American Society of Clinical Oncology Clinical Practice Guideline for the Use of Larynx-Preservation Strategies in the Treatment of Laryngeal Cancer

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ABSTRACT

Purpose To develop a clinical practice guideline for treatment of laryngeal cancer with the intent of preserving the larynx (either the organ itself or its function). This guideline is intended for use by oncologists in the care of patients outside of clinical trials.

Methods A multidisciplinary Expert Panel determined the clinical management questions to be addressed and reviewed the literature available through November 2005, with emphasis given to randomized controlled trials of site-specific disease. Survival, rate of larynx preservation, and toxicities were the principal outcomes assessed. The guideline underwent internal review and approval by the Panel, as well as external review by additional experts, members of the American Society of Clinical Oncology (ASCO) Health Services Committee, and the ASCO Board of Directors.

Results Evidence supports the use of larynx-preservation approaches for appropriately selected patients without a compromise in survival; however, no larynx-preservation approach offers a survival advantage compared with total laryngectomy and adjuvant therapy with rehabilitation as indicated.

Recommendations All patients with T1 or T2 laryngeal cancer, with rare exception, should be treated initially with intent to preserve the larynx. For most patients with T3 or T4 disease without tumor invasion through cartilage into soft tissues, a larynx-preservation approach is an appropriate, standard treatment option, and concurrent chemoradiotherapy therapy is the most widely applicable approach. To ensure an optimum outcome, special expertise and a multidisciplinary team are necessary, and the team should fully discuss with the patient the advantages and disadvantages of larynx-preservation options compared with treatments that include total laryngectomy.

INTRODUCTION

In 2005, an estimated 9,880 new cases of laryngeal cancer will be diagnosed in the United States, accounting for 3,770 deaths.[1] Squamous cell carcinoma is the predominant histologic type, and approximately 40% of patients will have stage III or IV disease when first evaluated.[2] Most cases of laryngeal cancer are associated with a history of tobacco and/or alcohol use, so the treatment of patients is complicated by medical comorbidity and the development of second primary cancers.[3-5]

Given the fundamental role the larynx plays in human speech and communication, determining the optimal management of laryngeal cancers must involve consideration of both survival and the functional consequences of a given treatment approach. The potential morbidity of curative treatment is a special consideration when total laryngectomy, either for primary therapy or as salvage treatment, is the recommendation. Total laryngectomy is widely recognized as one of the surgical procedures most feared by patients. Social isolation, job loss, and depression are common sequelae.[6,7] Pioneering work on patient preferences showed that approximately 25% of healthy individuals interviewed were willing to trade a 20% absolute difference in survival for the opportunity to save their voice.[8] Different voice rehabilitations exist,[9] but many patients are dissatisfied with the results and report associated restrictions in their daily lives. Although the impact of the procedure on voice often receives the greatest attention, the presence of the stoma may adversely affect quality life as much, if not more.[10] Accordingly, there has been keen interest in the development and refinement of organ-preservation therapies, such as radiation therapy alone, the combination of chemotherapy and radiation therapy (chemoradiation therapy), and function-preserving partial laryngectomy procedures. With all three of these approaches, total laryngectomy is reserved for tumor recurrence.

Although there is little argument that cure and preservation of function are both important goals of therapy for laryngeal cancer, there is considerable controversy about how to best achieve these goals through application of the aforementioned treatment options. For limited-stage disease, radiation therapy and surgery (including endoscopic cordectomy with or without the use of laser), and for advanced disease at the primary site, radiation therapy alone, chemoradiation therapy, and surgery (most commonly total laryngectomy) are all widely applied. The findings of practice variation studies confirm wide variations in practice and suggest that treatment selection may be influenced by physician specialty and nonmedical factors such as

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geography.[11,12] Practice variation is documented among university centers as well.[13] All the approaches require special expertise and careful integration of care to optimize outcomes.

In the context of larynx preservation, some might argue that total laryngectomy should be applied exclusively as salvage therapy. However, ill-advised application of a function-preserving approach may be associated with disappointing disease control and functional outcomes, and the morbidity and cost of treatment may increase. If salvage total laryngectomy is required, the patient would arguably have been best served by having total laryngectomy as the initial treatment. Furthermore, for most patients, cure is the highest priority, even in light of significant disability and adverse effects.[14]

The American Society of Clinical Oncology (ASCO) fully appreciates these issues and their applicability to the management of laryngeal cancer. Accordingly, as a service to patients, to its members, and to practicing physicians generally, ASCO convened an Expert Panel under the auspices of its Health Services Research Committee to develop recommendations regarding the appropriate application of larynx-preservation therapies. This report describes the aims, methods, and results of this Panel's deliberations.

Questions

For patients with squamous cell laryngeal cancer, the following questions were addressed by the Panel:

(1)   What are the larynx-preservation treatment options for limited stage (T1, T2) primary-site disease that do not compromise survival? What are the considerations in selecting among them?

(2)   What are the larynx-preservation treatment options for advanced stage (T3, T4) primary-site disease that do not compromise survival? What are the considerations in selecting among them?

(3)   What is the appropriate treatment of the regional cervical nodes for patients with laryngeal cancer who are treated with an organ-preservation approach?

(4)   Are there methods for prospectively selecting patients with laryngeal cancer to increase the likelihood of success of larynx preservation?

Practice Guidelines

"Practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances."[15] Attributes

of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation.[15] Guidelines may be useful in producing better care and decreasing its cost. Specifically, utilization of clinical guidelines may provide:

       (1) improvements in outcomes,

       (2) improvements in medical practice,

       (3) a means for minimizing inappropriate practice variation,

       (4) decision support tools for practitioners,

       (5) points of reference for medical orientation and education,

       (6) criteria for self-evaluation,

       (7) indicators and criteria for external quality review,

       (8) assistance with reimbursement and coverage decisions, and

       (9) criteria for use in credentialing decisions.

In formulating recommendations for the use of larynx-preservation strategies in the treatment of laryngeal cancer, ASCO considered these tenets of guideline development, emphasizing review of data from controlled clinical trials. However, it is important to realize that many management questions have not been comprehensively addressed in randomized trials and guidelines cannot always account for individual variation among patients. A guideline is not intended to supplant physician judgment with respect to particular patients or special clinical situations and cannot be considered inclusive of all proper methods of care or exclusive of other treatments reasonably directed at obtaining the same results.[*]

METHODS

Panel Composition

The Expert Panel was composed of experts in clinical medicine; medical, radiation, and surgical oncology; diagnostic imaging; clinical research; outcomes/health services research; and

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[*] Accordingly, ASCO considers adherence to this guideline to be voluntary, with the ultimate determination regarding its application to be made by the physician in light of each patient's individual circumstances. In addition, the guideline describes administration of therapies in clinical practice; it cannot be assumed to apply to interventions performed in the context of clinical trials, given that clinical studies are designed to test innovative and novel therapies in a disease and setting for which better therapy is needed. Because guideline development involves a review and synthesis of the latest literature, a practice guideline also serves to identify important questions for further research and those settings in which investigational therapy should be considered.

related disciplines (biostatistics, quality of life) with a focus on expertise in head and neck and laryngeal cancer. A patient representative was also included on the Panel. Both academic and community practitioners were included. A steering committee under the auspices of the Health Services Research Committee chose Panel participants to develop the Clinical Practice Guideline. Panel participants are listed in Appendix A.

Process Overview

The scope of the guideline, the clinical management questions to be addressed, and the literature search strategy were determined. Working groups within the Panel were created on the basis of interests and expertise, to focus on particular management questions and related review of the evidence. Each of these smaller groups developed applicable treatment recommendations and supporting text and identified areas of controversy and conflicting interpretations of the evidence. These subsections were the basis of the final document, which was then synthesized and further critiqued and revised by the Expert Panel.

Literature Review and Data Collection

Pertinent information from the published literature through November 2005 was retrieved and reviewed for the creation of the guideline. Articles published from 1990 onward were emphasized. Searches were performed of MEDLINE (National Library of Medicine, Bethesda, MD) and CANCERLIT (National Cancer Institute, National Institutes of Health, Bethesda, MD) for pertinent articles. The search strategy included the following key words: "larynx" plus "chemotherapy," "surgery," "radiation therapy," "organ preservation," "neck management," "diagnosis," "surveillance," "preservation," "head and neck," "staging," or "quality of life"; "organ preservation" plus "head and neck" or "neck management." Directed searches were made of the primary articles. Search results were limited to studies involving humans and English-language articles. The Cochrane Library (http://www.cochrane.org/) was searched using the phrase "larynx cancer." Directed searches based on the bibliographies of primary articles were also performed. Recent data presented at ASCO Annual Meetings were added to the evidence for this guideline at the discretion of members of the Expert Panel. The results of randomized controlled trials of site-specific disease were emphasized. Randomized trials that included some patients with laryngeal cancer as well as single-arm, disease site-specific studies were also considered.

Consensus Development Based on Evidence

The entire Panel met twice. The first meeting was designed to clarify the charge, identify topics to be addressed by the guideline, develop a strategy for completion of the guideline, perform a preliminary review of the initial literature search, and develop a strategy for refining the literature search. The purpose of the second meeting was to review the tentative recommendations and supporting evidence more critically. The guideline was circulated in draft form, and all members of the Panel had an opportunity to comment and address different interpretations of the evidence and related recommendations. A subgroup of Panel members met once to finalize guideline content. Final text editing was performed by David G. Pfister, MD, and Gregory T. Wolf, MD.

Guideline and Conflict of Interest

The content of the guideline were reviewed and approved by the Health Services Research Committee and by the ASCO Board of Directors before dissemination. All members of the Expert Panel complied with the ASCO policy on conflicts of interest, which requires disclosure of any financial or other interests that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel completed ASCO's disclosure form and were asked to identify ties to companies developing products that might potentially be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. No limiting conflicts with respect to the recommendations of the guideline were identified.

Revision Dates

At annual intervals, the Co-Chairs of the Expert Panel (D.G.P. and G.T.W.) and two Panel members designated by the Co-Chairs will determine the need for revisions to the guideline based on an examination of current literature. The entire Panel will be reconvened every 3 years to discuss potential changes, or more frequently, if new information suggests that more timely modifications may be warranted. When appropriate, the Panel will recommend a revised guideline to the Health Services Research Committee and the ASCO Board for review and approval.

Definition of Terms/Methodologic Issues

Squamous cell carcinoma is the histologic subtype of laryngeal cancer in more than 95% of cases. Accordingly, this guideline focuses only on invasive laryngeal cancers of this histologic subtype.

Tumors in other sites (such as the hypopharynx, oropharynx-base of tongue, or cervical esophagus) often necessitate resection of the larynx in part or in total. This guideline, however, is limited to cancer of the larynx.

The larynx is divided into three parts: the supraglottis (epiglottis, arytenoids, aryepiglottic folds, false cords), glottis (true cords, anterior and posterior commissures), and subglottis. Although tumors in these areas are frequently combined in studies, the natural histories of the tumors can differ. Subglottic tumors are especially uncommon. Most of the available evidence, especially the randomized trials, provides information primarily on the therapy of supraglottic and glottic cancers. Accordingly, the guideline will be most applicable to these two anatomic subsites.

The tumor-node-metastasis (TNM) system for staging of laryngeal cancer is mutually agreed on by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC; Table 1).[16] However, the version of the staging system used in studies may differ because substantial revisions to the system have been made periodically over the past 20 years. Furthermore, the increased availability and use of cross-sectional imaging over time can affect staging, leading to stage migration and an impact on reported results.[16] Although T stage is a prognostic factor commonly used for comparing results, it is widely appreciated that there remains clinical and prognostic heterogeneity within T stages, and that patients selected for surgery or radiation-based therapy may represent very different manifestations of the disease. The treatment of M1 disease will not be considered in this guideline, because the adverse prognostic implications of distant metastasis clearly has an impact on the approach to the primary site.

The concept of larynx or organ preservation is applicable only to patients with resectable disease. For example, it is not accurate to state that total laryngectomy is avoided if the procedure is not feasible. As such, studies of radiation-based "larynx preservation" imply that all patients have resectable disease and should be distinguished from studies with more generic eligibility criteria that may include a mixture of patients with resectable and unresectable disease.

Organ preservation or conservation surgery for laryngeal cancer includes techniques that involve resection of the lesion and allow for speech and swallowing without a permanent tracheostomy. The goal is to obtain negative margins while preserving structures key to the preservation of function. Organ-preservation surgery includes both endoscopic resections (with and without laser) as well as open techniques (larynx-conservation surgery). The T-staging system is useful for treatment planning for nonoperative organ-preservation techniques, such as radiation therapy with or without chemotherapy, but it has less of a role in planning for organ-preservation surgery. Simple T-staging classifications do not reflect tumor extent precisely enough to be directly correlated with specific organ-preservation procedures in all cases.

Summary of Outcomes Assessed

Overall survival, rates of disease control and larynx preservation, and treatment toxicities were the primary outcomes assessed, as these were the end points most commonly provided in the clinical studies reviewed (Table 2). With larynx-preservation therapies, however, rates of local control and larynx preservation are intermediate and imperfect markers for the more fundamental end points of treatment success: speech and swallowing function and quality of life. Despite improvement in these outcomes being a central goal of larynx-preservation therapy, more rigorous, site-specific data regarding functional and quality-of-life outcomes in this setting derived from studies in which the compared therapies were randomly assigned are limited. Similarly, data on cost comparisons of different treatment options are limited. In the Panel's view, more information on the impact of therapy on symptoms, quality of life/function, and costs are needed.

GUIDELINE FOR LARYNX-PRESERVATION TREATMENT

We have summarized the recommended treatment strategies by T stage, along with the basis for the recommendations and the quality of the supporting evidence (Table 3).

1. What are the larynx-preservation treatment options for limited stage (T1, T2) primary-site disease that do not compromise survival? What are the considerations in selecting treatment options in this setting?

Summary of Recommendations

Question 1	2005 Recommendations
What are the larynx-preservation treatment options for limited-stage (T1, T2) primary-site disease that do not compromise survival? What are the considerations in selecting treatment options in this setting?	All patients with T1-T2 laryngeal cancer should be treated, at least initially, with intent to preserve the larynx.
	T1-T2 laryngeal cancer can be treated with radiation or larynx-preservation surgery with similar survival outcomes. Selection of treatment depends on patient factors, local expertise, and the availability of appropriate support and rehabilitative services. Every effort should be made to avoid combining surgery with radiation therapy because functional outcomes may be compromised by combined-modality therapy; single-modality treatment is effective for limited-stage, invasive cancer of the larynx.
	Surgical excision of the primary tumor with intent to preserve the larynx should be undertaken with the aim of achieving tumor-free margins; so-called narrow-margin excision followed by postoperative radiation therapy is not an acceptable treatment approach.
	Local tumor recurrence after radiation therapy may be amenable to salvage by organ-preservation surgery but total laryngectomy will be necessary for a substantial proportion of patients, especially those with index T2 tumors.
	Concurrent chemoradiation therapy may be used for larynx preservation for selected patients with stage III, T2 N+ cancers for whom total laryngectomy is the only surgical option, when the functional outcome after larynx-preservation surgery is expected to be unsatisfactory, or when surgical expertise in such procedures is not available.
	Limited-stage laryngeal cancer constitutes a wide spectrum of disease. The clinician must exercise judgment when recommending treatment in this category. For a given patient, factors that may influence the selection of treatment modality include extent and volume of tumor; involvement of the anterior commissure; lymph node metastasis; the patient's age, occupation, preference, and compliance; availability of expertise in radiation therapy or surgery; and history of a malignant lesion in the head and neck.

Evidence Review

There are no randomized studies in which radiation therapy was compared with conservation surgery with respect to local control or survival for patients with limited-stage laryngeal cancer. Similarly, there are no randomized controlled data on comparison of functional outcomes, specifically quality of voice and swallowing ability, after surgery or radiation therapy for patients with this stage of disease. Unlike the case with local control and survival, assessment of the quality of voice is more difficult to standardize and compare. The issue is further complicated by the fact that the quality of voice after treatment depends on a number of patient-

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and tumor-related variables. Available data and clinical experience indicate that all patients with T1-T2 laryngeal cancer should be treated, at least initially, with the intent of larynx preservation.

Induction chemotherapy has been investigated as treatment for patients with limited-stage laryngeal cancer. After long-term follow-up, disease has been controlled with chemotherapy alone for selected patients treated with this approach.[16,17] However, insufficient data are currently available to recommend such an approach for patients with T1-T2 disease outside the context of a clinical trial.

The limited data available regarding the relative impact of different therapeutic modalities on the quality of life consist of case series of small numbers of patients, most of which are retrospective studies. In three prospective studies, of which the largest enrolled 84 patients, quality-of-life measures using different standardized scales were obtained at diagnosis and then again at various time points after completion of treatment.[18-20] The majority of patients in these studies had T1-T2 disease and were treated with radiation. Overall, the findings of the studies suggest that although there are detectable treatment-emergent symptoms, these do not appear to have a significant effect on overall quality of life.

T1 Cancer of the Glottis

Endoscopic excision of T1 cancers, usually not involving the anterior commissure, has yielded control rates of 89% to 100%.[21-28] The local control rate for T1 lesions of the larynx after radiation therapy ranges from 78% to 94%.[29-40] Involvement of the anterior commissure results in poorer local control rates irrespective of treatment modality. Adequate delivery of radiation dose to this region of the larynx has been difficult with traditional techniques. Similarly, the anterior commissure is not easy to access endoscopically, although the findings of recent studies have indicated the effectiveness of endoscopic laser resection.[41,42] More importantly, however, tumors in this region are at risk of being undertreated if invasion of the thyroid cartilage is not recognized. If clinical examination reveals tumor at the anterior commissure, high-resolution computed tomography (CT) of the larynx should be performed to determine if there is invasion of the cartilage. Radiation therapy and endoscopic laser resection are both acceptable options in the absence of such invasion.

Both radiation therapy and surgery may result in an abnormal voice by causing edema, stiffness, scarring, atrophy, and mucosal changes of the vocal cord or cords. Changes after endoscopic laser surgery are confined to the site of resection, but changes after open surgery and

radiation therapy are generally more extensive. The quality of voice after treatment depends on the interplay of numerous factors related not only to the type of treatment but also to the tumor (location and depth of invasion of tumor) and to host characteristics (eg, age, smoking, comorbidity, voice abuse). In most studies in which a direct comparison of the quality of voice has been attempted, the quality after endoscopic laser resection is comparable to that after radiation therapy for limited stage glottic cancer,[25,43-47] although a few investigators have reported that the quality of the voice is better after radiation therapy.[25,46] If voice outcome is predicted to be good after endoscopic laser resection (eg, a superficial tumor located in the middle third of the cord, especially on its free edge), this modality is more efficient and thus preferred. The addition of radiation therapy is unnecessary when the presence of microinvasive cancer is noted after the complete endoscopic excision of a discrete glottic lesion.[22,48] Lesions that are indistinct, especially those arising in the context of widespread, abnormal-appearing mucosa, are more suitable for radiation therapy than for surgery.

A consideration in making surgical excision a priority is that radiation therapy is reserved for treatment of a subsequent primary head and neck tumor. Fujita et al[49] noted that a second primary tumor developed in 22% of patients with a T1 glottic cancer who had had primary treatment with radiation therapy; 67% of these second lesions were in the upper aerodigestive tract. For many of these second primary tumors, the likelihood of lymph node involvement is higher than for the index glottic tumor and therefore benefit from the availability of radiation therapy.

Comparison of treatment costs for surgical excision and radiation therapy have been reported with varying conclusions that must be interpreted cautiously, because all have methodologic drawbacks. In general, endoscopic surgical excision is the least expensive modality.[21,50-52]

T2 Cancer of the Glottis

T2 cancers of the glottis can be described prognostically as either favorable or unfavorable. A favorable T2 glottic lesion is defined as a superficial tumor on radiographic imaging, with normal cord mobility; an example is a superficial glottic lesion that extends along the mucosa to the supraglottic larynx. For favorable T2 disease, available data support the use of either radiation therapy or organ preservation surgery for initial treatment. The local control rate after radiation therapy for T2 glottic cancer in series with a minimum of 100 patients and 2 years

of follow-up has ranged from 70% to 80%.[53-56] Local control rates after endoscopic laser resection of T2 glottic cancer are lower than those for T1 tumors (75% to 85%).[24,28,57,58] Vertical hemilaryngectomy yields local control rates that are slightly better than those after radiation therapy.[59,60] The supracricoid partial laryngectomy yields a local control rate of greater than 90%.[61-63] Although the supracricoid partial laryngectomy with cricohyoidoepliglottopexy has definite advantages compared with radiation therapy in terms of local control, the long-term result is permanent hoarseness. When pathologic findings mandate postoperative radiation therapy, the risk of compromise in anticipated functional outcomes increases.

Some investigators have noted compromised survival after failure of radiation therapy for T2 glottic cancer, indicating the importance of obtaining initial local control.[64,65] In addition, when T2 disease fails to respond to radiation therapy, total removal of the larynx for surgical salvage is most often necessary.[64,65] Supracricoid partial laryngectomy with cricohyoidoepliglottopexy remains a reasonable alternative for patients with a favorable T2 glottic cancer who, after participating in counseling, would be willing to sacrifice the quality of the voice in an effort to improve local control and possibly survival.

An unfavorable T2 glottic lesion is defined as a deeply invasive tumor on radiographic imaging, with or without subglottic extension, with impaired cord mobility (indicating deeper invasion). The optimal management of T2 glottic cancer with these characteristics has been controversial.[56,66-68] In series with a minimum of 100 patients and 2 years of follow-up, the local failure rate after radiation therapy ranges from 20% to 49% for T2b lesions.[53-56] The quality of the voice after treatment may be a lesser concern for these patients if function of the vocal cord is irreversibly compromised by tumor invasion. Given local control and survival concerns with the use of radiation therapy as a single modality in this setting, the suggested initial treatment is organ-preservation surgery. Supracricoid partial laryngectomy with cricohyoidoepliglottopexy is the organ-preservation surgery of choice for most unfavorable T2 glottic cancers.[61-63]

The local control rate associated with radiation therapy (66 to 70 Gy at 2 Gy/fraction/day or 63 to 65.25 Gy at 2.25 Gy/fraction/day, 5 days per week, are commonly used in this setting) is related to total radiation dose, fraction size, and overall treatment time.[32,69-72] In general, for a similar total dose, the local control rates are higher for fraction sizes of more than 2 Gy and shorter overall treatment time. The efficacy of twice-daily hyperfractionated radiation therapy is currently under study.

Chemoradiation therapy may be used for selected patients with unfavorable T2 N+ glottic cancers in whom function of the larynx is likely to be lost after primary radiation therapy or surgery (see Evidence Review for T3, T4 tumors).

T1 and T2 Cancers of the Supraglottis

Supraglottic cancers can also be described prognostically as favorable or unfavorable. A favorable supraglottic lesion is defined as a T1 or T2 tumor with superficial invasion on radiographic imaging and preserved cord mobility, and/or a tumor of the aryepiglottic fold with minimal involvement of the medial wall of the pyriform sinus. These supraglottic cancers can be treated with radiation therapy alone or organ-preservation surgery plus neck dissection, with excellent local control and preservation of voice. Anticipated local control rates for T1-T2 supraglottic cancers treated with definitive radiation therapy alone are greater than 80%.[73,74] Organ-preservation surgery, including supraglottic laryngectomy and supracricoid partial laryngectomy yields a local control rate of more than 90%.[61,62,75-78] Some patients with severe pulmonary dysfunction may not tolerate supraglottic laryngectomy because of postoperative difficulty with swallowing and consequent complications of aspiration. Endoscopic laser resection can achieve comparable local control rates for selected patients and has the advantage of avoiding tracheostomy in most instances.[79-83] A T1 or T2 tumor that is largely exophytic with minimal invasion, especially if it arises from locations such as the mobile epiglottis or the aryepiglottic fold, is easily amenable to endoscopic resection, with minimal postoperative morbidity and local control rates comparable to those associated with open resection.

For more locally advanced and invasive, and thus unfavorable, T2 supraglottic lesions, radiation therapy and surgery are the accepted treatment options. There are no randomized trials in which the efficacy of these two approaches has been compared in this setting. Single-arm studies suggest that primary surgery is associated with a better local control rate,[59,62,75-78,84] but potential differences in patient selection complicate interpretation of these data.

Rates of local control and preservation of laryngeal function after radiation therapy decrease with increase in tumor volume measured on CT scans made before treatment.[85] With conventional fractionated radiotherapy, 2 Gy/fraction/day, 5 days per week, for a total dose of 66 to 70 Gy, is usually delivered to the primary tumor and positive lymph nodes. An additional boost of 2 to 5 Gy may be administered to large primary tumors and neck nodes through reduced fields. Retrospective comparisons have suggested that local control rates are higher with twice-

daily hyperfractionated radiation therapy for T2-T3 laryngeal cancer than with historical controls treated with once-daily fractionated radiation therapy.[86,87] A randomized trial by the Radiation Therapy Oncology Group (RTOG 9003) [88] demonstrated that local-regional control was better with hyperfractionated radiation therapy or accelerated fractionated radiation therapy using a concomitant boost technique than with conventional once-daily fractionated radiotherapy for patients with squamous cell carcinoma of various head and neck primary sites at the expense of more acute toxicity.

For patients with stage III T2 N+ supraglottic cancers for whom organ-preservation surgery is contraindicated and total laryngectomy is the only surgical option, evidence supports the use of concurrent chemoradiation therapy regimens for these patients.[89]

2. What are the larynx-preservation treatment options for advanced-stage (T3, T4) primary-site disease that do not compromise survival? What are the considerations in selecting among them?

Summary of Recommendations

Question 2	2005 Recommendations
What are the larynx-preservation treatment options for advanced-stage (T3, T4) primary-site disease that do not compromise survival? What are the considerations in selecting among them?	Organ-preservation surgery, concurrent chemoradiation therapy, and radiation therapy alone, all with further surgery reserved for salvage, offer potential for larynx preservation without compromising survival. Anticipated success rates for larynx preservation, associated toxicities, and suitability for a given patient will vary among these approaches. Selection of a treatment option will depend on patient factors, local expertise, and the availability of appropriate support and rehabilitation services.
	All patients should be evaluated regarding their suitability for a larynx-preservation approach, and they should be apprised of these treatment options. No larynx-preservation approach offers a survival advantage compared with total laryngectomy and appropriate adjuvant treatment.
	A minority of patients with T3-T4 primary-site disease will be suitable for specialized organ-preservation procedures, such as a supracricoid partial laryngectomy. The addition of postoperative radiation therapy will compromise anticipated functional outcomes. Induction chemotherapy before organ-preservation surgery is not recommended outside of a clinical trial.

	Concurrent chemoradiation therapy offers a significantly higher chance of larynx preservation than does radiation therapy alone or induction chemotherapy followed by radiation, albeit at the cost of higher acute in-field toxicities. The best available evidence supports the use of cisplatin as the drug of choice in this setting.
	There is insufficient evidence to indicate that survival or larynx-preservation outcomes are improved by the addition of induction chemotherapy before concurrent treatment or the use of concurrent chemotherapy with altered fractionated radiation therapy in this setting.
	For patients who desire larynx-preservation therapy but are not candidates for organ-preservation surgery or chemoradiation therapy, radiation therapy alone is an appropriate treatment. With this last approach, survival is similar to that associated with chemoradiation therapy when salvage surgery is incorporated, but the likelihood of larynx preservation is lower.

Evidence Review

Larynx-preservation treatment options in this setting include variations on organ-preservation surgery, chemoradiation therapy, and radiation therapy alone. Although one provider can review options with the patient, a formal multidisciplinary assessment and discussion is arguably the best way to ensure a comprehensive discussion of the risks and benefits of these options. In all cases, the discussion with the patient must include the possibility of total laryngectomy, because failure of organ-preservation strategies will require salvage total laryngectomy if feasible and is part of the treatment strategy for avoiding a compromise in survival. It must be emphasized that no larynx-preservation strategy has been shown to offer superior survival compared with immediate total laryngectomy and adjuvant therapy as indicated.

Organ-Preservation Surgery

Success of a surgical approach to larynx preservation depends on the extent of the tumor, the experience of the surgeon, and patient selection. Potential contraindications to organ-preservation surgery include bilateral arytenoid involvement, extension of tumor to the subglottis, invasion of the cricoid cartilage, and extralaryngeal spread/massive invasion of thyroid cartilage. Patients must have an adequate performance status and sufficient pulmonary reserve to tolerate the episodes of aspiration that will occur, at least transiently, in the perioperative and rehabilitation periods. Furthermore, conditions that preclude a long period of

anesthesia, as well as psychologic or neurologic issues that would preclude functional rehabilitation, represent contraindications to organ-preservation surgery. Given these limitations and challenges, the minority of patients with advanced-stage (T3-T4) disease are suitable candidates for such an approach.

There are no randomized, disease site–specific studies in which the outcomes after organ-preservation surgery and total laryngectomy were compared. Data on outcomes with organ-preservation surgery consist of retrospective/prospective case series, often with only a few patients who have T3 or T4 lesions. For example, in a group of 118 patients (100 of whom received platinum-based induction chemotherapy) with T3 lesions who had supracricoid partial laryngectomy, the 5-year local control rate was 91%.[90] In an earlier report of 64 patients from the same institution (54 patients with T3 disease and six with T4 disease), the rate of larynx preservation was 92%.[91] Other case series of this procedure have included only small numbers (fewer than 15 patients) with T3 or T4 lesions.[92,93] However, in those series, the local control rate was more than 90% for all patients. These studies are not randomized, but survival does not appear to be compromised. Positive margins of resection are predictors for local recurrence.[90] Because radiation therapy to the laryngeal remnant leads to a high rate of complications, including laryngeal chondroradionecrosis, laryngeal stenosis,[94] and decrement in function, the presence of positive margins should prompt consideration of a completion total laryngectomy. If postoperative radiation therapy to the neck is indicated, care must be taken to avoid radiating the laryngeal remnant.

There are conflicting data regarding the quality of swallowing after partial laryngectomy, and difficulties have been reported.[95,96] However, satisfactory function has been reported in more recent series.[78,92,97,98] Published data have also indicated that swallowing function recovers differently within specific subgroups of patients with a partial laryngectomy, with swallowing ability recovered earlier in the postoperative period by patients who had hemilaryngectomy than by patients with any type of supraglottic laryngectomy.[99] In general, the results of nonrandomized comparisons of partial and total laryngectomy with regard to functional and quality-of-life outcomes favor partial laryngectomy, but there are inconsistencies.[100-102] The strength of the conclusions of each of these studies is limited by small numbers and nonrandomized trial designs.

Induction chemotherapy with organ-preservation surgery has been explored in this setting with different intents: to render patients who would otherwise need total laryngectomy suitable for organ-preservation surgery, to improve survival, and to decrease the need for radiation therapy.[17,91,103] The use of induction chemotherapy for these purposes, while promising, requires further evaluation in prospective studies before it can be recommended outside of a clinical trial.

Radiation-Based Treatment

Initial chemoradiation therapy approaches focused on the use of induction chemotherapy. In randomized studies, the addition of induction chemotherapy proved disappointing as a way to improve overall survival compared with surgery and postoperative radiation therapy alone,[104] but pilot data demonstrated that response to chemotherapy seemed predictive of response to radiation therapy, thus providing a basis for a potential larynx-preservation strategy.[105,106] More recently, concurrent chemoradiation therapy approaches have been the focus of attention.

Induction Chemotherapy and Radiation Therapy

Three randomized trials were identified which compared induction chemotherapy (cisplatin/fluorouracil infusion) followed by radiation with surgery reserved for disease persistence or relapse versus total laryngectomy and postoperative radiation (Tables 4a and 4b). In the initial report of The Veterans Administration (VA) Laryngeal Cancer Study[107] (median follow-up, 33 months), the estimated 2-year survival was the same for both treatment arms (Table 4b). A more recent analysis of long-term survival (median follow-up, 98 months) demonstrated that there continued to be no significant difference between treatment groups, with an overall survival rate of 35% ($P = .345$). Analysis of data from patients who had salvage laryngectomy also showed similar overall survival compared with the larynx-preservation group, although survival was better for patients who had early salvage (within 6 months) compared with patients who had late salvage.

Overall, the larynx was preserved in 101 of 166 patients who were randomly assigned to chemotherapy (61%; median follow-up, 43 months). Standardized assessments of functional outcomes for two years after therapy demonstrated significantly better speech and communication ability among patients in the chemotherapy arm, with significantly fewer requirements for individualized voice and speech rehabilitation. In contrast, there were very few differences between groups with respect to swallowing and nutrition-related measures.

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In 1998, a long-term (at 8 to 13 years) assessment of quality of life for 46 surviving patients determined that, compared with patients in the surgery arm, patients in the chemotherapy arm had significantly better scores on the Medical Outcomes Study Short Form (SF) -36 general health survey mental health domain, and less pain as measured by the University of Michigan Head and Neck Quality of Life instrument; in addition, fewer patients were depressed according to scores on the Beck Depression Inventory.[108] Similarly, patients with an intact larynx had less pain and higher emotional and mental health scores than those who had laryngectomy (either as part of the primary surgery plus radiation therapy arm or as salvage laryngectomy after failure of chemoradiation therapy) and fewer patients with an intact larynx were depressed.

These data suggest that larynx preservation after chemoradiation therapy is associated with better quality of life compared with total laryngectomy plus postoperative radiation therapy. Although quality-of-life scores associated with an intact larynx were higher, the difference does not appear to be attributable to preservation of speech function, as there were no significant differences between the groups with respect to speech scores on long-term follow-up. Instead, the better quality of life in the chemoradiation therapy arm appears to be related to better emotional well-being, freedom from pain, and lower levels of depression.

The Groupe d'Etude des Tumeurs de la Tète et du Cou (GETTEC) Study[109] included patients with previously untreated T3 disease (according to 1986 UICC and AJCC staging systems), all with a fixed vocal cord. In order to proceed with definitive radiation after three cycles of standard cisplatin and fluorouracil, the primary tumor had to shrink by at least 80% (the VA study required a partial or 50% response). The median duration of follow-up was 8.3 years. Total laryngectomy was avoided in 15 of 36 patients in the chemoradiation therapy arm. However, chemoradiation therapy was associated with more local-regional recurrence (six compared with three) and more distant failure (six compared with none). This led to a significant advantage for the surgery arm in terms of disease-free and overall survival (84% v 69% at 2 years; $P = 0.006$).

In the European Organisation for Research and Treatment of Cancer (EORTC) Hypopharynx Trial [110] patients with cancer of the lateral epilarynx (aryepiglottic fold and medial pyriform) were also eligible and represented 22% of those who were randomly assigned. If managed surgically, all patients would have required total laryngectomy with partial

pharyngectomy. To proceed with definitive radiation therapy after three cycles of cisplatin and fluorouracil, a complete response at the primary site was required, including normalization of vocal cord mobility. There was no significant difference in survival, despite a notable difference in median survival in favor of the chemoradiation therapy arm (44 months compared with 25 months), but 5-year survival rates were the same. At 3 and 5 years, the rate of larynx preservation (local control, no tracheostomy or feeding tube) was better for the chemoradiation-therapy arm. A functional larynx was retained in approximately half of the long-term survivors in the chemoradiation-therapy arm.

The three trials discussed in the preceding paragraphs were compiled into a meta-analysis[104] that included 602 patients. Significant statistical heterogeneity was noted among the studies. The 5-year survival rate was 6% lower for the chemoradiation therapy arm (39% compared with 45%; pooled hazard ratio, 1.19; 95% CI, 0.97 to 1.46; $P = .10$). The rate of larynx preservation among survivors was 58%. Collectively, these studies suggest that the larynx can be preserved with the outlined approach without a significant compromise in survival. That being said, there was clearly no evidence of a survival advantage for a larynx-preservation approach with chemoradiation therapy. Furthermore, it was unclear whether chemotherapy provided independent therapeutic effect or functioned simply to select patients more likely to ultimately preserve their larynx with radiation.

Concurrent Chemoradiation Therapy

The findings of randomized trials that were not disease-site specific suggest that concurrent chemoradiotherapy is more effective than radiation therapy alone. For example, in the meta-analysis of chemotherapy in head and neck cancer (MACH-NC), Pignon et al analyzed updated data on individual patients in studies that had completed accrual by December 31, 1993.[104] There was an absolute survival benefit of 8% at 5 years with the use of concurrent chemoradiation therapy compared with radiation therapy alone (hazard ratio, 0.81; 95% CI, 0.76 to 0.88; $P < .0001$). Significant statistical heterogeneity among studies was noted. Analysis of data for a subset of 861 patients from six randomized studies in which the same drugs were administered either concurrently with radiation or as induction before it demonstrated a nonsignificant difference in favor of concurrent treatment (hazard ratio, 0.91; 95% CI, 0.79 to 1.06; $P = .23$). The Expert Panel identified two randomized studies particularly relevant to the use of concurrent chemoradiation therapy with intent to preserve the larynx (Tables 5a and 5b).

In the Cleveland Clinic Trial,[111,112] the 3-year relapse-free survival and the rate of distant metastasis were better in the concurrent chemoradiation therapy arm (67% compared with 52%, $P = .03$; and 10% compared with 21%, $P = .04$, respectively; median follow up of 36 months). The 3-year survival rate without surgery to the primary site was also superior (57% compared with 35%, $P = .02$), an advantage that persisted in the laryngeal and hypopharyngeal cancer groups on subset analysis. With the contribution of salvage surgery, however, overall survival was not significantly different between the arms. The improved rate of organ preservation came at the expense of greater grade 3 to 4 acute toxicity.

In a separate analysis, surgical complications for the two arms were evaluated.[113] The total number of procedures and the number of major complications were the same for both arms. When only salvage surgery was considered, the complication rates were similar; when only major complications were considered, the rates were 16% for radiation therapy alone and 27% for chemoradiation therapy ($P = .79$).

The National Cancer Institute Cooperative Trials Head and Neck Intergroup Trial (RTOG 91-11)[89] was designed to specifically assess the contribution of chemotherapy added to radiation therapy and the optimal timing of chemotherapy (induction v concurrent) for achieving larynx preservation (Tables 5a and 5b). Patients with T1 disease or high-volume T4 disease (defined as more than 1 cm of invasion of the base of the tongue or tumor penetration of thyroid cartilage into soft tissues) were excluded.

Data for 497 patients were analyzed after a median follow-up of 3.8 years. At 2 years, the rate of larynx preservation was significantly higher for patients in the concurrent chemoradiation therapy arm (Table 5b). The rate of larynx preservation did not differ significantly between the induction-chemotherapy and radiation therapy–alone arms. Similarly, laryngectomy-free survival at 2 years was superior for the concurrent-chemoradiotherapy arm (66%) compared with either the induction-chemotherapy arm (59%) or the radiation therapy–alone arm (53%), as was local-regional control (78%, 61%, and 56%, respectively). Distant metastatic failure rates and disease-free survival were both better with concurrent and induction-chemotherapy approaches compared with radiation therapy alone. Overall survival was similar for all three arms.

Grade 3 to 4 mucosal toxicity was twice as frequent with concurrent treatment as with the other two arms. The incidence of in-field acute toxicity during radiation therapy was not increased in the induction chemotherapy arm compared with the radiation therapy alone arm, but

the overall rate of high-grade acute toxicity was comparable to that seen with concurrent treatment because of the toxicity associated with induction chemotherapy. There was no difference in late toxicity among the three arms.

At 1 year after the completion of therapy, a higher proportion of patients in the concurrent arm had moderate to severe difficulty with swallowing compared with the other arms. However, these differences were not apparent at 2 years. Speech dysfunction for patients with an intact larynx was not problematic across treatment arms, with 3% to 8% of patients reporting moderate dysfunction. Available speech and swallowing data suggest that concurrent chemoradiation therapy does not confer significant speech or swallowing impairment (at least at 2 years) when used for the treatment of advanced laryngeal cancer.

Weber et al[114] studied survival, local-regional control, and complications after salvage total laryngectomy for the patients in the Head and Neck Intergroup trial. There were no differences in overall survival among the various treatment groups for patients who had salvage surgery. An analysis of data for all patients who had salvage laryngectomy and survived for at least 1 year demonstrated that survival was significantly worse for patients who had salvage surgery than for patients who had organ preservation. The incidences of major and minor complications did not differ among the treatment arms, but pharyngocutaneous fistula developed in more than 30% of patients who had chemoradiation therapy and subsequent salvage laryngectomy.

Definitive Radiation Therapy

The Head and Neck Intergroup Trial[89] has been instrumental in clarifying the efficacy of radiation therapy alone compared with integrated chemoradiation therapy for advanced laryngeal cancer. In that study, once-daily, conventionally fractionated radiation was shown to produce overall survival that was equivalent to that with concurrent chemoradiation therapy and with less acute toxicity, but the rate of larynx preservation was lower. Nevertheless, patients who are not medically suitable for concurrent chemoradiation therapy may be treated with definitive radiation therapy alone.

A randomized trial from Tata Memorial Hospital in India is of interest with regard to the efficacy of single-modality radiation.[115] Seventy-two patients (64 assessable) with locally advanced (86% T3) supraglottic larynx/pyriform sinus cancer were randomly assigned to surgery and postoperative radiation versus definitive radiation with surgery for disease persistence or

salvage. With a mean follow up of 24 months, disease-free survival favored the surgery treatment arm ($P = .04$). Overall survival was reported to be similar ($P = .79$), although the modest sample size limits the power of this comparison. Voice/laryngeal preservation occurred in 62% of patients treated on the primary radiation arm.

In RTOG 9003,[88] more than 1,000 previously untreated patients with stage II-IV squamous cell carcinoma of the head and neck (16% of enrolled patients had supraglottic cancer) were randomly assigned to one of four different, definitive-dose, radiation therapy–only arms: standard fractionation, hyperfractionation, accelerated fractionation with a split, and accelerated fractionation with concomitant boost. With a median follow-up of 41.2 months for surviving patients, the overall survival did not differ significantly across the four arms. However, the continuous hyperfractionation and concomitant boost arms produced significantly better rates of local-regional control ($P = .045$ and $.050$, respectively) compared with the standard fractionation arm, albeit at the expense of more acute in-field toxicity. However, the higher acute toxicity did not translate into more late adverse effects.

Of note, in a recent meta-analysis of 15 randomized trials (6,515 patients, not site specific) in which altered fractionation programs were evaluated, such programs led to an absolute improvement in survival of 3% at 5 years (pooled hazard ratio, 0.91, $P = .003$).[116] The greatest effect on disease control was found for schedules in which a higher total dose of radiation was delivered.

Although these data demonstrating an improvement in local control with altered fractionation programs were not from studies that were disease site-specific, the Panel believed that such approaches may be considered for patients receiving definitive radiation therapy alone with intent of larynx preservation. Patients must be able to tolerate the anticipated increase in acute in-field toxicities.

Other Considerations

The feasibility of induction chemotherapy before concurrent chemoradiation is supported by the efficacy results of phase II studies that are not disease-site specific.[117] Randomized trials in which induction chemotherapy followed by concurrent chemoradiation therapy was compared with concurrent chemoradiation therapy alone for patients with locally-regionally advanced disease are in progress. Until more data become available, however, there is insufficient evidence

to recommend the addition of induction chemotherapy before concurrent treatment in the larynx-preservation setting.

Similarly, given the superiority in local control obtained with the use of altered fractionation programs, such radiation schemes are increasingly being investigated in combination with concurrent chemotherapy. The question of whether the use of an altered fractionated radiation schedule negates the added improvement in local-regional control of concurrent chemotherapy has been evaluated in non–disease-site specific randomized trials. Available data still support that concurrent chemotherapy adds benefit.[118,119] The relative efficacy of standard versus altered fractionated radiation therapy, both with concurrent chemotherapy, requires further study. As such, there currently is insufficient evidence to recommend the use of concurrent chemotherapy with altered fractionated radiation rather than a more conventional concurrent chemotherapy-standard fractionated approach in the larynx-preservation setting.

The potential role of newer targeted agents in the management of head and neck cancers and other types of cancers is of great interest. A randomized trial of radiation therapy alone compared with radiation therapy with concurrent cetuximab (a chimerized monoclonal antibody against the epidermal growth factor receptor) for patients with local-regional advanced squamous cell carcinoma of the head and neck was reported in an abstract.[120] The preliminary results of this non–disease-site specific study demonstrate a significant survival advantage for concurrent treatment. More data are needed, however, before such an approach can be recommended as a larynx-preservation treatment option outside of the clinical trial setting.

A common challenge is what to do if a patient has a good performance and clinical status, is not a candidate for organ-preservation surgery, and concurrent chemoradiation therapy is planned, but the potential toxicity of cisplatin poses concerns because of pre-existing hearing loss, neuropathy, or renal dysfunction. Certainly, one option is to pursue radiation therapy alone. However, Browman et al[121] reported a meta-analysis of 1,514 patients with locally advanced squamous cell carcinoma (not limited to the larynx) who were treated in randomized trials in which different concurrent chemoradiation therapy programs were evaluated. Compared with radiation therapy alone, better survival was associated with platinum-based regimens (odds ratio, 0.57; 95% CI, 0.46 to 0.71; $P < .00001$). Although overall survival was not improved significantly with concurrent chemotherapy and radiation compared with radiation alone in the

Cleveland Clinic[111,112] or Intergroup[89] trials after the contribution of salvage surgery, both studies showed a significant improvement in organ preservation rates with concurrent therapy. As such, the Expert Panel believes that the use of an alternative carboplatin-based regimen with a more favorable adverse-effect profile that has withstood the scrutiny of a randomized trial is appropriate to consider under the outlined circumstances.

The limited data available regarding the relative costs of surgery compared with radiation-based larynx preservation suggest that direct medical costs are less with primary surgical management.[122] However, potential cost savings related to increased productivity from improved function (ie, less indirect medical costs) have not been comprehensively assessed.

As mentioned previously, no difference in overall survival between surgery and radiation therapy and chemoradiation therapy (with surgery performed only for salvage) was found in the VA Laryngeal Cancer Study.[107] The recent poor-risk adjuvant data[123,124] in which surgery followed by concurrent cisplatin and radiation therapy was superior to surgery and radiation therapy (further discussion in the next section) raises the question of whether the survival equivalence assumption of current larynx-preservation approaches, strictly speaking, still applies, at least for patients with poor-risk disease. These recent data need to be carefully considered in the future design of larynx-preservation programs.

In summary, primary total laryngectomy is probably the best approach when larynx preservation is not likely to be successful, such as when tumor penetrates through cartilage into soft tissues (further discussion in later section) or when there is already substantial baseline laryngeal dysfunction unlikely to be reversed with tumor regression. When advanced metastasis is present in the neck, the actual extent of the primary tumor often precludes organ-preservation surgery, and modern comprehensive treatment would frequently include both radiation therapy and chemotherapy; the data particularly support concurrent chemoradiation therapy. For patients with less advanced T3 tumors, organ-preservation surgery should be considered, particularly if there is minimal or no disease in the neck. This approach is generally reserved for patients with good performance status and excellent pulmonary function.

3. What is the appropriate treatment of the regional cervical nodes in patients with laryngeal cancer who are treated with an organ-preservation approach?

Summary of Recommendations

Question 3	2005 Recommendations
What is the appropriate treatment of the regional cervical nodes in patients with laryngeal cancer who are treated with an organ-preservation approach?	Most patients with T1-T2 lesions of the glottis and clinically negative cervical nodes (N0) do not require routine elective treatment of the neck.
	Patients with advanced lesions of the glottis and all patients with supraglottic lesions should have elective treatment of the neck, even if clinically N0.
	Patients with clinically involved regional cervical nodes (N1) who are treated with definitive radiation therapy or chemoradiation therapy and who have a complete clinical response do not require elective neck dissection. Neck dissection should be performed for patients who do not have a complete clinical response to radiation therapy.
	Surgical treatment of the neck is recommended for patients with N2 or N3 disease who are treated with definitive radiation therapy or chemoradiation therapy, regardless of response. Some surgeons and patients are reluctant to risk the morbidity of neck dissection, given the prospect of a negative pathologic diagnosis in most cases, but there is no standard imaging approach in this setting that has been validated to significantly improve on this decision-making process. Salvage surgery for recurrent disease in the neck is rarely successful if subsequently required in this setting. These two points should be discussed with all patients who have an apparent complete clinical response to radiation therapy or chemoradiation therapy and choose to be followed up with expectant observation.
	Patients with clinically involved cervical nodes who are treated with surgery for the primary lesion should have neck dissection. If there are poor-risk features, adjuvant concurrent chemoradiation therapy is indicated.

Evidence Review

There are no randomized studies that address treatment of the neck for limited-stage disease in the primary site. The randomized studies of more advanced primary disease do not focus on treatment of the neck as a primary end point. Some of the key studies that guide treatment of the neck,[123-125] including the recently reported poor-risk adjuvant studies, are not disease-site specific.

Appropriate treatment of the neck is determined by the T stage, the site of the primary lesion, and the clinical status of the cervical nodes before treatment. Treatment of clinically positive nodes in the neck is the same, regardless of the site of the primary lesion. However,

when the cervical nodes are clinically negative for disease, the likelihood of occult metastases differs depending on the site of the primary tumor. The glottis has relatively few lymphatic vessels, but the supraglottis has a rich network of lymphatic vessels, raising the likelihood of occult metastasis in the nodes. In particular, the epiglottis (the site of most supraglottic cancers) has bilateral lymphatic drainage.

Clinically Negative Cervical Nodes

The likelihood of cervical node metastasis with T1 or T2 lesions of the glottis is very low.[36,126] In a series of 291 patients with T1 N0 lesions who received definitive radiation therapy only to the primary site, disease recurred in the neck in less than 1% of patients; for 228 patients with T2 N0 lesions, the rate of isolated recurrence in the neck was 3%.[38] In other series of more than 200 patients with T2 N0 lesions treated with radiation therapy only to the primary site, isolated node failure occurred in 4%.[127,128] With T2 N0 glottic lesions, the likelihood of recurrence in the neck does not appear to vary whether elective radiation to the node is administered, and it is difficult to delineate a clear and reproducibly determined subset of patients with T2 N0 glottic cancer who are at increased risk of disease in the neck.[129] However, the rate of isolated recurrence in the neck may be higher for T2 lesions with impaired vocal cord mobility (T2b).[38] Thus, for T1 and T2 lesions, routine elective treatment of the neck is not indicated, although it may be considered for bulkier T2 lesions with supraglottic or subglottic extension or impaired cord mobility. However, if radiation therapy fails to achieve local control, the risk of recurrence in the nodes increases to approximately 20%, necessitating neck dissection as well as treatment to control disease at the primary site.[129,130] For more advanced lesions of the glottis, the risk of occult metastases in the nodes may be greater than 20%, and thus, elective treatment of at least the ipsilateral neck is indicated.[131,132]

With supraglottic lesions, the risk of nodal metastasis is high, even with T1 and T2 disease. If the neck is not electively treated, recurrence rates of approximately 30% can be anticipated,[77,113,133,134] and recurrence in the neck is associated with a poor prognosis. In general, the contralateral neck should be treated.[77] Usually, the modality used to treat the primary site is the one used to treat the neck (eg, radiation therapy or neck dissection).

For patients treated with primary radiation therapy, the radiation portals for elective radiation of the clinically negative neck should include levels II, III, and IV on both sides.[131,135] For patients who were treated surgically, selective neck dissection of levels II, III, and IV have

been shown to be as effective as comprehensive elective neck dissection of all five levels for clinically node-negative supraglottic cancer.[136] Some controversy exists regarding the merit of bilateral or ipsilateral elective neck dissection in some settings.[137] Selective dissection of ipsilateral levels II, III, and IV may be considered for early stage lesions that are clearly lateralized, but these levels should be dissected on both sides when the supraglottic lesion approaches or involves the midline (even if the lesion is small).[138] Also, adjuvant therapy is indicated if poor-risk pathologic features are found during surgery (eg, extracapsular node extension).

Clinically Positive Cervical Nodes

The treatment for clinically positive cervical nodes is the same for patients with glottic and supraglottic cancers. If the initial treatment for the primary lesion is surgical, neck dissection should be performed, followed by adjuvant radiation or concurrent chemoradiation therapy, as dictated by the pathologic findings at neck dissection.[123,124] Patients with N1 disease treated with primary radiation or chemoradiation therapy do not need neck dissection if a complete clinical response is achieved. In a review of 121 patients with node-positive cancer (mostly N1, less than 10% N3) of the supraglottis who were treated with definitive radiation therapy, neck dissection was not performed if a complete clinical response was achieved; the incidence of recurrent disease in the neck was 7.5%.[139] Of note, in this retrospective analysis, the rate of regional control was higher with the use of hyperfractionated radiation. Others have reported a low incidence of recurrent disease in the neck for patients with N1 disease who have had a complete response to concomitant boost hyperfractionated radiation.[140,141] Similar outcomes have been reported for patients who had a complete response to induction chemotherapy and received only radiation to the neck.[142,143] In two studies of concurrent chemoradiation therapy that included patients with laryngeal cancer, there was no recurrence in patients with N1 disease who had a complete response.[134,144] Thus, the data suggest that when a complete clinical response to radiation or chemoradiation therapy is achieved, elective neck dissection can be avoided, because the risk of isolated recurrence in the neck is low. Patients with clinically detectable residual disease in the neck should undergo neck dissection after completion of definitive radiation or chemoradiation therapy.[139,144]

A planned neck dissection improves regional control for patients with more advanced nodal disease compared with radiation to the neck alone.[145] This also appears to be true for

concurrent chemoradiation therapy. In series that include patients with laryngeal cancer (N2 or N3 disease), pathologic residual disease has been documented after neck dissection in 20% to 30% of patients who had a complete clinical response to concurrent chemoradiation therapy,[134,144,146] and up to 44% of those patients who did not have a planned neck dissection relapse in the neck. Planned neck dissection after concurrent chemoradiation therapy appears to improve regional control for patients with advanced nodal disease,[134,147] and results also suggest that survival is better for patients with N2 or N3 disease who have planned neck dissection compared with patients who do not.[144] As additional evidence to support elective treatment of the neck to decrease the risk of recurrence there for patients with initial N2 or N3 disease (even in patients who had complete response to radiation-based treatment), salvage surgery for recurrent node disease is only rarely successful,[148,149] and recurrent disease in the neck is detrimental to survival.[150,151] Although there may be concerns regarding the potential for increased surgical morbidity in the period after radiation or chemoradiation therapy, this is not routinely the case.[111,144,152] Despite these data, routinely performing neck dissection for patients who have a complete clinical response in the neck does generate some controversy, with others reporting no increased risk of isolated recurrence in the neck in patients with N2 disease[140,147] or N3 disease[140] who have a complete response. Given the prospect of a potentially negative pathologic specimen in most cases, some surgeons and patients are reluctant to risk the morbidity of neck dissection.

Attempts have been made to use imaging to better clarify which patients with an apparent complete clinical response will most likely benefit from neck dissection. Some investigators have performed CT 1 month after completion of hyperfractionated radiation therapy to assess the likelihood of a complete pathologic response and the need to perform neck dissection[153]; this approach has had some success, but confirmation in prospective studies is needed. There has been great interest in positron emission tomography (PET) with 18-fluorodeoxyglucose (FDG), but the optimal timing of scanning after treatment is unclear. Radiation therapy may decrease uptake of FDG without sterilizing the tumor, leading to an unacceptable false-negative rate if the scan is performed too soon, whereas inflammation after treatment may lead to false-positive results.[154-156] Waiting 3 to 4 months until inflammation decreases will enhance the reliability of the findings, but the period for optimal timing of neck dissection may have passed. Most studies of the use of PET after treatment of head and neck cancer include small retrospective cohorts, are not site specific to the larynx, and involve evaluating the utility of PET for either detecting a

suspected recurrence or for early detection of recurrence. Thus, although some investigators have reported that negative findings on PET performed after radiation therapy is an accurate predictor of pathologically negative nodes in the neck,[157] even if a complete clinical response is not achieved, the data are insufficient to support the routine use of PET in this setting. As such, there is no standard imaging approach in this setting that has been validated to substantially improve the decision-making process about whether neck dissection can be safely withheld.

For patients who had an incisional or excisional biopsy of a positive node before definitive surgery, the risk of recurrence and death may be increased because of the open biopsy procedure.[126] However, if radiation-based therapy is the next step, there is no apparent adverse effect from open biopsy.[158] Therefore, if excisional biopsy is performed on a solitary node, the neck may be treated with radiation alone, with an approximately 95% likelihood of disease control in the neck.[159] Patients who have gross residual disease in the cervical nodes after an open biopsy in the neck are best treated with radiation therapy followed by neck dissection or with completion neck dissection followed by radiation therapy.[158,160]

Adjuvant Therapy After Primary Surgery

Adjuvant radiation therapy has traditionally been administered to patients with cancer of the larynx who had surgery but are found to have high-risk pathologic features, such as positive margins, extranodal spread, or more than two positive lymph nodes. The findings of two recent non–disease-site specific studies indicated a benefit to postoperative chemoradiation therapy compared with radiation therapy alone. The first study, undertaken by the RTOG, randomly assigned 459 patients with high-risk features (as just described) to either adjuvant radiation therapy alone or to the same radiation with concurrent cisplatin (100 mg/m^2 on days 1, 22, and 43).[124] Local control at 2 years was greater in the chemoradiation therapy arm (82% compared with 72%, $P < .01$), as was disease-free survival; overall survival was not significantly different between the two arms. Toxicity was greater in the combined-modality arm, with a doubling of adverse events of grade 3 or greater (77% v 34%, $P < .001$), and there were four toxic deaths, compared with none in the radiation-alone arm. The incidence of late toxicity was not different in the two arms.

A similar trial performed in Europe enrolled patients with broader eligibility criteria.[123] A total of 334 patients were randomly assigned to treatment with either adjuvant radiation alone or the same radiation with concurrent cisplatin as administered in the RTOG trial. The median

duration of progression-free survival and median overall survival were both significantly longer in the chemoradiation therapy arm (progression-free survival, 55 months compared with 23 months, $P = .04$; overall survival, 72 months compared with 32 months, $P = .02$). The incidence of severe (at least grade 3) mucositis was doubled in the chemoradiation therapy arm (41% compared with 21%, $P = .001$). The cumulative incidence of late toxicities was not different.

For both studies, the results are not reported by primary site, and so the specific benefit for patients with laryngeal cancer cannot be determined. However, approximately 20% of patients in each trial had laryngeal cancer, and it is appropriate to offer adjuvant chemoradiation therapy to medically suitable patients with high-risk pathologic features. It should be noted however, that the patients enrolled in these trials were young (median age, 55 years, with almost all patients younger than 70 years) and had good performance status with no significant comorbidity. In addition, the significantly higher rate of acute toxicities in the chemoradiation-therapy arm warrants consideration.

4. Are there methods for prospectively selecting patients with laryngeal cancer to increase the likelihood of successful larynx preservation?

Summary of Recommendations

Question 4	2005 Recommendations
Are there methods for prospectively selecting patients with laryngeal cancer to increase the likelihood of successful larynx preservation?	There are no validated markers that consistently predict outcomes of larynx-preservation therapy. However, patients with tumor penetration through cartilage into soft tissues are considered poor candidates for a larynx-preservation approach. Primary surgery, usually total laryngectomy, is commonly recommended in this setting.
	Selection of therapy for an individual patient requires assessment by a multidisciplinary team, as well as consideration of patient comorbidity, psychosocial situation and preferences, and local therapeutic expertise.
	Continued cigarette smoking appears to be associated with a worse outcome after radiation therapy. Patients should be encouraged to abstain from smoking after the diagnosis and throughout treatment.

Evidence Review

There is much interest in determining pretreatment factors that will predict the success of the different organ-preservation strategies, to facilitate the selection of treatment for a given patient

that will result in the highest likelihood of local-regional control without necessitating total laryngectomy as a salvage procedure. Factors considered include clinical, anatomic, and related radiographic features, as well as histopathologic and molecular characteristics of the primary tumor. The former group remains the most commonly referenced.

Clinical, Anatomic, and Radiographic Features

Clinical parameters that have been associated with a poorer outcome after radiation therapy include male gender[55,161-163] and the presence of anemia at the beginning of treatment.[163-165] Smoking status may also be related to outcome.[166] In a prospective analysis of 115 patients with advanced squamous cell carcinoma of the head and neck (28% of whom had laryngeal cancer), the likelihood of a complete response to radiation therapy was lower for patients who continued to smoke during treatment, and the median survival was also lower compared with patients who did not smoke during treatment or had quit before treatment.[167] The findings of a follow-up prospective study to that trial which involved 148 patients (one third of whom had laryngeal cancer) did not confirm the association of smoking during radiation treatment and decreased response, but did confirm a lower overall and cause-specific survival for patients who continued to smoke compared with those who had quit.[168] Continued smoking may increase the late complications of radiation[72] and impair voice quality after therapy.[169]

Anatomic factors that have been reported to predict for a decreased likelihood of local control with radiation therapy include advanced T stage[55,161,162,165,170,171]; clinically detectable impaired vocal cord mobility[55,171]; subglottic extension[172]; involvement of the anterior commissure[172]; larger tumor volume[82,170,173,174]; and invasion of specific anatomic sites, such as the thyroid/cricoid cartilage,[175,176] paraepiglottic space,[170,173] or pre-epiglottic space,[82,170,176] as determined by CT or magnetic resonance imaging (MRI). However, many retrospective analyses did not include controlling for confounding variables, and the association with a negative outcome is inconsistent for most of these factors. Accordingly, such factors are limited as guides in making therapeutic recommendations for an individual patient. Significant invasion of the cartilaginous structures of the larynx (thyroid or cricoid cartilage) is the most accepted criterion for predicting a negative outcome for radiation therapy. The use of concurrent chemoradiation therapy may be more successful in achieving tumor eradication in this setting, but this has not been well studied. Indeed, patients with gross cartilage invasion were excluded from the three-

arm Head and Neck Intergroup trial.[89] Primary surgery, usually a total laryngectomy, is commonly recommended in this situation.

The concept that chemosensitivity can predict for radioresponsiveness formed the basis for randomized trials of organ-preservation discussed previously.[106,107,110] Disease-free survival has been better for patients who have a complete histologic response to induction chemotherapy.[177] A complete response to induction chemotherapy is more likely for patients who have disease of an earlier T stage[177] or a lower tumor burden. Although response to induction chemotherapy may predict for improved outcome with subsequent definitive radiation therapy, the relevance of these findings to a treatment strategy of concurrent chemoradiation therapy without induction chemotherapy is unknown.

Sherman and Pfister, in collaboration with the investigators of the VA Laryngeal Cancer Study, developed a prediction tool based on T stage, serum albumin level, alcohol consumption, and Karnofsky performance status (TALK score) that was particularly useful in determining which patients were most likely to have inadequate response to chemotherapy and radiation therapy administered with intent of larynx preservation. The tool was validated in the investigational arm of the VA Laryngeal Cancer Study. Data for this instrument has been presented in an abstract,[178] and publication in a peer-review journal is awaited.

There are fewer available data on the factors predicting success of organ-preservation partial laryngectomy procedures. Surgical expertise and patient selection are clearly important because the presence of positive surgical margins has been shown to be predictive of recurrence.[62,90,92] Furthermore, clinical factors, such as performance status and pulmonary reserve need to be carefully considered, given the risk of aspiration in the perioperative and rehabilitative periods. As with radiation-based treatment, local control, survival, and organ preservation are all negatively affected by advanced T stage and extension of tumor into the subglottis, cricoid, tongue base, and hypopharynx.[61,82,179]

Histopathologic and Molecular Characteristics

At present, there is no preponderance of evidence that supports the clinical use of cellular or molecular predictors of success for radiation therapy or chemotherapy. The absence of prospective standardized acquisition of materials for research or standardization of applied scientific methodology, including standardized handling of pathologic tissues and validation procedures, compromises the ability to determine the current utility of biomarkers. There are

limited data on predictors of outcomes of concurrent chemoradiation therapy, the organ-preservation strategy most broadly applicable to many T3-T4 lesions.

A histologic growth pattern of thin, irregular cords or single tumor cells at the tumor margin were predictive of response to induction chemotherapy in the cohort of patients enrolled to the experimental arm of the VA Laryngeal Cancer Study.[180] A low-grade histologic growth pattern and a lower DNA tumor content were both associated with an improved prognosis for patients who had total laryngectomy.[181] Many investigators have examined p53 status, but as a predictor of outcome, the results have not been consistent.[182-187]

FINAL COMMENTS

A summary of all recommendations made by the Expert Panel is provided in Table 6.

Larynx-preservation therapy is intended to offer improved function and quality of life for patients with laryngeal cancer, without compromising survival. Our review of the data indicated that there is commonly more than one treatment option to consider. A thorough discussion of the risks and benefits of larynx-preservation therapy is crucial. Organ-preservation treatments can be difficult to administer, given that many patients have underlying medical comorbidity. Optimal patient selection increases the likelihood of a successful outcome. Effective application of larynx-preservation treatment requires special expertise and a specialized support team. A typical treatment team will include expertise in head and neck surgery, radiation therapy, medical oncology, pathology, nursing, speech and swallowing physiology/rehabilitation, audiology, social services, nutrition, tobacco cessation, and management of relevant medical comorbidities.

Many important management decisions have not been addressed by randomized trials, or require further clarification. Reliable biologic markers and imaging techniques to facilitate assessment of patient prognosis and response to therapy are needed to guide therapy and select the patients most appropriate for organ preserving approaches. Defining optimal treatment combinations including the role of neoadjuvant/induction, concurrent, and adjuvant therapies, as well as newer targeted therapies, is a priority. The role of more targeted radiation approaches and newer fractionation schedules, the timing of surgery for persistent disease, and optimal surveillance for recurrence and prevention of second primary cancers are key research areas. Practical assessments and interventions for nutrition, speech, swallowing, risk factor modification, and rehabilitation/reconstruction are needed. The Expert Panel believes that

commitment to and support of relevant and important randomized studies will be fundamental to addressing these issues. The thoughtful incorporation of relevant correlative studies into the design of randomized studies such as tissue-specific investigations will maximize the value of the latter.

When treatments yield similar survival end points, other outcomes, such as function, quality of life, and cost, become increasingly relevant. For example, speech and swallowing are highly complex, finely coordinated neuromuscular processes, and may be disrupted by both the disease itself and its therapy. Preservation of the laryngeal structure is not considered a functional success if persistent dysphagia, aspiration, or chronic tracheostomy results from organ-preserving therapy. All organ-sparing therapies are not the same with regard to their anticipated functional and quality-of-life outcomes. Yet as is the case with more traditional biomedical end points, randomized, primary site-specific data comparing patient-reported outcomes are limited.

Available information highlights some issues to consider. Differences in outcome between surgical and radiation-based approaches are not necessarily found on all quality-of-life domains,[18,108] and some that do may be primary site dependent.[188] How each patient perceives an adverse sequelae of treatment is variable. Permanent gastrostomy or stoma is often a greater concern to patients than loss of speech[10,189]; other quality-of-life domains (eg, emotional, social, financial) besides the functional one may be affected by the disease and its treatment and deserve attention. Underestimation of significant functional morbidity and treatment-related toxicities such as dysphagia is a risk if patients are not followed for longer time periods.[20,190-192] Careful assessment of such outcomes is crucial to guide subsequent protocol development in hopes of minimizing the morbidity of treatment without compromising efficacy.[193,194]

The thoughtful incorporation of valid pretreatment and longitudinal post-treatment functional and quality-of-life assessments will enhance the value of future larynx preservation studies. Validated technologies are already available to quantitate such end points.[9,195] Considering patient-reported outcomes in a broader sense than has historically been the case, particularly in organ preservation studies where treatment is randomly assigned, will provide useful information and facilitate clinical decision making and subsequent treatment protocol improvement.

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Table 1. TNM Staging Criteria for Laryngeal Cancer: Definitions

Primary Tumor (T)

TX   Primary tumor cannot be assessed

T0   No evidence of primary tumor

Tis   Carcinoma in situ

Supraglottis

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

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

T3   Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues, paraglottic space, and/or minor thyroid cartilage erosion (eg, inner cortex)

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

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

Glottis

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

T1a   Tumor limited to one vocal cord

T1b   Tumor involves both vocal cords

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

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

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

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

Subglottis

T1   Tumor limited to the subglottis

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

T3   Tumor limited to larynx with vocal cord fixation

T4a   Tumor invades cricoid or thyroid cartilage and/or

invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)

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

Regional Lymph Nodes (N)

NX   Regional lymph nodes cannot be assessed

N0   No regional lymph node metastasis

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

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

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

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

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

N3   Metastasis in a lymph node, > 6 cm in greatest dimension

Distant Metastasis (M)

MX   Distant metastasis cannot be assessed

M0   No distant metastasis

M1   Distant metastasis

Stage Grouping

0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4b	N2	M0
	T1	N2	M0
	T2	N2	M0
	T4	N2	M0
	T4a	N2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

Table 2. Evidence Used to Develop Recommendations

Question	Type of Evidence	Outcomes
1. What are the larynx-preservation treatment options for early stage (T1, T2) primary-site disease that do not compromise survival? What are the considerations in selecting treatment options for these patients?	Prospective and retrospective cohort studies.[17-50 51-87], For T2 N+: Randomized controlled trials of chemoradiation therapy (with either induction or concurrent chemotherapy compared with radiation therapy alone or surgery followed by adjuvant radiation therapy.[89,107]	Overall survival Disease-free survival Rates of laryngeal preservation Local-regional control Toxicity of therapy Cost
2. What are the larynx-preservation treatment options for advanced-stage (T3, T4) primary-site disease that do not compromise survival? What are the considerations in selecting among them?	Randomized controlled trials of chemoradiation therapy (either sequential or concurrent) compared with radiation therapy alone or surgery followed by adjuvant radiation therapy (or meta-analyses/derivative analyses).[88,89,104,107-116,118-120] Prospective and retrospective cohort studies.[17,78,90-103,105,106,117]	Overall survival Disease-free survival Rates of laryngeal preservation Local-regional control Toxicity of therapy Cost
3. What is the appropriate treatment of the regional cervical nodes for patients with laryngeal cancer who are treated with an organ-preservation approach?	Derivative analyses of randomized controlled trials of chemoradiation therapy (either sequential or concurrent) compared with radiation therapy alone or surgery followed by adjuvant radiation therapy.[132,141] Randomized trial comparing different types of neck dissection.[136] Prospective and retrospective cohort studies.[36,38,77,126,133,135,137-142,144-160] For adjuvant therapy: randomized controlled trials of radiation therapy compared with concurrent chemoradiation.[123-125]	Overall survival Disease-free survival Local-regional control Toxicity of therapy

| 4. Are there methods for prospectively selecting patients with laryngeal cancer to increase the likelihood of successful larynx preservation? | Prospective and retrospective cohort studies of clinical, radiographic, and/or pathologic parameters associated with clinical outcomes.[51,61,62,72,82,90,92,161-166,168-176,179,182-184,186,187]

Derivative analyses of a randomized controlled trial using induction chemotherapy.[167,177,178,180,181,185] | Overall survival

Disease-free survival

Local-regional control

Rates of laryngeal preservation |

Table 3. Summary of Recommended Strategies for Treatment of the Primary Site for Larynx Preservation

Type of Cancer	Organ-Preservation Strategy		Basis for Recommendation	Quality of Evidence
	Recommended	Other Options		
T1 Cancer of the glottis	Endoscopic resection (selected patients) OR Radiation therapy	Open organ-preservation surgery	High local control rates and quality of voice after endoscopic resection compared with radiation therapy; possible cost savings; ability to reserve radiation for possible second primary cancers of the upper aerodigestive tract; however, not suitable for all patients	Comparison of outcomes from case series/prospective single-arm studies
T2 Cancer of the glottis, favorable*	Open organ-preservation surgery OR Radiation therapy	Endoscopic resection (selected patients)	Open organ-preservation surgery is associated with highest local control rates; however, leads to permanent hoarseness; local control rates after radiation therapy are also high, and functional outcomes may be better	Comparison of outcomes from case series/prospective single-arm studies

T2 Cancer of the glottis, unfavorable*	Open organ-preservation surgery OR Concurrent chemoradiation therapy (selected patients with node-positive disease)	Radiation therapy Endoscopic resection (selected patients)	Higher local control rates after surgery compared with radiation therapy alone; quality of voice after therapy of less concern if vocal cord function is irreversibly compromised by tumor invasion; endoscopic surgery requires careful patient selection For patients with T2 N+ disease, evidence from randomized trials supports concurrent chemoradiation therapy as an organ-preservation option	Comparison of outcomes from case series/prospective single-arm studies Randomized controlled clinical trials comparing concurrent chemoradiation therapy, and/or induction chemotherapy followed by radiation, and/or radiation therapy alone, and/or surgery followed by radiation
T1-T2 Cancer of the supraglottis, favorable*	Open organ-preservation surgery OR Radiation therapy	Endoscopic resection (selected patients)	Open organ-preservation surgery associated with highest local control rates; however, requires temporary tracheostomy and may lead to increased risk of aspiration after therapy; local control rates after radiation therapy are also high, and functional outcomes may be better	Comparison of outcomes from case series/prospective single-arm studies

| T2 Cancer of the supraglottis, unfavorable* | Open organ-preservation surgery OR Concurrent chemoradiation therapy (selected patients with node-positive disease) | Radiation therapy Endoscopic resection (selected patients) | Open organ-preservation surgery is more likely to yield higher local control rates than radiation therapy For patients with T2 N+ disease, evidence from randomized trials supports concurrent chemoradiation therapy as an organ-preservation option | Comparison of outcomes from case series/prospective single-arm studies Randomized controlled clinical trials comparing concurrent chemoradiation therapy, and/or induction chemotherapy followed by radiation, and/or radiation therapy alone, and/or surgery followed by radiation |

| T3-T4 Cancers of the glottis or supraglottis | Concurrent chemoradiation therapy OR Open organ-preservation surgery (in highly selected patients) | Radiation therapy | Highest rate of larynx preservation is associated with concurrent chemoradiation therapy compared with other radiation-based approaches, at the cost of higher acute toxicities but without more long-term difficulties in speech and swallowing; when salvage total laryngectomy incorporated, no difference in overall survival Organ preservation surgery is an option in highly selected patients (eg, there are patients with T3 supraglottic cancers that have minimal or moderate pre-epiglottic invasion and are candidates for organ preserving surgery) | Randomized controlled clinical trials comparing concurrent chemoradiation therapy, and/or induction chemotherapy followed by radiation, and/or radiation therapy alone, and/or surgery followed by radiation. Comparison of outcomes from case series/prospective single-arm studies |

*See **T2 Cancer of the Glottis** and **T1 and T2 Cancers of the Supraglottis** for definitions of "favorable" and "unfavorable."

Table 4a: Phase III Studies of Induction Chemotherapy Followed by Radiation for Larynx Preservation: Study Designs

Study	Stage III/IV Disease (%)	T3/T4 Cancer (%)	N0-N1 Disease (%)	Study Arms	Treatment of Disease in the Neck	Indications for Salvage Surgery after Chemoradiation Therapy
VA Laryngeal Cancer Study[107] (n = 332)	57/43 (2/3 primary lesions of the supraglottis)	65/26	72	Induction chemotherapy (3 cycles standard cisplatin and fluorouracil) followed by radiation therapy (66-76 Gy to primary site, 50-75 Gy to nodes) Standard total laryngectomy followed by radiation therapy (50 Gy [no residual disease], up to 73 Gy [residual disease])	Chemoradiation arm: Lymph node dissection if residual disease after radiation therapy Surgery arm: Lymph node dissection for all patients	Less than partial response to chemotherapy after 2 cycles Residual disease at biopsy 12 weeks after completion of radiation therapy
GETTEC Study[109] (n = 68)	Not provided	100/0	93	Induction chemotherapy (3 cycles standard cisplatin and fluorouracil)	Chemoradiation arm: Lymph node dissection if salvage surgery	Less than 80 % regression of tumor after chemotherapy

				followed by radiation therapy (65-70 Gy to primary site, 50-70 Gy to nodes) Standard total laryngectomy followed by radiation therapy (50 Gy [no residual disease], up to 70 Gy [residual disease])	only Surgery arm: Lymph node dissection for all patients	Lack of return of laryngeal mobility
EORTC Hypopharynx Trial[110] (n = 202)	57/37	72/5	65	Induction chemotherapy (3 cycles standard cisplatin and fluorouracil) followed by radiation therapy (70 Gy to primary site and nodes) Standard total laryngectomy and partial pharyngectomy followed by radiation therapy	Chemoradiation arm: Lymph node dissection if residual disease in nodes after chemotherapy; timing variable Surgery arm: Lymph node dissection for all patients	Less than complete response to chemotherapy

				(50 Gy [no residual disease], 64 Gy [residual disease])		

Abbreviations: VA,Veterans Affairs; GETTEC, Groupe d'Etude des Tumeurs de la Tête Et du Cou; EORTC, European Organisation for Research and Treatment of Cancer.

Table 4b: Phase III Studies of Induction Chemotherapy Followed by Radiation Therapy for Larynx Preservation: Outcomes

Study	Overall Survival		Rate of Larynx Preservation		Toxicity
	%	Timeframe	%	Timeframe	
VA Laryngeal Cancer Study[107]					One toxic death thought due to chemotherapy. Radiation toxicity similar in the two arms. Data on long-term quality of life provided in subsequent publication.[108]
Chemoradiation-therapy arm	68	2 years	66	2 years	
Surgery arm	68	2 years	—		
GETTEC study[109]					No data provided on quality of life, speech or swallowing.
Chemoradiation-therapy arm	69	2 years	42	Median 8 years	
Surgery arm	84	2 years (P = .006)	—		
EORTC Hypopharynx Trial[110]					One toxic death due to chemotherapy. No data on quality of life or speech and swallowing. Larynx preservation required local control without surgery to the primary site, no tracheostomy nor feeding tube.
Chemoradiation-therapy arm	57 30	3 years 5 years	42 35	3 years 5 years	
Surgery arm	43 35	3 years 5 years	—		

Abbreviations: VA, Veterans Affairs; GETTEC, Groupe d'Etude des Tumeurs de la Tête Et du Cou; EORTC, European Organisation for Research and Treatment of Cancer.

Table 5a: Phase III Studies of Concurrent Chemoradiation Therapy for Larynx Preservation: Study Designs

Study	Stage III/IV Disease (%)	T3/T4 Cancer (%)	N0-N1 Disease (%)	Study Arms	Treatment of Disease in the Neck	Indications for Salvage Surgery
Cleveland Clinic Trial[111,112] (n = 100*)	28/72	39/33	47	Primary radiation therapy: 66-72 Gy to primary site and neck Concurrent chemoradiation: cisplatin/fluorouracil (2 cycles) plus 66-72 Gy to primary site and neck	Lymph node dissection if residual disease for all patients Lymph node dissection recommended if N2 or N3 disease, regardless of clinical response	If no response or progressive disease at 55 Gy Less than complete response to therapy
Intergroup Head and Neck Trial[89] (n = 547)	65/35	79/10	71	Primary radiation therapy: 70 Gy to primary site, 50-70 Gy to nodes Induction chemotherapy: cisplatin/fluorouracil (3 cycles) followed by radiation therapy for those who had a response (If salvage	Lymph node dissection after completion of radiation therapy for in all patients with clinical involvement of nodes before beginning of treatment	Less than partial response to induction chemotherapy Residual disease found at biopsy after completion of radiation therapy

				surgery, 50-70 Gy administered postoperatively) Concurrent chemoradiation: high-dose cisplatin (days 1, 22, 43) plus 70 Gy to primary site, 50-70 Gy to nodes		

*Data given for all enrolled patients; 52 had laryngeal/hypopharyngeal cancer.

Table 5b: Phase III Studies of Concurrent Chemoradiation Therapy for Larynx Preservation: Outcomes

Study	Overall Survival		Rate of Larynx Preservation		Toxicity
	%	**Timeframe**	**%**	**Timeframe**	
Cleveland Clinic Trial[111,112]					
Radiation therapy–alone arm	48	5 years	Larynx: 16	5-year overall survival with organ preservation	
			Hypopharynx: 0	5-year overall survival with organ preservation	
Concurrent chemoradiation therapy arm	50	5 years	Larynx: 29	5-year overall survival with organ preservation (*P* = .03 *v* radiation therapy–alone arm)	Increased weight loss compared with radiation therapy–alone arm Feeding tube required in 58% (32% in radiation therapy–alone arm) Febrile neutropenia in 36% No data on speech or swallowing
			Hypopharynx: 14	5-year overall survival with organ preservation (*P* = .008 *v* radiation therapy–alone arm)	
Intergroup Head and Neck					

Trial[89]					
Induction chemotherapy arm	76 55	2 years 5 years	75	2 years (P = .27 v radiation therapy–alone arm)	Rate of grade 3 or 4 toxicity during radiation no different from that for radiation therapy–alone arm Swallowing difficulties in 9% at 1 year and 16% at 2 years
Concurrent chemoradiation therapy arm	74 54	2 years 5 years	88	2 years (P < .001 v radiation therapy–alone arm, P = .005 v induction chemotherapy arm)	Highest rate of grade 3 or 4 acute toxicity No increase in late toxic effects Swallowing difficulties in 26% at 1 year and in 15% at 2 years
Radiation therapy–alone arm	75 56	2 years 5 years	70	2 years	Swallowing difficulties in 18% at 1 year and in 14% at 2 years

Table 6: Summary of Recommendations for the Use of Larynx-Preservation Strategies in the Treatment of Laryngeal Cancer

Specific Recommendations	2005 Recommendations
What are the larynx-preservation treatment options for limited-stage (T1, T2) primary-site disease that do not compromise survival? What are the considerations in selecting treatment options in this setting?	All patients with T1-T2 laryngeal cancer should be treated, at least initially, with intent to preserve the larynx.
	T1-T2 laryngeal cancer can be treated with radiation or larynx-preservation surgery with similar survival outcomes. Selection of treatment depends on patient factors, local expertise, and the availability of appropriate support and rehabilitative services. Every effort should be made to avoid combining surgery with radiation therapy because single-modality treatment is effective for limited-stage, invasive cancer of the larynx and functional outcomes may be compromised by combined-modality therapy.
	Surgical excision of the primary tumor with intent to preserve the larynx should be undertaken with the aim of achieving tumor-free margins; so-called narrow-margin excision followed by postoperative radiation therapy is not an acceptable treatment approach.
	Local tumor recurrence after radiation therapy may be amenable to salvage by organ-preservation surgery but total laryngectomy will be necessary for a substantial proportion of patients, especially those with index T2 tumors.
	Concurrent chemoradiation therapy may be used for larynx preservation for selected patients with stage III, T2 N+ cancers for whom total laryngectomy is the only surgical option, when the functional outcome after larynx-preservation surgery is expected to be unsatisfactory, or when surgical expertise in such procedures is not available.
	Limited stage laryngeal cancer constitutes a wide spectrum of disease. The clinician must exercise judgment when recommending treatment in this category. For a given patient, factors that may influence the selection of treatment modality include extent and volume of tumor; involvement of the anterior commissure; lymph node metastasis; the patient's age, occupation, preference, and compliance; availability of expertise in radiation therapy or surgery; and history of a malignant lesion in the head and neck.

What are the larynx-preservation treatment options for advanced-stage (T3, T4) primary-site disease that do not compromise survival? **What are the considerations in selecting among them?**	Organ-preservation surgery, concurrent chemoradiation therapy, and radiation therapy alone, all with further surgery reserved for salvage, offer potential for larynx preservation without compromising survival. Anticipated success rates for larynx preservation, associated toxicities, and suitability for a given patient will vary among these approaches. Selection of a treatment option will depend on patient factors, local expertise, and the availability of appropriate support and rehabilitation services.
	All patients should be evaluated regarding their suitability for a larynx- preservation approach, and they should be apprised of these treatment options. No larynx-preservation approach offers a survival advantage compared with total laryngectomy and appropriate adjuvant treatment.
	A minority of patients with T3-T4 primary-site disease will be suitable for specialized organ-preservation procedures such as a supracricoid partial laryngectomy. The addition of postoperative radiation therapy will compromise anticipated functional outcomes. Induction chemotherapy before organ-preservation surgery is not recommended outside of a clinical trial.
	Concurrent chemoradiation therapy offers a significantly higher chance of larynx preservation than does radiation therapy alone or induction chemotherapy followed by radiation, albeit at the cost of higher acute in-field toxicities. The best available evidence supports the use of cisplatin as the drug of choice in this setting.
	There is insufficient evidence to indicate that survival or larynx-preservation outcomes are improved by the addition of induction chemotherapy before concurrent treatment or the use of concurrent chemotherapy with altered fractionated radiation therapy in this setting.
	For patients who desire larynx-preservation therapy but are not candidates for organ-preservation surgery or chemoradiation therapy, radiation therapy alone is an appropriate treatment. With this last approach, survival is similar to that associated with chemoradiation therapy when salvage surgery is incorporated, but the likelihood of larynx preservation is lower.
What is the appropriate treatment of the regional cervical nodes in patients with laryngeal cancer who are treated with an organ-	Most patients with T1-T2 lesions of the glottis and clinically negative cervical nodes (N0) do not require routine elective treatment of the neck.
	Patients with advanced lesions of the glottis and all patients with supraglottic lesions should have elective treatment of the neck, even if clinically N0.

preservation approach?	Patients with clinically involved regional cervical nodes (N1) who are treated with definitive radiation therapy or chemoradiation therapy and who have a complete clinical response do not require elective neck dissection. Neck dissection should be performed for patients who do not have a complete clinical response to radiation therapy.
	Surgical treatment of the neck is recommended for patients with N2 or N3 disease who are treated with definitive radiation therapy or chemoradiation therapy, regardless of response. Some surgeons and patients are reluctant to risk the morbidity of neck dissection, given the prospect of a negative pathologic diagnosis in most cases, but there is no standard imaging approach in this setting that has been validated to significantly improve on this decision-making process. Salvage surgery for recurrent disease in the neck is rarely successful if subsequently required in this setting. These two points should be discussed with all patients who have an apparent complete clinical response to radiation therapy or chemoradiation therapy and choose to be followed up with expectant observation.
	Patients with clinically involved cervical nodes who are treated with surgery for the primary lesion should have neck dissection. If there are poor-risk features, adjuvant concurrent chemoradiation therapy is indicated.
Are there methods for prospectively selecting patients with laryngeal cancer to increase the likelihood of successful larynx preservation?	There are no validated markers that consistently predict outcomes of larynx-preservation therapy. However, patients with tumor penetration through cartilage into soft tissues are considered poor candidates for a larynx-preservation approach. Primary surgery, usually total laryngectomy, is commonly recommended in this setting.
	Selection of therapy for an individual patient requires assessment by a multidisciplinary team, as well as consideration of patient comorbidity, psychosocial situation and preferences, and local therapeutic expertise.
	Continued cigarette smoking appears to be associated with a worse outcome after radiation therapy. Patients should be encouraged to abstain from smoking after diagnosis and throughout treatment.

Appendix A

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