Research Article

External beam radiation plus intraluminal brachytherapy in locally advanced, inoperable carcinoma esophagus: A retrospective study from tertiary cancer care center

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Received: November 02, 2019; **Accepted:** November 20, 2019

ABSTRACT

Background: Worldwide, an estimated 572,034 esophageal cancer cases and 508,585 deaths occurred in 2018 and it accounts for approximately 3.2% of all malignancy. 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. Unresectable or metastatic disease at the time of diagnosis is seen in approximately 80% of patients, with cure rate <15% and thus making carcinoma of esophagus is one of the most dreaded malignancies. As most of the patients are diagnosed in locally advanced or metastatic stage, so curative surgical resection is not an option. Hence, in these groups of patients, other treatment modalities including concurrent chemoradiation have been tried. However, many of these patients are in a poor general condition so that radical concurrent chemoradiation as an alternative surgical resection could not be offered. In this group of patients, only radiotherapy (RT) is an option in intention to improve quality of life and to increase disease-free survival (DFS) if possible. As there is more chance local failure when patients treated with only external beam RT (EBRT), increasing dose to tumor may improve local control. Intraluminal brachytherapy (ILBT) is an important treatment option for dose escalation along with EBRT in the treatment of locally advanced and inoperable carcinoma esophagus. ILBT provides focal dose escalation, rapid reduction tumor, rapid restoration of swallowing function with sparing of surrounding normal tissue, and potentially improving therapeutic ratio. Hence, based on these facts, following EBRT, ILBT is an effective adjuvant modality to delivered high tumoricidal dose which can facilitate good local control, DFS with acceptable toxicity. We have used ILBT alone as palliative RT and combined modality with EBRT as radical treatment approach. **Objectives:** The aim of our study is to evaluate efficacy and safety of external beam radiation plus ILBT in locally advanced, inoperable carcinoma of esophagus in terms of improving local control, DFS, toxicity, and quality of life. **Materials and Methods:** A total of 58 carcinoma esophagus patients treated with EBRT plus ILBT in our RT department from 2012 to 2015 analyzed retrospectively. EBRT, total dose of 40 Gy/20 fractions, delivered in 4 weeks, using anteroposterior posteroanterior portal in cobalt-60 machine. Two–three weeks after completion of EBRT, ILBT was done using esophageal budgie. The total dose of brachytherapy was 10 Gy in two fractions, 1 week apart, 5 Gy in each fraction. EBRT and ILBT treatment completed in 8–9 weeks. Response assessed by clinical assessment, upper gastrointestinal endoscopy, and contrast-enhanced computed tomography chest and abdomen initially at 3 months and then at 6 months. **Results:** Local disease control seen in 65% of patients. With a median follow-up of 15 months, the median DFS was 8 months and median overall survival was 14 months. Regional nodal failure and distant metastasis were seen in 35% and 46% of patients, respectively. The incidence of acute mucositis was seen in 75% of patients and late toxicity is seen in 25% of cases. Swallowing function preserved in >87% of patients. **Conclusion:** In patients with locally advanced carcinoma of esophagus and poor

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Website: http://www.ijmsph.com	Quick Response code
DOI:10.5455/ijmsph.2020.1131420112019	

performance status who are unable to tolerate radical concurrent chemoradiation, combination of EBRT plus ILBT produces good local control, DFS, and durable relief of dysphagia with acceptable toxicity.

KEY WORDS: Carcinoma; Esophagus; Radiotherapy; Toxicity; Brachytherapy; Dysphagia

INTRODUCTION

Worldwide, in 2008, non-communicable disease (NCD) is a leading cause of death; responsible for 63% of death.[1] In India, based on available evidence, 53% of death caused by NCD and cancer one of the leading causes of mortality and about 6% death caused by cancer.[1] Worldwide, an estimated 572,034 esophageal cancer cases and 508,585 deaths occurred in 2018 and it accounts for approximately 3.2% of all malignancy.[2-4] 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.[5] 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 carcinoma of esophagus is one of the most dreaded malignancies.[6] Surgical resection has been standard of care and benchmark to which other modalities are compared. Cure rate and 5-year survival following curative surgical resection are <15% despite advanced in surgical technique and reduction operative mortality.[5-8] High locoregional failure and distal metastasis explain low cure rates and 5-year survival rates. Moreover, most of the patients are diagnosed in locally advanced or metastatic stage so curative surgical resection is not an option. Hence, in these groups of patients, other treatment modalities including concurrent chemoradiation have been tried. However, local failure and survival rates appear similar between definitive chemoradiation and surgical approach in many published literature.[9] At the same time, many of these patients are in a poor general condition so that radical concurrent chemoradiation as an alternative surgical resection could not be offered. In this group of patients, only radiotherapy (RT) is an option in intention to improve quality of life and to increase disease-free survival (DFS) if possible. As there is more chance local failure when patients treated with only external beam RT (EBRT), many researchers felt that increasing dose to tumor may improve local control. However, high dose of EBRT is very difficult to deliver because surrounding vital structure such as spinal cord, lung, and heart by conventional RT technique. Intraluminal brachytherapy (ILBT) is an important treatment option for dose escalation along with EBRT in the treatment of locally advanced and inoperable carcinoma esophagus. ILBT is a technique where radioactive source introduced through applicator or nasogastric tube into esophagus. By the function of inverse square law, rapid fall of dose with increasing distance from source thereby decreasing dose to surrounding vital structures mainly spinal cord, lung, and heart; at the same time, brachytherapy (BT) delivers very high dose to local tumor confined to the esophageal, i.e., focal dose escalation, rapid reduction tumor, rapid restoration of swallowing function with sparing of surrounding normal tissue, and potentially improving therapeutic ratio.[10-12] Hence, based on these facts, following EBRT, ILBT is an effective adjuvant modality to deliver high tumoricidal dose which can facilitate good local control, DFS with acceptable toxicity. In a retrospective analysis of 43 patients of advanced inoperable or metastatic esophageal carcinoma by Das *et al*., combination of EBRT plus ILBT was effective treatment for relief of dysphagia.[12] In a systematic review and meta-analysis by Fuccio *et al.* concluded that BT was highly effective and relatively safe treatment option and high-dose rate (HDR)-BT is effective for controlling dysphagia. ILBT in curative approach along with EBRT produces equal results achieved with concurrent chemoradiation.[13] We have used ILBT alone as palliative RT and combined modality with EBRT as radical treatment approach. We are reporting results of external beam radiation plus ILBT in locally advanced, inoperable carcinoma esophagus in terms of improving local control, DFS, toxicity, and quality of life.

MATERIALS AND METHODS

A total of 58 carcinoma esophagus patients treated in our RT department from 2012 to 2015 analyzed retrospectively. All patients underwent through clinical examination, routine blood test, chest X-ray posteroanterior (PA), barium swallow esophagus, upper gastrointestinal (GI) endoscopy with biopsy, contrast-enhanced computed tomography (CECT) chest and whole abdomen, ultrasonography of whole abdomen and whole-body fluorodeoxyglucose positron emission tomography-computed tomography (CT) scan, whole-body bone scan, and bronchoscopy in indicated cases. Only locally advanced inoperable (Stages II and III) mid-thoracic carcinoma of esophagus cases treated with EBRT plus ILBT and included for retrospective analysis. EBRT, total dose of 40 Gy/20 fractions, delivered in 4 weeks using anteroposterior PA portal in cobalt-60 machine. The treatment field was set by adding 2 cm margin to tumor laterally and 5 cm margin in longitudinal direction along the esophagus. Two–three weeks after completion of EBRT, ILBT was done using esophageal budgie. The treatment length of ILBT in longitudinal direction along esophagus was determined by adding 2 cm margin to tumor visible in endoscopy, barium swallow, and CT scan. One centimeter away from central axis of applicator, dose of ILBT was calculated. The total dose of BT was 10 Gy in two fractions, 1 week apart, 5 Gy in each #.

EBRT and ILBT treatment completed in 8–9 weeks. Response assessed by clinical assessment, upper GI endoscopy, and CECT chest and abdomen initially at 3 months and then at 6 months. The treatment algorithm of locally advanced unresectable middle thoracic esophagus is depicted in Figure 1. Despite the fact that our study is a retrospective one and all the epidemiological and treatment-related data have been collected from our own old records section of the Department of Radiotherapy of NRS Medical College and Hospital only, we have received formal permission from our Institutional Ethics Committee stating the nature of the study and that no harm and no financial burden would occur to the patients and that the further management of the patients will also not be affected by this retrospective analysis.

RESULTS

Patients specific characteristics are depicted in Table 1. Local disease control is seen in 65% of patients. With a median follow-up of 15 months, the median DFS was 8 months and median overall survival (OS) was 14 months. Regional nodal failure and distant metastasis were seen in 35% and 46% of patients, respectively. Post-treatment toxicity is depicted in Table 2. The incidence of acute mucositis was seen in 75% of patients treated by EBRT plus BT. As compared to acute toxicity, the incidence of late toxicity is less, seen in 25% of cases. To assess the functional outcome, we assessed swallowing of food. Swallowing function assessed clinically by ability to take normal diet. In >87% of patients, swallowing function preserved.

DISCUSSION

In our study, the local disease control seen in 65% of patients and the median DFS was 8 months and median OS was 14 months. Regional nodal failure and distant metastasis were seen in 35% and 46% of patients, respectively. The incidence of acute mucositis was seen in 75% of patients treated by

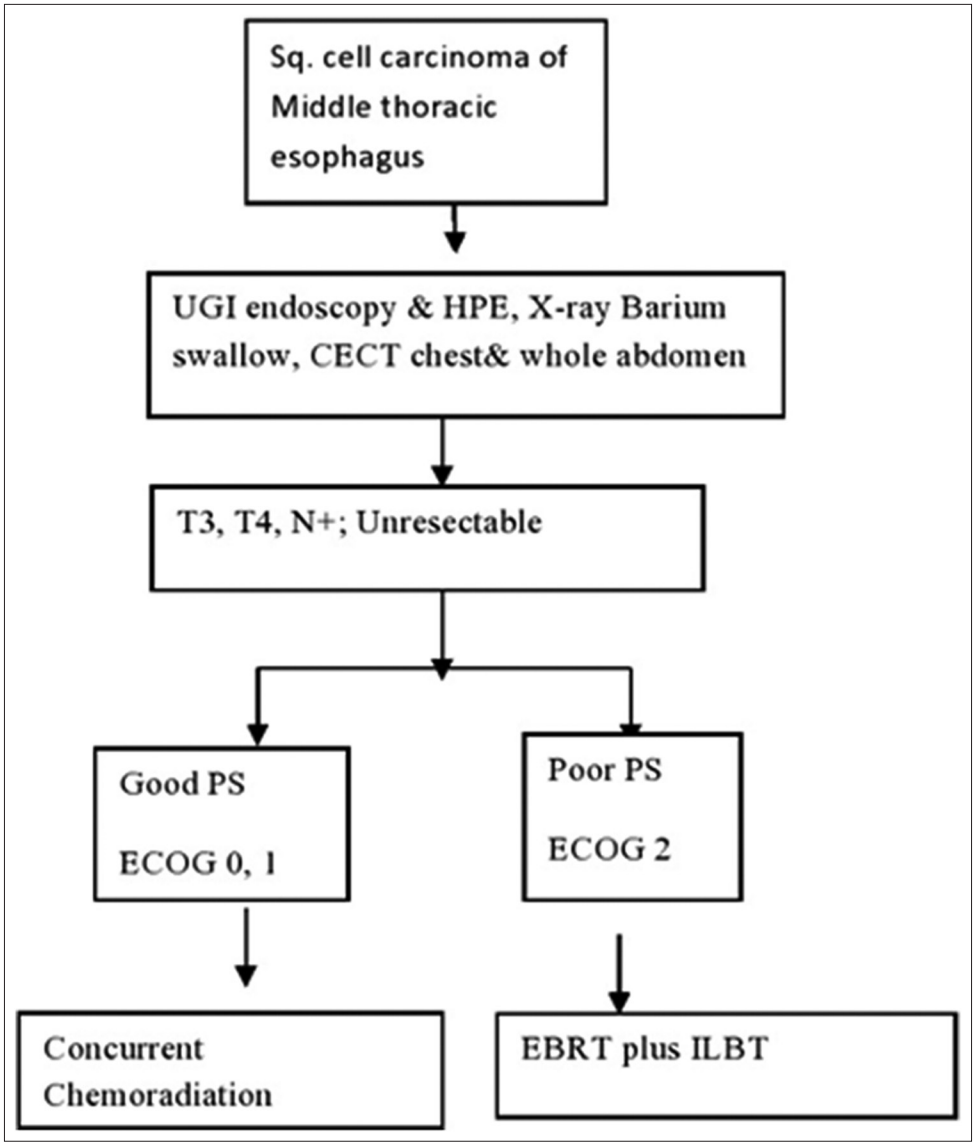

Figure 1: Treatment algorithm of locally advanced unresectable middle thoracic esophagus

Table 1: Patient's characteristics (*n*=58)

Variables	Value
Age (years)	
Range	36–78
Median	53
Sex (%)	
Male	48 (83)
Female	10 (17)
Stage (%)	
T3	28 (48)
T4	30 (52)
Tumor thickness (%)	
<2 cm	32 (55)
≥2 cm	26 (45)
Type of tumor (%)	
Exophytic	34 (59)
Infiltrative	24 (41)
Tumor length (%)	
≥5 cm	30 (52)
<5 cm	28 (48)

Table 2: Toxicity

Variables	Percentage
Acute toxicity	
Mucositis at 2-week post-brachytherapy (acute)–grade ≥2	75
Late toxicity	
Stricture	23
Fistula	2

EBRT plus BT. As compared to acute toxicity, the incidence of late toxicity is less, seen in 25% of cases. Swallowing function assessed clinically by the ability to take normal diet. In >87% of patients, swallowing function preserved.

In our study, 60% of patients of entire group were between 50 and 60 years of age. In SEAR, maximum incidence of carcinoma esophagus is seen in between 5th and 6th decades with male to female ratio of 2:1. The data obtained in this study closely correspond to published data.[5,6,8] As previously stated, unresectable or metastatic disease at the time of diagnosis is seen in approximately 80% of patients, prognosis remains poor, and meaning improvement of results remains to be challenging tusk for radiation oncologists. ILBT most frequently used as boost treatment after EBRT or as sole modality in palliative settings. In a systematic review and meta-analysis of prospective studies of ILBT by Fuccio *et al*.[13] concluded that BT is highly effective relatively safe treatment option that was currently underused. Clinical superiority of the combination of EBRT plus ILBT compared to EBRT alone has been reported by multiples randomized trials.[14-20] Failure in regional nodes was less in patients treated by both EBRT plus BT, but post-RT stenosis and fistula seen 12% and 8%, respectively. Vuong *et al*. suggested that relief dysphagia seen in up to 90% of patients.[21] In a randomized trial by Homs *et al*., patients treated with ILBT experience more days of no or mild dysphagia compared to patients with stent placements, i.e., long-term dysphagia relief was significantly improved in patients with ILBT.[22] In multiple published literature, swallowing ability is increased in majority of patients treated EBRT plus ILBT and this improvement persists for around 1 year.[23,24] In our study, symptomatic relief of dysphagia seen in 87% of patients and median duration was 10 months. Similarly, in multiple published literature, 1 year local disease control rate ranges from 45% to 79%.[14-19] In our study, local control rate seen in 65% of patients and the median DFS was 8 months and median OS was 14 months, which are comparable to published literature. Post-RT stenosis and fistula were seen in 23% and 2% of patients, respectively, and well-correlated above-mentioned studies. Post radiation fistula, ulceration, stricture formation ARE not uncommon late toxicity. Post-treatment stricture defined when narrowing detected 6 months after therapy in the absence of biopsy or in barium swallow X-ray; there is smooth tapering and constriction, but there is no evidence of malignancy in the biopsy. Factors influencing late toxicity include size of applicator, time gap between EBRT and ILBT, and interval between two ILBT fractions and fraction size. Large fraction size (>5 Gy in HDR), short interval between in between treatment (<2 weeks gap between EBRT and ILBT, <1 week gap between two fraction of ILBT) are associated with increased incidence of late toxicity. Various authors reported the incidence of post-RT stricture ranging from 12% to 44%.[14,15,17] In our series, interval between EBRT to ILBT was 2–3 weeks, interval between two # of ILRT was 1–2 weeks, and post-RT stricture seen in 23% of patients. We have used EBRT dose of 40 Gy in 20 fractions followed by DOSE OF 40 Gy in 20 followed by HDR-BT 10 Gy in 2 fractions in our study which may explain the low incidence of toxicity.

The major limitations are as follows: Our study is retrospective in nature, small number of patients, and shorter duration of follow-up. Another limitation of our study is all the patients treated in cobalt-60 machine with conventional RT technique.

CONCLUSION

In patients with locally advanced carcinoma of esophagus and poor performance status who are unable to tolerate radical concurrent chemoradiation, the combination of EBRT plus ILBT produces good local control, DFS, OS, and durable relief of dysphagia with acceptable toxicity. However, further randomized control trial with large number of patients needed before coming final conclusions.

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How to cite this article: Dutta S, Bera A, Mandal S, Banerjee C, Biswas L, Sadhya A. External beam radiation plus intraluminal brachytherapy in locally advanced, inoperable carcinoma esophagus: A retrospective study from tertiary cancer care center. Int J Med Sci Public Health 2020;9(1):79-83.

Source of Support: Nil, **Conflicts of Interest:** None declared.