

Pattern of clinical response after concurrent chemoradiotherapy in patients with esophagus carcinoma

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ABSTRACT

Background: Around the globe esophagus carcinoma is the 8th most common cancer with the incidence of 456,000 cases yearly & it is the 6th cause of mortality due to cancer. It is the 7th most common malignancy in men and 6th most common malignancy in females of Karachi. Chemoradiation therapy followed by surgery is the standard strategy for the treatment of locally advanced esophageal cancer. However, optimization of radiation dose, technique, chemotherapy, and patient selection is necessary to maximize its benefits. The objective of this study is to investigate the pattern of clinical response after concurrent chemoradiotherapy in patients with esophagus carcinoma.

Patients and methods: It was a longitudinal study conducted at the Department of Oncology of Jinnah Postgraduate Medical College from May 2017 to July 2018. The patients of age 19-70 years of either gender with histological proven esophagus carcinoma of stage IA-IIIB¹ were included in the study. Patients with metastasis disease were excluded from the study. Every patient underwent full disease staging at baseline that included PET-computed tomographic (CT) scans, endoscopic ultrasonography, blood tests, and endoscopic biopsies. The cross trial² was inducted in patients with lower and middle esophagus in which concurrent chemoradiotherapy was performed with radiations in which carboplatin and paclitaxel was given weekly. For the upper esophagus the RTOG 85-01 trial³ was inducted, in which concurrent chemoradiotherapy with cisplatin at day 1 and 5FU was administered on day 1 to 5. After 6 weeks at the end of chemoradiation, the clinical response was assessed on CT scan. The absence of visible tumor on CT scan and dysphagia was labelled as clinical complete response, a reduction of more than 30% of the tumor length on CT scan was labelled as partial response and appearance of new tumors or 30% increase in size of existence lesion was labelled as progression of disease and non-response, while patients with no change in index lesion was labelled as stable disease. Statistical analysis was performed using SPSS version 23.

Results: Total of 70 patients were included in the study. The median age of the patients was 43.32±14.24 years. The partial clinical response was achieved in majority of the patients after concurrent chemoradiation therapy (CCRT) (55.7%). However, 14 patients achieved complete response, 10 patients showed stable disease, 6 patients expired and only one patient showed disease progression with metastases.

Conclusion: The results showed that the achievement of complete clinical response was comparatively low after CCRT than partial response.

Keywords:

Esophagus carcinoma, Clinical response, Partial response, Complete clinical response, Concurrent chemoradiotherapy, Squamous cell carcinoma

INTRODUCTION

Around the globe esophagus carcinoma⁴ is the 8th most common cancer with the incidence of 456,000 cases yearly & it is the 6th cause of mortality due to cancer.⁵⁻⁷ In 2019, about 17,650 new cases of esophagus carcinoma (EC) are estimated to be identified in the United States, with 16,080 deaths.⁴ Data from Karachi

showed that it is the 7th most common malignancy in men and 6th most common malignancy in females.⁸⁻¹¹

The most well-known kind of EC in East Asia is Squamous cell carcinoma (SCC), while in Western (Barrett's esophagus) and smoking.^{12,13} The incidence of EC is 10 times more in certain countries including Iran, northern China, Russia, Hong Kong, Brazil and South Africa as compared to US. This variation may be due to nitrate rich foods like cured meats, pickled vegetables and fish and ingestion of alcoholic drinks.¹¹ or Concurrent Chemo radiotherapy (CCRT) is the main strategy for the management of inoperable cases of esophagus carcinoma established on

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the outcomes of the pivotal study of “Intergroup Radiation Therapy Oncology Group (RTOG)-8501” which showed significant improvement and survival of patients who had adenocarcinoma countries, adenocarcinoma is leading.^{9,10} The incidence of adenocarcinoma among Caucasians in the US has raised over the last 25 years.¹¹ The potential risk factors for adenocarcinoma include obesity, columnar metaplasia squamous cell of the esophagus with CCRT as contrast with radiotherapy (RT) only.¹⁴ Various studies have showed that high doses of radiation bring survival benefits. However some authors have found that dose-escalated radiotherapy don't benefit the CA esophagus patients and can prompt to more treatment related toxicities. Disparity in therapy response and outcomes have been observed in esophagus carcinoma patients after receiving chemo radiotherapy (CRT).¹⁵ Di Fiore and colleagues in their study showed that complete clinical response was seen in 86 patients after CRT, about 39.5% had local disease recurrence and 43% patients had metastatic disease and 19 patients experienced the both.¹⁶ Yamashita H and colleagues conducted study on 126 patients with esophageal squamous cell carcinoma, among them 69% had achieved complete clinical response after completion of CRT.¹⁷ Another CROSS trial showed overall survival of 24 months in the patients who had surgery and 49.4 months in the patients who had chemoradiotherapy along with surgery.¹⁸ Data on the patterns of esophagus carcinoma patients who achieved a complete clinical response after CRT remain scarce in Pakistan. So, the aim of our study was to determine the pattern of clinical response after concurrent CRT in patients with esophagus carcinoma.

PATIENTS AND METHODS

It was an interventional study conducted at the department of oncology of Jinnah Postgraduate Medical College (JPMC) from May 2017 to July 2018. The sample size of 70 patients was estimated using Open Epi online sample size calculator by taking frequency of complete clinical response after CRT among EC patients as 77%¹⁹, margin of error as 10% and 95% confidence level. Non-probability consecutive sampling technique was employed for sample selection. The patients of age 19-70 years of either gender with histological proven esophagus carcinoma of stage IA-IIIB¹ were included in the study. Patients with metastasis disease were excluded from the study. The ethical review committee approval was sought before

Table 1. Socio-demographic characteristics

Characteristics	Frequency n (%)
Age groups	
≤40 years	33 (47.1)
>40 years	37(52.9)
Median (Range)	43 (30-55)
Gender	
Male	32(45.7)
Female	38(54.3)
Occupation	
Housewife	38 (54.3)
Employed	29 (41.4)
Student	2 (2.9)
Retired	1 (1.4)
Addiction	
Pan	10 (14.3)
Huqqa	2 (2.9)
Betal Nut	5 (7.1)
Smoking	7 (10)
Gutka Chewing	7 (10)
Naswar	2 (2.9)
None	37 (52.9)
Dietary habits	
Spicy food	14 (20)
Junk food	5 (7.1)
Vegetables	11 (15.7)
Meat	10 (14.3)
Fruits	6 (8.6)
Normal	24 (34.3)

the conduct of study at multidisciplinary meeting at JPMC. Informed written and verbal consent was taken from all the patients. Information regarding socio-demographic and clinical factors were obtained from all the patients. Every patient underwent full disease staging at baseline that included CT scans, PET-computed tomographic (CT) scans, endoscopic ultrasonography, blood tests, and endoscopic biopsies. The cross trial² was inducted in patients with lower (Lower border of the inferior pulmonary vein to the stomach, including the esophagogastric junction) and middle esophagus (Lower border of the azygos vein to lower border of the inferior pulmonary vein) mass in which concurrent chemoradiotherapy was performed with total radiations dose delivered was 41.4 grays (Gy) in 23 fractions for 5 days in which carboplatin and paclitaxel was given once weekly.

For the upper esophagus (Cervical esophagus to lower border of the azygos vein) the RTOG 85-01 trial³ was inducted, in which concurrent chemoradiotherapy was performed with total radiations dose delivered was 50 Gy in 25 fractions with cisplatin at day 1 and 5FU was administered on day 1 to 5. Five to six weeks after completion of chemoradiation, all patients underwent a comprehensive restaging evaluation that included CT imaging, the clinical response was assessed on CT scan.

The absence of visible tumor on CT and dysphagia assessed clinically were labelled as clinical complete response, a reduction of more than 30% of the tumor length on CT scan was labelled as partial response and appearance of new tumors or 30% increase in size of existence lesion was labelled as progression of disease and non-response patients had no change in existence lesion was labelled as stable disease.¹⁹

Statistical analysis was performed using SPSS version 23. Mean and SD was calculated for all quantitative variables whereas frequency and percentage was calculated for all qualitative variables. Univariate analysis was performed to see the association between clinical response and other independent variables using chi-square test and $p < 0.05$ was considered as statistically significant.

RESULTS

Total of 70 patients were included in the study. The median age of the patients was 43.32 ± 14.24 years. Majority of the patients (52.9%) were more than 40 years of age and 47.1% of patients were less than and equal to 40 years of age. About 38 patients were female (54.3%) whereas 32 patients were male (45.7%). Most of the patients were housewives (54.3%) followed by employed (41.4%). Out of 70 cases, majority of the patients didn't have any addiction (52.9%) and 34.3% were taking normal food. (Table 1)

In all the cases of esophagus carcinoma, squamous cell carcinoma (SCC) was the most common histopathological tumor ($n=43$, 61.4%), whereas adenocarcinoma and adenosquamous cell accounted for 24 (34.3%) and 3 (4.3%) patients and 48 (68.6%) of the tumors were moderately differentiated and the most frequent site of tumor was lower (50%). According to stage of cancer, 34 patients were identified in IIA whereas according to the TNM staging of cancer, 26 (37.1%) were identified as T3N0M0. Among 70 patients, concurrent chemoradiotherapy was performed and majority of patients had 1-3 number of chemo cycles with median duration of CCRT as 49 (IQR: 37-71) days (Table 2).

The partial clinical response was achieved in majority of the patients after CCRT (55.7%). However 14 patients achieved complete response, 10 patients showed stable disease, 6 patients expired (Patients who did not get radiation on time) and only one patient showed progression with metastasis (lung metastasis). The patients were discussed in tumor board. The clinical response was stratified with respect to

Table 2. Clinicopathologic characteristics

Characteristics	Frequency n (%)
Histological type	
Squamous cell carcinoma	43 (61.4)
Adenocarcinoma	24 (34.3)
Adenosquamous cell	3 (4.3)
Tumor grade	
Well differentiated	10 (14.3)
Poorly differentiated	12 (17.1)
Moderately differentiated	48 (68.6)
Cancer stage	
IA	5 (7.1)
IIA	34 (48.6)
IIIA	13 (18.6)
IB	1 (1.4)
IIB	15 (21.4)
IIIB	2 (2.9)
Site	
Upper	12 (17.1)
Middle	23 (32.9)
Lower	35 (50)
TNM stage	
T1NoMo	6 (8.6)
T1N1Mo	2 (2.9)
T2NoMo	15 (21.4)
T2N1Mo	7 (10)
T3NoMo	26 (37.1)
T3N1Mo	11 (15.7)
T3N1M1	1 (1.4)
T3N2Mo	2 (2.9)
No. of chemo cycles	
1-3 cycles	43 (61.4)
4-7 cycles	27 (38.6)
Duration of CCRT (days [Median (IQR)])	
	49 (37-71)

histological type, grade, site of tumor & TNM stage Only TNM staging showed statistical difference when compared with clinical response ($p < 0.05$) (Table 3).

DISCUSSION

There is evidence in literature regarding treatment of esophageal cancer by combined chemoradiotherapy over radiotherapy alone.²⁰ In the study by Herskovic and coauthors revealed a significant benefit for survival of the patients who had received concurrent chemoradiation therapy.²¹ This study evaluated the clinical outcomes of CCRT among patients with esophagus carcinoma. In this study, the median age of EC patients was 43 years with interquartile range as 30-55 years. Whereas in a study conducted by Castoro found median age of EC patients was 58.8 (55.5–67.5) years.²² In another study conducted by Liao et al., the median age of the patients with EC was reported as 66 (24-87) years. The prevalence of EC is reportedly rising among elderly population because of aging population.²³ Hence no significant statistical difference has been found between younger and elderly patients for survival after esophageal resection ($p < 0.05$).^{23, 24} In a

Table 3. Stratification of clinical response after CCRT

Variables	Partial response n (%)	Complete response n (%)	Stable disease n (%)	Progression with metastasis n (%)	Expired n (%)	p-value*
Histological type						
Squamous cell carcinoma	23 (59)	9 (64.3)	6 (60)	1 (100)	4 (66.7)	0.395
Adenocarcinoma	15 (38.5)	5 (35.7)	2 (20)	0	2 (33.3)	
Adenosquamous cell	1 (2.6)	0	2 (20)	0		
Grade						
Poorly differentiated	6 (15.4)	1 (7.1)	3 (30)	0	2 (33.3)	0.751
Moderately differentiated	27 (69.2)	11(78.6)	5 (50)	1 (100)	4 (66.7)	
Well differentiated	6 (15.4)	2 (14.3)	2 (20)	0		
Site of tumor						
Upper	7 (17.9)	1 (7.1)	2 (20)	0	2 (33.3)	0.873
Middle	13 (33.3)	5 (35.7)	4 (40)	0	1 (16.7)	
Lower	19 (48.7)	8 (57.1)	4 (40)	1 (100)	3 (50)	
TNM staging						
T1N0M0	2 (5.1)	1 (7.1)	3 (30)	0	0	0.01
T1N1M0	0	1 (7.1)	0	0	0	
T2N0M0	9 (23.1)	3 (21.4)	1 (10)	0	2 (33.3)	
T2N1M0	4 (10.3)	2 (14.3)	1 (10)	0	0	
T3N0M0	15 (38.5)	4 (28.6)	4 (40)	0	3 (50)	
T3N1M0	6 (17.9)	2 (14.3)	1 (10)	0	1 (16.7)	
T3N1M1	1 (2.6)	0	0	1 (100)	0	
T3N2M0	1 (2.6)	1(7.1)	0	0	0	

*Chi square test was applied, p<0.05 level of significance

retrospective review of 263 cases of esophagus carcinoma seen at the Aga Khan University, the mean age at the time of diagnosis was 56 years and median age was 60 years (range 22–85), which higher than the present study.²⁵

In this study there were 32 males and 38 females. The proportion of women was slightly higher as compared to men. The dissimilar observations for female predominance has been reported in previous study by Meguid which showed out of 267 patients, 239 (89.5%) being males.²⁶ Another study conducted by Castoro²² also found the no. of males higher than females i.e. male: female = 29:9. In a study conducted at Karachi showed 59% of the males and 41% of the females were affected by esophagus carcinoma.²⁵ These studies showed that female may be a protective factor for progression to esophagus cancer. The factors responsible for the sex disparity in esophageal adenocarcinoma incidence have not been defined, and do not appear to be exclusively associated with changes in known risk factors, however recent reports suggest that hormonal factors may play a role in the observed sex disparity in esophageal adenocarcinoma incidence.²⁷

In a study conducted by Cheedella found majority of the patients were presented with poorly differentiated tumors (54.5%), followed by moderately differentiated tumors (44.7%) and only 2 patients were presented with well differentiated tumors. In their study adenocarcinoma was the most frequent cancer type and most of them belonged from stage II or III of cancer

before therapy.¹⁹ In another similar study 73 patients underwent for chemoradiation therapy, the most common histological subtype was squamous cell carcinoma (67%), the upper esophagus tumor was found in majority of the patients (34%) followed by gastroesophageal junction or lower esophagus (33%) and 31 patients had middle esophagus whereas majority of the patients had T3 stage (59%).²⁸ In the present study, majority of the patients had histological subtype as squamous cell carcinoma as 61.4% and most of the tumors were moderately differentiated (68.6%). The lower esophagus was the frequent site of tumor (50%) and had had stage IIA predominant before treatment (48.6%). About 37.1% patients had T3N0M0 stage. Among 70 patients, majority of patients had 1-3 chemo cycles (61.4%) with median duration of CCRT as 49 days (Range: 37-71).

Vernissia conducted a study in which 93 (30%) out of 308 EC patients received adjuvant chemotherapy. Partial response was observed in 50 out of 150 whom received adjuvant therapy, whereas patients with complete response or no response to trimodality therapy showed no difference in median survival with the addition of adjuvant chemotherapy. Authors also reported that patients with locally advanced stage of EC was related with 26 decrease in relative hazard for mortality than trimodality treatment alone. The study concluded that partial responders may advantage most from adjuvant chemotherapy.²⁹ Cheedela showed that 77 of the cases achieved complete clinical response after

preoperative chemoradiation therapy.¹⁶ In this study, majority of the patients achieved partial clinical response after CCRT (55.7%), complete clinical response (20%), stable disease (14.3%), progression with metastases in one patient. Out of 70 patients, 8.6% of the patients expired during or after the induction of CCRT. Nayan evaluated effect of CCRT in 28 esophageal cancer patients, among them 68% achieved complete clinical response, 14% achieved partial response & 18% of the cases had progression of disease.²⁹ In another research, 23.2% clinical complete response was achieved after CCRT for T4 SCC of the EC with median follow up time of 34 months.³⁰

CONCLUSION

Achievement of complete clinical response was comparatively low after CCRT than partial response. However, further follow-up and large sample size may be required to validate the current study conclusion.

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