EVIDENCE-BASED REVIEW OF TREATMENT OPTIONS FOR PATIENTS WITH GLOTTIC CANCER

Dana M. Hartl, MD, PhD,[1,2] Alfio Ferlito, MD, DLO, DPath, FRCSEd *ad hominem*, FRCS (Eng, Glasg, Ir) *ad eundem*, FDSRCS *ad eundem*, FHKCORL, FRCPath, FASCP, IFCAP,[3] Daniel F. Brasnu, MD,[4] Johannes A. Langendijk, MD, PhD,[5] Alessandra Rinaldo, MD, FRCSEd *ad hominem*, FRCS (Eng, Ir) *ad eundem*, FRCSGlasg,[3] Carl E. Silver, MD,[6] Gregory T. Wolf, MD[7]

[1] Department of Otolaryngology–Head and Neck Surgery, Institut Gustave Roussy, Villejuif, France. E-mail: dana.hartl@igr.fr
[2] Laboratoire de Phonétique et de Phonologie, Sorbonne Nouvelle, Paris, France
[3] Department of Surgical Sciences, ENT Clinic, University of Udine, Udine, Italy
[4] Department of Otolaryngology–Head and Neck Surgery, and Voice, Biomaterials and Head and Neck Oncology Research Laboratory, University Paris V, European Hospital Georges Pompidou, Paris, France
[5] Department of Radiation Oncology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[6] Departments of Surgery and Otolaryngology–Head and Neck Surgery, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York
[7] Department of Otolaryngology–Head and Neck Surgery, University of Michigan, Ann Arbor, Michigan

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Abstract: Evidence-based medicine integrates the best available data in decision making, with the goal of minimizing physicians' and patients' subjectivity. In 2006, the American Society of Clinical Oncology edited clinical practice guidelines for the use of larynx preservation strategies. The objective of this review was to evaluate the current levels of evidence for glottic squamous cell carcinoma. Current guidelines for early stage glottic cancer are based on low-level evidence. Conservation surgery (open or transoral) and radiation therapy are all valid options for T1 and selected T2 lesions. For advanced lesions, surgery and combined chemotherapy and radiation are options. High-level evidence favors combined chemotherapy and radiation therapy or altered fractionation radiation therapy as nonsurgical strategies for organ preservation, compared with radiation therapy alone. The optimal combination of chemotherapy, targeted therapy, and radiation therapy remains to be demonstrated, however, and for high-volume tumors, total laryngectomy may still be warranted. © 2011 Wiley Periodicals, Inc. *Head Neck* **33:** 1638–1648, 2011

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Evidence-based medicine is the "conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients," and "integrating experience with the best available data in decision making."[1] The role of clinical research is to allow us to rationalize and refine our practices for the benefit of our patients: "Experience is good but wisdom is better. On what should we rely for treatment decisions—anecdotes, opinions, and persuasion, or more objective data, systematic reviews, and thoughtful interpretation of available clinical reports? Use of the best information, thus minimizing bias and opinion, is the key element that separates ethical medical practitioners from quacks and charlatans."[2]

But why do we need evidence-based medicine? As technology advances, there is an increasing number of therapeutic options at our disposal. As globalization advances, we see the spectrum of the variations in clinical practice expand. Modern medicine includes the patient in therapeutic decision making, with informed consent obtained based on objective information and sound communication with healthcare providers. Finally, as knowledge in decision psychology progresses, it has become increasingly apparent that physicians are not as objective as they think they are when making decisions for patient treatment.[1]

Evidence in medicine can be classified as "high-level evidence," evidence with high statistical power and a low risk of bias, and "low-level evidence" with low statistical power (or none at all) and a high risk of bias. Between the highest and lowest levels, groups of experts throughout the world have developed various classification schemes, to compare different medical studies according to their methodology, statistical power, and risk of bias, generally with 4 or 5 levels.

In 2006, the American Society of Clinical Oncology edited clinical practice guidelines for the use of larynx-

Correspondence to: D. M. Hartl

preservation strategies, based on a systematic review of the literature.[3] The objective of this review was to evaluate the level of current evidence concerning these treatment options for glottic squamous cell carcinoma. For the purposes of this review, we have chosen a 5-level classification to rate levels of evidence[4]: level I, large randomized trials or meta-analyses of randomized trials; level II, small randomized trials; level III, nonrandomized studies with contemporaneous controls; level IV, nonrandomized studies with historical controls; level V, case studies with no controls.

QUESTIONS

1. What is the evidence in favor of any 1 particular type of treatment for early-stage glottic tumors (T1a)[5] without anterior commissure (AC) involvement?

High rates of local control and laryngeal function preservation have been shown for patients with early glottic tumors using radiation therapy (RT), transoral laser resection, or open partial laryngeal surgery. The reported rates of local control with conservation laryngeal surgery for T1 glottic carcinoma—transoral laser resection or traditional open partial laryngectomies—range from 85% to 100%,[6–46] and reported local control with RT alone ranges from 84% to 95% (Table 1).[47–66] These data are based on nonrandomized studies with historical or contemporaneous controls (levels III and IV). A systematic review in the Cochrane Database of Systematic Reviews found only 1 prospective randomized trial comparing RT and surgery.[67] That study was fraught with methodological flaws, however, leading the authors of the review to conclude that "there is currently insufficient evidence to guide management decisions on the most effective treatment." To date, no well-conducted prospective randomized study has been performed to provide level I or level II evidence in favor of any 1 of these different types of approaches. The best level evidence to date, comparing surgery (open or laser) to RT for T1a glottic carcinoma, shows no final local control or survival difference among these different treatments (Table 2),[46,50,68] although 1 study[46] (101 patients, level 3 evidence) found a significant improvement in final laryngeal preservation for patients initially treated surgically.

The current evidence regarding exclusive chemotherapy for treating glottic tumors is based on retrospective and prospective nonrandomized studies (level IV) and shows a rate of local control with chemotherapy alone to be in the range of 8% to 12% of all patients initially treated with induction chemotherapy for T1 to T3 glottic tumors.[69] Thus, in a comparison of treatment modalities, the (low-level) evidence suggests that surgery and RT provide higher initial local control rates than those of exclusive chemotherapy.

The majority of the evidence (level III) shows that RT and transoral laser resection provide comparable

Table 1. Retrospective studies (level IV evidence) of initial local control rates for T1–T2 glottic carcinoma.

T classification	Open cordectomy[12–14]	Frontal anterior laryngectomy[12,15,16]	Hemi-laryngectomy[11,17–23]	Frontal anterior laryngectomy[16,24,25]	SCPL[26–33]	Laser[6–11,34–46]	RT[47–66]
T1a	90% to 100%	93% to 96%	91% to 100%	100%	98% to 100%	85% to 100%	84% to 95%
T1a-b and T2 AC	—		86% to 98%			70% to 95%	T1: 43% to 91%
							T1T2*: 58% to 74%
T2	—	92%	69% to 78%	92% to 94%	88% to 96%	66% to 100%	50% to 85%

Abbreviations: AC, anterior commissure; SCPL, supracricoid partial laryngectomy; RT, radiation therapy.
**Mixed cohorts.*

Table 2. Highest-level evidence for treatment options for T1/T1a laryngeal carcinoma.

Reference	No. of patients	Methodology	Group	Outcome	Evidence level
Gourin et al[68]	89	Retrospective nonrandomized cohort, T1 all laryngeal sites	RT vs surgery	Survival: no difference	III
Jones et al[50]	364	Retrospective nonrandomized cohort, T1 glottic and supraglottic	RT vs surgery (laser or open resection)	Initial local control: no difference	III
Stoeckli et al[46]	101	Retrospective nonrandomized cohort, T1 glottic tumors	RT vs laser	Initial local control, survival: no difference Final laryngeal preservation: initial surgery better than RT	III

Abbreviation: RT, radiation therapy.

results in terms of voice outcomes and voice-related quality of life.[70–75] However, 1 study found a better voice handicap score after laser surgery versus RT,[76] and 2 other studies found that voice after RT was better than that after laser surgery[77,78] (all level III studies). Voice results depend on the depth of the laser resection, but level IV evidence shows that voice can return to normal for a number of patients (45% of patients in the study by Vilaseca et al[79]). This evidence reflects the fact that not all tumors classified as T1a are the same. They differ in depth of invasion of the thyroarytenoid muscle. Depth of invasion may constitute a bias in retrospective studies and a major bias when comparing retrospective studies from different centers. Level III evidence shows that the postoperative morbidity is lower with transoral laser resection than that with open conservation surgery, and that, despite comparable oncologic outcomes, transoral resection has for the most part replaced open surgery for tumors classified as T1a not involving the AC.[80]

What criteria then can be used to choose from among these 2 treatment options if there is no strong evidence in favor of 1 treatment over the other in terms of local control and voice-related quality of life? Cost is increasingly being integrated into medical decision making and expert-driven recommendations. Four level III studies (prospective nonrandomized) have shown that RT for T1 glottic carcinoma is significantly more costly than transoral laser resection, even though the calculation of cost varies among countries.[70–72,81] Technical aspects of both treatments are also a consideration. Transoral laser resection may not be possible because of patient morphology or comorbidities, or may not be possible because of the absence of a laser or a surgeon experienced in the technique. Alternatively, the availability and logistics of 6 to 7 weeks of RT and the need for careful cancer follow-up also become decision-making factors. Finally, after a full discussion and complete patient information, physician and patient preferences also may be taken into account.

2. What is the evidence for treatment of T1a or T1b glottic tumors involving the AC?

Cancers involving the AC pose a particular anatomical problem for tumor spread because of the proximity of the thyroid cartilage to the mucosa, the absence of perichondrium or conus elasticus, the absence of anatomic barriers to tumor spread toward the petiole of the epiglottis or to the cricothyroid membrane, and the early ossification of the cartilage at this level, which lowers its resistance to invasion by the tumor. Deep extension at this level may have no effect on vocal fold mobility, leading to a risk of understaging.[82,83] The small size of the region and the early ossification of the cartilage contribute to the difficulties in radiological staging and diagnosis of cartilage invasion. CT and MRI criteria to optimize the diagnosis of thyroid cartilage invasion are still being assessed, and under-staging or overstaging still occur in 25% to 50% of cases.[83–86] Finally, adequate exposure of the AC for transoral laser resection is challenging in some patients.[87]

As Bradley et al[83] clearly show in their comprehensive review, AC involvement for T1 tumors can mean many things. T1a tumors involving 1 cord up to the ipsilateral half of the AC are different from superficial T1b tumors involving both cords and the AC and from T1b tumors arising at the AC itself, with or without infiltration, ulceration, or spread to the vocal folds. It is also clear from this review that there has been no study directly comparing treatment modalities, such as RT, open surgery, or transoral laser surgery, for comparable tumors involving the AC, taking into account the differences in subtypes of AC involvement, which do not appear in the TNM classification. Scarring of the AC after either surgery or RT generally results in poor voice quality.

Furthermore, the existing literature includes heterogeneous populations of tumors, mixing the results of superficial and infiltrating tumors, and tumors classified T1a, T1b, and T2.[83]

The bulk of the literature concerning AC lesions aims at determining whether AC involvement is a risk factor for reduced local control. Most of these studies include T1a, T1b, and T2 tumors involving the AC, so that individualizing information regarding T1 tumors with AC involvement is difficult. These

retrospective studies provide conflicting level III and level IV evidence (Tables 1 and 3), but it would seem that at least certain subtypes of tumors involving the AC (infiltrating tumors arising at the AC itself) are of worse prognosis than tumors that do not involve the AC.[83] The literature, however, does not provide high-level evidence as to the optimum treatment for these lesions. Rates of local control and laryngeal preservation ranging from 75% to 98% have been reported from retrospective studies of T1 tumors involving the AC using RT,[47,48,83] open surgery,[12,88] and transoral laser resection.[34–39]

A recent retrospective study by Sachse et al[89] (level III, Table 3) found no difference between open surgery and transoral laser resection for T1 or T2 tumors involving the AC, but showed that local control was significantly decreased if the AC was involved, compared with tumors not involving the AC. Bron et al[7] and Zohar et al[90] both found that surgery provided better initial local control than RT. Rucci et al[91] retrospectively compared their surgical and radiotherapy cohorts of tumors with AC involvement and found that surgery as first-line treatment provided significantly better local control (86% vs 74%), but that for "pure AC cancers" RT provided better initial local control, although salvage surgery was less effective after RT. This study illustrates the heterogeneity of the subgroups of tumors involving the AC, the bias inherent in retrospective studies, and the limitations of comparing these studies.

In light of the above-cited evidence (levels III–IV) there is no evidence favoring surgery over RT for T1 tumors involving the AC. For laryngeal tumors in general, Silver et al[79] recently analyzed the decline in open surgery. As a result of the morbidity of open surgery compared with that of transoral laser resection or RT, these latter techniques have largely supplanted open conservation surgery for early stage laryngeal cancers. For early-stage tumors, open surgery is currently mostly reserved for recurrences.[80,92] In some cases, however, open surgery should still be considered an option as first-line treatment, in accord with the experience and technical possibilities of the surgeon and the radiation oncologist.[93] Other factors that can influence this decision include the ease of operative exposure and sufficient possibilities for close patient follow-up.

3. What treatment should be favored for higher classification glottic tumors (T2) with or without impaired vocal fold mobility?

Comparing retrospective case series with historical controls (level IV evidence), the initial local control for T2 tumors with normal vocal fold mobility treated with RT is comparable to the results of open surgery and transoral laser resection, ranging from 84% to 95% (Table 1).[8,9,19,40,41,47,48] Level III studies do not provide compelling evidence in favor of surgery versus RT (Table 4).[33,46,50,68] Level III evidence favors

Table 3. Highest-level evidence for treatment options for T1–T2 glottic carcinoma involving the anterior commissure.

Reference	No. of patients	Methodology	Group	Outcome	Evidence level
Sachse et al[89]	119	Retrospective nonrandomized cohort	Open surgery vs laser	Local control: no difference	III
Bron et al[7]	156	Retrospective nonrandomized cohort	Surgery (laser or open) vs RT	Initial local control and final laryngeal preservation: surgery better than RT	III
Zohar et al[90]	67	Retrospective nonrandomized cohort	Open surgery vs RT	Initial local control: open surgery better than RT	III
Rucci et al[91]	182	Retrospective nonrandomized cohort	Open surgery vs RT	Initial local control: RT better than surgery Final local control (after surgical salvage): initial surgery better than initial RT	III

Abbreviation: RT, radiation therapy.

Table 4. Highest-level evidence for treatment options for T2 glottic carcinoma.

Reference	No. of patients	Methodology	Group	Outcome	Evidence level
Gourin et al[68]	98	Retrospective nonrandomized cohort, T2 all laryngeal sites	RT vs surgery	Survival: no difference	III
Jones et al[50]	124	Retrospective nonrandomized cohort	RT vs surgery (laser or open resection)	Initial local control: no difference	III
Stoeckli et al[46]	39	Retrospective nonrandomized cohort	RT vs laser	Initial local control and final laryngeal preservation: surgery better than RT	III
Marandas et al[33]	66	Retrospective nonrandomized cohort, T2 with impaired mobility	RT vs open surgery	Initial local control surgery 88%, RT 79% (no statistical analysis)	III

Abbreviation: RT, radiation therapy.

supracricoid partial laryngectomy as opposed to a vertical laryngectomy to optimize local control if open surgery is chosen, however.[19]

For the subgroup of T2 tumors with impaired vocal fold mobility, local control with RT alone falls to 76% (at best).[47,48,94–96] Similarly, Peretti et al[40,41] found a significant decrease in local control with transoral laser resection for T2 tumors with deep extension involving the paraglottic space or extending to the roof of the ventricle and the false vocal fold (17%), compared with the entire group of tumors classified as T2 (77%). This evidence (level III) emphasizes, yet again, the bias inherent in comparing T2 tumors since not all T2 tumors are similar, and they do not have the same prognosis.

Retrospective studies (level IV) of supracricoid partial laryngectomy for patients with T2 tumors with impaired vocal fold mobility show a high rate of local control (88% to 94%), albeit at the cost of removing three fourths of the larynx and a large portion of the structures not involved by the tumor.[33,97,98] Thus, for T2 tumors with impaired mobility, level IV evidence seems to favor open conservation surgery over RT or transoral laser resection when local control is the endpoint. However, voice function, the risk of persistent aspiration, and the higher risk in elderly patients are other factors to integrate into decision making.

There is no evidence directly comparing conservation surgery (open or transoral) with chemoradiation or other nonsurgical organ preservation protocols (RT with cetuximab or altered fractionation schedules) for T2 tumors. Outcomes of prospective randomized studies (level I evidence) for stage III and stage IV tumors (including those classified as T2N+) show better results for primary chemoradiation with cisplatin versus RT alone or versus induction chemotherapy followed by RT,[99] but also for RT plus cetuximab versus RT alone,[100] and for altered-fractionation schedules versus RT alone.[101] When conservation surgery is not possible for a T2 tumor, attributed to tumor extensions or lack of local surgical possibilities, high-level evidence would favor chemoradiation, RT plus cetuximab, or altered-fractionation RT over RT alone for organ preservation.

For T2 tumors with impaired vocal cord mobility amenable to conservation surgery, there is only low-level evidence to guide treatment decisions. As stated in the American Society of Clinical Oncology's guidelines, tumor evaluation, patient selection, and "local expertise" are necessary but provide only subjective elements for decision making. The relative morbidity of each approach must be weighed, but has never been directly compared. Open conservation surgery exposes patients to permanent dysphonia and often some degree of dysphagia or aspiration, and requires an experienced surgical team. Nonsurgical organ preservation protocols incorporating chemotherapy

carry hematologic, renal, and/or cutaneous toxicities, and RT exposes patients to late complications such as laryngeal edema and fibrosis, which can lead to dysphagia, dysphonia, and/or dyspnea.[102,103]

4. Is there evidence favoring a particular organ preservation strategy for higher-classification (T3–T4) tumors arising at the glottic level?

There are no studies directly comparing organ-preservation surgery with nonsurgical organ-preservation protocols for advanced-stage laryngeal tumors in a prospective manner with comparable patient groups. Given the evidence (level IV) showing excellent local control, functional organ preservation, and survival for T3 laryngeal carcinoma using supracricoid partial laryngectomy,[27,104] this approach remains an option for eligible patients, providing that the surgical expertise is available. Supracricoid partial laryngectomy remains an alternative to total laryngectomy (TL) or nonsurgical organ preservation for selected patients with tumors classified as T3 and T4a.

Survival and local control by TL followed by RT have not been bettered by the use of nonsurgical organ-preservation strategies. In the only prospective randomized study comparing TL and RT with nonsurgical organ preservation, the Department of Veterans Affairs (VA) Laryngeal Cancer Study,[105] disease-specific survival was shown to be the same in the 2 groups (2-year overall survival 68% in both groups, level I evidence). A further prospective randomized trial, the Radiation Therapy Oncology Group (RTOG) 91-11 Study,[99] comparing 3 arms—concurrent chemoradiation (CRT), induction chemotherapy, and RT (the VA protocol) and RT alone—showed that overall survival did not differ among the 3 groups (2-year survival of 74%, 76%, and 75%, respectively). Disease-free survival was significantly better in the 2 arms with chemotherapy, however (61% and 52% vs 44% for RT alone). Organ preservation was better for the CRT arm (88% vs 75% vs 70% at 2 years). Local control and survival have also been shown to be higher with accelerated and hyperfractionated radiotherapy compared with conventional RT (level I evidence).[101] RT combined with cetuximab has been shown to improve survival for patients with advanced head and neck tumors (level I), although this improvement was not significant for the subset of patients with advanced laryngeal cancer.[100] Finally, the addition of docetaxel to induction chemotherapy improves oncological results and organ preservation in advanced-stage tumors compared with cisplatin and fluorouracil alone followed by chemoradiation (level I).[106,107] A meta-analysis of large randomized trials (level I evidence)[108,109] has shown improved survival for CRT using cisplatin, compared with sequential treatments or RT alone, but the role of newer therapies (taxanes and targeted therapies) remains to be examined.

Lower-level evidence, however, challenges the notion that nonsurgical organ preservation strategies provide survival rates comparable to the "gold standard" of total laryngectomy followed by RT (Table 5).[68,99–101,105–107,109–111] An analysis of the National Cancer Data Base (NCDB) information on laryngeal cancer led Hoffman et al[110] to demonstrate that, contrary to most other cancers, 5-year overall survival for laryngeal cancer had decreased significantly from the period of 1985 to 2001, from 68.1% to 64.7%. This decrease paralleled a decline in patients' socioeconomic status over that period. A subgroup analysis, however, showed that this decrease was significant for T3N0 supraglottic cancer, but not for T4N0 or T3N+ supraglottic tumors, and that the decrease for glottic tumors overall was significant only when comparing 1985–1987 with 1994–1996. Survival after chemoradiation was not significantly different from survival after surgery with RT for T3N0 laryngeal or T3N0 glottic tumors, but was worse after RT alone.[110,112,113] A smaller database study came to similar conclusions for stage III laryngeal tumors, showing no difference in survival between CRT and TL.[111] This study, however, showed significantly better survival after TL compared with CRT or RT for stage IV tumors.[111] This study also showed a significant association between survival and race, socioeconomic status, and access to healthcare. Finally, a recent large retrospective case series demonstrated improved survival for T4 tumors treated surgically compared with CRT or RT.[68]

Furthermore, despite the impeccable methodology and high statistical power of these randomized controlled trials, there still remains a certain risk in applying the results of these studies to all patients with stage III and stage IV tumors.[114] A close look at the patients included in the RTOG 91-11 study, for example, reveals that approximately two thirds of the tumors were supraglottic tumors, 40% of the patients had mobile vocal folds, only 10% of the tumors were classified as T4, and the performance status was >80% for approximately 95% of the patients.[99] This study specifically excluded "large volume" T4 disease, defined as "tumor penetrating through the cartilage or extending more than 1 cm into the base of the tongue."[99,112] The clinical guidelines, or "standard of care" determined by the American Society of Clinical Onology in 2006[3] state that "evidence supports the use of larynx-preservation approaches for appropriately selected patients without a compromise in survival; however no larynx-preservation approach offers a survival advantage compared with TL." The optimization of nonsurgical organ preservation (as with surgical organ preservation strategies) still relies on adequate patient selection. For appropriately selected patients, the options of CRT, induction chemotherapy with taxanes, RT and cetuximab, and altered fractionation RT all provide a high level of organ preservation without compromising survival, compared with RT.

Table 5. Highest-level evidence for treatment options for advanced stage (III–IV) laryngeal carcinoma.

Reference	No. of patients	Methodology	Group	Outcome	Evidence level
Wolf et al[105]	332	Prospective randomized, larynx	TL + RT vs Induction chemo* + RT in responders	Overall survival: no difference; 64% larynx preservation	I
Forastiere et al[99]	547	Prospective randomized, larynx	CRT vs chemo* + RT in responders vs RT	Overall survival: no difference. Disease-free survival: better if CRT or chemo. Larynx preservation best for CRT (88%)	I
Bonner et al[100]	424	Prospective randomized, all head and neck sites (1/4 larynx)	RT + cetuximab vs RT	Overall survival and locoregional control: RT + cetuximab better	I
Posner et al[106]	501	Prospective randomized, all head and neck sites (18% larynx)	Induction TPF vs chemo* both followed by CRT	Overall survival and locoregional control: TPF better	I
Pointreau et al[107]	213	Prospective randomized, larynx + hypopharynx	Induction TPF vs chemo* both followed by RT or CRT in responders	Organ preservation: TPF better (70% vs 58%) Overall and disease-free survival: no difference	I
Bourhis et al[101]	6,515	Meta-analysis prospective randomized trials (head and neck, all sites)	Hyperfractionated or accelerated RT vs RT	Overall survival and locoregional control: altered fractionation better	I
Pignon et al[109]	17,346	Meta-analysis prospective randomized trials (head and neck, all sites)	CRT vs sequential chemotherapy and RT vs RT	Overall survival better if chemotherapy; CRT better than other regimens	I
Hoffman et al[110]	158,426	Retrospective database (larynx all sites)	Treatments 1985–2001 (surgery vs RT vs CRT)	Overall survival: —decrease for T3N0 supraglottic but not for T4N0 or T3N+; —no significant decrease for T3N0 glottic and no difference between CRT and TL + RT (66%), but RT alone worse (48%)	III
Chen et al[111]	7,019	Retrospective database (larynx all sites)	TL vs RT vs CRT or sequential chemotherapy (chemo-RT)	Overall survival: stage III: TL and chemo-RT better than RT; stage IV: TL better than chemo-RT or RT	III
Gourin et al[68]	451	Retrospective database (larynx all sites)	Surgery vs RT vs CRT	Overall survival: stage III: no difference between surgery and CRT/RT but CRT better than RT; stage IV: surgery better than CRT or RT	III

Abbreviations: TL, total laryngectomy; RT, radiation therapy; Chemo, chemotherapy with cisplatin and 5-fluorouracil; CRT, concurrent chemoradiation with cisplatin; TPF, chemotherapy with docetaxel, cisplatin, and 5-fluorouracil.*

There is currently no evidence directly comparing these different nonsurgical organ-preservation protocols (chemoradiation, RT plus cetuximab, hyperfractionated or accelerated RT, or induction chemotherapy with taxanes) among each other, and only the VA study directly compared their protocol with TL plus RT, still considered as the "gold standard" in terms of local control and survival for locally advanced laryngeal carcinoma. Thus, for nonsurgical organ preservation, in light of these more recent treatment options, the optimal strategy is still unclear, and for "large volume" laryngeal carcinoma with widespread cartilage or tongue base infiltration, the current trend still tends to favor TL followed by RT.[112,113,115,116]

DISCUSSION

The aim of this review was to show that the levels of evidence for treatment selection remain very low. The American Society of Clinical Oncology published clinical practice guidelines in 2006, with recommendations based on current evidence. These guidelines admit that the recommendations for T1T2 lesions of the glottis are based on "comparison of outcomes from case series/prospective single-arm studies" (level III). The recommendations reflect this lack of high-level evidence. RT, open surgery, or transoral laser resection are all options for patients with tumors classified as T1T2 in these guidelines. The authors do make clear that multimodality therapy is not recommended for patients with these early-stage lesions, not because evidence shows a lack of advantage, but rather, it seems, from a risk–benefit analysis, where the morbidity of multimodality treatment probably outweighs the oncological benefit for these patients whose prognosis remains excellent with single-modality therapy. Although treatment selection may be single modality, all patients benefit from an expert multidisciplinary evaluation in which all treatment options and functional issues are evaluated and discussed.

A major advantage of the guidelines is to emphasize organ-preservation strategies, whether surgical or nonsurgical, and to emphasize the need for a multidisciplinary teamwork approach for each patient. The tracheostoma and loss of a physiological voice after TL decrease quality of life.[117–119] If similar oncological outcomes, without other functional morbidity, can be obtained with alternatives to TL, they are to be preferred, whether with organ-preservation surgery or nonsurgical organ-preservation strategies.

Future prospective randomized studies with adequate statistical power should aim to answer the questions not addressed in the current literature. It has become apparent that all T1a tumors are not equal, in terms of depth of vocalis muscle invasion. One question is: for T1a tumors with comparable depth of vocal fold invasion, which treatment provides the best voice quality and voice-related quality of life? It has become evident that not all tumors involving the AC are of worse prognosis, but that some subtypes are and may require more aggressive treatment. For each subgroup of T1 tumors involving the AC (T1a, T1b superficial and bicordal, or infiltrating T1b arising at the AC), which treatment provides the best local control? Which treatment provides the best ultimate laryngeal preservation? Which treatment provides the best voice outcome? From studies comparing different subtypes of tumors classified as T2, it is apparent that not all T2 tumors are the same. For superficial tumors classified as T2, how do different treatment modalities compare? For T2 tumors with impaired mobility amenable to conservation surgery, how does organ-preservation surgery compare with nonsurgical strategies in terms of local control, final organ-preservation, and quality of life? Finally, among the nonsurgical organ-preservation strategies for advanced laryngeal cancer now at our disposal, how do they compare in terms of local control, final organ preservation, and acute and late toxicities and when is a TL still preferable?

Prospective randomized trials with comparable cohorts are necessary to improve our levels of evidence for treatment decision making. Trials are currently under way concerning nonsurgical organ-preservation strategies for patients with advanced laryngeal cancer. These prospective multicenter trials providing a high level of evidence often involve support from the private sector, but even these trials may be fraught with bias in patient selection and evaluation of endpoints,[116] arising from the subjective nature of clinical tumor staging/classification (evaluation of tumor extensions and vocal fold mobility). Information from radiological studies is not always pertinent in the initial evaluation or evaluation of response to treatment for laryngeal cancer because of the complexities and subjectivity of the interpretation of laryngeal imaging. Finally, results of complex clinical trials may not be reproducible in the general setting, as a result of epidemiological factors, and patient self-selection for clinical trials that may constitute a bias toward better outcomes, in and of itself.[120] Because of the heterogeneity observed when comparing past clinical trials, new recommendations[115] attempt to redefine inclusion criteria, pertinent stratification variables, and acceptable endpoints for future larynx-preservation clinical trials. Developing clinical trials involving surgery meets with similar difficulties in selecting patients, in eliminating bias in patient selection and surgical expertise in different centers, and in financing studies involving surgery. Academic support for this type of prospective study is necessary. Finally, outcomes in laryngeal cancer are in part related to socioeconomic inequalities, or the "deprivation gap" described by Rachet et al[121] that healthcare systems and governments are currently striving to remedy.

The future holds even more questions. Molecular profiling for treatment selection is still in its infancy for laryngeal cancer, but research in this domain will

give way to new therapeutic paradigms. Robotic surgery, future miniaturization of robotic instruments, image-guided surgery, and other technological advances may improve tumor visualization and resection, and enlarge the indications for transoral minimally invasive surgery. Finally, and in the very near future, better patient selection based on tumor biology, new targeted treatments, and new combined modality therapies will be offering even more options for organ preservation.

CONCLUSIONS

Current treatment guidelines for early-stage glottic cancer are based on low-level evidence. Conservation surgery (open or transoral laser resection) and RT are all still valid options for treating T1 and selected T2 glottic lesions. Subjective selection criteria are still the basis for treatment choice for these early-stage lesions. For advanced lesions not amenable to conservation surgery, high-level evidence favors combined-modality therapy, chemotherapy and RT, or altered fractionation RT, as nonsurgical strategies for organ preservation, compared with RT alone. The optimal combination of chemotherapy, targeted therapy, and RT remains to be demonstrated. Finally, for large volume, infiltrating lesions, TL followed by RT still has its place in our armamentarium.

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