

A PROSPECTIVE STUDY TO COMPARE LOCAL CONTROL OF DISEASE BY DEFINITIVE CHEMORADIO THERAPY ALONE AND WITH INTRALUMINAL BOOST IN PATIENTS OF CARCINOMA ESOPHAGUS

Oncology/Radiotherapy

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KEYWORDS

INTRODUCTION

As per Globocan 2020, estimated no. of cases of carcinoma esophagus among men worldwide are 4,18,350 accounting 4.2 % of total cancer cases and in India, it ranks 5th with an incidence of 63,180 cases.^[1] Because esophagus has no serosal covering with extensive, longitudinal connecting system of lymphatic plexus, direct invasion to contiguous structures and lymph node metastasis occurs early.^[2] That is why, unresectable or metastatic disease at the time of diagnosis is seen in approximately 80% of patients, with cure rate <15% and thus making esophageal cancer one of the most dreaded malignancies with a death rate of 5.5% worldwide.^[1,3]

Squamous cell carcinoma is the most prevalent histological form accounting over 90 % of cases in the endemic regions of the world.^[4] The incidence of esophageal adenocarcinoma has increased sharply over the past few decades, both by period and birth cohort.^[5]

Primary treatment for localized esophageal cancer is radical excision but in majority of cases the tumor is in advanced stage and has already invaded through the esophageal wall. The current standard of care for inoperable esophageal cancer is concurrent chemoradiation with 50.4 Gy radiotherapy and paclitaxel and carboplatin-based chemotherapy. Further dose escalation to improve the outcome is limited due to critical surrounding structures. High Dose Rate Intraluminal Brachytherapy offers a simple, inexpensive method of conformal radiation therapy in this context of dose escalation with minimum morbidity.^[6-8]

HDRILBT allows the escalation of dose to the esophagus while protecting dose-limiting structure which is not possible even with the most conformal method of EBRT. In the definitive chemoradiation treatment of carcinoma esophagus, role of brachytherapy remains unclear and investigational.

MATERIAL AND METHODS

Objective:

- To assess the quality of life in both arms
- To compare local tumor control in both arms
- To compare toxicities in both arms

METHODS

Study population

This is a prospective randomized study in which 90 newly diagnosed cases of carcinoma esophagus were given curative chemoradiotherapy alone or along with Intraluminal brachytherapy boost.

Patients who were included in the study were histopathological proven patients of carcinoma esophagus stage II and III who had declined surgery. The age of patients were between 30 to 60 years having ECOG performance status of 0 to 3. They were physically fit to receive concurrent chemoradiotherapy with normal metabolic and haematological profile and were willing to give informed written consent.

The patients having multicentric cancer (skip lesions) in esophagus, lesion in the cervical esophagus, Any uncontrolled intercurrent

disease /pregnant woman/lactating woman/ immunocompromised state, double malignancy or any history of previous treatment with any of the following modalities surgery, radiotherapy, chemotherapy for esophageal cancer were excluded from the study.

Radiotherapy

All patients of locally advanced carcinoma esophagus were treated by external beam radiotherapy on Telecobalt-60 machine.

All patients received a total radiation dose of 50 Gy/ 25 fractions (2Gy/fraction, 5 days/week) on Telecobalt machine with concurrent chemotherapy (weekly Paclitaxel 50mg/m² and Carboplatin AUC 2).

In first phase, the patients were treated by 2 anterior-posterior field up to the dose of 40Gy. After that, in second phase, patients were treated by reduced posterior oblique fields so as to spare the spinal cord to the total dose of 50Gy. In the study arm, after a gap of 2-3 weeks of completion of CT-RT, HDR intraluminal brachytherapy was given of 5Gy in single fraction.

Concurrent chemotherapy

The patients received five weekly concurrent chemotherapy courses using Paclitaxel 50mg/m² and Carboplatin AUC 2. This was usually started after initiation of radiation treatment. The chemotherapy drugs given were Inj. paclitaxel 50 mg/m² 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 first day of the week, after proper premedication.

Evaluation after completion of treatment and follow up

Patient were evaluated for dysphagia at 1, 3 and 6 months. UGIE was done at 3 month for disease assessment and biopsy was done when indicated. CECT of chest and abdomen were obtained if any clinical suspicion of either local recurrence or metastasis. Toxicity was graded as per RTOG/EORTC criteria.

RESULT

90 patients were enrolled in the study which comprised of 23 (51.1%) male and 22(48.9%) female in the study arm, whereas 25(55%) male and 20(44%) female in the control arm. The age ranged between 30-60 years. Most common clinical presentation was dysphagia in all patients. Second most common symptom was pain in 30(66.7%) cases of study arm and in 27(60%) cases of control arm (Figure 1). 50% of patients in both study and control arm had ECOG performance status of 1. Patients characteristics have been shown in Table 1. 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 <5cm in more than half of the cases (57.8%) in study arm. In control arm number of cases who had ≤5 cm long tumor was almost equal to number of cases who had 6-10cm long tumor (Table 2). All patients received initial phase of EBRT, 50 Gy in 25 fractions, 5 days a week, by AP/PA portals without any interruption along with concurrent chemotherapy of Inj. Paclitaxel and carboplatin on Mondays of every week. All Patients were assessed for various treatment related toxicities on weekly basis.

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. Proportion of cases who had successful local control after 6 months in study arm was 83.72% (36/43) which was significantly higher than in cases of control arm 59.46%. ($X^2=4.718$, $Df=1$, P value=0.030). (Figure 2) All patients had a partial response locally after external radiation. The complete response rate was 32% in study arm and 40% in control arm (P value=0.64, not significant) on completion of treatment. The biopsy taken during endoscopy from the scarring area in these cases was negative for malignancy. Partial response was seen in 63% and 58% of cases in Group A and Group B respectively. Stable disease in 4% and 9% respectively and progression of disease was observed in 9% of cases in Group B. 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, 18 patients (40%) and 28 patients (62.2%) had dysphagia in Group A and Group B respectively. Two patients (4%) in Group A and eight (18%) in Group B had died, which reveals a survival advantage favouring Group A ($p=0.0441$). No distant metastases was observed in any patient during follow-up.

In Kaplan-Meier analysis, cumulative survival at the end of 6 months in study arm was 95.6% and in control arm it was 82.2%. Mean survival period in cases of study arm was 25.689 weeks (25.229-26.149) and in cases of control arm was 24.600 weeks (23.641-25.559). And, the difference in cumulative survival of both arms was found to be statistically significant (log rank Mantel cox- $X^2=4.017$, $Df=1$, p value=0.045)(Figure 3)

Table 1: Patient's characteristics of Ca esophagus patients

Variable	Study Arm	Control Arm
Sex		
Male	23(51.1)	25(55.6)
Female	22(48.9)	20(44.4)
Age group (Years)		
30-50	15(33.3)	18(40)
51-80	30(66.7)	27(60)
Socioeconomic status		
Low	22(48.9)	20(44.4)
High	23(51.1)	25(55.6)
Residential status		
Rural	28(62.2)	26(57.8)
Urban	17(37.8)	19(42.2)
ECOG score		
1	23(51.1)	24(53.3)
2	22(48.9)	21(46.7)
Hemoglobin		
Hb $\leq$ 10gm%	27(60)	29(64.4)
Hb $>$ 10gm%	18(40)	16(35.6)

Table 2: Variation of location and histopathology in both arms

		Study Arm	Control Arm
Type	SCC	41(91.1)	40(88.9)
	Adeno Ca	4(8.9)	5(11.1)
Location	Middle Thoracic	33(73.3)	35(77.8)
	Lower Thoracic	12(26.7)	10(22.2)
Length of tumour	$\leq$ 5 cm	26(57.8)	23(51.1)
	6-10 cm	19(42.2)	22(48.9)

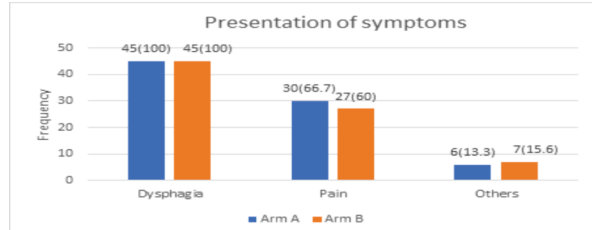


Figure 1 : Frequency of various presenting symptoms in both arms

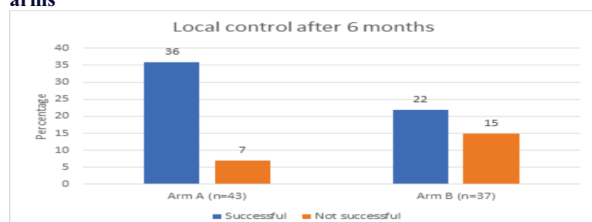


Figure 2 : Local control after 6 months in both arms

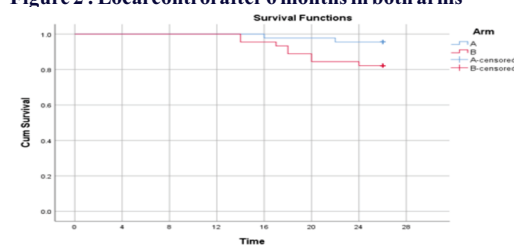


Figure 3 : Kaplan Meier Curves of ILBT and EBRT Boost

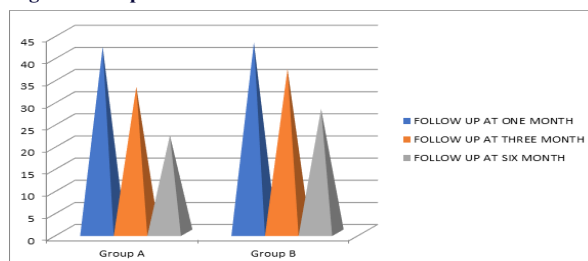


Figure 4: Prevalence of dysphagia in both arms

DISCUSSION

The curative treatment of carcinoma esophagus continues to be an elusive and a challenging target. As the patient presents with locally advanced case in around 70% of cases, the curative options are limited which in turn affects the prognosis^[9,10]

Intraluminal brachytherapy(ILBT) more frequently has been used as a boost after EBRT. There are various studies which claimed that use of ILBT has improved survival, local control and swallowing ability for patients. In study by Kapoor et al^[11] treated 86 patients with 35 Gray (Gy) EBRT followed by 6Gy/# (2#) and 4.67 Gy (3#) in two different arms. They experienced Local control 67.6% in 6 Gy/# arm and 89% in 4.67 Gy/# arm. Murakami et al^[12] treated 62 patients with 60 Gray (Gy) EBRT followed by 12Gy/# (2#). They experienced Local control 45% after 3 years. Tamaki et al^[13] in their study found that after EBRT and Brachytherapy with 10 Gy, local control was 49% after 5 year and overall survival was 31-84%. Gaspar et al^[14] presents sufficient clinical data to guide safe practice. Based on the clinical data available, the ABS has drawn up a set of guidelines to help in the selection of patients who are likely to benefit from intraluminal brachytherapy boost. They found 49% overall survival at one year. We also observed an improvement in local control in study arm as compared to control arm (86.66% vs 75%). There was also an improvement in OS at 6 months in study arm. 43 (96%) patients in study arm were alive as compared to 37 (82%) in control arm. Median survival was 95.6% and 82.2% in Group A and B as per Kaplan Meir survival method [Fig-3]. The current study also revealed statistically significant improvement in dysphagia ($p=0.03$) (Fig:4). Our results are compatible with other studies who reported better local control when HDR brachytherapy was used^[14-16].

Most of the toxicities were related to concurrent chemotherapy, which were managed conservatively without any treatment interruption. 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.^[17-18]

CONCLUSION

Intraluminal brachytherapy boost of 5Gy in single fraction has shown an improvement in local control, overall survival at 6 months and dysphagia status. The toxicity profile was mainly contributed to concurrent chemotherapy. No case of Post RT bleeding or fistula formation was observed. However further studies with a larger sample size and longer follow up is required to advocate the benefit of intraluminal brachytherapy boost.

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