

# A prospective comparative study between concurrent chemoradiation with brachytherapy boost with concurrent chemoradiation alone in locally advanced cancer esophagus

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## Abstract

**Context:** Carcinoma esophagus is a highly malignant disease with very low cure rate. Concurrent chemoradiation is the standard of care in patients deemed unfit for surgery. Intraluminal brachytherapy (ILRT) is effective for palliation of dysphagia and is also used as a boost to external beam radiotherapy (EBRT) in curative intent. **Aims:** The aim of the study was to compare the clinical outcome of definitive concurrent chemoradiation followed by ILRT boost with concurrent chemoradiation alone in locally advanced carcinoma esophagus in terms of tumor response and toxicities. **Settings and Design:** A single institutional prospective study was carried out between January 2014 and June 2015. **Subjects and Methods:** Fifty-seven patients of locally advanced carcinoma esophagus were allocated to study and control arms. Both groups were treated with definitive concurrent chemoradiation with 44 Gy of EBRT. The chemotherapy consisted of injection cisplatin 70 mg/m<sup>2</sup> intravenous on day 1 with capecitabine 800 mg/m<sup>2</sup> b.i.d. daily from day 1 to 4 orally on days 1 and 22 of EBRT. After 2 weeks, the control group was treated with EBRT boost of 10 Gy in 5 fractions, while the study group received intraluminal high-dose rate (HDR) brachytherapy boost of 10 Gy in 2 fractions. No concurrent chemotherapy was administered during ILRT. The treatment outcome was assessed in terms of tumor response and toxicities using the CTCAE version 4.0 criteria. **Results:** At a median follow-up of 10 months, the overall response rate was 89.2% in the control group (25/28) and 93.10% in the study group (27/29). Acute hematological and gastrointestinal toxicities were noted. **Conclusions:** HDR ILRT in combination with EBRT is effective for treating dysphagia in cancer esophagus with low incidence of severe complications.

**Key words:** Chemoradiation, esophageal cancer, external beam radiotherapy, intraluminal brachytherapy

## Introduction

Esophageal cancer is known to have dismal prognosis. The optimal management of locally advanced carcinoma esophagus is a controversial area. Only 30%–40% of patients have potentially resectable disease at presentation, and in many series, only, 5%–20% of those undergoing surgery are alive at 3–5 years.<sup>[1]</sup> Radiotherapy has conventionally played a major role, both as an adjunct and as an alternative to surgical approach, but is hampered by the fact that despite the inherent radiosensitivity of these tumors, locally curative doses are difficult to achieve because of the proximity to vital organs such as lungs, heart, and spinal cord.<sup>[2,3]</sup> Unsurprisingly, therefore, local failure is frequently observed as a result of underdosage of the tumor site. Intraluminal brachytherapy (ILRT) is an elegant method to achieve high doses to the esophageal wall with spatial precision. Therefore, this study aims to study the effects of dose escalation by ILRT after definitive concurrent chemoradiation in locally advanced cancer esophagus.

## Subjects and Methods

### Eligibility criteria

A prospective randomized comparative single-institutional study was carried out between January 2014 and June 2015. Untreated patients up to 70 years old with histologically proven locally advanced cancer of middle-third of the esophagus qualified for the study. Further eligibility criteria were adequate performance status, i.e., ECOG >2, no associated comorbidities, and written informed consent.

### Treatment

#### Control group

The patients in this arm were treated with external beam irradiation with conventional 2 Gy per fraction, 5 days a

week to a total dose of 56 Gy. Initially, 44 Gy was given by Anteroposterior-posteroanterior field; then in Phase II, dose escalation was done using three-field technique, i.e., one anterior and two posterior oblique fields. External beam irradiation was done using Theratron 780C.

#### Study group

The patients in this arm were treated with external beam radiation with conventional 2 Gy per fraction, 5 days a week to a total dose of 44 Gy using AP-PA fields, followed by high-dose rate (HDR) ILRT with 5 Gy per fraction weekly to a total dose of 10 Gy, with dose specified at 1 cm distance from the mid-dwell position. Brachytherapy was done by GammaMedPlus HDR Brachytherapy machine.

#### Chemotherapy

Patients in both the arms received chemotherapy with injection cisplatin 75 mg/m<sup>2</sup> intravenous on day 1 and oral capecitabine 1250 mg/m<sup>2</sup> b.i.d. daily from day 1 to 4 during external beam radiotherapy (EBRT) in a 3-weekly regimen.

#### Treatment planning for intraluminal brachytherapy

After applicator insertion, three-dimensional computed tomography (CT)-based planning is recommended. The reference isodose is usually placed at 5-mm tissue depth and a 2-cm longitudinal safety margin beyond the macroscopic tumor boundaries is added to account for microscopic tumor extension, and the spatial inaccuracy of the applicator.

In CT-based treatment planning, the clinical target volume (CTV) as well as organs at risk (OARs) are contoured, and consequently, the dose constraints for OARs, D<sub>90</sub>, and V<sub>100</sub> for the CTV can be analyzed and respected. For a given reference dose specified in relation to the applicator surface in

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case of smaller applicator, the dose gradient will be steeper, leading to higher doses at esophageal mucosa, which touches the surface, and lower doses in the esophageal wall beyond the reference isodose. This highlights the need to use applicators of sufficient size.<sup>[4]</sup>

Ideally, brachytherapy is to be started 2–3 weeks after completion of EBRT/chemoradiation to allow mucositis resolution. Concurrent chemotherapy is not recommended with brachytherapy.<sup>[5]</sup>

### Follow-up

Patients were seen for the first follow-up after 6 weeks of the end of treatment and then at 3 monthly intervals.

### Results

Case accrual was started from January 2014 and patients were enrolled till August 2014. All patients completed treatment within January 2015. Last follow-up was taken in June 2015. Patients with minimum follow-up of 6 months are included in this study.

The median follow-up was 10 months (range 8–14 months) for the control group and 10 months (range 7–15 months) for the study group. At the end of the study, 57 patients were eligible for analysis.

### Patient characteristics

Baseline profiles of both groups were comparable in terms of age distribution, sex, performance status, and stage. The patient and tumor characteristics are shown in Table 1.

### Toxicity profile

Radiation-induced esophagitis ranges from mild dysphagia or odynophagia requiring topical anesthetic or nonnarcotic analgesics to complete obstruction, ulceration, perforation, and fistula. The toxicity profile is shown in Table 2. No grade 3 and 4 toxicity was observed in any of the two groups.

Hematological toxicity was graded according to the CTCAE Criteria. Grade 1 anemia was seen in 12/28 (42.58%) patients of the control group and 11/29 (37.93%) patients of the study group. Grade 2 leukopenia was observed in 3 patients of both groups.

No late toxicities in the form of fibrosis or stricture were noted in either of the arms.

### Response evaluation

Response evaluation was done 6 weeks after the completion of treatment and was done by the RECIST criteria (version 1.1). Overall response rate (complete response [CR] + partial response) was 89.2% in the control group (25/28) and 93.10% in the study group (27/29). The response rates are shown in Table 3.

### Discussion

The treatment of esophageal cancer is still a challenge. Despite an 11% improvement in survival in the past 30 years, 5-year survival rates for patients with localized and regional involvement remain low at 33.7% and 16.7%, respectively.<sup>[6]</sup>

The disappointing rates of local control and survival associated with single modality therapy and the need for effective nonsurgical management led to the development of definitive chemoradiotherapy paradigms for esophageal cancer.

Chemoradiation not only improves the results compared with radiation alone but also is associated with a higher incidence of toxicity. In the 1997 report of the RTOG 85-01 trial, patients who received chemoradiation had a higher incidence of acute grade 3 toxicity (44% vs. 25%) and acute grade 4 toxicity (20% vs. 3%) compared with those who received radiation therapy alone. The incidence of total acute grade 3 + toxicity was 66%.<sup>[7]</sup> However, in our study, no high-grade acute toxicities were encountered.

Another approach to the dose intensification of chemoradiation is increasing the radiation dose above 50.4 Gy. There are two methods to increase the radiation dose to the esophagus: brachytherapy and external-beam radiation therapy.

RTOG conducted a multi-institutional Phase I/II trial to test the safety and efficacy of ILRT as a method of dose escalation in chemoradiation regimens.<sup>[8]</sup>

Series that combine brachytherapy with external beam radiation therapy or chemoradiation report results similar to those for conventional chemoradiation. This was seen in our study also that the response rates were equivocal in both the arms

In our study, overall response rate and CR both were equivocal in both the arms. The CR rates were seen to be 32.14% in

**Table 1: Pretreatment patient characteristics**

	Total (n=57), n (%)	Control group (n=28), n (%)	Study group (n=29), n (%)
Sex			
Males	47 (82.4)	23 (82.1)	24 (82.7)
Females	10 (17.5)	5 (17.8)	5 (17.2)
Age (years)			
41-50	9 (15.7)	7 (25)	2 (16.8)
51-60	32 (56.1)	13 (46.4)	19 (65.5)
61-70	16 (28)	8 (28.5)	8 (28.5)
Performance status			
ECOG 1	37 (64.9)	16 (57.1)	21 (72.4)
ECOG 2	20 (35)	12 (42.8)	8 (27.5)
Dysphagia			
Grade 1	17 (29.8)	6 (21.4)	11 (37.9)
Grade 2	32 (56.1)	16 (57.1)	16 (55.1)
Grade 3	8 (14.03)	6 (21.4)	2 (6.8)
Weight loss at presentation (%)			
<10	20 (35)	12 (42.8)	8 (27.5)
>10	37 (64.9)	16 (57.1)	21 (72.4)

ECOG=Eastern Cooperative Oncology Group

**Table 2: Toxicity profile**

Toxicity	Control group (n=28)	Study group (n=29)
Acute esophagitis		
Grade 0	14 (50)	16 (55.1)
Grade 1	10 (35.7)	10 (34.4)
Grade 2	4 (14.2)	3 (10.3)
Acute hematological toxicity (anemia)		
Grade 0	5 (17.8)	8 (27.5)
Grade 1	12 (42.8)	11 (37.9)
Grade 2	8 (28.5)	9 (31)
Grade 3	3 (10.7)	1 (3.4)
Acute hematological toxicity (leukopenia)		
Grade 0	9 (32.1)	13 (44.8)
Grade 1	16 (57.1)	13 (44.8)
Grade 2	3 (10.7)	3 (10.3)
Acute gastrointestinal toxicity		
Grade 0	15 (53.5)	17 (58.6)
Grade 1	8 (28.5)	9 (31)
Grade 2	5 (17.8)	3 (10.3)

**Table 3: Response evaluation**

Response	Control group	Study group	P
CR	16 (57.1)	17 (58.6)	0.562
PR	12 (42.8)	12 (41.3)	

CR=Complete response, PR=Partial response

the control group and 34.48% in the study group. The overall response rates were noted to be 89.2% in the control group and 93.1% in the study group and the difference was statistically insignificant.

The treatment in both the groups was very well tolerated with no high-grade toxicities. No fistulas were reported in the brachytherapy boost arm.

## Conclusion

Although our study gave equivocal results, the fact that dose escalation through brachytherapy boost is very precise cannot be denied. Therefore, further studies should be conducted to define the role of brachytherapy in the curative setting in esophageal cancer.

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## Conflicts of interest

There are no conflicts of interest.

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