

# Radical External Beam Radiotherapy With Intraluminal High Rate Dose Brachytherapy In Patients With Carcinoma Esophagus

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## Abstract

**Aims:** - Oesophageal carcinoma is an uncommon malignancy, accounting for approximately 1% of all malignancy and 6% of all gastrointestinal malignancies, patients with carcinoma oesophagus usually present with advanced disease. A combination of external and intraluminal radiation therapy is useful to palliate these patients. We report the findings of a retrospective study done on patients with carcinoma oesophagus who were treated with External radiation therapy Followed by Intraluminal brachytherapy. **Methods:** 21 patients who received ILBT followed by EBRT in year 2006-7, of unresectable carcinoma oesophagus without any history of previous anticancer treatment were given external radiotherapy, 40 Gy in 20 fractions over 4 weeks. After gap of two to three week all patients were given Intraluminal high dose rate brachytherapy (5 cGy /3fr/one week apart) were enrolled for this retrospective study. After completion of treatment patients were evaluated every months for clinical response, toxicity and survival. **Results:** Majority of patients were ranged 48-66, with median age of presentation was 57 years. 20 (95%) were male and 1(5%) was female patient. Dysphagia free survival was seen in 20 (95%) of patients. Recurrence was seen in one (5%) patient after completion of four months of follow up. Complete response seen in 19 patients (90.4%) at the completion of treatment. Two patients (9.52%) showed persistent disease. **Conclusions:** The use of HDR-ILBRT, as a treatment for unresectable oesophageal cancer, was significantly effective and HDR-ILBRT contributed to improve outcomes, as well as symptoms free survival in patients with advanced oesophageal cancer. Oesophageal stricture is a common late toxicity in IBT for oesophageal carcinoma. Late complications, including oesophageal ulcer and fistula, were not seen in the present study.

## INTRODUCTION

Oesophageal carcinoma is an uncommon malignancy, accounting for approximately 1% of all malignancy and 6% of all gastrointestinal malignancies.[1] Alcohol and tobacco use are the major risk factor for squamous cell carcinoma.[2] Most common presenting symptom is dysphagia seen in 90% of patients, odynophagia in 50%, weight loss 40%-70% of patients.[1, 3]

Carcinoma oesophagus is considered as aggressive disease as at the time of presentation most cases presents as advanced or metastatic disease with five year survival rate approximately is ranged from 5- 10 %, [4] with a median survival rate observed in 1990s approximately 9 months.[1]

Multidisciplinary treatment have been tried which includes surgery, concurrent chemoradiation, EBRT followed by high dose rate Intraluminal brachytherapy (HDR-ILBRT) in such patients to improve prognosis. The development of new

surgical techniques and better postoperative care has improved prognosis for patients undergoing surgery as the sole treatment, with 2-year survival rates ranging from 35 to 42%, and 5-year survival rates from 15 to 24%. [5,6,7] Historical series of external beam radiation therapy alone report 5-year survival rates of 0%–10%. [8-11] Low survival rate followed initial radiotherapy alone could be due to loco regional persistence or recurrence of tumour, which is seen in as high as 85% of cases. [8] The combination of radiotherapy and concurrent chemotherapy with cisplatin and fluorouracil has led to long-term survival in approximately 20%-30% of patients, an outcome similar to that associated with surgery alone but with a increased risk of late treatment related toxicity.[12]

Review of literature suggests high rates of local recurrence rate 32%-45% when treated with surgery alone and 77% when radiation therapy alone is used. [5, 7, 13, 14] So, the results of the treatment of Ca. of oesophagus have been poor

inspite of advances in various treatment modalities.

A high tumour dose is needed to achieve adequate local control, which is possible by an intraluminal boost following teletherapy. The advantage of intraluminal brachytherapy as a means of dose escalation following external beam radiotherapy centres on physical characteristic inverse square law and quick dose fall off results in relative sparing of surrounding normal tissues, and potentially improving the therapeutic ratio.

Based on the concept that Intraluminal Brachytherapy is an effective adjuvant to Teletherapy to facilitate high tumoricidal dose can achieve excellent local control rate and disease free survival with acceptable toxicities.

We report the findings of a retrospective study done on patients with carcinoma oesophagus who were treated with external radiation therapy followed by Intraluminal brachytherapy and evaluated its effectiveness, especially the HDR-ILBRT component.

## **MATERIAL AND METHODS**

This retrospective study was done in patients of cancer mid oesophagus treated in 2006 to 2007, who received definitive treatment, in form of external beam radiotherapy followed by intraluminal brachytherapy. Twenty one patients received 5 cGy in three fractions one week apart are included in this retrospective study. Other inclusion criteria were:

### **INCLUSION CRITERIA**

Those were unresectable due to medical region or not willing for surgery received definitive radiation therapy with ILBT alone enrolled in this study.

Previously untreated, histopathologically proved.

All lesions were in thoracic oesophagus.

Lesions were not more than 8 cm on barium swallow and endoscopy.

Karnofsky Performance status of more than 60%.

Age of the patients should be less than 62 years.

There was not significant interruption of treatment.

No evidence of metastasis, in Chest x - ray, USG abdomen normal, no palpable lymphadenopathy.

## **TREATMENT DESIGN**

### **EXTERNAL BEAM RADIOTHERAPY**

After proper positioning and immobilization on simulation and fluoroscopic visualization, to know extent of disease, patient was planned for external beam radiotherapy. EBRT delivered by Cobalt 60 Theratron 780-E machine. Minimum 5 cm of margins were taken from the initial tumour lesion with 8 -10 cm of width. Dose was given 40 Gy in 20 fractions over 4 weeks, 5 days per week by AP and PA field. After completion of EBRT two to three week rest was given to all patients.

### **INTRALUMINAL BRACHYTHERAPY**

ILBT was delivered by using High dose remote afterloading Microselectron (Nucletron, Netherlands) machine. Radioisotope used as a source was Iridium. (Stepping 192Ir. Source)

Patients were given premedication with Inj Glycopyrolate IV and mild sedatives. An after loading catheter was introduced through mouth into the oesophagus to the primary site under fluoroscopic guidance. The position of applicator was monitored by fluoroscopy and was adjusted to cover the tumour area by applicator. After a dummy source was inserted into the applicator, radiographs of the applicator were taken. In the current study, catheter was used with 6mm outer diameter with 995mm length. The geometrically optimized dose distributions were generated using a software program (PLATO; Nucletron Co.Ltd.)The reference point of dose calculation was at a distance of 5mm from the applicator surface. The length treated in all patients was 8 to 12 cm. The dose prescribed was 500 cGy in three fractions a week apart in all patients. The overall treatment time including external beam radiotherapy and brachytherapy ranged from 6-9 weeks. After completion of treatment response evaluated every month, in terms of local control, relief of symptoms like dysphagia, odynophagia. Barium swallow, endoscopy, and CT scan chest were performed in symptomatic patients to rule out residual disease. In asymptomatic patients all relevant investigation performed at 4 months. Local control was defined as a lack of either clinical or pathological evidence of tumour recurrence in oesophagus.

## **RESULTS**

The present study was done on 21 biopsy proven cases of carcinoma oesophagus treated by external beam radiotherapy and high dose rate brachytherapy from 2006 to 2007. The

majority of patient in this study were in 5th – 6th decade, mean age was 54 years. Male to female ratio in the study group was 20: 1 suggested the incidence of the disease was predominant amongst the males. Most common presenting symptom was dysphagia seen in all patients (100%). Weight loss was seen in 9(42%) of patients. Duration of symptoms ranged from 1-6 months.

**Figure 1**

Table - 1 Patient’s characteristics- Number of patients 21

No	Characteristic	
1.	Age	48-60 median (54 yrs)
2.	Sex	20:1(Male: Female)
3.	Dysphagia	21 (100%)
4.	Dysphagia (duration)	1-6 months
5.	Dysphagia (grade)	Grade I-8, Grade 2- 6 grade3- 6, grade 4- 1
6.	Weight loss	19 (82%)
7.	Location of tumour	Mid oesophagus -21 (100%)
8.	Length	5-8 cm median (6 cm)
9.	EBRT	40Gy/20# in 4 weeks
10.	ILBT	15Gy/3# in 3 weeks

**RESPONSE**

After completion of treatment, patients who had no clinical evidence of disease either at the primary site or in the regional lymphnodes nor had any evidence if distal metastasis, were considered as ‘complete remission’. Those who had > 50% decrease of the tumour size and regional lymph nodes were considered ‘partial remission’ (PR). Complete response was noted in 19(90.4%), persistent disease seen in 2(9.52%). After completion of fourth month of follow up only one patient had developed recurrence 1 (4.76%) for which the patient was given salvage chemotherapy. Dysphagia free survival observed in 20(95%) of the patients. Over all survival observed 10-12 months. (Table 2&3)

**Figure 2**

Table-2 Showing response

Sr. No.	Status	n	%
1.	Complete response	19	90.4%
2.	Persistent disease	2	9.52%
3.	Local recurrence*	1	4.76%

• \* Local recurrence seen after fourth month of follow up.

**TOXICITY**

Post radiotherapy stricture seen in 9(42%) of fistula. Among them 3 patients required dilatation .None of the patients developed ulcer or fistula.

**Figure 3**

Table -3 Complications After completion of EBRT and ILBT.

Sr. No.	Toxicity	n	%
1.	Post radiotherapy stricture	09	(42%)
2.	Ulcer and fistula	0	0
3.	Dysphagia free survival	20	(95.2%)*
4.	The medial overall survival	10-16	-

\*One patient with grade 4 dysphagia at the time of presentation, had grade 2 dysphagia after treatment.

**DISCUSSION**

The advantage of Brachytherapy over EBRT is Brachytherapy as compared to external beam radiation therapy offers rapid tumour reduction of luminal aspect thus rapidly restoring the swallowing function and at the same time delivers relatively low dose to surrounding normal tissues particularly lung, spinal cord and adjacent normal oesophageal mucosa from radiation while same time providing focal dose escalation. [15, 16]

Many studies have highlight the effect of ILBT boost following EBRT, four randomized trials have claimed

clinical superiority of ILBT following EBRT compared to EBRT alone.[17-20]

The other factor which determines the efficacy and toxicity of brachytherapy are treatment related factors such as sequencing, timing, and fractionation, total dose of EBRT and by brachytherapy parameters such as applicator diameter, dose rate, active length, interval and fractionation of brachytherapy. [21]

Kajanti et al analyzed the effects of overall treatment time on local control rates in 353 patients with oesophageal carcinoma treated with RT. They calculated RT doses for 10% probability of tumour control at 1 year (TCD10) and demonstrated that the TCD10 did not change significantly from 6 weeks to 7 weeks, but it increased at 8 weeks to 9 weeks. [22]

Stricture formation, fistula and oesophageal ulceration are the common late toxicities of HDR brachytherapy. Vivekananda et al reported post-radiation stricture in 59% in their study of 58 patients. [23]. Post radiation strictures reported by various authors in ranges from 11.8%-44%. In our series 42% of patients developed a stricture. Among them 3 patients required dilatation.

Strictures were defined as treatment related when barium swallow were smooth, and there were no malignant cells on biopsy examination, or when detected followed by 6 months survival considered as treatment related in absence of biopsy proof. However, fistula and ulceration have not seen in present study. Possibly that the short gap between EBRT HDR 3-14days and the short interfraction interval 3-7 days may explain the high incidence of severe morbidity. In current study the time between EBRT and HDR-ILBT was in ranges from 21-28 days and at least 7 days gap were present in every fraction. One other factor which influences late toxicity is the size of oesophageal applicator. Akagi et al in an optimization study treated patients with EBRT 5-61 Gy followed by HDR –ILBT in 2 fractions of 4 or 5Gy or 4-5 fractions of 2-2.5 Gy using a 15 mm or 20 mm diameter balloon applicator prescribed at 5 mm from the surface. They recommended the use of 4-5 fractions of 2-2.5 each for HDR-ILBT after 50-61 Gy EBRT based on a significantly lower probability of late morbidity.[24 ] In an another study 134 patients treated in 10 Italian centres with HDR-ILBT with or without EBRT, complication rates correlated with HDR-ILBT fraction size (for fraction size < 5 Gy, complication 9.5%, 20% with doses ranging 5-8 Gy and

38% with fraction doses >8 Gy), and on diameter of applicator tubes when narrower tubes used the oesophagus was more severely injured (24% with tube diameter < 2mm, 19% with tube diameter 2-6 mm and 5% with tube diameter >6mm).[25]

In present study EBRT doses were given 40 Gy followed by 15Gy (5 Gy per fraction) by HDR –ILBT could explain the absence of fistula and ulceration formation. However the stricture formation rate were high (42%), could have resulted from the use of narrower tube with diameter 6mm.

Caspers et al studied 35 patients with carcinoma oesophagus treated with external beam radiation therapy and low-dose-rate intraluminal brachytherapy. They reported dysphagia relief in almost 90% at six weeks. [26] In present study dysphagia relief was seen 95%. It has been demonstrated that HDR –ILBT also effective in palliation of dysphagia. Studies reported 90% relief in dysphasia in cases of palliative intention. [27]

Gasper et al in a prospective trial used EBRT 50 Gy with concurrent chemotherapy followed by brachytherapy after a gap of 2 weeks. Results showed a median survival of 11 months in all patients, local recurrence or persistence of disease observed in 63% of patients and 6 patients developed fistula.28

In current study complete response was observed in 19 (90%) while persistence disease observed in 2(9.52%) of the patients. One patient was developed local recurrence after fourth month of completion of treatment which was given salvage chemotherapy with Carboplatin and Paclitaxel after completion of 6 cycles of Chemotherapy, patients became asymptomatic. Median overall survival observed in current study in ranged of 10- 16 months. None of the patient developed oesophageal ulceration or fistula formation. However, concurrent chemotherapy was not given in current study.

Someya M. in their study observe that In patients with tumours of 5 cm or less in length, the results of treatment with 60 Gy ERT and 20 Gy ILBT were promising and did not cause severe late complications, in tune with present study.[29]

In the multi-institutional analysis a slightly higher 2- year local control rate was obtained in the group that received external beam RT with ILBT (90%) than in the group that received external beam radiotherapy alone with superficial

oesophageal carcinoma (77%).[30]

In a study conducted in patients with T1 and T2 tumours, found that the brachytherapy group showed a trend ( $p = 0.088$ ) toward better overall survival and a significant survival benefit in those with tumours smaller than 5 cm ( $p = 0.025$ ). [31] Another study, including only patients with superficial oesophageal tumours, found a significantly improved survival for the group that received a boost of intraluminal brachytherapy instead of continued external radiation. [32]

Review of literature showed swallowing ability is improved in the majority of patients treated with radiotherapy, and with ILBT to the same extent as externally delivered radiation, and the improvement has been reported to have duration of approximately 10 months.[18,33]

Moreover, swallowing function and general well-being both appear to be better for patients receiving brachytherapy with acceptable toxicity. The other strategy for improved treatment outcome is concurrent chemotherapy, but this combined modality resulted in high incidence of severe toxicity, including treatment related fistulas. [34]

With the concept that high tumoricidal dose for adequate tumour control achieved by ILBT, as a mean of dose escalation, at the same time sparing surrounding normal tissue, and potentially improving therapeutic ratio, EBRT followed by ILBT could be better choice for carcinoma oesophagus. This study indicates gives better response and found to be well tolerated and showed encouraging response in terms of complete and partial response. However, there are some drawbacks in this study; it included only 21 patients, short study period. Although the results in the present study are encouraging and suggest the use of HDR-ILBRT, as a component of multidisciplinary treatment for unresectable oesophageal cancer, was significantly effective and HDR-ILBRT contributed to improve outcomes in patients with advanced oesophageal cancer. Stenosis, ulcer, fistula and stricture are the most common late side effects following radiation therapy, but in present study ulcer and fistula formation were not seen. Despite advances in treatment of carcinoma oesophagus, radiation continues to be an important means of treatment with carcinoma oesophagus in radical as well as palliative setting.

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