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Research Article

Palliation of advanced/metastatic carcinoma esophagus with radiotherapy

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ABSTRACT

Background: Esophageal carcinoma carries an overall poor prognosis. Most patients present with lo¬cally advanced, unresectable or metastatic disease. The main objective in advanced disease is the palliation of dysphagia. Treatment options include surgery (bypass, resection), laser, stent placement, external beam radiotherapy (EBRT), brachytherapy and systemic chemotherapy. We have focused on our experience with EBRT followed by brachytherapy.
Methods: From January 2013 to December 2014, 29 patients of advanced/metastatic esophageal cancer were treated by HDR Brachytherapy following EBRT. All patients received 2# of 5Gy HDR brachytherapy. EBRT was 40Gy/20# (18 patients) and 36Gy/12# (11 patients). Disease remission and relief of dysphagia along with toxicity assessment were carried out at 1, 3 and 6 months after completion of treatment.
Results: Evaluation at 1 month after brachytherapy showed complete remission (CR) of the disease in 6 patients, partial remission (PR) in 17 patients and no remission (NR) in 6. Overall improvement in swallowing status was seen in 22(75.86%) patients. 7 patients showed no improvement and 1 reported worsening of dysphagia score at 1 month after ILRT. The improvement in swallowing was maintained by 55.17% of patients at 6 months. Strictures had developed in 5 patients, ulceration in 3 patients and fistula in 1.
Conclusions: A combination of EBRT and HDR brachytherapy affords effective palliation in advanced esophageal cancer with acceptable toxicity.

Keywords: Cancer oesophagus, Palliation, External beam radiotherapy, HDR Brachytherapy

INTRODUCTION

Esophageal carcinoma constitutes 4.1% of all cancer cases in the Indian population.[1] They are usually associated with poor prognosis owing to late presentation with advanced disease (which is seen in 60 - 70% of cases). For such cases, curative options are limited and the main objective of treatment becomes palliation of dysphagia. Palliation also aims at diminishing pain & bleeding, as well as improving the patient's well-being.[2]

Common treatment options for the alleviation of dysphagia include surgery (bypass, resection), laser, stent placement, external beam radiotherapy (EBRT), brachytherapy and systemic chemotherapy. The appropriate modality would depend upon the stage of disease at presentation, tumor location, patient's functional status, and the experience of the treating physician. Radiotherapy for palliation can be external beam (EBRT) alone, intraluminal brachytherapy (ILRT) alone or combination of both.[3]

METHODS

This retrospective study was done in patients of cancer esophagus treated from January 2013 to December 2014, who received external beam radiotherapy (EBRT) followed by intraluminal brachytherapy (ILRT) with

palliative intent. Twenty nine patients were included in this retrospective study. Inclusion criteria were:

1. Previously untreated, histopathologically proved cases of carcinoma esophagus
2. Lesions in upper /mid / lower thoracic esophagus
3. Eastern Cooperative Oncology Group (ECOG) performance status 1 to 2
4. Advanced /metastatic disease.
5. Intraluminal Brachytherapy (ILRT) feasible.

Patients had received EBRT either to a dose of 40 Gy/20# or 36 Gy/12# by Cobalt-60 Theratron 780-E machine by AP and PA fields.

HDR (High Dose Rate) Intraluminal Brachytherapy (ILRT) was started 2 or 3 weeks after completion of EBRT and consisted of placing a standard 3mm diameter (outer) universal catheter into a nasogastric tube in the lumen across the lesion using X-ray imaging to confirm catheter position and determine dummy source positions. Patients were given premedication with Inj. Glycopyrolate IV before the procedure. The prescribed dose was 5Gy at 1-cm from the active dwell positions and the treatment length included the tumor plus a 2 cm margin at each end. Planning was done with the help of HDR plus Version 2.5.3 treatment planning system. Treatment was delivered by HDR remote after loading unit which used Cobalt-60 source (Multisource HDR Brachytherapy, Bebig). Each patient received 2# of 5Gy each at an interval of one week.

Dysphagia (at presentation) and subsequent change in score was measured as per the following table.[4]

After completion of treatment, disease response, remission of dysphagia and treatment complications were assessed in the first month post treatment, and then at 3 and 6 months. To evaluate the obtained results, general clinical examination, assessment of performance status, symptom scoring, X-rays, CT scans, and endoscopy were performed.

The ECOG Performance Status is also included.

RESULTS

From January 2013 to December 2014, a total of 29 patients with advanced/metastatic carcinoma esophagus were treated with EBRT and HDR (high dose rate) intraluminal brachytherapy (ILRT). All patients received 2# of 5Gy each HDR Brachytherapy one week apart. A minimum interval of 2 weeks after EBRT was given before commencement of ILRT.18 patients had received EBRT to a dose of 40Gy/20# and 11 had received EBRT of 36Gy/12#. All 29 patients completed their ILRT schedule. The clinical profiles of the patients are given in the table below.

Table 1: Dysphagia grading and ECOG performance status.

Dysphagia	**Able to eat normal Diet**	**0**
	Able to swallow some solids	1
	Able to swallow only semisolid foods	2
	Able to swallow liquids only	3
	Unable to swallow anything/complete obstruction	4
ECOG performance Status scale	Asymptomatic, normal activity	0
	Symptomatic but fully ambulatory	1
	Symptomatic, in bed less than 50% of the time	2
	Symptomatic, in bed more than 50% of the time	3
	Bedridden	4

Overall improvement in swallowing status was seen in 22(75.86%) patients. 7 patients showed no improvement and 1 reported worsening of dysphagia score at 1 month after ILRT. The improvement in swallowing was maintained by 68.96% of patients at 3rd month and by 55.17% of patients at 6 months after ILRT. Evaluation at 1 month after brachytherapy showed complete remission (CR) of the disease in 6 patients, partial remission (PR) in 17 patients and no remission (NR) in 6.

Adverse effects reported during treatment and follow up period included chest pain (reported by 20.68% of the patients), cough (17.24%), loss of appetite (13.8%) and nausea (6.8%). None of these was severe enough to warrant hospitalization. Strictures had developed in 5 patients, ulceration in 3 patients and fistula in 1.

DISCUSSION

The prognosis in patients with advanced esophageal cancer remains poor despite the introduction of improved treatment modalities such as surgery, radiotherapy, and chemotherapy. The reported 2- and 5-year survival rates range from 30–40% and 10–25%, respectively, regardless of the disease status at presentation and treatment options.[5,6]

The majority of cancer esophagus patients coming to our department present with advanced clinical stages. They invariably present with dysphagia and palliation of dysphagia becomes a major objective.

A randomized trial of 50 patients, 25 of whom received 55 Gy of external beam therapy alone, and 25 patients who were administered 35 Gy of external beam therapy, supplemented with 12 Gy of HDR brachytherapy in two HDR treatments, 1 week apart.[7] The group receiving brachytherapy had better relief of dysphagia (70.6% vs.37.5% in the external-beam-therapy-only modality), improved local control (70.6% vs. 25%), and better

actuarial survival (78% vs. 47%) at 1 year. However, the incidence of strictures (8% vs. 4%) was higher for the brachytherapy modality.

Table 2: Patient characteristics.

No. of patients	29
Age (in years)	28-70 (Mean: 50.55)
Sex	18 Males, 11 Females (62%:38%)
Performance Status (ECOG)	1 (20 patients), 2 (9 patients)
Dysphagia Grade (Gr.)	Gr1- 11 Gr2- 9 Gr3- 9
Distant metastasis	2
Histology	Squamous Cell carcinoma (93.10%)
	Adenocarcinoma (6.89%)
Site of lesion	Upper 1/3rd 8 (27.5%)
	Middle 1/3rd 12 (41.3%)
	Lower 1/3rd 9 (31%)
Length of lesion	<5cm 2 (6.9%)
	5-10cm 23 (79.3%)
	>10cm 4 (13.8%)
EBRT Schedule	36Gy/12# (11 patients)
	40Gy/20# (18 patients)

ECOG: Eastern Cooperative Oncology Group; EBRT: External Beam Radiotherapy

A study by Isawa et al. reported significant improvement in 2-year local control in the treatment of carcinoma esophagus with external beam therapy (median, 50 Gy) and HDR brachytherapy with 18 Gy in 3 fractions, compared with 50 Gy or more of external beam therapy alone.[8]

A study by N. R. Vishnu Prasad et al, using for palliation, EBRT and ILRT in 33 patients of advanced esophageal carcinoma, reported decrease in median dysphagia score from 4 to 3 after treatment ($p = 0.002$) in 17 (89.5 %) patients. 26.3 % had persistent chest pain, increased cough with expectoration in 15.8 % and evidence of residual stricture was observed in 57.9 %.[9]

Brachytherapy causes rapid tumor reduction of luminal aspect thus rapidly restoring the swallowing function and at the same time delivers relatively low dose to the surrounding normal tissues particularly lung, spinal cord and adjacent normal esophageal mucosa.[6] Brachytherapy has been widely performed for the palliation of dysphagia due to esophageal cancer. Several reports have suggested that palliation of this type can be achieved with brachytherapy alone.

Caspar et al have recommended the HDR (High Dose Rate) doses of 15-20 Gy in 2 - 4 fractions for palliation, with similar schedule for patients who have failed previous external radiation or if life expectancy was short.[10]

Harvey et al reported mean dysphagia relief duration of 4.5 months and survival of 5.8 months in their experience with HDR brachytherapy.[11]

Ghosh S et al reported significant improvement in swallowing status in 20 patients (57.14%) since just after treatment and up to 7.5 months. 3 patients (out of 35) developed ulceration and 2 developed fistula immediately after treatment and 5 patients developed stricture. Median dysphagia-free survival was 6 months.[12]

Table 3: Treatment related complications.

Chest Pain	21%
Cough	17%
Loss of appetite	14%
Nausea	7%
Stricture	17%
Ulceration	10%
Fistula	3%

A multicenter, prospective randomized study was conducted under the International Atomic Energy Agency to evaluate two HDR brachytherapy regimens used in the treatment of surgically inoperable patients with squamous cell carcinoma. Patients were randomized to receive 18 Gy in 3 fractions on alternate days (6 Gy per fraction, Group A) or 16 Gy in 2 fractions on alternate days (8 Gy per fraction, Group B). A total of 232 patients were entered into the study (112 in Group A and 120 in Group B).The overall survival was 7.9 months for the whole group (Group A, 9.1 months; Group B, 6.9 months; $p > 0.05$). In the univariate analysis, weight, gender, race, dysphagia score, the treatment center, and tumor grade had an impact on dysphagia-free survival, whereas gender and performance score had an impact on dysphagia-free survival in multivariate analysis. Only age had an impact on the overall survival in both univariate ($p = 0.0430$) and multivariate ($p = 0.0331$) analyses. The authors concluded that fractionated HDR brachytherapy alone is an effective method of palliating advanced esophageal cancers, surpassing the results of any other modality of treatment presently available. Dose fractions of 6 Gy x 3# and 8 Gy x 2# produce similar results for dysphagia-free survival, overall survival, strictures, and fistulas and are equally effective in palliation of advanced esophageal cancer.[13]

Although brachytherapy alone may alleviate dysphagia in patients with a short life expectancy, it has been shown by some studies that the addition of teletherapy may significantly prolong the duration of palliation.[14-16]

The following scheme has been suggested by American Brachytherapy Society for palliative treatment of esophageal cancer:[10]

A. Recurrent after external beam radiation (EBRT) and short life expectancy.

For such patients, HDR Brachytherapy as a single modality can be given to a total dose of 10 to 14 Gy in one or two fractions

B. No previous EBRT

EBRT: 30 to 40 Gy in 2- to 3-Gy fractions

Brachytherapy (HDR): 10 to 14 Gy, one or two fractions

C. No previous EBRT, life expectancy > 6 months

EBRT: 45 to 50 Gy in 1.8- to 2-Gy fractions, 5#/week, week 1 to 5

Brachytherapy (HDR): total dose of 10 Gy, 5Gy/#, I #/week

All Brachytherapy doses were specified 1cm from the midsource or mid-dwell position. LDR (Low Dose Rate) dose-schedules were also described in the consensus guidelines.[10]

CONCLUSION

Radiotherapy affords effective palliation in patients of advanced esophageal carcinoma. Improvement in dysphagia was observed in most patients. Treatment was tolerated well by majority of patients and the complications rates were within acceptable limits.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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