

## Neoadjuvant Chemotherapy for Larynx Preservation: Has it Lost Importance?

### Abstract

Over the time, the aim of treatment for locally advanced laryngeal and hypopharyngeal carcinoma has changed from cure to cure with the functional larynx. Chemoradiation has emerged as the most important therapeutic modality for patients with locally advanced disease. However, systemic failure remains an important area of concern. Induction chemotherapy has emerged as promising organ preservation approach as it gives an window to select responders and continuing treatment with nonsurgical approach as well as reduces systemic recurrence and improve survival with a functional larynx. However, there are questions about the efficacy of this approach. In this context, we aim to evaluate the trials for locally advanced laryngeal and hypopharyngeal cancer attempting to optimize therapeutic outcome with addition of induction chemotherapy. This present review intends to look into the therapeutic ratio of induction chemotherapy for disease control, organ preservation.

**Keywords:** Chemoradiotherapy, induction chemotherapy, larynx preservation, locally advanced laryngeal carcinoma, squamous cell carcinoma

### Introduction

Head and neck cancer is the fifth most common cancer worldwide.<sup>[1]</sup> More than two third of these patients present in advanced stage disease and has limited treatment options with guarded prognosis.<sup>[2]</sup> Radical chemoradiotherapy (CRT) has emerged as the preferred combination of chemotherapy and radiation in head and neck cancers.<sup>[3,4]</sup> Chemotherapy and radiotherapy (RT) have also emerged as an important option for organ preservation in laryngeal and hypopharyngeal cancers.<sup>[5]</sup> The various organs in head and neck work in a coordinated manner and are important in respiration, swallowing, speech, hearing and functional, and cosmetic aspects of various structures in head and neck are important in providing good quality of life in patients. Surgery in advanced laryngeal or pharyngeal cancers leaves the patient with a tracheostomy tube, loss of his voice as well as a tube for enteral feeding for the patients. The cosmetic disfigurement associated with a massive surgery adds to the insult. Most of these patients also require postoperative RT as they are in advanced stages and usually have high-risk features, adding to the cell carcinoma of the head and neck is a acute and late effects side

effects in addition. Squamous moderately radiosensitive tumor and organ preservation are feasible in these patients. However, note should be made that local tumor control of with RT is critical in organ preservation and never matches that of surgery. Ultimately, a large fraction of patients will require surgery. The role of chemotherapy in organ preservation can be viewed in two aspects; one is chemotherapy given with RT where it is given along with RT as a radiosensitizer where it increases the efficacy of RT, thus improving local control and providing improved larynx preservation rates. The reduction in systemic metastasis and thus improved survival may come as an additional benefit in these patients. The second approach is to use chemotherapy alone in the upfront situation with the primary aim of selecting good candidates for the organ preservation approach. The good responders are taken up for larynx preservation with RT alone or with concurrent chemoradiotherapy (CCRT). The reduction in systemic metastasis and thus improved survival may be expected in these studies but has not been convincingly proved.

Among these two approaches the optimum or best approach is often debated. The Radiation Therapy Oncology

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Group (RTOG) trial has shown maximum benefit with the CCRT strategy. In this review, we would like to review the various trials which have used neoadjuvant chemotherapy (NACT) for larynx preservation with special emphasis on ideal regimen, larynx preservation rates, number of cycles, and the role of concurrent chemotherapy and future of NACT in larynx preservation.

### Who All should be Selected for the NACT Approach?

The patients who are selected for larynx preservation approach with neoadjuvant chemotherapy include patients with locally advanced laryngeal or pharyngeal cancer who may require total laryngectomy if a surgical approach is taken. This would basically include stage III and IV (T2-T4, N0-N2) larynx or hypopharyngeal cancer.<sup>[6]</sup> It is better to avoid patients with tumors that penetrated through cartilage with gross invasion to the base of the tongue.<sup>[7]</sup> Inner cartilage invasion patients may be taken up for larynx preservation strategies.<sup>[8]</sup> There are small series that have shown feasibility of larynx preservation even in patients with cartilage invasion.<sup>[9]</sup> The patients with N3 nodal disease and those with transglottic tumors should be carefully assessed before taking up for larynx preservation.<sup>[10]</sup> There are retrospective series in which N3 disease patients were also given NACT for organ conservation.<sup>[8]</sup>

As the treatment is associated with significant toxicity only patients with good performance status (Karnofsky performance status >70), with controlled comorbidities, good renal and liver functions must be selected for this approach. Metastatic patients should also be not taken up for this approach. Adequate bone marrow reserves must be ensured before taking the patient for NACT with the aim of organ preservation. The patient selection characteristics of major trials which have evaluated NACT for organ preservation is summarized in Table 1.

### What should be the Ideal Regimen?

Although initial larynx preservation trials used the doublet regimen of cisplatin and 5-fluorouracil (5 FU) for induction, the later trials used a triplet regimen adding docetaxel to the doublet. The doublet regimen consisted of cisplatin 100 mg/m<sup>2</sup> on day 1 and 5 FU 1000 mg/m<sup>2</sup> day 1–5 as a 24 h infusion daily.<sup>[6,7,14]</sup> In triplet regimen, the cisplatin dose reduced to 75 mg/m<sup>2</sup> on day 1 plus 5 FU 75 mg/m<sup>2</sup> day 1–5 and docetaxel 75 mg/m<sup>2</sup>.<sup>[10]</sup> The only trial that has compared head on between the two is the GORTEC 2000–01 trail which randomized 213 patients of laryngeal and hypopharyngeal cancer to receive three cycles induction chemotherapy with Taxol, Platinum, 5Fu (TPF) or Platinum, 5Fu (PF). Patients with >50% regression of tumor were then treated with CRT or RT alone.<sup>[12]</sup> 3-year larynx preservation was significantly improved in the TPF arm compared to PF arm (70.3% vs. 57.5%,  $P = 0.03$ ). 3 year OS was 60% in both the arm with 3-year disease-free survival (DFS) also not different (58% vs. 44%,  $P = 0.011$ ). The TPF-treated patients had higher rate of neutropenia (31.5% vs. 17.6%) and more febrile neutropenia (10.9% vs. 5.8%). However, only 62.7% and patients in the TPF and 32% patients in the PF group completed the treatment without delay or dose reduction. Thus, the addition of one-third agent is associated with significant toxicity but improves laryngeal preservation rates. This can be seen in parallel to the trails comparing doublet versus triplet chemotherapy in head and neck cancer where significant survival benefit was seen with the triplet regimen but at the cost of increased toxicity.<sup>[15-17]</sup> Thus, in patients with good performance status, a triplet regimen should be preferred, keeping in mind the higher laryngeal preservation rates associated with it.

Some smaller series have also evaluated doublet regimens such as docetaxel plus cisplatin/carboplatin for organ preservation.<sup>[18]</sup> A small study by Rubio Suárez *et al.* had evaluated the combination of vinorelbine, cisplatin,

**Table 1: Patient selection characteristics of major trials which have evaluated neoadjuvant chemotherapy for larynx preservation**

Trial/year	Number of patients	Patient selection	
		Subsite	Characteristics
VA trial, 1991 <sup>[6]</sup>	332	Larynx	Stage III/IV larynx cancer excluding T1N1 cancers, inoperable and metastatic cases
EORTC 24891, 1996 <sup>[11]</sup>	202	Hypopharynx	T2-T4, N0-N2b squamous cell carcinoma of the pyriform sinus or aryepiglottic fold
RTOG 91-11, 2003 <sup>[7]</sup>	547	Larynx	Stage III/IV larynx cancer T1 primary tumors were ineligible as well as T4 tumors that penetrated through cartilage or >1 cm into the base of tongue
GORTEC 2000-01, 2009 <sup>[12]</sup>	220	Larynx/hypopharynx	Stage III or IV
EORTC 24954, 2009 <sup>[13]</sup>	450	Larynx/hypopharynx	Larynx T3-T4, N0-N2 Hypopharynx T2-T4, N0-N2
TREMPIN, 2013 <sup>[10]</sup>	153	Larynx/hypopharynx	Stage III to IV larynx/hypopharynx squamous cell carcinoma T2-T3, N0-resectable N3

VA – Veterans affairs; EORTC – European Organization for Research and Treatment of Cancer; RTOG – Radiation Therapy Oncology Group

and Tegafur/uracil. Had a good laryngeal preservation rate of 50% in laryngeal primaries.<sup>[19]</sup>

Pfreundner *et al.* evaluated paclitaxel + cisplatin as NACT for organ preservation in patients with advanced laryngeal and hypopharyngeal carcinomas and reported a larynx preservation rate of 84% at 25 months.<sup>[20]</sup>

Response assessment after NACT should be done after 2–3 cycles of chemotherapy. It would be more logical to go for response assessment after 2 cycles as followed by the Veterans affairs (VA) trial and then go for a third cycle in responders.<sup>[6]</sup> It gives enough time for RT planning and prevents gap in the treatment. Smaller series have also reported assessment after 1 cycle of chemotherapy and reported a high response rate of >70% with 1 cycle.<sup>[21]</sup> A maximum of 3 cycles must be given as giving >3 cycles may prolong the overall treatment time and may increase the accelerated repopulation of tumor cells. The response rate to triplet chemotherapy has been reported to be as high as 85%.<sup>[22]</sup>

### Who should be Selected for Larynx Preservation versus Surgery?

The patients after receiving 2–3 cycles of NACT must undergo a response assessment and should be properly selected for a further RT for organ preservation or surgery. The trials have varied in their approach of selection of

patients for organ preservation. The European Organization for Research and Treatment of Cancer Head and Neck Cooperative Group (EORTC) 24891 selected only patients with a complete response (CR) after NACT for organ preservation approach while those without a CR went on to have a surgery.<sup>[11]</sup> However, the VA trial and the RTOG 91–11 trial took patients at least who had a partial response (PR) ( $\geq 50\%$  reduction in size of the primary) for RT approach.<sup>[6,7]</sup> However, when we analyze the results the rate of larynx preservation was higher in the VA and the RTOG trial than the EORTC trial. This may be because some of the patients who might have had larynx conservation underwent surgery due to strict cutoff for response in the EORTC trial. The trials that followed these three land mark trials also used the criteria of at least a PR to chemotherapy as a indication for RT over surgery. Thus, it is logical to evaluate the patient after 2–3 cycles of NACT and those patients who have at least a PR be selected for further RT.

A summary of various chemotherapy schedules and selection criteria for larynx preservation used in various trials is given in Table 2.

### Expected Survival and Larynx Preservation Rates

When we analyze the larynx preservation in various trials, it

**Table 2: Summary of various chemotherapy schedules and selection criteria for larynx preservation used in various trials**

Trial/year	Treatment regimen	NACT dose	Number of cycles	Selection of patient for radiotherapy
VA trial, 1991 <sup>[6]</sup>	A: Surgery→PORT B: PF (>50 regression) → RT	Cisplatin 100 mg/m <sup>2</sup> day 1 5-FU 1000 mg/m <sup>2</sup> day 1-5	3 (2 followed by 1 in responders)	Patients with a PR in primary and no progression in the node
EORTC 24891, 1996 <sup>[11]</sup>	A: Surgery→PORT B: PF (If CR) → RT	Cisplatin 100 mg/m <sup>2</sup> day 1 5-FU 1000 mg/m <sup>2</sup> day 1-5	3	Patients who showed a CR
RTOG 91-11, 2003 <sup>[7]</sup>	A: PF (If CR, PR) → RT B: CTRT C: RT alone	Cisplatin 100 mg/m <sup>2</sup> day 1 5-FU 1000 mg/m <sup>2</sup> day 1-5	3	$\geq 50\%$ reduction of the primary tumor and at least stable disease in the neck
GORTEC 2000-01, 2009 <sup>[12]</sup>	A: 3TPF → CTRT 70 Gy within 4-7 weeks B: 3PF → CTRT 70 Gy within 4-7 weeks	Docetaxel 75 mg/m <sup>2</sup> day 1 Cisplatin 75 mg/m <sup>2</sup> day 1 5-FU 750 mg/m <sup>2</sup> day 1-5 Cisplatin 100 mg/m <sup>2</sup> day 1 5-FU 1000 mg/m <sup>2</sup> day 1-5	3	Patients with CR at the primary site or PR and recovered normal larynx mobility
EORTC 24954, 2009 <sup>[13]</sup>	A: Sequential PF → RT 70 Gy B: Alternating PF/RT 60 Gy	Cisplatin 100 mg/m <sup>2</sup> day 1 5-FU 1000 mg/m <sup>2</sup> day 1-5	4 (2 followed by 2 in responders)	Responders with >50% response in sequential arm went on to have 2 more cycles of chemo and then RT
TREMPIN, 2013 <sup>[10]</sup>	All patients received 3-TPF induction then if >PR A: RT + cisplatin B: RT + cetuximab If <PR - surgery	Docetaxel 75 mg/m <sup>2</sup> day 1 Cisplatin 75 mg/m <sup>2</sup> day 1 5-FU 750 mg/m <sup>2</sup> day 1-5	3	Responders >50% response

5-FU – 5-fluorouracil; RT – Radiation therapy; PORT – Postoperative radiation therapy; VA – Veterans affairs; EORTC – European Organization for Research and Treatment of Cancer; RTOG – Radiation Therapy Oncology Group; PR – Partial response; CR – Complete response; NACT – Neoadjuvant chemotherapy; CTRT – Chemoradiotherapy; RT – Radiotherapy; TPF – Taxol, Platinum, 5Fu; PF – Platinum, 5Fu

is basically the anatomically intact larynx that we consider as preserved larynx. The various functions of larynx include phonation, prevent aspirations while deglutition. Provide a safe pathway for air into the lung. Ideally, these various functions of larynx must be intact reasonably to call the patient has a functionally preserved larynx. However, also to be careful is that the survival of the patient should not be compromised in an attempt to improve larynx preservation rates. A delicate balance of these various factors is the key to successful implementation of larynx preservation protocols.

One the earliest trial reported was the VA trial.<sup>[6]</sup> This trial randomized 332 patients of locally advanced, but resectable SCC of larynx to surgery followed by adjuvant radiation or induction chemotherapy followed by radiation for those achieving >50% response. 2-year survival was 68% in both the treatment arm. However, DFS was nonsignificantly inferior in the treatment arm. The most important finding was larynx preservation in 64% cases with estimated rate of 2-year larynx preservation was 66%. It was also noted that patients in the chemotherapy arm experienced more local recurrence (12% vs. 2%,  $P = 0.001$ ) but less distant metastasis (11% vs. 17%,  $P = 0.001$ ). A similar trial was conducted by the EORTC - 24891 Trial. This trial randomized 202 patients of locally advanced hypopharyngeal cancer patients to surgery followed by radiation or NACT followed by radiation for the complete responders. Those achieving less than a CR underwent immediate surgery.<sup>[11]</sup> At a median follow-up of 10.5 years, there was no significant difference in locoregional failures ( $P = 0.84$ ) or distant metastases ( $P = 0.14$ ) between the two groups. The 5- and 10-year OS was 38.1% and 13.1% in the chemotherapy group compared to 32.6% and 13.8% in the surgery group. The 5- and 10-year DFS was 31.7% and 10.8% in the chemotherapy group compared to 26.4% and 8.5% in the surgery group. 5- and 10-year survival with a function larynx was 21.9% and 8.7%.<sup>[14]</sup> Hence, larynx preservation was found possible in patients treated with induction chemotherapy followed by radiation for hypopharyngeal cancer also without adversely impacting survival.

The GETTEC study randomly assigned 68 patients to either upfront total laryngectomy or induction PF chemotherapy followed by radiation for patients with >80% response. Larynx preservation rate was 42% at 2 years. However, this trial reported 2-year overall survival (OS) (84% vs. 69%,  $P = 0.006$ ) and DFS (78% vs. 60%,  $P = 0.02$ ) significantly better in the surgical arm and recommended chemotherapy followed by radiation should not be considered for larynx preservation.<sup>[23]</sup> Subsequently, RTOG and the Head and Neck Intergroup (RTOG 91-11) conducted a large randomized controlled trial. At a median follow-up of 3.8 years, the rate of larynx preservation was 84%, 72% and 67%, respectively, in the three treatment arm and was significantly better in the CTRT arm compared to induction arm or radiation alone arm. However, it was not different

in induction arm or radiation alone arm ( $P = 0.27$ ). There was no difference in the speech at 1 and 2 year in the three groups.<sup>[7]</sup> Updated results of this trial at a median follow up of 10.8 years reported larynx preservation at 10 year was 81.7% in the CTRT arm compared to 67.5% and 63.8% in the NACT and RT alone arm. Locoregional control (LRC) was significantly better with CCRT (65.3%) compared to NACT + RT (48.9%,  $P = 0.0037$ ) and RT (47.2%,  $P = 0.0015$ ).<sup>[24]</sup>

Subsequently, the GORTEC 2000-01 a randomized 213 patients with laryngeal and hypo pharyngeal cancer trial, randomly assigned to receive three cycles induction chemotherapy with TPF or PF. Patients with >50% regression of tumor were then treated with CTRT or RT alone.<sup>[12]</sup> 3-year larynx preservation was significantly improved in the TPF arm compared to PF arm (70.3% vs. 57.5%,  $P = 0.03$ ). 3-year OS was 60% in both the arm with 3-year DFS also not different (58% vs. 44%,  $P = 0.011$ ). The TPF treated patient's higher rate of neutropenia (31.5% vs. 17.6%) and more febrile neutropenia (10.9% vs. 5.8%). However, only 62.7% and patients in the TPF and 32% patients in the PF group completed the treatment without delay or dose reduction. Lefebvre *et al.* randomly assigned 450 patients with resectable laryngeal and hypopharyngeal cancer to receive either sequential or alternating chemotherapy or radiation therapy.<sup>[13]</sup> In the sequential arm, patients were allowed to receive two cycles induction PF followed by radiation if tumor regression was >50%. In the alternating arm, patients were allowed to receive cisplatin and fluorouracil in week 1, 4, 7, and 11 with radiation of 20 Gy in the interval 2 weeks to a total of 60 Gy. Nonresponders were allowed to undergo surgery with adjuvant radiation. With a median follow-up of 6.5 years, OS (4.4 and 5.1 years) and progression-free survival (3.0 and 3.1 years) were not different between the two groups. The primary end-point was survival with a functional larynx. The median survival with a functional larynx was 1.6 years in the sequential arm compared to 2.3 years in the alternating arm (hazard ratio of event = 0.85, 95% confidence interval = 0.68-1.06). Estimated 5-year survival with a functional larynx was 30.5% versus 36.2% for the sequential and the alternating arm, respectively. There was also a trend toward the better quality of preserved larynx in the alternating arm. Acute objective mucosal reactions were significantly higher in the sequential treated arm; however, late toxicity was not different. Estimated 5-year survival was not significantly different between two groups (48.5% vs. 51.9%,  $P = 0.446$ ).<sup>[13]</sup>

Retrospective series have also reported high rates of organ preservation up to 70% with NACT followed by CTRT approach.<sup>[25]</sup> Similarly, a study by Franchin *et al.* which used an approach of NACT followed by hyper fractionated/accelerated RT achieved a larynx preservation rate of 73.5%.<sup>[26]</sup>



Table 3 summarizes survival outcomes and larynx preservation rates of important trials evaluating induction chemotherapy for laryngeal preservation.

### Addition of Targeted Therapy with Chemotherapy for Organ Preservation

Cetuximab has been evaluated for organ preservation after induction chemotherapy in stage III and IV laryngeal or hypopharyngeal cancers.<sup>[10]</sup> This phase II trial enrolled 116 patients to receive 3 cycles were used for induction chemotherapy with TPF and patients with >50% response were randomized to chemo-RT with cisplatin or RT with Cetuximab. When data were analyzed, there was no significant difference in larynx preservation at 3 months between the two arms. There was also no significant difference in OS at 18 months between the two arms. There was no difference in Grade 3–4 mucositis between the two arms, but more grade 3–4 in-field skin toxicity was observed in the cetuximab arm. Hematological toxicity and protocol modification due to toxicity were higher in cisplatin arm compared to cetuximab. Although this trial showed no difference in outcomes in bio-RT versus chemo-RT in organ preservation, further phase III data may be required before routinely incorporating bio RT in organ preservation protocols. However, one may argue that bio-RT may be an option in patients not suitable for chemotherapy without compromising the outcome. In developing countries, cost of bio, RT is a limiting factor for routine use.

### Toxicity

The main toxicity associated with NACT is hematotoxicity and mucositis. Neutropenia and febrile episodes can be dose limiting. As high as 10% febrile neutropenia and 30% Grade III neutropenia has been reported.<sup>[12]</sup> Mucositis of up to 8% and renal toxicity up to 3% have been reported with NACT.<sup>[11,12]</sup> The GORTEC 2000–01 which compared doublet to a triplet chemotherapy in larynx preservation had found that neutropenia and febrile neutropenia was more common with triplet regimen while stomatitis, thrombocytopenia, and renal abnormalities were more with doublet regimen.<sup>[12]</sup> The toxicity associated with NACT for organ preservation in laryngeal and pharyngeal cancers are summarized in Table 4.

### Comparison of Chemoradiotherapy versus Neoadjuvant Chemotherapy followed by Radiotherapy

The only randomized that compared CTRT versus NACT followed by RT was the RTOG 91-11 randomized controlled trial. Patients of carcinoma larynx with resectable locally advanced disease were randomly assigned to one of the three treatment arm: (1) Induction cisplatin plus fluorouracil followed by RT, (2) RT with concurrent cisplatin, and (3) RT alone.<sup>[7]</sup> The primary end-point was larynx preservation. At a median follow-up of 3.8 years, the rate of larynx preservation was 84%, 72%, and 67%, respectively, in the three treatment arms and was significantly better in the CTRT arm compared

**Table 3: Summary of trials evaluating induction chemotherapy for laryngeal preservation; survival outcomes and larynx preservation rates**

Trial/year	n	OS	LP	Comments
VA trial, 1991 <sup>[6]</sup>	332	A: 68% B: 68%	LP 66% at 2 years	
EORTC 24891, 1996 <sup>[11]</sup>	202	13.1% (10 years)	LP 28% at 3 years LP 17% at 5 years LP 8.5% (more than half of the survivors) were able to have a functional larynx at 10 years	The 3- and 5-year rate of retaining a functional larynx in the patients who completed treatment in the induction chemotherapy arm were 64% and 58% respectively
RTOG 91-11, 2003 <sup>[7]</sup>	547	55%-53% at 5 years versus 27%-31% at 10 years	LP 81.7% (10 years) versus 63.8% (10 years), $P < 0.001$	Radiotherapy with concurrent administration of cisplatin is superior to induction chemotherapy followed by radiotherapy or radiotherapy alone for laryngeal preservation and locoregional control
GORTEC 2000-01, 2009 <sup>[12]</sup>	220	30.1% CR + 29.1% PR versus 41.8% CR + 38.2% PR	LP 57.5% (3 years) versus 70.3%, $P = 0.03$	
EORTC 24954, 2009 <sup>[13]</sup>	450	NR	LP 39.5% (3 years) and 30.5% (5 years) versus LP 45.4% (3 years) and 36.2% (5 years), $P = 0.155$	
TREMPIN, 2013 <sup>[10]</sup>	153	NR	LP 93%-95% (3 months) Larynx function preservation-82%-87% (18 months)	Fewer local treatment failures in conventional chemoradiotherapy arm

OS – Overall survival; LP – Larynx preservation; VA – Veterans affairs; EORTC – European Organization for Research and Treatment of Cancer; RTOG – Radiation Therapy Oncology Group; PR – Partial response; CR – Complete response; NR – No response

**Table 4: Toxicity associated with neoadjuvant chemotherapy for organ preservation in laryngeal and pharyngeal cancers as reported in various trials**

Study	Subsite	Toxicity to NACT
VA trial, 1991 <sup>[6]</sup>	Larynx	7% in the induction arm - discontinued chemotherapy due to toxicities
EORTC 24891, 1996 <sup>[11]</sup>	Hypopharynx	Dose limiting toxicity Cardiovascular 6% Renal 3% Hematologic 3% Impairment of general condition - 1%
RTOG 91-11, 2003 <sup>[7]</sup>	Larynx	Mucosal toxicity of concurrent radiotherapy and cisplatin: Of the other two treatments during radiotherapy 2:1
GORTEC 2000-01, 2009 <sup>[12]</sup>	Larynx/hypopharynx	Triplet arm had more Grade 4 neutropenia 31.5% versus 17.6% Febrile neutropenia 10.9% versus 5.8% Doublet arm had more Grade 3 and 4 stomatitis 7.8% versus 4.6% Grade 3 and 4 thrombocytopenia 7.8% versus 1.8% Grade 4 creatinine elevation 2.0% versus 0%
EORTC 24954, 2009 <sup>[13]</sup>	Larynx/hypopharynx	5.3% patients received only one cycle of chemotherapy 21.8% patients received two cycles of chemotherapy
TREMPIN, 2013 <sup>[10]</sup>	Larynx/hypopharynx	26% received <3 cycles due to toxicity during NACT 23.5% experienced some Grade 3 to 4 toxicity during NACT

NACT – Neoadjuvant chemotherapy; VA – Veterans affairs; EORTC – European Organization for Research and Treatment of Cancer; RTOG – Radiation Therapy Oncology Group

to induction arm or radiation alone arm. Updated results of this trial at a median follow-up of 10.8 years reported larynx preservation at 10 year was 81.7% in the CRT arm compared to 67.5% and 63.8% in the NACT and RT alone arm. LRC was significantly better with CCRT (65.3%) compared to NACT + RT (48.9%,  $P = 0.0037$ ) and RT (47.2%,  $P = 0.0015$ ).<sup>[24]</sup> However, twice as many patients require laryngectomy when treated with NACT or RT alone compared to CRT. The rate of distant metastasis was not different in any of the chemotherapy treated arms.

Similarly, a small phase III trial by Prades *et al.* involving 71 patients laryngeal preservation rates at 2 years were significantly higher with CRT group than NACT group (92% vs. 68%,  $P = 0.016$ ).<sup>[27]</sup> Smaller series also report similar advantage of CRT over NACT but with higher toxicity.<sup>[28]</sup> Hence, compared to NACT arm CRT does provide better larynx preservation, disease control and survival. However, the advantage of NACT lies in the fact that it helps in proper selection of patients for surgical salvage. In addition, a salvage surgery after radical RT may be more difficult due to the radiation associated fibrosis and healing issues. This makes NACT still a valid option for the selection of patients for larynx preservation. The further trials have evaluated the role of CRT after NACT and have achieved larynx preservation rates similar to the RTOG trial.<sup>[12]</sup>

## Conclusion

NACT for organ preservation still remains an important modality for the selection of patients for larynx

preservation. The availability of less toxic drugs, inclusion of biological agents holds promise to improve outcome with NACT. Emerging molecular biology of HNSCC may drive us to a personalized the use of NACT for larynx preservation.

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## Conflicts of interest

There are no conflicts of interest.

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