

Current Status of Organ Preservation in Carcinoma Larynx

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Abstract

Organ preservation in carcinoma larynx is a long debated topic. There are multiple organ preserving approaches in the management of carcinoma larynx depending on various factors. Radical radiotherapy (RT) and conservation laryngeal surgery have shown equivalent results in early laryngeal cancer. Concurrent chemoradiation (CTRT) is the standard treatment in stage III and IV laryngeal cancer with intact cartilage and functional larynx. Patients with cartilage destruction or dysfunctional larynx are not the candidates for organ preservation. This systematic review is aimed at discussing the evolution of different organ preserving approaches, their efficacy, impact on voice quality, their pitfalls and future directions.

Keywords: Organ preservation; Larynx

Introduction

Laryngeal cancer consists of 1.1% of all new cancers worldwide. It is the seventh most common cause of cancer in males in India [1]. The incidence of laryngeal cancer has been reported to be 1.26 - 8.18 per 100,000 population in different regions in the country [2]. Early stage laryngeal cancers include T1 and most T2 squamous cell cancers of glottis and supraglottic regions. Subglottic cancers are relatively rare. Multiple treatment options exist for early stage squamous cell carcinoma of the larynx. Multidisciplinary approach is highly encouraged for the management.

Organ Preserving Approach in Early Glottis Cancer (T1, T2N0M0)

Treatment options include radical radiotherapy (RT), transoral laser surgery (TLS), and function preserving open partial laryngectomy [3]. Treatment selection depends on various fac-

tors including disease extent into supraglottis and subglottis, anterior commissure involvement, patient's preference, occupational considerations, voice quality, performance status, patient's compliance, comorbidities, physician's expertise, treatment cost and physician's bias. All the treatments are associated with excellent tumor control. Mendenhall et al discussed this particular issue in three angles: local control, voice quality and cost [3]. In University of Florida, patients with limited well-defined T1a N0M0 glottic cancers are treated with either RT or TLS. The remaining all patients with T1N0 and T2N0 lesions are treated with definitive RT. They concluded that the rates of local control, voice preservation and survival are comparable for patients treated with RT, TLS and open partial laryngectomy. Open partial laryngectomy is preferred in those who experience local disease recurrence.

Radical RT Versus Conservation Laryngeal Surgery in Early Glottic Cancer

The goal of treatment in early glottic cancer is to achieve cure with best functional outcome. At present, radical RT and TLS are standard upfront treatments for early glottic cancer [4]. As both the modalities offer excellent and equivalent cure rates, there is long standing debate on the merit of each modality in the treatment of early glottic cancer with regard to its efficacy and functional outcome.

In a study by Aaltonen et al [5], male patients with carcinoma limited to one mobile cord were randomized to receive either laser surgery or external beam radiotherapy (EBRT). EBRT dose was 66 Gy with 2 Gy/# over 6.5 weeks. Overall the voice qualities between the groups were rated similar but patients treated with RT reported less hoarseness-related inconvenience in daily living 2 years after treatment. They concluded that RT may be the treatment of choice for patients whose requirements for voice quality are demanding. Dinapoli et al [6] compared the oncological outcome and voice quality among a uniform and well-defined subset of patients with T1 glottic carcinoma. No statistically significant differences were found between the two groups in terms of overall survival and disease-free survival; even sub-classifying patients into stages T1a and T1b also made no difference. The median voice handicap index (VHI) score for patients undergoing RT was 4, while for surgical patients, it was 18 ($P < 0.0001$). Rimmelts et al [7] showed comparable oncological outcome between the TLS and RT arm. VHI scores were 12.4 ± 8.9 for laser surgery and 8.3 ± 7.7 for RT ($P < 0.05$), with a higher score reflecting a worse outcome. VHI scores per tumor stage for laser surgery and RT were 12.0 ± 9.9 and 7.9 ± 7.5 in T1a

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Table 1. Radiotherapy Versus TLS in Stage I Glottic Cancer

Author	Year	No. of patients	Local control	Larynx preservation	Voice quality
Aaltonen et al [5]	2014	RT 28; TLS 32	At 2 years, 88% in RT vs. 90% TLS	Not available	Overall voice quality similar in both arms. Voice more breathy in TLS; less hoarseness-related inconvenience in RT.
Remmelts et al [7]	2013	RT 159; TLS 89	At 5 years, 86% in RT vs. 75% in TLS (P = 0.07)	5-year 83% in RT vs. 93% in TLS (P < 0.05)	VHI 12.4 ± 8.9 in TLS vs. 8.3 ± 7.7 in RT (P < 0.05) suggestive of poor outcome of TLS
Milovanovic et al [8]	2013	RT 74; TLS 72	Equal in both arms	Equal in both arms	Shimmer score mean 3.75 in TLS; 4.07 in RT
van Gogh et al [9]	2012	RT 39; TLS 67	At 2 years, 95% in RT vs. 97% in TLS	At 2 years, 95% in RT vs. 100% in TLS	Shimmer score mean 5.06 in TLS vs. 5.39 in RT; voice outcome recovery earlier in TLS.
Dinapoli et al [6]	2010	RT 70; TLS 73	Equal oncological outcome		Median VHI 18 in TLS vs. 4 in RT (P < 0.0001)

(P = 0.06), 16.7 ± 9.0 and 4.9 ± 6.6 in T1b (P < 0.05), respectively. Depth of laser resection has impact on voice deficiency and patients with T1b lesion had higher voice deficiency if treated with laser surgery. Abdurehim et al [4] in their meta-analysis showed that no significant differences were observed between TLS and RT with respect to local control, survival and voice quality. Results of latest studies on RT vs. TLS are shown in Table 1 [5-9].

RT is a time tested approach. RT planning for early glottic cancer is simple and it does not require sophisticated technology. RT has proven to be of high efficacy with better or equivalent voice outcome. TLS is quicker and repeatable and has many salvage options. Moreover, this kind of studies has some limitations because of their small sample size, retrospective nature and selection bias. It is still unclear which of these modalities is to be considered optimum and the differences in outcome between the groups are too subtle.

The vertical partial laryngectomy comprises of vertical transection of thyroid cartilage and glottic resection extending into the paraglottic space. The goal of this surgery is resection of a portion of thyroid cartilage with the cancer at glottic level, while preserving the posterior paraglottic space. Hence, it is most suitable for early glottic cancer without anterior commissure involvement [10]. In 1994, Thomas et al [11] reported a series of 159 patients with T1 glottic cancer who underwent vertical partial laryngectomy at the Mayo Clinic between 1976 and 1986. The 5-year local control rate was 93% and in 94% of the patients, the larynx could be preserved. Spector et al [12] treated 404 patients with T1 glottic cancer with a 5-year local control rate of 92% and larynx preservation rate of 93%. In 71 patients with T2 glottic carcinoma, the 5-year disease-specific survival rate was 92%. The larynx preservation rate was 92%. The updated Cochrane review [13] identified only one randomized controlled trial, which compared open surgery and RT in 234 patients with early glottic laryngeal cancer. For T1 tumors, the 5-year survival was 91.7% following RT and 100% following surgery and for T2 tumors, 88.8% following RT and 97.4% following surgery. There were no significant differences in survival between the two groups. For T1 tumors, the 5-year disease-free survival rate was 71.1% following RT and 100.0% following surgery, and for the T2 tumors, 60.1% following RT

and 78.7% following surgery. Only the latter comparison was statistically significant (P = 0.036), but statistical significance would not have been achieved with a two-sided test. Data on voice quality and quality of life are not available. To conclude RT and conservation laryngeal surgery provides equivalent local control and functional outcome. Narrow margin followed by postoperative RT is not considered as an acceptable treatment approach.

Organ Preserving Surgeries for Early Supraglottic Cancers (T1, T2N0M0)

The primary difference between supraglottic cancers and true glottis cancers is the likelihood of developing cervical lymph node metastasis. The rate of cervical lymph node metastasis from supraglottic larynx ranges from 10% to 50% with an average of 33%. Hence neck treatment is mandatory [14]. Surgical treatment options for supraglottic carcinomas comprise open supraglottic laryngectomy, transoral laser microsurgery, and supracricoid partial laryngectomy with cricohyoidopexy (SCPL-CHEP). The open supraglottic laryngectomy consists of a resection of the entire supraglottis such as the epiglottis, the preepiglottic fat, and the ventricular folds together with the supraglottic part of the thyroid cartilage. The oncologic results of open supraglottic laryngectomy in early supraglottic carcinomas are excellent. The local control rate is between 90% and 100% for T1 tumors and 80% and 97% for T2 tumors [10]. Prades et al [15] report on 110 patients with T1-T3 supraglottic carcinomas. The local control rate was 90.3% and the 5-year overall survival rate was 52%.

The indication for this SCPL-CHEP comprises supraglottic tumors with limited infiltration of the preepiglottic fat, limited erosion of the thyroid cartilage and tumors with fixation of one vocal cord but without fixation of the arytenoid cartilage. This operation was used for surgical treatment of T1, T2 and selected T3 and T4 supraglottic tumors. Schwaab et al [16] report on 146 patients mostly with T2 and T3 carcinomas who underwent SCPL-CHP. The local control rate was very good, with only 4% developing local recurrence. The larynx could be

preserved in 85% of patients. The 5-year overall survival rate was 88%. The local recurrence reported in other studies is also very low ranging from 0% to 7% [17, 18].

Always those patients who are taken up for organ preservation should be treated with a single modality treatment. Every effort should be made to avoid combining surgery with radiation therapy because functional outcomes may be compromised by combined modality therapy; single modality treatment is effective for limited stage disease. Treatment options include radical RT or organ preserving surgery.

Organ Preserving Approaches in Locally Advanced Laryngeal Cancer (Stage III and IV)

Approximately 25 years ago, the standard treatment of locally advanced laryngeal cancer was total laryngectomy plus conventional postoperative RT. There was a paradigm shift with the emergence of induction chemotherapy as a part of larynx preserving treatment in 1991 when veteran affairs (VA) trial was published [19]. The landmark VA trial [19] enrolled 332 patients which were randomized to receive three cycles of chemotherapy (cisplatin + 5FU) and RT versus surgery and RT. The clinical tumor response was assessed after two cycles of chemotherapy and patients with partial response received third cycle of chemotherapy followed by definitive RT of 66 - 70 Gy. Patients who were not able to achieve partial response underwent surgery followed by postoperative RT. The combined rates of partial and complete response in the primary tumor and the regional nodes after two or three cycles of chemotherapy were 85% and 98%, respectively. After a median follow-up of 33 months, the estimated 2-year survival was 68% for both the arms. More local relapse and fewer distant relapse were seen in the chemotherapy group as compared to surgery group. The larynx was successfully preserved in 64% without jeopardizing the 2-year survival as compared to upfront surgery group. One-fourth of the patients had T4 disease and patients with cartilage erosion were also included in this study. Salvage laryngectomy was required in 44% patients with stage IV as compared with 29% of patients with stage III disease ($P = 0.048$). A total of 56% patients with T4 disease underwent salvage laryngectomy compared to 29% with smaller primary tumors ($P = 0.001$). Hence, patients with cartilage destruction are not the candidates for organ preservation approach. This landmark trial established induction chemotherapy followed by RT as an alternative to laryngectomy for locally advanced laryngeal cancer. To determine the contribution of chemotherapy and RT to larynx preservation and the optimum sequence of chemotherapy and RT, the RTOG and Head and Neck Inter-group conducted a randomized trial [20] to investigate three radiation-based schedules.

Induction cisplatin plus 5FU followed by RT (good responders to chemotherapy) experimental group in VA trial, chemoradiation (CIRT) and RT alone. The rationale for the second group was based on enhancement of radiation effect on tumor cells with concurrent administration of injection cisplatin. The primary objective was to compare trials of laryngeal preservation in three arms. Patients with large volume T4

disease (defined as penetration through cartilage) or extending more than 1 cm base of tongue were excluded from this study. Most of the patients (72%) were of carcinoma supraglottis. Most of the patients presented with T3 with fixed cord involvement (44%). At a median follow-up of 3.8 years, patients receiving CIRT had a significantly higher rate of larynx preservation rate (84%) vs. induction chemotherapy followed by RT (72%; $P = 0.005$) or RT alone (67%; $P \leq 0.001$). There was no difference between induction chemotherapy group versus RT alone group in terms of laryngeal preservation. There was no difference among the three treatment groups with regard to speech at either 12 or 24 months of follow-up.

In the long term update of the landmark RTOG 91-11 study [21], 520 patients were analyzed. Median follow-up period was 10.8 years. Both the chemotherapy regimens significantly improved laryngectomy free survival compared with RT alone (induction chemotherapy versus RT alone; hazard ratio (HR), 0.75; 95% CI, 0.59 - 0.95; $P = 0.02$; concurrent CIRT versus RT alone: HR, 0.78; 95% CI, 0.78 - 0.98; $P = 0.03$). Overall survival did not differ significantly in any of the treatment arm, with 5- and 10-year estimates of 58% and 39% for induction, 55% and 28% for CIRT and 54% and 32% for RT alone, respectively. After about 4.5 years, the curves begin to separate favoring induction, although the difference is not statistically significant. However, deaths in the CIRT arm was laryngeal cancer unrelated deaths. This occurred without increase in late toxicities.

Outcome of Salvage Total Laryngectomy Following Organ Preservation Therapy

Weber et al [22] evaluated the incidence of morbidity, mortality and disease control for patients requiring salvage total laryngectomy following organ preservation in RTOG 91-11 trial. From 1992 - 2000, 517 evaluable patients were randomized to receive chemotherapy followed by RT (arm 1), CIRT (arm 2) or RT (arm 3). Overall total laryngectomy was required in 129 patients. The salvage laryngectomy rates were 28%, 16% and 31% in arms 1, 2 and 3, respectively ($P = 0.002$). Following total laryngectomy, the incidence of major and minor complications ranged from 52% to 59% and did not differ significantly among the three arms. Locoregional control following salvage total laryngectomy was 74% for arms 1 and 2 and 90% for arm 3. At 24 months, the overall survival was 69% (arm 1), 71% (arm 2) and 76% (arm 3) ($P > 0.73$). Laryngectomy following organ preservation treatment was associated with acceptable morbidity. Survival following salvage laryngectomy was not influenced by the initial organ preservation treatment.

Induction Chemotherapy in Laryngeal Preservation

The Groupe Oncologie Radiotherapie Tete et Cou (GORTEC) trial [23] showed the effect of adding docetaxel to the PF (cisplatin, 5FU) induction chemotherapy regime on larynx preservation. Patients with laryngeal or hypopharyngeal cancers

Table 2. Results of Organ Preserving Approaches in Advanced Laryngeal Cancer

Study	Year	Arms	Outcome	Laryngeal preservation
VA trial [19]	1991	Induction chemo followed by RT vs. surgery + RT	After two cycles of chemo clinical CR 31%, PR 54%, 2-year survival 68% in both the groups. 36% of the patients of chemotherapy group required total laryngectomy.	Overall larynx preservation was 64% in the nonsurgical arm.
GORTEC trial [23]	2000 - 2001	Induction chemo with TPF vs. PF followed by radiotherapy or surgery according to the response	Overall response rate after induction chemotherapy was higher with TPF (80% versus 59% (P = 0.002). There was no significant difference between the treatment arms in the 3-year rate of overall (60% in each arm) or disease-free (58% with TPF versus 44% with PF) survival	The 3-year larynx preservation rate was significantly higher in the TPF arm than in the PF arm (70% versus 58%; P = 0.03).
RTOG 91-11 [20]	2003	RT vs. induction chemo followed by RT vs. CTRT	At a median follow-up of 3.8 years local control significantly better in CTRT arm (78%) vs. induction chemo followed by RT (61%) vs. RT alone (56%). Overall survival similar in all three groups	Larynx preservation was significantly higher in the CTRT arm (88%) as compared to induction chemo followed by RT (75%; P = 0.005) or RT alone (70%; P ≤ 0.001).
RTOG 91-11 update [21]	2013	RT vs. induction chemo followed by RT vs. CTRT	Median follow-up for surviving patients is 10.8 years. Both chemotherapy regimens significantly improved LFS compared with RT alone (induction chemotherapy vs. RT alone: hazard ratio (HR), 0.75; 95% CI, 0.59 to 0.95; P = 0.02; concomitant chemotherapy v RT alone: HR, 0.78; 95% CI, 0.78 to 0.98; P = 0.03). Overall survival did not differ significantly, although there was a possibility of worse outcome with concomitant relative to induction chemotherapy (HR, 1.25; 95% CI, 0.98 to 1.61; P = 0.08)	Concomitant cisplatin/RT significantly improved the larynx preservation rate over induction PF followed by RT (HR, 0.58; 95% CI, 0.37 to 0.89; P = 0.0050) and over RT alone (P < 0.001), whereas induction PF followed by RT was not better than treatment with RT alone (HR, 1.26; 95% CI, 0.88 to 1.82; P = 0.35).

requiring total laryngectomy were randomized to receive induction therapy with three 21-day cycles of either PF or TPF (docetaxel, cisplatin, 5FU). Patients responding to induction chemotherapy received conventionally fractionated RT (total dose of 70 Gy). Non-responders underwent total laryngectomy followed by RT. In this trial, a total of 213 patients were randomized. After induction chemotherapy, 20% of patients in the TPF arm and 16% patients in the PF arm received CTRT. At a median follow-up of 36 months, the 3-year larynx preservation rate was significantly higher in the TPF arm (70%) as compared to PF arm (58%) (P = 0.03). The overall response rate after induction chemotherapy was also higher in the TPF arm as compared to PF arm (80% vs. 59%; P = 0.002). There was no significant difference in overall survival or disease-free survival in both the arms. This laryngeal preservation trial is somewhat unique in that it includes a mix of larynx and hypopharynx patients. It is somewhat problematic to compare this study with previous laryngeal preservation trials, as the patient inclusion and treatment criteria are different (hypopharynx patient inclusion and stipulation of functional larynx). The PF induction chemotherapy arm in the RTOG 91-11 study showed better laryngeal preservation than the GORTEC trial (75% at 3.8 years vs. 58% at 3 years) because hypopharyngeal cancers were also included in the GORTEC trial.

TAX 324 and EORTC 24971/TAX 323 showed that TPF

induction chemotherapy significantly improves survival compared with PF [24, 25]. The subset analysis of patients with laryngohypopharyngeal cancer in TAX324 trial showed that TPF improves progression-free survival (PFS) and overall survival (OS), reduces the rates of locoregional surgery, and, in operable patients, results in a significant improvement in laryngectomy free survival (LFS) with an absolute improvement of 20% (52% vs. 32%; P = 0.030) at 3 years compared with PF [26].

Induction Chemotherapy Followed by CTRT

Those trials decided the optimum induction chemotherapy regime but did not answer the important question regarding the relative efficacy of adding induction chemotherapy followed by CTRT compared with CTRT alone, the current standard of care. Newer studies such as DeCIDE [27] (Docetaxel-Based Chemotherapy Plus or Minus IC to Decrease Events in Head and Neck Cancer) and PARADIGM [28] suggest no overall benefit from the addition of induction chemotherapy vs. concomitant RT alone. Budach et al [29] in their meta-analysis showed that induction treatment with TPF followed by CTRT does not result in significant improvement in OS or PFS.

The comparison of landmark studies on laryngeal preservation in locally advanced laryngeal cancer is provided in

Table 2 [19-21, 23].

Biological Therapy in Organ Preservation

Bonner et al [30] in their randomized trial of cetuximab with RT (CRT) vs. RT alone in head neck cancers (nearly 40% were laryngopharynx) demonstrated significant improvement in locoregional control (24.4 months vs. 14.9 months in cetuximab with RT and RT alone, respectively) as well as OS (49 months vs. 29.3 months) in those patients who received targeted therapy with RT. Although, these results were best seen in the subset of oropharyngeal cancers, there was a positive trend even in laryngopharynx. In a recent subgroup analysis of patients with hypopharyngeal and laryngeal cancers, Bonner et al analyzed the impact of cetuximab and RT in laryngeal preservation. The rates of laryngeal preservation were 87.9% at 2 and 3 years in the CRT group compared with 85.7% at 2 years and 76.8% at 3 years in the RT alone group. The 2.2% and 11.1% absolute improvements in the rates of laryngeal preservation at 2 and 3 years respectively favored CRT compared with RT alone but this improvement was not statistically significant (HR, 0.57; 95% CI, 0.23 - 1.42; P = 0.22). In addition, there was a 4% and 8.9% absolute improvement in laryngectomy free survival at 2 and 3 years, respectively. However, this difference also could not reach statistical significance (HR, 0.78; 95% CI, 0.54 - 1.11; P = 0.17) [31]. The targeted therapy plus radiotherapy approach has never been compared head on to concurrent CRT, which still remains the standard of care.

Consensus Panel Recommendation

An international consensus panel was convened to develop guidelines for the conduct of phase III clinical trials of larynx preservation in patients with locally advanced laryngeal and hypopharyngeal cancer. According to their recommendations, future trial populations should include patients with T2 or T3 laryngeal or hypopharyngeal squamous cell carcinoma not considered for partial laryngectomy and should exclude those with laryngeal dysfunction or aged > 70 years. Baseline and post-treatment functional assessments should include speech and swallowing evaluations. Furthermore, voice should be routinely assessed with a simple, validated instrument. Regarding endpoints, the primary endpoint should capture survival and function. As a result, the panel created a new endpoint of laryngesophageal dysfunction (LED)-free survival, which includes the events of death, local relapse, total or partial laryngectomy, tracheostomy at > 2 years, or feeding tube at > 2 years. Recommended secondary endpoints are freedom from LED, OS, PFS, locoregional control, time to tracheostomy, time to laryngectomy, time to discontinuation of feeding tube, and quality of life/patient-reported outcomes [32].

Emerging Approach

All patients with locally advanced head and neck cancer may not

benefit from concurrent CRT. The data regarding the reliable molecular markers predicting the response to CRT is scarce. The excision repair cross-complementation group 1 (ERCC1) enzyme is a key element of the nucleotide excision repair pathway that removes cisplatin-induced DNA adducts and has been associated with resistance to platinum-based chemotherapy. Jun et al showed that in SCCHN patients, those with ERCC1-negative tumors were more likely to derive a substantial benefit from cisplatin-based induction chemotherapy, translating to a lower risk for cancer-related death than in patients with ERCC1-positive tumors [33]. As a result, the evaluation of ERCC1 is recommended for future correlative biomarker studies.

Conclusion

The goal of treatment of laryngeal cancer is to achieve best oncologic outcome with optimum functional preservation. The treatment of early laryngeal cancer is radical RT or organ preserving surgery. However, RT is preferred because of excellent and equivalent tumor control, larynx preservation and better or equal voice quality and it is a time tested approach. For advanced laryngeal cancer, concurrent CRT is the best organ preserving modality. Induction chemotherapy followed by RT/CRT has not shown benefit over upfront CRT. Biological therapy is better as compared to RT alone in terms of laryngeal preservation; however, there is no head on comparison with CRT. Emerging molecular markers are coming up which promise to individualize further treatment with optimum laryngeal preservation.

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