvement identified after failed irradiation recurred a second time. They argue that an endoscopic approach is not adequate to address recurrent or persistent disease at this site due to the presence of deep nests of cancer cells. This diseased tissue could be hidden by superficial healing of the overlying mucosa allowing cancer to spread deeply into the visceral compartments through the laryngeal framework.

In the management philosophy espoused by Stoeckli *et al.* [53] the initial primary therapy was selected by the patient based on counseling regarding the relative advantages of each of the competing approaches. In a comparison study of 65 patients treated with laser surgery with 75 treated with radiotherapy during the period from 1990 to 1998 they found that for T1 and T2 glottic cancers laser surgery resulted in better laryngeal preservation rates. These investigators acknowledged that a selection bias may have influenced their conclusion that local tumor control is significantly better for T2 glottic cancer following endoscopic laser resection than when the initial treatment is with irradiation.

Quality of life

Jonathan Smith *et al.* [54] in 2003 published a quality of life and cost analysis of 101 patients retrospectively identified as having had treatment for cis and T1 glottic cancers between 1990 and 2000 at their institution. A larger proportion (59%) of the 74 patients treated surgically was contacted for response to a questionnaire than among the 11% of the 27 patients who were identified as having treatment with irradiation. Endoscopic laser excision (86%) was the most common surgical procedure and was followed in frequency by hemilaryngectomy (12%) and total laryngectomy (1%). Excellent quality of life and functional outcomes were reported from 'almost all patients' whether they were treated with surgery or irradiation. Hidden costs, in terms of number of hours of work lost, total travel time, total travel miles were greater for patients treated with irradiation. Actual costs were also higher for the irradiated group. These authors commendably identify that significant selection biases cloud the interpretation of their analysis. For example, quality of life was assessed not based on intent-to-treat, but following treatment. As a result, outcome is likely to be worse among the patients they were unable to contact, including those deceased patients who would therefore be rated with a very poor quality of life.

Conclusion

There has not yet been a randomized prospective study completed that successfully compares the effectiveness of endolaryngeal resection with either radiotherapy or open surgery [55]. Hopefully the completion of an ongoing randomized prospective multicenter study directed by William Coman from Brisbane Australia will provide useful data to permit analysis of the comparative value of these two treatment modalities [Coman W, personal communication]. Coman's study randomizes patients with early glottic cancer to treatment with either radiotherapy or endoscopic laser resection and evaluates multiple endpoints but directs its most detailed analysis to voice and quality of life outcomes. Another large study addressing endoscopic laser resection of upper aerodigestive tract cancer by a multicenter coalition in the US is nearing completion and is also prospective, but without

an arm randomized to nonsurgical treatment [56]. Studies such as these will hopefully offer insight to reduce the unknowns that now dominate the counseling and decision-making regarding endoscopic management of laryngeal cancer.

Endoscopic techniques in the management of laryngeal cancer continue to undergo modifications designed to improve oncologic efficacy in a manner that maximally preserves function. The modifications reported over the past two years have included the introduction of new diagnostic techniques, surgical approaches, endoscopes, and management philosophies. Despite these innovations and strong advocacy for their use, debate continues regarding the role that endoscopic management should play in the context of other competing options. Stoeckli *et al.* [57] offered a logical management philosophy for glottic carcinoma that addresses this debate. These investigators propose that the individual patient be the arbitrator in assessing the advantages and shortcomings to the alternative treatments in an open discussion.

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