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Palliative radiotherapy and quality of life in patients with locally advanced thoracic esophageal cancer: a single centre experience from Central India

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ABSTRACT

Background: Patients with locally advanced esophageal squamous cell carcinoma (LAESCC) have decreased quality of life (QoL) and, thus, require palliative external beam radiotherapy (EBRT). The present study was performed to evaluate the QoL in patients with LAESCC undergoing palliative EBRT.

Materials and methods: This was a prospective, observational study performed over a period of 18 months (from December 2018 to May 2020) in the Department of Radiation Oncology. Seventy patients with LAESCC received EBRT (30 Gy in 10 fractions, at 3 Gy per fraction over 2 weeks). Patients were followed-up at monthly intervals for 3 months. The dysphagia and odynophagia scores were calculated at baseline and follow-up visits. The QoL was assessed with 18-item EORTC QLQ-OES questionnaire at baseline and 3 months.

Results: Over the study period, significant decrease in mean dysphagia and odynophagia score was observed (p-value < 0.0001). On post-hoc analysis, significant decrease in both dysphagia and odynophagia score was observed between baseline and at the end of study and between various follow-up visits (p-value < 0.0001). Moreover, there was a significant increase in mean body weight (p-value < 0.0001). At 3 months, there was a significant decrease in dysphagia (p-value < 0.0001), eating (p-value < 0.0001), reflux (p-value = 0.005), pain (p-value < 0.0001), and saliva (p-value = 0.01) domains of EORTC QLQ-OES18 questionnaire.

Conclusion: In patients with LAESCC, EBRT leads to significant decrease in dysphagia and odynophagia, and increase in body weight. These changes indirectly lead to improved QoL.

Key words: esophageal squamous cell carcinoma; external beam radiotherapy; dysphagia score; quality of life

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Introduction

Esophageal cancer (EC) is a dreaded malignancy that leads to fatal outcome in majority of cases [1]. Globally, it is the 7th most common cancer (3.2%), and 6th most common cause of cancer related mortality (5.3%) [2]. Between 1990 and 2017, the total number of new cases, deaths, and total disability adjusted life years due to EC increased by 52.3%, 40.0%, and 27.4%, respectively [3]. In India, EC is the 6th most common cancer with incidence of 5.04% [2]. Moreover, it results in around 47,000 new cases each year with yearly mortality of up to 42,000 [4]. A variant of EC, esophageal squamous

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cell carcinoma (ESCC), accounts for 85% of global cases and is the most common type of EC in the Indian subcontinent [5–7].

In the initial stage, patients with EC often remain asymptomatic. However, in the advanced stage, patients may present with continuously aggravating dysphagia followed by inadvertent weight loss, odynophagia, new-onset dyspepsia, heartburn unresponsive to antacids, and chest pain [8]. Moreover, more than half of patients with locally advanced EC or distant metastases generally present with progressive cancer-related complications resulting in poor nutrition, decline in performance status, and decreased quality of life (QoL) [9].

The majority of patients with advanced EC are candidates for palliative therapy [10]. Currently, radiotherapy (RT), as monotherapy, is suitable for patients with good performance status, tumor not suitable for more radical procedures because of length and position, and regional and distant spread [11]. RT is documented to be associated with long-term symptomatic relief of dysphagia, less complication rates, and better QoL [12]. A study reported that RT results in a significantly relived dysphagia and improved QoL in 90% of patients with ESCC [13]. Another study reported dysphagia-free survival with RT in the majority of patients with advanced incurable EC [14].

Moreover, a study comparing brachytherapy (BT) and external beam radiotherapy (EBRT) reported that EBRT results in a significantly greater proportion of patients with improvement in dysphagia and smaller proportion of patients with severe toxicity [15]. Another study reported that EBRT resulted in significantly favorable outcomes, such as nausea, vomiting, pain, and appetite loss; however, both BT and EBRT resulted in a significantly improved QoL [16].

In India, 35–97% patients with EC present with dysphagia [5]. Considering the significant disease burden and number of patients with symptomatic presentation, the role of RT in palliation of dysphagia becomes crucial. Moreover, the studies evaluating the effect of RT on QoL in patients with ESCC residing in Central India are scarce and most of the patients present at our tertiary care centre in advanced stage of EC with dysphagia to liquids. Thus, this study was undertaken to assess the QoL in patients with advanced stage thoracic EC treated with palliative RT.

Materials and methods

This was a single centre, prospective, observational, follow-up study performed over a period of 18 months (from December 2018 to May 2020) in the Department of Radiation Oncology of a tertiary care teaching hospital situated in Central India. Before initiating, the study protocol was approved by the institutional ethics committee and written informed consent was obtained from the patients.

Seventy consecutive patients of either gender, aged between 30 and 65 years, with newly diagnosed and histologically proven stage III or IV (advanced stage) SCC of thoracic esophagus, Eastern Cooperative Oncology Group (ECOG) performance score of 0–2, and moderate anaemia (Hb > 8 gm%) were included in the study. Excluded from the study were patients with adenocarcinoma or any other histological variant of EC other than SCC, non-thoracic EC, ECOG performance score of 3 or more, abnormal kidney function test (KFT) and liver function test (LFT), tracheo-esophageal fistula, and pregnant or lactating women.

EBRT was delivered with conventional 2D technique through Teletherapy Cobalt 60 Unit (Theratron 780E, MSD Nordion, Canada). Each patient received 30 Gy in 10 fractions, at 3 Gy per fraction, with anteroposterior-posteroanterior field for 5 fractions a week, with total treatment duration of 2 weeks. During RT, a margin of 2 cm was considered both proximal and distal to the tumor. At 1-month interval after completion of EBRT, barium swallow, upper gastrointestinal endoscopy (UGIE), and contrast-enhanced computed tomography CT (CECT) of thorax were repeated. Patients were called for follow-up at monthly interval for 3 months from completion of the treatment to look for any change in dysphagia, odynophagia, and QoL following the therapy.

To understand the degree of dysphagia, dysphagia score was calculated at the time of enrolment of the patients. Moreover, to evaluate the degree of improvement, dysphagia score was calculated at each follow-up visits, i.e., at 1, 2, and 3 months. The dysphagia scoring system used to evaluate the effect of RT was:

- 0: able to eat normal diet/no dysphagia;
- 1: able to swallow some solid foods;
- 2: able to swallow only semi solid foods;
- 3: able to swallow liquids only;

- 4: unable to swallow anything/total dysphagia [17].

Similar to dysphagia, odynophagia was evaluated at the time of enrolment and at each follow-up visit. Odynophagia was scored with the help of Visual Analogue Scale (VAS) ranging from 10 to 0, where 0, 5, and 10 represented no, moderate, and worst possible pain, respectively [18].

Finally, QoL of patients with ESCC was evaluated at the time of enrolment and at the end of study, i.e., at 3 months. The improvement, deterioration, or no change following RT was noted. The QoL was assessed with the help of the European Organization for Research and Treatment of Cancer quality of life questionnaire esophageal-specific scales (EORTC QLQ-OES18). The EORTC QLQ-OES18 questionnaire is a 18-item self-rating instrument that aggregates into four multi-item scales of dysphagia (three items), eating (four items), reflux (two items), and pain (three items); and six single-item scales of trouble swallowing saliva, choking, dry mouth, taste, cough, and speech [19].

Sample size calculation

Sample size was calculated on the basis of the prevalence of EC in India and the following formula was used:

$$\frac{Z^2_{1-\frac{\alpha}{2}}p(1-p)}{d^2} = \frac{(1.96)^2 \times 0.042(1-0.042)}{(0.05)^2} = \frac{3.84 \times 0.0402}{0.0025} = 61.75$$

where,

p = prevalence of EC in India = 4.2% [20], d = absolute precision required on either side of the proportion = 5% = 0.05 (2-sided), $Z_{0.025}$ = 1.96 for 95% confidence interval.

Thus, the sample was calculated to be 62. However, considering the drop-out rate of 10%, the sample size obtained was 68, which was rounded off to 70. So, for the present study, the final sample size of 70 was considered.

Statistical analysis

The data was analysed with SPSS (IBM, Armonk, NY, USA) version 23.0 for Windows. Continuous and categorical variables were represented in terms of mean ± standard deviation (SD) and frequency (percentages), respectively. Association between continuous and categorical variables was assessed with independent sample t-test and Chi-Square test, respectively. Change in body weight, dysphagia score, and odynophagia score was assessed with repeated measures ANOVA with post-hoc analysis by Bonferroni's multiple comparison test. Finally, change in QoL scores in the EORTC QLQ-OES18 questionnaire was assessed with a paired t-test. A two-tailed probability value of < 0.05 was considered as statistically significant.

Results

Out of 70 patients, 3 were lost to follow-up. Of these 3 patients, 2 did not have any improvement in dysphagia and odynophagia and, thus, declined to continue the study after 1st follow-up visit (1st month). While, the remaining 1 patient had moved to another state and, thus, could not come for the follow-up after the 2nd month. Intention-to-treat analysis was performed and last observations of all these 3 patients were carried forward. Thus, the number of patients under analysis remained 70.

The majority of the patients were males (54.29%) and belonged to the age group of 51–60 years (34.29%). The male to female ratio was 1.2. In males, majority of the patients belonged to the age group of 61–70 years (39.47%) followed by 51–60 years (34.21%). While, in females, majority of the patients belonged to the age group of 51 – 60 years (34.38%) followed by 41–50 years (31.25%). There was no significant difference between the genders in terms of age distribution (p-value = 0.266). Though the mean age of males was numerically older than females, there was no significant difference between them (p-value = 0.147). Similarly, the mean time to diagnosis (TTD), and time to treatment (TTT) was numerically longer in females, but it did not reach a statistically significant level (p-values = 0.817, and 0.527, respectively). There was no significant difference between the genders in terms of location, length, and stage of tumor (TNM classification) (all p-values > 0.05). Compared to females, a significantly greater number of males were found to be addicted to tobacco (p-value < 0.0001) and alcohol (p-value < 0.0001) (Tab. 1).

Over the study period, the mean body weight was found to be significantly increased (p-value < 0.0001). On post-hoc analysis, a significant increase in body weight was observed between baseline and 1st month, baseline and 2nd month, baseline and 3rd month, 1st and 2nd month, 1st and 3rd month, and 2nd and 3rd month (all p-values < 0.0001)

Table 1. Comparison of demographic characteristics

Characteristics	Male (Nn = 38)	Female (n = 32)	p-value
Age [years]	56.82 ± 8.81	53.50 ± 10.11	0.147*
Age groups (years)			
31–40	4 (10.53%)	4 (12.50%)	0.266#
41–50	5 (13.16%)	10 (31.25%)	
51–60	13 (34.21%)	11 (34.38%)	
61–70	15 (39.47%)	6 (18.75%)	
71–75	1 (2.63%)	1 (3.12%)	
Location of tumor in thoracic esophagus			
Middle thoracic	25 (65.79%)	23 (71.88%)	0.286#
Middle + upper thoracic	2 (5.26%)	4 (12.50%)	
Middle + lower thoracic	11 (28.95%)	5 (15.62%)	
Length of tumor (cm)	7.49 ± 1.49	7.51 ± 1.29	0.967*
Stage of tumor			
T category			
T3	11 (28.94%)	12 (37.50%)	0.128#
T4a	17 (44.74%)	7 (21.88%)	
T4b	10 (26.32%)	13 (40.62%)	
N category			
N1	5 (13.16%)	5 (15.63%)	0.930#
N2	12 (31.58%)	9 (28.12%)	
N3	21 (55.26%)	18 (56.25%)	
M category			
M0	20 (52.63%)	12 (37.50%)	0.236#
M1	18 (47.37%)	20 (62.50%)	
Time to diagnosis [months]	2.61 ± 1.33	2.69 ± 1.64	0.817*
Time to treatment [days]	14.74 ± 10.75	16.88 ± 17.11	0.527*
Addiction			
Tobacco	35 (92.11%)	8 (15%)	< 0.0001#
Alcohol	24 (63.16%)	0 (0.00%)	< 0.0001#

*Independent sample t-test; #Chi-Square test; p-value < 0.05 was considered as statistically significant

(Fig. 1). Similarly, significant decrease in mean dysphagia and odynophagia score was observed (p-value < 0.0001). On post-hoc analysis, significant decrease in dysphagia (Fig. 2) and odynophagia score (Fig. 3) was observed between baseline and 1st month, baseline and 2nd month, baseline and 3rd month, 1st and 2nd month, 1st and 3rd month, and 2nd and 3rd month (all p-values < 0.0001).

Finally, the change in QoL scores was evaluated. At the end of study i.e., 3 months, there was a significant decrease in dysphagia (p-value < 0.0001), eating (p-value < 0.0001), reflux (p-value = 0.005), pain (p-value < 0.0001), and saliva (p-value = 0.01) domains. A slight decrease in the mean choking, and dry mouth domains was observed, but it did not reach a statistically significant level (both p-values > 0.05). However, a slight increase in the mean taste, cough, and speech domains was observed, but it did not reach a statistically significant level (all p-values > 0.05) (Tab. 2). None of the patients reported any RT-related toxicity. Moreover, none of the patients required a subsequent stent or feeding tube placement.

Discussion

The principal findings of the present study suggest that EBRT results in a significant decrease in

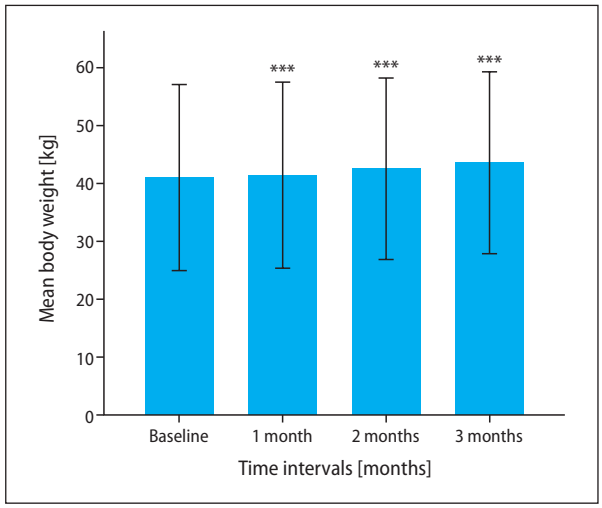

Figure 1. Change in mean body weight over the study duration. *Repeated measures ANOVA followed by post-hoc analysis by Bonferroni's multiple comparison test; ***< 0.0001 was considered as statistically significant

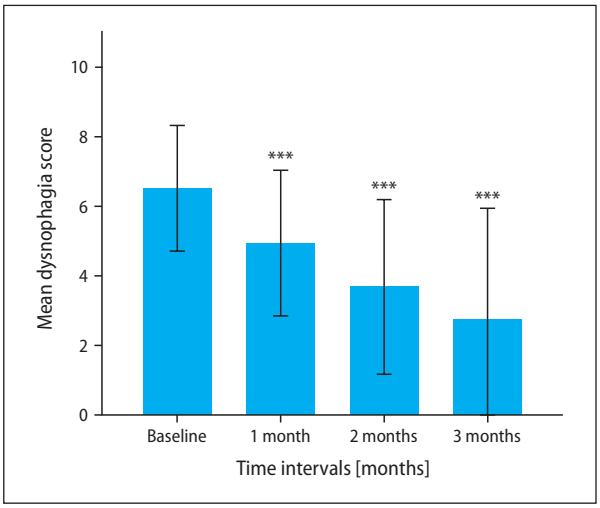

Figure 3. Change in mean odynophagia score over the study duration. *Repeated measures ANOVA followed by post-hoc analysis by Bonferroni's multiple comparison test; ***< 0.0001 was considered as statistically significant

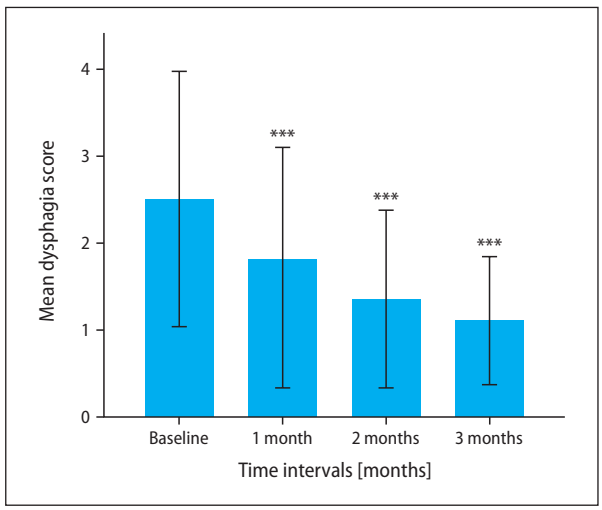

Figure 2. Change in mean dysphagia score over the study duration. *Repeated measures ANOVA followed by post-hoc analysis by Bonferroni's multiple comparison test; ***< 0.0001 was considered as statistically significant

dysphagia and odynophagia scores and simultaneous increase in body weight and QoL score in patients with advanced ESCC.

Dysphagia, an important symptom, is reported in 80–90% of patients with EC [21]. As QoL of these patients is mainly affected by the swallowing and eating problems, the primary aim of the palliative therapy is to relieve dysphagia symptoms. In their study, Murray et al. reported that 75% of the patients with EC had improvement in dysphagia with palliative EBRT (20 Gy in 5 fractions) [22]. In another study, Prasad et al. demonstrated that EBRT (40 Gy in 20 fractions) resulted in a significantly decreased mean dysphagia score and significantly improved mean QoL score at the end of a 6-week follow-up [13]. In their study, Suzuki et al. reported that EBRT [50 Gy (30–60 Gy) with 2.0–3.0 Gy/day, once daily five times a week] led to an improved dysphagia score in 73% of patients. Moreover, they observed that factors such as age less than 67 years at presentation, tumor length less than 7 cm, location in the middle third of the thoracic esophagus were linked to a significant improvement in swallowing scores [23].

In the present study, all the included patients had advanced stage ESCC in the thoracic esophagus, ECOG performance score of 0–2, Grade 3 dysphagia, odynophagia, more than 20% loss of body weight, tumor length of at least 5 cm, and poor prognosis. In these patients, relief of symptoms was a sole reason for which the patients sought treatment. Relief of symptoms with the least possible adverse effects is obtained through RT, as occurrence of adverse effects leads to discontinuation of treatment and decreased QoL. Thus, all the patients were treated with a palliative intent.

As per available literature, curative chemoradiotherapy (CRT) is ideal for patients with unresectable EC that has not yet metastasized, with significantly better local control and overall survival

Table 2. Change in quality of life (QoL) scores over the study duration

Characteristics	Baseline	3rd month	p-value*
Dysphagia	51.56 ± 9.29	48.23 ± 9.57	< 0.0001
Eating	35.80 ± 6.42	34.28 ± 6.75	< 0.0001
Reflux	37.14 ± 4.73	36.50 ± 4.65	0.005
Pain	24.81 ± 4.62	23.31 ± 4.67	< 0.0001
Saliva	28.53 ± 4.91	28.04 ± 5.01	0.010
Choking	25.98 ± 4.54	25.78 ± 4.76	0.199
Dry mouth	39.46 ± 8.52	38.93 ± 9.33	0.387
Taste	33.64 ± 6.82	33.73 ± 6.73	0.584
Cough	44.41 ± 7.99	44.53 ± 8.23	0.822
Speech	27.43 ± 5.25	27.74 ± 5.33	0.105

*Paired t-test; p-value < 0.05 was considered as statistically significant

advantages than RT alone [24–26]. In the present study, majority of the patients had metastatic disease (54.29%). Moreover, a recent randomized controlled trial by Penniment et al. compared RT alone with CRT for dysphagia relief in a palliative setting. They demonstrated that the use of CRT results in non-significantly better complete dysphagia relief; however, it was associated with non-significantly higher risk of undergoing additional treatment and significantly greater incidence of grade 3–4 adverse events [27]. Based on these findings, RT alone is a better approach for palliation of dysphagia and improving QoL.

In the present study, each patient received EBRT in a dose of 30 Gy in 10 fractions and none of them required retreatment with RT or stent placement during the study period. Walterbos et al. evaluated the palliative dose of EBRT and compared 3 EBRT schedules (20 Gy in 5 fractions, 30 Gy in 10 fractions, or 39 Gy in 13 fractions) for symptom control. They reported symptomatic improvement in 72% of patients with no differences between the schedules. However, higher dose schedule was found to be associated with longer overall survival and longer time to second intervention [28], thus supporting the findings of the present study.

Some of the studies have compared EBRT with BT and reported better outcomes with EBRT. van Rossum et al. compared patient-reported outcomes (PROs) after EBRT (20 Gy in 5 fractions) and BT (single-dose 12 Gy). At 3 months, treatment with BT resulted in a significant deterioration in functioning (i.e. physical, role, social), loss of appetite, pain, and altered taste sensation, while those treated with EBRT had deterioration only in role functioning, and had a significant improvement in dysphagia and odynophagia. Comparison of both treatments revealed mostly comparable changes in PRO, but significantly favored EBRT in terms of nausea, vomiting, pain, and appetite loss [16]. In another study, Jeene et al. compared the outcome with EBRT (5 fractions of 4 Gy) and intraluminal BT (single dose of 12 Gy). Significantly greater proportion of patients reported improvement in dysphagia with EBRT. Moreover, greater proportion of patients with dysphagia reported early initiation and peak effect of EBRT than BT [15].

The long-term efficacy of RT in palliation of dysphagia was reported by Hanna et al. They compared stenting with EBRT and reported that stenting resulted in earlier relief in dysphagia (first 2 weeks), but led to recurrent dysphagia in a significant number of patients after 10 weeks. Whereas RT had slow onset of action; but after 10 weeks, dysphagia was relieved in a significantly greater number of patients [29]. Thus, palliative RT resulted in a significant relief in dysphagia and improved QoL in patients with incurable and advanced ESCC and findings are comparable to those observed in literature.

In the present study, there was a significant increase in body weight over the study duration and the mean rise in body weight was 2.54 ± 0.25 kg. Similar to the present study, following RT, Fleischman et al. reported a mean rise in body weight by 1.5 kg [30]. In another study, Murray et al. used palliative EBRT (20 Gy in 5 fractions) in patients with incurable EC and reported that 25% of patients

gained weight [22]. In the present study, there was a significant decrease in odynophagia score over the study duration. Similarly, Welsch et al. reported a statistically significant improvement in the odynophagia score [14]. Review of literature revealed that gain in body weight and relief in odynophagia following palliative EBRT is seldom studied. Thus, findings of the present study add to the existing knowledge regarding the effect of EBRT on body weight and odynophagia in patients with advanced stage ESCC.

In the present study, the mean TTD was 2.64 ± 1.46 months. Similarly, in a study by Wang et al., mean duration between the first symptom and first contact with health-care system was 2 months and that between the first contact and histological diagnosis was 0.6 month. Thus, the total mean duration between the first symptoms and diagnosis was nearly equal to that observed in the present study [31]. In a study by Cavallin et al., the median TTD was 90 (60–150) days. In their study, out of 3613 symptomatic EC patients, 1201 patients were not considered resectable due to advanced stage. TTD was not associated with resectability. However, longer TTD was an independent predictor of severe malnutrition at diagnosis [32]. In the present study, though TTD was less than that reported by Cavallin et al., all the patients were in advanced stage of EC and, thus, were considered for RT. The reason for the delay in the diagnosis was patients' negligence toward their symptoms, as most of the patients were from remote rural areas.

In the present study, the mean TTT was found to be 15.71 ± 13.95 days. The reason for this delay could be negligence towards the symptoms and trial of alternative medicine such as traditional medicines, quack treatment, etc. A study by Grotenhuis et al. reported a median duration between diagnosis and initiation of treatment of 53 days (5–175) [33]. In another study, Rothwell et al. reported the delay in treatment initiation in terms of symptoms. They observed a median delay of 15 weeks for patients with dysphagia, and 17 weeks for patients with other symptoms. The most common reason for delay was late presentation to the family doctor (44%) [34]. However, in the present study, the shorter interval between diagnosis and initiation of treatment could be due to an advanced nature of the disease and worsened symptoms at presentation. This might have resulted in patients seeking the treatment on a relatively emergency basis.

The present study had several limitations. Firstly, this was a single centre study with limited sample size, therefore, these findings cannot be generalized. Secondly, limited risk factors (such as smoking and alcohol) associated with ESCC were studied. Thirdly, symptom free survival and overall survival was not evaluated. Fourthly, due to limited follow-up period, long-term outcome and complications of RT could not be assessed. Finally, residual disease at the end of study was not quantified.

Apart from the limitations, some of the strengths of the study were: Firstly, use of specific 18-item EORTC QLQ-OES questionnaire for quantifying the change in QoL. Secondly, the study findings related to change in body weight and odynophagia add to the existing literature. Thirdly, inclusion of patients with ECOG performance score of 0–2 suggests that patients were ambulatory and capable of self-care and, thus, ideal candidates for a follow-up study. Finally, lack of adverse events at the dose used suggests an acceptable toxicity profile of EBRT.

Conclusion

In patients with advanced ESCC, EBRT leads to significant decrease in dysphagia and odynophagia. Moreover, significant increase in body weight is also observed in these patients due to increased appetite and decreased pain during swallowing. All these changes collectively result in improved QoL. Due to limited toxicity and advantages in logistics, EBRT should be the palliative therapy of choice in ESCC patients presenting with dysphagia and decreased QoL.

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Conflict of interest

Authors declare that they have no conflict of interest.

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