

## ORIGINAL ARTICLE

# MODERATE HYPOFRACTIONATION RADIATION THERAPY IN ESOPHAGEAL CANCER

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## ABSTRACT

**Background:** Esophageal cancer is an aggressive disease with high mortality, mainly due to late stage diagnosis. Radiation therapy alone cannot cure patients who are either reluctant or medically unfit to receive chemotherapy or surgery. Moreover there is no evident optimal dose fraction schedule to treat these patients. We evaluated the outcomes of these esophageal cancer patients who were treated with moderate hypofractionation radiation therapy alone.

**Method:** This retrospective study was conducted at Department of Radiation Oncology, Ziauddin University Hospital. A total of 52 patients from the year 2011 to 2015 were treated with moderate hypofractionation radiotherapy in two phases. In the first phase 30 Gy in 10 fractions were delivered and in the second phase 20 Gy in 10 fractions were given. We evaluated the treatment outcomes in these patients.

**Results:** There were 27 (51.9%) males and 25 (48.1%) females with a mean age of  $52.78 \pm 14.54$  years. Mortality was observed in 47 (90.4%) patients with overall survival of  $10.51 \pm 1.25$  months. Overall survival was found to be significantly associated with grading ( $p$ -value = 0.030) and stages of cancer ( $p$ -value <0.001), and response to treatment ( $p$ -value = 0.031).

**Conclusion:** According to this study, moderate hypofractionation radiotherapy alone has reasonable outcomes in esophagus cancer patients who are medically unfit or refuse chemotherapy or surgery due to personal choice.

**KEYWORDS:** Esophageal Neoplasms, Survival Rate, Hypofractionated Dose, Radiotherapy.

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## INTRODUCTION

Worldwide, Esophageal cancer is ranked eighth among the most common cancers, and the sixth leading cause of mortality from cancer.<sup>1,2</sup> For classification and reporting of cancer, esophagus is divided into four regions namely: cervical, upper thoracic, mid thoracic and lower thoracic.<sup>3</sup> Moreover, esophageal cancer has two main histologic types; esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). ESCC predominate in developing world and usually occur due to chronic irritation caused by smoking, alcohol

consumption or hot beverages.<sup>4-6</sup> People who are obese and have Barrett's esophagus are at a higher risk of developing adenocarcinoma, which is swiftly growing in the developed world.<sup>7-12</sup>

Esophageal cancer is an aggressive disease with 5-year survival less than 20% and hence poor prognosis.<sup>13</sup> Chemoradiation therapy combined with surgery are multimodal approaches generally recommended for the loco-regional advanced disease.<sup>14</sup> However, limitations occur because of patients' comorbidities, advanced age and sometimes patients' refusal for surgery or chemotherapy,

leaving radiation therapy as the only choice of treatment. Although, no evidence supported sole radiation therapy treatment as 5-year overall survival rates were 0% to 20% in loco-regional advanced disease.<sup>15</sup> but in early stage disease favorable local control were found.<sup>16</sup> There is no established radiotherapy dose fraction schedule for these patients. Conventionally, 1.8 to 2 Gy per fraction is delivered but in efforts to get maximum benefit with radiation therapy in these patients various altered fractionation schedules have been tested. In moderate hypofractionation high dose is delivered in short time duration.

The aim of our study is to evaluate treatment outcomes of moderate hypofractionation schedule using 3 Gy per fraction for 10 days in first phase then 2 Gy per fraction for 10 days in second phase in those patients of esophageal cancer who either refused or were medically unfit for surgery or chemotherapy.

## METHODS

A retrospective study was conducted at Department of Radiation Oncology, Ziauddin University Hospital, Karachi. A total 52 esophageal cancer patients, who were treated with moderate hypofractionation radiotherapy from January 2011 to December 2015, were included in this study.

All esophageal cancer patients of both gender, aged 18 to 75 years with Eastern Cooperative Oncology Group (ECOG) Performance score of 0 to 2 were included in the study. Patients, who were previously irradiated in the same region, having a perforation or a fistula and ECOG Performance Status  $\geq 3$  were excluded.

All patients were biopsy proven squamous cell carcinoma or adenocarcinoma. The extent of tumor was evaluated by physical examination, endoscopy, and computed tomography. Clinical stage was assigned according to the 7th American Joint Committee on Cancer (AJCC) staging system for esophageal cancer. Total given dose was 50 Gy in 20 fractions which were delivered in two phases. In the first phase, 30 Gy in 10 fractions were delivered followed by one week gap. In the second phase, 20 Gy were delivered in 10 days. Patients were evaluated after one month then every 3 to 4 months and the response was measured by assessing improvement in symptoms. Endoscopy or CT scan were performed depending upon patient's status.

Statistical package for social sciences (SPSS) version 22 was used for the purpose of statistical analysis. Overall survival was calculated from day first of radiation therapy till the time of death by any cause. Mean and standard deviation was calculated

for age and overall survival in months, while frequency and percentages were calculated for gender, grading, histopathological findings, nodules, metastasis, staging, response at the end of the treatment, and stent placement. Independent t-test and one-way ANOVA test were applied to see the difference between overall survival with baseline characteristics. Chi-square test was also applied to see the association of survival status with baseline characteristics. P-value  $<0.05$  was taken as significant.

## RESULTS

A total of 52 patients were included with a mean age of  $52.78 \pm 14.54$  years. There were 27 (51.9%) females and 25 (48.1%) males. Addiction of smoking/betel nut/areca nut was found in 23 (44.2%) patients.

Moderately differentiated cancer was reported in majority (39; 75%) of the patients, followed by poorly differentiated (7; 13.5%) and well differentiated cancer (6; 11.5%). Histopathological findings revealed that patients with squamous cell carcinoma (SCC) were more (n=49, 94.2%) as compared to adenocarcinoma (n=3, 5.8%).

T3 was observed in 44 (84.6%) while T4 in 8 (15.4%) patients. N1 was found in the majority (n=27, 51.9%), followed by N2 in 16 (30.8%), N0 in 8 (15.4%) while N3 was observed in only 1 (1.9%) patient. There were 10 (19.2%) patients with metastasis.

Stage IIIA was found in 23 (44.2%), III B in 15 (28.8%), IV in 12 (23.1%) while II in 2 (3.9%) patients.

Cervical esophagus was site of involvement in 1 (1.9%) patient, upper thoracic in 6 (11.5%), mid thoracic in 22 (42.3%), lower thoracic in 35 (67.3%), gastro-esophageal junction in 20 (38.5%), while stomach involvement was seen in 3 (5.8%) patients. Stent was placed in 20 (38.5%) patients.

Overall response at the end of the treatment showed that 15 (28.8%) were normal, 9 (17.3%) were on semi-solid diet, 17 (32.7%) on a soft diet, 6 (11.5%) on liquids while 5 (9.6%) patients presented with absolute dysphagia.

The mortality was observed in 47 (90.4%) of the patients.

The overall survival among patients was found to be  $10.51 \pm 1.25$  months. Overall monthly survival was found significantly associated with stages of cancer (p-value  $<0.001$ ), grades (p-value 0.030) and response to treatment (p-value 0.031). In particular, there were only 2 patients with stage II disease, which had the mean survival of 60 months while

patients with stage III A had an overall survival of  $9.58 \pm 4.97$  months, III B had an overall survival of  $11.53 \pm 10.56$  months, and stage IV had an overall survival of  $6.91 \pm 3.47$  months. (Figure 1)

Overall monthly survival was found significantly higher in patients with poorly differentiated grading ( $21.71 \pm 20.84$ ) as compared to moderately differentiated grading ( $8.66 \pm 4.37$ ) and well differentiated grading ( $9.33 \pm 6.37$ ).

A significant difference was also observed between

overall survival in months and response of the patients (p-value 0.031). In particular, overall survival in months was found significantly higher in normal intake patients ( $18.6 \pm 17.6$ ) as compared to semi-solid ( $9.22 \pm 2.86$ ), soft diet ( $8.01 \pm 4.31$ ), liquid ( $4.16 \pm 2.04$ ), and absolute dysphagia ( $4.61 \pm 2.31$ ).

Comparison of survival status with baseline characteristics of the patients showed that staging was the only variable found significantly associated with survival status (p-value 0.024). (Table 1)

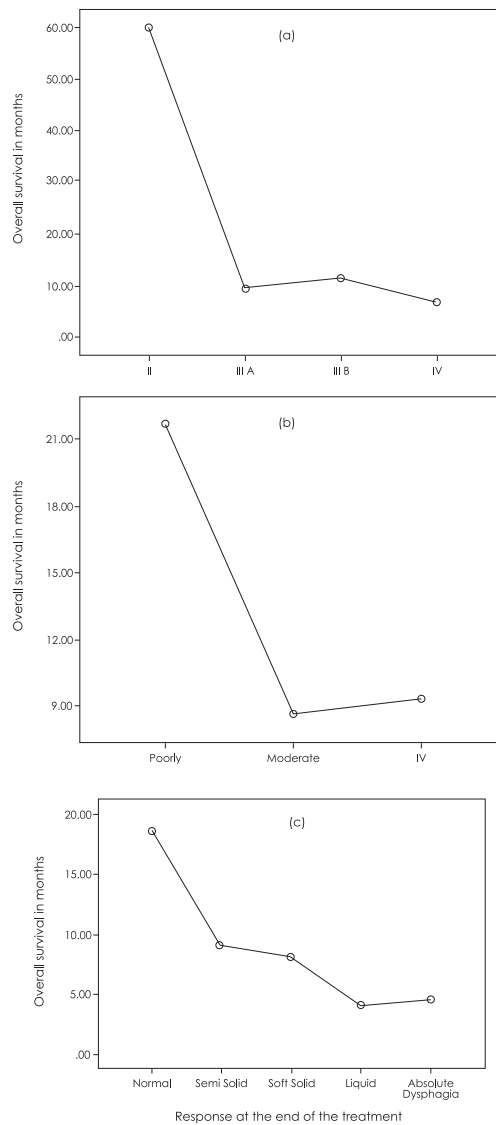


Figure 1: Means plot of overall monthly survival (a) with staging (b) gradings and (c) response at the end of treatment

**Table 1: Comparison of survival status with general characteristics of the patients (n=52)**

		Survival Status		p-value
		Expired	Alive	
		n (%)	n (%)	
Age, years	mean ±SD	52.91 ±14.95	44.75 ±12.84	0.296 <sup>l</sup>
Gender	Male	22 (88)	3 (12)	0.575 <sup>‡</sup>
	Female	25 (92.6)	2 (7.4)	
Addiction	Yes	20 (87)	3 (13)	0.455 <sup>‡</sup>
	No	27 (93.1)	2 (6.9)	
Grade	Poorly	5 (71.4)	2 (28.6)	0.126 <sup>‡</sup>
	Moderate	37 (94.9)	2 (5.1)	
	Well	5 (83.3)	1 (16.7)	
Histopathology	SCC	45 (91.8)	4 (8.2)	0.151 <sup>‡</sup>
	Adenocarcinoma	2 (66.7)	1 (33.3)	
T	T3	39 (88.6)	5 (11.4)	0.316 <sup>‡</sup>
	T4	8 (100)	0 (0)	
N	N0	6 (75)	2 (25)	0.45 <sup>‡</sup>
	N1	25 (92.6)	2 (7.4)	
	N2	15 (93.8)	1 (6.3)	
	N3	1 (100)	0 (0)	
Metastasis	Yes	10 (100)	0 (0)	0.569 <sup>‡</sup>
	No	37 (88.1)	5 (11.9)	
Stage	II A	1 (50)	1 (50)	0.024 <sup>‡</sup>
	III A	20 (87)	3 (13)	
	III B	14 (93.3)	1 (6.7)	
	IV	12 (100)	0 (0)	
Grade at the end of the treatment	Normal	12 (80)	3 (20)	0.505 <sup>‡</sup>
	Semi-Solid	8 (88.9)	1 (11.1)	
	Soft Diet	16 (94.1)	1 (5.9)	
	Liquid	6 (100)	0 (0)	
	Absolute Dysphagia	5 (100)	0 (0)	
Stent Placement	Yes	19 (95)	1 (5)	0.372 <sup>‡</sup>
	No	28 (87.5)	4 (12.5)	

\* Independent t-test applied, †Chi-square test applied, p-value <0.05 was taken as significant

**DISCUSSION**

Esophageal cancer is an aggressive disease with poor prognosis, as even with the standard treatment protocol of concurrent chemo-radiation, median survival is only 17.7 months.<sup>17</sup> In medically unfit patients who are unsuitable or those who are reluctant for chemotherapy or surgery, cure is challenging to achieve with radiation therapy alone. Before the era of concurrent chemoradiation, sole treatment with radiation therapy was considered effective. Nowadays, radiation therapy alone is only limited to those patients who are unwilling to go through standard protocol or are medical-

ly unfit. In Radiation Therapy Oncology Group (RTOG) study<sup>18</sup> radiation therapy alone was compared with concurrent RT and 3 years OS rate was 0%. Thereafter, radiation therapy alone was only used for palliative intent and no evident curative dose fraction schedule was established in these medically unfit patients. Study of JASTRO<sup>19</sup> evaluated that RT alone could be given with good survival in early stage esophagus cancer. Several studies evaluated nonconventional schedules in efforts to improve the survival of esophageal cancer patients. A recent study<sup>20</sup> revealed that high dose moderate hypofractionation radiotherapy is curative alternative option in treatment of superfi-

cial esophagus cancer, although, in our study we have only two patients of stage II but their mean survival is 60 months. Moderate hypofractionated radiotherapy usually treats the gross disease as a whole and not just the symptom. In the current study, we report a single institution experience of utilization of moderate hypofractionated radiotherapy for treatment in those patients who did not receive standard protocol. The optimum dose fraction schedule for moderate hypofractionation radiotherapy is still controversial in the literature.<sup>21,22</sup>

The results of the study showed that moderate hypofractionation radiotherapy alone gives an overall survival of  $10.51 \pm 1.25$  months. Our results are different from another study<sup>20</sup> which employed a different dose fraction schedule with delivered dose of 60Gy. They used 3Gy per fraction in whole treatment and in our study 50Gy in two phases were given as 3Gy per fraction for 10 days followed by 2Gy per fraction for 10 days.

This study also showed that moderate hypofractionated radiotherapy is useful in symptomatic relief of dysphagia. Following completion of treatment, majority of the patients were on a normal or semi-solid or soft diet while a small number of patients were on liquids or with absolute dysphagia. Our results matched with the study conducted by Aggarwal et al.<sup>23</sup>

In our study, mortality was observed in 90.4% of the cases. This may be related to treatment toxicity or treatment failure. Tumor progression as a result of treatment failure is primarily responsible for death. According to a previous study<sup>23</sup> approximately 65% of the cases of death were due to the progression of tumor. In another study by Laskar et al the cause of death was esophageal carcinoma.<sup>24</sup> Majority of patients in our study had squamous cell carcinoma, which has been observed as a major type in previous studies as well.<sup>25,26</sup> Our study results have shown that after treatment, patients having histologically proven squamous cell carcinoma showed a higher rate of recovery. Although this was an insignificant finding, such information can aid in tailored dose administration to further improve the quality of radiotherapy in such histological types of carcinoma.

This study showed the deep value of an approach based upon radiation therapy in a population not suited to radical treatment such as curative surgery or concurrent chemoradiotherapy. The results of this study have given an overall survival in different stages along with other variables of age, gender, tumor location, histologic type, grade and also grading of symptomatic relief of symptoms. To the best of our knowledge, these variables have not been studied in context of radiation therapy and esophageal cancer in Karachi, Pakistan.

## CONCLUSION

Our findings suggest that the overall survival of esophageal cancer patients who refused standard treatment protocol was considerably higher in response to moderate hypofractionation radiotherapy. Moreover moderate hypofractionation radiotherapy was also shown to relieve cancer symptoms, especially dysphagia, efficiently.

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