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REVIEW ARTICLE

Organ Preservation Protocols in T4 Laryngeal Cancer: a Review of the Literature

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Abstract
Population-based studies indicate that chemoradiation has become the most popular treatment for advanced laryngeal cancers; however, by extrapolating trial results to the general population, several issues have emerged, such as reduced overall survival, non-functional laryngeal preservation, and poor response to treatment. Although included in these trials, T4 laryngeal and hypopharyngeal cancers with cartilage invasion formed a small percentage of these patients and questions over whether they were appropriately staged remain unanswered. Literature on the use of chemoradiation in this set of patients, including the challenges, treatment considerations, and factors predicting response to treatment and outcomes, was reviewed. Current evidence indicates that all patients of T4 laryngeal and hypopharyngeal cancer are not suitable candidates for organ preservation; this modality should be offered only to select patients with good performance status and access to rehabilitative care and regular follow-up in order to achieve good results.

Keywords Advanced laryngeal cancer · Organ preservation · Chemoradiotherapy · Chemoselection · Induction chemotherapy

Introduction

The landmark trials in organ preservation for laryngeal cancer were by the Veterans Affairs (VA) Laryngeal Cancer Study Group in 1991 [1], followed by the Groupe d'Etude des Tumeurs de la Tête et du Cou (GETTEC) group study in 1998 [2] and the Radiation Therapy Oncology Group (RTOG) 91-11 trial in 2001 [3].

The VA study [1] showed that in stages III and IV, laryngeal squamous cell carcinoma (SCC) induction chemotherapy (IC) followed by definitive radiotherapy (RT) could help preserve the larynx in 64% of patients, with a comparable 2-year overall survival (OS) seen in the organ preservation and surgical treatment arms. The GETTEC study [2] was on the use of IC in T3 SCC of the larynx to determine if patients were likely to respond to RT. They concluded that IC was unable to predict suitability for organ preservation protocols (OPP) and that that patients who underwent surgery with adjuvant radiotherapy (SRT) had a better 2-year OS than those who underwent IC+RT; this challenged the notion of organ preservation protocols for patients who responded to IC. The RTOG 91-11 study [3] then found that concurrent chemoradiotherapy (CCRT) improved laryngectomy-free survival when compared to IC+RT or RT alone. However, the concept of functional preservation was not explored in these trials; functional preservation refers to the presence of an in situ larynx with preserved breathing, speech, and swallowing function [4].

The results of the VA and the RTOG 91-11 studies have resulted in the increasing use of OPP for the treatment of advanced laryngeal cancer, as reflected in a number of population-based studies. Carvalho [5] showed that the percentage of patients treated with organ preservation protocols increased from 37.4 to 50.6%, between 1974 and 1997. Hoffman [6] also found an increase in preservation therapy from 2.3 to 13.2% from 1985 to 2001, as did Megwalu [7] who demonstrated an increase from 8 to 48% from 1992 to 2009.

Another important consideration is the long-term survival of patients treated with OPP; as the number of patients being treated with non-surgical therapy increased, long-term outcome data began to appear. Hoffman [6] published the first

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study to show statistically significant worse OS for patients with T3 laryngeal SCC managed with OPP. Research by Megwalu [7], Chen et al. [8], O'Neill [9], and Timmermans [10] showed significant decreased overall survival in the OPP group by 5%, 18%, 13%, and 6% respectively. These studies, although retrospective were large, and raised the question as to why patients on OPP had worse survival outcomes when compared to surgery, in direct contradiction to trial findings.

These reasons were explained at least in part, Sanabria [11], who referred to the selection bias associated with randomized control trials, and complexity bias, which refers to the complex interdisciplinary care that patients receive in a trial setting, which may not be feasible in a non-academic, community setting. Sanabria also suggested that there was bias for physicians to opt for organ preservation protocols in advanced laryngeal cancers, as laryngectomy is seen as a "mutilating treatment," even when surgery should be considered. The significant variation in the number of patients with advanced laryngeal tumors in the major trials, the heterogeneity in the nature of laryngeal cancers under the umbrella of stage III and stage IV disease, combined with the small numbers of patients in trials, may explain the difficulty in extrapolating trial data to suggest that all patients would be good candidates for organ preservation strategies. Our study aims to review the available data on the use of OPP in patients of T4 laryngeal or hypopharyngeal SCC.

Extrapolating Trial Results to the General Population

The VA study [1] included 216 patents (65%) with T3 tumors, of which 117 patients (54%) had fixed vocal cords, and 85 patients (25%) with T4 tumors, with 30 patients (35%) of them having gross cartilage invasion. RTOG 91-11 [3] excluded large-volume tumors (those with grossly penetrated cartilage or with > 1-cm tongue base extension); their study included only 51 patients (9%) with T4 tumors; 79% of patients had T3 tumors, 46% of whom had vocal cord fixation. The GETTEC trial [2] only included T3 patients with vocal cord fixation and did not specify percentage of patients with cartilage invasion. This could help account for the difference in response to OPP; the VA trial showed a higher incidence of salvage laryngectomy in those with T4 compared to other T-stages. RTOG 91-11 did not have a surgical arm in the trial and whether patients with fixed cords had a higher requirement for salvage laryngectomy has not been specified. The GETTEC study showed better survival in the SRT group compared to the CCRT group. These conflicting results can be explained by the innate difficulties in staging laryngeal SCC.

Staging of laryngeal tumors has intrinsic challenges; it has been shown that clinical differentiation between vocal cord restriction and fixity has a wide inter-observer variation [12] and radiographic staging of cartilage invasion has a wide variation in sensitivity and specificity between centers, even when the modality used is the same [13]. These difficulties in staging disease can cause stage migration with an impact on prognostication. Since both the VA trial [1] and the RTOG 91-11 [3] had T3 patients with and without vocal cord fixation, whether some of these patients were T2 and hence represented a better response to CCRT is a cause for concern [11]. Cartilage invasion is also particularly problematic, since accurate determination of degree of cartilage invasion has been difficult [14]. This may account for the contrasting results in the trials and the observed patient data. As a result, understaging of patients may result in an expectation of better outcome and possible delay in salvage laryngectomy, which may have prognostic ramifications [15].

The concern with T4 disease is the hypothesis that cartilage invasion by the tumor is a marker of clinical aggression, and that these tumors have intrinsic hypoxia which make them naturally resistant to treatment with CCRT [16]. This is reflected in the recommendation by the American Society of Clinical Oncology that patients with cartilage invasion should undergo total laryngectomy as the primary modality of treatment [4]. The National Comprehensive Cancer Network guidelines make a similar recommendation [17]; however, CCRT continues to be a more popular choice than surgery for the treatment of T4 tumors in the large observational studies [5–10].

Outcomes in T4 Laryngeal Cancer Based on Treatment Modality

Very few patients from prospective trials had T4 disease; it is likely that the data from T3 tumors is being extrapolated to justify OPP in T4 disease. Observational data, however, suggests that T4 patients have shown improved survival when treated with surgical treatment [18–21]. Table 1 summarizes the findings of large studies (having over a hundred patients) comparing OS in CCRT and SRT in laryngeal cancer.

Upfront prospective comparisons between a surgical and non-surgical arm in advanced laryngeal cancer are improbable; the end-points for laryngeal cancer trials are laryngeal preservation rate or laryngectomy-free survival (LFS) rather than OS as the aim of these trials is organ preservation. However, retrospective comparisons are available.

Choi et al. [27] in their multi-centric retrospective review compared patients ($n = 89$) who received either SRT ($n = 56$) or non-surgical therapy ($n = 36$), which included CCRT, IC+RT, or RT alone. They noted that the SRT group had better progression-free survival and OS. Additionally, 33% of those treated with organ preservation therapies required surgical salvage. Interestingly, the survival benefit afforded by surgery was only noted in stages N0–1 and not beyond, likely to be due to the distant pattern of failure in those with advanced nodal disease.

Table 1 Large observational studies showing comparison of overall survival with concurrent chemoradiotherapy (CCRT) and surgery for advanced laryngeal cancers

Author	Number of patients	Subsite and stages included	Overall survival at 5 years		*p* value
			CCRT	Surgery	
Gourin et al. [19]	451	Stage I–IV laryngeal cancer	25	55	$p < 0.0001$
Dziegielewski et al. [18]	258	T3 and T4 laryngeal cancer	15	49	$p < 0.04$
Elegbede et al. [22]	225	Stage III and IV supraglottic laryngeal cancer	52	52	$p = 0.60$
Rosenthal et al. [20]	221	T4 laryngeal cancer	48	60	$p = 0.70$
Karlsson et al. [23]	176	Stage III and IV laryngeal cancers	42	58	$p = 0.93$
Rades et al. [24]	122	T3 and T4 laryngeal and hypopharyngeal cancer	66	75	$p = 0.95$
Vengalil et al. [21]	107	T4 laryngeal cancers	41	70	$p < 0.01$
Dyckhoff et al. [25]	107	T4 laryngeal cancers	12	48	$p = 0.036$
Stokes et al. [26]	3542	T4 laryngeal cancer	38	52	$p < 0.01$

Similar findings were noted in an observation cohort of advanced laryngeal cancer patients by Dyckhoff et al. [25] treated with CCRT where chemoradiotherapy had twice the risk of death compared to patients treated with SRT.

Patel [28] retrospectively studied 34 patients of T4 laryngeal/hypopharyngeal SCC, of whom 21 completed CCRT (with cisplatin or carboplatin) and 13 underwent SRT. In the CCRT group, 19 patients (90%) had a complete response determined either by direct laryngoscopy or imaging; however, of these, 4 (19%) had a local recurrence within the first 9 months. The remaining 15 patients (71%) remained free of local disease with a mean follow-up of over 1 year. In the SRT group, there was 100% local control with a mean follow-up of over 1 year. They stated that although the initial local response rate to CCRT was 90%, the response was not durable. The corresponding local control for those who underwent surgery was 100%.

Stokes et al. [26] studied patients ($n = 3542$) of T4M0 laryngeal cancer from the National Cancer Data Base who received either surgery with adjuvant radiotherapy ($n = 1597$) with those who received with either CCRT ($n = 1597$) or multi-agent IC+RT ($n = 386$). They found that those treated with CCRT had the worst OS compared to those treated with IC+RT (hazard ratio (HR) 1.55, $p < 0.01$) or SRT (HR, 1.25, $p < 0.01$). A peculiar finding, however, was that those treated with IC+RT had a comparable overall survival to those treated with SRT ($p = 0.10$). They were unable to explain these findings based on their data and stated that surgery should remain the standard of care for T4 laryngeal cancer.

Selection of Patients for Organ Preservation Protocols

Several tools have been used to determine susceptibility to organ preservation protocols with varying degrees of success. Response to IC is a commonly used tool and has shown to be a reliable indicator of CCRT sensitivity [29] and has been included in the NCCN guidelines [17] for the management of T3/T4 supraglottic and glottis SCC. IC can help determine whether to offer SRT or CCRT as the definitive treatment modality.

Knab [30] retrospectively studied a series of 32 patients with T4 laryngeal cancer, of whom 23 had large-volume tumors defined by cartilage invasion or invasion > 1 cm into the base of tongue. These patients were treated with multiple cycles of weekly carboplatin and paclitaxel IC, followed by concomitant paclitaxel, 5-fluorouracil, hydroxyurea, and hyperfractionated radiotherapy. The 4-year overall survival for patients with large-volume tumors was 56% with 81% larynx preservation. After minimum of 1-year follow-up, 13% of patients were gastrostomy tube dependent and 20% were tracheostomy dependent. They noted that there was no statistical difference in the disease-free survival or OS when comparing large-volume and non-large-volume T4 tumors and induction chemotherapy did not provide any survival benefit. When comparing functional outcomes in the two groups, there was no difference in gastrostomy tube or tracheostomy requirement at 12 months follow-up; however, speech impairment in those with large-volume tumors was more common than in non-large-volume tumors (40% vs 27%).

A study by Worden [31] retrospectively examined a group of T4 patients in their two sequential phase II randomized control trials. This was done to determine the use of chemoselection as a strategy for determining patient suitability for organ preservation protocols [28]. They studied 36 patients, 16 with cartilage invasion alone and 20 with cartilage invasion and extralaryngeal spread, who as per protocol received one cycle of 5-fluorouracil with either cisplatin or carboplatin. Those achieving > 50% response at the primary tumor, as determined by direct laryngoscopy, received concurrent chemoradiation within 3 weeks, with 3 cycles of cisplatin

(or carboplatin) on days 1, 22, and 43 of radiation, administered to a total of 70 Gy. Of these 36 patients, 29 (81%) had a > 50% response to induction chemotherapy at the primary site, of whom 27 received CCRT. Of those who received CCRT, 23 (85%) were complete histological responders (CHRs). Only 8 patients out of the 23 CHRs (34.6%) received adjuvant chemotherapy—the remaining patients refused further chemotherapy or were no longer suitable candidates for chemotherapy. The 3-year OS and LFS was 78% and 58% respectively. The 3-year disease-specific survival (DSS) for those who received adjuvant chemotherapy was 100% compared to 73% for those who did not. Six (17%) patients out of the total 36 patients of T4 laryngeal cancer were gastrostomy tube dependent.

Both Knab [30] and Worden [31] concluded that induction chemotherapy was a reasonable strategy to determine suitability for organ preservation protocols but neither study had a surgical arm in their study design.

Popovtzer et al. [32] used a single cycle of induction TPF (docetaxel, cisplatin, and 5-fluorouracil) to determine treatment of their T3/4 laryngeal cancer cohort with either SRT or concurrent CCRT. Those who responded (> 50% as assessed clinically and by PET) were administered CCRT while the remainder underwent SRT. Eighty-three percent of patients responded to the induction chemotherapy and the 2-year disease-specific survival was 86%, with a larynx preservation rate of 83%. Two years of overall survival was 92% for those who responded to induction chemotherapy while 50% for those who did not ($p = 0.02$). T-stage did not predict survival.

Pre-treatment positron emission tomography (PET) appears to be a promising tool in predicting the response of laryngeal and hypopharyngeal SCC to organ preservation strategies with either radiation or chemoradiation. Several studies showed the value of PET-derived metabolic tumor volume (MTV) in determining locoregional control and overall survival ([33–38], Table 2). Hanamoto [42] showed that total lesion glycolysis (TLG) was also an independent predictor of complete response to treatment. A meta-analysis of 1180 patients by Pak [43] also showed MTV and TLG were independent indicators of progression and recurrence. Evidence would suggest consideration of incorporating pre-treatment PET into treatment planning, especially for high-risk patients.

Discussion

McNeil first discussed the concept of organ preservation therapy in laryngeal cancer in an article [44] in 1981. It was a survey of 12 fire fighters and 25 executives in good health who were asked to imagine they had T3 laryngeal SCC; they answered that they were willing to trade 15–30% of their life expectancy to preserve their larynx. The criticism was the small sample size, and the bias arising from the fact that they were asked to imagine that they suffered from disease, but were otherwise healthy.

A more recent study by Laccourreye [45] summarized the findings of a detailed survey of 269 patients of advanced laryngeal cancer about their choice of treatment and had different findings. In contrast to McNeil, they found that 28.6% of subjects were not willing to consider any trade-off of survival in exchange for preserving their larynx. The patients willing to trade-off survival in exchange for preserving their larynx expressed a very wide range of desired survival from 5 to 100% (median of 33%). Nearly half of the patients wanted additional information on their option before taking a decision on their treatment, which was more common in patients with an education beyond a secondary school level or patients with a family history of cancer. On receiving information on the percentage risk of permanent tracheostomy and gastrostomy after CCRT, the percentage of patients unwilling to accept any trade-off in survival to preserve the larynx increased to 31.2% and 56.1% respectively.

These findings are especially relevant in the context of the long-term results of the RTOG 91-11 [46], which showed 34% of patients who received CCRT patients died of unknown causes, possibly a reflection on the long-term toxicity; this must be taken into account and made known to the patient while discussing treatment options.

Currently, there is no level I evidence comparing SRT and CCRT in advanced laryngeal cancers for survival. Additionally, when facing the potential risk of decreased life expectancy associated with long-term toxicity of CCRT, the

Table 2 Studies showing use of PET-derived parameters to predict response to chemoradiotherapy in head and neck squamous cell carcinoma

Author	Number of patients	No of patients with laryngeal/ hypopharyngeal cancer (%age)	End-points	PET parameters	Statistical significance
Romesser et al. [39]	41	15 (37%)	LC, OS	GTV, MTV	Yes
Tang et al. [40]	83	12 (14%)	DP, PFS, OS	MTV	Yes
Park et al. [36]	81	61 (100%)	LP, DFS	SUV_{max}, MTV	Yes
Minn et al. [41]	72	22 (31%)	LRFS, DFS, MFFS, OS	SUV_{max}, MTV, TLG	Yes
La et al. [34]	85	12 (14%)	DFS, OS	MTV	Yes

decision regarding treatment *needs* to be discussed with the patient. The likelihood of permanent tracheostomy and gastrostomy tube dependence has also been shown to influence the treatment decision and needs to be explained. Given that the primary goal of any treatment is control of disease, and that patients have a wide variation in their priorities, organ preservation should not necessarily be offered to patients of T4 laryngeal cancer as a default therapy in lieu of the perceived functional benefits. The pros and cons of all therapeutic modalities must be discussed with the patients, who should be allowed to make an informed decision.

Studies to determine the quality of life (QoL) in patients with total laryngectomy and radiation therapy when compared to organ preservation therapies have failed to demonstrate a significant difference between the groups. Hanna [22] showed that the QoL scores as measured by European Organization for Research and Treatment of Cancer (EORTC) questionnaires were comparable. Patients who received SRT had greater difficulties with social functioning relative to the CCRT group. They also had greater sensory disturbances of smell and taste, use of painkillers, and coughing. Those treated with CCRT had significantly greater problems with dry mouth. It is to be noted, however, that most patients in the study had primary voice restoration and speech rehabilitation following laryngectomy. Similar findings have been noted in other studies [23, 24].

Another important consideration in success of treatment is the facilities available to the patient. Organ preservation trials were conducted in tertiary-care level academic centers with access to multi-disciplinary, often state-of-the-art care. This is likely a major contribution to the successful functional outcomes in patients treating with CCRT. However, all centers offering CCRT may not have access to swallowing therapists or the rehabilitative support required to achieve these results, as reflected by worse outcomes [39]. These centers also need strict surveillance and the option of salvage surgery as and when required to maintain an adequate standard of care, which may not be in the case in all situations [8, 40].

Conclusion

Current data is insufficient to show that CCRT has an equal overall or disease-free survival when compared to surgery with adjuvant radiation in the treatment of T4 laryngeal SCC. Observational population-based studies have showed worse overall survival in patients treated with CCRT compared to those treated with SRT, which raises the concern of mortality associated with long-term toxicity of CCRT. Given that organ preservation is not always a patient concern, both options must be offered to patients and they should be allowed to make an informed decision.

Amongst organ preservation protocols, CCRT is the standard of care. Standard IC protocols have been shown to predict response to CCRT, but the response may not be durable, generating interest in more sensitive and durable predictors of response. Pre-treatment PET has been shown to be of value in several studies, but has yet to be incorporated into trial settings. Prospective trials are required to determine the best treatment for patients of advanced laryngeal cancer.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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