Organ Preservation for Advanced Larynx Cancer: Issues and Outcomes

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A B S T R A C T

Purpose

To provide a review of the clinical data, controversies, and limitations that underpin current recommendations for approaches to larynx preservation for locally advanced larynx cancer requiring total laryngectomy.

Methods

The key findings from pivotal randomized controlled trials are discussed, including quality of life, late effects, and function assessments. Trials investigating taxane inclusion in induction chemotherapy and trials of epidermal growth factor receptor inhibition for radiosensitization are put into perspective for larynx cancer. Controversies in the management of T4 primaries and the opportunities for conservation laryngeal surgery are reviewed.

Results

There are data from clinical trials to support induction chemotherapy, followed by radiotherapy (preferred approach in Europe) and concomitant cisplatin plus radiotherapy (preferred in North America) for nonsurgical preservation of the larynx. Treatment intensification by a sequential approach of induction, followed by concomitant treatment, is investigational. Transoral laryngeal microsurgery and transoral robotic partial laryngectomy have application in selected patients.

Conclusion

The management of locally advanced larynx cancer is challenging and requires an experienced multidisciplinary team for initial evaluation, response assessment, and support during and after treatment to achieve optimal function, quality of life, and overall survival. Patient expectations, in addition to tumor extent, pretreatment laryngeal function, and coexisting chronic disease, are critical factors in selecting surgical or nonsurgical primary treatment.

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INTRODUCTION

Preservation of the larynx for locally advanced head and neck squamous cell cancer (HNSCC) by combining chemotherapy and radiation has more than a 30-year clinical trial history. The negative physical and psychosocial impact of a permanent tracheostomy and loss of natural voice are powerful drivers for patients to want and to choose a treatment that will preserve their larynx.¹ Hence, the availability of alternatives to performing a total laryngectomy represents an enormous achievement in head and neck oncology. This review focuses on the key findings and limitations of randomized controlled trials that underpin current treatment recommendations for larynx preservation (LP) in the management of advanced larynx cancer (T2N+, T3, and T4), patient selection factors for considering function-preserving surgical approaches, and issues surrounding the management of T4 disease. LP also pertains to cancers of the

hypopharynx; however, these cancers have a distinctly different biology. The overall prognosis is poor, with a high rate of metastases and poor ability to salvage late recurrence with surgery. In contrast to larynx cancer, larger target volumes and higher doses of radiation to pharyngeal constrictors increase the risk of pharyngeal dysfunction and gastrostomy tube dependence. Extrapolation of concomitant chemoradiotherapy (CCR) trial results from larynx cancer to the hypopharynx may not be appropriate because of these differences, and there is a paucity of data from adequately powered trials to inform management recommendations.

NONSURGICAL STRATEGIES FOR LP

By the mid-1980s, the cisplatin and infusional fluorouracil (PF) regimen administered before resection was established as highly effective, achieving response rates of 85% to 90% and complete response

rates of 35% to 55%.^{2,3} Half of clinical complete responses were pathologically confirmed, and response correlated with success of subsequent therapy.^{4,5} These findings suggested that chemotherapy could possibly serve as a substitute for functionally debilitating surgery and potentially improve survival.^{6,7}

During the succeeding decades, two general approaches have evolved for the treatment of locally advanced cancers that require total laryngectomy: induction chemotherapy (ICT) with taxane, cisplatin, and fluorouracil (TPF), followed by radiation therapy (RT), which is favored in Europe; and concomitant cisplatin and standard fractionation RT (CCR), which is favored in North America.⁸⁻¹⁴ The details of these phase III trials are shown in Table 1. More importantly, none has demonstrated a survival advantage compared with a control arm of either surgery or an integrated chemotherapy and radiation strategy that reserves surgery for salvage. Most trials used simple two-dimensional treatment plans and lateral opposed fields for RT, definitions for the end point of LP differed, and reporting of late effects and function outcomes varied.

VETERANS' ADMINISTRATION LARYNGEAL CANCER STUDY GROUP AND INTERGROUP RTOG 91-11

The landmark Veterans' Administration Laryngeal Cancer Study Group (VALCSG) trial established the feasibility of LP without jeopardizing survival.¹²

Induction PF, followed by RT (in chemotherapy responders), was directly compared with total laryngectomy. The trial tested the concept that a favorable response to ICT, leaving no gross disease or small-volume tumor, would facilitate tumor eradication by RT and allow preservation of a functioning larynx. In addition, an impact of chemotherapy on metastases¹⁵ could improve overall survival. Early salvage laryngectomy of poor responders after two cycles of PF and those with persistent tumor after completion of RT was integral to the design. This mandated a multidisciplinary team led by a surgeon for evaluation of response during treatment, follow-up monitoring, and assessments of speech and swallowing.^{16,17}

After 10 years, there was no significant difference in overall survival.¹⁸ LP was proved feasible and expressed as the crude rate of surviving patients who were randomly assigned to induction PF and had retained their larynx. This was 62% at 3 years.

Other key findings included the pattern of failure that revealed more local recurrences for the ICT group but a significantly lower rate of metastases. The control rates for T3 cancers (65% of enrolled patients) were similar to historic published results with radiation alone^{19,20} and were a basis for criticism by radiation oncologists who argued that a comparator radiation-alone arm was needed. Other published data informed the design, eligibility criteria, and management of the neck in subsequent trials.²¹⁻²³

Table 1. Randomized Larynx Preservation Trial Designs and Outcomes

Study	No. of Patients (accrual period)	Site	Stage	Treatment	Response of Primary to Induction Chemotherapy	Larynx Preservation	Overall Survival
VALCSG Phase III ¹²	332 (1985-1988)	Larynx SG (63%) G (37%)	III (57%) ^a IV (43%)	a) TL → RT b) PF × 3 → RT ^b	NA 85% CR + PR	NA 3-year, 62% ^c Composite end point	3-year, 5-year a) 56%, 45% b) 53%, 42%
RTOG 91-11 Phase III ^{13,14}	547 (1992-2000)	Larynx SG (69%) G (31%)	III (64%) ^a IV (36%) ^e	a) PF × 3 → RT ^b b) RT + P c) RT	85% CR + PR NA NA	5-year, 10-year a) 71%, 68% b) 84%, 82% ^f c) 66%, 64%	5-year, 10-year ^d a) 58%, 39% b) 55%, 28% c) 54%, 32%
EORTC 24954-22950 Phase III ¹⁰	450 (1996-2004)	Larynx (48%) Hypopharynx (52%)	II (4%) III (39%) IV (58%)	a) PF × 4 → RT (70 Gy) ^b b) PF alternating/RT (60 Gy)	89% CR + PR NA	3-year ^g a) 40% b) 45% Composite end point	3-year a) 62.2% b) 64.8%
GORTEC 2000-01 Phase III ¹¹	213 (2000-2005)	Larynx (46%) Hypopharynx (54%)	III, IV	a) PF × 3 → RT ^h b) TPF × 3 → RT ^h	59.2% CR + PR 80% CR + PR (<i>P</i> = .002)	3-year a) 57.5% b) 70.3% (<i>P</i> = .03)	3-year a) 60% b) 60%
EORTC 24891 Phase III ^{8,9}	202 (1986-1993)	Hypopharynx	II (7%) III (57%) IV (37%) ^k	a) TLP → RT b) PF × 3 → RT ⁱ	NA 54% CR	3-year, 10-year ⁱ a) NA b) 42%, 27% Composite end point	3-year, 10-year a) 43%, 14% b) 57%, 13%

Abbreviations: CR, complete response; EORTC, European Organisation for Research and Treatment of Cancer; G, glottic; GORTEC, Groupe Oncologie Radiothérapie de la Tête et du Cou; NA, not applicable; P, cisplatin; PF, cisplatin plus fluorouracil; PR, partial response; RT, radiation therapy; RTOG, Radiation Therapy Oncology Group; SG, supraglottic; TL, total laryngectomy; TLP, total laryngectomy with partial pharyngectomy; TPF, docetaxel plus cisplatin plus fluorouracil; VALCSG, Veterans' Administration Laryngeal Cancer Study Group.

^aT1N1 excluded.

^bAt least a partial response of the primary and no progression in nodes after cycle 2 required to proceed with RT.

^cLarynx preservation reported as crude rate of the No. of patients with a preserved larynx among survivors.

^dDifferences are not statistically significant.

^eT4 with tumor penetrating through cartilage or > 1 cm into base of tongue excluded.

^fDifference statistically significant compared with arms a and b.

^gLarynx preservation reported as a composite end point: survival with larynx and no g-tube or tracheotomy for > 3 months.

^hAt least partial response and normal cord mobility after cycle 3 required to proceed with RT.

ⁱLarynx preservation reported as a composite end point: disease-specific survival with larynx and no g-tube or tracheotomy.

^jClinical CR of the primary and no progression in nodes required to proceed with RT.

^kBilateral neck nodes N2c excluded.

Those results propelled the Intergroup RTOG 91-11 trial that separately compared concomitant cisplatin (100 mg/m² on days 1, 22, and 43) plus RT and RT alone with the induction PF approach.¹³ T4 cancers that penetrated through cartilage or extended more than 1 cm into the base of the tongue were excluded.

Intergroup RTOG 91-11 established a new standard for LP by demonstrating the superiority of concomitant cisplatin plus RT for achieving local control and LP (Table 1). The primary end point used for sample size calculation was the composite end point, laryngectomy-free survival (laryngectomy or death as events). However, because this end point does not account for patients dying from non–cancer-related causes with a retained larynx, for clarity, all end points were separately reported.

After a median follow-up period exceeding 10 years, there was no significant difference in overall survival.¹⁴ LP and local control rates were significantly higher with concomitant cisplatin and RT: –42% relative risk reduction (hazard ratio [HR], 0.58; 95% CI, 0.37 to 0.89; *P* = .005) for undergoing laryngectomy compared with induction PF, and 54% risk reduction (HR, 0.46; 95% CI, 0.30 to 0.71; *P* < .001) compared with RT alone. By contrast, there was no advantage to adding ICT to RT. These results are consistent with the VALCSG and Groupe Oncologie Radiotherapie de la Tête et du Cou (GORTEC) trials, which have not shown an improvement in local control with ICT as an organ preservation strategy.¹¹

Although there was no significant difference in overall survival, the survival curves did separate after 4.5 years, favoring ICT.¹⁴ Also, the composite end point of laryngectomy-free survival for the comparison of induction versus RT changed from nonsignificant to significant (10 years, –28.9% v 17.2%; *P* = .02). The explanation for both lies with the CCR group that had the lowest rate of deaths from larynx cancer but also had the highest rate of non–cancer-related deaths. This outcome remains unexplained. It is possible that unrecognized or under-reported late toxicity affecting swallowing function could have contributed to some of the non–cancer-related deaths that emerged with long follow-up periods. This nonsignificant trend for better overall survival with ICT, despite inferior local control and LP, has fueled controversy among proponents of the two approaches. Whether late normal tissue toxicity (other than to the parotids) is reduced with modern conformal radiation delivery systems in use today remains to be established.²⁴

EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER TRIALS

The European Organisation for Research and Treatment of Cancer (EORTC) conducted two trials that established ICT as the evidence-based standard for hypopharynx cancer (Table 1).^{9,10} EORTC 24891 compared induction PF followed by RT with surgery (total laryngectomy, partial pharyngectomy, and neck dissection) in patients with cancer of the pyriform sinus. A long-term follow-up report confirmed the initial findings of equivalence of the two approaches for overall survival and pattern of failure.⁸

EORTC 24954-22950 compared a regimen of alternating PF and 2-week courses of RT with ICT and RT.²⁵ LP was conservatively defined as survival with a retained larynx without a tracheostomy or gastrostomy tube in place longer than 3 months. The results were identical to the induction PF group in the previous trial, and the alternating approach was not pursued.

TAXANES AND EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITION

The demonstration in locally advanced HNSCC mixed-site trials of a higher response rate to TPF compared with PF²⁶⁻²⁸ led investigators to postulate that induction TPF would improve the rates of LP and local control. This concept was tested by the GORTEC 2000-2001 trial, a phase III comparison of induction PF versus induction TPF enrolling patients with larynx and hypopharynx cancers (Table 1).¹¹ The results confirmed a significantly higher response rate with induction TPF (80% v 59%), thereby selecting more patients to undergo definitive RT, which translated to a significantly higher LP rate (3-year estimates, 70% v 57.5%). No other outcome was improved with TPF; the rates of local recurrence, late salvage surgery, metastases, and overall survival were the same in both groups. The small sample size precluded analysis by primary site. The results lend support for TPF in an induction (selection) organ preservation approach.

The US Food and Drug Administration approval of cetuximab in combination with RT was another milestone in the treatment of HNSCC.^{29,30} Building on the pivotal trial report of no added toxicity from cetuximab and the outcome of GORTEC 2000-2001, the TREMPLIN (Radiotherapy with Cisplatin versus Radiotherapy with Cetuximab after Induction Chemotherapy for Larynx Preservation) randomized phase II trial evaluated the feasibility of a sequential approach for LP.³¹ A total of 153 operable patients with larynx or hypopharynx cancer (T2-3 and N0-3) received three cycles of induction TPF. Responders would then be randomly assigned to either cetuximab or cisplatin concurrent with RT. The primary end point was LP 3 months after treatment, with an expected rate of 80%.

The TREMPLIN study did not meet the prespecified LP end point because of a high dropout rate (24%) before random assignment that was related to both substantial toxicity from TPF and insufficient tumor response. Also, cetuximab/RT proved as toxic as cisplatin/RT, causing the same rate of grade 3 to 4 acute mucositis but worse in-field skin toxicity. More local failures among patients treated with cetuximab raised the possibility that for larynx cancer, epidermal growth factor receptor inhibition/RT may be inferior to cisplatin/RT for achieving local control. This feasibility trial demonstrated that both cetuximab/RT and cisplatin/RT were difficult to administer after induction TPF. Moreover, the LP rate was no better than that observed with TPF, followed by RT alone in GORTEC 2000-2001.

Using response to ICT as a surrogate predictive biomarker for successful organ preservation, followed by RT plus cisplatin to maximize local control, is an appealing concept.^{32,33} However, the results of randomized controlled trials comparing sequential therapy with CCR in HNSCC have yet to demonstrate an advantage over CCR alone. Similarly, intensifying the treatment of larynx cancer by using sequential therapy is experimental.

QUALITY OF LIFE, LATE EFFECTS, AND FUNCTION ASSESSMENT

A range of tools and methods have been used for reporting quality of life (QOL), late effects, and function in trials of LP. Approximately 40% of patients with larynx cancer are dead by 5 years—approximately 50% of those patients die as a result of primary or secondary malignancy, approximately 25% die as a result of non–

Table 2. Late Effects and Function Assessments

Study	Site	Treatment Groups	Toxicity Scale	Late Effects	Function Assessment
VALCSG ^{12,16,17}	Larynx	a) TL → RT b) PF → RT	Not specified in report	Not reported	Voice quality and communication* Swallowing and eating related†
RTOG 91-11 ^{13,14}	Larynx	a) PF → RT b) RT + P c) RT	NCI-CTC and RTOG late toxicity scoring system	NSD in 10-year cumulative grade 3-5 late toxicity: 30.6% v 33.3% v 38%	Voice quality,† swallowing,† and QOL
EORTC 24954-22950 ¹⁰	Larynx Hypopharynx	a) PF → RT (70 Gy) b) PF alternating/RT (60 Gy)	Not specified in report	NSD in grade 3-4 mucosal: 35% v 34%; connective tissue: 41% v 35%	Measures not specified; % of patients with intelligible voice and normal intake reported
GORTEC 2000-01 ¹¹	Larynx Hypopharynx	a) PF → RT b) TPF → RT	NCI-CTC and RTOG late toxicity scoring system	Grade 3 to 4 subcutaneous tissue: 7% v 4%	Not reported
EORTC 24891 ^{8,9}	Hypopharynx	a) TLP → RT b) PF → RT	Not specified in report	Not reported	Not reported

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; GORTEC, Groupe Oncologie Radiotherapie de la Tête et du Cou; NCI-CTC, National Cancer Institute Common Toxicity Criteria; NSD, differences not statistically significant; P, cisplatin; PF, cisplatin plus fluorouracil; QOL, quality of life; RT, radiation therapy; RTOG, Radiation Therapy Oncology Group; TL, total laryngectomy; TLP, total laryngectomy with partial pharyngectomy; TPF, docetaxel plus cisplatin plus fluorouracil; VALCSG, Veterans' Administration Laryngeal Cancer Study Group.

*Objective measures.
†Questionnaire.

cancer-related causes, and 15% to 20% die as a result of unknown reasons.¹⁴ This diminishes the number of patients available for long-term effects analysis and reduces statistical power. QOL and function assessments were not performed in the GORTEC, TREMP-LIN, or EORTC 24891 trials.³¹

As shown in Table 2, in the VALCSG trial, communication, swallowing, and eating-related functions were obtained prospectively using descriptive methods.^{16,17} At 24 months, there was a significant difference in communication profiles and speech intelligibility between the surgery group and the larynx-preserved group, confirming that patients were better off with treatment that preserved their natural speech. By contrast, there were no significant differences in swallowing and eating-related functions on the basis of self-report. At baseline, 43% and 49% reported abnormal swallowing for the LP and surgery groups, respectively, decreasing to 24% and 32% at 24 months. Modification of diet texture, most frequently to a soft mechanical diet, was reported at 24 months in 13% and 24%, respectively; 2% and 4%, respectively, were able to swallow only liquids, and none reported using a gastrostomy tube.

Individuals with a preserved larynx also had better disease-specific QOL scores and general health status attributable to more freedom from pain, better emotional well-being, and lower levels of depression. Across seven general health status domains, scores of the larynx-preserved patients were similar to the US male population of comparable age, whereas surgery-treated patients had significantly lower general health status scores in all domains. QOL scores related to speech domains did not differ between those with and without a larynx. Nearly all of the long-term patients who underwent laryngectomy were communicating by means of an artificial larynx and presumably had adjusted their expectations.¹⁷

In the Intergroup RTOG 91-11 study, formal long-term QOL and function measures were collected using validated questionnaires (Functional Assessment of Cancer Therapy–Head and Neck Scale [HNS] version 2, University of Washington QOL instrument) in patients with a preserved larynx through 8 years of follow-up. No differences in swallowing function or diet alterations could be detected

among patients in the three treatment groups. Up to one quarter of patients reported diet alterations, but less than 4% were limited to liquids or could not swallow. Inability to swallow was reported in less than 3% of patients in all treatment groups. Similarly, no differences in speech or voice quality were found.¹⁴

Future trials should use formal grading of adverse events (National Cancer Institute–Common Terminology Criteria for Adverse Events [version 3]), as well as baseline assessments of function and patient-reported outcomes at follow-up: modified barium swallow, a patient-reported dysphagia tool (eg, MD Anderson Dysphagia Inventory), a patient-reported voice quality tool (eg, Voice Handicap Index), and a general QOL tool (eg, EORTC QOL Head and Neck 35).³⁴ Because of the need to cover the primary site and bilateral neck (levels II-IV) in most patients with advanced larynx cancer, advanced technology (eg, intensity-modulated RT) is not likely to significantly reduce toxicity.

OPPORTUNITIES FOR CONSERVATION LARYNGEAL SURGERY

The overarching goals of organ preservation laryngeal cancer surgery are to maximize survival and, whenever possible, preserve voice and swallowing function. End points for effective organ preservation surgery are similar to nonsurgical organ preservation: serviceable speech without a tracheostomy and oral nutrition without a gastrostomy tube. Surgical management has transitioned from open partial laryngectomy to transoral endoscopic laser resection, often referred to as transoral laryngeal microsurgery (TLM). Currently, open approaches (partial or total laryngectomy) are principally salvage procedures in patients with recurrence after primary therapy with radiation or chemoradiotherapy. One exception is open supracricoid partial laryngectomy that is used in some centers for primary treatment of T3 laryngeal cancers not deemed appropriate for transoral excision.³⁵ Weinstein et al³⁵ reported 5-year local control rates of 100% for T2 and 96% for T3 tumors for 96 patients, previously untreated or undergoing salvage supracricoid laryngectomy. For patients in whom

primary radiation treatment had failed, the 5-year laryngeal preservation rate was 89%. All but six patients were decannulated postoperatively, and 94% were able to swallow without a gastrostomy tube.

TLM compared with traditional open surgery is associated with lower morbidity because the surgery is performed from within the larynx, lessening injury to motor and sensory nerves and the supporting laryngeal framework. Oncologically effective endoscopic resection requires judgment, experience, a thorough knowledge of the endolaryngeal anatomy, and technical skill to accomplish tumor-free margins of resection.

TLM is optimally used as a single modality and, therefore, its primary role is in treatment of early disease that can be removed with an en bloc resection and a high rate of tumor-free margins. Administering radiation after surgery may delay or permanently impair swallowing recovery and will increase treatment morbidity.³⁶ This should be avoided through appropriate patient selection. When considering TLM for an individual patient, several factors must be considered. Is complete oncologic resection feasible through a transoral approach? Does the patient have the physiologic reserve to tolerate aspiration should it occur? Will surgery alone be adequate or will the patient require combined-modality therapy? What will be the expected voice outcome and what are the patient's expectations? T1 membranous vocal cord cancer and supraglottic tumors that do not involve the vocal cord or extend into the paraglottic space are amenable to TLM, with excellent vocal function. However, poorer voice quality can be expected for TLM excision of T1b cancers, those involving the arytenoid (T2) or extending into the paraglottic space (T3). Therefore, the patient whose voice quality is critical to his or her occupation or QOL may prefer a nonsurgical option.

When the tumor is large, visualization of both deep and surrounding structures is impaired and the tumor is removed piecemeal, increasing the potential for a positive margin and requirement for postsurgery RT. One third of patients with T1-4 lesions of the upper aerodigestive tract required revision surgery primarily for inadequate margins on final histopathology. Residual tumor found at the time of revision surgery was associated with worse tumor control but did not significantly affect survival.³⁷

Management of the neck is dependent on the primary site and cancer stage. For early glottic cancers, the risk of occult metastasis is low and observation is appropriate. However, supraglottic tumors have up to a 60% risk of occult unilateral or bilateral metastasis and require regional dissection, possibly postsurgery RT and increased complication rates. For early-stage larynx cancer, the complication rate is 0.3% to 6%.^{36,38,39}

The outcome with TLM for T1-2 glottic cancers is excellent, with a reported 5-year disease-free survival (DFS) rate of 88% and an overall survival rate of 92%.^{40,41} Outcome after TLM for supraglottic tumors is affected by T stage, with diminished local control and LP as T stage increases as well as the need for postoperative radiation or chemoradiotherapy.⁴² For T3 supraglottic tumors, patients experienced 60% DFS, 83% control with laser excision, and an 88% rate of organ preservation. A multi-institutional retrospective series of 117 patients with stage III or IV laryngeal cancer (64% supraglottic) reported a 5-year estimate of local control of 74% and locoregional control of 68%, with nearly 50% of patients requiring adjuvant radiation.³⁶

More recently, transoral robotic partial laryngectomy has been reported. Supraglottic tumors that can be visualized through a trans-

oral robotic approach are amenable to this new technology. The surgical robot offers excellent three-dimensional optics and motion scaling. Ozer et al⁴³ described 13 patients undergoing transoral robotic surgery for T2 supraglottic tumors. The operative time was 30 minutes or less and was associated with minimal blood loss and negative margins achieved in all cases.⁴³

MANAGEMENT OF T4 LARYNX CANCER

The indications for primary total laryngectomy for advanced laryngeal cancer remain controversial. RTOG 91-11 included patients with minimal cartilage erosion or tongue base involvement. Patients with T4a disease and penetration through cartilage were not eligible for inclusion in this study. Therefore, no level I evidence supports a nonoperative organ preservation strategy for these patients, and primary surgery followed by radiotherapy provides higher local-regional control rates over nonsurgical therapy. Patients with advanced laryngeal cancer who present with poor functional status, manifested by severe airway compromise requiring a tracheostomy or enteric feeding, are poor candidates for LP. Francis et al⁴⁴ described 30 patients who underwent total laryngectomy as primary treatment for T4a laryngeal cancer (20 glottic and 10 supraglottic). With a median follow-up of 37.5 months, 2-year overall survival and DFS rates were 81.3% and 78%, respectively. The 5-year overall survival and DFS rates were both 60%. The authors reviewed 24 published reports of treatment outcomes for advanced laryngeal cancer. All studies were retrospective, and no level I results were identified. Overall survival at 2 years ranged from 12% to 21.2% with RT alone, from 30% to 65% for chemoradiotherapy, and from 30% to 100% with surgery. At 5 years, overall survival was 0% to 75% with RT, 16% to 50.4% with chemoradiotherapy, and 10% to 80.9% with surgery.⁴⁴ The VALCSG trial found that 56% of patients with T4 disease underwent a laryngectomy as opposed to 29% of patients with less than T4 primary disease ($P = .001$).⁷ The 41 T4N0 patients had better survival when assigned to the surgical arm as opposed to assignment to the nonsurgical arm.⁴⁵

Initial treatment selection for T4 laryngeal carcinoma is critical because surgical salvage after failed nonoperative organ preservation therapy may adversely affect survival. Forastiere et al¹⁴ found no significant difference in overall survival comparing patients who did and did not undergo salvage laryngectomy within 1 year of completing treatment. However, in an exploratory analysis, significantly worse survival was found for patients who had a laryngectomy in both chemotherapy groups compared with those who did not. Chen et al⁴⁶ reviewed treatment trends from the National Cancer Database, noting increased administration of radiation with or without chemotherapy among 52,817 patients with advanced-stage laryngeal cancer from less than 7% to 45% between 1985 and 2007. Primary total laryngectomy decreased from 42% to 32%. The 4-year survival rates with total laryngectomy, chemoradiotherapy, and RT were 51%, 48%, and 38%, respectively.⁴⁶ The HR for risk of death comparing chemoradiotherapy with laryngectomy for advanced cancer was 1.13 (95% CI, 1.06 to 1.21; $P < .05$).⁴⁶ Hoffman et al⁴⁷ reported a significant decline in survival of patients with supraglottic cancers between 1985 and 1996 on the basis of analysis of the National Cancer Database. This was largely because of decreased survival of patients with early-stage cancers. There was no decrement in survival for T3N+M0 and T4N0M0 cancers and no significant difference in 5-year survival of patients with

T3N0M0 cancer treated with surgery (63.3%) or chemoradiotherapy (59.3%). On the basis of prospective clinical trial results, caution is appropriate when recommending nonoperative chemoradiotherapy for patients with T4 disease.

In conclusion, the management of locally advanced larynx cancer is challenging and requires a multidisciplinary team evaluation and a frank discussion of options and expectations with the patient. Patient selection by an experienced team is key to achieving good function outcomes and minimizing the risk for recurrence and salvage laryngectomy. Not only is the tumor extent and pretreatment laryngeal function critical but the expected tolerance of the treatment on the basis of performance status and comorbidities, particularly cardiopulmonary chronic disease that is common in this population.

Current evidence-based treatment algorithms for larynx cancer, T2N+, and T3 tumors requiring laryngectomy and selected low-volume T4 tumors endorse concomitant cisplatin and RT on the basis of level I randomized controlled trial data.⁴⁸ For patients who are not candidates for cisplatin, the substitution of carboplatin or cetuximab concurrent with RT is an accepted best practice in the absence of comparative data. Induction TPF, followed by RT, is an alternative on the basis of lower-level evidence from inadequately powered trials and retrospective analyses. Sequential ICT used as a biomarker for patient selection, followed by RT plus a sensitizer, is investigational. The optimal role for endoscopic resection (TLM) is as a single modality for

early-stage larynx cancer, in which the likelihood of radiation for a positive margin is low. For more advanced disease, patients suitable for endoscopic resection must be carefully selected by a skilled, experienced team, as discussed. Finally, there is a paucity of data on long-term functional outcomes and QOL. The importance of integrating longitudinal assessments using validated tools is now recognized. It is hoped that in conjunction with studies of transoral surgical approaches and deintensification strategies for other tumor sites in the head and neck (eg, oropharynx), standardized testing to assess function will result and become integrated into routine management.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors

Collection and assembly of data: All authors

Data analysis and interpretation: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Organ Preservation for Advanced Larynx Cancer: Issues and Outcomes

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