Original article

Pathological response rate in patients who achieve clinical response after neoadjuvant concurrent chemoradiotherapy in localized esophageal cancer

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ABSTRACT

Background: The incidence of esophagus carcinoma is raising and it is the 6th leading cause of mortality. The objective of this study is to determine pathological response rate in patients who achieve clinical response after neo-adjuvant concurrent chemoradiotherapy in locally advanced esophageal cancer presented at a single tertiary care centre in Karachi.

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. Thirty five patients with locally advanced carcinoma involving lower and middle esophagus had concurrent chemoradiotherapy. Induction of concurrent chemoradiotherapy with radiations in which carboplatin and paclitaxel was given weekly. After 6 weeks at the end of irradiation, the clinical response was assessed on CT scan. All patients who had achieved stable, partial and complete clinical response after completion of concurrent chemoradiotherapy (CCRT) underwent surgery within 6-8 weeks. After surgery, pathologist evaluated resected specimen and staging was done on the basis of residual tumor. To grade the response to therapy, the degree of histomorphologic regression classified into four categories as Pathological complete response (pCR), pathological partial response, stable disease as no pathological response and progression of disease. Statistical analysis was performed using SPSS version 23. Chi-square test was applied to assess association between effect modifiers and complete pathological response.

Results: Total of 35 patients were included in the study. Mean age of the patients was 42.42±14.16 years. There was female preponderance (57.4%) with male to female ratio of 17:18. Eleven patients (31%) achieved complete clinical response and 2 patients (6%) had stable disease. After surgery, complete pathological response was observed in 21 (60%) patients. However, 10 (28.6%) patients achieved partial pathological response, 1 (2.9%) patient had stable disease and 3 (8.6%) patients showed progression of disease.

Conclusion: The achievement of complete pathological response was comparatively higher than partial response among locally advanced EC patients who had neoadjuvant CCRT followed by surgery.

Keywords:

Pathological response; Clinical response; Esophagus carcinoma; Surgery; Neoadjuvant Chemoradiotherapy

INTRODUCTION

Globally, the annual incidence of esophagus carcinoma (EC) is raising and it is the 6th leading cause of mortality (overall 509,000 deaths).[1] The 5 years survival rate of 15-39% has been observed among patients with localized disease after curative therapy i.e. & partial or total esophagectomy & lymph node dissection. [2,3] Thus, neoadjuvant chemoradiotherapy along with surgery has become the standard for managing locally advanced EC.[3,4]

In clinical practice the trimodality approach which includes chemotherapy, radiotherapy and surgery is now widely accepted.[5,6] Previous meta-analyses showed significant efficacy of chemoradiotherapy (CRT) followed by esophagectomy for the treatment of localized tumor control and increased survival rate.[7,8] 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.[9] It is estimated that 25–30% of patients experience complete pathologic response following neoadjuvant chemoradiotherapy.[9-12] Rohatgi et al. reported that the response to preoperative chemoradiotherapy correlated strongly with overall survival and disease-free survival in patients with esophageal cancer. In their review of 235 cases, survival decreased progressively between patients who achieved

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a pathologic complete response, those who had a partial response (1-50% residual carcinoma in the resected specimen), and those with no response (greater than 50% residual carcinoma).[13]

Pakistan is a country where majority of the people suffer from advanced esophagus carcinoma due to lack of awareness, low socio economic status, limited access to health care services and late presentation.[14] Data from Karachi showed that EC is the 7th most common malignancy in men and 6th most common malignancy in females.[15] At the time of diagnosis, early-stage disease was found in 25%, locally advanced in 41% and metastatic in 34% of all cases.[16] The most common modality of treatment in Pakistan is radiation therapy with or without Cisplatin based chemotherapy.[15] The present study aims to evaluate complete pathological response rate in patients who achieve clinical response after neo-adjuvant concurrent chemoradiotherapy in locally advanced esophageal cancer at a single tertiary care centre in Karachi.

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. Non-probability consecutive sampling technique was employed for sample selection. Thirty-five patients of age 20-67 years of either gender with locally advanced esophagus carcinoma (histological proven esophagus carcinoma of stage IA-IIIB) who had achieved partial or complete clinical response or had stable disease after concurrent chemoradiotherapy and who were able to undergo esophagectomy were included in the study. Patients who had underwent only chemotherapy or radiotherapy prior to presentation, patients having deranged renal and hepatic profile or altered bone marrow reserves and patients with history of uncontrolled hypertension or diabetes mellitus or psychiatric illness or cardiac disease were excluded from the study. The ethical review committee approval was sought before the conduct of study. Informed written and verbal consent was taken from all the patients. Information regarding socio-demographic and clinical factors were obtained from all the patients. Thirty-five patients referred from gastroenterology department with locally advanced esophagus carcinoma (histological proven esophagus carcinoma of stage IA-IIIB) of lower (30-40 cm form the incisor teeth) and middle site (25-30 cm form the incisor teeth) were included. Most common type of tumors were squamous cell carcinoma followed by adenocarcinoma. Decision regarding concurrent chemotherapy was taken in tumor board by multi-discipline team. Induction of concurrent chemoradiotherapy 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. After 6 weeks at the end of irradiation, the clinical response was assessed on CT scan. The pathologic staging was done according to the American Joint Committee on Cancer (AJCC) staging criteria.[17] Post CCRT ToNoMo was labelled as complete clinical response, whereas post CCRT reduction in size of the tumor (such as from T4 to T3/T2/T1/To or from T3 to T2/T1/To or from T2 to T1/To or from T1 to To) or reduction in spread of cancer to nearby lymph nodes (such as from N3 to N2/N1/No or from N2 to N1/No or from N1 to No) was labelled as partial response. No change in size of the tumor or spread of cancer to lymph nodes post CCRT was labelled as stable disease whereas the increase in size of tumor (such as from To to T1/T2/T3/T4 or from T1 to T2/T3/T4 or T2 to from T3/T4 or T3 to T4) or increase in spread of cancer to nearby lymph nodes (such as from No to N1/N2/N3 from N1 to N2/N3, N2 to N3) was labelled progressive disease. All patients who had achieved stable, partial & complete clinical response after completion of CCRT underwent radical surgery within 6-8 weeks. A transthoracic approach with two-field lymph-node dissection was performed for tumors extending proximally to the tracheal bifurcation. For tumors involving the esophagogastric junction, a transhiatal resection was preferred. Peritruncal dissection was carried out with both approaches. The approach depended on the characteristics of the patient and on local preferences. Gastric-tube reconstruction with a cervical anastomosis was the preferred technique for restoring the continuity of the digestive tract. After surgery, pathologist evaluated resected specimen and staging was done on the basis of residual tumor. To grade the response to therapy, the degree of histomorphologic regression classified into four categories as Pathological complete response (pCR), pathological partial response (defined as 1–50% residual carcinoma in the resected specimen), stable disease as no pathological response (defined as greater than 50% residual carcinoma in the resected specimen) and progression of disease. Esophagitis and neutropenia, skin changes at area of radiation, nausea, fatigue, vomiting, diarrhea, dry mouth were the most commonly observed complications which were managed by best supportive care.

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. The association between pathological response and other independent variables using chi-square test was done and a p-value of ≤0.05 was considered as significant.

RESULTS

Total of 35 patients were included in the study. Mean age of the patients was 42.42±14.16 years. Majority of the patients were females (n=18, 57.4%) whereas 17 (48.6%) were males, with male to female ratio of 17:18.

Table 1. Baseline data of 35 study patients

Characteristics	*n* (%)
Age in years (mean±SD)	42.42±14.16
Gender	
Male	17 (48.6)
Female	18 (51.4)
Tumor grade	
Well differentiated	5 (14.3)
Poorly differentiated	2 (5.7)
Moderately differentiated	28 (80)
Histological type	
Squamous cell carcinoma	19 (54.3)
Adenocarcinoma	14 (40)
Adenosquamous cell	2 (5.7)
Site	
Middle	13 (37.1)
Lower	22 (62.9)
Stage	
IIA	20 (57.1)
IIIA	5 (14.3)
IA	9 (25.7)
IIIB	1 (2.9)
TNM stage	
T2NoMo	10 (28.6)
T3NoMo	11 (31.4)
T3N1Mo	4 (11.4)
T3N1M1	1 (2.9)
T1NoMo	3 (8.6)
T1N1Mo	1 (2.9%)
T2N1Mo	4 (11.4%)
T3N2Mo	1 (2.9%)
Surgical pathological report	
pT2NoMo	3 (8.6%)
pToNoMo	23 (65.7%)
pT3NoMo	6 (17.1%)
pT3N1Mo	2 (5.7%)
pT3N3Mo	1 (2.9%)

Microscopically, squamous cell carcinoma (SCC) was the most common histopathological tumor in 19 (54.3%) patients. Adenocarcinoma and adenosquamous cell accounted was present in 14 (40%) and 2 (5.7%) patients respectively. Total 28 (80%) of the tumors were moderately differentiated. Most frequent site of tumor was lower (n=22, 62.9%). According to stage of cancer, 20 patients were identified in IIA whereas according to the TNM staging of cancer, 11 (31.4%) were identified as T3N0M0. Among 35 patients, 23 (65.7%) had pT0N0M0 pathological stage. Table 1 summarizes the demographic details, tumour type, grade, location and staging for all patients included in the study. Partial clinical response was achieved in majority of the patients after CCRT (n=22, 63%). Eleven patients (31%) achieved complete clinical response and 2 patients (6%) had stable disease (Figure 1). After surgery, complete pathological response was achieved in 21 patients (60%). However, 10 patients (28.6%) achieved partial pathological response, 3 patients (8.6%) showed progression of disease and only 1 patient (2.9%) had stable disease (Figure 2).

The pathological response was stratified with respect to histological type, grade, site of tumor and stage. Among patients with squamous cell carcinoma 12 achieved complete pathological response and 6 achieved partial response whereas in patients with adenocarcinoma 8 patients achieved complete pathological response and 3 achieved partial response. Among patients with moderately differentiated tumor 17 achieved complete response and 8 achieved partial response. In patients with lower site, 14 achieved complete response and 5 achieved partial response (Table 2).

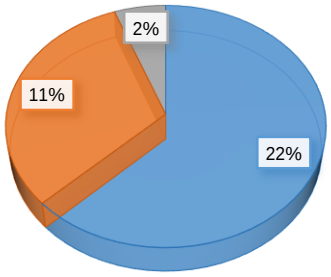

Figure 1. Clinical response after CCRT

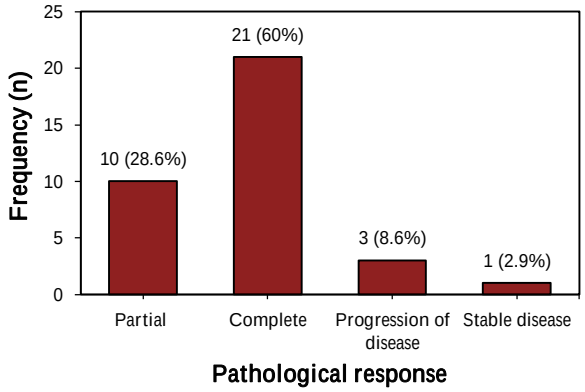

Figure 2. Pathological response

Table 2. Stratification of clinical response after CCRT

Characteristics	Partial response	Complete response	Stable disease	Progression of disease	p-value
Histological type					
Squamous cell carcinoma	6	12	0	1	0.788
Adenocarcinoma	3	8	1	2	
Adenosquamous cell	1	1	0	0	
Grade					
Poorly differentiated	1	1	0	0	0.390
Moderately differentiated	8	17	0	2	
Well differentiated	1	3	1	1	
Site of tumor					
Middle	5	7	0	1	0.694
Lower	5	14	1	2	

DISCUSSION

Esophageal cancer (EC) is highly life-threatening malignancy with overall 5-year survival rate of 10%.[18] In 2017 in USA, the overall estimate of 16940 of EC diagnosed and 15690 deaths occurred due to EC.[18] 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 & ingestion of alcoholic drinks.[19,20]

For the management of locally advanced EC surgery after CCRT is a well-established therapeutic measure but this treatment has significant association with complications and morbidity rate.[21-23] Consequences after surgery on the long term consist of significant gastroesophageal reflux disease, weight loss, dumping syndrome, and disconnect between brain center for hunger and restricted reservoir, leading to significant mental distress and postprandial pain.[24,25]

In a study conducted by Ilson and coworkers 55 patients of esophagus carcinoma, 75% of the patients had histological subtype as adenocarcinoma and 65% had T3N1 disease. About 16% of the patients achieved pCR among 38 EC patients who undergone surgery after CCRT.[26] Knox and group performed esophagectomy for locally advanced EC and evaluated the efficacy of induction chemoradiotherapy with irinotecan and cisplatin followed by resection.[27] Among 52 EC patients, complete clinical response was achieved in only 2% of the cases, 30% had partial response, 62% had stable disease and 6% had progressive disease. Esophagectomy was performed in 43 patients among which 16% achieved pCR.[27] In another study long-term outcomes following multimodal therapy for EC patients were evaluated among them 19% achieved pCR. Patients with a pCR have a 3-year survival rate of approximately 50%, as opposed to 37% for those without a pCR.[28] In the present study partial clinical response was achieved in 63% of the patients after CCRT and 31% had achieved complete clinical response. After surgery, complete pathological response was achieved in 60% patients.. In a similar study conducted in Pakistan, 45% of the patients achieved pCR, with overall 5 year survival in 38% of the patients with median survival time as 44 months.[29]

In this study pCR was achieved in 12 patients with histological type as squamous cell carcinoma (SCC). According to grade of tumor, 28 had moderately differentiated tumor among them 8 patients achieved partial response and 17 patients achieved complete clinical response. In a study by Crosby T et al. included 188 squamous, 65 adenocarcinoma and 5 undifferentiated tumor of esophagus. Fewer patients showed failure of treatment at 24 weeks in the CRT plus cetuximab arm than in the CRT alone group and they also had a shorter median survival (22.1 months versus 25.4 months, $p<0.05$).[30] Watanabe et al.[22], evaluated 63 patients who underwent esophagectomy after definitive chemoradiotherapy (dCRT) and concluded that R0 resection & pathologic T stage (T0–2) are favorable and independent predictive factors. The patients who had pretreatment dCRT had replased after complete clinical response and are good candidates for salvage esophagectomy.

In the present study we have small sample size. Further prospective, multicenter studies with larger sample size should be conducted along with different treatment regimens in order to recommend most safest and efficacious therapy.

CONCLUSION

Achievement of complete pathological response was comparatively higher than partial response among patients with neoadjuvant CCRT followed by surgery. Therefore all patients who have achieved partial or complete clinical response or had stable disease should be encouraged for surgery after recovery from chemoradiation for better outcomes.

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