

A clinical trial of neoadjuvant concurrent chemoradiotherapy followed by resection for esophageal carcinoma

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Background: Esophageal carcinoma is a common malignancy in the North East of Iran. Combined modality treatments have been adopted to improve survival in patients with esophageal carcinoma. In this trial, we evaluated the efficacy and toxicity of a preoperative concurrent chemoradiotherapy protocol in the patients with locally advanced esophageal carcinoma. **Materials and Methods:** Between 2006 and 2011, eligible patients with locally advanced esophageal carcinoma underwent concurrent radiotherapy and chemotherapy and 3-4 weeks later, esophagectomy. Pathologic response, overall survival rate, toxicity, and feasibility were evaluated. **Results:** One hundred ninety-seven patients with a median age of 59 (range: 27-70) entered the protocol. One hundred ninety-four cases (98.5%) had esophageal squamous cell carcinoma. Grades 3-4 of toxicity in patients undergoing neoadjuvant chemoradiotherapy were as follows: Neutropenia in 21% and esophagitis in 2.5% of cases. There were 11 (5.6%) early death probably due to the treatment-related toxicities. One hundred twenty-seven patients underwent surgery with postsurgical mortality of 11%. In these cases, the complete pathological response was shown in 38 cases (29.9%) with a 5-year overall survival rates of 48.2% and median overall survival of 44 months (95% confidence interval, 24.46-63.54). **Conclusion:** The pathological response rate and the overall survival rate are promising in patients who completed the protocol as receiving at least one cycle of chemotherapy. However, the treatment toxicities were relatively high.

Key words: Esophageal carcinoma, neoadjuvant chemoradiation, survival

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INTRODUCTION

Most patients with esophageal cancer present in the advanced stages. Esophagectomy as a classic standard treatment^[1,2] or radiotherapy alone^[3] have yielded a poor outcome in locally advanced esophageal cancer. There is controversy about the standard treatment of esophageal cancer. However, according to new studies, combined modality options has been proposed to improve the results. Multiple phase III randomized trials have been conducted to assess the survival benefit from tri-modality approaches including preoperative

concurrent chemoradiotherapy and esophagectomy as compared to surgery alone with controversial results.^[6] A meta-analysis by GebSKI *et al.* comparing neoadjuvant chemoradiotherapy and surgery versus surgery alone, showed a hazard ratio of 0.81 (95% confidence interval [CI]: 0.70-0.93, $P = 0.002$) for all-cause mortalities.^[7] Similarly, Urschel and Vasan in a meta-analysis on nine randomized trials that included 1116 patients showed a significant 3-year survival benefit and reduced local recurrence for neoadjuvant chemoradiotherapy and esophagectomy as compared to surgery alone.^[8]

The incidence of esophageal carcinoma is high in Iran, especially in North Eastern provinces.^[9] Genetic and

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environmental factors may contribute to the high incidence of esophageal cancer with squamous cell carcinomas (SCCs) constituting more than 90% of lesions in this country.^[10] It has been shown that low intake of micronutrients, vitamins, and minerals can increase the esophageal cancer risk.^[11] This malignancy is more prevalent in lower socioeconomic groups of society who usually take the insufficient amount of fruits and vegetable.^[12-14] It can be postulated that the background of malnutrition potentially enhances toxicity and alters treatment tolerability. Moreover, this malignancy might have a distinct genetic profile in Iranian patients with esophageal cancer which possibly affects treatment response. Overall, the results of tri-modality treatments might be different in this population in regards to toxicity, treatment response, and survival.

This clinical trial was designed to assess the feasibility and results of a tri-modality protocol containing cisplatin and 5-fluorouracil (5-FU) concurrent with radiotherapy in an Oncology Center in Mashhad a North Eastern City of Iran. We assessed the toxicity and feasibility as well as a pathological response to neoadjuvant chemoradiotherapy with our protocol and the treatment results. We also evaluated the effects of some potential prognostic factors on the overall survival rate.

MATERIALS AND METHODS

Place and time duration, ethical issue

This clinical trial was conducted at the Oncology Department, Cancer Research Center, Omid Hospital affiliated to Mashhad University of Medical Sciences (MUMS). The eligible patients with esophageal cancer were recruited for the preoperative chemoradiotherapy protocol between April 2006 and April 2011. This trial was approved by the Ethical Committee of MUMS. Neoadjuvant chemoradiotherapy had been previously investigated with various protocols and acceptable toxicity in other countries.^[4-8] All recruited patients were required to sign the informed consent.

Patients and primary investigations

The eligible patients had a histological confirmed carcinoma of the thoracic esophagus or gastroesophageal junction. The pretreatment investigation included flexible endoscopy, chest and abdominal computed tomography scan. The inclusion criteria were as follows: Resectable T2-T3 N0-N1 disease, lack of distant metastases including celiac and supraclavicular lymph nodes, maximum age 70, Karnofsky performance status of 70 or more, creatinine clearance ≥ 60 mL/min, normal liver function and blood biochemistry tests, and adequate baseline hematologic parameter including neutrophil count $>1500 \mu\text{l}$ and platelet count $>10 \times 10^5/\text{mL}$. The exclusion criteria were as follows: Concomitant another malignancy with the exception of

nonmelanoma skin cancers, severe pulmonary or cardiac diseases making the patient unsuitable for esophagectomy, and severe uncontrolled diabetes.

Treatment

Chemotherapy consisted of cisplatin 20 mg/m^2 for 4 days plus 5-FU 700 mg/m^2 24-h continuous infusion for 4 days on the 1st and 4th week of radiation therapy. The patients received the second course of chemotherapy if they had the neutrophil count $\geq 1500 \mu\text{l}$ and platelet count $\geq 10 \times 10^5/\text{mL}$, mucosal toxicity \leq Grade 2, and creatinine clearance $\geq 60 \text{ mL/min}$.

We used cobalt 60 unit for radiation therapy. The treatment volume was defined using conventional simulation as tumor volume revealing on esophagogram plus 5 cm cranial and caudal and 2 cm lateral margin. Lower cervical and bilateral supraclavicular lymph nodes were treated in upper thoracic tumors. For lower thoracic or GE junction tumors or mid thoracic tumors $\geq 5\text{cm}$, celiac lymph nodes were included in radiation fields. 40 Gy in 20 fractions was delivered using anterior and posterior fields. The radiation therapy stopped temporarily in the case of febrile neutropenia or Grade 4 of mucosal toxicity. The treatment toxicity was graded based on the National Cancer Institute Common Toxicity Criteria, version 2.

Esophagectomy was performed 3-4 weeks after radiation therapy termination using the transhiatal technique for mid and upper thoracic and for lower thoracic and GE junction tumors. The lymph nodes were dissected.

All the patients who were recruited and commenced the intended protocol were visited every week for evaluation of toxicity and tolerability. The patients who received at least one course of the chemotherapy protocol concurrent with radiation therapy and received at least 36 Gy of radiation therapy and underwent surgery were considered as appropriate for survival evaluations.

Patients were followed every 3 month following treatment termination. Follow-up evaluations including chest radiography, chest and abdominal computed tomography, and endoscopic evaluation were ordered based on the finding in physical examination and symptoms.

Pathological response assessment

Response of the primary tumor to preoperative chemoradiotherapy was graded on a 0-3 scale as follows; complete response (Grade 0) as no cancer cells, moderate response (Grade 1) as single cells or small groups of cancer cells, minimal response (Grade 2) as residual cancer cells outgrowth by fibrosis, and poor response (Grade 3) as minimal or no treatment effect.^[15]

Statistical analysis

The objectives of this trial were:

1. Toxicity and tolerability of the treatment protocol,
2. Chemoradiotherapy-related and surgical mortality/morbidity,
3. Pathologic response rates,
4. Disease-free survival rate,
5. Overall survival rate, and
6. Evaluation of some clinicopathological features affecting the overall survival including sex, age, tumor length (as revealed on esophagogram), tumor grade and pathological response, and the number of chemotherapy courses.

The survival rates were calculated using Kaplan-Meier method. The overall survival was measured from the time of diagnosis to the time of death to any cause or the last visit. The disease-free survival rate was measured from the time of diagnosis to the time of recurrence (loco-regional or distant) or the last visit. Log-rank test was utilized for comparing survival curves among groups. *P* value < 0.05 was considered as significant.

RESULTS

From April 2006 to April 2011, 197 patients with a median age of 59 years (Range: 27-70) and a male to female ratio 97/100 were recruited. The severity of dysphagia as graded from 1 to 5 was recorded in 10 (5.1%), 31 (15.7%), 113 (57.4%), 41 (20.8%) and 2 (1%) cases, respectively. The tumor was located in upper thoracic, middle thoracic, and lower thoracic/GEJ in 6 (3%), 112 (56.9%), and 79 (40.1%), respectively.

The acute adverse events that patients experienced during concurrent chemoradiotherapy are listed in Table 1. The reasons for patient disposition are listed in Figure 1. There were 11 early deaths at least partly due to the treatment toxicities. One hundred eighty patients finished

chemoradiotherapy protocol with 81 (45%) receiving two courses of chemotherapy. Despite completing the chemoradiotherapy, 53 cases refused to undergo surgery mostly because of relieving the dysphagia after neoadjuvant treatment, 25 of whom continued on radiotherapy and the remaining were not willing to follow any treatment. Finally, from 197 patients, 127 cases (64.5%) completed the treatment and underwent surgery, 60 of whom (47.2%) received 2 courses of chemotherapy.

Significant surgical complications were recorded in 17 patients (13.4%) as follows: Pneumonia in 4 (3.1%), atelectasis in 2 (1.6%), chylothorax in 6 (4.7%), and fistula in 5 (3.9%). There were 14 (11%) postsurgical mortalities. The postsurgical specimens were evaluated in 113 patients who was survived the surgery. Complete surgical resection was observed in 110 out of 113 postsurgical specimens (97.3%). Pathological response from Grade 0 to 3 was achieved in 38 (33.6%), 8 (7.1%), 22 (19.5%), and 45 (39.8%) available specimens respectively. As it is revealed in Table 2, lesion length and even the number of concurrent chemotherapy courses had no significant effect on the pathological response.

We excluded 59 patients who refused to continue on the protocol or undergo surgery for any reason from survival analysis. For the 138 remaining patients, with a median follow-up time of 18 months (range: 1-68), 65 instances of

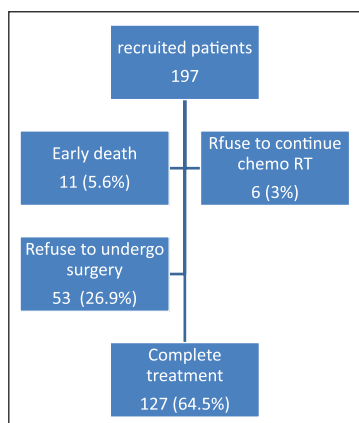


Figure 1: The reasons for patient disposition

Table 1: Acute toxicities in patients who commenced therapy

N = 197	Grade 1	Grade 2	Grade 3	Grade 4
	NO (%)	NO (%)	NO (%)	NO (%)
Neutropenia	62 (31.4)	61 (30.9)	40 (20.5%)	1 (0.5%)
Vomiting	71 (36)	18 (9.1)	6 (3)	1 (0.5)
Nausea	120 (60.9)	24 (12.1)	4 (2)	1 (0.5)
Esophagitis	76 (36.5)	7 (3.5)	5 (2.5)	0
Diarrhea	3 (1.5%)	0	0	0

Table 2: The association between some factors and pathological response to chemoradiotherapy in patients completing the trimodality therapy and surviving the surgery

Factor	Number	Pathological response		Chi-square <i>P</i> value
		Grade 0, 1	Grade 2,3	
Lesion length:				
< 5 cm	69	28 (40.6%)	41 (59.4%)	0.97
≥ 5 cm	42	18 (40.9%)	26 (59.1%)	
Site:				
Upper/mid thoracic	61	27(44.3%)	34(55.7%)	0.4
Lower/GEJ	52	19 (36.5%)	33 (63.5%)	
Pre operative Chemo course:				
1 course	62	23 (37.1%)	39 (62.9%)	0.38
2 course	51	23 (45.1%)	28 (54.9%)	

death, and a median overall survival time of 32 months (95% CI: 15.2-48.79) and a 3-year overall survival rate of 47.7% were recorded.

Figure 2 shows the outcome in 127 patients who completed the tri-modality therapy. In these cases, at a median follow-up time of 21 months (range: 2-68), the median overall survival time was 44 months (95% CI: 24.46-63.54) with a 3-year and 5-year overall survival rates of 51.8% and 48.2%, respectively. The 3-year and 5-year disease-free survival rates were recorded as 48.8% and 47.2%, respectively. Locoregional metastases developed in 25 cases including supraclavicular and cervical lymph nodes in 13 (52%), the anastomotic site in 8 (32%), and mediastinal lymph nodes in 4 (16%) patients. Twenty-two patients experienced distant metastasis. In these cases, the first site of metastasis was liver in 11, lung in 9, and brain in 2 patients.

The effects of some clinicopathological factors on overall survival were evaluated [Table 3]. Patients who achieved favorable pathological responses (Grade 0, 1) to preoperative chemoradiotherapy had relatively higher overall survival as compared to those achieving unfavorable responses, however, the difference did not reach statistical significance.

DISCUSSION

In this trial, we assessed the effectiveness and feasibility of a tri-modality therapy with two courses of chemotherapy consisting of cisplatin and 5FU concurrent with radiotherapy (40 Gy) followed by esophagectomy. More than half of our cases could not receive the second course of chemotherapy due to the hematological toxicity, severe mucositis and/or poor general conditions. One hundred eighty patients (91.3%) completed chemoradiotherapy. Fifty-three patients refused to undergo surgery. The reason for refusing surgery in this group of patients could at least partly due to satisfying

dysphagia relief, which made them reluctant to undergo a risky surgery. Grade 3-4 neutropenia was recorded in 21% of cases with only one case of febrile neutropenia which seems to be very satisfying. Eleven instances of early death (5.6%) was recorded which seems to be relatively high. Unfortunately, all of these cases had died at home; therefore, we could not clarify the exact causes of death. Considering that all of these patients were elderly, many of these patients might have had underlying undefined conditions including cardiovascular diseases. However, treatment-related toxicities could have aggravated their general condition and had a role in the death.

Among 127 patients who underwent esophagectomy, the mortality rate was 11%. The surgical mortality rate following chemoradiotherapy has been reported between 3% and 13% in other studies.^[16-19] There has been concern over the increased perioperative mortality with neoadjuvant chemoradiotherapy. Berger et al. reported their single center experience on 179 patient undergoing esophagectomy. They did not find any significant difference in mortality rates with (4.6%) and without (6.3%) induction therapy.^[20] A meta-analysis by Urschel and Vasan showed an improvement in 3-year overall survival and locoregional recurrences with neoadjuvant chemoradiotherapy as compared to surgery alone with a nonsignificant increase in surgical mortality rates.^[8]

We achieved pathological complete response of 33.6% in our series. Surprisingly, we did not find a significant difference in complete pathological response rates between those receiving one or two courses of chemotherapy. The pathological complete response to neoadjuvant chemoradiotherapy has been reported from 16% to 49% in published studies with various protocols.^[15-18,20] The various results in pathological response to induction therapy can be explained by using different protocols. However, in most trials, the complete pathological response has been associated with improved survival and control rates. We

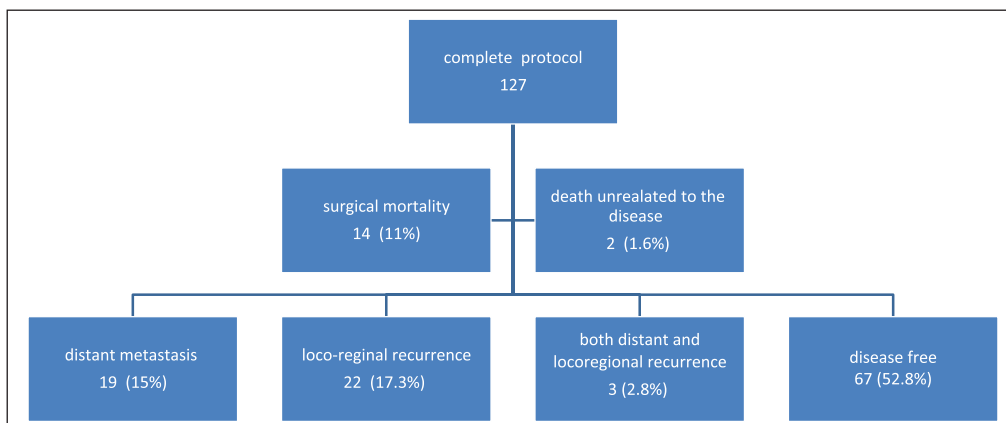


Figure 2: The treatment outcome in patients completing tri-modality therapy

Table 3: The association between some features and overall survival in patients completing the tri-modality therapy

Feature	NO	3- year OS % ± 1SE*	Log-rank P value
Age:			
≥ 60	59	49.3 ± 7.9	0.7
< 60	68	53.4 ± 6.8	
Sex:			
Male	59	55.1 ± 8	0.97
Female	68	5.6 ± 6.7	
Lesion length:			
< 5 cm	81	56 ± 6.2	0.89
≥ 5 cm	46	49.5 ± 8.7	
Grade:			
Well diff.	51	52.1 ± 9.1	0.45
Mod/poor diff.	68	50 ± 6.1	
Site:			
Upper/mid thoracic	69	56.2 ± 6.9	0.33
Lower/GEJ	58	46.6 ± 7.5	
Pre-operative Chemo course:			
1 course	69	49.9 ± 7.2	0.74
2 course	58	53.6 ± 7.2	
Pathological response:			
Grade 0/1	46	69.2 ± 7.6	0.22
Grade 2/3	67	49.8 ± 7.5	

*Standard Error

observed a trend for better survival for patients achieving significant pathological response (Grade 0, 1); however, the difference did not reach statistical significance. In our study, for patients who completed the tri-modality protocol, a median overall survival of 32 months with a 3-year overall survival of 47.7% was achieved, which compared well with previous trials that investigated the results of tri-modality treatment.^[4-6,8,16]

In a previous study in our center, the 3-year survival of 36.3% has been reported in 190 patients with nonmetastatic esophageal cancer undergoing definitive concurrent chemoradiotherapy.^[22] Although these two groups were not randomly compared, the results of tri-modality protocol seems to be superior over definitive chemoradiotherapy.

In our series, most cases could tolerate the chemoradiotherapy protocol with 45% receiving two courses of concurrent chemotherapy with radiation therapy. Neither pathological complete response rate nor overall survival rates were significantly superior in those receiving two courses of chemotherapy. It can be postulated that pathological response to concurrent regimens are more dependent on the inherent sensitivity of tumors (which is rooted in their genetic profile) than the intensity of chemotherapy protocols. The results of various trials suggested the effect of genetic factors on tumor sensitivity to chemoradiotherapy regimens.^[23-26]

Although using tri-modality therapies have improved treatment results in esophageal cancers, they have come with increased acute toxicities. Taken into consideration that the most patients with esophageal cancer are elderly, a thorough pretreatment medical investigation is warranted for a better selection of appropriate patients for combined therapies. Furthermore, the background of malnutrition might contribute to increased risk of treatment-related toxicity. Therefore, close monitoring of acute toxicities and nutritional support are crucial for obtaining the satisfying results.

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Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTION

KA, SAA contributed in the conception of the work, conducting the study, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MST contributed in revising the draft, approval of the final version of the manuscript. FSH, RS, GHN, SM and FN contributed in approval of the final version of the manuscript, and agreed for all aspects of the work.

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