



Impact of Hypofractionated Radiotherapy in Elderly Inoperable Carcinoma Esophagus Patients on: Dysphagia, Quality of life, and Toxicity profile

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Abstract

Aim: To assess the impact of hypofractionated radiotherapy on Dysphagia relief, to look for the Toxicity profile of the patients and to note the improvement in Quality of life post treatment

Material and Methods: This prospective study was done for two years. Baseline investigations were done. Performance status was assessed using EORTC Performance status. The grade of dysphagia and quality of life were assessed at diagnosis and post treatment. Toxicity was assessed using RTOG criteria. Radiotherapy consisted of EBRT with 35Gy/15 fractions @ 2.33Gy/#, 5 fractions per week by two AP/PA portals.

Results: Of 88 patients were included in the study, 71 patients completed the treatment. All 71(100%) patients had dysphagia relief following radiotherapy. 66 (93%) had grade I dysphagia followed by grade 2 dysphagia which was seen in 5 (7%) patients post treatment. Acute toxicities were seen in 18 (22.5%) patients, of which 11 (61.11%) had Grade I/II toxicity and 7 (38.88%) had Grade 3/4 acute toxicities. Late toxicities were seen in 4 (5.6%) patients. All 4 (5.6%) patients had late esophageal grade III toxicity. There was significant improvement in quality of life post treatment.

CONCLUSION: EBRT remains an effective, non-invasive and well-tolerated means to palliate dysphagia in selected patients with incurable esophageal carcinoma.

Keywords: hypofractionation, esophageal carcinoma, dysphagia, esophagitis, toxicities

Introduction

Cancer Esophagus is the seventh most common cancer worldwide, with an estimated 572,034 new cases in 2018 of which 399,699 in men and 172,335 in women. It's sixth most common cause of death with an estimated 508,585 deaths in 2018 [1]. In India, esophageal cancer is the sixth most common cancer with 52396 new cases diagnosed in 2018 and sixth most common cause of death with 46504 death in 2018 [2].

Squamous cell carcinoma and adenocarcinoma are the two predominant histological subtypes with varying geographical and racial distribution. Globally, squamous cell carcinoma remains the most common histological type, as 80% of esophageal cancers occurring in developing countries were squamous cell cancer. In Western countries including North America, Western Europe and Australia, however, adenocarcinoma has become the leading histological subtype[3], corresponding to a rise in the incidence of obesity, gastro-esophageal reflux disease

and Barrett's esophagus. The risk of esophageal adenocarcinoma conferred by Barrett's esophagus depends on factors such as genomic instability, race and gender of the patient

Dysphagia is the most common presenting symptom and is seen in 90% of the patients. Weight loss is seen in 40%-70% and odynophagia in 50% of the patients.

More than 50% of esophagus cancer patients present with locally advanced stage or distant metastases. Dysphagia is the most common symptom, leading to nutritional compromise, pain, reduced performance status and deterioration of quality of life.

Radiotherapy is a potent local treatment option, which can provide symptom relief and prolongation of survival. Its effects were the subject of this study. The primary endpoint of the study was to assess the impact of hypofractionated Radiotherapy on Dysphagia, to look for the Toxicity profile (RTOG CRITERIA) of the patient and to note the improvement in Quality of life(EORTC QLQ – OES18) post treatment

Material And Methods

This study was conducted in the Department of Radiation Oncology at Sher-i-Kashmir Institute of Medical Science, Srinagar, J&K, India.

It was conducted prospectively for 2 years from August 2018 to August 2020 with patients who fulfils inclusion criteria. The study was approved by the ethical committee of Sher i Kashmir Institute of medical sciences, Srinagar.

88 patients fulfilled the inclusion criteria were enrolled in this study.

Inclusion Criteria

1. ECOG PS \geq Grade I
2. Histologically confirmed carcinoma of the esophagus
3. Locally advanced stage III-IV with or without metastatic disease
4. Medically unsuitable for radical treatment
5. Dysphagia score of 1-4
6. Informed written consent

Exclusion Criteria

1. ECOG PS = 0-I
2. Previous radiochemotherapy, surgery

3. Presence of an esophageal fistula
4. Simultaneous other primary cancer
5. Not fit for radiotherapy
6. Stents in situ

Baseline investigations such as History and physical examination, CBC, LFT, KFT, esophagoduodenoscopy, computed tomographic scan were done

The degree of dysphagia and QoL were assessed at diagnosis. Dysphagia was scored from 0 to 4. The QoL was assessed using questionnaire based on the European Organization of Research and Treatment of Cancer (EORTC-QLQ-C30) [8, 9] and EORTC QLQ – OES18. The QLQ-C30 contained 30 questions, each carrying score of 1–4. The overall score ranges from 30 to 120. The questionnaire was based on functional scale, symptom scale and global health QoL scale. The QLQ-OES 18 contained 18 questions, each carrying score of 1-4. It was compartmentalized into six scales which are as follows: Dysphagia Score, Choking & coughing score, Satisfaction score, Dry mouth score, Oesophageal reflux score and Oesophageal pain score.

Toxicity was assessed using RTOG criteria.

Radiotherapy consist of EBRT with 35Gy/15 fractions @2.33Gy/#, 5 fractions per week, 5 days a week by two anteroposterior/posteroanterior portals.

Target volume consist of the primary esophageal tumor with margins of 3 cm in the cranial caudal direction and 1 cm circumferentially.

The response was measured in terms of dysphagia relief at 6 weeks after start of treatment, toxicity profile from start of treatment and improvement in quality of life post treatment.

Results And Observation

A total of 88 patients with carcinoma esophagus were included in the study. Mean age was 69.4 \pm 10.53 (28-90) years as shown in Fig1. There were 43 males (48.9%) and 45 (51.1%) female patients in the study group as shown in Fig 2. 82 (93.2%) patients belong to rural population and 6 (6.8%) belongs to urban population as shown in Fig 3.

Dysphagia was the most common symptom and was seen in all 88(100%) patients followed by, epigastric pain in 18(20.5%), chest pain in 6(6.8%), dyspnea in 5(5.7%), anorexia in 4 (4.5%), weight loss in

2(2.3%), hematemesis in 2(2.3%), melena in 2(2.3%), hoarseness of voice in 1(1.1%), cough in 1(1.1%), hemoptysis in 1(1.1%) and Other symptoms in 6(6.8%) patients as shown in Fig 4.

78(88.6%) patients were Illiterate as shown in Fig 5.

Majority of the patients 62(70.5%) belongs to lower class, 17(19.3%) belongs to Lower middle class and 9(10.2%) belongs to middle class as shown in Fig 6.

77(87.5%) patients were smoker and 11(12.5%) were nonsmoker in our study. Among the smokers 57(64.8%) were hookah smoker, 19(21.6) snuff abusers and 1(1.1%) patient smokes cigarette as shown in Fig 7.

26(20.54%) patients had ECOG PS 2 and 62(70.45%) patients had ECOG PS 3 as shown in Fig 8.

5(5.7%) patients had lesion in cervical esophagus, 12(13.6%) in Upper Thoracic esophagus, 27(30.7%) in mid Thoracic esophagus, 31(35.2) in lower Thoracic esophagus. In Cervical and upper thoracic esophagus 1(1.1%), Upper and mid thoracic esophagus 4(4.5%), Mid and lower thoracic esophagus 7(8.0%) and Upper, mid and lower thoracic esophagus 1(1.1%) as shown in Table 1.

Squamous cell carcinoma was seen in 85(96.6%) study patients, Adenocarcinoma in 2(2.3%) and Adenosquamous carcinoma in 1(1.1%) patient as shown in Fig 9.

42(47.7%) patients had metastasis at presentation and 46(52.3%) patients were non metastatic at presentation as shown in Fig 10

Majority of the patients 47(53.4%) had grade 3 dysphagia at presentation, 34(38.6%) had Grade 2 and 4(8%) had grade 4 dysphagia at presentation as shown in Fig 11

70(79.5%) patients completed the prescribed treatment without break, 1(1.1%) completed the treatment with breaks. In 8(9.1%) patients treatment was not started. In 9(10.2%) patients treatment was not completed as shown in Fig 12.

Dysphagia grade of study patients after treatment at six weeks is shown in Fig13.

71 patients who completed the prescribed treatment all show improvement in the dysphagia grade and it was statistically significant as shown in Fig 14.

Quality of life scale (EORTC QLQ-C30; Version 3) is summarized in Fig 15. The scale is compartmentalized into functional scales, symptom scales and a global health status / QoL scale. Decreased score after intervention was deemed good response in functional and symptoms scale and increase score in global health status was deemed good response. The improvement in global health status, physical functioning, role functioning, emotional functioning, social functioning, fatigue, nausea and vomiting, pain, insomnia, diarrhea and financial difficulties were statistically significant.

Quality of life scale pertaining to CA esophagus (EORTC QLQ-OES18) is summarized in Fig 16. It is also compartmentalized into six scales which are as follows: Dysphagia Score, Choking & coughing score, Satisfaction score, Dry mouth score, esophageal reflux score and esophageal pain score. Improvement of score in dysphagia scale was deemed positive response while decreased score after intervention was deemed good response in other scales. The improvement in dysphagia score and decreased in satisfaction score and esophageal pain score after treatment were statistically significant.

19 patients developed acute toxicities. 12(16.8%) patients had acute esophageal toxicities, 3(4.2%) patients with acute upper GI, 2(2.8%) patients had acute heart, 1(1.4%) patient had acute haematological toxicity and 1(1.4%) patient had acute lung toxicity as shown in Fig 17.

Late toxicities were seen in 6 patients. 5(7%) patients had late esophageal and 1(1.4%) patient had late lower GI toxicity as shown in Fig 18

At the completion of this study after 2 years, 55(68.75%) patients had expired and 25(31.25%) patients were still alive.

Discussion

The prognosis for patients with carcinoma of the esophagus remains poor despite recent advances in combined-modality therapies. More than 50% of esophageal cancer patients present with locally advanced stage or distant metastases with tumor related symptoms and/or poor general condition [4,5]. The most common cancer related complication in these patients is dysphagia with an increasing rate as the disease progresses, leading to nutritional compromise, pain, reduced performance status and

deterioration of quality of life[6,7]. Many of these patients with severe clinical symptoms are not fit enough to undergo surgical re-section or curative radiochemotherapy [8,9]. The latter approaches are not suitable for patients with distant metastases either [10]. In symptomatic patients, long-term palliation of dysphagia is an important goal of therapy. Recent literature reported that radiation increased the expression of cancer stem cells markers for radiation resistance which could lead to the local failure [11-13]. Trials have indicated hypofractionated radiation offered a clear advantage over conventional radiation, especially in local control [11-14].

A HRT schedule delivers a dose larger than 2 Gy per fraction (with a lower overall dose). Hypofractionation can achieve improved therapeutic index in one of two ways when compared with the conventional fractionated scheme [15]: (i) dose escalation to increase tumor control (ii) maintaining dose equivalence in terms of tumor cure probability while decreasing the normal tissue dose. Number of other advantages is conferred in terms of logistical, patient convenience and resource allocation considerations [16]. Reduced numbers of fractions will reduce radiotherapy costs in terms of work-hours and fewer fractions also results in fewer visits which is more convenient and less costly [17].

In our study, a total of 88 histologically confirmed patients of locally advanced or metastatic carcinoma esophagus were taken.

The mean age was 69.4 ± 10.53 (28-90) years which was in accordance with Indian studies exploring demographic profile of esophageal cancer [18-21]. Esophageal cancer has male predominance with male: female ratio in India being 2.4:1 [22]. But in our study there were 43 males (48.9%) and 45 (51.1%) female patients. This disparity could be explained by the fact that not all patients were included in the study. Only those patients who had locally advanced or metastatic disease with poor PS were included in the study. 82 (93.2%) patients belong to rural population and 6 (6.8%) belongs to urban population.

Dysphagia was the most common symptom and was observed in all 88 (100%) patients in our study which was in accordance with study done by Prasad NRV *et. al.* [23] which also showed dysphagia to be the most common presenting symptom.

62 (70.5%) patients belongs to lower class, 17 (19.3%) belongs to lower middle class and 9 (10.2%) belongs to middle class which is in accordance with the studies done by Khan NA *et. al.* [24] and Dar NA *et.al.* [25]

77 (87.5%) patients were smoker and 11 (12.5%) were non-smoker in our study. This was in accordance with various studies like those done by Khan NA *et.al.* [24], Vaughan *et. al* [26] and Sehgal S *et.al* [19] exploring the etiological factors of esophageal cancer. Among the smokers, 57 (64.8%) were hookah smoker, 19 (21.6) were snuff abusers (naswar) and 1 (1.1%) patient was cigarette smoker.

A significant family history of cancer was present in 7 (8%) patients and was insignificant in 81 (92%) patients in our study. In a study done by Khan NA *et.al.* [24] assessing risk factor for esophageal cancer in Kashmir valley, they found a significant family history of cancer in 27%. This difference between the presence of significant family history of cancer between the two studies can be explained by the fact that in our study we didn't took all esophageal cancer patients but only those who had locally advanced or metastatic disease.

62 (70.45%) patients had ECOG PS 3 and 26 (20.54%) patients had ECOG PS 2 which can be explained by the fact that only those patients with poor PS were included in the study.

5 (5.7%) patients had lesion in cervical esophagus, 12 (13.6%) in Upper Thoracic esophagus, 27 (30.7%) in mid Thoracic esophagus, 31 (35.2) in lower Thoracic esophagus. In Cervical and upper thoracic esophagus 1 (1.1%), Upper and mid thoracic esophagus 4 (4.5%), Mid and lower thoracic esophagus 7 (8.0%) and Upper, mid and lower thoracic esophagus 1 (1.1%). Lower thoracic esophagus was the most common site of carcinoma in our study followed by mid thoracic esophagus which was in accordance with other study done by Prasad NRV *et.al.* [23] in which also lower esophagus was the most common site of carcinoma.

A retrospective study published in 2007 looked at the trends in histology and site-specific distribution of esophageal malignancy between 1989 and 2004 in the state of Tamil Nadu in the Indian subcontinent. This study concluded that esophageal SCC remained the most common esophageal malignancy. In contrast

to reports of increasing incidence of esophageal adenocarcinoma from several countries worldwide, there was no such trend seen in our country. This was irrespective of the site, age, or gender [27]. Same was found in our study with Squamous cell carcinoma seen in 85 (96.6%) study patients, adenocarcinoma in 2 (2.3%) and adenosquamous carcinoma in 1 (1.1%) patient.

There were 42 (47.7%) patients who had metastasis at presentation. Same has been found in studies done by Torre LA, et.al [4] and Parkin DM et.al [5] which also found that more than 50% patients of esophageal cancer are locally advanced or metastatic at presentation. Majority of the patients 47 (53.4%) had grade 3 dysphagia at presentation, 34 (38.6%) had Grade 2 and 4 (8%) had grade 4 dysphagia at presentation. Similar dysphagia score at presentation was seen in the study done by Pinniment MG, et.al [28] in which he compared RT alone with chemoradiotherapy for dysphagia in advanced esophageal cancer.

70 (79.5%) patients completed the prescribed treatment without break, 1 (1.1%) completed the treatment with breaks as patient had severe anaemia and received blood transfusion for the same. In 8 (9.1%) patients treatment was not started. Among these 8, 5 patients died before treatment and 3 patients defaulted. In 9 (10.2%) patients treatment was not completed. Among these 9, 4 patients developed hypotensive shock and sepsis, 2 developed TOF, 1 had obstructive jaundice for which biliary stenting was done, 1 developed hepatic encephalopathy with jaundice and 1 had respiratory distress from the start of treatment which aggravated during treatment.

Studies done by Kassam Z et.al [28], Daly JM et.al [30] and Hayter CR et.al [31] indicated 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 in our study. The dysphagia scores significantly decreased after radiotherapy in 100 % of our patients, with majority of patients i.e. 66 (93%) having grade I dysphagia post treatment and 5 (7%) having grade II dysphagia. The improvement in dysphagia grade was statistically significant. Literature search showed varying response rate regarding dysphagia relief

following radiotherapy. Caspers et al. [32] reported dysphagia relief of 70.5 % following radiotherapy. 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% [29]. Another study from the UK reported improvement in dysphagia in 81.2% of patients [33]. Dysphagia response following palliative chemoradiation has been reported to vary from 76 to 78% [35,36]. Therefore, the dysphagia relief reported presently following isolated radiotherapy was comparable or even better than the response to chemoradiotherapy.

More than half (53.4 %) 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 [34]. Following treatment, dysphagia improved in 100% of our patients. In 93%, it improved to grade I (able to eat solid). In comparison, normal swallowing achieved in the Canadian trial was 43.6% [29].

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 QoL score. There was statistically significant improvement in global health status from 32.8 to 73.9. There was also statistically significant improvement in physical functioning, role functioning, emotional functioning and social functioning. There was statistically significant decrease in symptomology scale. In the Canadian study that evaluated the accelerated fractionated radiotherapy in palliation of malignant dysphagia, 42 % of patients had improvement in global QoL [29]. Maraju et al. [36] has shown significant rise in median score from 72 before stenting to 107 following self-expandable metallic stent placement for malignant esophageal strictures. Our study also found a similar significant increase in QoL score following radiotherapy. A randomized trial that compared the outcomes of brachytherapy and stent placement found favorable QoL with brachytherapy [37].

On comparison by using EORTC OES-18 scale, there was improvement in dysphagia score from 15.3 to 62.9 and decreased in satisfaction score from 23 to 1.2 and esophageal pain score from 14.2 to 0 after

treatment and these were statistically significant. Similar results were found in study done by Kabre RS et.al [38] in which they compared improvement in quality of life using EORTC OES-18 scale in Hypofractionated RT arm and conventional RT arm.

Out of 80 patients in whom the treatment was initiated, 18 (22.5%) patients developed acute toxicities. Almost similar toxicities were seen in a study done by Penniment MG, et.al. [28] in which 16% of patients developed acute toxicities. Of these 18 patients who developed acute toxicities in our study, 11 (61.11%) had Grade I/II toxicity and 7 (38.88%) had Grade3/4 acute toxicities. 11 (61.11%) patients had acute esophageal toxicities. 5 (6.3%) patients had grade I esophageal toxicity in form of mild dysphagia, 3 (3.8%) patients had grade II esophageal toxicity in form of moderate dysphagia, 1 (1.3%) with Grade III toxicity in form of severe dysphagia for which EGD dilatation was done and 2 patients developed grade IV toxicity in form of TOF due to which further treatment was stopped and for feeding Ryle’s Tube was placed. 3 (16.7%) patients developed acute upper GI toxicities grade III. All 3 had haematemesis and malena. 2 (11.2%) patients had acute heart toxicities with 1 having grade II toxicity in form of CCF and anaemia and other having grade III toxicity with pericardial effusion. 1 (5.6%) patient had acute haematological grade II

toxicity in form of anaemia and pedal edema and 1 (5.6%) patient had acute lung grade II toxicity with persistent cough and dyspnea. Late toxicities were seen in 4 (5.6%) patients. All 4 (5.6%) patients had late esophageal grade III toxicity. Out of these 4 patients, 2 developed stricture and two developed severe dysphagia for which SEMS was placed.

At the completion of this study, 55 (68.75%) patients had expired and 25 (31.25%) patients were still alive. Of these 55, 35 (63.63%) were those patients who were metastatic at presentation.

In a study similar to our study done by Penniment MG et al. [28] comparing RT alone (35Gy/15# or 30Gy/10#) with chemoradiotherapy for dysphagia relief, they found palliative chemoradiotherapy showed a modest, but not statistically significant, increase in dysphagia relief compared with radiotherapy alone, with minimal improvement in dysphagia progression-free survival and overall survival with chemoradiotherapy but at a cost of increased toxicity and concluded a short course of radiotherapy alone should be considered a safe and well tolerated treatment for malignant dysphagia in the palliative settings.

These data suggest that short course radiotherapy could be considered in patients with poor PS with incurable esophageal cancer.

Fig 1: Age wise distribution of sample

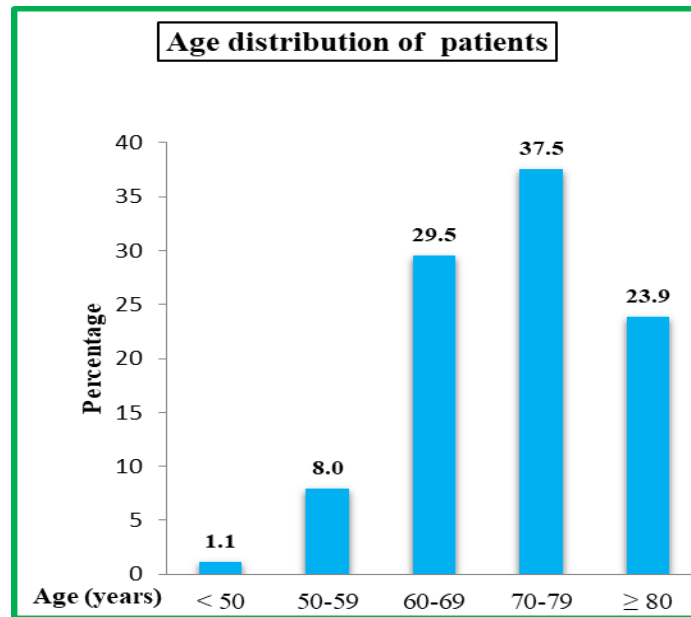


Fig 2: Gender wise distribution of sample

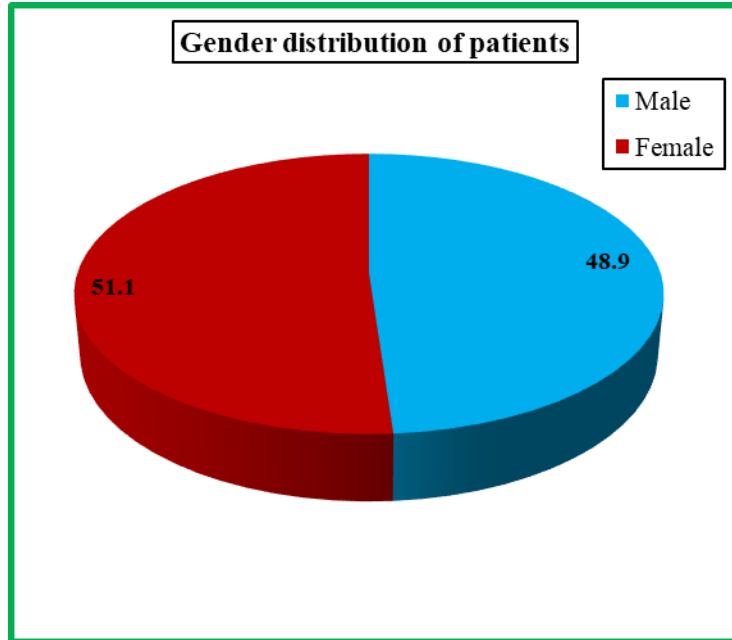


Fig 3: Distribution of patients as per residence

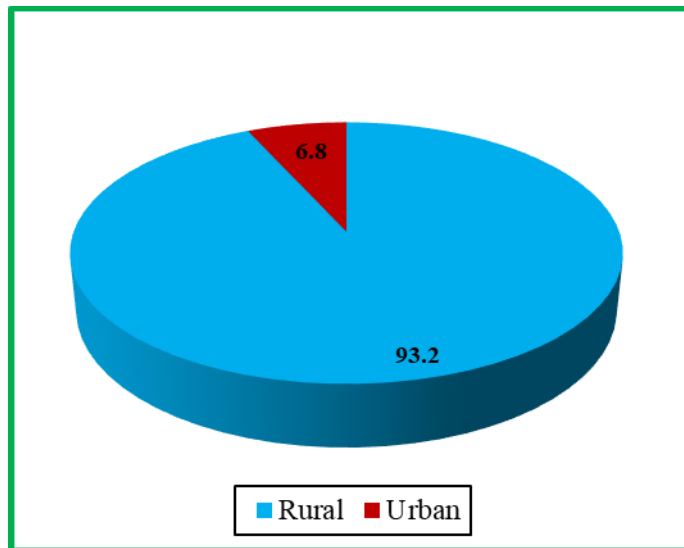


Fig 4: Presenting symptoms of patients

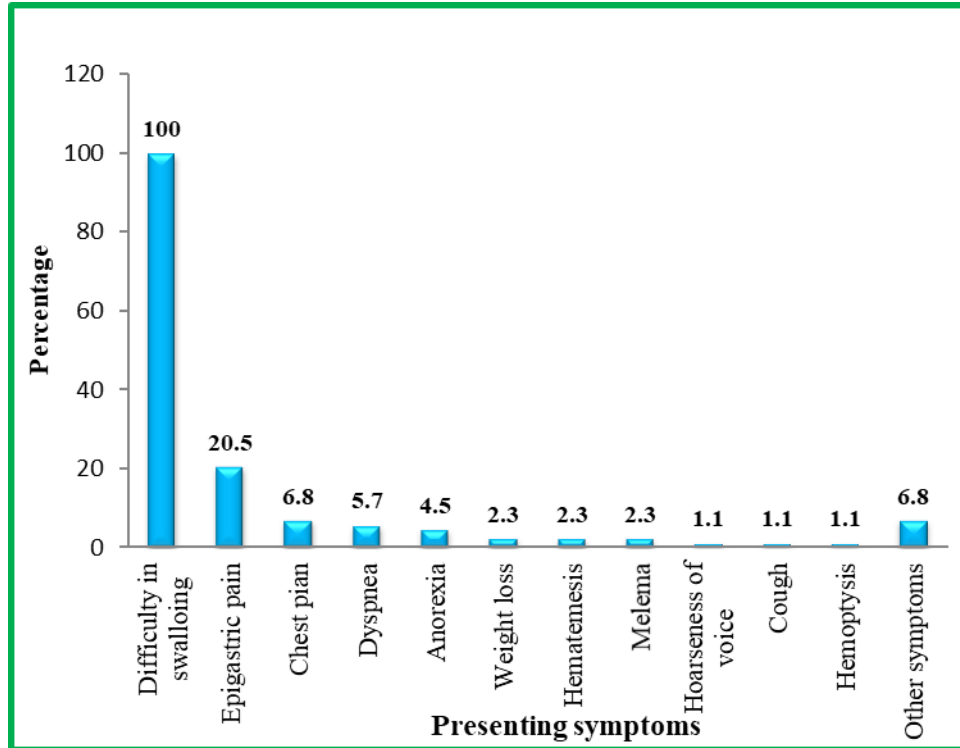


Fig 5: Educational status of patients

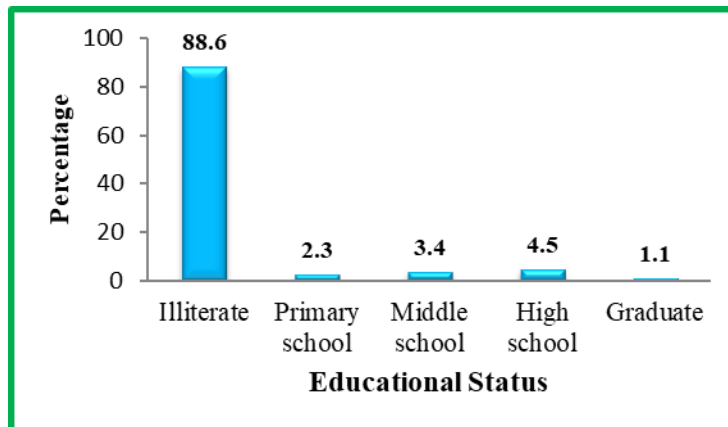


Fig 6: Socioeconomic status of patients

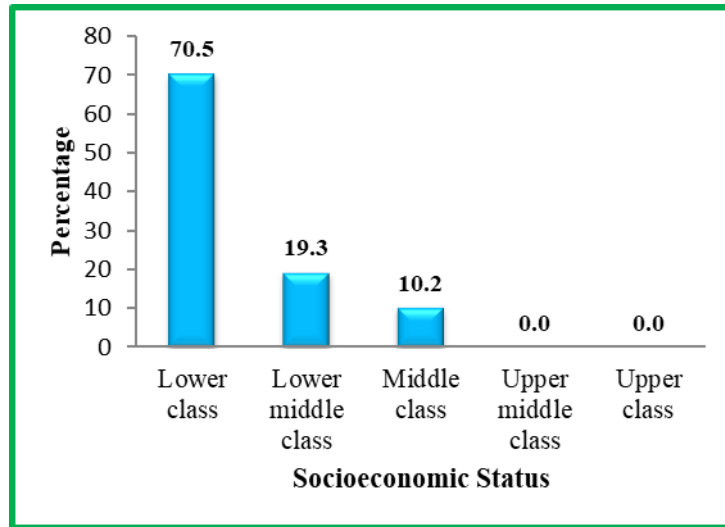


Fig 7: Smoking status of patients

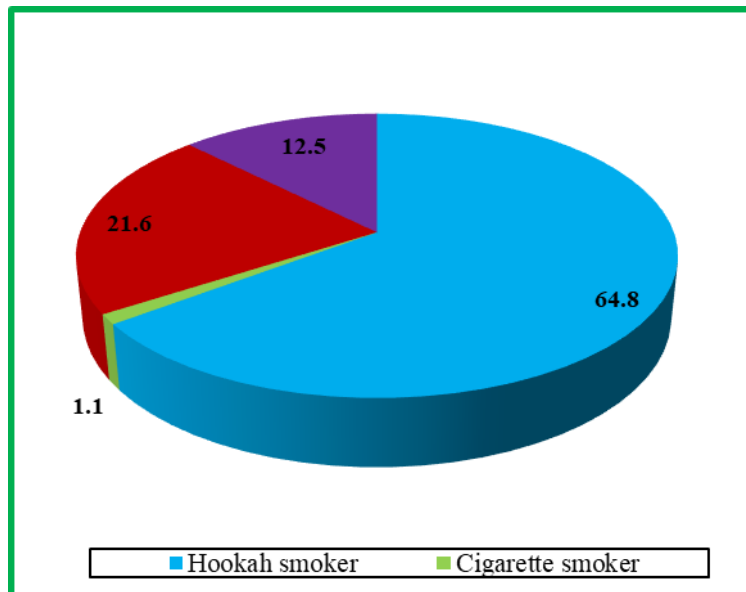


Fig 8: ECOG performance status of patients

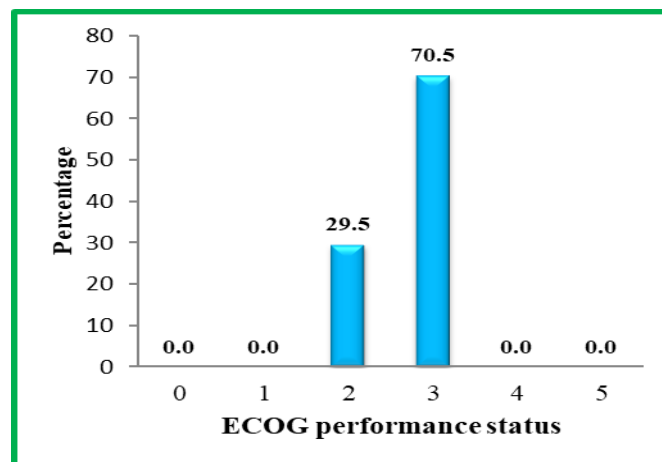


Table 1: Distribution of patients as per location of tumor			
Location of tumor		No. of patients	Percentage
Cervical esophagus		5	5.7
Thoracic esophagus	Upper	12	13.6
	Mid	27	30.7
	Lower	31	35.2
Overlapping	Cervical and upper thoracic esophagus	1	1.1
	Upper and mid thoracic esophagus	4	4.5
	Mid and lower thoracic esophagus	7	8.0
	Upper, mid and lower thoracic esophagus	1	1.1
Total		88	100

Fig 9: Tumor histology in patients

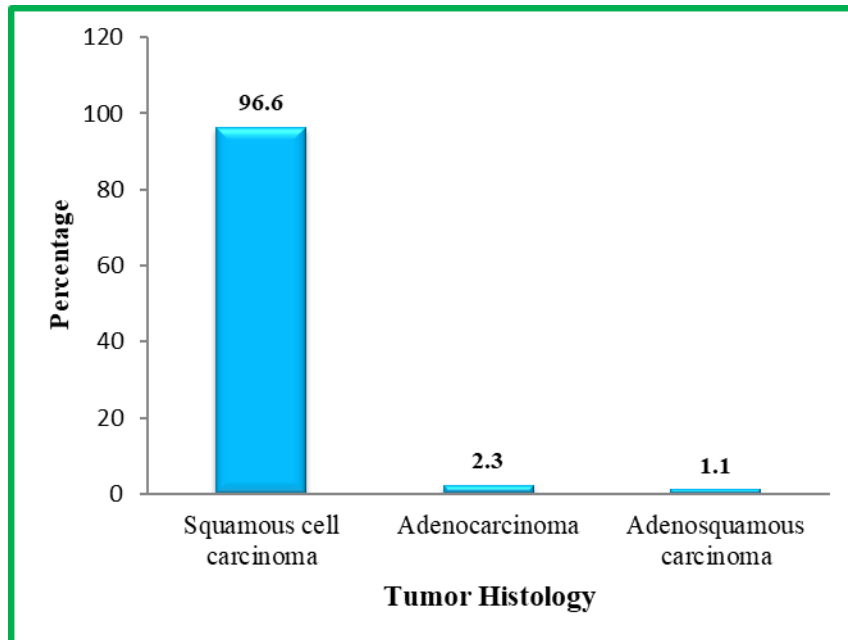


Fig 10: Metastasis at presentation in patients

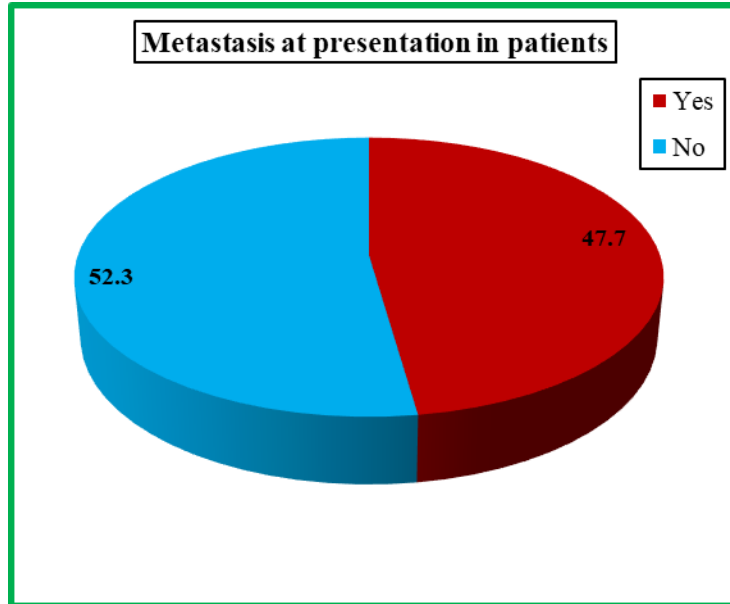


Fig 11: Dysphagia Grade of patients before treatment

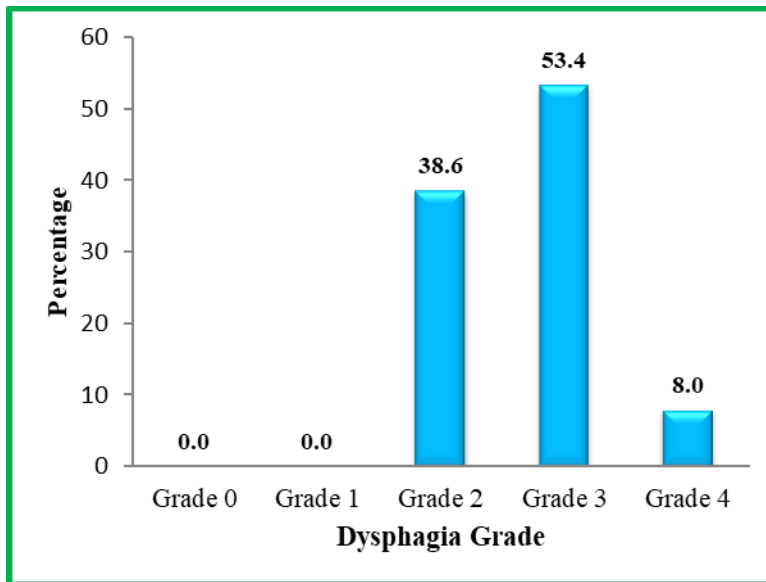


Fig 12: Treatment status of patients

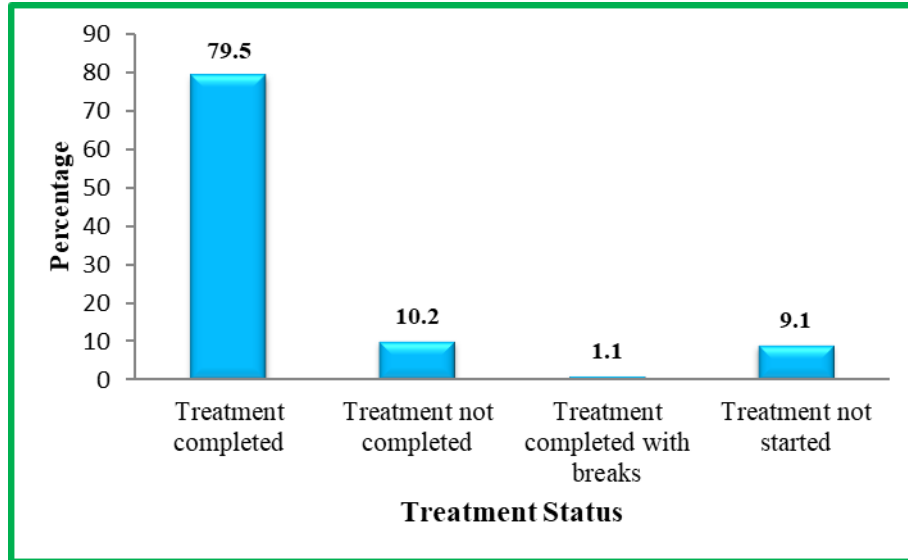


Fig 13: Dysphagia grade of patients at 6 weeks

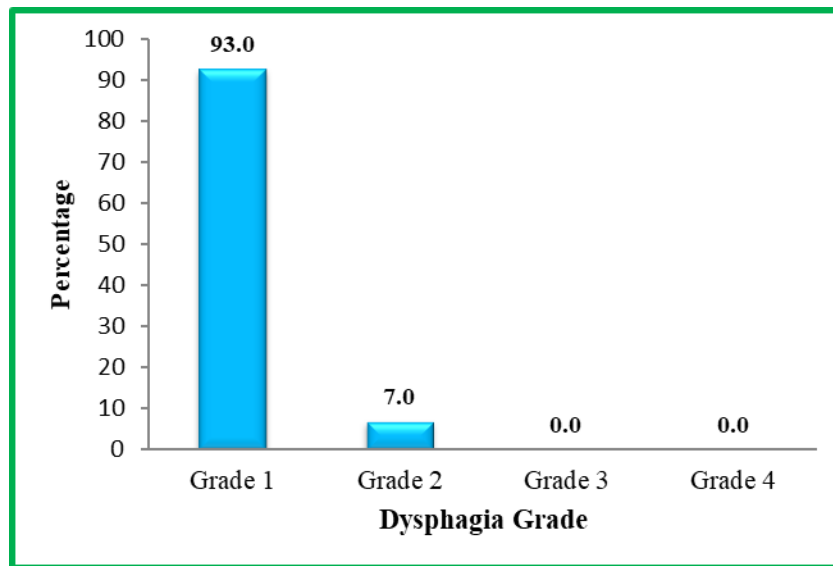


Fig 14: Comparison of dysphagia grade before and after treatment

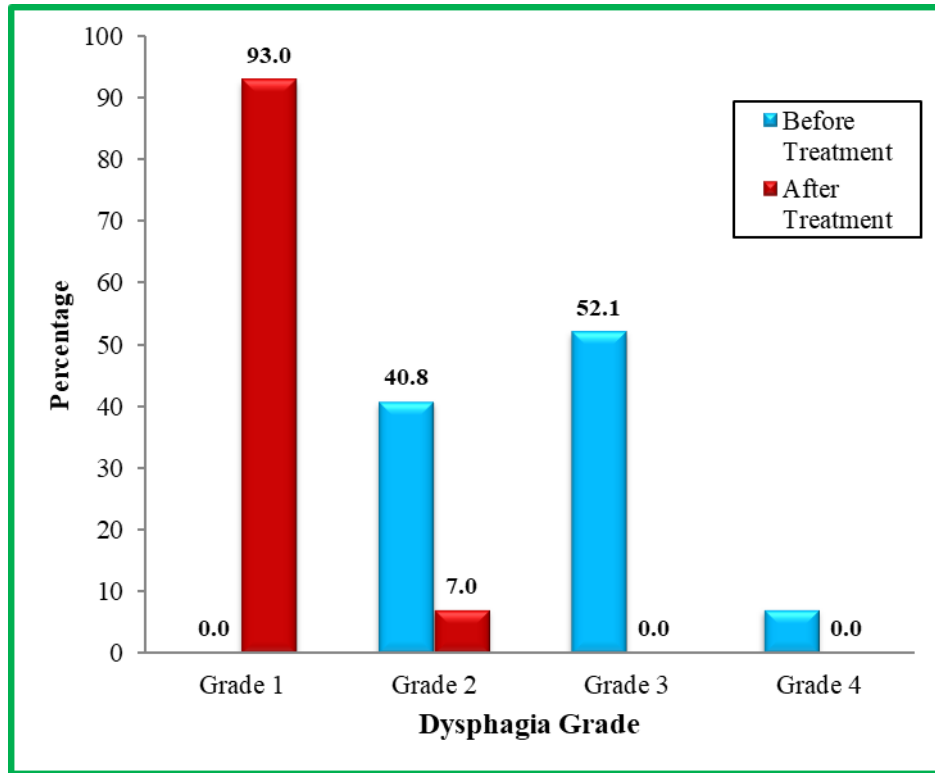


Fig 15: Comparison of improvement in EORTC QLQ-C30 before and after treatment

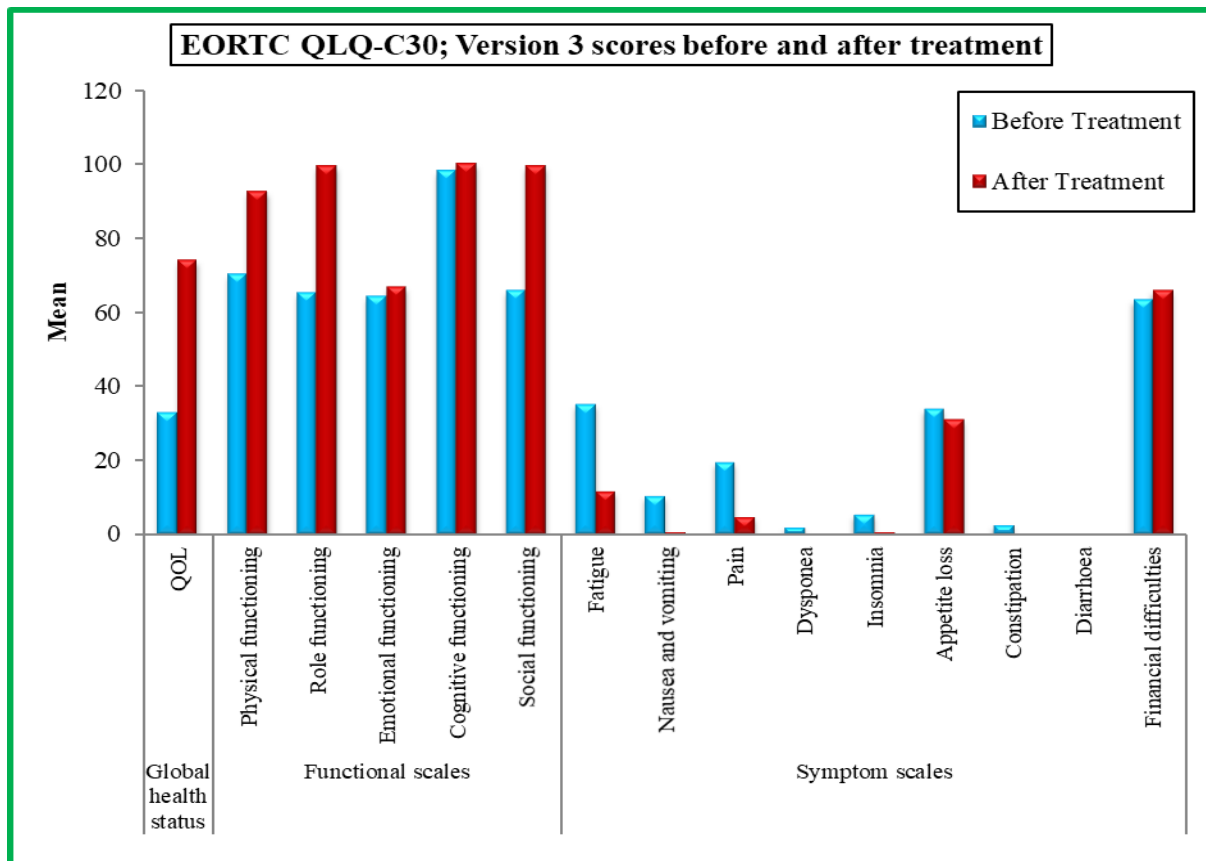


Fig 16: Comparison of improvement in EORTC QLQ-OES18 before and after treatment

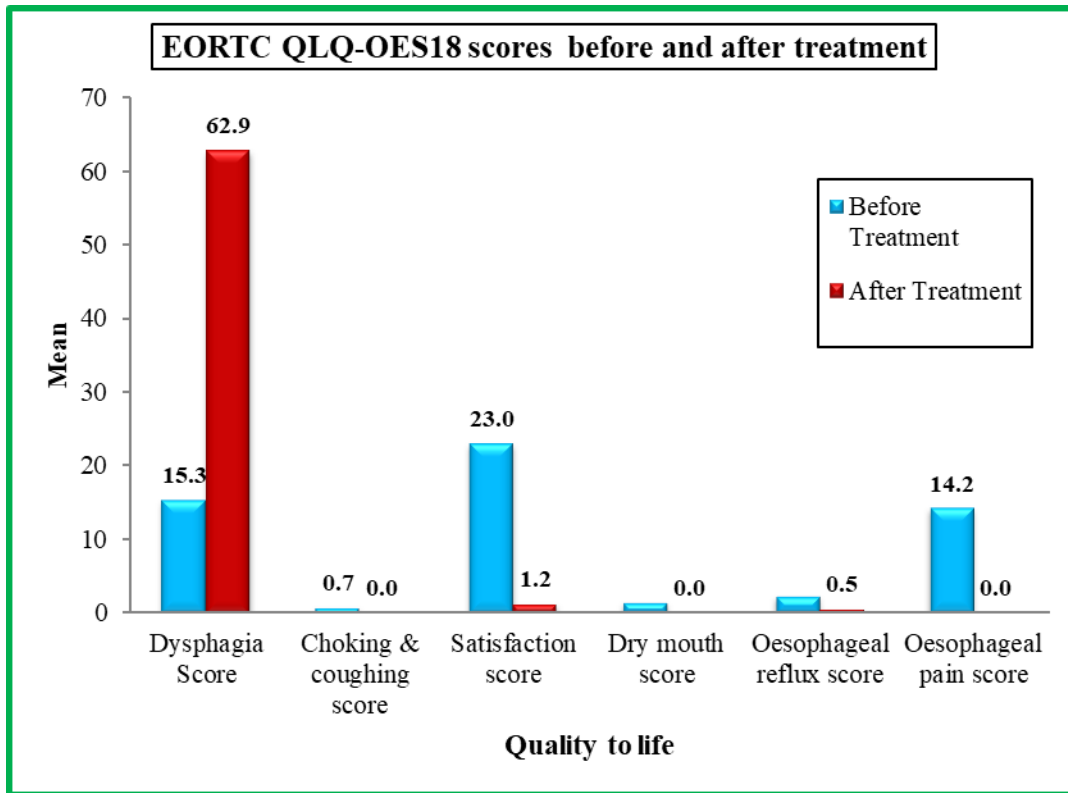


Fig 17: Showing acute toxicities

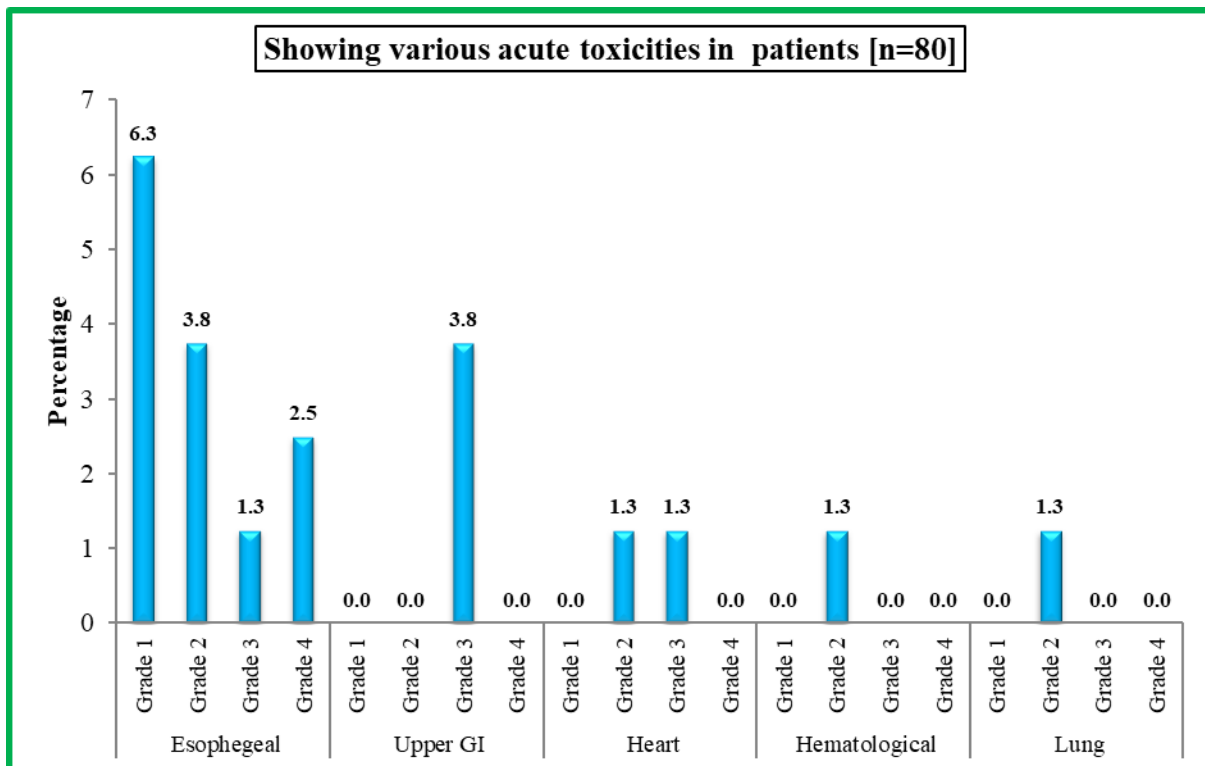


Fig 18: Showing late toxicities

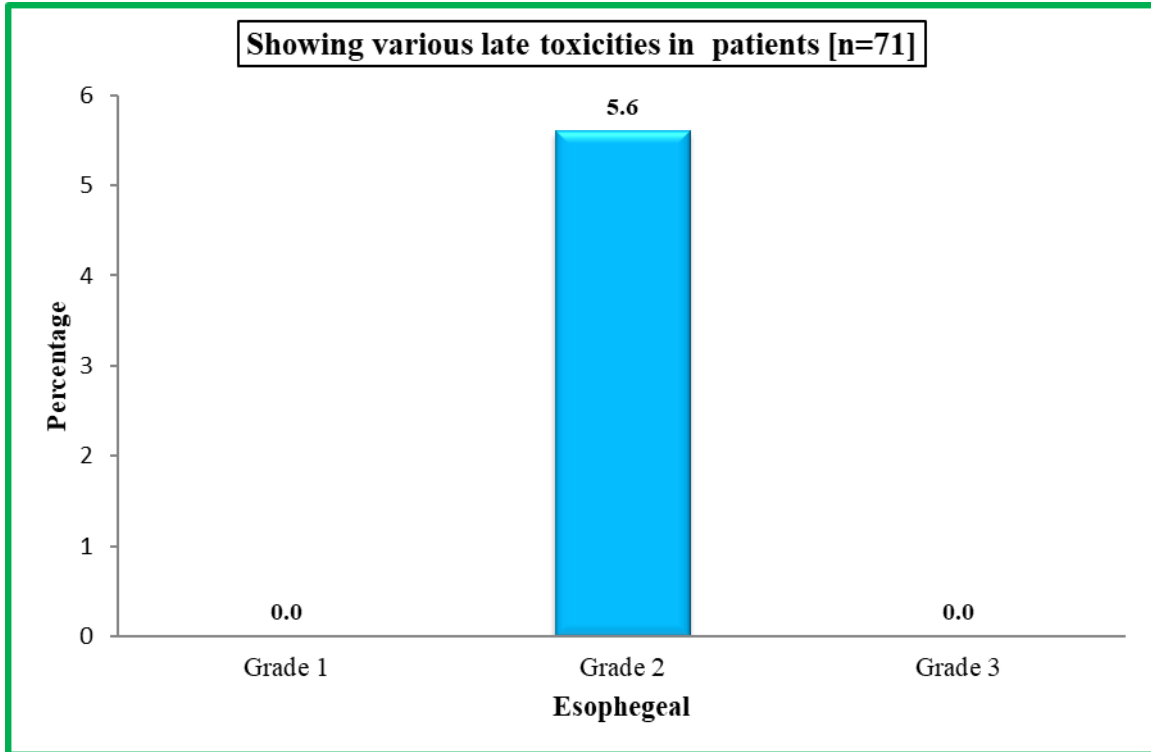
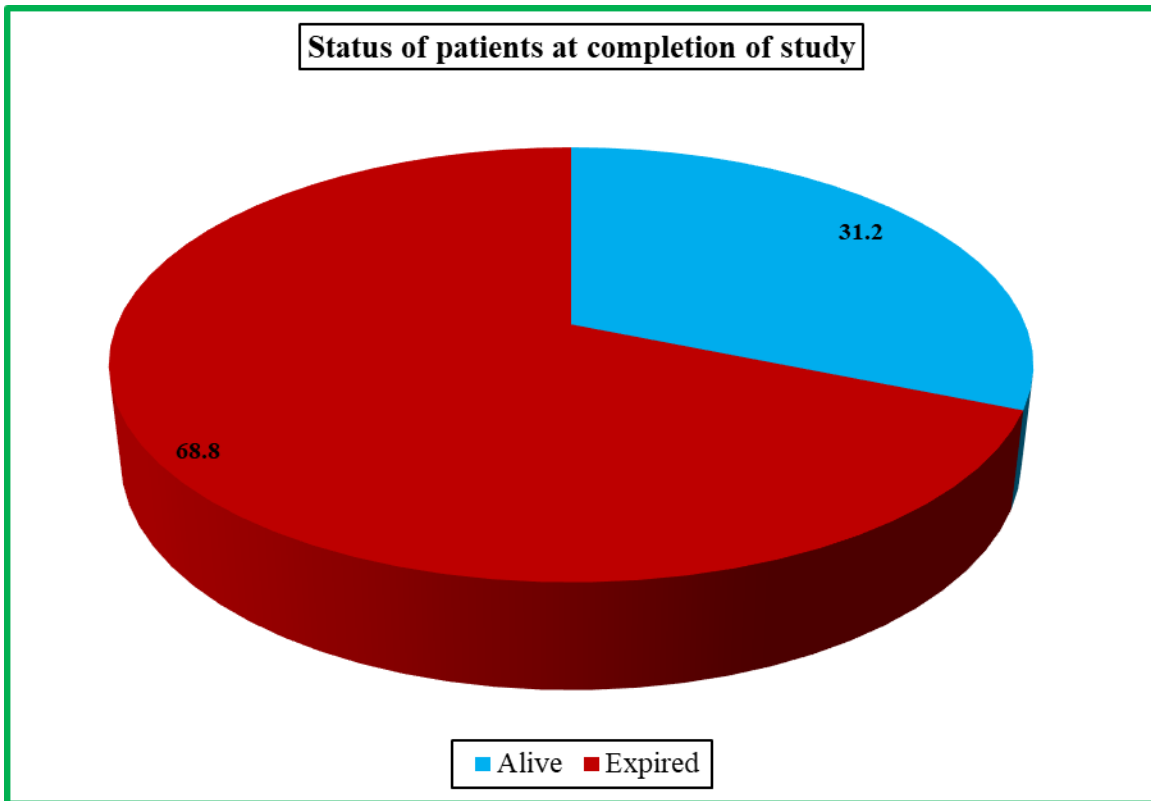


Fig 19 showing status of patients at completion of study



Conclusion

EBRT remains an effective, non-invasive and well-tolerated means to palliate dysphagia in selected patients with incurable esophageal carcinoma.

Hypofractionated regimen delivers a high biological dose in short time, with minimal toxicity, while offering a favourable response profile. This prospective trial shows that a short course of radiotherapy may produce complete relief of swallowing difficulties in a substantial proportion of patients with acceptable toxicity.

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