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ASCO SPECIAL ARTICLE

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

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Editor's note: This American Society of Clinical Oncology Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with additional evidence tables, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at: www.asco.org/head-neck-cancer-guidelines and www.asco.org/guidelineswiki.

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ABSTRACT

Purpose

To update the guideline recommendations on the use of larynx-preservation strategies in the treatment of laryngeal cancer.

Methods

An Expert Panel updated the systematic review of the literature for the period from January 2005 to May 2017.

Results

The panel confirmed that the use of a larynx-preservation approach for appropriately selected patients does not compromise survival. No larynx-preservation approach offered a survival advantage compared with total laryngectomy and adjuvant therapy as indicated. Changes were supported for the use of endoscopic surgical resection in patients with limited disease (T1, T2) and for initial total laryngectomy in patients with T4a disease or with severe pretreatment laryngeal dysfunction. New recommendations for positron emission tomography imaging for the evaluation of regional nodes after treatment and best measures for evaluating voice and swallowing function were added.

Recommendations

Patients with T1, T2 laryngeal cancer should be treated initially with intent to preserve the larynx by using endoscopic resection or radiation therapy, with either leading to similar outcomes. For patients with locally advanced (T3, T4) disease, organ-preservation surgery, combined chemotherapy and radiation, or radiation alone offer the potential for larynx preservation without compromising overall survival. For selected patients with extensive T3 or large T4a lesions and/or poor pretreatment laryngeal function, better survival rates and quality of life may be achieved with total laryngectomy. Patients with clinically involved regional cervical nodes (N+) who have a complete clinical and radiologic imaging response after chemoradiation do not require elective neck dissection. All patients should undergo a pretreatment baseline assessment of voice and swallowing function and receive counseling with regard to the potential impact of treatment options on voice, swallowing, and quality of life. Additional information is available at www.asco.org/head-neck-cancer-guidelines and www.asco.org/guidelineswiki.

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INTRODUCTION

Laryngeal cancer is a significant clinical problem that affects nearly 100,000 people in the United States. It is estimated that there were 13,430 new cases and 3,620 deaths attributed to cancer of the larynx in 2016.[1] With public awareness of tobacco and alcohol use as major predisposing factors, the incidence of laryngeal cancers has decreased 2.4% each year over the past 10 years.[1] Based on SEER data for the period of 2006 to 2012, the estimated overall 5-year survival rate for patients with laryngeal cancer was only 60.7% and has not changed appreciably over the past several decades. When analyzed by tumor stage, cure rates for patients diagnosed with limited disease (T1, T2) are excellent ranging from 80% to 90%. Unfortunately, a majority of patients are still diagnosed with locally advanced (T3, T4) disease or regional nodal metastases, where survival rates generally are < 50%. SEER data also show that the

ASSOCIATED CONTENT

Appendix
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Data Supplement
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THE BOTTOM LINE

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

Guideline Questions

1. What are the larynx-preservation treatment options for limited-stage (T1, T2) primary site disease that do not compromise survival?
   a. 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?
   a. 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?
5. [New] What are the best measures to evaluate airway, voice, and swallowing function?
   a. What are the considerations to determine best function-preservation treatment or to recommend laryngectomy?
   b. What are the best measures for the pre- and post-treatment assessment of function?

Target Population

Patients with laryngeal cancer.

Target Audience

Medical oncologists, radiation oncologists, surgeons, nurses, speech pathologists, oncology pharmacists.

Methods

An Expert Panel was convened to update clinical practice guideline recommendations based on a systematic review of the medical literature.

Key Recommendations

Clinical Question 1

Recommendation 1.1 [Unchanged]

All patients with T1, T2 laryngeal cancer should be treated, at least initially, with intent to preserve the larynx.

Recommendation 1.2 [Unchanged]

T1, T2 laryngeal cancer can be treated with radiation or larynx-preserving 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 (RT) because functional outcomes may be compromised by combined-modality therapy; single-modality treatment is effective for limited-stage, invasive cancer of the larynx.

Recommendation 1.3 [New]

The success of the larynx-preservation approach may be higher with initial larynx-preserving surgery compared with RT based on retrospective studies; however, this may be subjected to patient selection factors. In experienced hands, endoscopic resections are preferred because of equal or better outcomes compared with open partial laryngectomy, unless there are issues with tumor exposure or safety of the endoscopic approach (Type: evidence-based, benefits outweigh harms; Quality of evidence: intermediate; Strength of recommendation: moderate).

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THE BOTTOM LINE (CONTINUED)

Recommendation 1.4 [Updated]

Surgical excision of the primary tumor with intent to preserve the larynx should be undertaken with the aim of achieving tumor-free margins. Surgery that anticipates the need for postoperative RT to treat close or involved tumor margins or widespread dysplasia is not an acceptable treatment approach (Type: evidence-based, benefits outweigh harms; Quality of evidence: strong; Strength of recommendation: high).

Recommendation 1.5 [Unchanged]

Local tumor recurrence after RT 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.

Recommendation 1.6 [Unchanged]

Combined chemotherapy and RT may be used for larynx preservation for selected patients with limited-stage and (1) unfavorable or deeply invasive T2 cancer, (2) T2 N+ cancer, (3) for whom a total laryngectomy may be the only surgical option, (4) in whom the functional outcome after larynx-preserving surgery is expected to be unsatisfactory, and (5) for whom surgical expertise for such procedures is not available.

Recommendation 1.7 [Updated]

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; vocal cord mobility; involvement of the anterior commissure; lymph node metastasis; the patient's age, occupation, pretreatment voice, and swallowing function; patient preference and compliance; and the availability of expertise in RT or surgery. Optimal outcomes require specialized skills, judgment, and expertise. Poorly performed open or endoscopic surgery or RT will raise the risk for recurrence or the need for additional modalities of therapy to achieve disease control (Type: evidence-based, benefits outweigh harms; Quality of evidence: intermediate; Strength of recommendation: moderate).

Clinical Question 2

Recommendation 2.1 [Reworded]

Organ-preservation surgery, combined chemotherapy and RT, and RT alone, all with further surgery reserved for salvage, offer the potential for larynx preservation without compromising overall 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, including age, comorbidities, preferences, socioeconomic factors, local expertise, and the availability of appropriate support and rehabilitation services.

Recommendation 2.2 [New]

For selected patients with extensive T3 or large T4a lesions and/or poor pretreatment laryngeal function, better survival rates and quality of life may be achieved with total laryngectomy rather than with organ-preservation approaches and may be the preferred approach (Type: evidence-based, benefits outweigh harms; Quality of evidence: high; Strength of recommendation: strong).

Recommendation 2.3 [Unchanged]

All patients should have a multidisciplinary evaluation regarding their suitably 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.

(continued on following page)

THE BOTTOM LINE (CONTINUED)

Recommendation 2.4 [Updated]

A minority of patients with T3, T4 primary site disease will be suitable for specialized organ-preservation surgical procedures, such as a supracricoid partial laryngectomy. The addition of postoperative RT will compromise functional outcomes. Induction chemotherapy before organ-preservation surgery is not recommended outside a clinical trial (Type: evidence-based, benefits outweigh harms; Quality of evidence: intermediate; Strength of recommendation: moderate).

Recommendation 2.5 [Updated]

Concurrent chemoradiotherapy (CRT) offers a significantly higher chance of larynx preservation than RT alone or induction chemotherapy followed by RT, albeit at the cost of higher acute in-field toxicities and without improvement in overall survival. The best available evidence supports the use of cisplatin as the drug of choice in this setting (Type: evidence-based, benefits outweigh harms; Quality of evidence: strong; Strength of recommendation: high).

Recommendation 2.6 [Updated]

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 treatment with altered fractionation RT in this setting (Type: evidence-based, benefits outweigh harms; Quality of evidence: intermediate; Strength of recommendation: moderate).

Recommendation 2.7 [Unchanged]

For patients who desire larynx-preservation therapy but are not candidates for organ-preservation surgery or CRT, RT alone is an appropriate treatment. With this last approach, survival is similar to that associated with CRT when timely salvage surgery is incorporated, but the likelihood of larynx preservation is lower.

Clinical Question 3

Recommendation 3.1 [Unchanged]

Most patients with T1, T2 lesions of the glottis and clinically negative cervical nodes (N0) do not require routine elective treatment of the neck.

Recommendation 3.2 [Unchanged]

Patients with advanced lesions of the glottis and all patients with supraglottic lesions should have elective treatment of the neck, even if clinically N0.

Recommendation 3.3 [Updated]

Patients with clinically involved regional cervical nodes (N+) who are treated with definitive RT or chemotherapy and RT and who have complete clinical, radiologic, and metabolic imaging (positron emission tomography/computed tomography at 12 weeks or later after therapy) do not require elective neck dissection (Type: evidence-based, benefits outweigh harms; Quality of evidence: strong; Strength of recommendation: high).

Recommendation 3.4 [Updated]

Patients with equivocal [^{18}F]fluorodeoxyglucose uptake should undergo neck dissection. The risks and cost of expectant observation versus surgery should be discussed with the patient (Type: evidence-based, benefits outweigh harms; Quality of evidence: strong; Strength of recommendation: high).

Recommendation 3.5 [Unchanged]

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 CRT is indicated.

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THE BOTTOM LINE (CONTINUED)

Clinical Question 4

Recommendation 4.1 [Updated]

There are no validated markers that consistently predict outcomes of larynx-preservation therapy. However, patients with a nonfunctional larynx (eg, extensive T3 or T4a) or tumor penetration through cartilage into surrounding soft tissues are considered poor candidates for a larynx-preservation approach. Primary surgery, usually total laryngectomy, is commonly recommended in this setting (Type: evidence-based, benefits outweigh harms; Quality of evidence: intermediate; Strength of recommendation: moderate).

Recommendation 4.2 [Updated]

Selection of therapy for an individual patient requires assessment by the multidisciplinary team as well as consideration of voice and swallowing function; patient comorbidity, psychosocial situation, and preferences; and local therapeutic expertise. The multidisciplinary team should include surgical oncology, medical oncology, radiation oncology, speech pathology, radiology, pathology, nursing, dietetics, psychology, and a variety of rehabilitative services, including dental/prosthodontics, smoking cessation, and other ancillary services as required for such things as pain management and psychosocial support (Type: evidence-based, benefits outweigh harms; Quality of evidence: intermediate; Strength of recommendation: moderate).

Recommendation 4.3 [Unchanged]

Continued cigarette smoking is associated with a worse outcome after therapy. Patients should be encouraged to abstain from smoking after the diagnosis and monitored and recommended for smoking cessation programs as necessary throughout and following treatment.

Clinical Question 5 [New]

Recommendation 5.1

As part of a comprehensive pretreatment evaluation, all patients should undergo a baseline assessment of voice and swallowing function, voice (use and requirements), and counseling with regard to the potential effect of treatment options on voice, swallowing, and quality of life (Type: evidence-based, benefits outweigh harms; Quality of evidence: intermediate; Strength of recommendation: moderate).

Recommendation 5.2

Pretreatment voice and swallowing assessments should establish the functional impact of tumor volume and extent and stage of disease on voice and swallowing outcomes (Type: evidence-based, benefits outweigh harms; Quality of evidence: intermediate; Strength of recommendation: moderate).

Recommendation 5.3

Instrumental, performance status, and quality-of-life measures of voice and swallowing should be used to evaluate pre- and post-treatment function. Multiple assessment tools are available for voice and swallowing. Routine methods of assessment include self-recorded and/or expert-rated voice-quality measures, voice-related quality-of-life tools, videostroboscopy, radiographic (videofluoroscopic) or fiber-optic laryngoscopic evaluation of swallowing, and dietary assessment (Type: evidence-based, benefits outweigh harms; Quality of evidence: intermediate; Strength of recommendation: moderate).

Additional Resources

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/head-neck-cancer-guidelines and www.asco.org/guidelineswiki. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

overall survival of patients diagnosed with stage III/IV laryngeal cancer in the years 2004 to 2009 was significantly improved compared with those diagnosed before 2004, yet the 5-year rate was only 44%.[2] Although laryngeal cancer constitutes only 0.8% of all new cancer cases in the United States, it has significant social importance because of the critical role laryngeal function plays in voice production, swallowing, and quality of life for afflicted patients. This is particularly true for patients with advanced disease where traditional treatments have included radical surgery (total or near total laryngectomy) and intensive radiotherapy (RT) and/or chemotherapy combined with RT. Because of the morbidity associated with laryngeal cancers and its multimodality treatment, clinical research emphasis over the past 25 years has focused on efforts to preserve laryngeal function through improvements in single-modality treatment of patients with limited cancers and increasing use of combinations of chemotherapy and RT in the majority of patients with advanced disease as an alternative to total laryngectomy.

Unfortunately, these efforts have not met with improvements in overall survival rates even though preservation of laryngeal function can be achieved in $>$ 50% of patients. In 2006, an ASCO Expert Panel reviewed evidence that supports treatment strategies intended to preserve laryngeal function and published comprehensive guidelines for the use of such strategies in both limited and advanced disease settings.[3] The 2006 guidelines reflected the considerable nuances in selecting larynx-preservation treatment approaches and comprehensively reviewed factors that might influence decision making. Readers are referred to that publication for the detailed supporting literature review.[3] Since that time, additional clinical progress has been made in defining situations best suited for differing larynx-preservation treatment strategies and the individualization of treatment approaches. Over the past 10 years, there has been increased appreciation of the long-term complications and morbidity of larynx-preservation treatment approaches and enhanced understanding of the importance of the assessment of voice and swallowing functions in treatment decision making.[4]

The purpose of this guideline update is to review the recent literature since the publication of the 2006 guidelines and evaluates the prior recommendations to determine whether they still represent the state of the art in larynx-preservation treatment approaches for patients with laryngeal cancer. The goal is to confirm prior recommendations where appropriate and provide updated and new recommendations as necessary to reflect current practice and promote treatment excellence and consistency across institutions and practices.

GUIDELINE QUESTIONS

This clinical practice guideline addresses five overarching clinical questions: What are the larynx-preservation treatment options for limited-stage (T1, T2) and advanced-stage (T3, T4) primary site disease that do not compromise survival, and what are the considerations in selecting among them? What is the appropriate treatment of the regional cervical nodes for patients with laryngeal cancer who are treated with an organ-preservation approach? Are there methods for prospectively selecting patients with laryngeal cancer to increase the likelihood of success of larynx preservation? What are the best measures to evaluate airway, voice, and swallowing function to determine the best function-preservation treatment or to recommend laryngectomy and for the pre- and post-treatment assessment of function?

METHODS

Guideline Update Development Process

The Expert Panel (Appendix Table A1, online only) convened through teleconference and/or webinar and corresponded through e-mail. With consideration of the evidence, the authors were asked to contribute to the development the guideline, provide critical review, and finalize the guideline recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review and submitted to *Journal of Clinical Oncology* for editorial review and consideration for publication. All American Society of Clinical Oncology (ASCO) guidelines are ultimately reviewed and approved by an Expert Panel and the ASCO Clinical Practice Guideline Committee before publication. All funding for the administration of the project was provided by ASCO.

The 2006 recommendations were reviewed and updated by an Expert Panel with multidisciplinary representation. MEDLINE was searched from January 2005 to May 2017. The updated systematic review included phase III randomized clinical trials (RCTs), phase II studies, and prospective and retrospective studies. Articles were selected for inclusion in the systematic review of the evidence according to the following criteria:

- Population: patients with laryngeal cancer.
- Interventions: surgery, RT, chemotherapy, targeted therapy, and organ-preserving surgery.
- Fully published English-language reports of phase III RCTs, rigorously conducted systematic reviews or meta-analyses, phase II studies, prospective and retrospective studies, and longitudinal studies.
- Studies with sample sizes $\geq$ 50.

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, or narrative reviews; or (3) published in a non-English language.

The updated search was guided by the signals[5] approach designed to identify only new, potentially practice-changing data signals that might translate into revised practice recommendations. The approach relies on targeted routine literature searches and the expertise of ASCO Expert Panel members to help to identify potential signals. The Methodology Supplement (available at www.asco.org/head-neck-cancer-guidelines) provides additional information about the signals approach.

The new guideline recommendations are crafted, in part, by using the Guidelines Into Decision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software.[6] In addition, a guideline implementability review was conducted. On the basis of the implementability review, revisions were made to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each new recommendation.

Detailed information about the methods used to develop this guideline update is available in the Methodology Supplement at www.asco.org/head-neck-cancer-guidelines, including an overview (eg, panel composition, development process, revision dates), the literature search and data extraction process, the recommendation development process (GLIDES and BRIDGE-Wiz), and quality assessment.

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of substantive updates to the guideline. On the basis of formal review of the emerging literature, ASCO will determine the need to update.

This information is the most recent as of the publication date. Visit the ASCO Guidelines Wiki at www.asco.org/guidelineswiki to submit new evidence.

In some selected cases where evidence is lacking but there was a high level of agreement among the Expert Panel, informal consensus is used (as noted with the Recommendations).

Guideline Disclaimer

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Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria; consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

Characteristics of Studies Identified in the Literature Search

A total of 150 studies met eligibility criteria and form the evidentiary basis for the guideline recommendations.[2,4,7-154] The identified trials included 13 systematic reviews,[8,30,37,44,48,60,62,74,94,98,138,152,153] 16 RCTs,[7,13,16,45,75,77,89,90,110,111,133,144-146,148,150] four phase II studies,[29,49,56,134] 29 prospective studies,[15,22,23,34,41,46,50-54,58,59,73,78,79,81,83,91,99,102,107,117,119,128,130,135,136,151] two prospective-retrospective studies,[4,57] and 86 retrospective studies[2,9-12,14,17-21,24-28,31-33,35,36,38-40,42,43,47,55,61,63-72,76,80,82,84-88,92,93,95-97,100,101,103-106,108,109,112-116,118,120-127,129,131,132,137,139-143,147,149,154] as shown in Figure 1. The primary outcomes reported in these studies were larynx-preservation rate, overall survival, locoregional control rate, response rate, voice- and swallowing-related quality of life, and health-related quality of life. Additional details about the study characteristics and outcomes can be found in the Data Supplement.

Study Quality Assessment

Study design aspects related to individual study quality, strength of evidence, strength of recommendations, and risk of bias were assessed. Refer to the Methodology Supplement for more information and for definitions of ratings for overall potential risk of bias.

RECOMMENDATIONS

The Expert Panel reviewed the 2006 recommendations and found some of the recommendations to be valid despite the updated evidence. The recommendations that were revised, updated, or newly added are discussed in this section.

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

The Expert Panel reaffirmed most of the prior 2006 recommendations and added endoscopic surgical resection as an initial recommended treatment option for patients with limited (T1, T2) disease. Since the 2006 report, a large number of studies have reported outcomes for endoscopic treatment approaches, even though overall use of RT for localized glottic cancer has increased.[139] Similar overall survival outcomes and voice and swallowing functionalities were confirmed for both initial endoscopic surgical and radiation treatment approaches. Additional clarifications were added to existing recommendations regarding the selection of combined chemotherapy and RT as treatment of selected patients with T2 tumors. Factors for consideration in treatment selection were expanded to include vocal cord mobility, patient morbidity, and pretreatment voice and swallowing function. A history of prior head and neck malignancy was removed as a consideration because the Panel believed that this had only been included previously as a cautionary factor for re-irradiation of neck tissues.

Recommendation 1.1. [Unchanged]. All patients with T1, T2 laryngeal cancer should be treated, at least initially, with intent to preserve the larynx.

Clinical interpretation of literature review. Three recent large systematic reviews have compared various initial treatment options and confirmed similar high cure rates regardless of initial larynx-preservation strategy.[8,44,138] Because of the essential role of the larynx in voice production and swallowing, optimal management of limited lesions includes consideration of both survival and functional consequences of a given initial treatment approach. Treatments that minimize the long-term treatment consequences on voice production, swallowing, and quality of life and the likelihood of requiring a total laryngectomy as a secondary salvage procedure are generally favored.

The goals in treatment of patients with limited-stage laryngeal cancer are curing the cancer, preserving laryngeal functions, and maximizing quality of life. The major treatment modalities traditionally have included primary larynx-preserving surgery or RT as single modalities; however, with the introduction of chemotherapy into the treatment of patients with more advanced laryngeal cancers, this recent review included some newer reports of combined chemotherapy and RT for selected patients with T2 disease.[9,50-52,105] Optimal treatment of patients with limited cancer

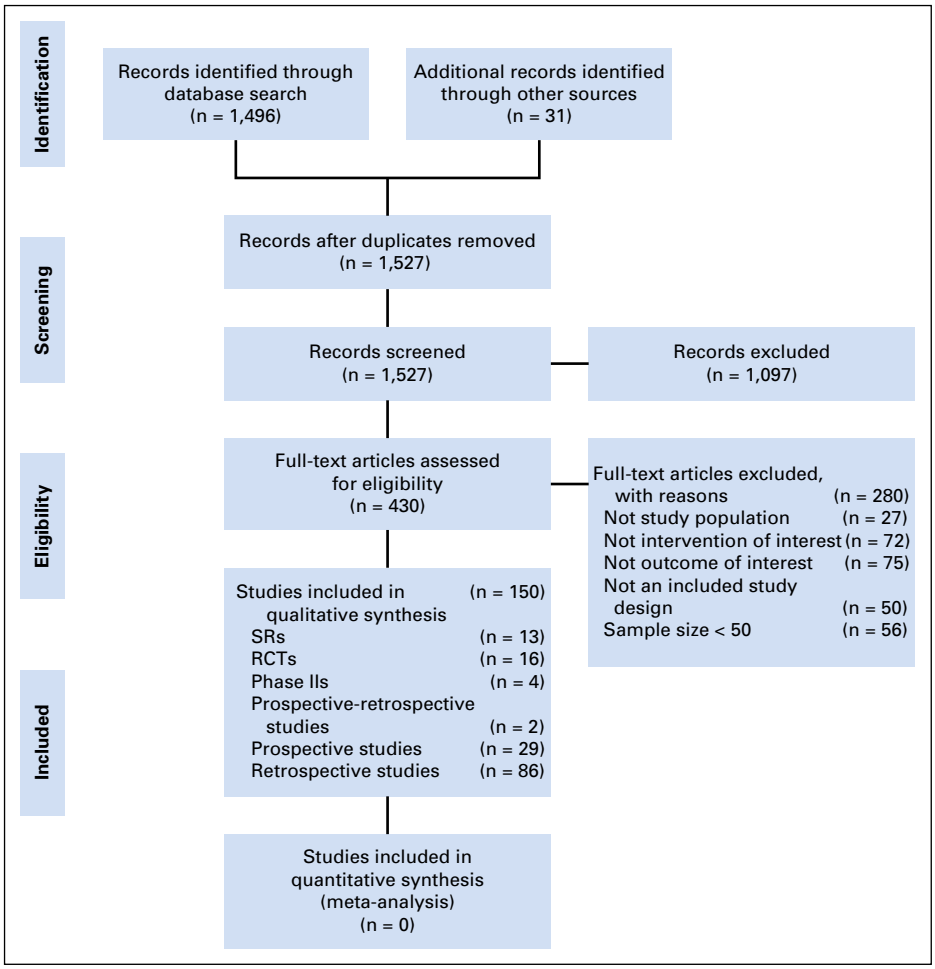

Fig 1. Study selection flow diagram. RCT, randomized controlled trial; SR, systematic review.

is achieved through careful cancer staging and comprehensive pretreatment evaluations of clinical, behavioral, psychologic, socioeconomic, and logistic issues, including patient desires, as part of a multidisciplinary evaluation. A particular new emphasis has been placed on pretreatment evaluation of voice and swallowing function. All patients with T1, T2 cancers should be treated, at least initially, with intent to preserve the larynx and laryngeal function. The general treatment options include endoscopic resection, open surgical partial laryngectomy, or RT. Total laryngectomy is reserved for surgical salvage of local tumor recurrences that are not optimally treated with additional partial surgery.

Recommendation 1.2. [Unchanged]. T1, T2 laryngeal cancer can be treated with radiation or larynx-preserving 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 RT because functional outcomes may be compromised by combined-modality therapy; single-modality treatment is effective for limited-stage, invasive cancer of the larynx.

Clinical interpretation of literature review. No randomized trials have compared survival outcomes among differing initial single-modality treatments for patients with T1 or T2 laryngeal cancers; however, since the 2006 guidelines were developed, a large number of prospective cohort[22,34,50-53,73,83,91,128] and retrospective studies[9-11,14,17,19,21,24,25,28,36,40,43,64-67,70,71,76,86,87,92,93,95,97,105,106,108,120,122,123,129,131,132,137,139,141] have been published comparing larynx-preserving surgical approaches to RT with respect to local control, survival, and voice outcomes. One small randomized trial (60 patients) from Finland compared voice outcomes after laser resection with RT and found no significant differences in overall voice quality but increased breathiness in the laser surgery cohort.[6] Three systematic reviews compared endoscopic resection to RT and found no significant differences in overall survival or voice outcomes or evidence that favors one modality over another.[8,44,138] Selection of initial treatment will be influenced by various factors, such as tumor site (glottic *v* supraglottic); ability to achieve adequate endoscopic visualization; risk of occult regional metastases; availability of RT; skill and experience of the treatment team; patient comorbidities; and local extent of the cancer, including subsites within the larynx and presence of regional metastases. Regional lymph node involvement in T1, T2 glottic cancers is unusual; therefore, single-modality treatment directed at the primary site generally is successful. Some limited-extent glottic tumors are considered unfavorable, including rare N+ cancers and some glottic T2 tumors with deep-tissue invasion or impaired vocal cord mobility indicative of deeper invasion. For such patients, either open surgical resection (larynx-preserving surgery) or combined chemoradiation may be an option. Supracricoid partial laryngectomy with cricohyoidoepiglottopexy is the organ-preserving surgery of

choice for most unfavorable T2 glottic cancers.[155-157] For T1, T2 supraglottic tumors, occult regional metastases or clinically positive regional nodes are more common, and initial treatment planning should include treatment of the neck. In most cases, comprehensive initial treatment favors RT as a single modality and either endoscopic resections in selected patients[22,34,120] or open surgical resections[24] combined with treatment of the neck as indicated. Single-modality therapy that provides the best functional outcomes is recommended for favorable tumors, which include superficial or exophytic T1, T2 tumors with minimal invasion of pre-epiglottic or paraglottic spaces, intact vocal cord mobility, and minimal extension to base of tongue or hypopharynx. Multimodality treatment with surgery and RT for patients with limited disease generally is avoided because of higher complication rates, added toxicities with poorer functional results, and an increased necessity for total laryngectomy as salvage after local recurrence (see Recommendation 1.3). Some T1, T2 supraglottic cancers are considered unfavorable because of deep invasion in laryngeal spaces and/or larger tumor volumes that make local control with RT alone or endoscopic approaches less successful. 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 open surgery is associated with a better local control rate,[156,158-163] but potential differences in patient selection complicate the interpretation of these data. Chemotherapy for treatment of patients with limited disease has been investigated, including induction chemotherapy[164,165] alone or chemotherapy combined with RT. Insufficient data are currently available to recommend these approaches outside a clinical trial, and the added toxicities of chemotherapy must be balanced against expected benefit. In a few recent studies reviewed, selected patients with deeply invasive (unfavorable) glottic T2 cancers or local advanced T2 supraglottic cancers have been successfully treated with concurrent chemoradiation.[9,50,52,54,105]

Recommendation 1.3. [New]. The success of the larynx-preservation approach may be higher with initial larynx-preserving surgery compared with RT based on retrospective studies; however, this may be subjected to patient selection factors. In experienced hands, endoscopic resections are preferred because of equal or better outcomes compared with open partial laryngectomy, unless there are issues with tumor exposure or safety of the endoscopic approach (Type: evidence-based, benefits outweigh harms; Quality of evidence: intermediate; Strength of recommendation: moderate).

Clinical Interpretation of literature review. Larynx preservation may be higher in patients treated initially with endoscopic resection compared with initial RT,[8,95,138] and costs of treatment are lower.[44] However, these results are based on retrospective studies and may be somewhat biased by patient selection factors. There is only one small randomized trial that compared voice outcomes between laser resection and RT and showed no overall survival differences by initial treatment modality.[8,14,44,138] Although patient age has been reported to be a negative prognostic factor for patients treated initially with RT,[64] it may not be a negative factor for endoscopically treated patients.[132] Surgical salvage of RT treatment failure is highly effective when close follow-up surveillance detects early recurrence, and success often can be achieved with endoscopic or open larynx-preserving surgery.[19,53,66,83] However, in many cases, total laryngectomy is required as salvage therapy after initial RT, particularly for patients with T2 disease.[71,95,166,167] Initial local tumor control is higher with primary surgical resections,[129,138] and positive margins or local recurrences can be effectively managed with re-resection, which results in long-term larynx-preservation rates $\geq$ 90%.[19,21,24,25]

Recommendation 1.4. [Updated]. Surgical excision of the primary tumor with intent to preserve the larynx should be undertaken with the aim of achieving tumor-free margins. Surgery that anticipates the need for postoperative RT to treat close or involved tumor margins or widespread dysplasia is not an acceptable treatment approach (Type: evidence-based, benefits outweigh harms; Quality of evidence: strong; Strength of recommendation: high).

Clinical Interpretation of literature review. Consistent with the overall goals of treatment, initial surgical excisions should be planned to remove all of the cancer with an adequate safety margin yet preserving as much residual tissue as possible to enhance speech and swallowing functions postoperatively. Single-modality treatment without planned adjuvant RT or chemoradiation is recommended. When suspicious or positive margins are identified, re-resection is recommended rather than adjuvant RT, which should be reserved for future use.[17,67] Adequate margins for successful local control generally are considered to be 4 to 5 mm[52,53,120] for open surgical resections and $\leq$ 2 mm for endoscopic resections.[67,87,123] Although local control with open partial laryngectomy procedures is excellent, endoscopic resections are preferred when feasible because more tissue is spared and functional results are generally better. The experience of the surgical team and the ability to visualize the larynx and tumor adequately for safe endoscopic management are critical factors for both resection and later cancer surveillance.

Recommendation 1.5. [Unchanged]. Local tumor recurrence after RT 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.

Recommendation 1.6. [Unchanged]. Combined chemotherapy and RT approaches may be used for larynx preservation for selected patients with limited-stage and (1) unfavorable or deeply invasive T2 cancer, (2) T2 N+ cancers, (3) for whom a total laryngectomy may be the only surgical option, (4) in whom functional outcome after larynx-preserving surgery is expected to be unsatisfactory, and (5) for whom surgical expertise for such procedures is not available.

Recommendation 1.7. [Updated]. 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; vocal cord mobility; involvement of the anterior commissure; lymph node metastasis; the patient's age, occupation, pretreatment voice, and swallowing function; patient preference and compliance; and the availability of expertise in RT or surgery. Optimal outcomes require specialized skills, judgment, and expertise. Poorly performed open or endoscopic surgery or RT will raise the risk for recurrence or the need for additional modalities of therapy to achieve disease control (Type: evidence-based, benefits outweigh harms; Quality of evidence: intermediate; Strength of recommendation: moderate).

Clinical interpretation of literature review. Because of the numerous factors that enter into treatment decision making for patients with limited disease, careful tumor staging is supplemented

by comprehensive pretreatment evaluation of voice production and swallowing in a multidisciplinary fashion that incorporates the patient's desires, lifestyle needs, and social and psychological support. The guideline revision adds emphasis on vocal cord mobility, which represents deep invasion or large tumor volume, and consideration of socioeconomic and behavioral factors, such as smoking cessation, with regard to long-term outcomes and airway protection and quality of voice and life.[10,11,66] In recent publications, involvement of the anterior commissure without cartilage invasion was reported to be less important as a prognostic factor for both endoscopic resections and RT, which probably is due to improvements in surgical and RT treatment techniques.[71,87,93,106] Specialized surgical skill and experience are particularly important in endoscopic and open organ-preserving surgical approaches and have been emphasized. History of a malignant lesion in the head and neck was removed from the recommendation because it was unclear how this would influence selection of an initial larynx-preservation approach unless it was previously included in the guidelines as a surrogate to represent prior head and neck radiation. It was recognized that the consideration for recommending endoscopic surgical resection as an initial approach (new Recommendation 1.3) was based, in part, on the fact that RT could be reserved for treatment of a subsequent primary head and neck tumor.[168]

CLINICAL QUESTION 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?

Recommendation 2.1. [Reworded]. Organ-preservation surgery, combined chemotherapy and RT, and RT alone, all with further surgery reserved for salvage, offer the potential for larynx preservation without compromising overall 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, including age, comorbidities, preferences, socioeconomic factors, local expertise, and the availability of appropriate support and rehabilitation services.

Recommendation 2.2. [New]. For selected patients with extensive T3 or large T4a lesions and/or poor pretreatment laryngeal function, better survival rates and quality of life may be achieved with total laryngectomy rather than with organ-preservation approaches and may be the preferred approach (Type: evidence-based, benefits outweigh harms; Quality of evidence: strong; Strength of recommendation: high).

Clinical interpretation of literature review. Two factors are critical to ensure that the survival of patients with locally advanced laryngeal cancer is not jeopardized. These are (1) the appropriate selection of patients for a larynx-preservation approach and (2) active follow-up care to ensure early salvage laryngectomy for treatment failures. Over the past two decades, there has been increasing use of nonsurgical larynx-preservation approaches in the management of patients with stage III and IV laryngeal cancer. The recommendation that a combined chemotherapy and RT approach is appropriate for patients with T3 and selected T4a primary tumors is based on the results of the Department of Veterans Affairs (VA) Laryngeal Cancer Study Group trial[162] and the Intergroup Radiation Therapy Oncology Group trial (RTOG 91-11).[161] The VA trial found that 56% of patients with T4 cancers ultimately required salvage laryngectomy, which was associated more frequently with the glottic subsite than supraglottic and gross cartilage invasion more often than no cartilage involvement. The subsequent design of RTOG 91-11 took these findings into consideration because RT alone was one of the treatment arms; thus, the RTOG 91-11 trial excluded high-volume T4 cancers (extensive supraglottic tumors with invasion deep into the tongue musculature and extensive cancers with tumor penetration through the cartilage). Only 10% of patients enrolled in RTOG 91-11 had T4 disease, which precluded subset analysis. Thus, concurrent chemotherapy and RT has been recommended specifically for selected, low-volume T4 cancers, which is consistent with the eligibility criteria for RTOG 91-11. It has been increasingly clear that multidisciplinary evaluation that includes pretreatment speech and swallowing assessment is critically important for determining which select patients with T4 cancers are candidates for a larynx-preservation approach and which with T3 cancers would be better served with a total laryngectomy. Thus, this guideline update adds a new section on the evaluation of function (Recommendation 5.0).

The ASCO guideline literature review for this recommendation concerning extensive T3 and T4 cancer yielded three population-based, national registry retrospective studies[2,63,104] and 10 retrospective, single-institution cohort studies[27,31,42,61,104,118,126,130,142,143] that addressed survival outcomes and factors predictive of outcome for stage III and IV laryngeal cancer and T3 and T4a disease treated with total laryngectomy or nonsurgical therapy. The findings of the largest and most informative reports are discussed in this summary of the literature review.

Chen and Halpern[27] conducted a retrospective observational cohort study of data collected in the National Cancer Database (NCDB) for all patients with stages III and IV laryngeal cancer diagnosed from 1995 to 1998 (American Joint Committee on Cancer [AJCC] staging system, 5th edition). A total of 7,019 patients were included in the analysis of whom 53.6% were treated with total laryngectomy, 30.6% with RT alone, and 15.8% with chemotherapy and RT (induction or concurrent approaches). In the overall population analysis, total laryngectomy was significantly associated with an increased likelihood of survival compared with either nonsurgical approach ($P < .001$). In all analyses, the risk of death was significantly higher for patients treated with RT alone compared with total laryngectomy ($P < .001$). Controlling for clinical and demographic factors such as ethnicity, sex, and insurance status among patients with stage III disease, the risk of death was similar for treatment with chemotherapy and RT compared with total laryngectomy (hazard ratio [HR], 1.15; $P = .09$), but for stage IV disease, the risk of death was significantly greater with chemotherapy and RT (HR, 1.43; $P < .001$). The HR for risk of death was nearly identical for T3 (HR, 1.18; $P = .03$) and stage III disease treated with chemotherapy and RT, which indicates that much of the difference in survival in the overall analysis was attributable to stage IV disease.

Grover et al[63] used the NCDB to focus on survival outcome of T4a laryngeal cancer diagnosed from 2003 to 2006 (AJCC staging system, 6th edition). Before 2003, the AJCC staging system did not distinguish between T4a and T4b disease. A total of 969 cases were included in the analysis, which was limited to patients who received chemotherapy and RT (induction or concurrent approaches; 64%) or total laryngectomy and postoperative RT (36%). On multivariable regression analysis, patients with advanced nodal disease (N2, N3) or a supraglottic subsite were more likely to be treated

with chemotherapy and RT; those treated at a high-volume facility were more likely to undergo total laryngectomy. Unadjusted Kaplan-Meier survival estimates showed a median overall survival of 61 months for the total laryngectomy treatment group and 39 months for the larynx-preservation group ($P < .001$). By using a propensity score–adjusted Cox proportional hazards regression model, a larynx-preservation approach for treatment of T4a disease was associated with an increased risk of death (adjusted HR, 1.31; 95% CI, 1.10 to 1.57; $P = .003$).

Megwalu and Sikora[2] used the SEER database of 18 registries across the nation to conduct a population-based cohort study of 5,394 patients with stage III or IV laryngeal cancer diagnosed during three time periods (1992 to 1997, 1998 to 2003, and 2004 to 2009). Stage IVB and T1 cancers were excluded, and patients with medical contraindications to surgery were excluded to match the inclusion criteria of the VA Laryngeal Cancer Study.[162] Cancers were coded according to the AJCC staging (6th edition); for cases before 2004, TNM stage was reconstructed on the basis of International Classification of Diseases codes that reflect tumor extent because TNM and stage grouping was not coded in SEER until 2004. Surgical therapy and laryngeal conservation (RT with or without chemotherapy) were compared for disease-specific and overall survival outcomes. The use of nonsurgical therapy increased with each year-of-diagnosis cohort (32% for 1992 to 1997, 45% for 1998 to 2003, and 62% for 2004 to 2009), and disease-specific survival and overall survival increased with each cohort. Patients diagnosed in 2004 to 2009 had significantly better survival outcomes ($P < .001$) than those diagnosed before 2004. A comparison of surgical and nonsurgical treatment revealed that survival outcomes were significantly better with surgical treatment (2-year and 5-year overall survival, 64% *v* 57% and 44% *v* 39% [$P < .001$], respectively; 2-year and 5-year disease-specific survival, 70% *v* 64% and 55% *v* 51% [$P < .001$], respectively). The difference in survival outcomes narrowed with each year-of-diagnosis cohort, which suggests a potential effect of improvements in RT and more use of chemotherapy plus RT. The SEER database does not specify chemotherapy; therefore, it is not possible to separate treatment with RT alone from chemotherapy plus RT, or whether chemotherapy was given in a neoadjuvant or concurrent fashion. Multivariable analysis adjusted for year of diagnosis, stage, and other clinical factors showed a 30% higher risk of death for patients treated nonsurgically (disease-specific survival HR, 1.33 [$P < .001$]; overall survival HR, 1.32 [$P < .001$]) compared with surgical therapy. Favorable factors included stage III disease, glottic subsite, female sex, married status, and treatment in 2004 to 2009. Subset analysis specific for T3N0 and T4aN0 cancers showed better disease-specific and overall survival with surgery ($P < .001$), although the difference compared with nonsurgical treatment was most pronounced for T4a disease.

The advantage of these retrospective cohort studies that use data collected in national cancer registries is the large number of cases included. However, all have limitations that can affect survival results, and the limitations differ among the databases and the diagnosis years included in the cohort. Hence, the results may have little or limited relevance to today's treatment with modern RT and clinical staging that incorporates advanced imaging. For example, the pattern of care for the diagnosis year cohort analyzed by Chen and Halpern[27] from >20 years ago (1996 to 1998) was dominated by surgery with only a small minority of patients (16%) treated with chemotherapy and RT. Moreover, the AJCC staging system (5th edition) definitions did not distinguish T4a and T4b. Thus, selection bias may be great, and it is conceivable that during those years, patients who received nonsurgical therapy were largely those with unresectable or medically inoperable disease. Grover et al[63] also used the NCDB, but chose a later diagnosis year period (2003 to 2006) to identify T4a disease and strictly defined the study cohort to exclude patients treated with single-modality surgery, or RT, or with incomplete treatment. Sensitivity and landmark analyses were used to assess the effects of potential confounders on the HR and to minimize bias. Even with the robust statistical methods, other patient-specific characteristics that could influence survival and treatment choice, such as medical inoperability and tumor volume, cannot be discerned from the NCDB database. The SEER registry has the advantage of providing disease-specific survival data but does not code chemotherapy and lumps RT and RT plus chemotherapy together. Although RCTs show no difference in overall survival among patients treated with RT or combined chemotherapy and RT, selection bias for patients who are inoperable or have a poor performance status to undergo single-modality RT alone cannot be discriminated. Even with these inherent limitations, these analyses of large numbers of patients reinforce the conclusion that no larynx-preservation approach results in better survival than total laryngectomy and adjuvant RT, and T4 cancers specifically have a substantially worse outcome with nonsurgical treatment. It is noteworthy and deserving of emphasis that overall survival of patients with stage III/IV laryngeal cancer diagnosed from 1992 through 2009, irrespective of treatment, has significantly improved over time.

Retrospective single-institution chart review cohort studies also suffer from selection bias and nonuniform stage definitions over time, but they have the potential advantage of including information on tumor volume and function that is absent from national database registries. Gourin et al[61] reported survival outcomes from a retrospective chart review of patients with laryngeal cancer treated at the Medical College of Georgia from 1985 to 2002. A total of 451 patients with stage I to IV disease were included of whom 57% underwent surgery as primary therapy, 27% received RT alone, and only 16% received chemotherapy and RT (induction or concurrent approaches). For stage I to III disease, the overall survival rate did not differ on comparison of surgical versus nonsurgical treatment ($P = .4$); however, patients with stage IV disease had significantly better survival with surgery (5-year estimate, 49% *v* 21% for chemotherapy plus RT and 14% for RT alone, $P < .001$). Analysis by primary tumor stage revealed that survival of patients with T1 to T3 primary tumors was independent of treatment modality. For T4 disease, after controlling for operability, surgical treatment was associated with significantly better survival (55%) than either chemotherapy plus RT (25%) or RT alone (0%; $P < .001$). Cox proportional hazards regression models indicated significantly worse disease-specific survival for T4 cancers, advanced nodal disease (N2 or N3), and nonsurgical treatment. The authors noted that in performing their retrospective case review, it was not possible to determine whether T4 cancer was predominantly associated with cartilage invasion, extralaryngeal spread, or low-volume T4 disease.

Vengalil et al[142] from the Princess Margaret Cancer Center of the University of Toronto identified 106 patients from their Head

and Neck Prospective Anthology database who were diagnosed with T4 laryngeal cancer from 2003 through 2010. The goal of the study was to assess tumor control and functional outcomes of patients treated with total laryngectomy and postoperative RT compared with RT with and without chemotherapy. All patients had multidisciplinary evaluation and baseline speech and swallowing function assessment, which were integral to the treatment decisions. Patients with supraglottic cancers with base-of-tongue involvement were not considered candidates for primary surgery. Sixty-one percent of the cohort was treated with total laryngectomy and 39% with RT (mostly intensity-modulated radiotherapy [IMRT]) with or without concurrent chemotherapy. In this setting, the 3-year overall survival for T4 cancers was significantly worse in the nonsurgical cohort than in the surgical cohort (41% *v* 70%; $P < .01$), as was the local control rate (63% *v* 88%). However, with restriction of the comparison to smaller-volume tumors and minimal cartilage involvement, the 3-year overall survival rate was the same (70%), and the local control rate was not statistically different compared with the surgery group.

Investigators from the MD Anderson Cancer Center published two retrospective chart review cohort analyses to investigate survival, patterns of treatment failure, and functional outcomes for patients with T3 and T4 laryngeal cancer diagnosed from 1985 to 2011.[118,143] Tumors were restaged, as needed, to conform with the AJCC staging system (7th edition) definitions. As part of institutional policy, all patients had a multidisciplinary team evaluation that included speech and swallowing studies. Patients with poor baseline airway function, such as demonstrable aspiration on barium swallow test, or extensive cartilage destruction were considered poor candidates for larynx preservation, and total laryngectomy was recommended. The analysis of T3 laryngeal cancers consisted of 412 patients of whom 70% received a larynx-preservation approach (combined chemotherapy and RT or RT alone) and 30% had total laryngectomy and postoperative RT. The 5- and 10-year overall survival rates were 56% and 35%, respectively, and disease-specific survival rates were 69% and 61%, respectively. Multivariable analysis showed that chemotherapy use (HR, 0.66; $P = .003$), node-negative status (HR, 0.69; $P = .002$), Eastern Cooperative Oncology Group performance status < 2 (HR, 0.57; $P = .03$), and glottic subsite (HR, 0.54; $P < .001$) were independently associated with improved overall survival for T3 laryngeal cancer. Disease-specific survival, overall survival, and functional outcomes were significantly better ($P < .006$) for the combined chemotherapy and RT compared with RT alone and with surgery and postoperative RT. The rate of ultimate locoregional control with RT and chemotherapy was equivalent to treatment with primary surgery and better than treatment with RT alone. These investigators also found that for patients treated with a larynx-preservation approach, modern RT with IMRT resulted in better tumor control and disease-specific survival than conventional RT.[143]

The MD Anderson Cancer Center retrospective analysis of T4 primary tumors consisted of 221 patients of whom 73% underwent total laryngectomy and postoperative RT and 27% were treated with a larynx-preservation approach, most with combined chemotherapy and RT. The 5- and 10-year estimated rates of overall survival were 52% and 29%, respectively, and disease-specific survival rates were 57% and 48%, respectively. Multivariable analysis showed that lymph node–positive disease was associated with an increased risk of mortality for both treatment approaches ($P < .001$). Median overall survival was the same (64 months) for the surgical and larynx-preservation groups, whereas locoregional control was significantly better with initial surgery. In terms of functional outcomes, rates of dysphagia were significantly worse after a larynx-preservation approach. Crude feeding tube rates at last contact were 17% with larynx preservation and 7% for surgery. The observed composite rate of survival with a functional, intact larynx (no gastrostomy tube or tracheotomy) at 5 and 10 years was 32% and 13%, respectively. Thus, even at an academic center with carefully selected patients with T4 cancer for a larynx-preservation approach, the rate of survival with a good functional outcome was low.[118]

SEER data demonstrate that overall survival and disease-specific survival rates have significantly increased over time in cohorts with stage III/IV laryngeal cancer diagnosed from 1992 through 2009.[2] This improvement corresponds with the increasing use of nonsurgical larynx-preservation approaches, concurrent chemotherapy and RT, and advances in RT delivery systems. Also important are the increased use of advanced imaging to more precisely stage patients with extensive primary tumors and the incorporation of pretreatment functional assessments. Analyses of large numbers of patients through SEER data and NCDB hospital data have shown a significant survival advantage with total laryngectomy and postoperative RT compared with nonsurgical treatment, and SEER data have shown that this difference has narrowed over time. The difference is greatest and most consistent for stage IV disease (advanced nodal involvement N2, N3) and T4 primary status. The findings are not uniform for stage III and T3 primary status, with some analyses finding comparable survival results for treatment with total laryngectomy or combined chemotherapy and RT. In addition, the adoption of free vascularized tissue transfer as part of surgical reconstruction for salvage laryngectomy after failure of organ preservation with chemoradiation has resulted in decreased serious surgical wound complications and may have contributed to the narrowing of overall differences, particularly for patients with stage IV disease. The lack of information on tumor volume and medical inoperability creates selection bias, which is a major limitation of these analyses.

Retrospective single-institution case series that can assess tumor volume show that the overall survival of selected patients with T4a cancers managed at centers of excellence with combined chemotherapy and RT is similar to treatment with total laryngectomy and postoperative RT. These patients generally have low-volume disease, minimal cartilage destruction, and adequate airway function as determined by multidisciplinary evaluation and speech and swallowing assessments. Although the mortality risk associated with nonsurgical treatment of all T4 cancers may be lessened with careful patient selection, locoregional control is lower than with total laryngectomy, and the potential for poor functional outcome is greater.

For stage III disease (T3N0 to T3N1), single-institution retrospective series would support the conclusion that survival outcomes for treatment with chemotherapy plus RT are not inferior to those achieved with total laryngectomy and that both quality of life and function are better with a preserved larynx. For these patients, selection of an organ-preservation approach versus laryngectomy should be determined by lifestyle factors and pretreatment speech and swallowing studies that can predict functional outcome (see Recommendation 5.0). For patients with extensive T3 primary

tumors, laryngectomy and postoperative RT may provide better long-term disease control and function. Pretreatment speech and swallowing function should be considered in decision making.

Recommendation 2.3. [Unchanged]. All patients should have a multidisciplinary evaluation regarding their suitably 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.

Recommendation 2.4. [Updated]. A minority of patients with T3, T4 primary site disease will be suitable for specialized organ-preservation surgical procedures, such as a supracricoid partial laryngectomy. The addition of postoperative RT will compromise functional outcomes. Induction chemotherapy before organ-preservation surgery is not recommended outside a clinical trial (Type: evidence-based, benefits outweigh harms; Quality of evidence: intermediate; Strength of recommendation: moderate).

Clinical interpretation of literature review. Success of a surgical approach to larynx preservation depends on the extent of the tumor, the technical skill and experience of the surgeon, and careful patient selection. With technical advances, surgical management has shifted from open partial laryngectomy to transoral, minimally invasive endoscopic surgery, which is referred to as transoral laryngeal microsurgery (TLM) for patients with early- to intermediate-stage laryngeal cancer.

For this update, there are no randomized, 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.

Endoscopic surgery is associated with lower morbidity than open surgery, and functional results are optimal when TLM is used as a single modality. The need for RT after surgery to treat a positive margin will increase treatment morbidity and may substantially impair swallowing recovery.[169] Thus, the importance of selecting patients for whom a complete oncologic resection is feasible through a transoral approach is paramount. In a retrospective chart review of 122 pT3 glottic cancers, the 5-year overall, recurrence-free, and disease-specific survival rates were comparable with open surgery or chemoradiation (58.6%, 57.8%, and 84.1%, respectively) and a larynx-preservation rate of 83%.[25] T3 supraglottic tumors are more difficult to control because of an up to 60% risk of occult neck metastases. The literature reports of TLMs are limited to clinical stages I, II, and selected III (T1 to T2N1M0) with or without RT.[170,171] In a prospective Southwest Oncology Group trial, 34 patients with early- to intermediate-stage supraglottic cancer treated with TLM and RT had estimated 3-year progression-free and overall survival rates of 79% and 88%, respectively. Seventy-one percent recovered adequate swallowing function and were free from tube feeding within 7 days of surgery, whereas 9% were gastrostomy tube dependent long term. Voice quality after TLM varies with tumor extent. The results are excellent for T1 membranous vocal cord cancer and supraglottic cancer that do not involve the vocal cord. Voice quality is poorer for cancer that involves the arytenoid or is extend into the paraglottic space.

The open supracricoid partial laryngectomy is used in some centers for primary treatment of T3 supraglottic cancers not appropriate for transoral excision.[172] A 5-year local control rate of 100% for T2 tumors and 96% for T3 tumors was reported for 96 patients who underwent supracricoid partial laryngectomy as salvage or initial treatment. Ninety-four percent had adequate swallowing function without the need for a gastrostomy tube. The outcomes for supracricoid partial laryngectomy for T2 and selected T3 cancers seem comparable to chemoradiation or total laryngectomy, with local control rates $>$ 90%.[173]

In summary, select patients with T3 cancers are candidates for larynx-preserving surgical procedures, including partial laryngectomy or endoscopic surgery. Functional outcomes are optimal when the tumor can be completely resected without the need for RT. Reports from experienced centers suggest that the local control rates are comparable to total laryngectomy.

Recommendation 2.5. [Updated]. Concurrent chemoradiotherapy (CRT) offers a significantly higher chance of larynx preservation than RT alone or induction chemotherapy followed by RT, albeit at the cost of higher acute in-field toxicities and without improvement in overall survival. The best available evidence supports the use of cisplatin as the drug of choice in this setting (Type: evidence-based, benefits outweigh harms; Quality of evidence: strong; Strength of recommendation: high).

Clinical interpretation of literature review. The nonsurgical approaches for larynx preservation of stage III/IV glottic or supraglottic primary tumors that have been evaluated in RCTs are induction chemotherapy followed by RT in responders, concurrent chemoradiation, and RT as a single modality. The updated literature review included initial and long-term reports of three RCTs and an updated meta-analysis that evaluated these approaches. In addition, there are two retrospective cohort analyses evaluating late effects and cause of death in patients receiving concurrent chemoradiation and modern conformal radiation. No RCTs compared radiosensitizing agents with cisplatin. A retrospective subset analysis of cetuximab and RT is relevant.

Trials of induction chemotherapy followed by RT. The European Organization for Research and Treatment of Cancer (EORTC) Hypopharynx Trial (EORTC 24891) that included patients with cancer of the lateral epilarynx (aryepiglottic fold and medial pyriform) and had a surgery control arm was updated after a median follow-up of 10.5 years.[144] The long-term analysis confirmed the 5-year results, which showed no significant difference in overall survival for patients treated with induction cisplatin and fluorouracil (FU) for three cycles compared with initial laryngopharyngectomy and RT. The feasibility of preserving the larynx was demonstrated in patients who achieved a complete response of the primary tumor, as was required to proceed with RT. Patients who received induction chemotherapy had fewer distant metastases. The complete response to induction correlated with T stage (82% for T2, 48% for T3, and 0% for T4).

The two phase III trials of induction chemotherapy without a surgery control group published since the 2006 ASCO guideline included in the literature review were EORTC 24954[90,146] and Groupe Oncologie Radiotherapie de la Tete et du Cou (GORTEC) 2000-01.[110,145] Patients with operable stage III/IV laryngeal or hypopharyngeal cancer who required total laryngectomy were eligible for both trials. EORTC 24954 compared alternating sequences of cisplatin and FU (total of four 5-day courses) and 2-week courses of 20-Gy RT (total of three courses at 60 Gy) with the control arm of induction cisplatin and FU for a maximum of four

cycles followed by RT (70 Gy) in responders. Enrolled patients had T3 to T4 laryngeal cancer (n = 118) or T2 to T4 hypopharyngeal cancer (n = 231) and N0 to N2 disease. Substantial regression of tumor volume and at least partial recovery of larynx mobility defined a partial response. This was assessed after two cycles of cisplatin and FU. Responders received two more cycles of chemotherapy followed by RT; nonresponders underwent immediate laryngectomy and adjuvant RT.

The initial results were reported in 2009[90] after a median follow-up of 6.5 years and updated in 2016[146] with a median follow-up of 10.2 years. No statistically significant difference was found in the primary end point of survival with a functional larynx (local control, no tracheotomy or feeding tube) or the secondary end points of larynx preservation, progression-free survival, and overall survival according to treatment. The median survival time with a functional larynx was 1.6 years (95% CI, 1.1 to 2.3 years) for the induction group and 2.3 years (95% CI, 1.6 to 3.3 years) for the alternating treatment group. The median overall survival was 5.1 years (95% CI, 3.5 to 6.5 years) and 5.0 years (95% CI, 4.1 to 5.9 years) for the induction and alternating treatment groups, respectively. Analysis of larynx-preservation rates showed a trend for a higher rate with the alternating treatment; 25.2% required salvage laryngectomy compared with 31.7% in the induction group. A trend for better laryngeal function (phonation, swallowing, and breathing) that favored the alternating treatment at 1 and 5 years post-treatment also was found. Acute mucosal and skin toxicities were significantly worse in patients in the induction control group, presumably because of the higher RT dose, but late toxicities were similar. The alternating approach with a total radiation dose of 60 Gy did not significantly improve outcomes and was not pursued. The larynx-preservation results for the induction group confirmed the previously tested approach for cancer of the hypopharynx.[144]

Since the publication of the previous guideline, the higher response rate achievable with cisplatin and FU plus a taxane compared with cisplatin and FU as an induction regimen was demonstrated in mixed-site trials.[174-176] This led the GORTEC to conduct a phase III trial that compared induction cisplatin and FU plus docetaxel versus cisplatin and FU (control group) for selection of patients for larynx preservation. Patients with stage III/IV operable laryngeal (n = 98) and hypopharyngeal (n = 115) cancer were randomly assigned to receive three cycles of induction chemotherapy followed by response evaluation and then RT for those with at least a partial response and recovery of cord mobility. The initial results published in 2009[110] and updated in 2016[145] after a median follow-up of 8.75 years showed a significantly higher response rate after three cycles of the cisplatin, FU, and docetaxel regimen compared with three cycles of cisplatin and FU (80% *v* 59%, respectively). This resulted in larynx-preservation rates that were significantly higher with the docetaxel-containing regimen compared with cisplatin and FU (74% [95% CI, 0.64% to 0.82%] *v* 58% [95% CI, 0.47% to 0.68%], respectively, at 5 years; 70.3% [95% CI, 0.58% to 0.80%] *v* 46.5% [95% CI, 0.31% to 0.63%]; $P = .01$], respectively, at 10 years). However, overall survival, disease-free survival, locoregional control, distant control, and rates of late salvage surgery did not differ by treatment. Although collectively, these results and the data from comparative mixed-site trials of cisplatin and FU with or without docetaxel provide level 1 (strong) evidence for using cisplatin, FU, and docetaxel over doublet cisplatin and FU induction chemotherapy, the evidence is based solely on the consistently higher response rate. For laryngeal cancer, no data as yet suggest that the pattern of treatment failure or survival is altered by the addition of a taxane to induction cisplatin and FU. Furthermore, the natural history and prognosis of cancers of the larynx and hypopharynx are quite different, and the GORTEC 2000-01 trial was not powered to separately analyze outcomes on the basis of primary site.

Concurrent Chemoradiation Trials. The updated Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) Collaborative Group report published in 2009 comprised updated individual patient data on 17,346 patients enrolled in 93 randomized trials conducted between 1965 and 2000. The trials compared locoregional treatment versus locoregional treatment and chemotherapy (induction, concurrent, or adjuvant).[177] An absolute survival benefit of 6.5% at 5 years with concurrent chemotherapy (HR, 0.81; 95% CI, 0.78 to 0.86; $P < .001$) was found, whereas no overall survival benefit with induction chemotherapy was observed (absolute survival benefit, 2.4%; HR, 0.96; 95% CI, 0.90 to 1.02; $P = .18$). The benefit of concurrent administration of chemotherapy on locoregional treatment failure was also significant (HR, 0.74; 95% CI, 0.70 to 0.79; $P < .001$) in contrast to induction chemotherapy where no such effect was seen (HR, 1.03; 95% CI, 0.95 to 1.13; $P = .43$). Both approaches reduced the risk of distant failure, although the effect from induction chemotherapy was more pronounced. In terms of type of chemotherapy, no significant variation ($P = .23$) was found of the effect on 5-year overall survival or event-free survival for platin plus FU, other multidrug chemotherapy, or monotherapy. For concurrent chemotherapy, the magnitude of the benefit was similar for cisplatin alone or cisplatin plus FU or carboplatin plus FU but was inferior with monotherapy other than cisplatin. Of note, trials that evaluated the effect of cetuximab concurrent with RT and the effect of induction with a taxane added to cisplatin plus FU were not included in this meta-analysis.

The RTOG 91-11 trial was updated after a median follow-up of > 10 years for surviving patients.[45] The trial was designed to specifically assess the contribution of chemotherapy added to RT and the optimal timing of chemotherapy (induction *v* concurrent) for achieving larynx preservation. Patients with T1 disease or high-volume T4 disease (defined as > 1 cm of invasion of the base of the tongue or tumor penetration of thyroid cartilage into soft tissues) were excluded. Of the 547 patients enrolled, 79% had T3 disease.

The long-term results continued to show that the rates of larynx preservation were significantly higher for patients in the concurrent cisplatin and RT group (81.7%). By contrast, no significant difference was detected for the comparison of the induction chemotherapy arm (67.5%) with the RT alone arm (63.8%). The superior outcome for concomitant treatment also was seen for local control (69.2%, 53.7%, and 50.1%, respectively, for concurrent therapy, induction therapy, and RT alone). At 10-years, no significant difference was found in the composite end point of laryngectomy-free survival for treatment with concurrent cisplatin and RT (23.5%) compared with induction cisplatin plus FU (28.9%), and treatment with RT alone was significantly inferior (17.2%) to both chemotherapy approaches. No significant difference was found in overall survival among the three treatment arms at 5 and 10 years, but the survival curves did separate after 4.5 years in favor of the induction treatment group (HR, 1.25; $P = .08$)

compared with the concurrent treatment group. With long follow-up, the concurrent cisplatin and RT group had the lowest rate of deaths as a result of laryngeal cancer but a higher rate of noncancer deaths. This outcome could not be explained. In long-term follow-up, no difference was found in the overall survival of patients who underwent salvage laryngectomy within 1 year ($P = .21$) or within 2 years ($P = .23$) of completing treatment compared with those who did not undergo laryngectomy.[45] In addition, no difference was found in the cumulative incidence of late toxicities among treatments (grade 3 to 5 range, 31% to 38%), quality of life, or function (swallowing ability, diet, speech, and voice quality) as assessed through the collection of validated questionnaires (Functional Assessment of Cancer Therapy head and neck scale version 2 [University of Washington quality-of-life instrument]) for 8 years. Although data on gastrostomy tube usage was not specifically tracked, inability to swallow was reported by $< 3\%$ in all treatment groups.

The unexplained higher rate of noncancer deaths with concurrent treatment raised the possibility of unrecognized chronic toxicities and late treatment morbidity associated with, for example, late radiation–associated dysphagia and aspiration. Although this remains speculative, it should be noted that radiation was delivered by using two-dimensional treatment plans. The use of modern conformal three-dimensional and IMRT plans and contemporary regimens of proactive swallowing therapy offer promise in reducing late-occurring dysphagia. The outcomes of these methods continue to be studied.

To address this issue, investigators from the Cleveland Clinic and University Hospitals published a retrospective cohort analysis evaluating the incidence of severe late dysphagia and its relationship to cause of death in patients with laryngeal cancer treated with concurrent chemoradiation.[147] The 84 patients included in the analysis met the eligibility criteria for RTOG 91-11 and were treated between 1993 and 2013 by using three-dimensional or IMRT plans, daily or twice-daily fractionation, and concurrent cisplatin or cisplatin plus FU. The cumulative incidence rate of severe late dysphagia at 5-years was substantial at 26.5% (95% CI, 15.2% to 37.8%); however, no deaths could be directly related to severe dysphagia. Four (18%) of a total of 22 patients with late dysphagia experienced their first event beyond 5 years, including three first stricture dilations, two aspiration admissions, and five late feeding tube insertions. The only statistically significant factor associated with increased severe late dysphagia was twice-daily fractionation.

Investigators from the Peter MacCallum Cancer Centre published a retrospective analysis of the outcomes of nonsurgical treatment of locally advanced laryngeal cancer by using data from their prospective collection database.[32] A total of sixty patients with stage III/IVa disease treated from 2002 through 2006 for whom the goal of treatment was larynx preservation were included. Patients with low probability of preserving a functional larynx, such as those with T4 primary tumors with extensive cartilage destruction, were managed with total laryngectomy per institutional practice. Most patients received high-dose cisplatin or cisplatin plus FU. Radiation was given using three-dimensional conformal planning and once-daily fractionation. At 3 and 5 years, the rates of larynx preservation with local disease control were 83% and 77%, respectively; overall survival rates were 67% and 45%, respectively. Few severe late complications were observed—5% required pharyngeal dilatations and 3% had permanent gastrostomy feeding tubes. All the patients with an intact larynx had a functional voice. None of the noncancer deaths could be related to late toxicity.

No prospective phase III trials have evaluated therapeutics other than cisplatin as radiosensitizers for larynx preservation. Cetuximab specifically has not been compared with cisplatin or systematically studied in laryngeal cancer. It is worth noting the results of a secondary analysis of the landmark multisite phase III trial of RT with or without cetuximab.[148] This unplanned analysis included 62 patients with hypopharyngeal cancer and 106 patients with laryngeal cancer, resectability status unknown. A trend was found for better rates of larynx preservation and laryngectomy-free survival at 3 years that favored cetuximab plus RT, but differences were not statistically significant. Survival rates at 3 years were 41.9% for cetuximab plus RT and 39% for RT alone.

Individual randomized trials to date have not demonstrated improved survival with any organ-preservation approach. The data from meta-analysis of prospective controlled clinical trials support feasibility without survival compromise and an effect of timing of chemotherapy on patterns of locoregional control and distant treatment failure, which has implications for the success of various approaches to larynx preservation. Induction (cisplatin plus FU) followed by RT, concurrent cisplatin and RT, and RT alone have been studied in RCTs. The major advantage of induction chemotherapy is that it selects patients with relatively resistant disease for early laryngectomy and can reduce the risk of systemic failure. Concurrent cisplatin and RT has its greatest impact on locoregional control and, hence, has resulted in significantly higher rates of larynx preservation compared with the other two approaches. Responders to induction cisplatin plus FU who proceed to RT show less-acute mucocutaneous toxicity than occurs with concurrent cisplatin and RT, but the overall rates of local control and larynx preservation are inferior and not significantly improved over treatment with RT alone.

Preservation of the larynx without jeopardizing overall survival is paramount. The composite end point of laryngectomy-free survival is a reporting measure used to reflect this concept. In the RTOG 91-11, with 10-year follow-up, this end point became significant for the comparison of induction cisplatin and FU versus RT alone as a result of a nonsignificant trend for better survival with induction therapy (absent improvement in larynx preservation and local control outcomes). Laryngectomy-free survival with concurrent cisplatin and RT was significantly better than treatment with RT alone at 2-, 5-, and 10-year outcome reporting. Differences between treatment approaches for late toxicity and functional outcomes were not detected in any trials, although this could be due to limitations in methodology. In the RTOG 91-11 trial, both locoregional and distant control were improved with concurrent treatment compared with RT alone. This did not translate to a survival benefit because of the unexplained increase in noncancer deaths that became apparent with long follow-up. Retrospective, single-institution studies have looked at late swallowing toxicity and cause of death in patients treated with concurrent cisplatin-based chemotherapy who met eligibility criteria for RTOG 91-11. Modern conformal RT techniques were used. These small cohort studies did not find complications of late toxicity to be a cause of noncancer deaths, and larynx preservation and survival results were in line with RTOG 91-11.

The results of induction cisplatin, FU, and docetaxel as evaluated in 98 patients with laryngeal cancer compared with cisplatin

plus FU in the GORTEC trial along with the higher response rate observed in multisite cisplatin, FU, and taxane comparative trials support its use in an induction approach. Whether the addition of a taxane to cisplatin plus FU induction leads to improved survival and larynx-preservation outcomes compared with concurrent cisplatin and RT is unknown and requires a direct comparative trial.

By using the composite end point of laryngectomy-free survival, induction cisplatin plus FU and concurrent cisplatin and RT are both more effective than RT alone in a nonsurgical larynx-preservation approach. The induction approach is favored in Europe on the basis of the sequence of EORTC and GORTEC trials in cancers of the larynx and hypopharynx. However, after assessing the individual end points of larynx preservation and locoregional control, concurrent cisplatin and RT has a clear advantage. The panel views the randomized phase III trials reported since the publication of the 2006 ASCO guideline, including the update of RTOG 91-11, as continuing to support concurrent cisplatin and RT as the preferred approach and standard of care for achieving larynx preservation. This applies to intermediate- and advanced-stage (T2N+, T3, and limited T4) operable cancers of the supraglottic and glottic larynx that meet the inclusion criteria for RTOG 91-11. Patient selection is a critical determinant of the success of organ-preservation treatment. When patients are poorly selected (ie, have tumors that are more advanced than those eligible for RTOG 91-11), a greater risk of treatment failure and decrement in survival are likely (see Recommendation 2.2). Determination of the most effective combined-modality strategy to preserve a functional larynx, minimize late effects, and optimize survival will continue to evolve. Presently, no data support a radiosensitizing agent other than cisplatin. The panel recommends the use of carboplatin in patients with contraindication to cisplatin.

Recommendation 2.6. [Updated]. 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 treatment with altered fractionation RT in this setting (Type: evidence-based, benefits outweigh harms; Quality of evidence: intermediate; Strength of recommendation: moderate).

Clinical interpretation of literature review: trials of sequential chemotherapy followed by chemoradiation. Combining induction chemotherapy and concurrent chemoradiation is an appealing concept to optimize the effect of systemic therapy (ie, to reduce the risk of distant metastases and improve locoregional control). In the setting of operable cancer with the goal of larynx preservation, response to induction chemotherapy serves as a surrogate predictive biomarker for successful organ preservation with subsequent RT plus cisplatin. However, intensification of treatment by adding multiple cycles of induction chemotherapy to concurrent cisplatin and RT has yet to show a benefit in survival or organ-preservation rate compared with a control group of concurrent cisplatin and RT. The literature review for this updated analysis yielded one randomized phase II trial,[89] a single-institution, single-arm phase II trial,[134] and a retrospective unplanned subset analysis of a phase III multisite trial comparing two sequential regimens.[111]

Building on the pivotal trial report of survival benefit without additional toxicity for cetuximab and RT versus RT alone[178] and the outcome of the GORTEC 2000-01 trial,[110] the Radiotherapy With Cisplatin Versus Radiotherapy With Cetuximab After Induction Chemotherapy for Larynx Preservation (TREMPLIN) randomized phase II trial was conducted to determine the feasibility of a sequential approach for larynx preservation.[89] The trial explored the efficacy and tolerability of cisplatin and RT and cetuximab and RT after three cycles of induction cisplatin, FU, and docetaxel. A total of 153 operable patients with either laryngeal or hypopharyngeal cancer (T2 to T3, N0 to N3) who required total laryngectomy received induction cisplatin, FU, and docetaxel. Those with sufficient response were to be randomly assigned to receive either cetuximab and RT or cisplatin and RT. The TREMPLIN study did not meet its prespecified larynx-preservation end point of 80% at 3 months post-treatment. There was a high dropout rate (24%) before random assignment because of both substantial toxicity from cisplatin, FU, and docetaxel and insufficient tumor response. Cetuximab and RT proved as toxic as cisplatin and RT, which caused the same rate of grade 3 and 4 acute mucositis but worse in-field skin toxicity. The 3-month larynx-preservation rate and survival at 18 months were not statistically different for concurrent cisplatin or cetuximab; however, as pointed out by the Lefebvre et al, these results were inflated because only those randomly assigned to sequential concurrent drug and RT (116 of 153 initiated on induction cisplatin, FU, and docetaxel) were included in the analysis. More local treatment failures occurred among those administered cetuximab, which raised the possibility that for larynx preservation and achievement of local control, EGFR inhibition and RT may be inferior to cisplatin and RT. This feasibility trial demonstrated that intensification of treatment with a sequential approach of multiple cycles of cisplatin, FU, and docetaxel risks substantial added toxicity and that both cetuximab and RT and cisplatin and RT were difficult to administer after this induction regimen. The larynx-preservation rate was no better than that observed with induction cisplatin, FU, and docetaxel followed by RT in the GORTEC 2000-01 trial. TREMPLIN did not establish a role for cetuximab and RT in the treatment of laryngeal cancer, nor did the results support further testing of either sequential regimen.

A retrospective, unplanned subset analysis of operable cancers of the larynx and hypopharynx (n = 123) in the TAX-324 trial was published in 2009.[111] This small cohort analysis compared three cycles of cisplatin and FU with or without docetaxel followed by RT and concurrent carboplatin (in responders) and suggested that the addition of docetaxel improved laryngectomy-free survival and progression-free survival but not overall survival. The rate of larynx preservation specifically was not reported.

In contrast to the administration of multiple cycles of induction chemotherapy, investigators at the University of Michigan used the response to a single cycle of platinum plus FU as a predictive biomarker for selecting patients for larynx preservation with concurrent platinum and RT.[134] This integrated approach focused on the speed of tumor response as prognostic and on shortening the overall treatment time to reduce accelerated repopulation of surviving tumor clones. Ninety-seven patients with stage III/IV laryngeal cancer were enrolled in this prospective phase II trial. One third of patients had T4 high-volume or deeply invasive cancers. After one cycle of platinum and FU, 75% achieved at least a partial response of the primary tumor. The larynx was preserved in 70% of the 97 patients. Estimated overall survival at 2 and 3 years was 88% and 85%, respectively, and estimated disease-free survival was 80% and 78%, respectively. The laryngectomy-free survival rate at 2 and 3 years was 63% and 61%, respectively. Early patient selection and timely integration of surgery were believed to be key to the excellent

overall survival rates for this population with advanced disease. It is noteworthy that although two cycles of adjuvant cisplatin plus FU was planned, this was feasible in only 28% of 68 patients eligible for adjuvant chemotherapy. This neoadjuvant bioselection experience was recently expanded and validated in a retrospective cohort of 71 additional patients with advanced disease treated outside a clinical trial setting, which included 45% with T4a disease. An overall 5-year survival rate of 76% (95% CI, 63% to 85%) and disease-specific survival rate of 79% (95% CI, 67% to 88%) was confirmed.[149] A total of nine percent of patients required total laryngectomy after poor response to induction chemotherapy, and none of these patients experienced treatment failure. A total of 18% of patients required later salvage surgery after completion of chemoradiation with excellent survival rates and an overall larynx preservation rate of 66%, but only a 48% functional preservation rate was observed when the presence of tracheostomy or feeding tube at 1-year post-treatment was considered. This individualized bioselection approach mitigates the potential disadvantages of multiple cycles of induction chemotherapy (ie, delay in definitive local therapy, associated toxicity that may preclude or compromise definitive chemoradiation, potential selection of resistant clones and accelerated repopulation). There is an implicit assumption that patients who require two or three cycles of induction chemotherapy to achieve a partial response would ultimately experience treatment failure and require a laryngectomy. The results support a broader evaluation of this approach.

The sequential approach of one to three cycles of induction chemotherapy (now cisplatin, FU, and a taxane) for selection of patients for larynx preservation with definitive platinum and RT requires more data to be considered a standard option. The optimal combined-modality approach to achieve larynx preservation, which balances survival and quality of life, may not be uniform for all TN stages and subsites. RCTs that are adequately powered for site-specific analyses are needed.

Recommendation 2.7. [Unchanged]. For patients who desire larynx-preservation therapy but are not candidates for organ-preservation surgery or chemoradiation, RT alone is an appropriate treatment. With this last approach, survival is similar to that associated with CRT when timely salvage surgery is incorporated, but the likelihood of larynx preservation is lower.

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

Management of disease in the neck is one of the most critical factors in overall survival for patients with laryngeal cancer, and thus, appropriate management of the neck is a critical consideration in all larynx-preservation strategies. Neck metastases are uncommon in early-stage glottic cancers but frequently occur in patients with limited or advanced supraglottic cancer. Rates of occult metastatic disease vary by tumor site and are highest for supraglottic primary tumors. Elective treatment is indicated in most cases of supraglottic cancer and if not performed, recurrence rates of approximately 30% can be expected.[161,179-181] In the majority of patients with advanced disease who undergo organ-preserving chemoradiation, the at-risk regional lymphatics are routinely treated, and attention is therefore directed at early and appropriate surgical salvage of persistent or recurrent neck disease. This review has updated the 2006 ASCO guideline with respect to management of clinically positive neck metastases after chemoradiation. Prior data suggested that patients with a complete response of clinically positive neck nodes do not require subsequent neck dissection, but patients with clinically detectable residual disease in the neck should undergo neck dissection after completion of definitive RT or CRT.[182,183] It was not clear whether neck dissection was still required after apparent clinical resolution of disease in settings of advanced nodal metastases (N2, N3) because data suggested that planned elective dissections for such patients decreased recurrence rates and avoided potentially unresectable neck disease later on. How the use and timing of modern imaging techniques could assist in decision making with regard to neck management after organ preservation were more recently clarified, and therefore, several prior guidelines have been updated.

Recommendation 3.1 [Unchanged]. Most patients with T1, T2 lesions of the glottis and clinically negative cervical nodes (N0) do not require routine elective treatment of the neck.

Recommendation 3.2 [Unchanged]. Patients with advanced lesions of the glottis and all patients with supraglottic lesions should have elective treatment of the neck, even if clinically N0.

Recommendation 3.3 [Updated]. Patients with clinically involved regional cervical nodes (N+) who are treated with definitive RT or chemotherapy and RT and who have complete clinical, radiologic, and metabolic imaging (positron emission tomography [PET] and computed tomography [CT] at 12 weeks or later after therapy) do not require elective neck dissection (Type: evidence-based, benefits outweigh harms; Quality of evidence: strong; Strength of recommendation: high).

Recommendation 3.4. [Updated]. Patients with equivocal [^{18}F]fluorodeoxyglucose uptake should undergo neck dissection. The risks and cost of expectant observation versus surgery should be discussed with the patient (Type: evidence-based, benefits outweigh harms; Quality of evidence: strong; Strength of recommendation: high).

Clinical interpretation of literature review. The literature review yielded one RCT,[150] one single-institution prospective study,[151] and two meta-analyses[152,153] that analyzed the role of PET-CT imaging in the follow-up of patients with head and neck cancer after RT with or without chemotherapy. Patients who underwent PET-CT–guided surveillance 12 weeks after completion of CRT had similar survival to those who underwent planned neck dissection, but surveillance was more cost-effective over a 2-year minimum follow-up period and resulted in considerably fewer operations. The per-person cost saving was approximately $2,190, with an additional 0.08 quality-adjusted life-years per person.[150]

PET-directed management of the neck after definitive chemoradiation in N+ head and neck squamous cell carcinoma (HNSCC) appropriately spares neck dissections in patients with PET-negative, residual nodal abnormalities without compromising isolated nodal control.[151]

PET imaging is highly accurate for detecting recurrent or residual HNSCC after chemoradiation, with a sensitivity of 94% and specificity of 82%. Positive and negative predictive values were 75% and 95%, respectively.[152]

The sensitivity, specificity, positive predictive value, and negative predictive value of post- treatment [^{18}F]fluorodeoxyglucose PET-CT imaging of the neck were 72.7%, 87.6%, 52.1%, and 94.5% respectively. Because of a high negative predictive value, a negative post-treatment scan result is highly suggestive of the absence of viable disease that can guide the decision of neck dissection versus observation.[153] Argiris et al[154] found no survival benefit from planned

neck dissection in patients who showed complete response to chemoradiation, with a 5-year progression-free survival of 68% with neck dissection and 71% without.

Recommendation 3.5. [Unchanged]. 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 CRT is indicated.

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

The tremendous growth in use of combined chemotherapy and RT as primary treatment of larynx preservation in patients with advanced disease has confirmed high rates of larynx preservation but without significant improvement in survival. Studies have suggested that complications of initial therapy and poorer outcomes are associated with larger tumor volumes and with surgical salvage of chemoradiation treatment failures. It is clear that none of the primary organ-preservation approaches have achieved survival rates superior to primary total laryngectomy and that timely salvage of organ-preservation treatment failures is essential to maintaining survival rates comparable to primary surgery. There is, therefore, great interest in the identification of factors or biomarkers that predict success of therapy and that would guide selection of appropriate treatment modalities. The updated literature review confirms many of the clinical, behavioral, and socioeconomic factors previously identified as predictive of survival or local recurrence. A composite score (TALK score) that includes one point for clinical T stage (T4), nutrition (albumin $<$ 4 g/dL), alcohol use ($>$ 6 drinks/day), and Karnofsky performance status ($<$ 80%) has been validated as a simple prognostic tool, with only 6% of patients with scores $\geq$ 3 experiencing successful larynx preservation.[121] Others have found clinical tumor stage to be less reliable in predicting larynx preservation, even for patients with T4a disease.[49,116,130] Additional reports have emphasized comorbidities, smoking and smoking cessation, anemia,[40] prior tracheostomy,[103] age,[40] and ethnicity as important factors. Anatomic factors traditionally associated with poorer outcomes include advanced T or N stage, large tumor volume, involvement of the anterior commissure or invasion through cartilage, impaired vocal cord mobility, deep invasion into preepiglottic or paraglottic spaces, and airway obstruction requiring tracheostomy.[103,118] Significant invasion of the major cartilaginous structures of the larynx (thyroid or cricoid cartilage) is the most accepted criterion for predicting a negative outcome for RT. Although the use of combined chemoradiation has been used in this setting, the results have been inconsistent, and concerns exist that long-term larynx preservation with adequate function may be compromised. Most prior studies have focused on larynx-preservation strategies for patients with tumor stage less than IV. The less-favorable results in patients with stage IV disease has been a contributing factor in recommending primary surgery, which usually is total laryngectomy in those with advanced local disease (T4a).

Recommendation 4.1. [Updated]. There are no validated markers that consistently predict outcomes of larynx-preservation therapy. However, patients with a nonfunctional larynx (eg, extensive T3 or T4a) or tumor penetration through cartilage into surrounding soft tissues are considered poor candidates for a larynx-preservation approach. Primary surgery, usually total laryngectomy, is recommended in this setting (Type: evidence-based, benefits outweigh harms; Quality of evidence: intermediate; Strength of recommendation: moderate).

Clinical interpretation of literature review. Since 2006, considerable experience has been gained in the application of organ-preservation approaches for patients with both limited and advanced disease. For patients with limited disease, the emphasis has been on increased use of endoscopic techniques as initial treatment because they achieve similar survival rates, acceptable speech, and higher local control and long-term larynx-preservation rates compared with initial RT. Expert review confirmed that optimal selection of an initial approach for patients with limited disease is based on the multitude of factors described in Recommendation 1.2. Treatment selection and consideration of these factors is best facilitated by comprehensive multidisciplinary evaluation in all patients. Although no single factor predominates in decision making, increased tumor volume, and extent of invasion as reflected in the tumor staging classification, vocal cord mobility and pretreatment speech and swallowing function were confirmed as the major factors associated with decreased success rates for preservation of laryngeal function.[184,185]

Not all patients with advanced disease will have successful larynx preservation, and the search for reliable predictive factors is ongoing. The most consistent biologic factor that has correlated with poor prognosis in laryngeal cancer has been the lack of a significant decrease in tumor volume in response to multiple cycles of induction chemotherapy. Nonresponse, generally in 15% of patients who receive two to three cycles of induction chemotherapy, has characteristically been associated with poor response to subsequent RT and eventual failure of organ preservation and poor overall survival.[186-188] Recently, a biologic response after a single cycle of chemotherapy has been used to select patients for early total laryngectomy, with promising results that require validation.[149] Because of higher larynx-preservation rates, concurrent chemoradiation is the preferred treatment for which some progress has been reported in using clinical characteristics to identify potential treatment failures and to select patients for primary surgery. After concurrent chemoradiation, local tumor recurrences and the risks of long-term sequelae of aspiration and chondronecrosis in successfully treated patients are increased and seem related to pretreatment tumor volume, cartilage invasion, and pretreatment laryngeal dysfunction.[189-195] Numerous retrospective studies have identified patients with high-volume T4a disease as poor candidates for organ-preservation approaches, which results in a shift to primary total laryngectomy for such patients. Surgically treated patients have shown higher overall survival rates compared with concurrent chemoradiation in similar settings in retrospective studies.[27,39,47,61,104,118] However, some trials that investigated induction chemotherapy for T4 cancers have reported encouraging results, even in patients with T4a cancers.[49,134] When significant pretreatment laryngeal dysfunction is evident (insufficient airway and/or significant aspiration), post-treatment function after chemoradiation often is equally poor and can exacerbate comorbidities that lead to death or a sufficiently dysfunctional larynx that requires either a long-term tracheostomy or a feeding tube. Generally, these situations are not believed to represent successful larynx preservation, even if speech function is maintained and a remnant of laryngeal structure remains.[196] Thus, selection criteria, overall survival, and expected functional outcomes for organ-preservation

approaches in patients with advanced (T4a) local disease need to be carefully considered and discussed with patients.

Recommendation 4.2. [Updated]. Selection of therapy for an individual patient requires assessment by the multidisciplinary team as well as consideration of voice and swallowing function, patient comorbidity, psychosocial situation and preferences, and local therapeutic expertise. The multidisciplinary team should include surgical oncology, medical oncology, radiation oncology, speech pathology, radiology, pathology, nursing, dietetics, psychology, and a variety of rehabilitative services, including dental/prosthodontics, smoking cessation, and other ancillary services as required for such things as pain management and psychosocial support (Type: evidence-based, benefits outweigh harms; Quality of evidence: intermediate; Strength of recommendation: moderate).

Clinical interpretation of literature review. For patients with advanced disease, accepted larynx-preservation approaches include organ-preserving surgery (subtotal laryngectomy or, in selected patients, endoscopic resection), RT alone, or combined chemotherapy and RT. Multidisciplinary evaluation is essential because multimodality treatment is the norm, and combinations of chemotherapy and RT have become the most frequent treatment approach.[104] Furthermore, in all larynx-preservation approaches, successful salvage of local recurrences is a critical element in achieving the highest survival rates and demands careful multidisciplinary surveillance. The multidisciplinary team typically includes surgical, medical, and radiation oncology, speech pathology, radiology, pathology, nursing, dietetics, and psychology, and a variety of rehabilitative services, including dental/prosthodontics, smoking cessation, and other ancillary services as required for such things as pain management and psychosocial support.

Recommendation 4.3. [Unchanged]. Continued cigarette smoking is associated with a worse outcome after therapy. Patients should be encouraged to abstain from smoking after the diagnosis and monitored and recommended for smoking cessation programs as necessary throughout and following treatment.

CLINICAL QUESTION 5. [New]. What are the best measures to evaluate airway, speech, and swallowing function to determine best function-preservation treatment or laryngectomy and post-treatment assessment of function?

Recommendation 5.1. As part of a comprehensive pre-treatment evaluation, all patients should undergo an assessment of voice and swallowing function, voice (use and requirements), and counseling with regard to the potential effect on quality of life, voice, and swallowing (Type: evidence-based, benefits outweigh harms; Quality of evidence: intermediate; Strength of recommendation: moderate).

Clinical interpretation of literature review. The goal of functional evaluation and intervention is to establish baseline airway, speech, and swallowing status to guide treatment selection and organ preservation versus total resection and to minimize post-treatment dysfunction, thereby optimizing quality of life during survivorship. Although patients with early-stage (T1, T2) disease have similar voice and swallowing quality-of-life outcomes, considerable heterogeneity exists among T1 and T2 lesions that influence treatment selection.[197,198] Experience has shown that the depth of invasion and the glottic site of the cancer are key determinates in treatment selection. Cancers that deeply invade the vocal cord or ones that involve the anterior commissure often are better treated with nonsurgical alternatives that avoid large defects and impede vocal fold closure, which result in glottic incompetency, poor vocal quality, and risk of aspiration. Specifically, cancers that affect the anterior commissure generally result in patient complaints related to weak, breathy vocal quality and problems with pitch variation. Patients with larger-volume invasive lesions treated with surgery that results in sizeable glottic defects have worse functional outcomes (more so for voice than for swallowing) than those with smaller-volume lesions. In contrast, superficial cancers of the true vocal cords generally are better candidates for laser resection. Superior voice outcomes have been documented in patients with early glottic cancers treated with RT alone and CRT compared with laser surgery in the first year after treatment (with a gradual decline in voice-related quality of life thereafter related to late adverse effects of RT) compared with patients treated with laser surgery. The lowest voice outcomes have been shown uniformly in patients treated with total laryngectomy.[107]

Meta-analytic data demonstrate a survival benefit after combined-modality treatment compared with local single-modality treatment alone for patients with head and neck cancers,[177] but a high incidence of acute toxicity commonly is acknowledged.[199] The exact magnitude of dysphagia and aspiration as common post-treatment toxicities are unknown; however, it has been estimated that up to 50% of survivors of advanced head and neck cancer have dysphagia,[200] and studies have reported aspiration rates between 47% and 84% among symptomatic patients after RT or CRT.[193,201,202] Dysphagia after RT or CRT most commonly results from edema, fibrosis, and sensory alterations associated with acute and chronic soft tissue changes. The amount of dysfunction varies with the total dose, schedule, and duration of RT as well as the size of the radiation field. The ability of dose-limiting treatments to reduce normal tissue damage and preserve function offer promise to avoid long-term functional deterioration.[188,203] Patients with difficulty swallowing before treatment are at higher risk for chronic dysphagia and permanent feeding tube dependency.[201] Likewise, prolonged intervals of nothing per oral for $>$ 2 weeks during RT or CRT are associated with poorer swallowing outcomes.[204] Therefore, patients should be encouraged to swallow throughout the course of RT or CRT as much as possible, and even brief nothing per oral intervals should be avoided.[205] Aspiration is commonly reported in clinical studies on the basis of instrumental swallowing evaluation, particularly the modified barium swallow(MBS) study. Much of our knowledge of aspiration and physiologic impairment comes from data of larynx-preservation trials that aggregate functional outcomes from multiple sites of HNSCC and show aspiration rates of up to 40% in unselected cohorts and in up to 80% of symptomatic patients. These data are based on findings from MBS studies confirm that when physiology is impaired, patients have high rates of aspiration, much of which are undetected by patient report because of a lack of sensory awareness. Hence, there is general agreement that aspiration rates are likely underreported because of the lack of detection of silent episodes of aspiration in asymptomatic patients who do not report dysphagia and has been reported in $>$ 50% of patients who aspirate.[193,201,206,207]

In recent years, a growing awareness of the potential for long-term functional sequelae of chemoradiation has been documented. To date, most estimates of functional outcomes have been derived from single-institution clinical studies. The most common swallowing

outcome reported in the clinical literature is the rate of feeding tube dependence. However, feeding tube dependence may, in fact, underestimate the burden of dysphagia because patients often eat despite evidence of dysphagia or aspiration on instrumental examination.[201] Most clinical trials, have reported rates of < 10% at 1 year and < 5% at 2 years, with the exception of RTOG 9914 (concurrent cisplatin with concomitant boost radiation), which found 41% and 22% of patients to be feeding tube dependent at 1 and 2 years, respectively.[16,29,56,90] In long-term follow-up of RTOG 91-11, non-cancer–related deaths were higher in the chemoradiation arm relative to RT alone or induction followed by RT, and this may represent morbidity of chronic aspiration and pneumonia.[208] The SEER-Medicare analysis estimates lifetime risk of aspiration pneumonia after chemoradiation is 25% and 30% in patients with laryngeal and hypopharyngeal cancers, respectively, and is associated with a 42% increased risk of death during survivorship.[209] The practice of prophylactic feeding tube placement for patients with cancer of the head and neck has changed within the past decade because evidence has shown that patients who receive prophylactic gastrostomy tubes are more likely to have late esophageal toxicity and dysphagia that lead to long-term dependence on enteral feedings and often depression, which ultimately complicates recovery.[191,210,211] Recent findings suggest that reactive versus prophylactic feeding tubes are associated with favorable swallowing outcomes and thus, may help to prevent dysphagia that requires long-term feeding tube dependence.[212]

For patients who are not candidates for larynx preservation or who have experienced failure of nonsurgical organ-sparing protocols, total laryngectomy remains the procedure of choice for cancer cure and survival. Successful rehabilitation has been associated with good quality of life. The selection of the optimal alternative (artificial larynx [electrolarynx], esophageal speech production, tracheoesophageal voice restoration) depends on appropriate patient selection, patient motivation, and clinician expertise with the chosen alaryngeal speech alternative. Not all approaches are appropriate for every patient with a laryngectomy. The decision about the best alaryngeal speech option should be patient driven and not a unilateral decision made by the physician, family, or speech pathologist. In large part, clinician experience and familiarity with the specific alaryngeal voice alternative will significantly affect overall success. Thus, patients with laryngectomy must seek out rehabilitation from experienced clinicians who are familiar with the nuances of multiple available methods and who are familiar with the unique complications and problems often experienced by alaryngeal speakers. Given the current state of rehabilitation, no patient should be without some method of functional speech restoration after total laryngectomy.

Recommendation 5.2. Pretreatment voice and swallowing assessments should establish the functional impact of tumor volume and extent and stage of disease on voice and swallowing outcomes (Type: evidence-based, benefits outweigh harms; Quality of evidence: intermediate; Strength of recommendation: moderate).

Clinical interpretation of literature review. Patients with early-stage disease who undergo larynx-preserving surgery or RT generally have similar voice and swallowing quality-of-life outcomes. However, considerable heterogeneity exists between T1 and T2 lesions that influence treatment selection. After RT, larger-volume lesions tend to have worse functional outcomes compared with smaller-volume lesions and more so for voice than for swallowing. However, both voice and swallowing generally show worse outcomes after extended organ-preserving surgery.

Post-treatment assessment of function is recommended to evaluate the adequacy of airway, voice and swallowing, and aspiration status. Function changes over time and voice quality and swallowing function may not stabilize for at least 6 months post-treatment. For surviving patients treated for advanced-stage disease, worse long-term swallowing outcomes may occur with the addition of chemotherapy to RT.

For surgical and nonsurgical patients with advanced-stage (III/IV) disease, baseline assessments of airway, voice, and swallowing function are recommended to assess laryngopharyngeal function, counsel patients, predict morbidity as a result of treatment, and select the best treatment modality. This assessment should include the necessity for feeding or tracheostomy tubes. Routine serial assessments on an annual basis are necessary to evaluate long-term effects and late toxicities, but the frequency of assessment in a given year may vary according to patient symptoms. Generally, patients with large-volume, deeply infiltrative, extensive lesions (large T3, T4a tumors) that have significant pretreatment dysfunction will show poor function after organ-preservation treatment approaches and, therefore, are potentially better candidates for total laryngectomy. Pretreatment gross or recurring aspiration, extensive laryngeal cartilage destruction, a nonfunctional voice or airway, and severe laryngeal dysfunction favor total laryngectomy.[213] For instance, baseline vocal fold fixation, tracheostomy dependence, gastrostomy dependence, and aspiration detected on high-grade fluoroscopy have all been shown to portend poor functional outcome after larynx preservation.[201,214,215]

Recommendation 5.3. Instrumental, performance status, and quality-of-life measures of voice and swallowing should be used to evaluate pre- and post-treatment function. Multiple assessment tools are available for voice and swallowing. Routine methods of assessment include self-recorded and/or expert-rated voice quality measures, voice-related quality-of-life tools, videostroboscopy, radiographic (videofluoroscopic) or fiber-optic laryngoscopic evaluation of swallowing, and dietary assessment (Type: evidence-based, benefits outweigh harms; Quality of evidence: intermediate; Strength of recommendation: moderate).

Clinical interpretation of literature review. As part of a comprehensive pretreatment evaluation of patients with laryngeal disease, all patients who present with or are at risk for post-treatment speech and swallowing dysfunction should undergo a thorough assessment of voice and swallowing that includes counseling about the potential impact on quality of life along with available rehabilitative options. Specifically, patients with complaints about dysphagia, postprandial cough, unexplained weight loss, and/or pneumonia should be referred to an experienced speech language pathologist for clinical and instrumental evaluation of swallowing function. Patients with early glottic tumors who are being considered for surgical versus nonsurgical treatment and whose prognosis for survival is comparable regardless of treatment modality should also receive videostroboscopic examination of vocal function to facilitate best treatment selection to optimize voice preservation. At a minimum, the patient's physiologic function, functional performance status (eg, how the patient routinely eats and communicates in daily life), and the patient's perceived function should be examined.[216]

A variety of measures to assess vocal functioning are available. Among them are the Voice-Related Quality of Life,[217] Voice Symptom

Scale,[218] and the Voice Handicap Index 30[219] and its shortened version Voice Handicap Index 10.[220] The Consensus Auditory-Perceptual Evaluation of Voice[221] and the GRBAS (grade, roughness, breathiness, asthenia, strain) scale[222] are frequently used measures of voice perception. Videostroboscopy provides overall visualization of the laryngeal anatomy and allows observation and assessment of the degree and symmetry of true vocal fold movement and vibratory patterns during phonation.

Reliance on patient report to determine swallowing competence is not recommended because the patient's account of his or her functional status frequently is unreliable and more often does not accurately reflect physiologic performance and actual abilities.[223] Patients frequently indicate normal swallowing despite abnormal findings of silent aspiration shown on videofluoroscopic examination. Conversely, patients also report abnormal swallowing function associated with radiation-induced xerostomia despite functional videofluoroscopic findings.[204,224]

The evaluation of swallowing incorporates a variety of measures that include instrumental examinations, such as the MBS study[225] and fiber-optic endoscopic evaluation of swallowing.[226] MBS and fiber-optic evaluation of swallowing should be conducted in accordance with standard protocols. The MBS Impairment Profile[227] and Dynamic Imaging Grade of Swallowing Toxicity[228] are quantitative measures that evaluate the severity and pathophysiology of dysphagia on the basis of observations obtained from the MBS study. In addition, a comprehensive examination of swallowing function must also include clinician-rated and patient-reported outcome measures. These include the Performance Status Scale–Head and Neck, which assesses three areas (normalcy of diet, understandability of speech, and eating in public),[229] and the MD Anderson Dysphagia Inventory.[230] The Functional Oral Intake Scale[231] is a simple, validated tool that helps to quantify the functional status of the patient with regard to feeding tube dependence and level of oral intake. Multidimensional swallowing evaluation also is important. A longitudinal study of CRT for head and neck cancer identified complementary, distinct, normal toxicity complication probabilities on the basis of the specific method of swallowing evaluation used.[232] In addition, specific recommendations to incorporate multidimensional evaluation of swallowing in phase III organ-preservation trials are found in the current radiation oncology literature.[233]

PATIENT AND CLINICIAN COMMUNICATION

The past 10 years have seen tremendous changes in the adoption of new therapeutic approaches to patients with laryngeal cancer that have included endoscopic approaches for patients with limited disease, advances in diagnostic imaging, and reinvigorated interest in total laryngectomy for patients with advanced disease who previously had been considered candidates for organ preservation. The nuances of treatment selection, assessments of pretreatment voice and swallowing, and public awareness of new organ-preservation treatment and decision making have increased to the point that careful and individualized discussion with patients and families with the multidisciplinary treatment team is a critical element of modern care. Good communication among the members of the treatment team is essential to minimize patient confusion. Written copies of discussion summaries that can be shared with the patient should be considered.

Integral to these recommendations is communication of these therapeutic decisions to the primary care team and ancillary care practitioners, such as nurses, speech pathologists, dieticians, and social workers, who will be involved in ongoing supportive care. Establishment of good communication practices among all members of the care team is essential to a good outcome, and good communication is a shared responsibility. The following are some basic guidelines for clinicians. Advances in care and electronic medical documentation have encouraged greater participation by patients in communication and the coordination of care by the other members of a modern treatment team. Many institutions have already instituted electronic patient access portals to allow patient's direct viewing of their medical records. Treatment plans need to be articulated in the medical record. Responsibilities for each component of care and follow-up need to be defined and understood by the patient and primary care providers. These expectations should be shared with the patient. The availability of online educational materials also has increased dramatically, and any discrepancies in patient understanding of the proposed treatment plans and what he or she may have learned from other sources need to be thoughtfully discussed. Good record keeping by patients, families, and caregivers should be encouraged, and any changes in symptoms or other health conditions should be noted and reported. Patients should be empowered to participate in their care, treatment plans, and surveillance schedules and to share any other concerns about ongoing care, adverse effects, overall prognosis, and other issues that may affect cancer recovery and quality of life.

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving poor-quality care than other Americans. A number of large-scale population-based studies have identified more advanced disease and lower survival rates in low-income groups and in African American patients.[27,122,139] Some studies have reported less access to RT,[139] whereas others have reported that use of radiation is increased.[122] Access to sophisticated multidisciplinary care and skilled surveillance are essential to successful organ-preservation therapies and may be limited by geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

MULTIPLE CHRONIC CONDITIONS

Comorbidities and patient performance status have been consistently identified as significant overall prognostic factors for survival in patients with laryngeal cancer. Often, comorbidities (especially

hepatic, pulmonary, and cardiac) may limit the acceptability of aggressive treatment strategies that incorporate intensive chemotherapy or even suitability of organ-preserving surgery. The creation of evidence-based recommendations to inform treatment of patients with additional chronic conditions (a situation where the patient may have two or more such conditions referred to as multiple chronic conditions [MCCs]) is challenging. Patients with MCC are a complex and heterogeneous population, which makes it difficult to account for all possible permutations for developing specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials wherein study selection criteria may exclude these patients to avoid potential interaction effects or a confounding of results associated with MCCs. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

Because many patients for whom guideline recommendations apply present with MCCs, any treatment plan must take into account the complexity and uncertainty created by the presence of MCCs and highlight the importance of multidisciplinary shared decision making with regard to guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions the patient has and take those into account while formulating the treatment and follow-up plan.

In light of these considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCCs, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied as determined by best practice in consideration of any MCC.

COST IMPLICATIONS

Cost of care is a major consideration that should take into account the frequency and necessity of surveillance activities and cost of secondary salvage procedures in addition to the cost of initial treatment modalities. For patients with limited (T1, T2) disease, the increasing use of endoscopic surgery as initial therapy has been associated with lower costs.[44,95,150,234-237] The assessment of cost implications of chemoradiation versus total laryngectomy as initial treatment of patients with advanced disease is more difficult because type of chemotherapy, hospital setting, and likelihood of high-cost complications will determine overall costs of organ-preservation approaches. Generally, costs of preserving the larynx will be higher. True costs in terms of patient burden and quality of life, return to work, and health utility for loss of laryngeal function, however, are difficult to measure and compare.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners, cancer survivors, and caregivers and to provide adequate services in the face of limited resources. The guideline Bottom Line box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/head-neck-cancer-guidelines and www.asco.org/guidelineswiki. Patient information is available at www.cancer.net. Visit www.asco.org/guidelineswiki to provide comments on the guideline or to submit new evidence.

Related ASCO Guidelines

- Integration of Palliative Care Into Standard Oncology Practice[238] (http://ascopubs.org/doi/full/10.1200/JCO.2016.70.1474)
- Head and Neck Cancer Survivorship Care Guideline[239] (http://ascopubs.org/doi/full/10.1200/JCO.2016.71.8478)
- Antiemetics[240] (http://ascopubs.org/doi/full/10.1200/JCO.2017.74.4789)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

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REFERENCES

1. National Cancer Institute, SEER: Cancer Stat Facts: Larynx Cancer, 2016. http://seer.cancer.gov/statfacts/html/laryn.html
2. Megwalu UC, Sikora AG: Survival outcomes in advanced laryngeal cancer. JAMA Otolaryngol Head Neck Surg 140:855-860, 2014
3. Pfister DG, Laurie SA, Weinstein GS, et al: American Society of Clinical Oncology clinical practice guideline for the use of larynx-preservation strategies in the treatment of laryngeal cancer. J Clin Oncol 24:3693-3704, 2006
4. Rütten H, Pop LA, Janssens GO, et al: Long-term outcome and morbidity after treatment with accelerated radiotherapy and weekly cisplatin for locally advanced head-and-neck cancer: Results of a multidisciplinary late morbidity clinic. Int J Radiat Oncol Biol Phys 81:923-929, 2011
5. Shojania KG, Sampson M, Ansari MT, et al: How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med 147:224-233, 2007
6. Shiffman RN, Michel G, Rosenfeld RM, et al: Building better guidelines with BRIDGE-Wiz: Development and evaluation of a software assistant to promote clarity, transparency, and implementability. J Am Med Inform Assoc 19:94-101, 2012
7. Aaltonen LM, Rautiainen N, Sellman J, et al: Voice quality after treatment of early vocal cord cancer: A randomized trial comparing laser surgery with radiation therapy. Int J Radiat Oncol Biol Phys 90:255-260, 2014
8. Abdurehim Y, Hua Z, Yasin Y, et al: Transoral laser surgery versus radiotherapy: Systematic review and meta-analysis for treatment options of T1a glottic cancer. Head Neck 34:23-33, 2012
9. Akimoto T, Nonaka T, Kitamoto Y, et al: Radiation therapy for T2N0 laryngeal cancer: A retrospective analysis for the impact of concurrent chemotherapy on local control. Int J Radiat Oncol Biol Phys 64:995-1001, 2006
10. Al-Mamgani A, van Rooij PH, Mehilal R, et al: Radiotherapy for T1a glottic cancer: The influence of smoking cessation and fractionation schedule of radiotherapy. Eur Arch Otorhinolaryngol 271:125-132, 2014
11. Al-Mamgani A, van Rooij PH, Woutersen DP, et al: Radiotherapy for T1-2N0 glottic cancer: A multivariate analysis of predictive factors for the long-term outcome in 1050 patients and a prospective assessment of quality of life and voice handicap index in a subset of 233 patients. Clin Otolaryngol 38:306-312, 2013
12. Al-Mamgani A, Tans L, van Rooij P, et al: A single-institutional experience of 15 years of treating T3 laryngeal cancer with primary radiotherapy, with or without chemotherapy. Int J Radiat Oncol Biol Phys 83:1000-1006, 2012
13. Andreadis C, Iliopoulou C, Sidiras T, et al: Neoadjuvant chemotherapy followed by radiotherapy versus concurrent chemoradiotherapy for larynx preservation in patients with advanced laryngeal cancer. J BUON 12:341-347, 2007
14. Ansarin M, Cattaneo A, Santoro L, et al: Laser surgery of early glottic cancer in elderly. Acta Otorhinolaryngol Ital 30:169, 2010
15. Azevedo EH, Montoni N, Gonçalves Filho J, et al: Vocal handicap and quality of life after treatment of advanced squamous carcinoma of the larynx and/or hypopharynx. J Voice 26:e63-e71, 2012
16. Bensadoun RJ, Bénézery K, Dassonville O, et al: French multicenter phase III randomized study testing concurrent twice-a-day radiotherapy and cisplatin/5-fluorouracil chemotherapy (BiRCF) in unresectable pharyngeal carcinoma: Results at 2 years (FNCLCC-GORTEC). Int J Radiat Oncol Biol Phys 64:983-994, 2006
17. Bertino G, Degiorgi G, Tinelli C, et al: CO_2 laser cordectomy for T1-T2 glottic cancer: Oncological and functional long-term results. Eur Arch Otorhinolaryngol 272:2389-2395, 2015
18. Bhattacharyya T, Ghoshal S, Dhanireddy B, et al: Efficacy of radical radiotherapy alone for functional preservation of larynx in laryngeal carcinoma: A retrospective analysis. Indian J Cancer 51:10-14, 2014
19. Bocciolini C, Presutti L, Laudadio P: Oncological outcome after CO2 laser cordectomy for early-stage glottic carcinoma. Acta Otorhinolaryngol Ital 25:86-93, 2005
20. Boscolo-Rizzo P, Maronato F, Marchiori C, et al: Long-term quality of life after total laryngectomy and postoperative radiotherapy versus concurrent chemoradiotherapy for laryngeal preservation. Laryngoscope 118:300-306, 2008
21. Breda E, Catarino R, Monteiro E: Transoral laser microsurgery for laryngeal carcinoma: Survival analysis in a hospital-based population. Head Neck 37:1181-1186, 2015
22. Bumber Z, Prgomet D, Janjanin S: Endoscopic CO2 laser surgery for supraglottic cancer—ten years of experience. Coll Antropol 33:87-91, 2009
23. Burnip E, Owen SJ, Barker S, et al: Swallowing outcomes following surgical and non-surgical treatment for advanced laryngeal cancer. J Laryngol Otol 127:1116-1121, 2013
24. Caicedo-Granados E, Beswick DM, Christopoulos A, et al: Oncologic and functional outcomes of partial laryngeal surgery for intermediate-stage laryngeal cancer. Otolaryngol Head Neck Surg 148:235-242, 2013
25. Canis M, Ihler F, Martin A, et al: Transoral laser microsurgery for T1a glottic cancer: Review of 404 cases. Head Neck 37:889-895, 2015
26. Caudell JJ, Schaner PE, Meredith RF, et al: Factors associated with long-term dysphagia after definitive radiotherapy for locally advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 73:410-415, 2009
27. Chen AY, Halpern M: Factors predictive of survival in advanced laryngeal cancer. Arch Otolaryngol Head Neck Surg 133:1270-1276, 2007
28. Chera BS, Amdur RJ, Morris CG, et al: T1N0 to T2N0 squamous cell carcinoma of the glottic larynx treated with definitive radiotherapy. Int J Radiat Oncol Biol Phys 78:461-466, 2010
29. Cmelak AJ, Li S, Goldwasser MA, et al: Phase II trial of chemoradiation for organ preservation in resectable stage III or IV squamous cell carcinomas of the larynx or oropharynx: Results of Eastern Cooperative Oncology Group Study E2399. J Clin Oncol 25:3971-3977, 2007
30. Cohen SM, Garrett CG, Dupont WD, et al: Voice-related quality of life in T1 glottic cancer: Irradiation versus endoscopic excision. Ann Otol Rhinol Laryngol 115:581-586, 2006
31. Connor KL, Pattle S, Kerr GR, et al: Treatment, comorbidity and survival in stage III laryngeal cancer. Head Neck 37:698-706, 2015
32. Corry J, Rischin D, Cotton S, et al: Larynx preservation with primary non-surgical treatment for loco-regionally advanced larynx cancer. J Med Imaging Radiat Oncol 55:229-235, 2011
33. Costa L, Pedretti S, Foscarini F, et al: Clinical outcomes and toxicity after exclusive versus postoperative radiotherapy in supraglottic cancer: New solutions for old problems? The case of stage III and IV disease. Radiol Med (Torino) 121:70-79, 2016
34. Csanády M, Czigner J, Vass G, et al: Transoral CO2 laser management for selected supraglottic tumors and neck dissection. Eur Arch Otorhinolaryngol 268:1181-1186, 2011
35. Czecior E, Orecka B, Pawlas P, et al: Comparative assessment of the voice in patients treated for early glottis cancer by laser cordectomy or radiotherapy. Otolaryngol Pol 66:407-412, 2012
36. Pérez Delgado L, El-Uali Abeida M, de Miguel García F, et al: CO2 laser surgery of supraglottic carcinoma: Our experience over 6 years. Acta Otorrinolaringol Esp 61:12-18, 2010
37. Denaro N, Russi EG, Lefebvre JL, et al: A systematic review of current and emerging approaches in the field of larynx preservation. Radiother Oncol 110:16-24, 2014
38. Dinapoli N, Parrilla C, Galli J, et al: Multidisciplinary approach in the treatment of T1 glottic cancer. The role of patient preference in a homogenous patient population. Strahlenther Onkol 186:607-613, 2010
39. Dziegielewski PT, O'Connell DA, Klein M, et al: Primary total laryngectomy versus organ preservation for T3/T4a laryngeal cancer: A population-based analysis of survival. J Otolaryngol Head Neck Surg 41:S56-S64, 2012 (suppl 1)
40. Eldeeb H, Abdel-Khalk S: Does treatment interruption and baseline hemoglobin affect overall survival in early laryngeal cancer treated with radical radiotherapy? 10 years follow up. J BUON 19:124-129, 2014
41. El-Deiry M, Funk GF, Nalwa S, et al: Long-term quality of life for surgical and nonsurgical treatment of head and neck cancer. Arch Otolaryngol Head Neck Surg 131:879-885, 2005
42. Elegbede AI, Rybicki LA, Adelstein DJ, et al: Oncologic and functional outcomes of surgical and nonsurgical treatment of advanced squamous cell carcinoma of the supraglottic larynx. JAMA Otolaryngol Head Neck Surg 141:1111-1117, 2015
43. Ermiş E, Teo M, Dyker KE, et al: Definitive hypofractionated radiotherapy for early glottic carcinoma: Experience of 55Gy in 20 fractions. Radiat Oncol 10:203, 2015
44. Feng Y, Wang B, Wen S: Laser surgery versus radiotherapy for T1-T2N0 glottic cancer: A meta-analysis. ORL J Otorhinolaryngol Relat Spec 73:336-342, 2011
45. Forastiere AA, Zhang Q, Weber RS, et al: Long-term results of RTOG 91-11: A comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. J Clin Oncol 31:845-852, 2013
46. Franchin G, Vaccher E, Politi D, et al: Organ preservation in locally advanced head and neck cancer of the larynx using induction chemotherapy followed by improved radiation schemes. Eur Arch Otorhinolaryngol 266:719-726, 2009
47. Francis E, Matar N, Khoueir N, et al: T4a laryngeal cancer survival: Retrospective institutional analysis and systematic review. Laryngoscope 124:1618-1623, 2014
48. Fu X, Zhou Q, Zhang X: Efficacy comparison between total laryngectomy and nonsurgical organ-preservation modalities in treatment of advanced stage laryngeal cancer: A meta-analysis. Medicine (Baltimore) 95:e3142, 2016
49. Fung K, Lyden TH, Lee J, et al: Voice and swallowing outcomes of an organ-preservation trial

for advanced laryngeal cancer. Int J Radiat Oncol Biol Phys 63:1395-1399, 2005

50. Furusaka T, Matsuda A, Saito T, et al: Concurrent chemoradiation therapy with docetaxel (DOC) for laryngeal preservation in T2N0M0 glottic squamous cell carcinomas. Acta Otolaryngol 133: 99-112, 2013

51. Furusaka T, Matsuda A, Tanaka A, et al: Superselective intra-arterial chemoradiation therapy for functional laryngeal preservation in advanced squamous cell carcinoma of the glottic larynx. Acta Otolaryngol 133:633-640, 2013

52. Furusaka T, Matsuda H, Saito T, et al: Long-term follow-up and salvage surgery in patients with T2N0M0 squamous cell carcinoma of the glottic larynx who received concurrent chemoradiation therapy with carboplatin (CBDCA) - AUC 1.5 vs AUC 2.0. Acta Otolaryngol 132:1215-1223, 2012

53. Furusaka T, Matuda H, Saito T, et al: Long-term observations and salvage operations on patients with T2N0M0 squamous cell carcinoma of the glottic larynx treated with radiation therapy alone. Acta Otolaryngol 132:546-551, 2012

54. Furusaka T, Susaki Y, Saito T, et al: Long-term follow-up and salvage surgery in patients with T2N0M0 squamous cell carcinoma of the glottic larynx following concurrent chemoradiation therapy with cisplatin and 5-fluorouracil for laryngeal preservation. Acta Otolaryngol 133:91-98, 2013

55. Ganly I, Patel SG, Matsuo J, et al: Predictors of outcome for advanced-stage supraglottic laryngeal cancer. Head Neck 31:1489-1495, 2009

56. Garden AS, Harris J, Trotti A, et al: Long-term results of concomitant boost radiation plus concurrent cisplatin for advanced head and neck carcinomas: A phase II trial of the radiation therapy oncology group (RTOG 99-14). Int J Radiat Oncol Biol Phys 71: 1351-1355, 2008

57. Givens DJ, Karnell LH, Gupta AK, et al: Adverse events associated with concurrent chemoradiation therapy in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 135: 1209-1217, 2009

58. van Gogh CD, Verdonck-de Leeuw IM, Boon-Kamma BA, et al: A screening questionnaire for voice problems after treatment of early glottic cancer. Int J Radiat Oncol Biol Phys 62:700-705, 2005

59. Goguen LA, Posner MR, Norris CM, et al: Dysphagia after sequential chemoradiation therapy for advanced head and neck cancer. Otolaryngol Head Neck Surg 134:916-922, 2006

60. Goudakos JK, Markou K, Nikolaou A, et al: Management of the clinically negative neck (N0) of supraglottic laryngeal carcinoma: A systematic review. Eur J Surg Oncol 35:223-229, 2009

61. Gourin CG, Conger BT, Sheils WC, et al: The effect of treatment on survival in patients with advanced laryngeal carcinoma. Laryngoscope 119: 1312-1317, 2009

62. Greulich MT, Parker NP, Lee P, et al: Voice outcomes following radiation versus laser microsurgery for T1 glottic carcinoma: Systematic review and meta-analysis. Otolaryngol Head Neck Surg 152: 811-819, 2015

63. Grover S, Swisher-McClure S, Mitra N, et al: Total laryngectomy versus larynx preservation for T4a larynx cancer: Patterns of care and survival outcomes. Int J Radiat Oncol Biol Phys 92:594-601, 2015

64. Gultekin M, Ozyar E, Cengiz M, et al: High daily fraction dose external radiotherapy for T1 glottic carcinoma: Treatment results and prognostic factors. Head Neck 34:1009-1014, 2012

65. Hafidh M, Tibbo J, Trites J, et al: Radiotherapy for T1 and T2 laryngeal cancer: The Dalhousie University experience. J Otolaryngol Head Neck Surg 38: 434-439, 2009

66. Harada A, Sasaki R, Miyawaki D, et al: Treatment outcomes of the patients with early glottic cancer treated with initial radiotherapy and salvaged by conservative surgery. Jpn J Clin Oncol 45: 248-255, 2015

67. Hartl DM, de Monès E, Hans S, et al: Treatment of early-stage glottic cancer by transoral laser resection. Ann Otol Rhinol Laryngol 116:832-836, 2007

68. Haugen H, Johansson KA, Ejnell H, et al: Accelerated radiotherapy for advanced laryngeal cancer. Acta Oncol 44:481-489, 2005

69. Hinerman RW, Mendenhall WM, Morris CG, et al: T3 and T4 true vocal cord squamous carcinomas treated with external beam irradiation: A single institution's 35-year experience. Am J Clin Oncol 30: 181-185, 2007

70. Hirasawa N, Itoh Y, Ishihara S, et al: Radiotherapy with or without chemotherapy for patients with T1-T2 glottic carcinoma: Retrospective analysis. Head Neck Oncol 2:20, 2010

71. Holsinger FC, Funk E, Roberts DB, et al: Conservation laryngeal surgery versus total laryngectomy for radiation failure in laryngeal cancer. Head Neck 28: 779-784, 2006

72. Hou WH, Daly ME, Lee NY, et al: Racial disparities in the use of voice preservation therapy for locally advanced laryngeal cancer. Arch Otolaryngol Head Neck Surg 138:644-649, 2012

73. Ijichi K, Hanai N, Kawakita D, et al: Selection of therapeutic treatment with alternating chemoradiotherapy for larynx preservation in laryngeal carcinoma patients. Jpn J Clin Oncol 44:1063-1069, 2014

74. Jacobi I, van der Molen L, Huiskens H, et al: Voice and speech outcomes of chemoradiation for advanced head and neck cancer: A systematic review. Eur Arch Otorhinolaryngol 267:1495-1505, 2010

75. Janssens GO, Rademakers SE, Terhaard CH, et al: Accelerated radiotherapy with carbogen and nicotinamide for laryngeal cancer: Results of a phase III randomized trial. J Clin Oncol 30:1777-1783, 2012

76. Karatzanis AD, Psychogios G, Zenk J, et al: Comparison among different available surgical approaches in T1 glottic cancer. Laryngoscope 119: 1704-1708, 2009

77. Karlsson T, Johansson M, Andréll P, et al: Effects of voice rehabilitation on health-related quality of life, communication and voice in laryngeal cancer patients treated with radiotherapy: A randomised controlled trial. Acta Oncol 54: 1017-1024, 2015

78. Kasper C, Schuster M, Psychogios G, et al: Voice Handicap Index and voice-related quality of life in small laryngeal carcinoma. Eur Arch Otorhinolaryngol 268:401-404, 2011

79. Kennedy JT, Paddle PM, Cook BJ, et al: Voice outcomes following transoral laser microsurgery for early glottic squamous cell carcinoma. J Laryngol Otol 121:1184-1188, 2007

80. Kerr P, Mark Taylor S, Rigby M, et al: Oncologic and voice outcomes after treatment of early glottic cancer: Transoral laser microsurgery versus radiotherapy. J Otolaryngol Head Neck Surg 41: 381-388, 2012

81. Killguss H, Gottwald F, Haderlein T, et al: Voice handicap and health-related quality of life after treatment for small laryngeal carcinoma. Folia Phoniatr Logop 63:122-128, 2011

82. Koss SL, Russell MD, Leem TH, et al: Occult nodal disease in patients with failed laryngeal preservation undergoing surgical salvage. Laryngoscope 124:421-428, 2014

83. Kujath M, Kerr P, Myers C, et al: Functional outcomes and laryngectomy-free survival after transoral CO_2 laser microsurgery for stage 1 and 2 glottic carcinoma. J Otolaryngol Head Neck Surg 40: S49-S58, 2011 (suppl 1)

84. Laoufi S, Mirghani H, Janot F, et al: Voice quality after treatment of T1a glottic cancer. Laryngoscope 124:1398-1401, 2014

85. Ledda GP, Grover N, Pundir V, et al: Functional outcomes after CO2 laser treatment of early glottic carcinoma. Laryngoscope 116:1007-1011, 2006

86. Ledda GP, Puxeddu R: Carbon dioxide laser microsurgery for early glottic carcinoma. Otolaryngol Head Neck Surg 134:911-915, 2006

87. Lee HS, Chun BG, Kim SW, et al: Transoral laser microsurgery for early glottic cancer as one-stage single-modality therapy. Laryngoscope 123: 2670-2674, 2013

88. Lee WT, Yoo DS, Puscas L, et al: Treatment-induced changes in vocal cord mobility and subsequent local recurrence after organ preservation therapy for laryngeal carcinoma. Head Neck 34: 792-796, 2012

89. Lefebvre JL, Pointreau Y, Rolland F, et al: Induction chemotherapy followed by either chemoradiotherapy or bioradiotherapy for larynx preservation: The TREMPLIN randomized phase II study. J Clin Oncol 31:853-859, 2013

90. Lefebvre JL, Rolland F, Tesselaar M, et al: Phase 3 randomized trial on larynx preservation comparing sequential vs alternating chemotherapy and radiotherapy. J Natl Cancer Inst 101:142-152, 2009

91. Lei WB, Jiang AY, Chai LP, et al: Middle frontal horizontal partial laryngectomy (MFHPL): A treatment for stage T1b squamous cell carcinoma of the glottic larynx involving anterior vocal commissure. PLoS One 8:e52723, 2013

92. Lester SE, Rigby MH, Taylor SM: Transoral laser microsurgery outcomes with early glottic cancer: The Dalhousie University experience. J Laryngol Otol 125:509-512, 2011

93. Lucioni M, Bertolin A, Rizzotto G, et al: CO(2) laser surgery in elderly patients with glottic carcinoma: Univariate and multivariate analyses of results. Head Neck 34:1804-1809, 2012

94. Luo XN, Chen LS, Zhang SY, et al: Effectiveness of chemotherapy and radiotherapy for laryngeal preservation in advanced laryngeal cancer: A meta-analysis and systematic review. Radiol Med (Torino) 120:1153-1169, 2015

95. Mahler V, Boysen M, Brøndbo K: Radiotherapy or CO(2) laser surgery as treatment of T(1a) glottic carcinoma? Eur Arch Otorhinolaryngol 267:743-750, 2010

96. Majem M, Mesia R, Mañós M, et al: Does induction chemotherapy still have a role in larynx preservation strategies? The experience of Institut Catala d'Oncologia in stage III larynx carcinoma. Laryngoscope 116:1651-1656, 2006

97. Marcotullio D, de Vincentiis M, Iannella G, et al: Surgical treatment of T1b glottic tumor, 10-years follow-up. Eur Rev Med Pharmacol Sci 18: 1212-1217, 2014

98. McCoul ED, Har-El G: Meta-analysis of impaired vocal cord mobility as a prognostic factor in T2 glottic carcinoma. Arch Otolaryngol Head Neck Surg 135:479-486, 2009

99. Milovanovic J, Jotic A, Djukic V, et al: Oncological and functional outcome after surgical treatment

of early glottic carcinoma without anterior commissure involvement. BioMed Res Int 2014:464781, 2014

100. Misono S, Marmor S, Yueh B, et al: Treatment and survival in 10,429 patients with localized laryngeal cancer: A population-based analysis. Cancer 120: 1810-1817, 2014

101. Misono S, Marmor S, Yueh B, et al: T1 glottic carcinoma: Do comorbidities, facility characteristics, and sociodemographics explain survival differences across treatment? Otolaryngol Head Neck Surg 152: 856-862, 2015

102. van der Molen L, van Rossum MA, Jacobi I, et al: Pre- and posttreatment voice and speech outcomes in patients with advanced head and neck cancer treated with chemoradiotherapy: Expert listeners' and patient's perception. J Voice 26:664. e25-664.e33, 2012

103. Mucha-Małecka A, Składowski K: High-dose radiotherapy alone for patients with T4-stage laryngeal cancer. Strahlenther Onkol 189:632-638, 2013

104. O'Neill CB, O'Neill JP, Atoria CL, et al: Treatment complications and survival in advanced laryngeal cancer: A population-based analysis. Laryngoscope 124:2707-2713, 2014

105. Niibe Y, Nakayama M, Matsubayashi T, et al: Effectiveness of concurrent radiation therapy with UFT or TS-1 for T2N0 glottic cancer in Japan. Anticancer Res 27(5B):3497-3500, 2007

106. Nomiya T, Nemoto K, Wada H, et al: Long-term results of radiotherapy for T1a and T1bN0M0 glottic carcinoma. Laryngoscope 118:1417-1421, 2008

107. Oridate N, Homma A, Suzuki S, et al: Voice-related quality of life after treatment of laryngeal cancer. Arch Otolaryngol Head Neck Surg 135:363-368, 2009

108. Peretti G, Piazza C, Ansarin M, et al: Transoral CO2 laser microsurgery for Tis-T3 supraglottic squamous cell carcinomas. Eur Arch Otorhinolaryngol 267:1735-1742, 2010

109. Peretti G, Piazza C, Del Bon F, et al: Function preservation using transoral laser surgery for T2-T3 glottic cancer: Oncologic, vocal, and swallowing outcomes. Eur Arch Otorhinolaryngol 270:2275-2281, 2013

110. Pointreau Y, Garaud P, Chapet S, et al: Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. J Natl Cancer Inst 101:498-506, 2009

111. Posner MR, Norris CM, Wirth LJ, et al: Sequential therapy for the locally advanced larynx and hypopharynx cancer subgroup in TAX 324: Survival, surgery, and organ preservation. Ann Oncol 20: 921-927, 2009

112. Potenza I, Franco P, Moretto F, et al: Exclusive radiotherapy for early-stage glottic cancer: A single-institution retrospective analysis with a focus on voice quality. Anticancer Res 35:4155-4160, 2015

113. Preuss SF, Cramer K, Klussmann JP, et al: Transoral laser surgery for laryngeal cancer: Outcome, complications and prognostic factors in 275 patients. Eur J Surg Oncol 35:235-240, 2009

114. Qian W, Zhu G, Wang Y, et al: Multi-modality management for loco-regionally advanced laryngeal and hypopharyngeal cancer: Balancing the benefit of efficacy and functional preservation. Med Oncol 31: 178, 2014

115. Remmelts AJ, Hoebers FJ, Klop WM, et al: Evaluation of lasersurgery and radiotherapy as treatment modalities in early stage laryngeal carcinoma: Tumour outcome and quality of voice. Eur Arch Otorhinolaryngol 270:2079-2087, 2013

116. Rodriguez CP, Adelstein DJ, Rybicki LA, et al: Clinical predictors of larynx preservation after multiagent concurrent chemoradiotherapy. Head Neck 30:1535-1542, 2008

117. Roh JL, Kim DH, Kim SY, et al: Quality of life and voice in patients after laser cordectomy for TIS and T1 glottic carcinomas. Head Neck 29:1010-1016, 2007

118. Rosenthal DI, Mohamed AS, Weber RS, et al: Long-term outcomes after surgical or nonsurgical initial therapy for patients with T4 squamous cell carcinoma of the larynx: A 3-decade survey. Cancer 121:1608-1619, 2015

119. Schindler A, Mozzanica F, Ginocchio D, et al: Voice-related quality of life in patients after total and partial laryngectomy. Auris Nasus Larynx 39:77-83, 2012

120. Sessions DG, Lenox J, Spector GJ: Supraglottic laryngeal cancer: Analysis of treatment results. Laryngoscope 115:1402-1410, 2005

121. Sherman EJ, Fisher SG, Kraus DH, et al: TALK score: Development and validation of a prognostic model for predicting larynx preservation outcome. Laryngoscope 122:1043-1050, 2012

122. Shin JY, Truong MT: Racial disparities in laryngeal cancer treatment and outcome: A population-based analysis of 24,069 patients. Laryngoscope 125:1667-1674, 2015

123. Sigston E, de Mones E, Babin E, et al: Early-stage glottic cancer: Oncological results and margins in laser cordectomy. Arch Otolaryngol Head Neck Surg 132:147-52, 2006

124. Smee RI, De-loyde KJ, Broadley K, et al: Prognostic factors for supraglottic laryngeal carcinoma: Importance of the unfit patient. Head Neck 35: 949-958, 2013

125. Stanković M, Milisavljević D, Stojanov D, et al: Influential factors, complications and survival rate of primary and salvage total laryngectomy for advanced laryngeal cancer. Coll Antropol 36:7-12, 2012 (suppl 2)

126. Stenson KM, Maccracken E, Kunnavakkam R, et al: Chemoradiation for patients with large-volume laryngeal cancers. Head Neck 34:1162-1167, 2012

127. Szuecs M, Kuhnt T, Punke C, et al: Subjective voice quality, communicative ability and swallowing after definitive radio(chemo)therapy, laryngectomy plus radio(chemo)therapy, or organ conservation surgery plus radio(chemo)therapy for laryngeal and hypopharyngeal cancer. J Radiat Res (Tokyo) 56:159-168, 2015

128. Taylor SM, Kerr P, Fung K, et al: Treatment of T1b glottic SCC: Laser vs. radiation—a Canadian multicenter study. J Otolaryngol Head Neck Surg 42:22, 2013

129. Thurnher D, Erovic BM, Frommlet F, et al: Challenging a dogma—surgery yields superior long-term results for T1a squamous cell carcinoma of the glottic larynx compared to radiotherapy. Eur J Surg Oncol 34:692-698, 2008

130. Timme DW, Jonnalagadda S, Patel R, et al: Treatment selection for T3/T4a laryngeal cancer: Chemoradiation versus primary surgery. Ann Otol Rhinol Laryngol 124:845-851, 2015

131. To K, Qureishi A, Mortimore S, et al: The role of primary transoral laser microsurgery in laryngeal cancer: A retrospective study. Clin Otolaryngol 40: 449-455, 2015

132. Tuna B, Katilmiş H, Oztürkcan S, et al: Outcome of conservation surgery for laryngeal carcinoma: An 8-year trial. Eur Arch Otorhinolaryngol 266: 1681-1686, 2009

133. Tuomi L, Andréll P, Finizia C: Effects of voice rehabilitation after radiation therapy for laryngeal cancer: A randomized controlled study. Int J Radiat Oncol Biol Phys 89:964-972, 2014

134. Urba S, Wolf G, Eisbruch A, et al: Single-cycle induction chemotherapy selects patients with advanced laryngeal cancer for combined chemoradiation: A new treatment paradigm. J Clin Oncol 24:593-598, 2006

135. Vilaseca I, Ballesteros F, Martínez-Vidal BM, et al: Quality of life after transoral laser microresection of laryngeal cancer: A longitudinal study. J Surg Oncol 108:52-56, 2013

136. Vilaseca I, Bernal-Sprekelsen M, Him R, et al: Prognostic factors of quality of life after transoral laser microsurgery for laryngeal cancer. Eur Arch Otorhinolaryngol 272:1203-1210, 2015

137. Wilkie MD, Lightbody KA, Lythgoe D, et al: Transoral laser microsurgery for early and moderately advanced laryngeal cancers: Outcomes from a single centralised United Kingdom centre. Eur Arch Otorhinolaryngol 272:695-704, 2015

138. Yoo J, Lacchetti C, Hammond JA, et al: Role of endolaryngeal surgery (with or without laser) versus radiotherapy in the management of early (T1) glottic cancer: A systematic review. Head Neck 36: 1807-1819, 2014

139. Zhang H, Travis LB, Chen R, et al: Impact of radiotherapy on laryngeal cancer survival: A population-based study of 13,808 US patients. Cancer 118:1276-1287, 2012

140. Zhang SY, Lu ZM, Luo XN, et al: Retrospective analysis of prognostic factors in 205 patients with laryngeal squamous cell carcinoma who underwent surgical treatment. PLoS One 8:e60157, 2013

141. Zumsteg ZS, Riaz N, Jaffery S, et al: Carotid sparing intensity-modulated radiation therapy achieves comparable locoregional control to conventional radiotherapy in T1-2N0 laryngeal carcinoma. Oral Oncol 51:716-723, 2015

142. Vengalil S, Giuliani ME, Huang SH, et al: Clinical outcomes in patients with T4 laryngeal cancer treated with primary radiotherapy versus primary laryngectomy. Head Neck 38:E2035-E2040, 2016 (suppl 1)

143. Fuller CD, Mohamed AS, Garden AS, et al: Long-term outcomes after multidisciplinary management of T3 laryngeal squamous cell carcinomas: Improved functional outcomes and survival with modern therapeutic approaches. Head Neck 38:1739-1751, 2016

144. Lefebvre JL, Andry G, Chevalier D, et al: Laryngeal preservation with induction chemotherapy for hypopharyngeal squamous cell carcinoma: 10-year results of EORTC trial 24891. Ann Oncol 23: 2708-2714, 2012

145. Janoray G, Pointreau Y, Garaud P, et al: Long-term results of a multicenter randomized phase III trial of induction chemotherapy with cisplatin, 5-fluorouracil, ± docetaxel for larynx preservation. J Natl Cancer Inst 108: 108, 2015

146. Henriques De Figueiredo B, Fortpied C, Menis J, et al: Long-term update of the 24954 EORTC phase III trial on larynx preservation. Eur J Cancer 65:109-112, 2016

147. Ward MC, Adelstein DJ, Bhateja P, et al: Severe late dysphagia and cause of death after concurrent chemoradiation for larynx cancer in patients eligible for RTOG 91-11. Oral Oncol 57:21-26, 2016

148. Bonner J, Giralt J, Harari P, et al: Cetuximab and radiotherapy in laryngeal preservation for cancers of the larynx and hypopharynx: A secondary analysis of a randomized clinical trial. JAMA Otolaryngol Head Neck Surg 142:842-849, 2016

149. Wolf GT, Bellile E, Eisbruch A, et al: Survival rates using individualized bioselection treatment methods in patients with advanced laryngeal cancer. JAMA Otolaryngol Head Neck Surg 143:355-366, 2017

150. Mehanna H, Wong WL, McConkey CC, et al: PET-CT surveillance versus neck dissection in advanced

head and neck cancer. N Engl J Med 374:1444-1454, 2016

151. Porceddu SV, Pryor DI, Burmeister E, et al: Results of a prospective study of positron emission tomography-directed management of residual nodal abnormalities in node-positive head and neck cancer after definitive radiotherapy with or without systemic therapy. Head Neck 33:1675-1682, 2011

152. Isles MG, McConkey C, Mehanna HM: A systematic review and meta-analysis of the role of positron emission tomography in the follow up of head and neck squamous cell carcinoma following radiotherapy or chemoradiotherapy. Clin Otolaryngol 33:210-222, 2008

153. Gupta T, Master Z, Kannan S, et al: Diagnostic performance of post-treatment FDG PET or FDG PET/CT imaging in head and neck cancer: A systematic review and meta-analysis. Eur J Nucl Med Mol Imaging 38:2083-2095, 2011

154. Argiris A, Stenson KM, Brockstein BE, et al: Neck dissection in the combined-modality therapy of patients with locoregionally advanced head and neck cancer. Head Neck 26:447-455, 2004

155. Hinerman RW, Mendenhall WM, Amdur RJ, et al: Carcinoma of the supraglottic larynx: Treatment results with radiotherapy alone or with planned neck dissection. Head Neck 24:456-467, 2002

156. Iro H, Waldfahrer F, Altendorf-Hofmann A, et al: Transoral laser surgery of supraglottic cancer: Follow-up of 141 patients. Arch Otolaryngol Head Neck Surg 124:1245-1250, 1998

157. Kim RY, Marks ME, Salter MM: Early-stage glottic cancer: Importance of dose fractionation in radiation therapy. Radiology 182:273-275, 1992

158. Eckel HE: Endoscopic laser resection of supraglottic carcinoma. Otolaryngol Head Neck Surg 117:681-687, 1997

159. Yu E, Shenouda G, Beaudet MP, et al: Impact of radiation therapy fraction size on local control of early glottic carcinoma. Int J Radiat Oncol Biol Phys 37:587-591, 1997

160. Fu KK, Pajak TF, Trotti A, et al: A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: First report of RTOG 9003. Int J Radiat Oncol Biol Phys 48:7-16, 2000

161. Forastiere AA, Goepfert H, Maor M, et al: Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 349:2091-2098, 2003

162. Wolf GT, Fisher SG, Hong WK, et al: Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N Engl J Med 324:1685-1690, 1991

163. Brizel DM, Albers ME, Fisher SR, et al: Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. N Engl J Med 338:1798-1804, 1998

164. Dinshaw KA, Sharma V: Radiation therapy in early glottic carcinoma: Significance of prognostic factors and dose fractionation. Indian J Cancer 27:143-153, 1990

165. Eckel HE, Thumfart WF: Laser surgery for the treatment of larynx carcinomas: Indications, techniques, and preliminary results. Ann Otol Rhinol Laryngol 101:113-118, 1992

166. Le QT, Fu KK, Kroll S, et al: Influence of fraction size, total dose, and overall time on local control of T1-T2 glottic carcinoma. Int J Radiat Oncol Biol Phys 39:115-126, 1997

167. Lee NK, Goepfert H, Wendt CD: Supraglottic laryngectomy for intermediate-stage cancer: U.T. M.D. Anderson Cancer Center experience with combined therapy. Laryngoscope 100:831-836, 1990

168. McLaughlin MP, Parsons JT, Fein DA, et al: Salvage surgery after radiotherapy failure in T1-T2 squamous cell carcinoma of the glottic larynx. Head Neck 18:229-235, 1996

169. Hinni ML, Salassa JR, Grant DG, et al: Transoral laser microsurgery for advanced laryngeal cancer. Arch Otolaryngol Head Neck Surg 133:1198-1204, 2007

170. Agrawal A, Moon J, Davis RK, et al: Transoral carbon dioxide laser supraglottic laryngectomy and irradiation in stage I, II, and III squamous cell carcinoma of the supraglottic larynx: Report of Southwest Oncology Group Phase 2 Trial S9709. Arch Otolaryngol Head Neck Surg 133:1044-1050, 2007

171. Davis RK, Kriskovich MD, Galloway EB III, et al: Endoscopic supraglottic laryngectomy with postoperative irradiation. Ann Otol Rhinol Laryngol 113:132-138, 2004

172. Sperry SM, Rassekh CH, Laccourreye O, et al: Supracricoid partial laryngectomy for primary and recurrent laryngeal cancer. JAMA Otolaryngol Head Neck Surg 139:1226-1235, 2013

173. Dufour X, Hans S, De Mones E, et al: Local control after supracricoid partial laryngectomy for "advanced" endolaryngeal squamous cell carcinoma classified as T3. Arch Otolaryngol Head Neck Surg 130:1092-1099, 2004

174. Vermorken JB, Remenar E, van Herpen C, et al: Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 357:1695-1704, 2007

175. Posner MR, Hershock DM, Blajman CR, et al: Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 357:1705-1715, 2007

176. Hitt R, López-Pousa A, Martínez-Trufero J, et al: Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. J Clin Oncol 23:8636-8645, 2005

177. Pignon JP, le Maître A, Maillard E, et al: Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother Oncol 92:4-14, 2009

178. Bonner JA, Harari PM, Giralt J, et al: Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 354:567-578, 2006

179. Brazilian Head and Neck Cancer Study Group: End results of a prospective trial on elective lateral neck dissection vs type III modified radical neck dissection in the management of supraglottic and transglottic carcinomas. Head Neck 21:694-702, 1999

180. Mendenhall WM, Parsons JT, Stringer SP, et al: Squamous cell carcinoma of the head and neck treated with irradiation: Management of the neck. Semin Radiat Oncol 2:163-170, 1992

181. Mendenhall WM, Villaret DB, Amdur RJ, et al: Planned neck dissection after definitive radiotherapy for squamous cell carcinoma of the head and neck. Head Neck 24:1012-1018, 2002

182. Weber PC, Johnson JT, Myers EN: The impact of bilateral neck dissection on pattern of recurrence and survival in supraglottic carcinoma. Arch Otolaryngol Head Neck Surg 120:703-706, 1994

183. Cooper JS, Pajak TF, Forastiere AA, et al: Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med 350:1937-1944, 2004

184. Timmermans AJ, Lange CA, de Bois JA, et al: Tumor volume as a prognostic factor for local control and overall survival in advanced larynx cancer. Laryngoscope 126:E60-E67, 2016

185. Issa MR, Samuels SE, Bellile E, et al: Tumor volumes and prognosis in laryngeal cancer. Cancers (Basel) 7:2236-2261, 2015

186. Weinstein GS, El-Sawy MM, Ruiz C, et al: Laryngeal preservation with supracricoid partial laryngectomy results in improved quality of life when compared with total laryngectomy. Laryngoscope 111:191-199, 2001

187. Weber RS, Berkey BA, Forastiere A, et al: Outcome of salvage total laryngectomy following organ preservation therapy: The Radiation Therapy Oncology Group trial 91-11. Arch Otolaryngol Head Neck Surg 129:44-49, 2003

188. Eisbruch A, Schwartz M, Rasch C, et al: Dysphagia and aspiration after chemoradiotherapy for head-and-neck cancer: Which anatomic structures are affected and can they be spared by IMRT? Int J Radiat Oncol Biol Phys 60:1425-1439, 2004

189. Spaulding MB, Fischer SG, Wolf GT: Tumor response, toxicity, and survival after neoadjuvant organ-preserving chemotherapy for advanced laryngeal carcinoma. J Clin Oncol 12:1592-1599, 1994

190. Truelson JM, Fisher SG, Beals TE, et al: DNA content and histologic growth pattern correlate with prognosis in patients with advanced squamous cell carcinoma of the larynx. Cancer 70:56-62, 1992

191. Gillespie MB, Brodsky MB, Day TA, et al: Swallowing-related quality of life after head and neck cancer treatment. Laryngoscope 114:1362-1367, 2004

192. Terrell JE, Ronis DL, Fowler KE, et al: Clinical predictors of quality of life in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 130:401-408, 2004

193. Eisbruch A, Lyden T, Bradford CR, et al: Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys 53:23-28, 2002

194. Nguyen NP, Moltz CC, Frank C, et al: Dysphagia following chemoradiation for locally advanced head and neck cancer. Ann Oncol 15:383-388, 2004

195. Smith RV, Kotz T, Beitler JJ, et al: Long-term swallowing problems after organ preservation therapy with concomitant radiation therapy and intravenous hydroxyurea: Initial results. Arch Otolaryngol Head Neck Surg 126:384-389, 2000

196. Strojan P, Haigentz M Jr, Bradford CR, et al: Chemoradiotherapy vs. total laryngectomy for primary treatment of advanced laryngeal squamous cell carcinoma. Oral Oncol 49:283-286, 2013

197. Osborn HA, Hu A, Venkatesan V, et al: Comparison of endoscopic laser resection versus radiation therapy for the treatment of early glottic carcinoma. J Otolaryngol Head Neck Surg 40:200-204, 2011

198. Benninger MS, Gillen J, Thieme P, et al: Factors associated with recurrence and voice quality following radiation therapy for T1 and T2 glottic carcinomas. Laryngoscope 104:294-298, 1994

199. Trotti A, Bellm LA, Epstein JB, et al: Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: A systematic literature review. Radiother Oncol 66:253-262, 2003

200. Nguyen NP, Sallah S, Karlsson U, et al: Combined chemotherapy and radiation therapy for head and neck malignancies: Quality of life issues. Cancer 94:1131-1141, 2002

201. Hutcheson KA, Barringer DA, Rosenthal DI, et al: Swallowing outcomes after radiotherapy for

laryngeal carcinoma. Arch Otolaryngol Head Neck Surg 134:178-183, 2008

202. Nguyen NP, Frank C, Moltz CC, et al: Aspiration rate following chemoradiation for head and neck cancer: An underreported occurrence. Radiother Oncol 80:302-306, 2006

203. Feng FY, Kim HM, Lyden TH, et al: Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: Early dose-effect relationships for the swallowing structures. Int J Radiat Oncol Biol Phys 68:1289-1298, 2007

204. Gillespie MB, Brodsky MB, Day TA, et al: Laryngeal penetration and aspiration during swallowing after the treatment of advanced oropharyngeal cancer. Arch Otolaryngol Head Neck Surg 131: 615-619, 2005

205. Rosenthal DI, Lewin JS, Eisbruch A: Prevention and treatment of dysphagia and aspiration after chemoradiation for head and neck cancer. J Clin Oncol 24:2636-2643, 2006

206. Carrara-de Angelis E, Feher O, Barros AP, et al: Voice and swallowing in patients enrolled in a larynx preservation trial. Arch Otolaryngol Head Neck Surg 129:733-738, 2003

207. Francis DO, Weymuller EA Jr, Parvathaneni U, et al: Dysphagia, stricture, and pneumonia in head and neck cancer patients: Does treatment modality matter? Ann Otol Rhinol Laryngol 119:391-397, 2010

208. Forastiere AA, Weber RS, Trotti A: Organ preservation for advanced larynx cancer: Issues and outcomes. J Clin Oncol 33:3262-3268, 2015

209. Xu B, Boero IJ, Hwang L, et al: Aspiration pneumonia after concurrent chemoradiotherapy for head and neck cancer. Cancer 121:1303-1311, 2015

210. Chen AM, Li BQ, Jennelle RL, et al: Late esophageal toxicity after radiation therapy for head and neck cancer. Head Neck 32:178-183, 2010

211. Nguyen NP, Frank C, Moltz CC, et al: Impact of dysphagia on quality of life after treatment of head-and-neck cancer. Int J Radiat Oncol Biol Phys 61: 772-778, 2005

212. Bhayani MK, Hutcheson KA, Barringer DA, et al: Gastrostomy tube placement in patients with oropharyngeal carcinoma treated with radiotherapy or chemoradiotherapy: Factors affecting placement and dependence. Head Neck 35:1634-1640, 2013

213. Hutcheson KA, Lewin JS: Functional outcomes after chemoradiotherapy of laryngeal and pharyngeal cancers. Curr Oncol Rep 14:158-165, 2012

214. Staton J, Robbins KT, Newman L, et al: Factors predictive of poor functional outcome after chemoradiation for advanced laryngeal cancer. Otolaryngol Head Neck Surg 127:43-47, 2002

215. Solares CA, Wood B, Rodriguez CP, et al: Does vocal cord fixation preclude nonsurgical management of laryngeal cancer? Laryngoscope 119: 1130-1134, 2009

216. Starmer H, Gourin C, Lua LL, et al: Pretreatment swallowing assessment in head and neck cancer patients. Laryngoscope 121:1208-1211, 2011

217. Hogikyan ND, Sethuraman G: Validation of an instrument to measure voice-related quality of life (V-RQOL). J Voice 13:557-569, 1999

218. Deary IJ, Wilson JA, Carding PN, et al: VoiSS: A patient-derived voice symptom scale. J Psychosom Res 54:483-489, 2003

219. Jacobson BH, Johnson A, Grywalski C, et al: The Voice Handicap Index (VHI) development and validation. Am J Speech Lang Pathol 6:66-70, 1997

220. Rosen CA, Lee AS, Osborne J, et al: Development and validation of the Voice Handicap Index-10. Laryngoscope 114:1549-1556, 2004

221. Kempster GB, Gerratt BR, Verdolini Abbott K, et al: Consensus auditory-perceptual evaluation of voice: Development of a standardized clinical protocol. Am J Speech Lang Pathol 18:124-132, 2009

222. Hirano M. Clinical Examination of Voice. New York, NY, Springer Verlag, 1981

223. Hunter KU, Lee OE, Lyden TH, et al: Aspiration pneumonia after chemo-intensity-modulated radiation therapy of oropharyngeal carcinoma and its clinical and dysphagia-related predictors. Head Neck 36:120-125, 2014

224. Rogus-Pulia NM, Pierce MC, Mittal BB, et al: Changes in swallowing physiology and patient perception of swallowing function following chemoradiation for head and neck cancer. Dysphagia 29:223-233, 2014

225. Logemann JA. Evaluation and Treatment of Swallowing Disorders (ed 2). Austin, TX, Pro-Ed, 1998

226. Langmore SE, Schatz K, Olsen N: Fiberoptic endoscopic examination of swallowing safety: A new procedure. Dysphagia 2:216-219, 1988

227. Martin-Harris B, Brodsky MB, Michel Y, et al: MBS measurement tool for swallow impairment—MBSImp: Establishing a standard. Dysphagia 23: 392-405, 2008

228. Hutcheson KA, Barrow MP, Barringer DA, et al: Dynamic Imaging Grade of Swallowing Toxicity (DIGEST): Scale development and validation. Cancer 123:62-70, 2017

229. List MA, Ritter-Sterr C, Lansky SB: A performance status scale for head and neck cancer patients. Cancer 66:564-569, 1990

230. Chen AY, Frankowski R, Bishop-Leone J, et al: The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: The M. D. Anderson dysphagia inventory. Arch Otolaryngol Head Neck Surg 127:870-876, 2001

231. Crary MA, Mann GD, Groher ME: Initial psychometric assessment of a functional oral intake scale for dysphagia in stroke patients. Arch Phys Med Rehabil 86:1516-1520, 2005

232. Eisbruch A, Kim HM, Feng FY, et al: Chemo-IMRT of oropharyngeal cancer aiming to reduce dysphagia: Swallowing organs late complication probabilities and dosimetric correlates. Int J Radiat Oncol Biol Phys 81:e93-e99, 2011

233. Lefebvre JL, Ang KK: Larynx preservation clinical trial design: Key issues and recommendations—a consensus panel summary. Head Neck 31:429-441, 2009

234. Hayakawa K, Mitsuhashi N, Akimoto T, et al: The effect of overall treatment time of radiation therapy on local control of T1-stage squamous cell carcinoma of the glottis. Laryngoscope 106:1545-1547, 1996

235. Piquet JJ, Chevalier D: Subtotal laryngectomy with crico-hyoido-epiglotto-pexy for the treatment of extended glottic carcinomas. Am J Surg 162: 357-361, 1991

236. Motta G, Esposito E, Cassiano B, et al: T1-T2-T3 glottic tumors: Fifteen years experience with CO2 laser. Acta Otolaryngol Suppl 527:155-159, 1997

237. Rudert HH, Werner JA: Endoscopic resections of glottic and supraglottic carcinomas with the CO2 laser. Eur Arch Otorhinolaryngol 252:146-148, 1995

238. Ferrell BR, Temel JS, Temin S, et al: Integration of palliative care into standard oncology care: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 35:96-112, 2017

239. Nekhlyudov L, Lacchetti C, Davis NB, et al: Head and neck cancer survivorship care guideline: American Society of Clinical Oncology clinical practice guideline endorsement of the American Cancer Society guideline. J Clin Oncol 35: 1606-1621, 2017

240. Hesketh PJ, Kris MG, Basch E, et al: Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 35: 3240-3261, 2017

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Table A1. Use of Larynx-Preservation Strategies in the Treatment of Laryngeal Cancer Expert Panel Membership

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Abbreviation: PGIN, Practice Guidelines Implementation Network.