CLINICAL REVIEW

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RECENT CHANGES IN THE TREATMENT OF PATIENTS WITH ADVANCED LARYNGEAL CANCER

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Abstract: Since the original data from the Department of Veterans Affairs Laryngeal Cancer Study Group demonstrated that nonsurgical therapy could achieve survival rates comparable to total laryngectomy in selected cases, there has been a progressive increase in employment of nonsurgical therapy for the management of advanced laryngeal cancer. Both neoadjuvant chemotherapy followed by conventionally fractionated or hyperfractioned radiotherapy for chemotherapy responders, or simultaneously administered chemoradiation has resulted in a significant number of patients who achieved cure while preserving their larynges. Nevertheless, combined chemotherapy and external beam radiation is associated with a variety of acute and chronic sequelae that can have a debilitating impact on function and quality of life. Although no therapeutic option is without risk, the decision regarding the modality of therapy for a patient with advanced laryngeal cancer should prompt a careful review of

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the current surgical techniques available for treatment. Data on quality of life and aging, as well as advances in minimally invasive surgical techniques, are available today that were not available at the time of the Veterans study. Selection of optimal therapy is often complex and raises the question whether the pendulum may have swung too far in the direction of nonsurgical therapy for advanced laryngeal cancer. This article reviews the current options available for a patient with advanced laryngeal cancer and discusses the impact of therapy. ©2007 Wiley Periodicals, Inc. *Head Neck* **30:** 103–110, 2008

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Cancer of the larynx is among the most common cancers of the upper aerodigestive tract and is diagnosed in nearly 10,000 men and women in the United States annually.[1] In the Developed World, 50% to 60% of patients present with early laryngeal cancer, defined by the American Joint Committee on Cancer as a T1 or T2 tumor without nodal involvement or distant metastases.[2] Advanced laryngeal cancer has been classified as locally advanced laryngeal cancer, locoregionally advanced laryngeal cancer, and disseminated laryngeal cancer.[3] It is generally accepted that the term "advanced" corresponds to stages III and IV of the TNM classification.

The current recommendations for the management of advanced laryngeal cancer have been published by the National Comprehensive Cancer Network (NCCN).[4] These recommendations reflect the results of several phase II and phase III studies as well as the opinions of the members of the committee assigned to the NCCN on head and neck cancer. Although the guidelines are revised every 2 years to reflect changing therapeutic trends, new data on the management of advanced laryngeal cancer and the impact of therapy are constantly being published in an effort to improve survival outcomes and quality of life (QOL). This review is an update of current data and thinking with regard to management of advanced laryngeal cancer.

NEOADJUVANT THERAPY, CHEMORADIATION, AND LARYNX PRESERVATION

The Department of Veterans Affairs Laryngeal Cancer Study Group (VALCSG)[5] was the first to demonstrate that nonsurgical therapy could achieve survival rates comparable to the "gold standard" of total laryngectomy, when neoadjuvant (or "induction") chemotherapy was employed to select those cases most likely to respond to radiation therapy (RT). The study demonstrated little difference in survival between total laryngectomy with postoperative RT, and induction chemotherapy followed by RT with surgery reserved for chemotherapy nonresponders. This landmark work demonstrated the potential value of nonsurgical therapy in achieving laryngeal preservation (64%) with survival rates comparable to surgery as primary treatment. Since this pioneering publication, the percentage of advanced-stage patients treated with combined-modality chemotherapy and RT, either sequentially or as chemoradiation, increased from 8.3% to 20.8%, whereas the proportion treated with RT alone decreased from 38.9% to 23.0%.[2] The Radiation Therapy Oncology Group (RTOG) (Head and Neck Intergroup) (RTOG 91-11)[6] subsequently demonstrated that concomitant chemoradiation achieved higher laryngeal preservation rates when compared with induction chemotherapy followed by RT, or RT alone. However, 5-year overall survival rates did not differ by treatment.

Although these randomized trials have changed the standard of care for advanced laryngeal cancer, there have been several criticisms of these trials. These include the fact that many of the tumors were considered "advanced" because of nodal status, not because of primary stage. Therefore patients with mobile cords might have been candidates for conservation laryngeal surgery, rather than total laryngectomy. It has also been suggested that many of the patients in the RTOG 91-11 trial had earlier stage disease than those in the original VALCSG study, again suggesting that these patients might have been candidates for conservation laryngectomy, not total laryngectomy. Given the documented excellent results with transoral laser microsurgery and supracricoid partial laryngectomy,[7–9] many argue that these confounding factors may have favorably influenced the overall survival rates and the rate of laryngeal preservation. In 2006, Foote et al[10] addressed these concerns and found that it is unlikely that the inclusion of patients with a mobile vocal cord would have significantly affected overall survival or laryngeal preservation rate for either the VALCSG or RTOG 91-11 studies. Despite this report, and several others examining the results of these studies,[8,11] many head and neck oncologists have conflicting views about optimal candidatures for nonsurgical therapy.

Although the VALCSG data[5] suggested that neoadjuvant chemotherapy failed to exert a signif-

icant impact on overall survival, it and several other studies have demonstrated that induction chemotherapy may have an important role in the contemporary management of advanced laryngeal cancer. It has become clear that while some patients benefit from chemoradiation, there is another subgroup that will not respond to chemoradiation and would benefit from initial total laryngectomy and postoperative RT. This would suggest that appropriate patient selection might be the key to optimizing treatment outcome. The VALCSG study employed 3 cycles of chemotherapy to make this selection, thus delaying the institution of definitive treatment by several months. In 2006, Urba et al[12] conducted a phase II organ preservation trial in 97 patients to determine if late salvage surgery rates could be decreased and survival improved by selecting patients for organ preservation predicated on the response to a single cycle of induction chemotherapy. One third of the patients had T4 (cartilage invasion) primary cancers. Of the 97 eligible patients, 73 (75%) achieved more than 50% response and consequently were treated with chemoradiation. Twenty-nine (30%) of the total group underwent salvage surgery. Twenty percent had early salvage surgery after the single cycle of induction chemotherapy produced less than a 50% response. Three percent of patients had late salvage surgery after failure of chemoradiation, and 6% of patients had salvage surgery for recurrence. Larynx preservation was achieved in 70% of patients, and the 3-year cause-specific survival rate was 87%, significantly better than an immediately previous historical control cohort of comparable patients. This study confirmed the benefit of single cycle induction chemotherapy in predicting response to chemoradiation and suggested that overall survival rates could be improved with such an induction regimen.

In 2006, Majem et al[13] studied 71 patients with advanced laryngeal cancer who received induction chemotherapy with 3 cycles of cisplatin plus fluorouracil. Patients who experienced a complete response received hyperfractionated RT, whereas those without complete response were offered a total laryngectomy. Thirty-three (46.5%) of patients achieved complete response to induction chemotherapy and were irradiated. Four of these patients experienced a tumor relapse, and all underwent salvage surgery. Seventy-six percent of the surviving patients had a functional larynx. Despite not achieving complete response, 15 patients refused total laryngectomy and received hyperfractionated RT. Seven patients demonstrated tumor relapse and salvage surgery was performed in 3 of them. Fifty percent of surviving patients had a functional larynx. Twenty-two patients without complete response underwent total laryngectomy. No differences in overall survival were observed between groups. However, 10 patients in whom the larynx had been anatomically preserved developed functionless larynges because of chronic toxicity from the treatment. Majem et al[13] concluded that patients with complete response to induction chemotherapy for laryngeal cancer have a high probability of cure after hyperfractionated RT. Nevertheless, hyperfractionated RT is accompanied by a high degree of toxicity that reduces preservation of laryngeal function and may jeopardize QOL and overall survival.

Although induction chemotherapy offers the ability to predict response and outcome of nonsurgical treatment, the results of the RTOG 91-11 study showed that induction chemotherapy followed by conventionally fractionated RT is not the most effective nonsurgical approach for laryngeal preservation.[6] In this 3-arm phase III study, patients with locally advanced cancer of the larynx were randomly assigned to receive either RT alone, or induction chemotherapy with cisplatin followed by RT, or concomitant chemoradiation with cisplatin. After 2 years, the rate of larynx preservation was highest among those who received concomitant chemoradiation (88%) and was significantly higher than after RT alone (70%) or induction chemotherapy followed by RT (75%). However, although locoregional control was also highest after concomitant chemoradiation, this difference did not translate into an overall survival benefit. Five-year survival rates were similar among all 3 treatment groups and were highest in the group receiving induction chemotherapy. Generally, survival rates were lower in patients who required surgical salvage in comparison to those who achieved successful larynx preservation.[14] Although this study has been criticized, as previously mentioned, concomitant chemoradiation is currently the most popular and widely applied nonsurgical approach for larynx preservation.[9,15]

CHEMOTHERAPY ALONE

In 2007, Bonfils et al[16] evaluated, in a retrospective study, the results of chemotherapy alone in patients with invasive squamous cell carcinoma of

the larynx had achieved a complete clinical response after an induction chemotherapy protocol. The survival rate of the complete responder group was significantly higher than that of the incomplete responder group subsequently treated with conventional modalities. No statistically significant difference was noted between the 2 groups in terms of local and nodal recurrence. The authors suggested that chemotherapy alone is a viable option in selected patients with carcinoma of the larynx who achieved a complete clinical response after an induction chemotherapy protocol. This therapeutic approach allows surgery and/or RT to be reserved for the management of metachronous second primary tumors.

Recently, Worden et al[17] used the response to an initial course of induction chemotherapy in patients with stages III or IV cancers, to select complete histologic responders for exclusive chemotherapy treatment. Preliminary analysis indicated excellent primary site control and organ preservation but inadequate regional tumor control with chemotherapy alone.

Although the results of these studies are of interest, current treatment guidelines indicate that chemotherapy alone should be used only in clinical trials, in patients with a complete clinical response following 3 courses of neoadjuvant chemotherapy.

MOLECULAR THERAPY

For patients who experience treatment failure with first-line therapy for recurrent or metastatic disease, a median overall survival of 3 to 4 months has been observed after treatment with second-line chemotherapy.[18] There is, therefore, a need for new therapeutic strategies focused on molecular targets. The 2 targeting strategies that have proven most successful in clinical applications thus far have been small-molecule tyrosine kinase inhibitors (gefitinib and erlotinib) or monoclonal antibodies directed against the epidermal growth factor receptor (EGFR), such as cetuximab. The EGFR and its ligands have been recognized as critical proteins in the development and survival of epithelial tissues, and the great majority of squamous cell carcinomas of the head and neck (SCCHN) express EGFR. Inhibition of EGFR signaling by small molecules, monoclonal antibodies directed against ligands or receptors, immunotoxin conjugates, or antisense oligonucleotides has demonstrated important activity in different models of SCCHN.[19] Recently, a multinational, randomized study comparing the effect of RT alone with RT plus cetuximab showed that the median duration of loco-regional control was 24.4 months among patients treated with cetuximab plus RT and 14.9 months among those given RT alone. Similar results were observed concerning the median duration of overall survival, which were 49.0 months among patients treated with combined therapy and 29.3 months among those treated with RT alone.[20] These results were most prominent in patients with oropharyngeal primary tumors, with little difference in outcome for patients with laryngeal or hypopharyngeal cancers.

On the other hand, reports of the combination of gefitinib or erlotinib with cytotoxic chemotherapy have been presented showing a 50% and 78% overall response rate, respectively.[21] It is also apparent that these agents and many others have, on average, more limited toxicity than do traditional chemotherapeutic agents. Their efficacy must be assessed using additional parameters, including disease stabilization and QOL instruments, as well as phase III trials.

FUNCTION, QUALITY OF LIFE, AND COST OF TREATMENT

Improved cure rates, prolonged disease-free survival, and organ preservation are 3 of the primary goals of the treatment of advanced laryngeal cancer. While improved cure rates and prolonged disease-free survival are the primary focus of all cancer therapy, the implicit purpose of organ preservation is improved function and QOL. However, preservation of an organ does not equate to conservation of organ function.[22,23] Therefore, the literature related to this topic must be interpreted carefully. Preservation of the larynx says nothing about the presence of a tracheotomy, the quality of voice, or the presence of dysphagia and dependence on gastrostomy feedings.

There are few studies evaluating the QOL specifically related to swallowing. In 2006, Dworkin et al[24] evaluated a series of subjects treated for advanced laryngeal cancer with nonsurgical therapy for swallowing function, time from treatment to swallowing, and sequelae of nonsurgical therapy. The study included 14 patients, all of whom were treated with 7000 cGy using standard external beam RT to the primary site, and 5000 cGy to the ipsilateral neck (1 patient excluded). Two patients received RT alone, whereas several patients received 3 courses of neoadjuvant cisplatin

and 5-fluorouracil, followed by 3 courses of concurrent cisplatin and RT. Patients were evaluated retrospectively using fiberoptic endoscopic evaluation of swallowing and patient interviews to evaluate the patients' perceived swallowing function and diet. In this study, 10 of 14 patients had mild to severe dysphagia, and there was no significant difference between those evaluated early in the course of therapy (less than 1 year) or later (more than 1 year after therapy). Five patients required a tracheotomy during the course of therapy, and only 2 patients were decannulated following therapy. Four patients required gastrostomy tubes, and only 2 patients had the tubes removed following therapy. One patient suffered an RT-induced oropharyngeal stricture. In this study, all the patients suffered from "substantial swallowing difficulties" following organ preservation therapy. Not unlike other studies,[25–27] more than 90% of patients suffered abnormal swallowing function, including pooling of secretions and trace aspiration following treatment.

These findings are in stark contrast to those reported by Fung et al,[28] who also evaluated the impact of organ preservation therapy on voice and swallowing therapy in patients with advanced cancers. They found that voice-related QOL was better in patients after chemoradiation when compared with total laryngectomy. They also found that while swallowing function was good in all patients, those with an intact larynx were more likely to obtain nutrition by oral intake without supplements. An explanation of the differing conclusions of these studies might be inferred from the criteria employed to define satisfactory swallowing function. In the study by Fung et al,[28] the definition of satisfactory function was nutritional mode consisting of oral intake alone without nutritional supplements. Such factors as pooling of saliva or minimal aspiration, employed in many of the other studies, were not considered.

In 2007, Nguyen et al[29] compared incidence and degree of aspiration by barium swallow examination in 43 patients, free of tumor after treatment, who complained of aspiration after chemoradiation (22 patients) or RT alone (21 patients). Aspiration occurred in 12 patients (54%) of the chemoradiation group, and 7 patients (33%) of the RT alone group. The difference was not statistically significant ($p = .13$). There was a high proportion of patients with large tumors in the chemoradiation group, although not statistically significant. The authors suggest that this trend toward aspiration may be related to tumor size, as well as the additional toxic effects of chemotherapy, and that the lack of significance was due to small sample size. The article does not make clear the overall incidence of dysphagia and aspiration among all patients treated, as the study was confined only to patients who complained of dysphagia.

Loss of laryngeal function is often attributed to chondronecrosis. In 2006, Zbären et al[30] performed a retrospective study on 341 patients treated by RT alone or radiochemotherapy. The incidence of chondroradionecrosis in 341 irradiated patients was 5%. Tumor was present in 6 of 10 patients who underwent surgery for chondronecrosis. Chondronecrosis was often undetectable on radiographic examination. The authors concluded that chondronecrosis was rare. When present, tumor recurrence often was situated beneath an intact mucosa and was not evident on endoscopic examination.

Because the overall survival rates associated with surgical and nonsurgical therapies are not appreciably different, the focus of recent literature has been on the impact of therapy on QOL, the cost of therapy, and the ability to achieve reproducible results with nonsurgical treatment regimens. Assessing QOL is a difficult task. Hanna et al[31] reviewed 42 patients with advanced stages III or IV cancer of the larynx that were treated with either concurrent chemoradiotherapy or laryngectomy with postoperative RT. QOL was measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) in tandem with the head and neck module (EORTC QLQ-H&N35). Hanna et al[31] found no statistically significant differences in the overall QOL between the 2 groups. This study is unique in that a functional subscale analysis was performed and the authors found that surgery patients reported significantly greater difficulties with smell and taste, use of painkillers, and coughing, whereas chemoradiation patients reported significantly greater problems with xerostomia. The authors concluded that both chemoradiation and laryngectomy impact negatively on QOL in different ways. Although differences in QOL could be detected by functional and subscale analyses, the overall QOL scores of both groups were similar.

The conflicting data on QOL has prompted some to consider the cost of therapy as a consideration for choice of therapy. Davis et al[32] set out to perform a cost minimization analysis of total laryngectomy with postoperative RT versus induction chemotherapy with subsequent RT in

patients with advanced (stages III or IV) squamous cell carcinoma of the larynx. The authors employed a decision-analysis model using data from peer-reviewed trials, case series, meta-analyses, and Medicare diagnosis-related group reimbursement rates. The authors found that total laryngectomy with postoperative RT cost nearly $3000 U.S. dollars less than organ preservation treatment for advanced laryngeal cancer. The authors suggested that cost and patient preference should be considered when establishing a treatment modality for patients with advanced laryngeal cancer.

AGE

In addition to the factors of function, QOL, and cost, consideration must be given to the age and comorbid status of the patient. According to the Department of Health and Human Services report on aging,[33] persons 65 years or older numbered 36.3 million in 2002 and represented 12.4% of the United States population; or about 1 in every 8. By 2030, there will be about 71.5 million older persons, constituting 20% of the population. The elderly represent the fastest growing subpopulation in North America and Europe. As the aging population grows, the number of aged with advanced laryngeal cancer will also grow. Many of the physiologic changes associated with age do not represent a direct risk for surgical complications or complications related to chemoradiation. Nevertheless, the physiologic changes that are characteristic of advanced age can result indirectly in a higher risk of morbidity. The normal age-related decline in immunologic function, renal function, and vascular compliance may predispose elderly patients to complications of therapy and therefore must be carefully evaluated. Emerging data from meta-analyses of concurrent chemoradiation protocols indicate a decreasing benefit with increasing patient age and lack of significant benefit when chemotherapy is added to RT in patients over the age of 70 years.[34]

The shift toward nonsurgical therapy for the management of advanced laryngeal cancer has generated considerable debate as to whether elderly patients can tolerate chemoradiation therapy for a period of 2 to 3 months. The majority of chemotherapy protocols do not include elderly patients in their studies. Often not addressed is the anecdotal observation that salvage surgery in elderly individuals may be extremely complex and such patients may not tolerate salvage surgery. Clayman et al[35] reviewed 43 patients aged 80 years and older in a case-controlled study. Only 23.3% of the octogenarians were treated with adjuvant therapy, whereas 44.1% of the younger controls received adjuvant therapy. Clayman et al[35] found that multimodality therapy among the octogenarian population may be limited by a patient's ability to tolerate therapy. Similarly, postoperative RT may not be tolerated well by elderly patients. The authors point out that following major surgery, the patient may refuse postoperative RT, especially if postoperative complications had occurred. Clayman et al[35] state that the psychosocial status of elderly patients has a significant impact on the course of the disease, highlighting both the predilection for less aggressive and substandard therapy in the elderly and the likely misperception that age may adversely affect disease-free survival.

There is a paucity of data to suggest that age alone is associated with a higher risk of surgical complications and in fact, the great majority of studies assessing the impact of age on surgical morbidity suggest no relationship between advanced age and surgical morbidity.[36–39] However, as mentioned earlier, the comorbidities associated with age may indirectly affect an elderly patient's ability to tolerate surgery and prolonged anesthesia. One recent study reviewed the American College of Surgeons National Surgical Quality Improvement Program database for patient demographics, preoperative risk factors, intraoperative risk factors, and 30-day outcomes with a focus on those aged 80 years and older.[40] The authors reviewed 7696 surgical procedures and found that hypertension and dyspnea were the most frequent risk factors in those aged 80 years and older. Preoperative transfusion, emergency operation, and weight loss best predicted morbidity for those 80 years of age and older. They also noted the American Society of Anesthesiologists' classification, which predicts mortality across all age groups. A 30-minute increment of operative duration increased the odds of mortality by 17% in patients older than 80 years, and postoperative morbidity and mortality increased progressively with age. Age was statistically significantly associated with cardiovascular, renal, respiratory, and wound-healing complications. This study is highlighted because it is one of the few studies that suggest that age may be related to surgical morbidity. More importantly, this study defines factors that can be controlled prior to surgery in an effort to reduce the risk of surgery.

CONCLUSIONS: SELECTION OF OPTIMAL TREATMENT

There is excellent data to support the use of induction chemotherapy as a predictor of radiosensitivity and for selection of patients for definitive RT or laryngectomy. Concomitant chemoradiation offers the highest chance of laryngeal preservation, but with a significant incidence of functional problems affecting deglutition, need for tracheotomy, and QOL. There is also data to suggest that other factors, including cost, age, and patient comorbidity, should be considered in the decision-making process. In the final analysis, every patient is unique, and therefore, no single therapeutic modality is ideal for every patient.

Organ preservation protocols and endoscopic resection have demonstrated clear progress concerning posttreatment function of patients with laryngeal carcinomas. However, according to the National Cancer Data Base, survival has decreased among patients with laryngeal cancer during the past 2 decades in the United States.[41] The most notable decline in the 5-year relative survival occurred among advanced-stage glottic cancer, early-stage supraglottic cancers, and supraglottic cancers classified as T3N0M0. An increase in the use of chemoradiation has paralleled increased mortality of patients with laryngeal cancer. Although there has been an increase in endoscopic surgery for laryngeal cancer, lack of data about surgical detail prevents conclusions being drawn in relation to mortality.[41] Therefore, it is of paramount importance to critically evaluate treatment protocols and continue to seek more effective strategies to provide both better QOL and improved survival rates.

Thus choice of treatment has to take into consideration patient factors, such as performance status, access to support services and to close follow-up, and institutional factors such as swallowing and nutritional support, and post-chemoradiation salvage surgery expertise. As we gain an appreciation of the long-term morbidity associated with nonsurgical therapy, the impact of our therapeutic options should be carefully considered, particularly if survival rates are not enhanced. It may be that primary surgical therapy for some patients offers advantages that cannot be realized by nonsurgical techniques. The ability to perform conservation partial laryngectomy procedures using open and transoral approaches holds promise insofar as that a proportion of patients with advanced cancers may benefit from surgery with postoperative adjuvant therapy at a dose that may be more favorably tolerated.

The future of treatment of advanced laryngeal cancer should include better patient selection and identification of the most appropriate treatment modalities for defined populations.[42]

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