Outcomes of organ preservation treatment in advanced laryngeal carcinoma: A retrospective analysis from a single institution

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Abstract. Chemoradiation is the standard treatment for patients with locally advanced laryngeal carcinoma with intact cartilage and functional larynx. The aim of this retrospective study was to assess overall survival (OS) and disease-free survival (DFS) of patients with locally advanced (stage III and stage IV) squamous cell carcinoma of the larynx who have been treated with definitive radical radiotherapy (RT) with or without chemotherapy in a tertiary cancer center in India between January 1, 2006 and December 31, 2015. Data were collected using structured proforma. The patients were treated with RT alone, induction chemotherapy (IC) followed by RT, concurrent chemoradiation therapy (CCRT) or IC followed by CCRT. Response assessment was conducted at 3-4 months post-treatment. Patient-, tumor- and treatment-related factors were documented and were associated with DFS and OS. Survival curves were generated using the Kaplan-Meier method and the statistical significance of survival curves was assessed using the log-rank test. Prognostic factors were assessed using the Cox proportional hazards regression model. A total of 630 patients were included in the present study. The most common age group at presentation was 50-70 years (n=477; 75.7%) and 95.4% (n=601) patients were male. The most common stage at presentation was stage III (n=367, 58.1%). The median follow-up period for the entire group of was 59 months (range, 2-175 months). A complete response after treatment was seen in 549 patients (87.1%). Salvage surgery was performed for 11 patients with residual disease. A total of 134 patients (21.3%) had developed locoregional and distant relapses, and salvage surgery was performed for 31 out of 102 patients with locoregional relapse. The 5-year OS was 48.7% and the 5-year DFS was 45.7%. The stage-wise OS rates were 58.9, 34.9 and 30.4% (P=0.001) and the stage-wise DFS rates were 56.3, 32.0 and 21.7 (P=0.001) for stage III, IVa and IVb, respectively. Results from the present study demonstrated the feasibility of delivery of chemoradiation protocols with good results in a developing country.

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Introduction

Laryngeal cancer constitutes 1.1% of all new cancer diagnoses worldwide; there are ~177,000 new laryngeal cancer cases and ~94,000 deaths annually (1). In India, laryngeal cancer is the seventh most common cancer, whereas it ranks ninth in Asia (2). The incidence of laryngeal cancer is 1.26-8.18 per 100,000 population in different regions in India (3). Laryngeal cancer is divided into supraglottic (epiglottis, false vocal cords, ventricles, aryepiglottic folds, arytenoids), glottic (true vocal cords, anterior commissure), and subglottic (located below the vocal cords) cancer for staging and prognostication purposes. Of these types of cancer, glottic cancer has the best 5-year relative survival rate (77%), due to a higher percentage of patients presenting with localized disease (83%) (4). The 5-year relative survival rate of subglottic cancer is 53% (4). Furthermore, supraglottic primary tumors more often recur when compared with glottic primary tumors (5,6). Supraglottic tumors are also associated with higher rates of regional nodal metastasis, whereas the glottic site is less prone to nodal spread as the lymphatic drainage is sparse at this site.

It is estimated that 75% of laryngeal cancer cases are attributable to cigarette smoking and alcohol use. For several years, alcohol and tobacco were thought to act synergistically (7); however, more recent data have suggested that the two are independent risk factors (8). The effect of smoking and alcohol is greater for supraglottic cancer than glottic cancer (9). People who employ their voices extensively in their work also appear to be at a higher risk of developing laryngeal cancer. In addition, occupational exposure to asbestos, diesel fumes, rubber and wood dust (9), vitamin and nutrient deficiencies (10), and gastroesophageal reflux disease (11,12) may also lead to the development of laryngeal cancer. A molecular etiology for laryngeal cancer is emerging (13,14) and mutations in p53,

Ki-67, Chek-2, EGFR, h-TERT, cyclin D1, cathepsin D and TGF-β have been identified (15-17).

Locally advanced cancer of the larynx includes TNM stages T3, T4 and N1-N3. Until the early 1990s, the standard treatment for locally advanced disease was total laryngectomy followed by adjuvant radiation. Crucial changes in the treatment approaches have come about in the management of these types of cancer as a result of definitive evidence supporting the role of organ preservation (18-20). The role of radiotherapy (RT) was established with the publishing of the Veterans Affair trial in 1991 (18). With the use of induction chemotherapy (IC), and subsequently concurrent chemoradiation therapy (CCRT), organ preservation approaches have become the standard of care in stage III and stage IV laryngeal cancer with intact cartilage and functional larynx (21-28). Although these changes have been incorporated in the treatment of laryngeal cancer worldwide, their clinical outcomes and tolerance in the Indian population have not been adequately quantified. The present retrospective study aimed at analyzing the overall survival (OS) and disease-free survival (DFS) of patients with locally advanced (stage III and stage IV) squamous cell carcinoma of the larynx who have been treated with definitive radical RT with or without chemotherapy in a tertiary cancer center between January 1, 2006 and December 31, 2015. The results may provide detailed insight on the success rates of the current treatment protocols in laryngeal cancer, which may in turn open up areas of focused research aiming at improving the outcome further.

Materials and methods

Ethics approval. The retrospective study protocol was approved by the scientific review committee institutional review board of Regional Cancer Centre, Thiruvananthapuram (IRB no. 09/2019/04). Data were retrieved from case files using a structured proforma.

Patient cohort. A retrospective analysis was conducted on 630 patients with biopsy-proven locally advanced (stage III and IV) squamous cell carcinoma of the larynx who were treated with definitive RT with or without chemotherapy between the period January 1, 2006 and December 31, 2015 in Regional Cancer Centre (Thiruvananthapuram, India) Patients with histology other than squamous cell carcinoma, patients who presented after primary treatment elsewhere for salvage procedures, patients with stage T4a disease with cartilage destruction who underwent primary surgical management and patients having received palliative treatment were excluded from the study.

The work-up after flexible endoscopy and biopsy included routine hemogram, creatinine clearance test, dental checkup, neck CT, chest X-ray and baseline cardiac evaluation. The patients were staged according to American Joint Committee on Cancer (AJCC) TNM staging 7 edition (29).

Treatment. The patients who received radiotherapy (RT) alone, CCRT, IC followed by RT, or IC followed by CCRT were included in the present study.

RT. All patients receiving RT were treated with either a two-dimensional (2D) technique using X-ray simulator with customized MLC shielding with 6 MV photons or cobalt 60 or with intensity-modulated RT. The different dose fractionations used were 60 Gy/26 fractions, 66 Gy/33 fractions, 55 Gy/20 fractions or 66 Gy/30 fractions. Patients were reviewed weekly during RT for any acute complications and were managed accordingly. Any interruption in treatment was corrected after giving adequate gap correction.

IC. The IC regimens used were 5-fluorouracil (5-FU) + cisplatin (PF) or PF + docetaxel (TPF). The IC regimens were administered every 3 weeks. The CCRT regimens were 3-weekly cisplatin (80-100 mg/m^2), 3-weekly carboplatin (area under the curve, 5) or weekly cisplatin (40 mg/m^2).

Follow up of patients. Patients underwent the first clinical review at 2 months after completion of RT, and response assessment was done at 3-4 months. Further follow-up was done every 3 months in the first year of completion of treatment, every 4 months in the second year, followed by every 6 months until 5 years post-RT and annually thereafter. Patients were clinically examined and an evaluation with indirect laryngoscopy/70-degree laryngeal endoscopy was done at each visit. If patients were lost to follow-up, details were updated through telephonic conversation. Salvage surgery was planned for patients who had residual disease or who had developed locoregional relapse.

Statistical analysis. Details of the patients, their tumor and their treatment-related characteristics were retrieved from the hospital database using a structured proforma. Follow-up data were updated until October 30, 2020. The primary endpoints analyzed were disease-free survival (DFS) and overall survival (OS). DFS was defined as the period from the date of registration to the date of locoregional relapse, distant relapse or death, whichever occurred earlier. OS was defined as the period from the date of registration to the date of death from any cause. Compliance to treatment was assessed based on whether the patient completed the planned course of treatment or whether there were any interruptions. Evaluation of toxicity was not included in the present study.

Survival curves were generated using the Kaplan-Meier method and statistical significance was assessed using the log-rank test. For univariate analysis, the patient factors with potential prognostic value with respect to OS and DFS were recorded and analyzed. Age, sex, smoking and drinking habits, comorbidity, T stage, N stage, composite stage, and sequencing of chemotherapy were tested for statistical significance. Prognostic factors were assessed using Cox proportional hazards regression model. Patients were stratified into three age groups (<50, 50-70 and >70 years) for analysis of outcomes. With respect to chemotherapy, the use of IC alone, IC followed by CCRT, CCRT alone or no chemotherapy were separately analyzed for any significant association with outcomes.

Results

Baseline characteristics. A total of 630 patients were included in the present retrospective study; the baseline characteristics of the study population are provided in Table I. The median age of the target population was 61 years (range, 30-89 years), and the majority of the patients were in the 50-70-years age group (n=477; 75.7%). Most of the patients were male (n=601;

Table I. Baseline clinicopathological characteristics of the patients with laryngeal carcinoma.

Clinicopathological characteristic	Patients, n=630	%
Age, years		
<50	67	10.6
50-70	477	75.7
>70	86	13.7
Sex		
Male	601	95.4
Female	29	4.6
Habit		
Smoking	384	61.0
Alcohol consumption	263	41.0
Comorbidity		
Diabetes mellitus	274	43.5
Hypertension	156	24.8
Heart disease	112	17.8
Disease characteristic (laryngeal subsite)		
Supraglottis	496	78.7
Glottis	126	20.0
Subglottis	8	1.3
T stage		
T1	23	3.7
T2	93	14.8
T3	413	65.6
T4a	81	12.9
T4b	20	3.2
N stage		
N0	257	40.8
N1	162	25.7
N2a	66	10.5
N2b	85	13.5
N2c	57	9.0
N3	3	0.5
Composite stage		
Stage III	367	58.1
Stage IVa	240	38.3
Stage IVb	23	3.6
Tracheostomy		
No	482	76.5
Yes	148	23.5
Dose of RT		
60 Gy/26 fractions	483	76.7
66 Gy/33 fractions	38	6.0
55 Gy/20 fractions	86	13.7
66 Gy/30 fractions	23	3.7
Technique		
2D	606	96.2
IMRT	24	3.8
Sequencing of chemotherapy		
CCRT	295	46.8
IC followed by CCRT	139	22.1
IC followed by RT	17	2.6
RT alone (no chemotherapy)	177	28.1
Unknown	2	0.4
Induction chemotherapeutic agent		
No IC	455	72.2
PF	160	25.4
TPF	9	1.4
5-FU + carboplatin	5	0.8
MTX	1	0.2
Treatment interruption		
No	576	91.4
Yes	54	8.6

2D, two-dimensional; 5-FU, 5-fluorouricil; CCRT, concurrent chemoradiation therapy; IC, induction chemotherapy; IMRT, intensity-modulated radiotherapy; PF, cisplatin + 5-FU; MTX, methotrexate; RT, radiotherapy; TPF, 5-fluorouracil + cisplatin + docetaxel.

95.4%). In addition, 61% (n=384) of the patients were habituated to smoking and 41% (n=263) to alcohol consumption.

In the majority of the patients, the supraglottis was the primary site of disease (n=496; 78.7%). A total of 257 patients (40.8%) were N0 at presentation, and 367 patients (58.1%) had stage III disease at presentation. A tracheostomy was performed for 148 (23.5%) patients. Out of the total 630 patients, 451 (71.5%) received chemotherapy. Most patients (46.8%) received CCRT. The most common IC agents used were PF and the majority of patients (96.2%) had cisplatin as the concurrent chemotherapy. Conventional 2D RT was delivered to 606 patients (96.2%). Only 54 patients (8.6%) had treatment interruption exceeding 7 days (reasons including machine failure, toxicity and poor compliance), whereas the remaining patients completed the planned treatment without interruptions.

Treatment outcomes are detailed in Table II. After the planned radical treatment, 549 patients (87.1%) had complete response at 3-4 months post-treatment. Out of the total 630 patients, 75 (11.9%) had residual disease, of which 35 patients had residual disease in the primary site, 37 in the nodal site and three in both sites. A total of 11 patients with residual disease underwent salvage surgery.

The median follow-up period for the entire group of 630 patients was 59 months (range, 2-175 months). The 5-year follow-up information was available for 84% of patients. At the median follow-up of 59 months, 134 patients (21.2%) relapsed and the median time to relapse was 16 months (range,

Table II. Results of treatment outcome.

Treatment outcome	Patients, n=630	%
Status at 3-4 month follow-up		
Complete response	549	87.0
Partial response	75	12.0
Unknown	6	0.9
Residual disease (partial/no response)	75	12.0
Primary site	35	47.0
Nodal site	37	49.0
Primary and nodal	3	4.0
Salvage surgery for residual disease	11	14.7
Primary	6	54.5
Nodal	3	27.3
Both primary and nodal	2	18.2
Pattern of relapse	134	21.3
Local	65	48.5
Regional	32	23.9
Locoregional	5	3.7
Distant	32	23.9
Salvage surgery for relapse	31	4.9
Local	21	67.7
Regional	9	29.0
Locoregional	1	3.2
Second malignancy		
No	602	95.6
Yes	21	3.3
Unknown	7	1.1

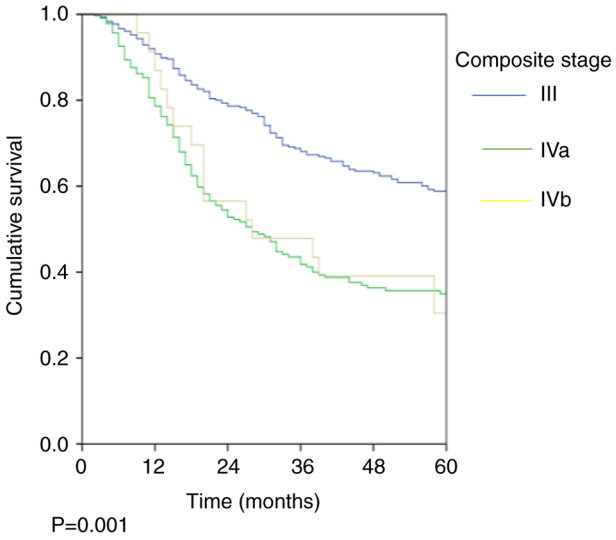

Figure 1. Kaplan-Meier curves showing the 5-year stage-wise overall survival for patients with stage III, IVa and IVb laryngeal carcinoma. P=0.001.

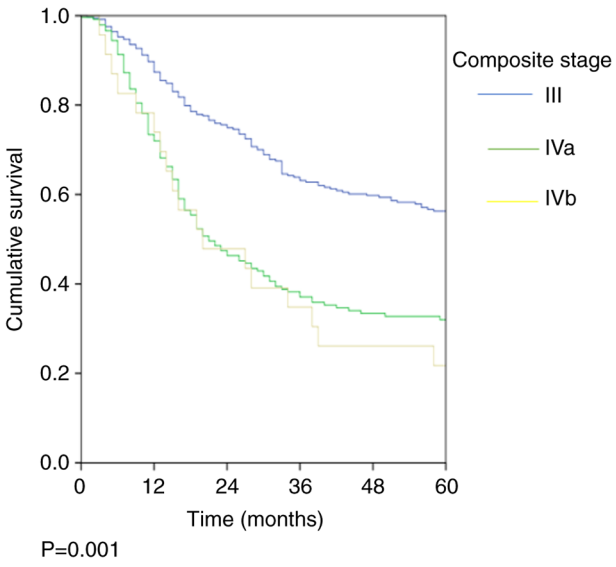

Figure 2. Kaplan-Meier curves showing the 5-year stage-wise disease-free survival for patients with stage III, IVa and IVb laryngeal carcinoma. P=0.001.

6-87 months). Of those patients that relapsed, 65 (11.48%) relapsed locally, 32 (5.6%) relapsed in the nodal site, 5 (0.8%) relapsed locoregionally and 32 (5.6%) had distant recurrence. In the patients who relapsed, salvage surgery was performed for 21 patients with local recurrence, nine patients with nodal recurrence and one patient with locoregional recurrence. The remaining 103 patients that relapsed were treated with palliative chemotherapy or best supportive care. During the follow-up period, 21 patients (3%) developed a second malignancy, with the most common being lung cancer.

Survival outcomes. The 5-year OS rate was 48.7% and the 5-year DFS rate was 45.7%. The stage-wise OS rates were 58.9, 34.9 and 30.4% (P=0.001; Fig. 1; Table III) and the stage-wise DFS rates were 56.3, 32 and 21.7% (P=0.001; Fig. 2; Table III) for stage III, Iva and Ivb, respectively.

The outcome measures of univariate analysis for OS and DFS were associated with various patient factors and treatment-related factors, and were tested for significance (Table IV). With respect to age, patients <50 years old had better 5-year DFS (P=0.050), but there was no statistically significant difference in 5-year OS (P=0.147). The 5-year OS (P=0.003) and DFS (P=0.002) were higher in non-smokers when compared with smokers. Patients with hypertension had significantly lower OS (P=0.001) and DFS (P=0.002), and those with diabetes mellitus had lower DFS (P=0.043). Heart disease was associated with slightly lower OS (P=0.247) and DFS (P=0.077) but it was not statistically significant. With respect to disease stage, the DFS and OS were significantly lower with advanced T4, N2+3 and Stage IVb disease (all P=0.001). Sex, alcohol consumption, heart disease and sequencing of chemotherapy did not show any significant association with OS or DFS.

The factors found significant on univariate analysis were subjected to multivariate analysis. On multivariate analysis, T stage (T3 vs. T4; P=0.001), N stage (N2 + N3 vs. N0; P=0.001) and smoking status (P=0.012) were shown to have significant association with OS (Table V), whereas smoking

Table III. Stage-wise OS and DFS rates.

Stage	OS, % (SEM, %)	P-value	DFS % (SEM, %)	P-value
All patients	48.7 (2.2)		45.7 (2.2)	
Stage III (n=367)	58.9 (2.9)	0.001	56.3 (2.9)	0.001
Stage IVa (n=240)	34.9 (3.5)		32.0 (3.4)	
Stage IVb (n=23)	30.4 (9.6)		21.7 (8.6)	

DFS, disease-free survival; OS, overall survival.

Table IV. Univariate analysis of OS and DFS.

Clinicopathological characteristic	Patients, n=630	%	OS, % (SEM %)	P-value	DFS, % (SEM, %)	P-value
Age, years						
<50	67	10.6	60.3 (6.8)	0.147	60.2 (6.8)	0.05
50-70	477	75.7	47.2 (2.6)		43.2 (2.5)	
>70	86	13.7	48.3 (6.3)		48.0 (6.3)	
Sex						
Male	601	95.4	48.0 (2.3)	0.199	45.1 (2.3)	0.218
Female	29	4.6	65.9 (10.7)		60.9 (11.0)	
Habit						
Smoking						
Yes	384	61.0	42.9 (2.9)	0.003	39.8 (2.8)	0.002
No	246	39.0	57.1 (3.5)		54.4 (3.5)	
Alcohol consumption						
Yes	263	41.0	43.9 (2.7)	0.261	42.1 (2.6)	0.071
No	367	59.0	57.6 (4.1)		57.4 (4.1)	
Comorbidity						
Diabetes						
Yes	274	43.5	45.7 (2.5)	0.075	42.5 (2.5)	0.043
No	356	56.5	59.5 (4.6)		57.3 (4.7)	
Hypertension						
Yes	156	24.8	44.3 (2.6)	0.001	41.9 (2.6)	0.002
No	474	75.2	61.1 (4.3)		56.9 (4.3)	
Heart disease						
Yes	112	17.8	47.9 (2.4)	0.247	44.6 (2.4)	0.077
No	518	82.2	55.1 (6.6)		55.1 (6.6)	
Disease characteristics						
T stage						
T1 + T2	116	18.5	44.5 (5.2)	0.001	42.8 (5.1)	0.001
T3	413	65.6	54.0 (2.8)		51.4 (2.8)	
T4	101	16.1	32.1 (5.2)		26.2 (4.9)	
N stage						
N0	257	40.8	59.1 (3.5)	0.001	56.2 (3.5)	0.001
N1	162	25.7	55.8 (4.3)		51.4 (4.3)	
N2 + N3	211	33.5	30.2 (3.6)		28.5 (3.5)	
Stage						
III	367	58.1	58.9 (2.9)	0.001	56.3 (2.9)	0.001
IVa	240	38.3	34.9 (3.5)		32.0 (3.4)	
IVb	23	3.6	30.4 (9.6)		21.7 (8.6)	

Table IV. Continued.

Clinicopathological characteristic	Patients, n=630	%	OS, % (SEM %)	P-value	DFS, % (SEM, %)	P-value
Sequencing of chemotherapy						
CCRT	295	46.8	48.6 (3.3)	0.785	45.7 (3.2)	0.729
IC + CCRT	139	22.1	48.9 (4.8)		43.9 (4.7)	
IC alone followed by RT	17	2.6	62.5 (12.1)		50.0 (12.5)	
No chemotherapy	177	28.1	47.6 (4.3)		46.8 (4.3)	
Unknown	2	0.4	n/a			n/a

CCRT, concurrent chemoradiation therapy; DFS, disease-free survival; IC, induction chemotherapy; OS, overall survival.

status (P=0.005) and composite stage (IVa and IVb; both P=0.001) had significant association with respect to DFS (Table VI).

Discussion

Until the early 1990s, the standard treatment for locally advanced laryngeal carcinoma was total laryngectomy followed by adjuvant RT. A fundamental change in the management of laryngeal cancer began in 1991 when the Veteran Affairs laryngeal cancer study was published (18). This trial included 332 patients who were randomized to receive either three cycles of IC (PF) followed by RT or undergo primary surgery followed by postoperative RT. The 2-year OS was 68% for both arms and 64% of patients receiving PF + RT had successfully preserved larynx without compromising survival. This study demonstrated that IC followed by RT is a reasonable alternative to laryngectomy for patients with locally advanced laryngeal cancer. Another phase 2 trial for patients with stage III and IV laryngeal cancer reported that one cycle of IC (PF) followed by CCRT in responders resulted in excellent larynx preservation and improved OS rates compared with historical results (19). A voice-related quality of life analysis was conducted in the patients of the aforementioned trial, and quality of life was found to be better in those who received chemoradiation therapy compared with salvage laryngectomy (20).

A meta-analysis of chemotherapy in head and neck cancer and its subsequent updates established the role of CCRT along with RT in squamous cell cancer of the head and neck region, with an absolute 5-year OS benefit of 5.4% for laryngeal cancer in the subset analysis (21-25). The role of CCRT as an organ preservation approach for laryngeal cancer was studied in the Radiation Therapy Oncology Group (RTOG) 91-11 trial and its update (26,27). This study showed that the 10-year laryngeal preservation rate was significantly higher in the CCRT arm compared with the IC followed by RT or RT-alone arms. Thus, the standard treatment for patients with stage III and IV laryngeal cancer who have intact cartilage and a functional larynx is CCRT. Those with cartilage destruction or dysfunctional larynx are not ideal candidates for organ preservation (28).

The superiority of the three-drug IC (TPF) in locally advanced head and neck cancer in terms of OS and DFS was established by TAX 323 (30) and TAX 324 (31) trials. The GORTEC 2000-01 trial evaluated the role of TPF in organ preservation in laryngeal and hypopharyngeal cancer in which patients were randomized to receive IC with either TPF or PF regimens (32). The responders to IC were given radical RT, whereas non-responders underwent total laryngectomy followed by adjuvant RT. The overall response was higher in the TPF arm (80%) compared with the PF arm (59.2%) (P=0.002). The study had a median follow-up of 105 months, and the long-term efficacy and safety of the trial reported significant differences in the 5-year (74.0 vs. 58.1%) and the 10-year (70.3 vs. 46.5%) larynx preservation rates in the TPF and PF arms (both P=0.01) (33). A number of studies have shown that TPF IC is not superior to CCRT alone in head and neck squamous cell carcinoma (HNSCC) in terms of survival (34-36). The ongoing phase 3 French trial (GORTEC 2014-2103-SALTORL) is continuing to compare the role of TPF IC followed by RT with CCRT in patients with laryngeal and hypopharyngeal cancer (37).

Based on these previous reports, the present study analyzed the profiles, the main modalities of treatment used for locally advanced laryngeal cancer, the outcome of various modalities of treatment with regard to survival, as well as patient- and treatment-related factors predicting the outcome for patients admitted to Regional Cancer Centre, Thiruvananthapuram. The significance of various prognostic factors in the present study are detailed below.

In the present study, the patients were stratified into three age groups (<50, 50-70 and >70 years), with the majority belonging to the 50-70 years group. No significant difference in OS was identified between the three groups; however, there was a significant difference in terms of DFS favoring the younger group. It may be that the younger patients tolerated aggressive chemoradiation better than the elderly patients. Previous studies have also shown that age is an important predictor of survival outcome. Lacy *et al* (38) found that younger patients (≤40 years) had a significantly better 5-year OS rate compared with middle-aged or older patients. In a large retrospective study from Norway, Brandstorp-Boesen *et al* (39) reported that the OS was better in patients aged <60 years.

With respect to smoking, the present study showed that the OS rate was significantly higher in smokers compared with non-smokers. Similarly, Browman *et al* (40) demonstrated a better 2-year OS rate for non-smokers (66% for abstainers vs. 39% for active smokers; P=0.005) with a risk difference of 27%. Similarly, Fortin *et al* (41) revealed the following a 5-year OS rates for 1,871 patients with locally advanced HNSCC:

Table V. Multivariate analysis of overall survival.

		95.0% CI for HR		
Factor assessed	HR	Lower	Upper	P-value
T stage (T1 + T2 vs. T3)	1.05	0.75	1.47	0.796
T stage (T4 vs. T3)	1.69	1.24	2.31	0.001
N stage (N1 vs. N0)	1.04	0.73	1.48	0.832
N stage (N2 + N3 vs. N0)	2.21	1.63	3	0.001
Smoking status (yes vs. no)	1.39	1.07	1.79	0.012

HR, hazard ratio.

Table VI. Multivariate analysis of disease-free survival.

		95.0% CI for HR		
Factor assessed	HR	Lower	Upper	P-value
Composite stage (IVa vs. III)	1.98	1.55	2.53	0.001
Composite stage (IVb vs. III)	2.58	1.58	4.22	0.001
Smoking status (yes vs. no)	1.43	1.12	1.82	0.005

HR, hazard ratio.

68% for patients that never smoked, 55% for former smokers and 50% for active smokers (P=0.001).

In the present study, comorbidities such as diabetes mellitus, heart disease and hypertension were present; however, a statistically significant reduction in OS was determined only for patients with hypertension, and a lower DFS was indicated for those with hypertension and diabetes mellitus. Previous studies have shown an association between coexisting comorbidities (diabetes mellitus, hypertension, heart disease, pulmonary diseases and neurological disease) and low OS in patients, although there are limited data on comorbidities and DFS in patients with laryngeal cancer. Fong *et al* (42) showed incidence in comorbidity was associated with inferior OS (HR=1.24; P<0.001) and inferior progression-free survival (HR=1.14; P=0.007). Bøje *et al* (43) studied the impact of comorbidity on treatment outcome in a series of 12,623 patients in a Danish head and neck cancer study and found that comorbidities, such as heart disease and diabetes mellitus, significantly decreased the 5-year OS (P<0.001).

The present study showed that high T and N stages were associated with poor outcome. Fong *et al* (42) also showed that advanced N stage was associated with worse OS (HR, 3.52; P<0.001) and DFS (HR, 3.23; P<0.001), and a higher T stage was associated with inferior OS and (HR 1.61; P=0.02). The majority of patients in the present study had stage III (58.1%) at presentation, followed by stage IVa (38.3%) and stage IVb (3.6%). Analysis of different disease stages in the present study revealed a significant difference in survival probability with advanced stages in both univariate and multivariate analyses.

In the present study organ preservation strategies used were radical RT alone, IC followed by radical RT, CCRT and IC followed by CCRT. No significant difference was observed for OS or DFS between any of the treatment groups. Although IC followed by RT showed a non-significant improved outcome compared with other chemotherapy sequence groups with regard to OS and DFS, the number of patients in this group was too small to identify the significance. In the RTOG 91-11 study, even though there was no statistically significant difference in OS in any of the three treatment arms, locoregional control and laryngeal preservation were significantly higher in the CCRT-alone arm compared with the other two arms (IC followed by RT or RT-alone) (26,27).

In the present study, the 5-year OS and DFS rates for all patients combined were 48.7 and 45.7%, respectively, and a stage-wise decrease in OS was observed from 58.9 to 30.4%. These results were similar to other studies that have shown 5-year survival rates of 40-50% in stage III and 30-35% in stage IV locally advanced laryngeal carcinoma (44,45). A total of 134 patients (23.6%) had recurrence in the present study, the most common being local recurrence. In the RTOG 91-11 study (26), the proportion of patients in the IC, CCRT and RT-alone groups with recurrence were: Local, 33.3, 22.3 and 35.8%; regional, 7.6, 3.3 and 11.5%; and distant, 10.4, 11.2 and 14.9%, respectively.

The best sequence of chemotherapy and radiation to achieve optimum results could not be determined from the present study results, as no difference in OS was determined. It must be noted that treatment comparison based on non-randomized data are generally not recommended as they are prone to bias, and hence no conclusion could be reached on the outcomes

with different organ preservation approaches in laryngeal cancer from the present study.

Weber *et al* (46) studied the outcome of salvage surgery in patients following organ preservation and concluded that salvage surgery was associated with acceptable morbidity with excellent locoregional control In the present study, only 31 patients with recurrence and 11 patients with residual disease underwent salvage surgery. Others were offered either palliative chemotherapy or best supportive care in view of poor general condition and/or advanced disease. This is likely the main reason that the OS and DFS closely correspond with each other in the present study.

In the present study, univariate analysis showed that the factors associated with OS were smoking, hypertension, T stage, N stage and composite stage, and those associated with DFS were age, smoking, diabetes, hypertension, T stage, N stage and composite stage. On multivariate analysis, T stage, N stage and smoking habit were associated with OS, whereas composite stage and smoking habit were associated with DFS. In a study by Daneshi *et al* (47), multivariate Cox regression analysis suggested that age at diagnosis, cancer stage, type of treatment, N stage and tumor grade affected the survival of patients with locally advanced laryngeal carcinoma.

The retrospective nature of the present study, the small number of patients in various treatment groups and non-uniform treatment decisions for the entire population were the major limitations of the present study. The heterogenous treatment received by the study group made it unfeasible to derive the best treatment modality for the patients. However, in this single-institution study, the total number of patients in the cohort was high, and the majority of the patients completed the planned course of treatment without interruptions.

Anti-EGFR therapy has not shown any added benefit in locally advanced head and neck cancer in addition to standard CCRT (48-50); however, it is a reasonable option in patients who cannot tolerate platinum-based chemotherapy (51,52). The role of immune checkpoint inhibitors has shown promising results in the first-line and second-line treatments for recurrent or metastatic HNSCC (53-55), but they have not shown any effect on locally advanced head and neck cancer (56).

In the present study, a major concern was the high relapse rate (21.3%), even in patients who had completed the planned course of treatment. Newer approaches to detect the various biomarkers in patients with advanced laryngeal cancer, and thus offer a better personalized treatment approach, may help to overcome the relapse challenges. For example, Jun *et al* (57) showed that low expression of ERCC1 was an independent predictor for prolonged survival in HNSCC, and ERCC1 expression may be a useful biomarker for these tumors in patients treated with cisplatin-based CCRT. Hence, the evaluation of ERCC1 is recommended for future correlative biomarker studies. A consensus panel summary on laryngeal preservation suggested a new endpoint called laryngo-esophageal dysfunction-free survival, and also suggested that correlative biomarker studies for near-term trials should include EGFR, ERCC-1, E-cadherin and β-catenin, epiregulin and amphiregulin, as well as TP53 mutation (58).

In conclusion, the present retrospective study evaluated the outcomes of patients with locally advanced laryngeal carcinoma who received chemoradiation/radiation. Chemoradiation is the standard of care in locally advanced laryngeal carcinoma. The aim of the present study was to demonstrate the feasibility of delivering chemoradiation protocols in developing countries with poor resources, and it has shown good results with a 5-year OS rate of 48.7% and DFS rate of 45.7% in locally advanced laryngeal cancer. The salvage rates were poor for those with recurrence (4.9%) and/or residual disease (14.7%). Ideal sequencing of chemotherapy with RT is an ongoing area of research.

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Availability of data and materials

All data analyzed during this study are included in this published article.

Authors' contributions

KCT made substantial contributions to the conception and design of the study. AF performed acquisition of the data. Data analysis was mainly done by PG and the interpretation of data was performed by AF, RRK, MR, FN, AMP, NK and KR. KCT and AF confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The retrospective study protocol was approved by the scientific review committee institutional review board of Regional Cancer Centre, Thiruvananthapuram. Data were retrieved from case files using a structured proforma.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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