



Organ Preservation in Advanced Laryngeal Cancer Using Radical Radiotherapy: A Case Series

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Abstract

Introduction: Advanced laryngeal cancers are conventionally treated by total laryngectomy but surgical intervention has a profound impact on quality of life. Role of radiotherapy in laryngeal cancer with extensive extra laryngeal spread is limited. Therefore, we did a study of the case series to investigate the survival outcomes and laryngeal preservation after radical radiotherapy in advanced laryngeal carcinomas with extensive extra laryngeal spread.

Methodology: 10 patients with biopsy proven carcinoma of larynx associated with extra laryngeal spread were included. Only patients with a KPS score of ≥ 70 points and good voice quality were studied. All patients reported addiction history. All patients underwent radical radiotherapy by IMRT technique to a total dose of 66 Gy in 30 fractions. 7 patients underwent NACT before radiotherapy and 6 patients were administered concurrent chemotherapy. The clinical endpoints examined were LRC, OS and laryngeal preservation.

Results: Median age of presentation was 52 years. The median follow-up time was 26 months. Male to female ratio was 4:1. 70% patients had supraglottic cancers. Median tumor size before radiotherapy was 4.5 cm. Overall survival is 60%. LRC was 70%. Organ preservation was achieved in all patients. 30% patients had hoarseness of voice during RT. Grade 1 dysphagia was seen in 50% of patients. 30% patients had Grade 3 mucosal and skin toxicity.

Conclusion: We conclude that radical radiotherapy has the potential to preserve larynx in advanced laryngeal cancers with extensive extra laryngeal spread and good voice quality. Further prospective clinical trials are needed to solidify role of radiotherapy in high volume advanced laryngeal cancers.

Introduction

Advanced squamous cell carcinoma of larynx was conventionally treated by total laryngectomy or a combination of surgery and postoperative radiotherapy. But loss of larynx has a profound impact on quality of life [1]. And therefore after the landmark trial by Wolf et al [4], an alternative standard of treat-

ment which consisted of induction chemotherapy followed by radiation therapy was introduced. In contrast to this, RTOG 91-11 demonstrated induction chemotherapy followed by RT was not superior than RT alone and reported concurrent chemotherapy was better than induction chemotherapy in T4 laryn-



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geal cancers [5]. But these trials included low volume disease with minimal extra laryngeal extension. Also, studies emphasizing the role of radiotherapy with curative intent in patients with significant extra laryngeal extension is uncommon. Thus, a general reluctance to pursue radiotherapy in high volume advanced laryngeal disease persist in India.

The role of radiotherapy and its optimal timing in the treatment paradigms of laryngeal cancer with extensive extra laryngeal spread remain controversial. Therefore, we studied 10 cases of advanced laryngeal carcinomas with extensive extra laryngeal spread, treated by curative chemoradiation to investigate the effect of radiotherapy on survival, loco regional control and laryngeal preservation in this presentation.

Table 1: Characteristics of patients included in the study.

Age	Karnofsky performance	Diagnosis	stage	NACT (0,1)	RT(0,1)	Concurrent chemotherapy (0,1)	Grade 3/4 mucosal & skin reaction	Dysphagia	death
30	100	CA SUPRAGLOTTIS	CT4aN0	1	1	1	1	1	Alive
63	90	CA GLOTTIS	CT4aN2c	0	1	1	0	0	Alive
75	80	CA GLOTTIS	CT4aN0	0	1	0	0	0	Dead
44	90	CA SUPRAGLOTTIS	CT4aN2c	1	1	1	1	0	Alive
42	90	CA SUPRAGLOTTIS	CT4aN3b	1	1	1	1	1	Alive
55	90	Ca Supraglottis	CT4aN2c	1	1	1	0	1	Alive
48	80	CA SUPRAGLOTTIS	CT4aN2c	1	1	0	0	0	Dead
48	90	Ca AEF--> PFS	CT4aN2b	1	1	0	0	1	Alive
60	80	CA SUPRAGLOTTIS	CT4aN2c	1	1	0	0	0	Dead
57	70	CA AEF	CT4aN2c	0	1	1	0	1	Dead

Staging

Patients were staged according to AJCC 2019 laryngeal carcinoma staging. All patients underwent endoscopic tumor staging and CT PNS+Neck+Thorax to assess initial T and N stage and rule out any metastasis. 70% patient had disease epicentre in the supraglottis and 30% in the glottis. Histopathological examination revealed squamous cell carcinoma with well to moderate differentiation. All patients had T4a disease with median tumor size of 4.5 cm (largest diameter). Nodal status ranged from N0 to N3b with 60% presenting with N2c disease. All were non metastatic at presentation.

Early stage carcinomas, advanced stage carcinomas with fungating lesions, patients who had undergone surgical resection, history of previous irradiation to head and neck and poor voice quality were excluded.

Radiotherapy

All patients received External beam radiotherapy to a total dose of 66 Gy in 30 fractions, 2.2 Gy per fraction, 1 fraction per day, 5 fractions per week, over a period of 6.5 weeks was given by IMRT technique. Six patients received concurrent chemotherapy of cisplatin of dose 50 mg IV or Carboplatin of dose 150 mg IV. There was no treatment delays attributed to skin and mucosal toxicities.

7 out of these 10 patients had initially underwent induction chemotherapy consisting of 2 cycles of paclitaxel (260 mg) and cisplatin (60 mg). Thereafter, these patients were evaluated by DLE & CT imaging to determine disease status. The patients either had a stable disease or a partial response to induction chemotherapy, and subsequently received EBRT.

Methods and Methodology

Patient characteristics

We included 10 patients with biopsy proven carcinoma of larynx associated with extra laryngeal spread. Median follow-up was 26 months. All patients with a performance status of ≥ 70 points on Karnofsky performance scale and had good voice quality. All patients gave addiction history for a median of 23 years. 5 patients had history of addiction to smoking, 5 patients to Pan masala and 3 patients were addicted to alcohol in addition to others. 4 patients had history of comorbidities (**Table 1**).

Target volumes for IMRT planning varied according to the disease extension. GTV Primary and node were contoured according to the disease extension on CT scan. 5 mm volumetric expansion to GTVp & GTVn comprised the High Risk CTV (HR-CTV). Intermediate Risk CTV (IR-CTV) included 10 mm expansion to GTVp & GTVn. Unilateral or bilateral nodal stations were included either in the IR-CTV or low risk CTV (LR-CTV) based on the gross nodal involvement. 66 Gy (2.2 Gy per fraction) was prescribed to HR-CTV, 60 Gy (2 Gy per fraction) to IR-CTV and 54 Gy (1.8 Gy per fraction) to LR-CTV (**Table 2**).

Table 2: Normal tissue dose constraints.

Organ at risk (OAR)	Constraints
Parotid gland	Mean dose <26Gy
Mandible	Maximum dose <70Gy
Larynx	Mean <45Gy
Esophagus	Mean <34Gy
Spinal cord	Maximum point dose <45Gy
Lung	Mean dose <21Gy

All patients were assessed by CT imaging after 3 months of Radiotherapy. If persistent disease was suspected, a DLE with biopsy was performed. Patients were kept on monthly follow up for first 3 months, 3 monthly follow up for next 6 months and 6 monthly thereafter. Loco Regional Failure (LRF) and Distant Metastases (DM) were assessed by either clinical or radiographic progression. The time to LRF and DMs was defined from the start of RT to the date of detection on radiological imaging.

Kaplan-Meier estimates were performed for LRC and Overall Survival (OS) probabilities. The mean, median, and range were used to describe the patient and treatment characteristics.

Results

Median age of presentation was 52 years. 70% of the patients belonged to 40-60 years of age. The median follow-up time was 26 months. Male to female ratio was 4:1. 70% patients had supraglottic cancers. All patients had history of addiction to either tobacco or alcohol or both. Overall treatment was completed within 7 weeks and no break in treatment was recorded. Median tumor size before radiotherapy was 4.5 cm. Among the 7 patients who underwent induction chemotherapy, 5 patients had persistent disease and 2 patients had stable disease after chemotherapy.

The clinical endpoints examined were LRC, OS and laryngeal preservation. 2 year Overall survival is 60%. One patient died due to COVID related health deterioration. Mean survival time is 27.6 months \pm 1.3 (95% CI- 25 to 30 months). Average survival time among patients who underwent RT alone was 25.3 months compared to 26.3 months in the patients who were administered concurrent chemotherapy, but the difference was not significant (p value-0.46). No survival benefit was observed in patients who underwent neoadjuvant chemotherapy (25.6 months vs 26 months, p value- 0.72). Age, histopathological grade of the disease, location of tumor, lymph node involvement did not have any significant correlation with overall survival (**Figure 1**).

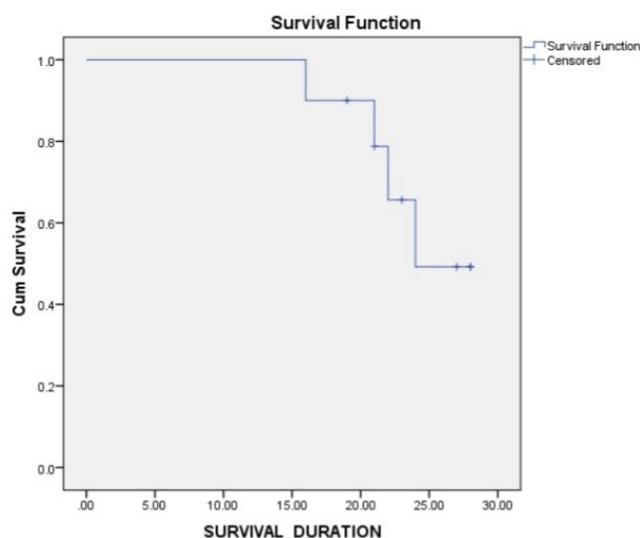


Figure 1: Loco regional control was 70%. Two patients had residual disease 4 months following Radiotherapy. Another patient had persistent disease which responded poorly to chemoradiation and patient eventually succumbed to disease even though patient was started on palliative chemotherapy. Loco regional control did not have significant difference among patients who underwent induction chemotherapy to those who did not (72%vs 66%, p value-1.12). Also, LRC was better in patients who were administered concurrent chemotherapy vs. those who underwent only RT but the difference was not significant (80% vs 50%, p value- 0.53).

None of the patients developed distant metastases during the study period. Organ preservation was achieved in all patients and 5 patients underwent temporary tracheostomy. 30% patients had hoarseness of voice during RT but resolved completely within 2 months of RT. Grade 1 dysphagia was seen in 50% of patients. 30% patients had Grade 3 mucosal and skin toxicity and was seen in patients who underwent concomitant

chemotherapy. Grade 4 toxicity was not reported in the sample population.

Discussion

Total laryngectomy followed by post operative radiotherapy was the norm for advanced laryngeal cancer. While surgery assured a favourable survival especially in T3 & T4 disease [7] the quality of life was severely affected. Radiotherapy, even though was initially considered inferior to surgery in terms of survival, its superiority in providing a better quality of life was apparent. While the answer to whether quantity or quality of life is principal should be best left to patients' purview¹, as a clinician our paramount challenge is to find an optimum modality of treatment which can preserve laryngeal function while simultaneously providing non inferior survival.

Gourin et al. demonstrated a five-year survival rates of 51% for stage III and 35% for stage IV disease. They observed survival for patients with stage I-III disease was similar for patients treated operatively or nonoperatively but stage IV disease had significantly better survival with surgery (49%) than chemoradiation (21%) or radiotherapy alone (14%). Significantly worse survival was seen in nonoperative treatment. For T4 disease, after controlling for nodal status, non operative treatment was the only significant predictor of worse survival [7].

Spector et al. Demonstrated none of the standard treatment modalities namely total laryngectomy, total laryngectomy with neck dissection, radiation therapy alone (median dose, 69.5 Gy), total laryngectomy combined with radiation therapy, and total laryngectomy and neck dissection combined with radiation therapy, has a statistical advantage regarding survival, recurrence, complications, or quality of life. The overall 5-year Observed Survival (OS) rate was 39%, and the 5-year Disease-Specific Survival (DSS) rate was 45%. The overall loco regional control rate was 69% [9]. The advancement of Radiotherapy techniques and development of efficient imaging techniques has helped in achieving better target coverage without geographic miss. Thus it is now possible to achieve comparable survival with radiotherapy, along with added benefit of better quality of life.

In the current study, 70% of the malignancy was localized to supraglottis, but tumor site didn't have any significant effect on survival. This is in accordance to the existing literature which states glottic or subglottic involvement doesn't affect duration of survival [3]. Studies have been conducted over the past three decades to access the benefits of organ preservation in T3, T4 disease and its influence on overall survival of patient. Radical radiotherapy was able to achieve a local control of 56% in T4 disease [2]. And 5-year adjusted actuarial survival of 75% in T4N0 group [3]. Bhalavat et al suggested that radical radiotherapy +/- salvage surgery provided a feasible option in low volume, respectable stage III and IV supraglottic lesions for better quality of life, while achieving similar overall survival as compared to patients who underwent upfront surgery followed by post op radiotherapy [6].

Various studies have insisted on induction chemotherapy followed by radiotherapy as a standard alternative. A 1991 study conducted by department of Veterans Affairs Laryngeal Cancer Study Group emphasised on induction chemotherapy followed by radiation therapy as a treatment strategy for advanced laryngeal cancers. They randomized patients with Stage III or IV laryngeal cancer to induction chemotherapy followed by de-

definitive radiotherapy. Patients who did not respond to 2 cycles of cisplatin and fluorouracil underwent salvage laryngectomy. They reported a 31 percent complete and 54 percent partial response to induction chemotherapy. They concluded that induction chemotherapy followed by radiotherapy was an effective in preserving larynx without compromising overall survival [4]. Contrary to this, in our study, patients had poor response to induction chemotherapy and did not have any significant effect on overall survival, local control or distant metastases.

RTOG 91-11 demonstrated induction chemotherapy followed by RT was not better than treatment with RT alone [5]. Wolf et al have estimated 2-year survival of 68 percent after induction chemotherapy followed by radiotherapy. More local recurrences and fewer distant metastases were seen in patients who underwent induction chemotherapy than in the patients who underwent laryngectomy. The larynx was preserved in 64 percent of the patients [4].

Chemotherapy can decrease frequency of distant metastasis and local therapy will truncate the high rate of local recurrence in advanced laryngeal carcinomas. RTOG 91-11 claimed that concurrent chemotherapy was superior to induction chemotherapy in low volume T4 primaries. They randomized 520 patients with stage III or IV glottic or supraglottic squamous cell cancer to induction cisplatin/fluorouracil followed by RT, concomitant cisplatin/RT, or RT alone. Overall survival did not differ significantly but concomitant chemo radiation improved the larynx preservation rate over induction chemotherapy followed by RT and over RT alone. They observed no difference in late effects, but deaths not attributed to larynx cancer or treatment were higher with concomitant chemotherapy. Loco regional control was achieved better with concurrent chemoradiation than sequential chemotherapy and then radiotherapy or radiotherapy alone [5]. Also, Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) emphasized the benefit of the addition of chemotherapy to loco regional treatment. Concomitant administration of chemotherapy demonstrated 5-year absolute benefit of 5.4% in larynx tumours [8].

In our sample group, chemotherapy was deferred in some patients in view of their age, comorbidities and general condition. It was observed loco regional control and survival was numerically better in the patients who underwent concurrent chemotherapy, albeit not being significant. Laryngeal preservation was achieved in all patients throughout the study period. Acute mucosal and skin toxicity tends to be higher in patients administered concurrent chemo radiation than radiotherapy alone [5]. This affects oral intake of patient which in turn compromise patient's quality of life. In our study group, only 30% of patients developed grade 3 toxicity. But all the patients recovered from mucosal toxicity fully within 1 month post radiotherapy.

Almost all the existing studies have focused on role of radiotherapy in organ preservation in advanced laryngeal carcinomas but with low volume T4 diseases and minimum extra laryngeal extension. In this study series, we have included patients with high volume diseases with extensive extra laryngeal spread and we were able to achieve laryngeal preservation with promising loco regional control (70%) and overall survival (60%). We believe radiotherapy has the potential to be a safe and effective alternative to surgery in T4 laryngeal cancers with extensive extra laryngeal spread.

This study is limited by its low sample size. It is a case series studying the role of radiotherapy in advanced laryngeal cancer with extra laryngeal extension. Due to the short median follow-up of around 2 years, long term toxicities, loco regional and distant failures are not fully assessed. This study should encourage prospective studies focusing on the survival outcomes, organ preservation, quality of life and toxicity profile in patients with extensive extra laryngeal spread in carcinoma of larynx.

Conclusion

The profound effect of loss of larynx on quality of life should encourage oncologists to find a better modality of management in carcinoma of larynx independent of disease stage. Radiotherapy provides a effective alternative to surgical interventions in such advanced cancers while maintaining superior quality of life and it is pertinent to widen the scope of radiotherapy to include the treatment in these patients.

We conclude that Radiotherapy with concomitant chemotherapy offers an alternate standard of management in advanced laryngeal cancer with extensive extra laryngeal spread and good quality. We hope this study will encourage prospective trials to deduce potential role of radiotherapy in laryngeal preservation in advanced laryngeal cancer and achieve better quality of life with non inferior survival in these patients.

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Ethics statement: Informed written consent have been procured from patients to publish their data. Due approval has been obtained from Institute review committee of GCRI Ahmedabad.

Consent to publish: All patients have given written informed consent to publish the study.

Conflicts of interest: The authorship has no Conflicts of Interest to declare.

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