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Randomised controlled trial comparing clinical response between hypo fractionated verses conventional fractionated radiotherapy in early stage Ca Larynx

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Abstract
Aim: *The objective of the study is to compare the locoregional control in patients of early Ca larynx treated with hypofractionated versus conventional fractionated radiotherapy.*
Material and Methods: *Patients with histo-pathologically proven cases of early stage Ca larynx (T1N0M0 and T2N0M0) attending Radiotherapy OPD of our institute between November 2015 and November 2016. Total of 30 patients in each arm were allocated and total of 60 patients were enrolled.*
Result: *In this study, the most common site of primary tumor was supraglottic (53.3%) followed by glottis (46.7%). Complete response (CR) in hypofractionated (Arm A) was (96.7%) with a partial response (PR) of (3.3%) versus Complete response (CR) of (93.3%) in conventional fractionated radiotherapy (Arm B) with a partial response (PR) of (6.7%). Locoregional control at median follow-up of 1yr was (93.3%) in hypofractionated radiotherapy (Arm A) and in conventional radiotherapy (Arm B) was of (96.7%) in patients of Early Ca larynx.*
Conclusion: *Most of our patients were Males with stage II disease. Major subsite was supraglottic followed by glottis. In early treatment response assessment response was comparable to similar studies.*
Keywords: *Conventional radiotherapy, Early Ca larynx, hypofractionated radiotherapy.*

Introduction

Larynx cancer is the most common cancer of head and neck and accounts for 2% of all cancer. The vocal cord glottis represents the most common sub- site and represents 75% of all laryngeal cancers[1]. Glottic cancer represent Glottic carcinoma presents early and unlike many other head and neck cancers subsites paucity of lymphatic drainage in the glottis mucosa conveys a low risk of lymphatic dissemination[2]. The incidence of laryngeal cancer in India is 8.5/ lac in males and constitutes 7.4% of all cancer in males. The Male:Female ratio is 4:1. In the Indian subcontinent, supraglottic cancer is twice more common than compared to glottis cancers. Laryngeal carcinoma is predominatly a male disease. The male:female ratio is 12:1 for glottis cancer and 4:1 for supraglottic cancers[3].[4]. Persistent hoarseness is the most common symptom. The goal of conservative management is the control of disease while maintaining the voice quality. Radiation therapy has comparable

cure rates for selected T1 and T2 early stage glottis cancer with laser excision, cordectomy and hemilaryngectomy[3]. Carcinoma Larynx is strongly related to smoking.[4] Alcohol has synergistic effects if consumed along with smoking. Local control may be inferior after laser excision in cases with anterior commisure involvement[2]. Voice quality after laser resection relates to the extent of resection[2,5]. A wide range of radiotherapy dose- fractionation schedules have been employed for treatment of early glottis carcinoma[6,7,8,9,10,11] Local control rates of 80-95% for T1and 50-80% for T2 early glottis cancer have been ranged. The use of hypofractionation to minimize potential for tumor repopulation during radiotherapy is particularly important for early larynx in view of small field size potentially allowing large dose per fraction without excessive late morbidity.

Materials and Methods

From November 2015 to November 2016 patients with biopsy of histo-pathologically proven cases of early stage carcinoma larynx (T1N0M0 and T2N0M0) attending the radiotherapy OPD of Medical College Kolkata. Total of 74 were included in the study with age from 18-70 yrs of age having ECOG performance status of <1 with no existing comorbidities and having features that were indications of radiotherapy.

Methods

Detailed history and physical examination with proper pre-radiotherapy dental check-up was done for all eligible patients. Proper indirect and direct laryngoscopy was performed to evaluate the disease extent. Metastatic work up was also done to rule out distant mets if any. A total dose of 55Gy in 20 fractions was delivered in the hypofractionated arm (A) where as total dose of 66Gy in 33 fractions was delivered in conventional fractionation arm (B).

Result and Analysis

Population Parameters of Hypofractionated and Conventional Radiotherapy Arms.

Table 1 Population Parameters of the two Arms

n-60

Distribution	Hypofractionated Arm(A)	Conventional Arm(B)	Total (60)
Sex			
Male	25	23	48
Female	5	7	12
Site			
Glottic	14	16	30
Supraglottic	16	14	30
Tumor Size			
T1	8	11	19
T2	22	19	41
ECOG			
1	9	12	21
2	14	13	27
3	7	5	12
Stage			
Stage II	7	11	18
Stage III	23	19	42
Histopathology			
Mod differentiated	20	17	37
Well differentiated	10	13	23

Table 2 Distribution of Response in the two Arms

Respone	Hypofractionated Arm(A)	Conventional Arm(B)	Total
Complete Response(CR)	29	28	57
Partial Response(PR)	1	2	3
Total	30	30	60

Chi-square value:0.3509; p-value: 0.55361

In ARM-A 29(96.7%) patients had CR and 1(3.3%) patient had PR. In ARM-B 28(93.3%) patients had CR and 2(6.7%) patients had PR. There was no significant difference in response in two ARMS. Association between response in two groups was not statistically significant (p=0.55361).

Table 3 Distribution of Mean disease free survival in months in both ARMS

		NUMBER	Mean	SD	Minimum	maximum	median	p-value
DFS	Arm A	30	9.7167	2.6382	0.0000	12.0000	9.5000	
	Arm B	30	9.8617	2.6272	0.0000	12.0000	10.5000	0.8836

Difference of mean disease free survival in two groups was not statistically significant (p-0.8836).

Table 4 Distribution of Locoregional Control in two Arms
n=60

Loco regional control at 1yr	Hypofractionated Arm(A)	Conventional Arm(B)	Total
No	2	1	3
Yes	28	29	57
Total	30	30	60

Chi-square:0.3509; P- value:0.5536

In ARM-A, 28(93.3%) Patients had Loco Regional control at 1 yr and 2(6.7%) patient had no loco-regional control at 1yr. In ARM-B,29 (96.7%) patients had 1yr and 1 patient (3.3%) had loco-regional control at 1yr.There was no difference in loco-regional control at 1yr in two ARMS.

Toxicity outcomes

Documented RTOG grade 3 skin toxicity occurred in 12 (4 %) of patients. RTOG grade 3 mucositis requiring enteral nutrition (via nasogastric tube feeding in all cases) occurred in 13 (9.8 %) patients. No deaths occurred within 90 days of completion of radiotherapy. Documented late toxicity in included post-cricoid stenosis in one patient managed with repeated dilatations, anterior glottic webbing in two patients, and one patient requiring a emergency tracheostomy 3 years post radiotherapy with progressive laryngeal symptoms and there was no evidence of disease recurrence. No patients required long term enteral feeding.

Discussion

Glottis the hub of voice population accounts for 60-65% of all laryngeal carcinoma. Squamous cell carcinoma is the predominant histology and nearly 40% of the patients are often stage III and stage IV at initial evaluation. Patients with early glottis squamous cell carcinoma of the larynx are generally considered to have good prognosis. The aim of the early glottis carcinoma are cure, voice preservation, optimal voice quality with minimal morbidity, expense and inconvenience. Given the fundamental role of larynx in human speech and communication the optimal treatment has to be considered. The potential morbidity of curative treatment is a special consideration when total laryngectomy for primary therapy or as a salvage therapy is recommended. Total laryngectomy is widely recognized as one of the procedure mostly feared by the patients. Accordingly there has been keen interest in the development of and refinement of organ preservation therapies, such as radiation therapy alone. With all these

approaches, total laryngectomy is usually preserved for primary site tumor recurrence. With this treatment approach, organ preservation is possible without compromising locoregional control and survival rates. Our study was designed to asses response, organ preservation and locoregional control with radiotherapy in patients with early stage carcinoma of the larynx.

We evaluated 30 patients in each Arm of early glottis cancer presenting to our OPD. Most of the patients presented with hoarseness of voice (52.2%) followed by dysphagia (19%) and respiratory distress.In our study most common site of primary tumor was supraglottic (53.3%) followed by glottis (46.7%). Similar results were also seen by Guadagnolo BA et al and Forastiere AA et al reported majority of supraglottic with supraglottic being majority with 60% and 66% respectively.But this was contradiction to the study by Jamshed A et al which reported majority of glottis carcinoma (78.2%).

In our study as per TNM staging (AJCC 2010) Arm A Stage I (38.9%), Stage II(54.8%) that is the hypofarctionated Arm and Arm B stage I(61.1%) and stage II (45.2%).

Early treatment response – In our study complete response (CR) in Arm A (96.7%) with partial response of (3.3%) that was the hypofractionated radiotherapy. In Arm B complete response was seen in (93.3%) and partial response was seen in Arm B was of (6.7%).

Late treatment response- In our study, Locoregional control at median follow up of 1year in Arm A was (93.3%) and Arm B was (96.7%). Di Nicola et al analysed the voice quality and local control in patient with cT1a squamous cell carcinoma of true vocal cords treated with conventional radiotherapy or hypofractionated radiotherapy, and showed that overall voice quality returned to normal levels in 75% of patients 12 months after radiotherapy while modest modification was observed were observed in 25% of the patients. After 3 years of follow-up, the LRC was 100% for the patients treated with >2Gy/fraction and 96% for the patients treated with 2Gy/fraction. In addition, a randomised controlled trial from South Korea[12] compared a conventional 2Gy per fraction arm (66Gy in 33 fractions for T1 and 70Gy in 35 fractions for T2) with a hypofractionated 2.25Gy per fraction arm (63Gy in 28 fractions for T1 and 67.5Gy in 30 fractions for T2); the study closed prematurely due to poor accrual with 156 of a planned 282 patients; 5-year local progression free survival was 77.8 % versus 88.5 % (non-significant) the regimes achieved similar results in terms of local control and complication. Arif jamshed et al found LRC after primary radiotherapy was 91%. Patients with T1a and T1b disease had LRC rates of 95% and 88%. They concluded that hypofractionated radiotherapy of 55Gy in 22# is comparable to conventional in terms of locoregional control and survival while offering potential for optimizing resources usage. Fraction size of ≥2.25Gy was a significant factor in local control for T2 tumors[8]. Increased fraction size appeared beneficial independent of total dose and treatment time[8,13]. Kim et al.[14] reported a retrospective analysis outcomes of a series of 157 patients with T1/2 glottic carcinomas treated with either 70Gy in 35 fractions or 67.5Gy in 30 fractions; disease free survival was significantly superior in the 2.25Gy/fraction arm. Overall this increasing body of evidence have established hypofractionation as the standard of care for definitive radiotherapy treatment of T1/2 glottic carcinomas, providing increased local control with acceptable toxicity.

Conclusion

The optimum fraction size/dose and treatment time for early glottic cancer has yet to be established, although in the published literature hypofractionated accelerated radiotherapy schedules appear to be highly effective. This series demonstrates that a schedule of 55Gy in 20 fractions over 4 weeks offers high rates of local control with acceptable long term toxicity for both T1 and T2 disease. Recent national guidelines acknowledge that for early glottis cancers, hypofractionated radiotherapy schedules have

equivalent outcomes to conventional fractionation. Without any increase in toxicity and therefore suggests using regimens with fraction regimes with fraction sizes between 2.65and 3.25Gy[15].

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