Multidisciplinary Care of Laryngeal Cancer

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Abstract

Treatment of larynx cancer has changed dramatically over the past several years. Novel modalities of treatment have been introduced as organ preservation has been developed. In addition, new targeted therapies have appeared, and improvements in radiotherapeutic and surgical techniques have been introduced. Thus, a large variety of treatment options is increasing local control rates and overall survival; however, selecting the most appropriate treatment remains a challenging decision. This article focuses on the multidisciplinary care of early-stage and locally advanced larynx cancer and attempts to sum up different approaches. Moreover, it reviews state-of-the-art treatment in larynx preservation, which has been consolidated in recent years.

EPIDEMIOLOGY AND ETIOLOGY

The incidence of head and neck cancer is increasing rapidly, accounting for > 550,000 cases annually worldwide,1 of which 130,000 are new laryngeal cancer cases.2 There are geographic differences in the incidence because of the different prevalence of risk factors, mainly tobacco and alcohol, among populations, which also makes the disease more common in men because of their greater exposure to those factors. Tumors can develop in any part of the larynx; the glottis is the most common site, followed by the supraglottis and the subglottis.3 The signs and symptoms, which include hoarseness, stridor, sore throat, persistent cough, or a neck mass, depend on the size and location of the tumor.4 Frequently, glottic tumors are diagnosed at early stages, because a change in voice quality is noted relatively early in the course of the disease. However, supraglottic and subglottic tumors often present with advanced disease because their symptoms are less obvious.

EARLY STAGE (STAGE I AND II)

Epidemiology

Approximately 60% of people diagnosed with larynx cancer have stage I or II cancer (no evidence of lymph node involvement or thyroid cartilage invasion).5 With radiotherapy (RT) or surgery, 10-year disease-specific survival rates are > 90% and 70%, respectively, for patients with stage I and II cancer.6,7 Larynx preservation should be considered in patients with early-stage cancer. Both treatments, RT and surgery, work well in abolishing early-stage cancer, with no differences in oncologic outcomes.8-10 However, RT is usually preferred because of its functional results.11 Factors such as tumor characteristics, logistics, and patient preferences should be considered in selecting the treatment.

Treatment of Early-Stage (Stage I and II) Disease

Larynx-preserving treatments with RT, partial laryngectomy, or transoral laser
surgery should be the initial approach for patients with early-stage larynx cancer. However, there are no randomized studies of RT and conservation surgery that compare local control or survival for patients with early-stage laryngeal cancer.

**Supraglottis**

Supraglottic cancers represent approximately one third of laryngeal cancers. Most studies suggest that RT improves functional outcomes and is better at preserving voice quality. RT is effective for stage I larynx cancer in the supraglottic region. Sykes et al12 showed a local control of 92% with RT (with surgery after recurrence) for patients with stage I supraglottic tumors, and regional lymph node control of 91% with a 5-year survival rate of 83%. Conversely, a retrospective study comparing radical RT (60 to 66 Gy) versus partial laryngectomy in patients with T1 to T2 N0 found that surgery is effective, with results comparable to those of RT.6

**Subglottis**

Subglottic cancers represent < 2% of laryngeal cancers. Most cases are diagnosed in patients with advanced disease, so data on treatment are based on few patients in each study. Early stages in this location are usually treated with RT. If RT is not successful, a hemilaryngectomy should be performed.13

**Glottis**

Cancer of the glottis represents approximately two thirds of all cases of laryngeal cancer. Patients with early-stage cancer should be treated using a larynx-preserving approach, with either RT or transoral laser surgery. Several studies have noted that transoral laser surgery offers an effective approach to early-stage glottic cancer. Stoeckli et al6 compared treatment between laser surgery and RT (68 to 70.2 Gy) involving 140 patients with T1 to T2 glottic cancer. Local control, progression-free survival, and overall survival were similar between groups in patients with T1. However, surgery had better local control for patients with T2 than did RT. Larynx preservation was superior in the surgery group (T1, 82% for RT v 96% for surgery; T2, 77% v 89%). In an Italian study with T1a and T1b glottic cancer, laser surgery resulted in a 90% local control.14

A comparative review of RT, transoral laser surgery, and partial open laryngectomy in T1 to T2 larynx cancer showed that patients treated with RT had 5-year local control rates of 85% to 94% and 70% to 80% for T1 and T2, respectively (Table 1). The overall survival was comparable for all treatments.9 These authors concluded that local control after RT is adversely influenced by increasing T stage, male sex, prolonged overall treatment time, poor histologic differentiation, and low pretreatment hemoglobin level.9,15,16 Other studies suggest the same results, showing no differences in local control, progression-free survival, and overall survival between laser surgery and RT in patients with T1b glottic cancer.16

In a meta-analysis involving 7,600 patients with early-stage glottic cancer that compared RT with laser surgery, no differences were found in local control. Nevertheless, laser surgery seemed to be superior to RT in improving overall survival (odds ratio, 1.48; 95% CI, 1.19 to 1.85).17

In a prospective study, Yamazaki et al18 evaluated different schemes of RT (small tumors [less than two thirds glottis], classic RT [60 Gy; 2 Gy/fr] v experimental RT [56 Gy; 2.25 Gy/fr]; big tumors [two thirds glottis or more], classic RT [66 Gy; 2 Gy/fr] v experimental RT [63 Gy; 2.25 Gy/fr]). Despite local control being superior in the experimental arm (92% v 77%, P = .004), there were no differences in overall survival. This technique can decrease the dose to healthy tissues and increase the dose to tumor with less toxicity; however, patient selection criteria are critical. Recently, in an analysis of the National Center Institute’s SEER, a benefit in terms of cancerspecific survival for intensity-modulated RT (84.1%) versus other techniques (66%) was observed.19 Moreover, additional retrospective data support the use of carotid-sparing intensity-modulated RT over conventional RT in T1 to T2 N0 larynx cancer, demonstrating no difference in efficacy with significantly lower doses to the carotid arteries.20 Whether this translates into improved long-term vascular outcomes is still unknown.

Therefore, patients with early-stage disease could be treated with either RT or transoral laser surgery. Those with a higher risk (because of involvement of the anterior or posterior commissures or bilateral disease) are usually treated with RT because of the risk of positive margins.21,22

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**Table 1. Local Control Rates**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>T1</th>
<th>T2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transoral laser resection</td>
<td>80-90</td>
<td>70-85</td>
</tr>
<tr>
<td>Open partial laryngectomy</td>
<td>90-95</td>
<td>70-90</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>85-94</td>
<td>70-80</td>
</tr>
</tbody>
</table>

NOTE. Local control rates were assessed from meta-analyses.9
TREATMENT OF LOCOREGIONALLY ADVANCED STAGE (STAGE III AND IV MO) DISEASE

Until 1990, laryngectomy was the standard treatment of locoregionally advanced disease. Currently, all patients with stage III and IV should be evaluated before treatment by a multidisciplinary tumor board, which can change the management and thus improve the survival of patients.23 Larynx preservation is considered critical. Functional organ preservation is recommended and usually involves a combination of chemotherapy and RT. Nevertheless, laryngeal preservation surgery could be an alternative treatment in carefully selected patients.10,24 It could be used in combination with chemoradiotherapy or postoperative RT as an alternative option for patients with a small T-stage primary tumor but with advanced disease owing to neck node disease. These kinds of approaches have not been compared with chemoradiotherapy; therefore they should be used for carefully selected patients only.

The locoregionally advanced group has two kinds of patients: those who are candidates for organ preservation and those who are not. Currently, the line between them is not clear and the decision depends on the surgeon and the institution. Most studies do not clarify resectability criteria. However, some anatomic criteria are unequivocal, as the following: involvement of the hyoid bone or cricoids cartilage, extralaryngeal dissemination, involvement of prevertebral fascia, vascular structure invasion, or complete resection is not possible.5 In addition to these criteria, other aspects of a resectable tumor must be considered, and these increase the relevance of a multidisciplinary tumor board.

TREATMENT OF LOCOREGIONALLY ADVANCED STAGE III AND IV DISEASE

In locally advanced laryngeal cancer, the traditional approach has been laryngectomy followed by adjuvant RT, resulting in a loss of natural voice production. However, this approach has important limitations: a suboptimal rate of disease control (35% to 75%), a 60% chance of locoregional relapse, and a 20% chance of metastasis after 5 years.25,26 Because of this, we began looking for alternatives to surgery.

Treatments for the head and neck have changed dramatically with the appearance of novel modalities such as combined therapy. The development of new chemotherapy agents (taxanes and cetuximab) and the introduction of new prognosis factors (margins and extracapsular nodal extension) have changed the way we treat these patients; these developments have become an important part of the whole process.

Surgery

The most common treatment of locoregionally advanced disease is chemoradiotherapy. Nevertheless, surgery is important for selected patients who are not candidates for or who choose not to undergo chemoradiotherapy.

Larynx preservation surgery

Larynx preservation surgery is used in combination with adjuvant RT or chemoradiotherapy. It is an option for patients with a small primary tumor but who have advanced disease owing to neck node burden.27

Conservation surgery

Conservation surgery is used as an aggressive treatment of locally recurrent disease after RT.28,29 In addition, endoscopic methods are used for early stages (see Treatment of Early-Stage [Stage I and II] Disease). In selected T3 or T4 tumors, transoral laser surgery, in combination with postoperative treatment, may be considered, leading to an excellent oncologic survival outcome.30

Total laryngectomy

Usually, total laryngectomy is used to treat locally recurrent disease after chemoradiotherapy. Moreover, it should be used in older or frail patients.31,32 However, bulky T4 tumors could be treated with upfront chemoradiotherapy.33

Adjuvant Treatment

After larynx preservation surgery, adjuvant RT is required for patients with locoregionally advanced disease, with or without chemotherapy.34

Adjuvant chemotherapy (cisplatin 100 mg/m² every 21 days) concurrent with RT has better local control, progression-free survival, and overall survival than does RT alone in patients with high-risk locoregionally advanced disease (the European Organisation for Research and Treatment of Cancer and Radiation Therapy Oncology Group studies included approximately 22% of patients with larynx cancer and both trials demonstrated a significant benefit in disease-free survival and locoregional control).35 Positive margins and extracapsular nodal extension are the risk factors that have benefit in overall survival and local control of concurrent chemoradiotherapy. There are no specific data for larynx cancer.
Functional Organ Preservation

The first exploratory study in this area was the landmark trial conducted by the Department of Veterans Affairs Laryngeal Cancer Study Group, in which patients were assigned to receive three cycles of induction chemotherapy (cisplatin plus fluorouracil) before definitive RT versus surgery (typically, total laryngectomy) plus adjuvant RT. Patients without at least a partial response were treated with surgery and adjuvant RT. The larynx was preserved in 64% of the patients who received chemotherapy followed by RT, and there were no differences in survival.

The European Cooperative Group trial (EORTC 24891) showed similar results in patients with hypopharynx cancer, in which induction chemotherapy (cisplatin plus fluorouracil) followed by definitive RT was compared with surgery followed by postoperative RT. Patients without a complete response to chemotherapy underwent salvage surgery and adjuvant RT. There were no significant differences in survival.

Concurrent chemoradiotherapy

Concurrent chemoradiotherapy was developed originally as a definitive treatment option for inoperable patients; it had excellent reported local control and survival rates. Concomitant chemoradiotherapy attempts to take advantage of the radiosensitizing properties of chemotherapy. The main problem with this treatment is an increase in grade 3 and 4 acute toxicities. Some trials using intensive chemoradiotherapy regimens have noticed a survival benefit without surgery.

The standard of treatment changed with the RTOG 91-11 study, and functional organ preservation with concurrent chemoradiotherapy became a preferred choice in larynx cancer (Table 2). This treatment approach improves disease control and laryngeal preservation. Nevertheless, is less effective than induction chemotherapy followed by radical RT in decreasing the development of metastasis. The study randomly assigned patients to investigate three treatments: induction cisplatin plus fluorouracil followed by RT, RT with concurrent administration of cisplatin, and RT alone. The results demonstrated that RT with concurrent administration of cisplatin is superior to the other treatments for laryngeal preservation and locoregional control. A trend toward improved overall survival in the induction group was noted that was not statistically significantly different.

Currently, target therapies such as cetuximab can be combined with RT as radical treatment in patients with locally advanced disease. This was investigated in a phase III trial, which compared RT with RT plus cetuximab as a radical treatment in patients with locally advanced disease. The local control was better using the combination

### Table 2. Chemoradiotherapy vs Other Modalities for Organ Preservation in Locally Advanced Head and Neck Cancer

<table>
<thead>
<tr>
<th>First Author</th>
<th>Trial</th>
<th>Tumor Location</th>
<th>No.</th>
<th>Induction CT</th>
<th>Local Therapy</th>
<th>Acute Toxicity, High Grade (%)</th>
<th>Survival Difference</th>
<th>Larynx Preservation at 2 Years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forastiere</td>
<td>Intergroup 91-11</td>
<td>Larynx</td>
<td>510</td>
<td>None</td>
<td>CRT (P)</td>
<td>82</td>
<td>No</td>
<td>88*</td>
</tr>
<tr>
<td>VA</td>
<td>VA 24891</td>
<td>Larynx</td>
<td>332</td>
<td>PF × 2</td>
<td>RT</td>
<td>81</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>None</td>
<td></td>
<td>RT</td>
<td>61</td>
<td>70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lefebvre</td>
<td>EORTC 24891</td>
<td>Hypopharynx</td>
<td>202</td>
<td>PF × 3</td>
<td>RT</td>
<td>NA</td>
<td>Not†</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td></td>
<td>None</td>
<td></td>
<td>S, RT</td>
<td></td>
<td></td>
<td></td>
<td>64</td>
</tr>
</tbody>
</table>

NOTE. Data adapted. Statistically significant at \( P = .005 \). No difference chronic toxicity.

Abbreviations: CRT, chemoradiotherapy; CT, chemotherapy; F, fluorouracil; NA, not available; P, cisplatin; PF, cisplatin + fluorouracil; RT, radiotherapy; S, surgery as local salvage therapy.

*Statistically significant, \( P = .005 \).
†Induction arm had higher local failure rate and lower distal failure rate.
‡Induction arm had fewer distant failures.
§At 3 years.
||No difference in chronic toxicity.
treatment (24.4 months v 14.9 months, \(P = .005\)), as was overall survival (45.6% v 36.4%; hazard ratio, 0.73). It should be noted that the trial was not designed for platinum-ineligible patients; the objective was to evaluate cetuximab in a broad population of patients with locally advanced disease.\(^{42}\)

Trials are underway in unresectable disease, but until further data become available, the treatment selection will depend on toxicity and patient fragility.

This approach seems to be effective for locoregional control, but some trials revealed a worse control in distant disease, especially in patients with an advanced nodal stage. For that reason, induction chemotherapy was developed (see Induction chemotherapy).

**Induction chemotherapy**

Induction chemotherapy is an option for functional larynx preservation in locoregionally advanced disease. Usually, the scheme is induction chemotherapy followed by definitive RT; however, this treatment is less effective than concomitant chemoradiotherapy treatment in terms of locoregional control.\(^{43}\) Induction chemotherapy has shown a survival benefit effect. That has been tested in several trials (Paccagnella et al\(^{44}\); Domenge et al\(^{45}\); Pignon et al\(^{34,46,47}\)), which have shown a consistent survival benefit and increased cure rates in a subset of nonoperable patients. In the Pignon et al\(^{34}\) meta-analysis, the researchers noted a 5% increase in survival, reaching statistical significance (\(P = .05\)), in trials using a cisplatin-plus-fluorouracil regimen only.

**Cisplatin plus fluorouracil.** In the earlier results of the Meta-Analysis of Chemotherapy in Head and Neck Cancer, there was no survival benefit for induction chemotherapy because of the heterogeneity of the studies and the platin absence in some of them. Nevertheless, the latest reports showed a significant benefit of 5% in overall survival for induction chemotherapy using cisplatin plus fluorouracil.\(^{34}\) In addition, other studies in the hypopharynx and oropharynx have shown good results in organ preservation (Table 3).

**Taxanes.** The incorporation of taxanes into induction treatment has improved larynx preservation and response rates. Therefore, induction chemotherapy that is based on taxanes and local treatment has become the new standard treatment.

In the TAX 323 trial, it was noted that the combination regimen of taxane, cisplatin, and fluorouracil improved overall survival compared with cisplatin plus fluorouracil, when both were followed by radical RT. The induction response has a prognostic and predictive value in deciding the following treatment, chemoradiotherapy or surgery.\(^{50}\)

The TAX 324 trial showed the effectiveness of induction with docetaxel, cisplatin, and fluorouracil followed by concomitant chemoradiotherapy using weekly carboplatin. In a subset of nonoperable patients, the overall survival was 40 months for patients treated with taxanes versus 21 months for the group treated with cisplatin plus fluorouracil.\(^{51}\) The GORTEC 2000-01 study had 213 patients with stage III to IV larynx or hypopharynx tumors who were candidates for

Table 3. Studies in Hypopharynx and Oropharynx Showing Good Results in Organ Preservation With Induction Cisplatin Plus Fluorouracil

<table>
<thead>
<tr>
<th>First Author</th>
<th>Trial</th>
<th>Trial Characteristics</th>
<th>Patient</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lefebvre(^{37,48})</td>
<td>EORTC 24891</td>
<td>Phase III Randomized Patients: resectable hypopharynx tumor with locoregional advance disease</td>
<td>202</td>
<td>Exp. arm: Induction CT (PF) → RT (if CR) or surgery + RT (if not CR)</td>
<td>No difference in overall survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control arm: Surgery → adjuvant RT</td>
<td></td>
</tr>
<tr>
<td>Worden(^{49})</td>
<td>UMCC 9921</td>
<td>Patients: resectable oropharynx tumors</td>
<td>66</td>
<td>Induction CT (PF or CBDCA + FU): → If CR or PR → CT + RT → If less than PR → Surgery + RT</td>
<td>7-year larynx-preservation rate, 73.4%</td>
</tr>
</tbody>
</table>

Abbreviations: CBDCA, carboplatin; CR, complete response; CT, chemotherapy; EORTC, European Organization for Research and Treatment of Cancer; Exp arm, experimental arm; FU, fluorouracil; PF, cisplatin + FU; PR, partial response; RT, radiotherapy.
They were randomly assigned to three cycles of induction chemotherapy (with or without taxane) followed by RT or surgery, depending on the response to chemotherapy. It was noted that there was a higher larynx preservation rate in the group receiving the taxane, cisplatin, and fluorouracil regimen than in the group receiving the cisplatin and fluorouracil regimen (70% vs 57%). Overall survival was 60% for both chemotherapy regimens.\(^{52}\)

A phase II trial by Gruppo di Studio sui Tumori della Testa e del Collo showed a benefit in locoregional control (50% vs 21.2%, \(P = .04\)), overall survival, and progression-free survival\(^{53}\) in the induction arm. Moreover, the phase III preliminary results were presented in 2014; they showed a benefit in progression-free survival (29.7 months vs 18.5 months) and 3-year overall survival (53.7 months vs 30.3 months) for the induction arm.

Thus, the triple combination of taxane, cisplatin, and fluorouracil is an effective treatment for reducing metastasis incidence and increasing local control. However, the main problem for these patients remains the locoregional recurrence, so evaluating the treatment after the induction seems to be important.

Cetuximab. Target therapies that decrease treatment toxicity have been studied. The TREMPLIN study is a phase II trial that analyzed induction chemotherapy (three cycles of taxane, cisplatin, and fluorouracil regimen) followed by RT plus cisplatin or plus cetuximab in patients with laryngeal and hypopharyngeal tumors. There were no differences in oncologic outcomes (3-month larynx preservation, overall survival, 18-month functional larynx preservation) with the exception of local control, which was superior in the cisplatin group.\(^{54}\) Target therapies such as cetuximab showed evidence of a benefit in resectable disease in the TREMPLIN trial; however, adequate evidence for patients with unresectable disease is not available currently. Until further data become available, the treatment selection will depend on toxicity and patient fragility.

**Induction chemotherapy followed by sequential chemoradiotherapy.** Several trials have evaluated different combinations of induction chemotherapy followed by concomitant chemoradiotherapy. Most of the studies were negative, and this approach remains controversial.

In conclusion, the treatment of larynx cancer has changed dramatically over the past 3 decades. The most important modification is the use of the multidisciplinary approach (Table 4; Fig 1). Before treatment, all patients with larynx cancer, especially those with locally advanced disease, should be evaluated by a multidisciplinary tumor board.

For the majority of patients with locally advanced (stage III or IV) laryngeal cancer, a functional organ preservation approach with chemoradiotherapy is recommended. However, surgery may be an option for selected patients and for those who are not candidates for larynx preservation. Targeted therapies play a role in chemoradiotherapy, but further comparative trials must be performed. Great advances have been made in larynx cancer treatment, but we must continue

### Table 4. Recommendations for the Treatment of Early-Stage Laryngeal Cancer

<table>
<thead>
<tr>
<th>Location</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supraglottis</td>
<td>Radical radiotherapy (60–66 Gy) or surgery (T1–T2 N0)</td>
</tr>
<tr>
<td>Subglottis</td>
<td>Radiotherapy; if radiation therapy is not successful, a hemilaryngectomy should be performed</td>
</tr>
<tr>
<td>Glottis</td>
<td>Patients with early-stage laryngeal cancer should be treated using a larynx-preserving approach, with either RT or transoral laser surgery.</td>
</tr>
</tbody>
</table>

Abbreviation: RT, radiotherapy.

FIG 1. Recommendations for the treatment of advanced-stage laryngeal cancer. CT, chemotherapy; PS, performance status; RT, radiotherapy.
improving our knowledge and quality standards to benefit as many patients as possible. JOP

Authors’ Disclosures of Potential Conflicts of Interest

Disclosures provided by the authors are available with this article at jop.ascopubs.org.

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Conception and design: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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References


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Volume 12 / Issue 8 / August 2016 • jop.ascopubs.org

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Multidisciplinary Care of Laryngeal Cancer

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No relationship to disclose

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Consulting or Advisory Role: Merck, Bristol-Myers Squibb, AstraZeneca, Human Longevity, Pfizer