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Original Article

Oncology Section

Assessment of Rate of Laryngeal Preservation in Patients undergoing Radiotherapy with Concurrent Chemotherapy for Advanced Squamous Cell Carcinoma of Larynx: A Prospective Interventional Study

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ABSTRACT

Introduction: Advanced laryngeal cancer carries significant morbidity with deterioration sinquality of life. The Radiation Therapy Oncology Group (RTOG) 91-11 study found that in the management of advanced laryngeal cancers, Concurrent Chemotherapy and Radiation (CCRT) produced significant organ preservation compared with other treatment modalities without compromising locoregional control and survival outcomes. These studies lead to the employment of CCRT for advanced laryngeal cancer with the aim of organ preservation.

Aim: To assess the rate of laryngeal preservation in patients undergoing CCRT in a tertiary care centre.

Materials and Methods: The present prospective, interventional study was conducted in the Department of Radiotherapy, Government Medical college, Thrissur, Kerala, India comprising the newly diagnosed patients with locally advanced laryngeal cancers from July 2019 to August 2020. Conventional radiotherapy with a dose of 66 Gray in 33 fractions over 6.5 weeks was given concurrently with injection cisplatin 100 mg/m^2 intravenously every three weeks and periodically followed-up for one year.

Results: Out of 50 study participants, 40% of the target population were between 51-60 years of age and 90% of the cases were males. The rates of laryngeal preservation were found to be 88% according to this study. The study proved that laryngeal preservation was significantly lower in cases with age 61-70 years, with those with Eastern Cooperative Oncology Group (ECOG) performance score of 2, nodal stage N3 and stage IV disease and in those with fewer chemo cycles. There was no relationship between laryngeal preservation sex, tumour stage, composite stage.

Conclusion: These results show that the rates of laryngeal preservation were found to be higher in advanced laryngeal cancers undergoing radiotherapy with concurrent chemotherapy. Locoregional control was higher without causing severe toxicities. This study shows that higher rates of laryngeal preservation could be achieved with good locoregional control thereby leading to organ preservation and avoidance of severe morbid surgical procedures.

Keywords: Eastern cooperative oncology group, Preservation of larynx, Radiation, Tumour stage

INTRODUCTION

Laryngeal cancer ranks the 9th leading cause of cancer in India and about 28,000 new cases of laryngeal cancers have been detected each year [1]. Laryngeal cancer can orginate from any of the epithelial and non epithelial structures of the larynx, of which 85-95% are squamous cell carcinomas [2]. Tobacco smoking and consumption of alcohol increases the risk for the manifestation of laryngeal cancers [3].

At the time of diagnosis, localised laryngeal tumours contributes to 52% and, 23% are locally advanced [4]. Earlier in 1873, advanced laryngeal cancers were managed by Total Laryngectomy (TL), which was first performed by Billroth. The combination of laryngectomy followed by postoperative radiotherapy were also practiced earlier which resulted in overall survival ranging from 0 to 50% [5]. This lead to creation of permanent tracheal stoma and mutilation of vocal function and had a significant impact on the patient with respect to severe morbidity owing to surgery and profound mental distress over losing their voices [6].

In 1991, Veteran Affairs (VA) trial was published which lead to the preference of laryngeal preservation by means of induction chemotherapy followed by radiotherapy over morbid surgeries in case of locally advanced laryngeal cancers [7].

The laryngeal preservation rates of induction chemotherapy with Docetaxel, Cisplatin and 5-Fluorouracil (TPF regimen) followed by Radiotherapy (RT) or surgery was significantly higher when compared with Cisplatin and 5-Fluorouracil (PF) followed by RT/surgery according to Groupe Oncologie Radiothérapie Tête et Cou (GORTEC) trial conducted from 2000 to 2001 [8].

In order to assess the role of RT in laryngeal preservation and the ideal sequencing of chemotherapy and radiotherapy, RTOG and Head and Neck Intergroup performed a randomised trial in 2003 which did a comparison of induction Cisplatin and 5-Fluorouracil (5-FU) followed by radiotherapy, concomitant cisplatin and radiotherapy, and radiotherapy alone. This study demonstrated an improved locoregional control rates with concurrent therapy [9].

RTOG 91-11 updated their study results in 2013, in which it was found that concomitant cisplatin with radiotherapy significantly improved the larynx preservation rate over induction cisplatin and 5-fluorouracil followed by radiotherapy and over RT alone [10]. A study conducted by Nair SV et al., in 2018 which compared total laryngectomy with Organ Preservation Protocol (OPP), the concurrent chemoradiotherapy arm showed an improvement in laryngeal preservation rate.

Concurrent Chemo Radiotherapy (CCRT) with high laryngeal preservation rates has led to an increase in the use of non operative treatment and a decrease in the use of primary surgery. This has led to increased rates of laryngeal preservation and improved the quality of lives, particularly in advanced stage of laryngeal cancer,

with improved locoregional control rates following concurrent chemoradiotherapy [9].

In the study institution according to Indian Council of Medical Research (ICMR) data authors had 156 new laryngeal cancer cases registered in 2018 of which 75% constituted to advanced stage. Treatment aim in such patients is to give laryngeal preservation with intent to cure. Authors routinely use the CCRT a regime of 66 Gy in 33 fractions based on RTOG 91-11 trial. Radiation is given as 2 gray per fractions for five days over 6-7 weeks to these advanced laryngeal cancer patients without cartilage invasion [11].

This study aimed to prospectively assess the benefit of the CCRT in the management of locally advanced laryngeal cancers. Comparing to vast data of laryngeal preservation with CCRT from west and paucity of data from kerala, the present study attempts to provide data regarding the rates of laryngeal preservation following CCRT from a tertiary care centre from mid kerala.

MATERIALS AND METHODS

This prospective, interventional study was conducted in the Department of Radiotherapy, Government Medical College, Thrissur, Kerala, India, from July 2019 to August 2020 comprising the newly diagnosed patients with locally advanced stage III and IV a squamous cell carcinoma based on American Joint Committee on Cancer (AJCC), 8th edition of larynx [12]. All patients were explained about the procedure and informed consent obtained. Ethical clearance was obtained from Institutional Ethical Committee {IEC no. B6-8772/2016/MCTCR(27)}.

Inclusion criteria: Patients with confirmed histology report of squamous cell carcinoma with age less than 70 years and Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 [13] were included in the study.

Exclusion criteria: Patients with cartilage invasion, renal impairment and moderate sensorineural hearing loss were excluded from the study.

Sample size calculation: Sample size is calculated using the formula:

$$(Z_\alpha)^2 PQ /d^2$$

P=84% (P is the percentage of patients who achieved target in the study RT0G 91-11

Z_α = 1.96, Q=100-P which equals to 16, Relative error d=20% of P which equals to 16.8

Significance level of 0.05 and power 90%

So sample size=$(1.96)^2 \times 84 \times 16/(16.8)^2$= 18

So the minimum sample size needed was 18

Hence, sample size for the study was 50

Study Procedure

Patients with carcinoma larynx was clinically assessed along with laryngoscopy to know the extent and measurement of the tumour. High-resolution computed tomography scanning of the primary tumour and the neck was done before starting treatment to confirm the stage of the disease. All the routine blood investigations including complete blood count, liver and kidney functions and 24 hour urine creatinine clearance test were performed. Pure tone audiogram was done prior to starting cisplatin chemotherapy. Prophylactic extraction of caries teeth was done prior to radiation. A ryles tube insertion was routinely done prior to radiation to counter the dysphagia during radiotherapy. Patients received radiation to a dose of 66 Gy in 33 fractions over 6 ½ weeks, with cobalt 60 teletherapy machine; along with three courses of chemotherapy with intravenous cisplatin at a dose of 75-100 mg/m^2 in divided doses for two consecutive days on days 1, 22, and 43 of radiotherapy. The primary site and upper cervical nodes were treated using opposing lateral fields to a dose of 66 Gy with a field size reduction after 44 Gy (22 fractions) to reduce toxicity to spinal cord. The lower neck and supraclavicular nodes were included in an anterior field and treated to a dose of 50 Gy which will be matched on the skin at 0.5 to 1 cm below the lateral fields to allow for beam divergence and penumbra, and prevent overdose at the junction. Patients were evaluated eight weeks after completion of therapy. They were followed-up monthly for two months, then once in two months during the study period direct laryngoscopy were done. Local recurrence was defined as those originating in the primary tumour area and regional lymph node. The disease-free survival was calculated in each case. All efforts were made to update the disease status of patients through telephonic contact. Chi-square test was used for statistical analysis and the p-value <0.05 was considered statistically significant.

STATISTICAL ANALYSIS

Descriptive analysis and logical regression was performed by Master 2.0 software. P value was calculated using chi square test and the value < 0.05 was considered significant.

RESULTS

Among 50 patients taken up for study evaluation, 40% of the target population were between 51-60 years of age and 90% of the cases were males. Patients with stage III disease accounted for 30% and 70% of the cases were stage IV. The rate of laryngeal preservation was 88% according to this study.

Patient characteristics: In this study, 6% of the cases belong to the age group up to 40 years, 30% of the cases belonged to the group 41-50 years and 24% of the cases belonged to the group 61-70 years. Among study participants, 18% of the cases have ECOG score 0, 72% of the cases have ECOG score 1 and 10% cases with ECOG score 2 were also noted.

Disease Characteristics: Out of 50 patients, 11 (22%) of the cases were Tumour (T) stage, T2 and 39 (78%) of the cases were T3. In this study, 10% of the cases were N0 and 20% of the cases were N1. The clinical nodal status was N0 in 10%, N1 in 20%, N2 in 42% and N3 in 28% patients.

Rate of laryngeal preservation: The distribution of laryngeal preservation was analysed. Among 50 patients taken for the study, 88% of the cases had laryngeal preservation and laryngeal preservation was not done for the remaining 12% of cases.

Factors affecting laryngeal preservation: The relationship between laryngeal preservation and age is significant. The study reveals that laryngeal preservation is significantly lower (50%) in cases with age 61-70 years compared to age below 40 years (100%), 41-50 years (100%) and 51-60 years (100%). The laryngeal preservation is significantly lower in cases with ECOG performance status 2 (20%) compared to the cases with ECOG performance status 0 (100%) and 1 (94.4%). There is no relationship between laryngeal preservation andT-stage [Table/Fig-1]. The study reveals that laryngeal preservation is almost same in T2 cases (90.9%) and T3 cases (87.2%). Laryngeal preservation is significantly lower in N3 (64.3%) compared to N0 (100%), N1 (100%) and N2 (95.2%). The association between laryngeal preservation and composite stage was not statistically significant (p-value>0.05). Laryngeal preservation is lower in stage IV (82.9%) compared to stage III (100%), which was statistically significant (p-value >0.05) [Table/Fig-1]. The association between laryngeal preservation and number of chemo cycles was significant with p-value <0.0001. Laryngeal preservation is significantly lower in cases with one chemo cycle (16.7%), compared to the cases with three chemo cycles (100%) and two chemo cycles (87.5%) [Table/Fig-1]. The table reveals that laryngeal preservation is more in those patients who received RT dose without treatment breaks (91.3%), compared to cases with treatment breaks (50%) but the association was not significant (p-value >0.05).

Factors affecting laryngeal preservation		Laryngeal preservation Yes n (%)	Laryngeal preservation No n (%)	Total (n)	p-value*
Patient characteristics					
Age group (years)	Up to 40	3 (100%)	0	3	<0.0001
	41-50	15 (100%)	0	15	
	51-60	20 (100%)	0	20	
	61-70	6 (50%)	6 (50%)	12	
ECOG performance status	Zero	9 (100%)	0	9	<0.0001
	One	34 (94.4%)	2 (5.6%)	36	
	Two	1 (20%)	4 (80%)	5	
Disease characteristics					
Tumour stage	T2	10(90.9%)	1(9.1%)	11	0.990
	T3	34 (87.2%)	5(12.8%)	39	
Nodal stage	N0	5 (100%)	0	5	0.026
	N1	10 (100%)	0	10	
	N2	20 (95.2%)	1 (4.8%)	21	
	N3	9 (64.3%)	5 (35.7%)	14	
Composite stage	Stage III	15 (100%)	0	15	0.160
	Stage IV	29 (82.9%)	6 (17.1%)	35	
Treatment characteristics					
Received radiotherapy dose	Without treatment break	42 (91.3%)	4 (8.7%)	46	0.066
	With treatment break	2 (50%)	2 (50%)	4	
Number of chemotherapy cycles	One	1 (16.7%)	5 (83.3%)	6	<0.0001
	Two	7 (87.5%)	1 (12.5%)	8	
	Three	36 (100%)	0	36	

[Table/Fig-1]: Factors affecting laryngeal preservation.
p-value <0.05 was considered statistically significant.

DISCUSSION

Radiotherapy with concurrent chemotherapy is the preferred modality of treatment in advanced laryngeal cancers. CCRT has led to an increase in the use of non operative treatment for organ preservation and a decrease in the use of primary surgery. The primary objectives of this study were to assess the rate of laryngeal preservation in patients undergoing CCRT. The study group included 50 patients with locally advanced laryngeal cancers.

The RTOG 91-11 trial 2013 compared the effects of RT alone, induction chemotherapy followed by RT and radiation therapy with concurrent chemotherapy for Stage III- IV laryngeal cancer patients [10]. The CCRT arms showed an improved 10 year laryngeal preservation rate of 82% over RT alone (64%) and induction chemotherapy followed by RT (68%). In a study by Al-Mamagami A et. al., conducted in Netherlands, 2012 showed a laryngeal preservation of 74% in CCRT arm [14]. Another study by Stenson KM et al., conducted in Chicago in 2011 showed a laryngeal preservation rate of 88% with CCRT [15]. In an indian study conducted by Nair SV et al., in 2018 which compared total laryngectomy with organ preservation protocol (OPP), the CCRT arm showed an improvement in laryngeal preservation rate of 65% [11]. Study conducted by Arain AA et al., in 2020 on organ preservation for advanced laryngeal cancer, experience with concurrent chemoradiation therapy the organ preservation was achieved in 84% of the patients. In the present study the laryngeal preservation rates were found to be 88%. The study proved that laryngeal preservation was significantly lower in cases with age 61-70 years (50%) (p-value <0.0001) and in those with ECOG performance score of 2 (20%) with p-value <0.0001. The N3 (64.3%) lesions tends to have significantly less(p value 0.026) laryngeal preservation rates when compared with N2 and N1 cases. There was no relationship between laryngeal preservation sex, T stage, composite stage. Those patients who could undergo only one cycle of chemo had less laryngeal preservation (16.7%) when compared with the other groups. This study was well comparable with other studies and also had better laryngeal preservation rates [Table/Fig-2] [10,11,14-16].

Study	Laryngeal preservation	Local regional recurrence
Stenson KM et al., [15], 2011	88%	33.3%
Al-Mamgani A et al., [14], 2012	74%	32%
RTOG 91-11 update [10], 2013	82%	35%
Nair SV et. al., [11], 2013	65%	Not applicable
Arain AA et al., [16], 2020	84%	Not applicable
Present study	88%	20%

[Table/Fig-2]: Comparison of laryngeal preservation rates with other studies.

Limitation(s)

The study was a prospective, interventional study among small group of 50 patients and the time period of conduction was less (1.5 years). The follow-up period was also limited hence the data cannot be extrapolated for a long-term result. Since the study group consisted of patients belonging to a small region the data cannot be generalised to a wider population.

CONCLUSION(S)

In advanced laryngeal cancers CCRT helps in laryngeal preservation along with adequate locoregional tumour control. CCRT hence has been practiced widely as an alternative to morbid surgical procedures.

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