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Comparison Of External Beam Radiotherapy Followed By Intra-Luminal Brachytherapy With External Beam Radiotherapy Alone In Locally Advanced Carcinoma Of Esophagus.

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Abstract

Aim: The aim was to compare the outcome of intraluminal boost brachytherapy following external beam radiotherapy with external beam radiotherapy alone in locally advanced carcinoma esophagus in terms of toxicity, response, andsurvival.

Material and Methods: A total of 80 patients with squamous cell carcinoma of esophagus were enrolled in the study between June 2014 to June 2016.Patients were treated with external beam radiotherapy (EBRT) of 40 Gy by AP/PA portals with concurrent chemotherapy. After completion of first phase of EBRT patients were divided into two groups. In Group A, boost was given by intraluminal brachytherapy (ILBT) and in Group B, boost was given by 3 field technique of EBRT.

Results: Out of 80 patients, 42 were males and 38 females in the age group of 51 – 70 years. After completion of treatment, residual disease was present in 60 % and 77.5 % in Group A and B respectively. Complete response was seen in 22.5 % and 15 % in Group A and B respectively. Dysphagia improvement was seen in 86.5% and 59.9 % in Group A and B respectively (P= 0.45). Median survival was 57% and 43% in Group A and B respectively.

Conclusions: Dysphagia improvement, local response and median survival was better and toxicities less in Group A, as compared to Group B,

Key words: Brachytherapy, intraluminal boost, External beam Radiotherapy. Carcinoma esophagus

Introduction

Esophageal cancer continues to be the least treatment responsive malignancies even in developed countries more than 85 % of patients die within two years of diagnosis, making it the sixth most common causes of cancer related deaths in the world.[1,2] Squamous cell carcinoma is the most prevalent histological form accounting over 90 % of cases in the endemic regions of the world.[3,4] The conventional treatment with surgery and radiation is limited with a five year survival of 10-25 % worldwide.[5,6] The prognosis continues to be poor because of high loco regional failure rates.[7,8] Good local control, can be achieved by external beam radiotherapy followed by intraluminal brachytherapy, which has an advantage of sparing surrounding normal tissues and potentially improving the therapeutic ratio.[9,10,11] We conducted this study to assess the clinical outcome of external beam radiation therapy alone and in combination with intraluminal brachytherapy in locally advanced carcinoma esophagus.

Material and Methods

A total of 80 patients with histologically proved squamous cell carcinoma of esophagus were enrolled in this study prospectively between June 2014 – June 2016. Pre-treatment evaluation included history, physical examination, CBC, KFT, LFT, Chest X-RAY, CECT Chest and Abdomen, Bone Scan (where-ever indicated), Barium swallow esophagus and upper GI Endoscopy. Patient's eligibility included; 1: locally advanced disease, Stage II- III, 2: ECOG performance status of 3 or less. Exclusion criteria included; 1: Double or multi-centre cancer (Skip lesion) in esophagus, 2: Lesions in the cervical esophagus and gastro-esophageal junction, 3: Histology of adenocarcinoma. All patients were treated with external beam radiotherapy of 40 Gy by an Anterior/posterior portals at the rate of 2 Gy/fraction, 5 fractions/week in 4 weeks concurrent with chemotherapy. The chemotherapy drugs given were Inj. paclitaxel 50 mg/m^2 i/v in 500 ml of normal saline over one hour and Inj. carboplatin (AUC 2) 225mg i/v in 200ml of 5% dextrose over 30 minutes. Both the drugs were given on Ist day of the week, after proper premedication. After completion of EBRT of 40 Gy patients were divided in two groups by simple randomization for receiving boost. Group A (40 patients) were treated by intraluminal brachytherapy (ILBT) of 10 Gy in two sessions of 5 Gy per week. Group B (40 Patients) were supplemented by external beam radiotherapy (EBRT) of 10 Gy in one week by one anterior and two posterior oblique portals on Co-60 unit. One to two week gap was kept between EBRT and ILBT. For ILBT, tumor localization was done with the help of endoscopy findings, barium swallow esophagus and CT scan findings. An after loading applicator along with a fiducial marker was introduced in to the Ryle's tube, small amount of xylocain jelly was put into one of the nostrils and on the tip of Ryle's tube. The Ryle's tube was then inserted through the nose into the esophagus up to GE junction. This procedure was performed with the patient on the CT simulation table. As per the endoscopic level of the lesion, external lead marker was placed on the body surface of the patient. The scan of entire area of interest with margins was obtained and images of 3 to 5 mm slices were taken thereby allowing accurate tumor characterization. CT images were transferred to the treatment planning system for dose calculation and delivery of treatment. After completion of treatment, patients were followed up to a period of six months, with respect to assess toxicities and response. After 4 – 6 weeks of completion of treatment, patients were subjected to endoscopy and CECT chest for assessing response to treatment.

Statistical analysis

Data were analyzed using SPSS Software package version 18.0.Quantitative data was expressed using MEAN & SD while qualitative data were expressed in frequency and percentage. Qualitative data was analyzed using chi-square test; also Fishers test was applied to compare the two groups. Survival analysis was done with the help of Kaplan Meier Method. The survival between two groups was analyzed with the Log Rank Test. P-value of less than 0.05 was considered statistically significant.

The study was approved by the Institute Ethical Committee (IEC).

Results

Among the 80 patients enrolled in the study comprised of 42 males (52.5%) and 38 females (47.5%) in the age range of 51 -70 years. Most common clinical presentation was dysphagia in all patients. 73.5% of patients had grade 1 dysphagia. Majority of the patients had lesion in the esophagus at the level of 25-30cm from incisor teeth as per endoscopy. The size of the lesion was between 2 to 5cm in 81% of cases. Stage III and II disease was seen in 76.2% and 23.8% of cases respectively. 80% of patients had ECOG performance status of 1. Patient characteristics are shown in Table 1. All (80) patients received initial phase of EBRT, 40 Gy in 20 fractions, 5 days a week, by AP/PA portals without any interruption. Out of these 64 (75%) received concurrent chemotherapy of Inj. Paclitaxel and carboplatin on Mondays of every week. However 16 (25%) did not receive concurrent chemotherapy either they had co- morbid medical conditions or did not give consent for chemotherapy. All Patients were assessed for various treatment related toxicities on weekly

basis and are shown in table 2. Toxicities were evaluated by using radiation injury evaluation criteria of radiotherapy oncology group (RTOG). Oral mucosites of Grade 2 was seen in 5% and 15% of cases in Group A and B respectively. Mucosites was mostly seen in those cases, which received concurrent chemotherapy over a period of five weeks (Group B). Grade 2 skin reactions in the irradiated field was observed in 15% of cases in Group B only. The other toxicities, gastrointestinal, hematological and non-hematological were managed conservatively [Table 2]. All patients successfully completed the prescribed treatment schedule in time. The follow-up was carried out at intervals of 1, 3 and 6 months after treatment. All patients had undergone clinical examination, endoscopy and CECT chest for assessing the response to treatment at 6 weeks of follow-up after receiving boost treatment [Table 3]. 22.5% and 15% of patients in Group A and B respectively had complete response, clinically and on imaging. The biopsy taken during endoscopy from the scarring area in these cases was negative for malignancy. Residual disease was seen in 60% and 77.5% of patients in Group A and B respectively. 6 patients in Group A and 3 patients in Group B did not give consent for undergoing endoscopy, hence disease assessment by endoscopy could not be ascertained in these cases. However CECT chest was done in all cases [Table 3]. Partial response was seen in 47.5% and 35% of cases in Group A and Group B respectively. Stable disease in 22.5% and 37.5% and progression of disease in 7.5% and 12.5% of cases was observed in Group A and Group B respectively. Progression of disease was seen in the form of appearing of regional/mediastinal nodes which were not present prior to treatment. At 6 months of follow-up, 38 patients (95%) and 35 patients (87.5%) were available for dysphagia assessment in Group A and Group B respectively. Two patients (5%) in Group A and five (12.5%) in Group B had died, which reveals a survival advantage favouring Group A (p=0.42). 34.2% and 25.7% of patients had no dysphagia (Grade 0) and 52.63% and 34.28% had Grade 1 dysphagia (p=0.04) in Group A and B respectively [Table 4]. No distant metastases was observed in any patient during follow-up. Median survival was in 57% and 43% in Group A and B respectively as per Kaplan Meir Method [Fig.1].

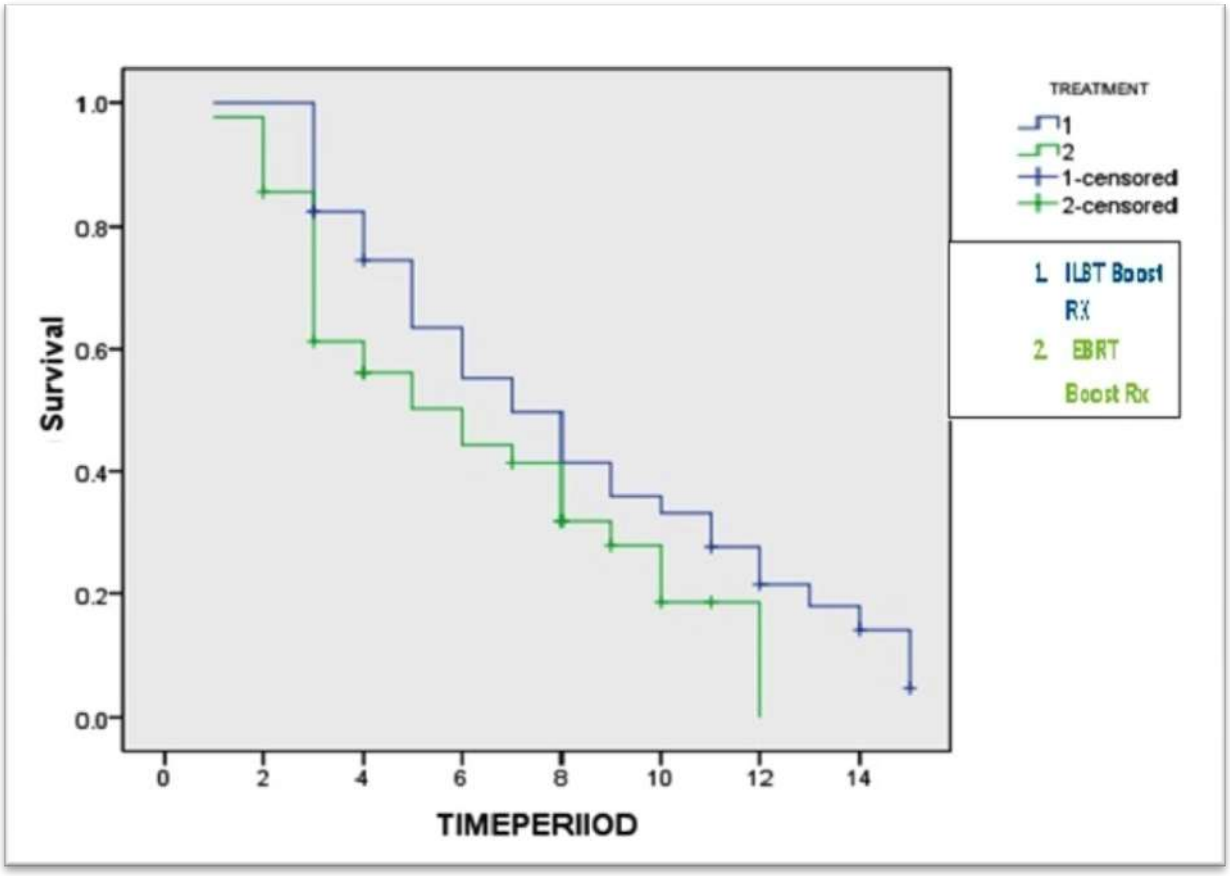

Figure 1; **Kaplan Meier curves of ILBT and EBRT Boost**

Discussion

The meaningful improvement in the treatment of carcinoma esophagus continues to be an elusive and a challenging target, the prognosis of esophageal cancer is poor, because the locally advanced disease at presentation is seen in around 70% of cases, when the curative options are limited. [12,13] More frequently intraluminal brachytherapy(ILBT) has been utilized as a boost after external beam radiotherapy (EBRT). Several studies comparing EBRT with or without brachytherapy claim improved survival, local control and swallowing ability for patients treated with brachytherapy.[12,14,15,16,17] We also observed an improvement in survival in Group A as compared to Group B. While analyzing the patients after completion of 6 months of follow up, 95% were alive in Group A and 87.5% in group B (p=0.42) [Table 4] Median survival was 57% and 43% in Group A and B as per Kaplan Meir survival method [Fig-1]. The current study also revealed statistically significant improvement in dysphagia (p=0.04) [Table 4]. Residual/ recurrence disease was seen in Group B (77.5%) verses (60%) in Group A thus justifying the benefit of ILBT boost [Table 3]. Our results are compatible with other studies who reported better local control when HDR brachytherapy was used.[18,19,20] Regarding toxicities, oral mucosites of Grade 2 was observed more 15% in Group B versus 5% in Group A. Most of the toxicities were related to concurrent chemotherapy, which were managed conservatively without any treatment interruption [Table 2]. We did not observe post treatment bleeding or fistula formation in any of the patients treated with intraluminal brachytherapy which is compatible with other studies, who did not report bleeding or fistula formation with concurrent chemotherapy followed by 10Gy in two fractions via brachytherapy. [21,22,23] Also the benefit with Brachytherapy boost was that patient had to come just two times to hospital while for EBRT patient had to visit five times.

Conclusions

Intraluminal Brachytherapy in the form of boost of 10Gy after EBRT is safe and well tolerated, besides showing an improvement in dysphagia status, local control and overall survival. However further studies with larger sample size, need to be conducted with longer follow-up for justifying the benefit of ILBT in locally advanced carcinoma of esophagus.

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Table 1: Patient Characteristics

Variable	Characteristic	Group A (n=40) % age		Group B (n=40) % age		P value
Gender	Male	19	47.5	23	57.5	0.50
	Female	21	52.5	17	40.5	
Performance status	P1	30	75	32	80	0.78
	P2	10	25	8	20	
Dysphagia	Grade 1	28	70	31	77.5	0.448
	Grade 2	9	22.5	7	17.5	
	Grade 3	3	7.5	2	5.0	
Size of Lesion	1-2cm	1	2.5	2	5.0	0.321
	2-5cm	34	85.0	31	77.5	
	5-7cm	5	12.5	7	17.5	
Stage	II.	09	22.5	10	25	0.794
	III	31	77.5	30	75	
Treatment	EBRT alone	9	22.5	7	17.5	0.77
	Concurrent (R+C)	31	77.5	33	82.5	

Group A (received boost by ILBT), Group B (received by 3 field technique EBRT)

Table 2: Acute Toxicities during treatment

Toxicity	Group A (n=40)	% age	Group B (n=40)	%age	p-value
Gastrointestinal					
Oral Mucosities	2	5	6	15	
Vomiting Nausea	23	57.5	25	62.5	
Epigastric Pain	8	20	7	17.5	<0.05
Loose Motion	7	17.5	2	5	
Hematological					
Anemia					
Grade 1	8	20	8	20	

Grade 2	6	15	4	10	<0.05
Grade 3	1	2.5	5	12.5	
Neutropenia					
Grade 1	10	25	16	40	
Grade 2	0		6	15	
Grade 3	0		2	5	0.007
Grade 4	1	2.5	4	10	
Thrombocytopenia					
Grade 1	15	37.5	9	22.5	
Grade 2	4	10	3	7.5	
Grade 3	0		2	5	0.09
Grade 4	1	2.5	4	10	

Table 3: Response assessment at 6 weeks

Variable	**Group A**		**Group B**		
	(n=40)	**% age**	**(n=40)**	**%age**	
P-value					
Endoscopic assessment					
Normal	9	22.5	6	15	
Residual lesion	24	60	31	77.5	<0.05
Structure	1	2.5	-	-	
Not done	6	15	3	7.5	
CECT- Chest					
Complete response	9	22.5	6	15	
Partial response	19	47.5	14	35	
<0.05					
Stable response	9	22.5	15	37.5	
Progression of disease	3	7.5	5	12.5	

Table 4: Assessment of dysphagia status at 6th month of follow-up

Variable	**Group A (n=40) % age**	**Group B (n=40) %age**	**p-value**
Alive	38 95	35 87.5	0.42
Expired	2 5	5 12.5	
Dysphagia status	(n=38) % age	(n=35) % age	
Grade 0	13 34.21	9 25.71	
Grade 1	20 52.63	12 34.28	
Grade 2	3 7.89	12 34.28	0.04
Grade 3	2 5.26	2 5.71	
Mean	2.06	2.64	
SD	1.11	1.29	