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Palliative Radiotherapy in Esophageal Cancer

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Abstract The present study was undertaken to evaluate the efficacy of radiotherapy in palliation of dysphagia in patients with squamous cell carcinoma (SCC) of esophagus and to see the quality of life (QoL) following radiotherapy. This was a prospective clinical study done between September 2006 and May 2008. All consecutive patients with SCC of the esophagus, who are not candidates for definitive treatment, were included in the study. Dysphagia and QoL were assessed using modified Takita's grading and modified questionnaire based on EORTC QLQ 30 respectively. External beam radiotherapy (EBRT) was delivered to all patients using linear accelerator 6 Mv photons. Patients who had good response with EBRT were further subjected to intraluminal brachytherapy (ILBT) at 700 cGy using Iridium-192. The cumulative dose each patient received was 65 Gy. Patients were followed up at 6 weeks from completion of treatment to look for any difference in dysphagia grade and QoL following therapy. Thirty-three patients were included in the study. The mean age among males and females was 60.9 and 49.8 years, respectively. Nineteen patients (57.6 %) received EBRT followed by ILBT; the remaining patients received only EBRT. Seven were lost during follow-up, and seven (21.2 %) died during the study period of 6 weeks. Nineteen (57.6 %) were followed up. On follow-up endoscopy, evidence of residual stricture was observed in 57.9 %, and growth in 36.8 %. Of the patients, 27.8 % had biopsy-confirmed residual disease. The median dysphagia score decreased from 4 to 3 after treatment ($p=0.002$) in 17 (89.5 %) patients. The mean QoL score improved from 107.5 to 114.1 at 6-week follow-up. Following radiotherapy, 26.3 % had persistent chest pain, increased cough with expectoration in 15.8 %, and hyperpigmentation of skin in 10.5 %. Radiotherapy gives significant relief of dysphagia and improves QoL in 90 % of patients with SCC of esophagus. However, following radiotherapy, a number of patients will have persistent stricture, ulceration, and residual disease.

Keywords Squamous cell carcinoma of esophagus · Dysphagia score · Quality of life · External beam radiotherapy · Intraluminal brachytherapy

Introduction

Esophageal cancer is the most frequent malignancy worldwide and the sixth leading cause of cancer-related deaths [1]. Squamous cell carcinoma (SCC) continues to be more prevalent in Asia, particularly in Indian subcontinent [2, 3]. A significant number of patients present with locally advanced or metastatic disease and are considered suitable only for palliative treatment [4, 5]. Radiotherapy is one of the main palliative approaches in patients with dysphagia. As limited reports are available documenting the efficacy of radiotherapy in carcinoma of esophagus from this part of the country, the present study was undertaken to evaluate the efficacy of radiotherapy in palliation of dysphagia in patients with SCC of esophagus and to see the quality of life (QoL) following radiotherapy.

Methods

This was a prospective clinical study done in the Departments of Surgery and Radiotherapy, between September 2006 and

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Table 1 Patient characteristics

Characteristics	Number
Number of patients	33
Age (years)	
Mean (SD)	56.8 (10.3)
Median (range)	60 (35–78)
Male/female ratio	1.8:1
Level of growth, *n* (%)	
Upper	3 (9.1)
Middle	13 (39.4)
Lower	17 (51.5)
Symptoms at diagnosis, *n* (%)	
Dysphagia	32 (97)
Loss of appetite	3 (9.1)
Loss of weight	8 (24.2)
Chest pain	5 (15.2)
Vomiting after food	6 (18.2)
Regurgitation of feeds	5 (15.2)
Odynophagia	1 (3)
Hoarseness of voice	1 (3)
Hiccups	1 (3)
Cough with expectoration	1 (3)
Neck swelling	1 (3)
Treatment, *n* (%)	
EBRT+ILBT	19 (57.6)
EBRT	14 (42.4)
Patients for follow-up, *n* (%)	19 (57.6)

EBRT external beam radiotherapy, *IBRT* intraluminal brachytherapy

May 2008, after obtaining clearance from the Institute Ethics Committee. All consecutive patients with SCC of esophagus who were not candidates for definitive treatment modality (surgery/chemo-radiotherapy), either due to advanced disease or poor general condition underwent radiotherapy. Patients with tracheo-esophageal fistula and those unfit for radiotherapy (Karnofsky performance status score <60 %) were excluded [6]. Informed consent was obtained. Patients were questioned about presenting symptomatology and underwent clinical examination. Relevant investigations such as barium esophagogram and computed tomographic scan were done. The degree of dysphagia and QoL were assessed at diagnosis. Modified Takita's grading used for the assessment of dysphagia has scores from 1 to 6; grade 1, ability to eat normally and grade 6 with absolute dysphagia [7]. The QoL was assessed using modified questionnaire based on the European Organization of Research and Treatment of Cancer (EORTC-QLQ-C30) [8, 9]. The QLQ-C30 contained 30 questions, each carrying score of 1–5. The overall score ranges from 30 to 150. The questionnaire was based on functional (cognitive, emotional, and social) and symptom scale, global health QoL scale, and economic independence.

External beam radiotherapy (EBRT) was delivered to all patients using linear accelerator 6 MV photons. Patients received 40 Gy in 20 fractions, at 200 cGy per fraction, with anteroposterior-posteroanterior field for 5 days a week, with total treatment duration of 4 weeks. A margin of 5 cm was considered both proximal and distal to the tumor. For lower third growth, L-shaped field with inclusion of esophagogastric (OG) junction was delivered with anteroposterior-posteroanterior field. At 1-week interval after completion of EBRT, barium esophagogram was repeated. Patients who had good response with EBRT were further subjected to intraluminal brachytherapy (ILBT). Those who had OG junction involvement were considered for further EBRT using oblique portals to deliver a dose of 24 Gy in 12 fractions, 200 cGy per fraction after careful planning with ASHA treatment planning system. Brachytherapy was delivered using high-dose rate (HDR) Iridium-192 microselectron machine. All patients received two fractions of ILBT at weekly interval. Dose delivered was 700 cGy HDR dose (equivalent to 1,250 cGy of low-dose rate) prescribed at 1 cm around the tumor. Therefore, the cumulative dose to the tumor (EBRT and ILBT) was 65 Gy. Patients with OG junction involvement received 40 Gy by anteroposterior-posteroanterior fields followed by 24 Gy using oblique portals, resulting in a total dose of 64 Gy.

Patients were called for follow-up at 6 weeks from completion of the treatment to look for any difference in dysphagia grade and QoL following the therapy. Upper gastrointestinal endoscopy (UGIE) and biopsy were performed to evaluate residual disease. Patients were also clinically assessed for side effects of radiation.

The Statistical Package for Social Sciences version 10 was used to analyze the data. Wilcoxon signed-rank test was used to compare the difference in median dysphagia scores and paired *t* test to compare mean scores of QoL before and after treatment. A *p* value of less than 0.05 was considered significant.

Table 2 Comparison of dysphagia/QoL score before and after treatment ($n=19$)

		Pre-treatment	Post-treatment	*P* value (CI)
Dysphagia	Median score	4	3	0.002
	Mean score (SD)	4.1 (1.2)	2.4 (1.1)	0.000 (0.89–2.58)
QoL	Median score	106	116	0.014
	Mean score (SD)	107.5 (10.1)	114.1 (7.5)	0.009 (1.91–11.33)

QoL quality of life, *CI* 95 % confidence interval

Results

A total of 33 consecutive patients with SCC of esophagus were prospectively included in the study. Overall, 91 % of the patients had carcinoma of lower and middle third esophagus. Among males, the distal third growth was found to be more common (57.1 %). In females, 58.3 % of the tumors were present in the middle third of the esophagus. Tumors of moderately differentiated type were predominant (60.6 %). Dysphagia was the most common presenting symptom observed in 97 % of patients (Table 1). Of the 33 patients who underwent treatment, 19 (57.6 %) received EBRT followed by ILBT, and the remaining received only EBRT. Seven of the 33 patients were lost to follow-up, and seven (21.2 %) died within the study period of 6 weeks. This left 19 patients (57.6 %) for follow-up.

On follow-up UGIE, 57.9 % had evidence of esophageal stricture. Residual growth was present in 31.6 % of the patients. Esophageal ulceration was seen in 36.8 % of the patients, and nodular appearance of the esophagus was noted in 10.5 %. Endoscopic biopsy confirmed residual disease in 27.8 % of patients.

The median dysphagia score showed a significant decrease from 4 to 3 after treatment (p=0.002) (Table 2). The mean dysphagia score significantly decreased from 4.1 (±1.2) to 2.4 (±1.1) (p<0.001; 95 % confidence interval (CI)=0.89–2.58]. Further analysis on comparison of individual grade of dysphagia before and after treatment was performed (Table 3). At diagnosis, 1 patient had grade I dysphagia, 3 had grade III, 11 had grade IV, and 4 had grade VI dysphagia (absolute dysphagia). Following radiotherapy, dysphagia improved in 17 patients with a response rate of 89.5 %. In 36.8 %, it improved to grade I (able to eat normally), and in 52.6 % to grade III. Fifty-three percent had improvement in dysphagia score by greater than one point (Table 4). The two patients who presented with dysphagia scores of I and III, respectively, worsened to grade IV after treatment.

Table 3 Comparison of dysphagia at each score before and after treatment (n=19)

Dysphagia grade	Pre-treatment		Post-treatment	
	N	%	*N*	%
1	1	5.3	7	36.8
2	–	–	–	–
3	3	15.8	10	52.6
4	11	57.9	2	10.5
5	–	–	–	–
6	4	21.1	–	–

Table 4 Point change in dysphagia score after treatment (n=19)

Point dysphagia score[a]	Number	Percentage
1	7	36.8
2	2	10.5
3	7	36.8
4	–	–
5	1	5.3
−1	1	5.3
−2	–	–
−3	1	5.3

[a] Difference between post-treatment and pre-treatment dysphagia scores

The QoL score varied from 89 to 127 at presentation and improved to 97–128 at 6 weeks follow-up. Post-treatment QoL score was less than 100 in one patient, 100–110 in five, 110–120 in nine, and greater than 120 in four patients. Median QoL score was 106 before and 116 after treatment (p=0.014) (Table 2). The mean QoL score significantly increased from 107.5 (±10.1) to 114.1 (±7.5) (p=0.009; 95 % CI=1.91–11.33).

The complications of radiotherapy were studied at 6 weeks follow-up (Table 5). Esophageal stricture was found in 57.9 % of patients, and persistent chest pain in 26.3 %. Increased cough with expectoration was present in 15.8 %, and hyperpigmentation of skin was observed in 10.5 %. One patient (5.3 %) complained of dry mouth. Over long term, two patients required stenting for esophageal stricture. A patient was found to have tracheoesophageal fistula when he presented 3 months after treatment with respiratory complaints.

Discussion

Prior studies indicate that the median time to respond following radiation therapy in patients with carcinoma of esophagus was around 4 to 5 weeks, hence the rationale for reassessing the patient for dysphagia relief after 6 weeks

Table 5 Adverse effects following radiotherapy (n=19)

Adverse effects	Number	Percentage
Stricture	11	57.9
Chest pain	5	26.3
Hyperpigmentation of skin	2	10.5
Cough with expectoration	3	15.8
Dry mouth	1	5.3
None	2	10.5

in our study [10–12]. The dysphagia scores significantly decreased after radiotherapy in 89.5 % of our patients, with median score decreasing from 4 to 3. Literature search shows varying response rate regarding dysphagia relief following radiotherapy. Caspers et al. reported dysphagia relief of 70.5 % following radiotherapy [13]. A Canadian phase I/II trial that tested the efficacy of accelerated fractionation radiotherapy in the palliation of dysphagia found a response rate of 67 % [10]. Another study from the UK reported improvement in dysphagia in 81.2 % of patients [14]. Dysphagia response following palliative chemoradiation has been reported to vary from 76 to 78 % [15, 16]. Therefore, the dysphagia relief reported presently following isolated radiotherapy was comparable or even better than the response to chemoradiotherapy, but the results should be interpreted considering the small sample size and the absence of long-term follow-up and study on survival, which are the limitations of the present study. More than half (57.9 %) of our patients presented with inability to swallow liquids. In an Australian study, the median score at presentation corresponded to difficulty in swallowing soft food, indicating late presentation of the disease in our patients [15]. Following treatment, dysphagia improved in 89.5 % of our patients. In 36.8 %, it improved to grade I (able to eat normally). In comparison, normal swallowing achieved in the Canadian trial was 43.6 % [10].

The QoL is dependent to a large degree on the ability of swallowing, and the relief of dysphagia is expected to improve the QoL. The present study showed significant increase in mean QoL score of 107.5±10.1 to 114.1±7.5. In the Canadian study that evaluated the accelerated fractionated radiotherapy in palliation of malignant dysphagia, 42 % of patients had improvement in global QoL [10]. Maroju et al. has shown significant rise in median score from 72 before stenting to 107 following self-expandable metallic stent placement for malignant esophageal strictures. Though our study also found a similar significant increase in QoL score following radiotherapy, the absolute increase in score was less compared to the other study [9]. A randomized trial that compared the outcomes of brachytherapy and stent placement found favorable QoL with brachytherapy [17]. More than half of our patients (57.9 %) on follow-up endoscopy showed stricture that was very high compared to the other study from India [18]. Homs et al., in his retrospective analysis, reported complications such as fistula formation and bleeding in 7 % of the patients treated with HDR brachytherapy. Eight percent had retrosternal pain compared to 26.3 % in our study [19].

In conclusion, radiotherapy effectively relieves malignant dysphagia in about 90 % of patients with SCC of esophagus and is useful in the palliation of dysphagia in these patients. It also improves QoL among these patients possibly because of dysphagia relief. However, following radiotherapy, a number of patients will have persistent stricture, ulceration, and residual disease. They may also develop complication of radiotherapy such as chest pain, cough, and radiodermatitis.

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