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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A B S T R A C T

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.

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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 of 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 (chemoradiotherapy therapy), and function-preserving partial laryngectomy procedures. With all three of these approaches, total laryngectomy is reserved for tumor recurrence.

The American Society of Clinical Oncology (ASCO) fully appreciates the controversy about how to best achieve the dual goals of cure and preservation of function for patients with laryngeal cancer. As a service to patients, to its members, and to practicing physicians generally, ASCO convened an Expert Panel under the auspices of the Health Services Committee to develop recommendations regarding the appropriate application of larynx-preservation therapies.

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.

QUESTIONS

The following questions about squamous cell laryngeal cancer 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?

METHODS

The members of the Expert Panel were selected for their expertise in clinical medicine; medical, radiation, and surgical oncology; diagnostic imaging; clinical research; outcomes/health services research; and related disciplines (biostatistics, quality of life) with a focus on expertise in head and neck and laryngeal cancer (Appendix A). To enhance the focus of the published guideline on the implications for clinical practice, the methodology of the guideline development is available online, at both www.jco.org and www.asco.org.

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 1). A complete review of the literature and discussion of study results are available online.

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?

Evidence base. 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 the quality of voice and swallowing ability, after surgery or radiation therapy for patients with this stage of disease.

The recommendations to address these questions are based on evidence from prospective and retrospective cohort studies.¹¹⁻⁷⁵ The recommendations for T2 N+ disease are based on data from randomized controlled trials of chemoradiotherapy therapy (with either induction or concurrent chemotherapy compared with radiation therapy alone or surgery followed by adjuvant radiation therapy).^{77,78} The outcomes assessed included overall survival, disease-free survival, rates of laryngeal preservation, local-regional control, toxicity of therapy, and cost.

Limited-stage disease represents a spectrum. Treatment selection can be challenging, as the evidence base for most decisions is derived from nonrandomized studies and various factors need to be considered when choosing therapy. Selected examples for glottic cancer are illustrative. If voice outcome is predicted to be good after endoscopic laser resection for a T1 glottic cancer (eg, a superficial tumor located in the middle third of the cord, especially on its free edge), then use of this modality is more efficient and thus preferred. However, lesions that are indistinct, especially those arising in the context of widespread, abnormal-appearing mucosa, are more suitable for radiation therapy than for surgery. Radiation therapy is preferred by many clinicians for treatment of T2 glottic carcinoma characterized as superficial on radiographic imaging, with preserved cord mobility, as local control rates are high and anticipated functional outcomes are good. But some investigators have noted compromised survival after the failure of radiation therapy in T2 glottic carcinoma indicating the importance of obtaining initial local control.^{56,59} As such, supracricoid partial laryngectomy with cricohyoidoepiglottopexy remains a reasonable alternative for patients with a T2 glottic carcinoma who after pretreatment counseling would be willing to sacrifice voice quality in an effort to improve local control. Induction chemotherapy has been investigated as treatment for patients with limited-stage laryngeal cancer. However, insufficient data are currently available to recommend such an approach outside the context of a clinical trial.

Recommendations

- 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,

Table 1. 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: 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	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*: T2—tumor extends to supraglottis and/or subglottis, or with impaired vocal cord mobility	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*: 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	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: T3 glottis—tumor limited to the larynx with vocal cord fixation, and/or invades paraglottic space, and/or minor thyroid cartilage erosion (eg, inner cortex) T3 supraglottis—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 glottis or supraglottis—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 glottis or supraglottis—tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures	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

*A favorable T2 glottic lesion is defined as a superficial tumor, on radiographic imaging, with normal cord mobility. 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). A favorable supraglottic lesion is defined as a T1 or T2 tumor with superficial invasion on radiographic imaging and preserved cord mobility, and/or tumor of the aryepiglottic fold with minimal involvement of the medial wall of the pyriform sinus. More locally advanced and invasive T2 supraglottic lesions are considered unfavorable.

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 chemoradiotherapy therapy may be used for larynx preservation for selected patients with stage III, T2 N+ cancers when 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?

Evidence base. The recommendations to address these questions are based on evidence from randomized controlled trials of different radiation fractionation schedules,⁷⁶ chemoradiotherapy therapy (either induction or concurrent) compared with radiation therapy alone or surgery followed by adjuvant radiation therapy,⁷⁷⁻⁸⁵ on meta-analysis or other secondary analysis of data from randomized clinical trials,^{86-88,102,105,108} and on prospective and retrospective cohort studies.^{22,58,89-101,103,104,106,107} The outcomes evaluated included overall survival, disease-free survival, rates of laryngeal preservation, local-regional control, toxicity of therapy, and cost.

Recommendations

- Organ-preservation surgery, concurrent chemoradiotherapy 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 (Table 2).

- 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 chemoradiotherapy 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 (Table 3).

- 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 chemoradiotherapy therapy, radiation therapy alone is an appropriate treatment. With this last approach, survival is similar to that associated with chemoradiotherapy 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-preservation approach?

Evidence base. 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.

The recommendations to address this question are based on evidence from derivative analyses of randomized controlled trials of chemoradiotherapy (either induction or concurrent) compared with radiation therapy alone or surgery followed by adjuvant radiation therapy,^{125,140} a randomized trial comparing the different types of neck dissection,¹¹³ and on prospective and retrospective cohort studies.^{25,35,66,109,124,126-139,141,142} With respect to adjuvant therapy, evidence was drawn from randomized controlled trials of radiation therapy compared with concurrent chemoradiotherapy.¹⁴³⁻¹⁴⁵ The outcomes assessed included overall survival, disease-free survival, local-regional control, and toxicity of therapy.

Recommendations

- 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 chemoradiotherapy 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 chemoradiotherapy 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

Table 2. Phase III Studies of Induction Chemotherapy Followed by Radiation for Larynx Preservation

Study and Patient Characteristics	Study Arms	Treatment of Disease in the Neck	Indications for Salvage Surgery After Chemoradiation Therapy	Overall Survival		Rate of Larynx Preservation		Toxicity
				%	Timeframe	%	Timeframe	
VA Laryngeal Cancer Study ⁷⁸ (n = 332) Stage III/IV disease (%), 57/43 (2/3 primary lesions of the supraglottis); T3/T4 (%), 65/26; N0-N1 (%), 72	Chemoradiation Arm							
	Induction chemotherapy (3 cycles standard cisplatin and fluorouracil) followed by radiation therapy (66-76 Gy to primary site 50-75 Gy to nodes)	Lymph node dissection if residual disease after radiation therapy	Less than partial response to chemotherapy after 2 cycles; residual disease at biopsy 12 weeks after completion of radiation therapy	68	2 years	66	2 years	One toxic death thought caused by chemotherapy; radiation toxicity similar in the two arms; long-term data on quality of life provided in subsequent publication ¹⁰²
	Surgery Arm							
	Standard total laryngectomy followed by radiation therapy (50 Gy [no residual disease], up to 73 Gy [residual disease])	Lymph node dissection for all patients	—	68	2 years	—		
GETTEC Study ⁸² (n = 68) Stage III/IV (%), not provided; T3/T4 (%), 100/0; N0-N1 (%), 93	Chemoradiation Arm							
	Induction chemotherapy (3 cycles standard cisplatin and fluorouracil) followed by radiation therapy (65-70 Gy to primary site 50-70 Gy to nodes)	Lymph node dissection if salvage surgery only	Less than 80% regression of tumor after chemotherapy, lack of return of laryngeal mobility	69	2 years	42	Median, 8 years	No data provided on quality of life, speech, or swallowing
	Surgery Arm							
	Standard total laryngectomy followed by radiation therapy (50 Gy [no residual disease], up to 70 Gy [residual disease])	Lymph node dissection for all patients	—	84	2 years			—
					<i>P</i> = .006			
EORTC Hypopharynx Trial ⁸¹ (n = 202) Stage III/IV (%), 57/37; T3/T4 (%), 72/5; N0-N1 (%), 65	Chemoradiation Arm							
	Induction chemotherapy (3 cycles standard cisplatin and fluorouracil) followed by radiation therapy (70 Gy to primary site and nodes)	Lymph node dissection if residual disease in nodes after chemotherapy; timing variable	Less than complete response to chemotherapy	57	3 years	42	3 years	One toxic death caused by chemotherapy; no data on quality of life or speech and swallowing; larynx preservation required local control without surgery to the primary site, no tracheostomy or feeding tube
				30	5 years	35	5 years	
	Surgery Arm							
	Standard total laryngectomy with partial pharyngectomy followed by radiation therapy (50 Gy [no residual disease] 64 Gy [residual disease])	Lymph node dissection for all patients	—	43	3 years			—
				35	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.

apparent complete clinical response to radiation therapy or chemoradiotherapy 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 chemoradiotherapy therapy is indicated.

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

Evidence base. The recommendations addressing this question are based on evidence from prospective and retrospective cohort stud-

ies of clinical, radiographic, and/or pathologic parameters associated with clinical outcomes^{44,47,62,73,89,91,146,147,149,151-168} and on derivative analyses of a randomized controlled trial.^{148,150,169-171} The outcomes assessed included overall survival, disease-free survival, local-regional control, and rates of laryngeal preservation.

Recommendations

- 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.

Table 3. Phase III Studies of Concurrent Chemoradiation Therapy for Larynx Preservation

Study	Study Arms	Treatment of Disease in the Neck	Indications for Salvage Surgery	Overall Survival		Larynx Preservation		Toxicity		
				%	Timeframe	%	Timeframe			
Cleveland Clinic Trial ^{79,80} (n = 100*) Stage III/IV (%), 28/72; T3/T4 (%), 39/33; N0-N1 (%), 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	48	5 years	Radiation therapy alone				
						Larynx				
						16	5-year overall survival with organ preservation			
						0	Hypopharynx 5-year overall survival with organ preservation			
				50	5 years	Concurrent chemoradiation therapy		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 .		
						Larynx (<i>P</i> = .03 v radiation therapy-alone arm)				
						29	5-year overall survival with organ preservation			
						Hypopharynx (<i>P</i> = .008 v radiation therapy-alone arm)				
						14	5-year overall survival with organ preservation			
Intergroup Head and Neck Trial ⁷⁶ (n = 547) Stage III/IV (%), 65/35; T3/T4 (%), 79/10; N0-N1 (%), 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 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	Lymph node dissection after completion of radiation therapy for 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	75	2 years	Radiation therapy alone		Swallowing difficulties in 18% at 1 year and in 14% at 2 years		
						70	2 years			
						56	5 years			
						76	2 years	Induction chemotherapy		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
								75	2 years	
						55	5 years	<i>P</i> = .27 v radiation therapy-alone arm		
		74	2 years	Concurrent chemoradiation		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				
				88	2 years					
				54	5 years	<i>P</i> < .001 v radiation therapy-alone arm; <i>P</i> = .005 v induction-chemotherapy arm				
*Data given for all enrolled patients; 52 had laryngeal/hypopharyngeal cancer.										

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

- 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.

FINAL COMMENTS

Larynx-preservation therapy is intended to offer improved function and quality of life for patients with laryngeal cancer, without compro-

mising 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 therapy, 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, such as tissue-specific investigations, into the design of randomized studies 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,^{26,102} and some that do may be primary site dependent.¹⁷² How each patient perceives an adverse sequela of treatment is variable. Permanent gastrostomy or stoma is often a greater concern to patients than loss of speech^{10,173}; 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 substantial functional morbidity and treatment-related toxicities such as dysphagia is a risk if patients are not followed up for longer time periods.^{30,174-176} Careful assessment of such outcomes is crucial to guide subsequent protocol development in hopes of minimizing the morbidity of treatment without compromising efficacy.^{177,178}

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.^{9,179} 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 improvement in treatment protocols.

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Appendix

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