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Prospective randomized comparative study between EBRT alone and EBRT with ILRT boost in locally advanced unresectable esophageal cancer - Tertiary rural Indian cancer center experience

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ABSTRACT

Background: Local recurrence within the gross tumor volume following a conventional radiation dose of 50 Gy is a major hurdle in achieving a better prognosis for esophageal carcinoma. Consequently, there remains a lack of consensus globally regarding the optimal dose for definitive concurrent chemoradiotherapy. Certain studies propose that radiation dose escalation could enhance clinical outcomes. **Aims and Objectives:** The current study aimed to compare the safety and effectiveness of external beam radiotherapy (EBRT) alone versus EBRT with intraluminal radiotherapy (ILRT) boost. **Materials and Methods:** A total of 60 patients with locally advanced unresectable squamous cell carcinoma of the esophagus were prospectively enrolled in this study. A comparison was conducted between 50 Gy EBRT alone and 50 Gy EBRT with 8 Gy ILRT boost, alongside weekly concurrent chemotherapy, to assess the response and toxicities. **Results:** On initial assessment, a complete response (CR) was achieved in 76.66% of patients in the ILRT boost arm and 70% in the EBRT alone arm (P = 0.559). At the 6th-month follow-up, 60% of patients in the ILRT boost arm and 50% in the EBRT alone arm still had a CR. No statistically significant differences were observed between the two arms in terms of leukopenia (P = 0.576), nephrotoxicity (P = 1.0), radiation dermatitis (P = 0.615), vomiting (P = 0.921), and diarrhea (P = 1.0). Five patients in the ILRT boost arm and three in the EBRT alone arm experienced stricture, while no cases of fistula formation were reported. **Conclusion:** Dose escalation with ILRT can result in an enhanced CR accompanied by manageable toxicity, ultimately leading to improved locoregional control.

Key words: Esophageal cancer; Concurrent chemoradiotherapy; Radiotherapy dose; Standard dose; High dose

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INTRODUCTION

Esophageal carcinoma is a deadly cancer with increasing incidence worldwide, causing over half a million deaths each year.[1] In India, it is the fifth-most common cause of cancer-related deaths.[2]

For locally advanced resectable esophageal carcinoma, neoadjuvant chemoradiotherapy followed by surgery is the preferred treatment option (The Chemoradiotherapy for Oesophageal Cancer followed by Surgery Study, CROSS Trial).[3] However, due to early invasion of adjacent structures and lymph node metastasis,[4] approximately

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80% of patients present with unresectable or metastatic disease.[5] Comorbidity, a low-performance status, or even a patient's unwillingness to undergo surgery are other factors that render a patient unresectable. Definitive concurrent chemoradiotherapy (CCRT) is considered a standard treatment modality for such locally advanced unresectable cases (The Radiation Therapy Oncology Group, RTOG 85-01 trial)[6] which showed improved local control and overall survival (OS) compared to radiotherapy alone. The RTOG 94-05 trial explored the optimal radiation dose for CCRT and found that there was no increase in OS or local regional control with dose escalation from 50.4 to 64.8 Gy.[7] After this trial, 50.4 Gy has been accepted as a standard dose for CCRT in the European and American guidelines but it is frequently observed that conventional radiation doses of 50.4 Gy for esophageal carcinoma result in a significant occurrence of locoregional failure (LRF) (ranging from 41% to 50%), with the primary tumor being the main site of failure in the majority of cases (ranging from 86% to 90%).[8] Other studies have also indicated that local recurrence within the gross tumor volume after CCRT is a major hurdle in achieving a better prognosis for esophageal carcinoma.[9-11] Hence, there is still a lack of consensus globally on the optimal dose for definitive CCRT for esophageal carcinoma.

Some theories suggest that to control microscopic tumous of squamous cell carcinoma (SCC) or adenocarcinoma, 45–50 Gy radiation dose can be used, but to control the gross tumor, at least a radiation dose of 60 Gy is required.[12,13] Many studies have shown improved outcomes with a radiation dose of 60 Gy or higher.[8,14-16] Zhang et al., conducted a study that revealed that patients in the higher radiation dose group (>51 Gy) exhibited a better 3-year local control rate (36% vs. 19%) and disease-free survival rate (25% vs. 10%) compared to those in the low-dose group (≤51 Gy).[17] Chen et al.,[14] conducted a study that demonstrated a higher radiation dose than the standard dose may lead to improved survival for non-operated, localized esophageal SCC undergoing CCRT. The study revealed that the optimal definitive radiation dose should be determined on an individual basis.

When it comes to increasing the radiotherapy dose for esophageal cancer patients, two approaches can be used: External beam radiotherapy (EBRT) and intraluminal radiotherapy (ILRT). Of the two, ILRT boasts a unique advantage – it allows for higher doses to be delivered directly to the tumor while minimizing exposure to healthy tissues. Consequently, numerous researchers from globally have investigated the combination of ILRT and EBRT for treating esophageal cancer with higher radiation dose.

With this background, our study aimed to evaluate and compare the efficacy and safety of a 50 Gy dose EBRT alone versus a 50 Gy dose EBRT with 8 Gy ILRT boost with concurrent chemotherapy (CCT) in locally advanced unresectable esophageal cancer. The findings of this study may contribute to a better understanding of the optimal radiation dose for definitive CCRT.

Aims and objectives

To evaluate and compare the efficacy and safety of a 50 Gy dose of EBRT alone versus a combined approach of 50 Gy EBRT with an 8 Gy ILRT boost, along with concurrent chemotherapy (CCT), in locally advanced unresectable esophageal cancer. The goal is to gain a better understanding of the optimal radiation dose for definitive CCRT.

MATERIALS AND METHODS

After receiving approval from the Ethical Committee of the Institution, we conducted a prospective randomized comparative study in our department from December 2019 to June 2021 on patients willing to provide informed consent.

The inclusion criteria included patients who had biopsy-proven esophageal carcinoma with SCC histology, carcinoma located 5 cm away from the cricopharyngeus muscle, tumor length ≤10 cm, tumor not involving the gastroesophageal junction (GEJ)/cardia, disease in a locally advanced stage (III and IVA) with unresectability due to being medically unfit for surgery or unwillingness to undergo surgery or due to advanced stage, treatment-naive status, age 18 years or older, and eastern cooperative oncology group (ECOG) 0–2. Patients who were excluded from the study were those who had AC histology, a tumor within 5 cm from the cricopharyngeus muscle, stenosis that could not be bypassed, esophageal fistula, a tumor >10 cm in length, a tumor involving the GEJ/cardia, distant metastasis (DM), or other synchronous malignancies, ECOG >2, pregnant or lactating women, hypersensitivity to paclitaxel and carboplatin.

All patients were initially evaluated, including clinical examination; routine blood tests; upper gastrointestinal endoscopy (UGIE) with biopsy; contrast-enhanced computed tomography (CECT) of the neck, chest, and whole abdomen; and whole-body fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET CT) scan in indicated cases. Then patients were staged according to the American Joint Committee on Cancer 8th edition staging system. Patients were randomized into two arms (30 patients in each arm) using a sequential randomization method based on their first visit to our

department. The randomization sequence was generated using computer-generated random numbers.

As per protocol, all patients in both arms received EBRT with a dose of 50 Gy in 25 fractions (2 Gy per fraction and 5 fractions per week). All treatment was stopped in the EBRT alone arm after giving this 50 Gy dose, but a boost of 8 Gy radiation dose was given using a high dose rate ILRT technique (4 Gy per fraction in two fractions) in the ILRT boost arm. ILRT was delivered through a flexible 1 cm diameter applicator, delivering a dose of 8 Gy prescribed to 0.5 cm from the applicator surface. The treatment length was defined as gross disease plus 1 cm proximally and distally. The treatment gap between the two fractions of ILRT was 1 week.

All patients received weekly CCT during treatment in both arms with intravenous paclitaxel 75 mg/m^2 and carboplatin (area under curve 2). Patients were reviewed once weekly or as needed to assess treatment-related toxicities. Toxicity was graded according to the Common Terminology Criteria for Adverse Events version 5. Response evaluation was performed according to the response evaluation criteria in solid tumor criteria (version 1.1). Response assessment was done by clinical examination, UGIE, and CECT thorax initially at the 4th week of treatment completion, then at 3 months and 6 months. Additional investigations were performed whenever necessary during follow-up. Statistical analysis was conducted using the SPSS version 2.0. The qualitative data were compared by applying the Chi-square test or Fisher's exact test, as appropriate. A P<0.05 was considered significant.

RESULTS

Both treatment arms were reasonably comparable in terms of baseline characteristics including age, sex, performance status, primary site, stage, and tumor differentiation (Table 1).

Locoregional response

Four weeks after completion of treatment, in the ILRT boost arm, 76.66% of patients achieved complete response (CR) and 23.33% had partial response (PR). In the EBRT alone arm, 70% of the patients achieved CR and 30% had PR. While a greater number of patients achieved CR in the ILRT boost arm compared to the EBRT alone arm, the difference was statistically non-significant (P=0.559) due to a smaller number of patients (Table 2). Within the ILRT boost arm, 11 patients had stage III disease, with 81.81% achieving CR and 18.18% achieving PR. Among the 19 patients with stage IVA disease, 73.68% achieved CR and 26.31% achieved PR. In comparison, within the EBRT alone arm, 13 patients had stage III disease, with 76.92% achieving CR and 23.07% achieving PR. Among the 17 patients with stage IVA disease, 64.70% achieved CR and 35.29% achieved PR.

Table 1: Baseline characteristics of patients

Characteristics	ILRT boost arm (n=30)	EBRT alone arm (n=30)
Median age	60	53.5
Male, No. (%)	16 (53.33)	19 (63.33)
Female, No. (%)	14 (46.66)	11 (36.66)
Rural: Urban	17:13	16:14
Performance status (%)		
ECOG 1	24 (80)	23 (76.67)
ECOG 2	06 (20)	07 (23.33)
Addiction in any form	21 (70)	22 (73.33)
Tobacco chewing	17 (56.66)	17 (56.66)
Smoking status	9 (30)	12 (40)
Alcohol	6 (20)	10 (33.33)
Tumor site (%)		
Upper 1/3rd	4 (13.33)	5 (16.66)
Middle 1/3rd	14 (46.66)	11 (36.66)
Lower 1/3rd	12 (40)	14 (46.66)
Stage at diagnosis, No. (%)		
III	11 (36.67)	13 (43.33)
IV A	19 (63.33)	17 (56.67)
T Stage		
T3	11	13
T4	19	17
N Stage		
N0	07	06
N1	17	21
N2	06	03
N3	0	0

Table 2: Response of primary tumor at 4 weeks of completion of treatment

Responses	ILRT boost arm (n=30)	EBRT alone arm (n=30)
CR (%)	23 (76.66)	21 (70)
PR (%)	07 (23.33)	09 (30)
PD		
LRF	0	0
DM	0	0
SD	0	0

CR: Complete response, PR: Partial response, PD: Progressive disease, LRF: Locoregional failure, DM: Distant metastasis, SD: Stable disease

At the 3rd-month follow-up (Table 3a), in the ILRT boost arm, out of 23 patients who showed CR at the 4th week of treatment completion, 21 remained in CR state and two showed progressive disease (PD) (one patient showed LRF and one showed DM in the form of brain metastasis). Among the seven patients who showed PR at the 4th week of treatment completion, four patients showed stable disease (SD) and three showed PD (in the form of LRF). Overall, at the 3rd-month follow-up (Table 3b), in the ILRT boost arm, 70% (21) of patients remained in CR, SD was found in 13.33% (4) patients, and PD was seen in

Table 3a: Responses at 3rd month follow-up

Responses	ILRT boost arm (n = 30)		EBRT alone arm (n = 30)	
	CR* (n = 23)	PR* (n = 07)	CR* (n = 21)	PR* (n = 09)
CR	21	00	16	00
PD				
LRF	01	03	05	02
DM	01	00	00	00
SD	00	04	00	07

*Response at 4th week of treatment completion, CR: Complete response, PR: Partial response, PD: Progressive disease, LRF: Locoregional failure, DM: Distant metastasis, SD: Stable disease

16.66% (5) of patients [13.33% (4) with LRF and 03.33% (1) with DM]. At the 3rd-month follow-up (Table 3a), in the EBRT alone arm, out of 21 patients who showed CR at the 4th week of treatment completion, 16 remained in CR state, while 5 patients showed PD (5 with LRF and no DM). Among 9 patients who showed PR at the 4th week of treatment completion, 7 showed SD and 2 showed PD (2 with LRF). Overall, at the 3rd-month follow-up (Table 3b), in the EBRT alone arm, 53.33% (16) of patients showed CR, SD was found in 23.33% (7) of patients, and PD was seen in 23.33% (7) of patients (7 with LRF and no DM).

All patients in both arms who showed PD were assigned for further chemotherapy. Patient with brain metastasis was given whole-brain radiotherapy.

At the next 3rd-month follow-up (6th-month post-radiotherapy) (Table 4a), in the ILRT boost arm, out of 21 patients who remained in CR at the first 3rd-month follow-up, 18 patients maintained CR, while three patients showed PD (in the form of LRF). No new patient showed DM, but there was one patient who died due to brain metastasis in the 5th month. Among the four patients who showed SD at the 3rd-month follow-up, one patient continued to have SD status and three showed PD (i.e., three with LRF). Out of the four patients who exhibited LRF in the 3rd month, three patients experienced PD (three with LRF) and one patient achieved SD with the use of chemotherapy. In the EBRT alone arm, out of 16 patients who remained in CR at the first 3rd-month follow-up, 15 patients maintained CR, while 1 patient showed PD (1 LRF and no DM). Among the 7 patients with SD at the 3rd-month follow-up, 1 patient remained in SD status and 6 showed PD (5 LRF and 1 DM in the form of liver metastasis). Out of the 7 patients who showed LRF in the 3rd month, 6 patients experienced PD (6 with LRF) and 1 patient achieved SD with the use of chemotherapy.

Overall, at the 6th-month follow-up (Table 4b), 60% of patients in the ILRT boost arm and 50% of patients in the EBRT alone arm had CR. PD was observed in 33.33% of patients (30% LRF and 03.33% DM) in the ILRT boost arm and in 43.33% (40% LRF and 3.33% DM) in the EBRT alone arm.

Table 3b: Overall response at 3rd month follow-up

Responses	ILRT boost arm (n=30)	EBRT alone arm (n=30)
CR (%)	21 (70)	16 (53.33)
PD (%)		
LRF	04 (13.33)	07 (23.33)
DM	01 (03.33)	00
SD (%)	04 (13.33)	07 (23.33)

CR: Complete response, PR: Partial response, PD: Progressive disease, LRF: Locoregional failure, DM: Distant metastasis, SD: Stable disease

Toxicities

The main acute toxicities associated with the treatment are summarized in Table 5.

The most common hematologic toxicity observed in our patients was leukopenia of Grade 1 and 2 severity. None of the patients in either arm experienced Grade 3 or 4 hematologic toxicity. Most cases of toxicity occurred during the 3rd and 4th week of treatment. Compared to the EBRT alone arm, patients in the ILRT boost arm exhibited slightly more toxicity in terms of vomiting and diarrhea. However, both groups had similar profiles of leukopenia, nephrotoxicity, and radiation dermatitis. Nevertheless, this difference in toxicity profile is statistically insignificant and can be effectively managed either on an outpatient basis or by hospitalization of patients. Regarding late toxicities, stricture formation was observed in 5 patients in the ILRT boost arm and in 03 patients in the EBRT alone arm, at the 3rd-month follow-up. No cases of fistula formation were reported in either arm.

DISCUSSION

Our study conducted a comparison and evaluation of the efficacy and safety of treatment between EBRT alone and EBRT with ILRT boost for locally advanced unresectable esophageal cancer. The results of our study demonstrated that an ILRT boost with EBRT led to improved CR and local-regional control without a significant rise in treatment-related mortality or toxicity.

The National Comprehensive Cancer Network guidelines for esophageal cancer recommend a radiation dose of 50 or

Table 4a: Response at 6th month follow-up

Response	ILRT boost arm (n=30)				EBRT alone arm (n=30)			
	CR+ (n=21)	LRF+ (n=04)	SD+ (n=04)	DM+ (n=01)	CR+ (n=16)	LRF+ (n=07)	SD+ (n=07)	DM+ (n=00)
CR	18	00	00	00	15	00	00	00
PD								
LRF	03	03	03	00	01	06	05	00
DM	00	00	00	01 (Death at 5th month)	00	00	01	00
SD	00	01	01	00	00	01	01	00

+Response at 3rd-month follow-up, CR: Complete response, PR: Partial response, PD: Progressive disease, LRF: Locoregional failure, DM: Distant metastasis, SD: Stable disease

Table 4b: Overall response in the 6th month

Responses	ILRT boost arm (n=30)	EBRT alone arm (n=30)
CR (%)	18 (60)	15 (50)
PD (%)		
LRF	09 (30)	12 (40)
DM	01 (03.33) (death occurred in the 5th month due to brain metastasis	01 (03.33)
SD (%)	02 (06.66%)	02 (06.66)

CR: Complete response, PR: Partial response, PD: Progressive disease, LRF: Locoregional failure, DM: Distant metastasis, SD: Stable disease

50.4 Gy for definitive CCRT.[18] These guidelines are based on the RTOG trial 94-05, which compared the responses of patients receiving radiotherapy doses of 64.8 Gy and 50.4 Gy with CCT.[7] This trial demonstrated that high-dose radiotherapy with CCT did not provide any advantages over standard-dose (50 or 50.4Gy) CCRT. In addition, the trial showed that treatment-related deaths were more frequent in the high-dose arm compared to the standard-dose arm. However, it is important to note that 7 out of the 11 deaths in the high-dose arm occurred in patients who received 50.4 Gy or less. Therefore, it cannot be concluded that high radiation dose was solely responsible for the increased mortality in the high-dose group. Further studies are necessary to ascertain the effectiveness and toxicities of high radiation doses for treating esophageal cancer.

To explore the potential advantages of different radiotherapy doses, numerous studies have been conducted. Song et al.,[19] reported that clinical outcomes may improve with 60 Gy CCRT compared to conventional-dose CCRT, particularly for SCC histology in esophageal carcinoma. He et al.,[20] conducted a study that revealed that the high-dose group had a significantly lower local failure rate (17.9% vs. 34.3%, P=0.024) than the low-dose group. Kim et al.,[21] performed a retrospective analysis to investigate the correlation between radiation dose and OS in patients with esophageal carcinoma treated with definitive CCRT. The results indicated that patients who received high-dose radiotherapy with CCT had significantly better survival than those who received <60 Gy radiotherapy during CCRT. The study conducted by McLoughlin et al.,[22] suggested that clinical CR was not highly indicative of pathological CR after chemoradiation treatment. Even after achieving clinical remission with chemoradiotherapy, residual lesions may still be present at the primary site. However, these residual lesions can be eliminated through high-dose radiotherapy, which can enhance local control and ultimately improve OS. Based on the aforementioned studies, we investigated the efficacy of radiotherapy with CCT using two different doses: 50 Gy EBRT alone and 50 Gy EBRT with 8 Gy ILRT boost. After careful consideration, we decided to utilize a high radiation dose by adding an ILRT boost to EBRT.

Numerous studies have indicated improved results when using CCRT with ILRT for patients with esophageal carcinoma.[23,24] Vuong et al.,[23] conducted a study on the efficacy of combining ILRT with external radiotherapy, demonstrating excellent local control with a rate of 75%. In our study, we observed a CR rate of 76.66% at 4 weeks after treatment completion in the ILRT boost arm, which is comparable to their findings. In addition, our study showed good tolerance to the treatment, with no instances of fistula formation observed. In contrast, one patient developed a fistula in the Vuong et al.,'s study.[23] This difference could potentially be attributed to the fact that our study utilized only two fractions of ILRT with a sufficient gap of 1 week between each fraction. In contrast, Vuong et al.,'s study[23] employed a higher radiation dose, administering an additional 20 Gy in 5 fractions (twice weekly) of high dose rate (HDR) brachytherapy, along with 50 Gy of EBRT. Similarly, Montravadi et al.,[25] also reported no instances of fistula formation in their study.

Therefore, in our study, compared to the EBRT alone arm, a greater number of the patients in the ILRT boost arm achieved CR, along with slight toxicity in some cases that can be easily handled. These findings suggest that a high-dose radiotherapy by adding ILRT to EBRT can be safely and feasibly used alongside CCT. However, it is important to note that the study had a small sample size and a short-term follow-up, rendering the data inconclusive. Further investigations involving a larger number of patients and long-term follow-up are necessary to conclusively

Table 5: Acute toxicity

Toxicity	ILRT boost arm (%)	EBRT alone arm (%)	P-value
Leukopenia			0.576
Grade 1	06 (20)	08 (26.66)	
Grade 2	09 (30)	08 (26.66)	
Nephrotoxicity			1.00
Grade 1	02 (6.66)	02 (6.66)	
Grade 2	00 (00)	00 (00)	
Radiation dermatitis			0.615
Grade 1	09 (30)	10 (33.33)	
Grade 2	03 (10)	02 (06.66)	
Vomiting			0.921
Grade 1	09 (30)	10 (33.33)	
Grade 2	13 (43.33)	12 (40)	
Grade 3	06 (20)	05 (16.66)	
Diarrhea			1.0
Grade 1	05 (16.66)	05 (16.66)	
Grade 2	04 (13.33)	03 (10)	
Grade 3	01 (03.33)	00 (00)	

ILRT: Intraluminal radiotherapy, EBRT: External beam radiotherapy

determine the efficacy of dose-escalated radiotherapy in increasing CR and loco-regional control, ultimately leading to improved OS.

Limitations of the study

A small sample size and a short-term follow-up.

CONCLUSION

ILRT boost, when added to EBRT, resulted in more patients achieving CR compared to EBRT alone, with manageable toxicities. These results indicate the safe and feasible use of high-dose radiotherapy by combining ILRT with EBRT in conjunction with CCT.

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