Original Article

High Dose Rate Intraluminal Brachytherapy (HDRILBT) as a Boost to External Beam Radiation Therapy (EBRT) in Advanced Inoperable Carcinoma Esophagus

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Abstract

Aim of study: In certain clinical situations HDRILBT may be an effective alternative modality as a boost to external beam radiation therapy in advanced inoperable carcinoma esophagus. In this study, we evaluated the feasibility, complications and short term response of HDRILBT used as a boost after completion of 40 Gy EBRT with curative intent in inoperable advance stage esophageal cancer. **Materials and Methods:** After 40 Gy EBRT, 28 patients who could be intubated with 16 F Levine's tube was given high dose rate (HDRILBT) and formed the study group. The prescription point was at 1 cm from the central axis of the oesophageal catheter. A total dose of 10 Gy in 2 fractions at weekly intervals was prescribed. **Results:** Treatment result was analysed after 3 months of completion of treatment. It was consisted of clinical evaluation, endoscopic evaluation and contrast enhanced CT scan thorax of the patients. Grade 1 & 2 oesophagitis was seen in 21 patients. 3 patients had Grade 3 & 4 oesophagitis (RTOG scale). Stricture formation was seen in 3 patients. In one patient, tracheoesophageal fistula was developed 3 months after treatment. Complete Response was seen in 20 patients (71%). Partial response was seen in 4 patients (14%). Stationary and progressive disease was seen in 4 patients (14%). Relief in dysphagia was seen in 22 (78%) patients. **Conclusion:** In selected cases use of HDRILBT as a boost to EBRT is a feasible option to obtain a higher dose for improved local control with acceptable complications.

Keywords: Inoperable advance stage esophageal cancer; High dose rate intraluminal brachytherapy

Introduction

Oesophageal cancer is the eighth most common cancer and the sixth leading cause of cancer deaths in the world. [1] In India most of the patients present in advanced and inoperable stage. They usually present in a nutritionally compromised state and mostly have poor performance status. The survival rate of these patients remains very poor.

In the curative setting primary treatment options for patients with locally advanced disease include preoperative chemoradiation, definitive chemoradiation and rarely preoperative chemotherapy. [2,3] Preoperative chemoradiation is preferred over preoperative chemotherapy for patients with adenocarcinoma (ACC) of the distal esophagus or esophgeogastric junction. [4] Definitive chemoradiation therapy has been demonstrated as the curative approach for patients with squamous cell carcinoma (SCC) of the esophagus whereas chemoradiation followed by surgery is the standard of treatment for adenocarcinoma of the distal esophagus or esophageogastric junction. [5] The current standard of care for inoperable esophageal cancer is concurrent chemoradiation with 50.4 [6] Gy radiotherapy and cisplatin/5-FU–based chemotherapy. [7]

However, in most of these cases, only the palliation of symptoms is possible. The various available options are palliative bypass surgery, endoscopic laser therapy, concomitant chemoradition therapy, intraluminal plastic tubes and the insertion of self-expandable stents. [8] High dose rate intraluminal brachytherapy (HDRILBT) is also an effective method for palliation of dysphagia. [9]

During definitive chemoradiation treatment, after the completion of 40 Gy external beam radiotherapy (EBRT), further dose escalation may take either of the two approaches to boost the primary tumour volume. One is use of three-dimensional conformal EBRT (3DCRT) and another is HDRILBT. While 3DCRT may help to conform the high dose region to the tumour volume, they are expensive, time consuming and not readily available in Indian scenario. HDRILBT offer a simple, inexpensive method of conformal radiation therapy. HDRILBT allows the escalation of dose to the oesophagus while protecting dose-limiting structure such as lung, heart and spinal cord. It is found in the literature that in certain clinical situations HDRILBT may be an effective alternative modality both as sole radiation therapy and as a boost to EBRT. [10-13] As a result of

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its many advantages such as dose conformity, short treatment duration, and out-patient treatment, HDRILBT could be a feasible option for dose escalation to improve the survival. [14-16]

In this study, we have evaluated the feasibility, complications and short term response of HDRILBT employed as a boost after completion of 40 Gy EBRT with curative intent in inoperable advanced stage esophageal cancer.

Methods and Patients

Patients having histologically proven SCC or ACC of the thoracic esophagus with stage 2 & 3 disease (advanced stage) were included. 52 patients with inoperable carcinoma esophagus were selected for chemoradiation treatment between January 2012 and September 2013 at our centre. They were inoperable due to local extension, old age or concomitant disease. Exclusion criteria included cervical esophageal cancers, extension of tumor to gastroesophageal junction, involvement of supraclavicular or more distant lymph node groups, and invasion of the tracheobronchial tree.

They were treated by chemoradiation as a primary treatment of modality. Patient's characteristics are shown in Table 1. The study was approved by local Research and Ethical Committee. Study was explained and written consent was taken from individual patient before the execution of treatment.

Table 1: Patient characteristics.

Age (years)	Mean	58.8
	Range	40-75
Sex	Male	18
	Female	10
Site	Upper third	6
	Middle third	13
	Lower third	6
	Upper & Middle	1
	Middle & lower	2
Histology	SCC	22
	Adenocarcinoma	6
Stage	II	11
	III	17

Initial treatment

These patients were given EBRT with the dose of 40 Gy/22 fractions by anteroposterior field with Co60 teletherapy machine. A fraction of 200cGy was given daily, five days per week. Patients were started on EBRT with a treatment volume covering the primary tumour with generous proximal and distal margins (5 cm margins above and below the tumour and mediastinal lymph nodes). Both portals were treated daily with patient in the supine position. Concurrent chemotherapy was given with Cisplatinum 75 mg/m^2 Day 1 and 5-FU 750 mg/m^2 Days 1-4 during weeks 1 and 4 of EBRT. Patients were weekly followed for acute toxicities of chemoradiation and were managed accordingly. After EBRT completion patients were evaluated for treatment response. Surgical opinion was taken for middle and lower 1/3 oesophageal disease. Patients who were still inoperable but well responded to radiotherapy were selected and planned for further radiation treatment.

Study design

After a total dose of 40 Gy with EBRT, further dose escalation was done by using HDRILBT. 28 patients in which intubation in esophagus with 16 F Levine's tube was feasible were selected for the delivery of HDRILBT.

2 patients in which intubation was not possible, were excluded from the final evaluation. In these patients dose escalation was done employing 3DCRT with three-field arrangement consisting of an anterior field and two posterior oblique fields to minimize the dose to spinal cord. A total dose of 50 Gy by EBRT was given in these patients.

HDRILBT

The prescription point was at 1 cm from the central axis of the oesophageal catheter. A total dose of 10 Gy in 2 fractions at weekly intervals was prescribed. The tumour length is determined using available information from the barium oesophagogram, computed tomography scans and endoscopy. The treatment length usually includes the entire tumour length at presentation with a margin of 2 cm on either side.

A graduated nasogastric tube was inserted to position the distal end of the tube at the distal end of the planned treatment length. During intubation local anaesthesia was produced by using Xylocaine spray. After verification that the tube is in the oesophagus and not in the airway, a dummy source was placed in the nasogastric tube and pushed up to its distal end. Radiographs were taken to verify the location of the nasogastric tube and check that its distal end is appropriately positioned to treat the desired segment of the oesophagus.

Computerized treatment planning was used to calculate the dwell time of the source at various positions along the oesophagus. The treatment time was calculated to deliver the prescribed dose at a uniform distance from the source. The tube in the patient was then connected to the remote afterloader and the HDRILBT was delivered using a remote afterloading unit with an Ir-192 source. These patients were evaluated for feasibility, complications and short term treatment response.

Results

In this study the mean age of the patients was 59 year. Male to female ratio was 2:1. Middle one third of the oesophagus was the commonest site and SCC was the commonest histopathology (78%). Treatment results were analysed after 3 months of completion of treatment. Response evaluation was done using clinical examination, endoscopic examinationn and contrast enhanced CT scan thorax of the patients.

Complications of the treatment are described in Table 2. After treatment completion grades 1 and 2 esophagitis was seen in 21 patients. 3 patients had Grades 3 and 4 esophagitis (RTOG scale). Stricture formation was seen in 3 patients. In one patient, tracheoesophageal fistula was developed after the 3 months of treatment.

Table 2: Complications of treatment.	
Complications	**No. of cases (%)**
Oesophagitis Grade 1&2	21 (75)
Oesophagitis Grade 3&4	3(14)
Stricture	3 (14)
Fistula	1 (3)

Response to treatment is described in Table 3. The Complete Response (CR), defined as no tumour seen on oesophagoscopy, was seen in 20 patients (71%). Partial response (PR) which is defined as <50% decrease in tumour growth on esophagoscopy, was seen in 4 patients (14%). Stationary and progressive disease was present in 4 patients (14%). Relief in dysphagia was present in 22 (78%) patients.

Table 3: Results of radical treatment in terms of response.	
Results of radical treatment (N=28)	
Complete response	20 (71%)
Partial response	4 (14%)
No change or progression of disease	4 (14%)

Discussion

The current standard of care for inoperable esophageal cancer is concurrent chemoradiation with 50.4 Gy radiotherapy and cisplatin/ 5-FU–based chemotherapy. Further dose escalation to improve the outcome is limited critical surrounding structures. HDRILBT offers a simple, inexpensive method of conformal radiation therapy in this context of dose escalation with minimum morbidity. HDRILBT allows the escalation of dose to the oesophagus while protecting dose-limiting structure which is not possible even with the most conformal method of EBRT.

In the definitive chemoradiation treatment of carcinoma oesophagus, role of brachytherapy remains unclear and investigational. Most of the studies are single centre experiences and done in palliative setting to relieve dysphagia.

According to the American brachytherapy society (ABS) guidelines [17] HDRILBT may be given in unifocal, localised SCC or ACC of thoracic esophagus, ≤ 10 cm in length. Cervical oesophagus location, tracheal or bronchial involvement and stenosis that cannot be bypassed are the contraindications for HDRILBT. HDRILBT in the palliative setting may be given in thoracic esophagus carcinoma with distant metastases, unresectable local disease progression and/or recurrence after definitive radiation treatment.

The esophageal brachytherapy applicator should have an external diameter of 6-10 mm. If 5FU-based chemotherapy and 45-50-Gy external beam are used, recommended dose of HDRILBT is 10 Gy in two weekly fractions of 5 Gy each. Dose should be prescribed at 1 cm from the midsource or mid-dwell position. Brachytherapy should follow and should not be given concurrently with chemotherapy. In palliative setting, 30 Gy EBRT followed by 10-14 Gy HDRILBT in one or two fractions is the recommendation of ABS. [17]

The use of HDRILBT with EBRT has been reported in a very few studies. [18-20] Hishikawa et al. reported a higher local control rate, 62% versus 20%, and higher two-year survival in stages 1 and 2, 44% versus 9%, when ILBT was added to EBRT as compared to EBRT alone. [15] There are two randomized trials supporting the use of HDRILBT as an adjunct to EBRT in cases treated with curative intent. From china, Wei-bo Yin [12] reported a statistically significant improvement in survival in 100 patients treated with 50Gy EBRT followed by 19-26Gy HDRILBT in 3-4 fractions (78% at one year) when compared to 100 patients treated with 70Gy EBRT alone (56% at one year, P<0.01). Sur et al. reported similar results from India in a smaller group of patients. [18] In our study Complete Response rate was 71% and Partial response rate was 14%. Stationary and progressive disease was seen in 4 patients (14%).

Various single centre experiences [21-25] of HDRILBT in palliative setting suggested that HDRILBT is a safe and feasible option in selected patients for the control of dysphagia. These studies reported dysphagia control in 50-80% of patients with acceptable toxicities. Homs et al. in their study compared HDRILBT with stent placement and concluded that single-dose HDRILBT gave better long-term relief of dysphagia and associated with fewer complications. [9] In our study percentage reduction of dysphagia was 78%.

RTOG 92-07 trial was a multiinstitutional prospective study, designed to determine the feasibility and toxicity of chemotherapy, EBRT and oesophageal brachytherapy with curative intent in ACC or SCC of the oesophagus. In this trial although swallowing function after EBRT and concurrent chemotherapy is satisfactory in most surviving patients (92%), incidence of fistulas was higher (12% within 7 month). Authors suggested cautious use of brachytherapy particularly when used in conjunction with chemotherapy. [26,27]

Esophagitis, stricture formation ulceration and fistula formation are the possible complications with HDRILBT. [19] Considerable variations are seen in complication rate reported in the previous studies because of variability in dosing schedules, fraction size and applicator size in these studies. [20] The most common complication reported with oesophageal radiation therapy is an esophageal stricture. This may occur in 17-43% of patients. [28] In our study grade 1&2 oesophagitis was seen in 21 (75%) patients. 3 patients had Grade 3 & 4 oesophagitis (14%). Stricture formation was seen in 3 patients (14%). In one patient, tracheoesophageal fistula was developed 3 months after treatment. We have found a lower complication rates as compared to other studies. The treatment was very well tolerated, with only one patient developing fistula following treatment. This shows the feasibility and better outcome of our HDRILBT dose fractionation schedule.

Patient's compliance was found to be a limitation in delivering HDRILBT as excessive gag reflex during intubation was very cumbersome in some patients.

Conclusion

This study did not aim to compare the HDRILBT with 3D conformal EBRT but result of this study show that in selected

cases use of HDRILBT with EBRT is a feasible option to obtain a higher dose for improved local control and acceptable complications. HDRILBT is feasible, effective, better tolerated and safe but patient compliance is needed. Long term follow up is required to comment on survival rates. Further research is necessary to determine the appropriate dose fractionation schemes and schedules for integration with EBRT.

Conflict of Interest

All authors disclose that there was no conflict of interest.

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