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Original Research Article

INDUCTION CHEMOTHERAPY FOLLOWED BY CONCURRENT CHEMORADIATION FOR ORGAN PRESERVATION IN LOCALLY ADVANCED LARYNGEAL CANCER: A PROSPECTIVE PHASE II STUDY

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ABSTRACT

Background: Laryngeal cancer often presents in advanced stages. Organ-preserving treatment using induction chemotherapy followed by chemoradiation shows promise; however, prospective data with cisplatin–5-fluorouracil regimens remain limited. This study aimed to evaluate the treatment response, survival outcomes, toxicity, and laryngeal preservation following induction chemotherapy followed by concurrent chemoradiotherapy in locally advanced laryngeal cancer. **Materials and Methods:** This prospective Phase II study was conducted at Dharan Hospital, Salem, Tamil Nadu, between October 2020 and September 2024. Thirty patients with previously untreated stage III–IV laryngeal squamous cell carcinoma received cisplatin and 5-fluorouracil induction chemotherapy, followed by concurrent chemoradiotherapy. Tumour response, toxicity, survival, and organ preservation were also assessed. The primary outcome was tumour response, and the secondary outcomes included disease-free survival, overall survival, laryngeal preservation, and treatment-related toxicity. Data were analysed using descriptive statistics only. **Result:** Patients aged 50–69 years comprised 22 of 30 (73.3%) patients. Supraglottic tumours were observed in 13 of the 30 patients (41.9%). Stage III disease was observed in 63.3% of patients, T3 tumours in 70%, and nodal involvement in 60%. After treatment, a complete response at the primary site was achieved in 80% of patients and a complete nodal response in 70% of patients, with no progressive disease observed. At a median follow-up of 27 months, the disease-free survival and overall survival rates were 76.7% and 83.3%, respectively. Laryngeal preservation was achieved in 86.7% of the patients, whereas 13.3% required salvage laryngectomy. Anaemia was the most frequent haematologic toxicity during induction, whereas grade III mucositis was the most common severe toxicity during chemoradiation. **Conclusion:** Sequential induction chemotherapy followed by concurrent chemoradiotherapy provides effective disease control, favourable survival, and high laryngeal preservation rates with acceptable toxicity. This approach may be feasible for routine clinical practice.

INTRODUCTION

Laryngeal cancer is a major health problem worldwide, with approximately 200,000 new cases and nearly 120,000 deaths reported globally in 2021, according to the Global Burden of Disease 2021 study.[1] Indian population-based cancer registries also show a high disease burden, with regional variation and high incidence in several registries.[2] Most laryngeal cancers are squamous cell cancers, developing mainly from long-term exposure to tobacco and alcohol, which work together to cause cancer formation.[3] Tumour subsites affect clinical presentation. Supraglottic tumours usually present with dysphagia, odynophagia, or foreign body sensation, while glottic tumours often appear earlier with hoarseness due to direct vocal cord involvement, allowing earlier detection in some patients.[1] In the past, total laryngectomy followed by radiotherapy was the standard treatment for locally advanced disease, providing reasonable cancer control but causing permanent loss of natural voice and significant functional morbidity.[4]

A major change in the treatment of advanced laryngeal cancer occurred after the Veterans Affairs (VA) Laryngeal Cancer Study showed that induction

chemotherapy followed by radiotherapy resulted in survival rates similar to those observed after surgery, while preserving the larynx in a large number of patients.[5] This study proved that non-surgical organ preservation was possible. Radiation Therapy Oncology Group (RTOG) 91-11 showed that concurrent chemoradiation was the most effective method for larynx preservation, with better loco-regional control and higher preservation rates than induction chemotherapy followed by radiotherapy alone.[6] Therefore, concurrent chemoradiation has become the standard non-surgical treatment for laryngeal preservation.

Induction chemotherapy still plays an important role in selected patients, especially those with large T3–T4 tumours, airway compromise, severe symptoms, or when rapid tumour reduction is needed. Induction chemotherapy can shrink the tumour, open the airway, improve oxygen supply to the tumour, and make the tumour respond better to radiation, while also providing early control of microscopic disease spread.[7] Induction treatment also helps in selecting patients, as tumours that respond well are more likely to respond to later chemoradiation. Many studies have shown good response rates and high laryngeal preservation when induction chemotherapy is followed by concurrent chemoradiation.[8-10]

Most of the available data on induction chemotherapy followed by concurrent chemoradiotherapy come from Western populations, use different induction regimens, or are based on taxane drugs. Therefore, the results may not apply well to settings where cisplatin and 5-fluorouracil are commonly used. There are limited prospective data on this induction followed by concurrent chemoradiation in locally advanced laryngeal cancer, especially from resource-limited settings, and issues related to toxicity, treatment compliance, and organ preservation are not clearly defined. This creates an important research gap because patient characteristics, disease stage at presentation, and treatment facilities often differ from those reported in large multicentre studies. This study aimed to prospectively evaluate tumour response, treatment-related toxicity, survival outcomes, and laryngeal preservation following cisplatin–5-fluorouracil-based induction chemotherapy followed by concurrent chemoradiation in patients with locally advanced laryngeal squamous cell carcinoma.

MATERIALS AND METHODS

This prospective Phase II study enrolled 30 patients with previously untreated stage III or IV laryngeal squamous cell carcinoma between October 2020 and September 2024 at Dharan Hospital, Salem, Tamil Nadu. The study was approved by the ethics committee, and informed consent was obtained from all patients.

Inclusion Criteria

Patients aged ≥ 30 years with a Karnofsky performance status of ≥ 60 and acceptable blood counts and kidney function were included.

Exclusion Criteria

Patients with distant metastasis who had received prior radiotherapy or surgery to the larynx, pregnant patients, individuals with another primary cancer, and patients with serious medical conditions that could interfere with chemotherapy were excluded.

Methods: Patients were treated using a fixed, stepwise treatment plan. Induction chemotherapy was administered first and included three cycles of cisplatin (50 mg/m²) on days 1 and 2, along with a continuous infusion of 5-fluorouracil (1 g/m²) from days 1 to 4. Patients who showed a complete response, partial response, or stable disease after induction were included in the study. These patients received concurrent chemoradiation with weekly cisplatin 40 mg/m² or carboplatin at area under the curve (AUC) 1.5, along with external beam radiotherapy at a total dose of 66–70 gray administered once daily. Radiotherapy was delivered five days per week using external beam techniques with curative intent.

The primary outcome was tumour response after completion of concurrent chemoradiotherapy, assessed using RECIST 1.1. Secondary outcomes included disease-free survival (DFS), overall survival (OS), laryngeal preservation, and treatment-related toxicity.

DFS was defined as the time from the completion of chemoradiotherapy to documented recurrence or death. OS was defined as the time from completion of chemoradiotherapy to death from any cause. Laryngeal preservation was defined as survival without a total laryngectomy.

Clinical details related to tumour response and treatment-related toxicity were collected prospectively. Tumour response was assessed one month after completion of chemoradiation using the RECIST 1.1 criteria. Blood-related and non-blood-related toxicities were recorded using CTCAE version 1.0, while radiation-related toxicities were assessed using standard RTOG scoring. Patients were followed up every month for the first six months and then once every two to three months.

Data were analysed using SPSS software v29. Data were summarised using descriptive statistics, such as frequencies and percentages. No inferential or survival statistical tests were performed.

RESULTS

A total of 30 eligible patients were enrolled during the study period, and all 30 completed induction chemotherapy followed by concurrent chemoradiotherapy and were included in the final analysis. Patients aged 50–69 years comprised 22 of 30 (73.3%) patients. Most patients were male (27, 90%). Supraglottic tumours were the most frequent

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subsites, seen in 13 patients (41.9%), followed by glottic tumours in 12 patients (38.6%) and transglottic tumours in 5 patients (19.4%) [Table 1].

Table 1: Baseline demographic and tumour subsite distribution

Variable	Category	N (%)
Age (years)	50–69	22 (73.3%)
Gender	Male	27 (90%)
	Female	3 (10%)
Presenting symptom	Hoarseness	18 (60%)
	Dysphagia / Odynophagia / Foreign-body sensation	12 (40%)
Tumour subsite	Supraglottic	13 (41.9%)
	Glottic	12 (38.6%)
	Transglottic	5 (19.4%)

Most patients presented with stage III disease (19, 63.3%). T3 tumours were the predominant tumour stage, observed in 21 patients (70%), and regional nodal involvement was present in 18 patients (60%) [Table 2].

Table 2: Stage and nodal status at initial presentation (n = 30)

Parameter	Category	N (%)
Overall stage	Stage III	19 (63.3%)
	Stage IV	11 (36.7%)
T stage	T3	21 (70%)
	T2	6 (20%)
	T4	3 (10%)
Nodal status	Node positive	18 (60%)
	Node negative	12 (40%)

A complete response was achieved in 24 patients (80%) at the primary tumour site and in 21 patients (70%) at the cervical nodes, with no cases of disease progression observed [Table 3].

Table 3: Tumour and nodal response after completion of concurrent chemoradiation

Response	Primary Tumour	Cervical Nodes
Complete response (CR)	24 (80%)	21 (70%)
Partial response (PR)	5 (16.7%)	8 (26.7%)
Stable disease (SD)	1 (3.3%)	1 (3.3%)
Progressive disease (PD)	0	0

At a median follow-up of 27 months, the DFS and OS rates were 76.7% and 83.3%, respectively. Laryngeal preservation was achieved in 26 patients (86.7%), whereas 4 patients (13.3%) required salvage laryngectomy during follow-up [Table 4].

Table 4: Survival and laryngeal preservation outcomes at follow-up (n = 30)

Outcome	Result
Median follow-up	27 months
Disease-free survival (DFS)	23/30 (76.7%)
Overall survival (OS)	25/30 (83.3%)
Laryngeal preservation rate	26/30 (86.7%)
Salvage laryngectomy required	4 patients (13.3%)

Anaemia was the most common haematologic toxicity, affecting 29 patients (96.7%), followed by leukopenia in 15 patients (50%) and thrombocytopenia in 13 patients (43.3%) [Table 5].

Table 5: Hematologic toxicities observed during induction chemotherapy

Toxicity	Incidence
Anaemia	29 (96.7%)
Leukopenia	15 (50%)
Thrombocytopenia	13 (43.3%)

Table 6: Grade III treatment-related toxicities during concurrent chemoradiation

Toxicity	Grade III (%)
Mucositis	20 (66.7%)
Dermatitis	4 (12%)

Grade III mucositis was the most frequent severe toxicity observed in 20 patients (66.7%). Grade III dermatitis occurred in four patients (12%) [Table 6].

DISCUSSION

This study shows that administering chemotherapy first, followed by chemoradiation, can effectively

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control advanced laryngeal cancer. Most patients responded to treatment, survival outcomes were encouraging, the larynx was preserved in many cases, and treatment-related side effects were generally manageable in routine clinical practice.

Most patients were middle-aged to elderly males, with supraglottic tumours being the most frequent laryngeal subsite at presentation. Similarly, Pal et al. found that among malignant cases, 65.8% were aged 51–70 years, 89% were males, and the supraglottis was the most common subsite (53.4%), followed by glottic tumours (45.2%).[11] Chauhan et al. reported that most patients were in the fifth–seventh decades (mean age 58.9 ± 10.0 years); males predominated (92.3%), and the supraglottis was the most common subsite (69.2%).[12] These studies support our results because they show the same patterns of age, male dominance, and supraglottic tumour location, confirming that our patient profile matches commonly reported laryngeal cancer characteristics.

Our study showed that most patients presented with locally advanced disease, characterised by predominant T3 tumours and frequent regional lymph node involvement at diagnosis. Similarly, Chauhan et al. found that most patients presented with locally advanced disease (Stage III–IV, 75.4%), had predominant T3–T4 tumours (75.4%), and regional nodal involvement in 56.9% at diagnosis.[12] Grasl et al. found that most patients presented with advanced disease, with T3–T4 tumours in 82.4% and regional nodal involvement in 54.5%, indicating the predominance of locally advanced presentation at diagnosis.[13] These studies support our results that many patients are diagnosed at an advanced stage, with large tumours and frequent lymph node involvement, similar to what we observed.

In our study, treatment resulted in high primary and nodal response rates, with effective disease control and no cases of progression observed. Similarly, Fasaludeen et al. reported that following definitive treatment, 87.1% of patients achieved a complete response, while 11.9% had residual disease involving the primary site (47.0%), nodes (49.0%), or both sites (4.0%).[14] Strojan et al. showed that after concurrent chemoradiotherapy, a complete response was achieved in 100% of patients at the primary site and 86% at the nodal sites, with no progressive disease at the first response evaluation.[8] These findings support a strong tumour response after treatment, good control at both primary and nodal sites, and very few or no cases of early disease progression.

In our study, at follow-up, survival outcomes were favourable, with high rates of laryngeal preservation and only a small proportion requiring salvage laryngectomy. Similarly, Strojan et al. reported that with a median follow-up of 3.8 years, DFS was 79% at 2 years and 70% at 5 years, whereas OS was 92% and 82%, respectively. Laryngeal preservation was maintained in 87% of patients at 2 years, and only a small proportion required salvage surgery.8 Katano et al. reported a median follow-up of 42.1 months, with a 3-year OS of 86.3% and a progression-free survival of 66.8%. Laryngeal preservation was achieved in 78.4% of patients, while salvage laryngectomy was required only in patients who developed local recurrence.[15] These studies showed similar survival outcomes, good laryngeal preservation, and few patients requiring further surgery, proving that organ-preserving treatment works well over time. However, differences in study design, chemotherapy regimens, and follow-up duration across these studies limit direct quantitative comparisons with the present cohort.

In this study, anaemia predominated during induction chemotherapy, while severe mucositis was the most common toxicity during concurrent chemoradiation, with dermatitis occurring less frequently. Similarly, in a dose-dense docetaxel-cisplatin-5-FU (TPF) induction study, Hsieh et al. reported that anaemia occurred in 10.3% of patients, while neutropenia was seen in 34.5%, including 25.9% with grade 3–4 toxicity; thrombocytopenia was not observed, consistent with the known myelosuppressive effects of induction chemotherapy.[16] In a study of 122 patients receiving definitive concurrent chemoradiotherapy, Iqbal et al. observed grade 3–4 mucositis in 33% and severe dermatitis in 41%, highlighting the high incidence of significant mucosal and skin toxicity during CRT.[17] These findings support similar blood-related side effects with induction chemotherapy and frequent mouth and skin reactions during chemoradiation, matching the toxicity patterns seen in our patients. This pattern is consistent with the known mucosal and myelosuppressive effects of platinum-based chemoradiotherapy.

Strengths: This prospective study used a uniform treatment approach, showed good follow-up, and provided practical evidence of effective larynx preservation with manageable toxicity. The prospective design and use of RECIST, CTCAE, and RTOG criteria strengthened the reliability of the outcome assessment.

Clinical implications: This treatment approach may preserve the larynx in many advanced cases while maintaining good disease control and acceptable side effects in routine practice. Future studies with more patients and longer follow-up are needed to better understand the long-term results and identify which patients benefit most from this treatment. Future studies should evaluate this sequential approach against upfront concurrent chemoradiotherapy using controlled comparative designs.

Limitations: The small sample size limits the generalisation of the results. The single-centre design may reflect local practice patterns. The lack of a comparison group restricts treatment comparison. Longer follow-up is needed to assess the late effects and durability of the outcomes. The absence of formal statistical comparisons limits inferences regarding the magnitude of the treatment benefit.

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CONCLUSION

Administering chemotherapy first, followed by chemoradiation, is effective for advanced laryngeal cancer. It effectively controls the disease, aids in laryngeal preservation, and has manageable side effects. This prospective Phase II study provides additional evidence supporting PF-based induction chemotherapy followed by concurrent chemoradiotherapy as an organ-preserving strategy for locally advanced laryngeal carcinoma. This treatment may be used in everyday hospital practice, even where resources are limited, and is suitable for carefully selected patients.

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