

# Organ preservation strategies: Review of literature and their applicability in developing nations

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## Abstract

There has been a change in practice in locally advanced laryngopharyngeal cancers toward non-surgical treatment modalities. Although, there have been landmark trials pertinent to organ preservation, their applicability in developing nations is a topic of much debate. The organ preservation concept was based on the findings of pivotal trials by the Veterans Affairs, European Organization for Research and Treatment of Cancer group and Radiation Therapy Oncology Group. Subsequently numerous studies have been designed to evaluate intensification of treatment as well as study toxicity and tolerability. This review critically analyses current evidence for larynx preservation, experience from various centers on organ preservation strategies as well as applicability of these protocols to developing nations.

**Key words:** Chemoradiotherapy, clinical protocols, developing countries

## Introduction

In the past three decades locally advanced laryngopharyngeal cancer management has undergone a paradigm shift from surgical dominance to non-surgical organ preservation strategies. Randomized controlled trials on larynx preservation approaches have contributed to this change in practice. Larynx preservation was possible without compromising survival against the time tested surgical approach of laryngectomy with adjuvant radiotherapy (RT). However, applicability of these trials out of a protocol setting was a cause of concern more so in the developing nations. Therefore, individual centers adopted these protocols some of them with certain modifications to increase their applicability. However, there remains a paucity of robust data from the developing world on non-surgical organ preservation strategies. This review aims at analyzing available literature and put forth current evidence as well as discuss applicability of these strategies especially in the developing countries.

## Current Evidence

Inception of organ preservation strategies took seed in the early 80s with initial trials demonstrating the potential of chemotherapy to cause tumor regression as well as predict response to RT.<sup>[1]</sup> Since, then chemotherapy is used in conjunction with RT as an approach to organ preservation in various combinations (neoadjuvant, concurrent and alternating).

The Veterans Affairs (VA) Laryngeal Cancer Study group was pivotal in establishing the role of non-surgical methods of treatment for advanced laryngeal cancers.<sup>[2]</sup> In this study, patients were randomized to the experimental arm of induction chemotherapy followed by RT in those with partial response against the standard of care i.e. surgery followed by adjuvant RT. This approach was able to achieve larynx preservation in 64% maintaining similar overall survival in both arms. This study set the stage for further larynx preservation studies and established induction chemotherapy as standard of care.

A study with similar design but predominantly focused on locally advanced hypopharyngeal cancers was conducted by the European Organization for Research and Treatment of

Cancer (EORTC).<sup>[3]</sup> The results of this trial, like the VA results strongly established the role of induction chemotherapy in hypopharyngeal cancers as well. With similar overall survival, larynx preservation was achieved in 48%. The group essentially concluded that larynx preservation protocol was a feasible option in hypopharyngeal cancers in the form of induction chemotherapy and RT. The authors however noted that the response was more favorable for T2 disease when compared to T3 and T4 disease. The 10 year update suggests similar overall survival in both the arms and survival with a functional larynx in 8.7%.<sup>[4]</sup>

Such was the popularity of larynx preservation approaches that a study conducted by Groupe d'Etude des Tumeurs de la TeÅ te et du Cou (GETTEC), Head and Neck Tumor Study Group had to be prematurely abandoned due to a strong patient preference for organ preservation over surgical resection.<sup>[5]</sup> Although, the findings were not adequately powered, the study demonstrated significantly poorer survival in the induction chemotherapy arm than those who underwent primary surgery (2 year survival 84% in the surgery group vs. 69% in the chemotherapy group).

In the 1990s, Forastiere *et al.* conducted a three armed study comparing induction chemotherapy, concurrent chemoradiotherapy (CRT) and RT alone in patients with locally advanced glottic and supraglottic cancers.<sup>[6]</sup> With comparable overall survival in the three arms, larynx preservation was best with concurrent CRT (2 year larynx preservation rate of 88%, 75% and 70% in the concurrent CRT, induction chemotherapy and RT alone arm). In addition, locoregional control was significantly better with concurrent CRT. This was further corroborated by the meta-analysis of chemotherapy in head neck cancer (MACH-NC) which demonstrated an absolute benefit of chemotherapy administered concomitantly.<sup>[7]</sup>

Similarly, Prades *et al.* compared induction chemotherapy versus concurrent CRT in hypopharyngeal cancers.<sup>[8]</sup> The induction chemotherapy regimen comprised of two drugs as in the EORTC trial. Amongst 71 patients with advanced pyriform sinus cancer, larynx preservation was superior for concurrent CRT group (2 year larynx preservation 92%) compared with induction chemotherapy (68%). However, there was no survival benefit with concurrent CRT.

A 10 year update of the Radiation Therapy Oncology Group (RTOG) 9111 trial gave some insight into the long-term effect of these approaches.<sup>[9]</sup> RT alone was significantly inferior to both the chemotherapy arms. With regards to toxicity, deaths

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unrelated to cancer or treatment were significantly higher in the concomitant chemotherapy arm (30.8% vs. 20.8% in the induction arm vs. 16.9% in RT alone arm). It could be attributed to late toxicity related to swallowing dysfunction along with silent aspiration.<sup>[10]</sup> Long-term interpretation of speech and swallowing showed acceptable results although available data was limited.

Thus while locoregional control and larynx preservation was significantly improved by concomitant use of chemotherapy with RT, the tolerance of such intensive regimens was a cause of concern. Since RT alone was proven to be inferior in treating such cancers, the search for alternative treatment strategies started.

Bonner *et al.* in their randomized trial of Cetuximab with RT 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 overall survival (49 months vs. 29.3 months) in those patients who received targeted therapy with RT.<sup>[11]</sup> Although, these results were best seen in the subset of oropharyngeal cancers, there was a positive trend even in laryngopharynx. However, the targeted chemotherapy approach has never been compared head on to concurrent CRT, which still remains the standard of care. This approach would seem logical however in elderly patients, those with compromised renal functions and patients with poor performance status in whom CRT is not tolerated. In an attempt to avoid the toxicities associated with chemotherapy, other approaches using altered fractionation have also been studied. Accelerated RT (6 days) is found to have better locoregional control when compared to conventional 5 day RT (70% vs. 60% 5 year locoregional control respectively). This was demonstrated by the Danish Head and Neck Cancer Group (DAHANCA) six and seven trial where more than 90% of patients were glottic, supraglottic or pharyngeal cancers.<sup>[12]</sup> More than 97% patients completed the intended treatment. Although, toxicity was higher in the 6 day RT arm, it was found to be transient.

Simultaneously, researchers explored alternate schedules incorporating aggressive induction chemotherapy in an attempt to improve preservation and survival results. Induction chemotherapy regimens became more intensive from the use of single agent chemotherapy (Platinum based) in the 1970s to doublet chemotherapy (addition of 5-fluorouracil) in the 1980s to three drug (addition of taxanes) in 1990s. (Taxotere) TAX 324 study had determined the benefit of three drug versus two drug chemotherapy as induction chemotherapy regimen for overall survival.<sup>[13]</sup> At about the same time, Groupe d'Oncologie Radiothérapie Tête Et Cou (GORTEC) 2000-01 trial compared three drug (Docetaxel, Cisplatin, 5-fluorouracil) versus two drug (Cisplatin, 5 fluorouracil) in laryngeal and hypopharyngeal cancers for larynx preservation.<sup>[14]</sup> Among 220 patients, 3 year larynx preservation rate was 73% in the Taxane, platinum, fluorouracil group compared to 63% in the platinum, fluorouracil arm.

While three drug chemotherapy did demonstrate superiority over doublet chemotherapy, concerns were raised about tolerance to CRT following three drug induction chemotherapy. These were addressed by the trial conducted

by the GETTEC and GORTEC group, TREMPIN trial (RT with cisplatin vs. RT with cetuximab after induction chemotherapy for larynx preservation).<sup>[15]</sup> It attempted to evaluate the feasibility of sequential chemotherapy i.e. induction chemotherapy followed by concurrent CRT versus induction chemotherapy followed by bioradiotherapy. Although larynx preservation and control rates were equal in both the arms, compliance was higher in the bioradiotherapy arm albeit high toxicity in both arms (nephrotoxicity in concurrent CRT and skin toxicity in targeted therapy arm). However, no conclusive proof exists on the role of sequential induction chemotherapy followed by concurrent chemotherapy.

### Critical Analysis of Literature

Non-surgical organ preservation was established following the VA and EORTC trial. Amongst non-surgical approaches to advanced laryngopharyngeal cancers, CRT has become the standard of care in view of its head on comparison with induction chemotherapy regimens. However, it may be kept in mind that long-term results of the RTOG 9111 study show a trend toward induction chemotherapy although not statistically significant. Furthermore, benefit of sequential three drugs over two drug induction chemotherapy remains to be compared with concurrent CRT.

A common critique for organ preservation trials remains the primary endpoint which in all the studies was larynx preservation. These trials would be inadequately powered to compare survival in the comparative arms. To add to that, the definition of larynx preservation is not standard across all the studies. Consequent to this, a consensus panel laid down recommendations on the trial design for future studies on larynx preservation.<sup>[16]</sup> The panel recommended the endpoint to be a combination of survival along with a functional larynx. Observations by Chen and Halpern, Hoffman *et al.* of trend toward decreasing survival in laryngeal cancers must be kept in mind particularly due to increased popularity of non-surgical approaches to such advanced cancers.<sup>[17,18]</sup>

### Outcomes of Organ Preservation in Individual Centers

Preferences for organ preservation strategies are diverse with North America and Australia preferring the concomitant CRT regimen while European centers preferring the induction chemotherapy approach.<sup>[10]</sup> Various authors have shared their individual center experiences, which are tabulated [Table 1]. Trends are by and large comparable to evidence from randomized controlled trials.

### Experience of Surgical Salvage after Organ Preservation

Major wound complications more than 60% have been reported in salvage surgeries after larynx preservation strategies.<sup>[24]</sup> Salvage laryngectomy reports from the RTOG 9111 study suggest major complications in more than 50% cases. Pharyngocutaneous fistulas were maximum for those who received concurrent CRT.<sup>[25]</sup>

### Experience from Developing Nations

Differences exist in several aspects, which preclude universal applicability of the larynx preservation strategies<sup>[26,27]</sup> viz:

1. Preponderance of advanced cancers in the form of bulky disease and large nodal burden (Stage IV). Larynx

**Table 1: Experience of individual centers on organ preservation strategies**

Author (year)	No. of patients	Subsite	Results	Protocol
Taguchi <i>et al.</i> <sup>[19]</sup>	102	Larynx	5 years O.S: 63.9% 5 years DSS with larynx preservation: 54.1%	CRT
Kogashiwa <i>et al.</i> <sup>[20]</sup>	32	Laryngeal and hypopharyngeal	3 years survival in all patients 67.1%, 82.9% in laryngeal cancer, 51.6% in hypopharyngeal carcinoma	NACT followed by CRT
Nishimura <i>et al.</i> <sup>[21]</sup>	23	Laryngeal and hypopharyngeal	5-year DSS rate 59.4% in all patients, 51.9% in hypopharyngeal carcinoma, 71.0% in the laryngeal carcinoma	CRT (cisplatin and 5 FU)
Rades <i>et al.</i> <sup>[22]</sup>	44	Laryngeal and hypopharyngeal	2 years locoregional control 66%	CRT
Lambert <i>et al.</i> <sup>[23]</sup>	82	Laryngeal and hypopharyngeal	3 years O.S and DFS was 63% and 73%	CRT

DSS=Disease-specific survival, O.S=Overall survival, CRT=Chemoradiotherapy, NACT=Neoadjuvant chemotherapy, FU=Fluorouracil, DFS=Disease free survival

preservation studies had limited number of such patients. The tumor characteristics of patients in RTOG 9111 showed that 42-47% patients were T2 or T3 without cord fixation in all 3 arms. Less than 10% of patients had T4 disease in stark contrast to those presenting in developing nations

- Poor performance status partially contributed by the preponderance of hypopharyngeal cancers resulting in dysphagia
- Hypopharyngeal cancers, which are traditionally known to be poor performers form the major subsite along with marginal zone cancer (supraglottis with hypopharynx).<sup>[28,29]</sup> This is in contrast to the areas from where these trials originated where the major burden is that of glottic and supraglottic cancers
- Limited availability of infrastructure and expertise to administer and monitor such intensive regimens.

Treatment modifications have been adopted to cater to such a patient profile as well as logistic limitations

- Weekly low dose chemotherapy (Cisplatin 30 mg/m<sup>2</sup>) was found to be a more feasible option with acceptable toxicity and lesser treatment interruptions (<15%). This regimen showed similar control rates when compared to routinely practiced 3 weekly high dose chemotherapy.<sup>[30]</sup> The feasibility of this regimen is based on the evidence that a cumulative therapeutic dose of chemotherapy (>200 mg/m<sup>2</sup>) is essential for therapeutic benefit.<sup>[31]</sup>
- Six day RT which was proven to give better locoregional control when compared to 5 day RT as a regimen was applicable in developing nations as was tested by the randomized controlled trial by the International Atomic Energy Agency (IAEA) ACC trial.<sup>[32]</sup> The control rates were found to be significantly higher and this strategy was found to be logistically feasible.
- Neoadjuvant chemotherapy to determine responders and feasibility to organ preservation particularly in patients with bulky disease, N3 nodes or exolaryngeal disease without cartilage erosion. As many as 73% patients could be further considered for organ preservation as was determined by an analysis of neoadjuvant chemotherapy on hypopharyngeal cancers.<sup>[33]</sup> This approach helps in determining RT responders since both chemo and RT response follow a similar mechanism of deoxyribonucleic acid strand breakage. This could behave as a surrogate marker avoiding potential salvage surgery related complications. This was demonstrated by the VA study in which amongst all those patients who underwent surgery

on the induction chemotherapy arm, 50% underwent surgery (30 patients) prior to RT while 50% (29 patients) underwent surgery after RT.

A large cohort of advanced hypopharyngeal cancers (more than 500 patients) treated with non-surgical approach was retrospectively reviewed.<sup>[34]</sup> There were varied treatment strategies adopted depending on the time period of presentation which influenced a change in treatment policy from RT alone to neoadjuvant to concurrent, weekly CRT in most recent cases. The 3 year locoregional control achieved was 47.1% comparable to published literature.

In a survey conducted among patients in a Tertiary Cancer Center from India, it was found that global quality-of-life was similar between those who underwent organ preservation strategies versus those with total laryngectomy except xerostomia affecting those on non-surgical treatment and voice related problems affecting those with total laryngectomy.<sup>[35]</sup> It must also be kept in mind that patients would rather prefer intact function after laryngectomy with deglutition without aspiration as well as good quality prosthetic voice as opposed to a functionless, frozen larynx.<sup>[36]</sup> Thus, total laryngectomy may still be considered a viable option with optimum prosthetic voice rehabilitation in such moderately advanced cancers.

#### Future trends

Determining molecular biomarkers as predictors for response to non-surgical treatment modalities has been attempted. The role of epidermal growth factor receptor, E-catherin and b-catenin Tp53 mutation has been explored.<sup>[37]</sup> Although, no conclusive evidence exists, protein profiling using tissue microarrays and immunohistochemistry could be exploited.<sup>[38]</sup> However, these approaches are investigational as of date.

#### Conclusion

Organ preservation protocols appear to be promising and are here to stay. Current evidence shows CRT to be standard of care. Feasible modifications have been adopted for improving applicability of these strategies like weekly concurrent chemotherapy with RT and altered fractionation RT. Future studies for organ preservation strategies should be designed with survival as the end point.

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