

Organ preservation in Ca Larynx/Hypopharynx

Dr. Manish Siddha

SRJ-CBCC Cancer Hospital

Indore

Introduction

- The larynx is involved in many vital functions such as breathing, speaking, and swallowing, and as a result, both larynx cancer and its treatment may significantly affect quality of life.
- The 5-year survival rate for patients with stage III/IV larynx cancer has significantly improved during the years 2004–2009 compared to those patients diagnosed before 2004. However, the current 5-year survival is only 44% for this population

- LP is also an important issue for patients with carcinomas of the hypopharynx. These carcinomas are biologically different from larynx carcinomas and have a higher tendency to disseminate distantly. As a result, patients with this disease usually have a poor performance status, and salvage surgery after radiation therapy or chemo-radiation is associated with increased morbidity

- preservation of the larynx without survival is not a meaningful outcome for patients.
- Therefore, for patients with larynx and hypopharynx cancer, the ultimate goal is survival with a functional larynx (defined as survival without local disease, tracheotomy, feeding tube, or gastrostomy)

Induction chemotherapy followed by radiation therapy (IC + RT)

- Cisplatin/ plus minus vincristine or bleomycin response rate of 80%, but with a complete response rate of only 30%.
- In the early 1980s, small phase II studies showed that IC with cisplatin and infusional 5-fluorouracil (PF) administered prior to surgery and/or radiation proved to be effective with a response rate of 85–90%.

- selected group of patients with advanced larynx cancer chemotherapy could be a substitute for surgeries that have a negative impact on the psychosocial well-being and quality of life of larynx cancer survivors

- The Veterans' Administration Laryngeal Cancer Study Group (1991) performed a randomized phase III study of 332 patients with stage III and IV locally advanced larynx cancer. Patients were randomized to one of two treatment arms: (1) IC with PF, followed by RT or (2) standard treatment with TL, followed by adjuvant RT. Patients randomized to IC with PF were assessed for response after 2 cycles of therapy, and those who achieved at least a partial response proceeded with a third cycle of chemotherapy followed by definitive radiation therapy

- Those with less than a partial response proceeded with TL followed by adjuvant radiation. Sixty-two percent of the patients randomized to the IC with PF group retained their larynx at 3-years post-treatment, suggesting that LP was feasible for these patients

- However, the study showed that patients with T4 cancers and gross cartilage invasion were at increased risk for salvage TL. The 10-year follow-up study found no survival difference between the two treatment groups

- (GETTEC) [15] reported different conclusions (Table 1). In this study, 68 larynx cancer patients with T3 disease and vocal cord fixation were randomized to (1) IC with PF, followed by RT for patients who experienced a tumor regression of at least 80% or (2) TL surgery followed by adjuvant RT. The trial was closed to accrual prematurely when the majority of patients refused entry because they wished to receive chemotherapy. Results showed reduced survival rates for the group undergoing a LP strategy, with 2- year survival rates of 69% for the IC with PF group and 84% in the upfront TL surgery group [15]. The contradictory results of the Department of Veterans Affairs and the GETTEC studies stress the importance of patient selection, including a thorough evaluation of the larynx function prior to considering a LP approach

(EORTC) conducted a phase III randomized trial similar in design to the Department of Veterans Affairs study
hypopharynx cancer

- In patients who underwent IC with PF treatment, the 3- and 5-year LP rates were 42% and 35%. However, the survival estimates with a functional larynx (defined as survival without local disease, tracheotomy, feeding tube, or gastrostomy) were 28% and 17% respectively
- Similar to the Department of Veterans Affairs trial (1991), the EORTC study showed that IC with PF could preserve the larynx in a subgroup of patients with hypopharyngeal cancers with no detrimental effect on overall survival. Specifically, the 3-year and 10-year post-treatment survival rates were 57% and 13% in the IC arm and 43% and 14% for the TL arm, respectively

Randomized trials of induction chemotherapy followed by radiation.

Study	N	Site	Treatment	Response to chemotherapy	LP	OS
Veterans [13,14]	332	Larynx	(1) TL → RT (2) IC → RT	NA 85% (CR + PR)	NA 62% at 3Y	45% at 5Y 42% at 5Y
EORTC 24891 [4,5]	202	Hypopharynx	(1) TL → RT (2) IC → RT	NA 54% (CR)	NA 42% at 3Y	43% at 3Y 57% at 3Y
GETTEC [15]	68	Larynx	(1) TL → RT (2) IC → RT	NA 39% (PR ≥ 80%)	NA Not stated	84% at 2Y 69% at 2Y
GORTEC 2000-01 [19,6]	213	Larynx/Hypopharynx	(1) PF → RT (2) TPF → RT	59% (CR + PR) 80% (CR + PR)	57% at 3Y 70% at 3Y	60% at 3Y 60% at 3Y

Docetaxel plus PF (TPF)

- These studies randomized patients into IC with TPF or IC with PF followed by RT alone (TAX 323) or RT plus weekly carboplatin (TAX324). Results from both trials confirmed the superiority of TPF compared with the PF regimen in terms of treatment response, progression-free survival, and overall survival. However, despite these results, the question of whether IC with CCRT has a benefit over CCRT alone remains

- In a phase III randomized trial, GORTEC 2000-2001, IC with TPF was compared to IC with PF, followed by definitive RT for patients achieving at least a partial response to therapy [19]. Patients who did not respond to IC were treated with TL and adjuvant RT (Table 1). The results confirmed a significantly higher response rate of 80% for the TPF arm compared to 59% for the PF arm. Because an increased number of patients achieved a partial response to therapy, more patients in the TPF arm were selected for definitive RT. It also is important to note that a percentage of patients in both groups received CRT in this study (20% and 16%, respectively in TPF and PF arms), making the subsequent results somewhat difficult to interpret. No difference in 3-year survival rates was observed between the two groups (60% in each arm) [19]. Data from the 10-year follow-up of this study showed that the LP rates at 5 and 10 years remained significantly higher for the TPF arm versus the PF arm (5 year LP rate: 74% and 58.1%; 10 year LP rate: 70.3% and 46.5% for the two arms, respectively).

- Importantly, the 5- and 10-year larynx dysfunction-free survival rates were also higher for the TPF arm, at 67.2% and 63.7% compared to 46.5% and 37.2% for the PF arm. However, there was no improvement in overall survival, dysfunctionfree survival or locoregional control between the two arms. Despite the larynx dysfunction-free survival rate benefit in this study, actual survival with a functional larynx remains low with overall survival at 10 years of 30.2% and 23.5% for the TPF and PF arms, respectively (P = 0.28) [6]. Nonetheless, if IC is the primary strategy for LP treatment, a three-drug regimen using IC with TPF should be considered to increase the chances of tumor response to therapy

Concurrent chemotherapy and radiation (CCRT)

- The initial reports of the Radiation Therapy Oncology Group (RTOG) showed that a cisplatin-based chemotherapy plus RT was feasible for patients with locally advanced and inoperable head and neck cancers, with more than 50% of the patients achieving a complete response to therapy

- Based on the aforementioned data, in the early 1990s, the RTOG launched the clinical trial RTOG 91-11 [23], designed to compare IC to RT for larynx preservation.
- This study thus consisted of three treatment approaches (1) CCRT with cisplatin-based chemotherapy (100 mg/m² on days 1, 22, and 43) (2) IC with PF, followed by RT, and (3) RT alone. RTOG 91-11 demonstrated the superiority of CCRT with cisplatin-based chemotherapy for achieving local control and LP and established a new standard of care for LP

- 80% of the patients who were enrolled in the study exhibited T3 disease.
- There was no difference in overall survival among the three treatment arms at 5 and 10-year follow-up, but the survival curves did separate after 5 years in favor of the IC treatment group ($P = 0.08$). However, the unexplained higher rate of non-cancer deaths in the CCRT treatment arm raised the possibility of unrecognized chronic toxicities and late treatment morbidity

Randomized trials of induction chemotherapy versus concomitant chemo-radiation.

Study	N	Site	Treatment	Response to chemotherapy	LP	OS
RTOG 91-11 [22-24]	547	Larynx	(1) IC → RT	85% (CR + PR)	71% at 5Y	58% at 5Y
			(2) CCRT	NA	84% at 5Y	55% at 5Y
			(3) RT	NA	66% at 5Y	54% at 5Y
EORTC 24954-22950 [25,26]	450	Larynx/Hypopharynx	(1) IC → RT	89% (CR + PR)	40% at 3Y	62% at 3Y
			(2) Alternating CCRT	NA	45% at 3Y	64% at 3Y

Induction chemotherapy followed by concurrent chemotherapy and radiation (IC followed by CCRT

- Based on the positive results for LP shown in studies using cisplatinbased concurrent CCRT according to RTOG 91-11[23,24] as well as the positive results obtained by TPF-based IC (GORTEC 2000-2001) [6,19], the French group GORTEC/GETTEC designed the phase II randomized trial TREMPLIN (Radiotherapy With Cisplatin Versus Radiotherapy With Cetuximab After Induction Chemotherapy for Larynx Preservation) [30]. This study aimed to evaluate the tolerability of and compliance to a sequential approach of TPF-based IC followed by CCRT

- Positive data was reported with the use of cetuximab concomitantly with RT in oropharynx cancer.
- The combination of cetuximab with RT proved to have higher rates of in-field skin toxicity and the same rate of severe mucositis as compared to cisplatin-based chemo-radiation. Furthermore, more local failures in patients in the cetuximab arm raised the possibility that an epidermal growth factor receptor inhibition/RT regimen may be inferior to a cisplatin/RT regimen for achieving local control in larynx cancer

- The TREMPLIN study demonstrated that both cetuximab/RT and cisplatin/RT were associated with toxicity after TPF-based IC. Moreover, the LP rate was no better than that observed with TPF followed by RT alone in GORTEC 2000-2001. The TREMPLIN study, however, compared two different CCRT regimens and therefore, whether IC with CCRT has a benefit over CCRT alone remains to be determined.

- A retrospective analysis of the TAX 324 trial randomized a subgroup of patients with resectable larynx and hypopharynx cancer (n = 123) to (1) IC with TPF or (2) IC with PF. After completion of IC, both treatment arms received definitive CCRT with weekly carboplatin (Table 3) [20]. This unplanned subgroup analysis showed that the 3-year laryngectomy-free survival rate was significantly higher for the group receiving TPF-based IC (52% vs 32%; HR 0.59; P = 0.03). This trial suggested the feasibility of using a less nephrotoxic concurrent chemotherapy regimen, such as carboplatin, with the intent to intensify the CCRT treatment in the LP setting.
- A potential role of CCRT after IC is for the group of patients with poor or no response to IC and refuse TL

- the overall benefit of CCRT after IC in comparison with RT after IC remains unclear, as exemplified by RTOG 91-11 in which eleven patients with less than partial response after induction chemotherapy received additional radiotherapy or chemotherapy treatment and all achieved a complete response. Furthermore, only one of these patients required a subsequent salvage laryngectomy

- An alternative approach to the use of 3 cycles of IC followed by CCRT was employed in a phase II trial of 97 patients [34]. In this study, patients received a single dose of IC to identify responders and select patients for definitive cisplatin-based CCRT. Patients who did not respond to one cycle of induction chemotherapy received TL followed by adjuvant radiation. After one cycle of PF, 75% of the patients achieved a partial response. At 3 years, the laryngectomy-free survival was 61% and the overall survival was 85% [34]. This approach may reduce the toxicity related to IC and improve the tolerance to the CCRT portion of the treatment. However, more data are needed to define the role for the sequential approach of IC followed by definitive CCRT as standard of care in the larynx preservation setting

Cisplatin-ineligible patients

- the efficacy and tolerability of concurrent carboplatin plus RT is unclear for head and neck cancer patients who are ineligible for cisplatin.
- the meta-analysis of chemotherapy in head and neck cancer showed that the benefit of concurrent chemotherapy is similar between cisplatin and carboplatin only when carboplatin is used in a doublet combination (i.e., carboplatin and fluorouracil) [27]. A retrospective study of 150 patients (25% had tumors of the larynx/hypopharynx) that received definitive CCRT with weekly carboplatin and paclitaxel showed that this combination was safe and active [40]. The 3-year loco-regional control rate for this group of patients was 83.2%, and the overall survival was 76.5%

- A randomized trial showed that patients with advanced oropharynx cancer treated with RT and cetuximab had superior loco-regional control and overall-survival compared to those receiving RT alone [31]. However, in an unplanned subgroup analysis, only patients 65-years-old and younger with good performance status seemed to benefit from the addition of cetuximab [41]. This data raises concern for the use of cetuximab in cisplatin-ineligible patients. Furthermore, in a retrospective analysis of 174 patients with head and neck cancer receiving definitive CCRT with cisplatin vs. cetuximab (25% larynx-hypopharynx cancer), it was found that patients receiving cisplatin-based CCRT achieved better loco-regional control and overall survival

- In summary, for patients that are ineligible for cisplatin-based CCRT but desire LP, the option of carboplatin-based (as single agent vs. doublet) CCRT should be discussed with the patient [27]. For patients who desire LP therapy but are not candidates for organ preservation surgery or CCRT, RT alone is an appropriate treatment. With this last approach, survival is similar to that associated with CCRT when timely salvage surgery is incorporated, but the likelihood of larynx preservation is low

Alternatives to larynx preservation

- A study using the SEER cancer registry data assessed 5394 patients with stage III or IV laryngeal squamous cell carcinoma treated between 1992 and 2009 and showed that patients who received surgery had superior disease specific survival (DSS) and overall survival (OS) at both 2 and 5 year time points (DSS at 2 and 5 years: 70% vs 64% and 55% vs 51%, $P < 0.001$; OS at 2 and 5 years: 64% vs 57% and 44% vs 39%, $P < 0.001$)

- Another SEER study of patients with advanced laryngeal cancer diagnosed between 1999 and 2007 who underwent TL or chemoradiation, showed that TL was associated with an 18% lower risk of death compared to a LP approach

- Choosing the optimal treatment strategy between LP and TL relies heavily on patients' individual characteristics and tumor-related factors

Conclusions

- Treatment decisions depend on patients' desires, tumor extent, experience of the treating physician, possibility of adequate follow-up to detect early recurrences in cases of LP treatments, and the functional status of the larynx prior to treatment

- The data from phase III studies suggests that patients with advanced T4 cancers will have better outcomes with a primary surgical approach [2,14,23,43,44]. On the other hand, for patients with T2N+ and T3 tumors, LP approaches such as definitive CCRT (the preferred treatment approach in the United States [23,24,29]) or IC with TPF followed by definitive RT (the preferred treatment approach in Europe [4,6,27]) are currently acceptable options. It is important to note that to date there have been inconsistencies in trial design, at times making interpretation of the available data more difficult. Though induction therapy remains an effective and feasible treatment option, there remains controversy in respect to the overall benefit of IC over the CCRT approach. The actively accruing GORTEC SALTORL trial comparing IC (with TPF) followed by RT vs CCRT (with TPF) will help to establish the best treatment regimen for locally advanced larynx and hypopharynx cancers and patient selection for laryngeal preservation

- At this junction, in order to proceed with LP therapy, a good pretreatment larynx function in the patient is requisite.