Journal of Gastrointestinal Cancer (2019) 50:907–912
https://doi.org/10.1007/s12029-018-0155-7

ORIGINAL RESEARCH

Outcomes of Neoadjuvant Chemoradiation in Patients with Gastro-esophageal Junction Adenocarcinoma: a Retrospective Cohort Study in Iran

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Published online: 7 November 2018

Abstract

Purpose The optimal treatment for locally advanced GEJ and cardia adenocarcinoma is controversial. Several studies have shown that treating these patients with neoadjuvant chemoradiotherapy followed by surgery leads to survival benefits, and there are also studies that have declared conflicting results. It seems that there is still room for discussion. We calculated the survival rates and pathologic responses in our patients with characteristics which we mentioned above.

Methods Patients with locally advanced, non-metastatic GEJ and cardia adenocarcinomas (only patients with Siewert's type I and II), who were referred to Imam Khomeini hospital (Institute of cancer) between 2005 and 2014 and received neoadjuvant chemoradiation and underwent surgery were enrolled in this retrospective cohort study. Evaluations were done every 3 months.

Results Thirty-two patients enrolled in this study. Median follow up time was 23 months (Reverse Kaplan-Meier method). The rates of 1-year survival, 2-year survival, 3-year survival, 4-year survival, and 5-year survival were 75%, 52%, 52%, 37%, and 37%, respectively. No local recurrences occurred among patients; however, four patients experienced distal recurrence in the following locations: two cases (6.3%) in the liver, one case (3.1%) in the lung, and one case (3.1%) in the peritoneum. The rate of complete pathologic response (T_0N_0) was 21.9%.

Conclusions Neoadjuvant chemoradiation in patients with locally advanced GEJ and cardia adenocarcinoma will lead to a survival benefit.

Keywords Chemoradiotherapy · Esophageal neoplasms · Gastrointestinal cancer · Iran · Neoadjuvant

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Introduction

Upper gastrointestinal tract malignancies are currently a significant health problem in the world [1]. Esophageal cancer is the eighth common cancer in the world [2] and the seventh most common cancer in Iran [3]. In Iran, it is estimated that out of a total of 35,000 deaths from cancer every year, about 5800 deaths are related to esophageal cancer. Meanwhile, Ardabil province has the highest incidence of cardia cancer in the world [4]. In recent years, the incidence of GEJ cancer has increased significantly [5]. Most patients with esophageal cancer present with locoregional invasion, and the optimal treatment in these patients is controversial [6]. Several studies have shown that treating these patients with neoadjuvant

chemoradiotherapy followed by surgery leads to a reduction in mortality and improvement in survival. However, there are also studies that have declared conflicting results comparing neoadjuvant chemoradiotherapy followed by surgery and surgery alone [7–10]. In several Phase I and II studies, concurrent pre-operative chemoradiation in resectable gastric carcinomas had stunning results [11–13]. There are few explanations why neoadjuvant treatment results in lower mortality rates and survival benefits including (1) neoadjuvant chemotherapy can eradicate pre-operative micrometastasis [14, 15], (2) it reduces the tumor cell shedding during surgery [15], (3) patient's tolerance for receiving full intensity chemotherapy is better before surgery compared with after surgery [15], and (4) it leads to significant downstaging and also increases resectability in several gastrointestinal cancers [15]. In a randomized clinical trial by Medical Council Oesophageal Cancer Working Group, 6% improvement in complete resection rate due to pre-operative chemotherapy has been reported (60% total resection rate in a group of patients who received pre-operative chemotherapy vs. 53% in a group of patients who treated by surgery alone ($p < 0.0001$)) [16]. According to a phase III trial study (CROSS study), the average survival rate in patients who underwent surgical treatment was 24 months, and in patients who received neoadjuvant chemoradiotherapy before surgery, it was 49 months [9]. Currently, the most commonly used treatment for patients with locally advanced esophageal adenocarcinomas is neoadjuvant chemoradiotherapy followed by surgery, although this approach is still under investigation [6].

It seems that there is still room for discussion. In Iran, despite the high prevalence of esophageal and gastric cancer and the increasing prevalence of GEJ cancer, studies on the outcomes of trimodality treatment are limited, which is why we decided to study the results and effects of pre-operative chemoradiation in patients with cardia and GEJ adenocarcinoma with locally advanced invasion. We will work on survival and measure the success rate of this method in our patients.

Materials and Methods

Patients and Tumors Characteristics

The population of this retrospective study was patients with biopsy-proven nonmetastatic locally advanced (patients whose tumors are T_3-$T_{4a}N_0$ or any T lymph node positive) cardia and GEJ adenocarcinoma (only patients with Siewert's type I and II), referring to the cancer institute of Imam Khomeini hospital between 2005 and 2014 which received neoadjuvant chemoradiation and then underwent surgery. All patients had been evaluated with complete medical history taking, physical examination, upper endoscopy (with biopsy), endo-ultrasonography (EUS) (to determine the clinical stage of the tumor), and chest and abdomen computed tomography (CT). Patients with metastatic or non-resectable tumors, as well as patients with tumors of other areas of the gastrointestinal tract, were not included in the study.

Treatment Protocols

All patients underwent pre-operative chemoradiation followed by surgery. The radiation dose was 41.4 Gy (1.8 Gy/fr) or 45 Gy (1.8 Gy/fr) or 50 Gy (2 Gy/fr) or 50.4 Gy (1.8 Gy/fr) according to the patients' condition. The radiation fields covered the GTV plus 3–5 cm longitudinal margin and 1.5–2.0 cm radial margin providing adequate coverage of involved nodes. Concurrent chemotherapy regimen was chosen from the following (standard regimens): Capecitabine (825 mg/m^2/PO/BID/d_1-d_5/weekly) (62.5%), 5-Flouracil (425 mg/IV/bolus/d_1/weekly) + Leucovorin (20 mg/m^2/IV/bolus/d_1/weekly) (9.4%), Cisplatin (30 mg/m^2/IV/d_1/weekly) + Capecitabine (800 mg/m^2/PO/BID/d_1-d_5/weekly) (9.4%), Carboplatin (AUC 6/IV/d_1/weekly) + Paclitaxel (150 mg/m^2/IV/d_1/weekly) (12.5%), and Capecitabine (625 mg/m^2/PO/BID/d_1-d_5/weekly) + Oxaliplatin (50 mg/m^2/IV/d_1/weekly) or (85 mg/m^2/IV/biweekly) (6.3%).

Assessment and Follow-up

All patients were evaluated every 3 months in a clinic. Each time, a complete history was taken, and a thorough physical examination was performed; then the reports were documented, and in case of any suspicious complaints or abnormal physical examination, upper gastrointestinal endoscopy or chest and abdominal computed tomography (CT) scans were requested as clinically indicated.

Statistical Analysis

All the data were analyzed using the Statistical Package for Social Sciences software (SPSS version 20.0, IBM Corporation, Chicago, IL, US). Disease-free survival (DFS) and overall survival (OS) rates were calculated based on Kaplan-Meier survival analysis algorithm. Log-rank test and Cox proportional hazards model were used to determine any significant predictors of OS. *P*-value significance was placed at < 0.05.

Results

A total number of 32 patients with locally advanced cardia and GEJ adenocarcinoma referred to the Institute of cancer of Imam Khomeini hospital complex between 2005 and 2014 and have received neoadjuvant chemoradiation and then have undergone surgery were enrolled in the study (see the detailed

Table 1 Patients' characteristics

Age	Mean (range)	63.4 (34–87)	SD = 10.9 (%)
Gender	Male	25	78.1
	Female	7	21.9
Clinical T	T_2	1	3.1
	T_3	25	78.1
	T_4	4	12.5
Clinical N	N_0	1	3.1
	N_1	13	40.6
	N_2	11	34.4
	N_3	5	15.6
Clinical stage	IIB	2	6.3
	IIIA	11	34.4
	IIIB	9	28.1
	IIIC	8	25
Surgical technique	Total gastrectomy	28	87.5
	Partial gastrectomy	4	12.5
Concurrent chemotherapy regimen	Xeloda	20	62.5
	5FU + LV	3	9.4
	Cisplatin/Xeloda	3	9.4
	Carboplatin/Taxol	4	12.5
	XELOX	2	6.3
Induction chemotherapy	Yes	10	31.3
	No	22	68.8

patients' characteristic in Table 1 and the clinical T*clinical N cross-tabulation of tumor in Table 2).

The median duration of neoadjuvant chemoradiation was 37 days (range 31–60). The median radiation dose was 50 Gy (range 41.4–52.2 Gy). The interval between neoadjuvant chemoradiation and surgery was a minimum of 20 days and a maximum of 413 days, and the median was 65.8 days. No patient received pre-operative chemotherapy. The mean tumor size was 2.8 cm ± 2.8 cm. The mean and median number of surgically resected lymph nodes were 9.3 ± 7.5 and 8.5, respectively. Twenty patients (62.5%) received adjuvant chemotherapy, and 12 patients (37.5%) did not receive adjuvant chemotherapy (see the detailed tumor characteristics in the surgical specimen in Table 3).

Among our patients, the rate of complete pathologic response (T_0N_0) was 21.9% (CI95% 9.4–37.5%) (7 cases), intermediate pathologic response ($T_{1–2}N_0$) was 43.8% (CI95% 25.0–59.4%) (14 cases), and poor pathologic response ($T_{3–4}N_0$ or $T_{any}N_+$) was 34.4% (CI95% 18.8–50.0%) (11 cases). TRG (Tumor Regression Grade) was 0 for 7 patients (21.9%) (CI95% 9.4–37.5%), 1 for 4 patients (12.5%) (CI95% 3.1–25.0%), 2 for 15 patients (46.9%) (CI95% 28.1–62.5%), and 3 for 6 patients (18.8%) (CI95% 6.3–34.4%) (see surgical T*Surgical N cross-tabulation in Table 4). Downstaging occurred in 27 (85.5%) patients. Median follow up time was 23 months (Reverse Kaplan-Meier method). The rates of 1-year, 2-year, 3-year, 4-year, and 5-year survival were 75% (CI95% 58.0–90.0%), 52% (CI95% 30.0–73.0%), 52% (CI95% 30.0–73.0%), 37% (CI95% 8.0–66.0%), and 37% (CI95% 8.0–66.0%), respectively. No local recurrences occurred among patients; however, four patients experienced distal recurrence in the following locations: two patients (6.3%) in the liver, one patient (3.1%) in the lung, and one patient (3.1%) in the peritoneum.

Table 2 Clinical T and N

EUS-N EUS-T	N_0	N1	N2	N3
T2	0 (0%)	1 (3.1%)	0 (0%)	0 (0%)
T3	1 (3.1%)	13 (40.6%)	9 (28.1%)	4 (12.5%)
T4	0 (0%)	1 (3.1%)	2 (6.2%)	1 (3.1%)

Discussion

There are different treatment options for a patient diagnosed with locally advanced GEJ and cardia adenocarcinoma which is surgery, definitive chemoradiation, and neoadjuvant chemoradiation followed by surgery. Though several studies have been shown improvement in survival and pathologic response

Table 3 Tumor characteristic in the surgical specimen

Surgical histology	Intestinal	4 (12.5%)
	Signet	1 (3.1%)
	Diffuse	3 (9.4%)
	Mucinous	2 (6.3%)
	Not specified	22 (68.7%)
Grade	Well differentiated	4 (12.5%)
	Moderately differentiated	5 (15.6%)
	Poorly differentiated	3 (9.4%)
	Undifferentiated	1 (3.1%)
	Not specified	19 (59.4%)
Stage	0	7 (21.9%)
	IB	2 (6.3%)
	IIA	3 (9.4%)
	IIB	5 (15.6%)
	IIIA	13 (40.6%)
	Not specified	2 (6.3%)
Surgery PNI	Absent	13 (40.6%)
	Present	14 (43.8%)
	Not specified	5 (15.6%)
Surgery LVI	Absent	20 (62.5%)
	Present	7 (21.9%)
	Not specified	5 (15.6%)
Margin	Free	31 (96.9%)
	Involved	1 (3.1%)

by treating patients with neoadjuvant chemoradiation followed by surgery, studies have also declared this to be contrary. We studied 32 patients with locally advanced cardia and GEJ adenocarcinoma, all of whom underwent neoadjuvant chemoradiation followed by surgery. Among these patients, the rate of complete pathologic response (T_0N_0) was 21.9% (seven patients). The 1-year, 2-year, 3-year, and 5-year survival rates were 75%, 52%, 52%, and 37%, respectively.

Van Hagen P et al. (2012) in their study known as CROSS trial introduced neoadjuvant chemoradiation followed by surgery as the gold-standard therapy for esophageal cancer. They have reported the 2-year and 5-year survival rates to be 67% and 47%, respectively, in patients with esophageal and esophagogastric junction cancer who underwent chemoradiation followed by surgery. In this study, the rate of complete pathologic response in patients with esophageal and GEJ cancer who received neoadjuvant chemoradiation was reported to be 29% [9]. In a study by Stahl et al. on patients with GEJ carcinoma, in a group of them who received pre-operative chemoradiation, the complete pathologic response rate was 15.6%, and the 3-year survival was 47.4% [17]. A randomized study was published in 1996 by Walsh et al. In this study, complete pathologic response and 3-year survival were reported being 25 and 37% ($P = 0.006$), respectively, in patients who underwent chemoradiation followed by surgery [18]. In another similar study, published by Urba et al. in 2001, 28% complete pathologic responses were observed with concurrent chemoradiation, and the 3-year survival rate was reported to be 30% ($P = 0.15$) [19]. By studying 256 patients, Burmeister et al. concluded that pre-operative chemoradiation had no effect on overall and disease-free survival but had a higher R0 resection rate and less chance of lymph node involvement, although the radiotherapy dose was not standard [20].

Table 4 Surgical T and N

Surgical-N Surgical-T	N_0	N_1	N_2
T_0	7 (21.9%)	1 (3.1%)	0 (0%)
T_2	4 (12.5%)	0 (0%)	0 (0%)
T_3	6 (18.8%)	10 (31.2%)	1 (3.1%)
T_4	3 (9.4%)	0 (0%)	0 (0%)

In Iran, in Yazd province, Ali Akhavan et al. conducted a study on patients with gastric and gastroesophageal junction adenocarcinoma (24.5% of them had GEJ adenocarcinoma), who referred to their center for post-operative radiation with or without chemotherapy (patients' clinical staging: T stages T_2b, T_3, and T_4 with or without positive lymph nodes and with no evidence of distant metastasis nor any previous history of cancer). In this study, the mean and the median survival rates were 50.9 and 51 months respectively. The 3-year and 5-year survival rates were 73 and 36%, respectively [21]. In a clinical trial by Kazem Anvari et al., in patients with locally advanced esophageal carcinoma (98.5% of patients had SCC) who underwent chemoradiotherapy followed by resection, the complete pathologic response rate was reported to be 29.9%. 5-Year survival rate was reported to be 48.2%, and the median overall survival duration was 44 months (CI95% 24.46–63.54) (Fig. 1) [22].

In a review article by Cellini et al., it was concluded that by accepting the reasonable toxicity rate of chemoradiotherapy, chemoradiation would be beneficial; it is highly recommended and will increase the survival rate of the patients [23]. In a phase III trial by Joel Tepper et al. in which they compared "Trimodality therapy with Cisplatin, Fluorouracil, radiotherapy" with surgery alone for non-metastatic esophageal cancer (23% of them were squamous cell carcinoma and 77% of them were adenocarcinoma), the median survival was 4.48 Vs. 1.79 years ($P = 0.002$) in favor of the first group and the 5-year survival was 39% Vs. 16% again in favor of the first group [24]. Also, in other studies, the superiority of pre-operative chemotherapy to surgery alone, in resectable GEJ adenocarcinoma, has been proved [25–33].

The results of our study were better compared with other studies which investigate the outcomes in patients who underwent upfront surgery. Despite this superiority in results, the outcomes of our patients are still less than that of similar studies, and the reasons can be the following: 1) poor

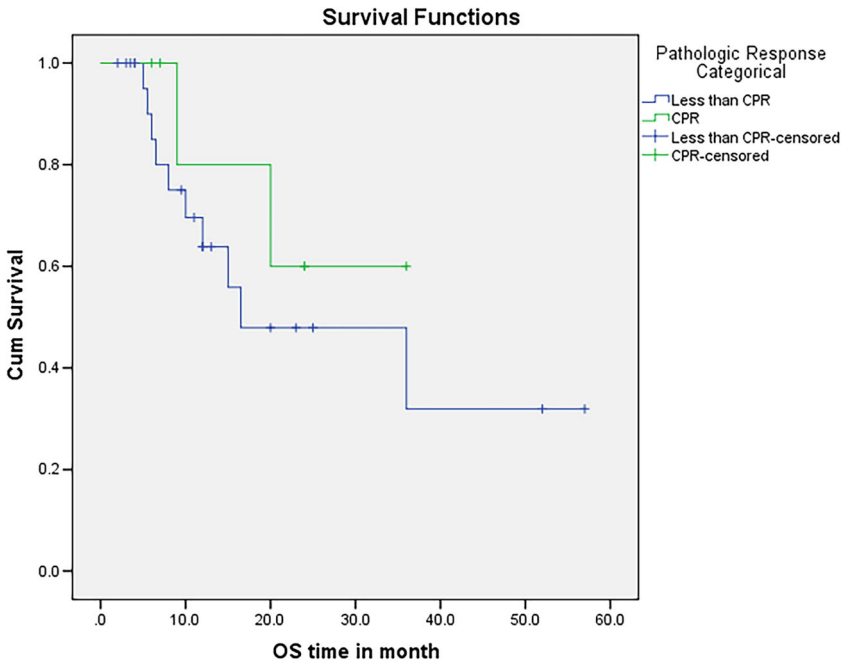

Fig. 1 5-Year overall survival

nutrition; 2) not doing laparoscopic staging (which leads to under staging); 3) our center is a referral center, and patients come from other provinces; therefore, there is lack of proper accommodation and nutrition while receiving treatment; 4) the long waiting list for surgery (which results in a long interval between neoadjuvant treatment and surgery); and 5) low sample size (as the study was performed in a single center). The weaknesses of the study can be noted as the following: 1) small sample size as mentioned and 2) short median follow-up duration. And as a strength of this study, we can mention the narrow inclusion criteria compared with other similar studies in Iran (as our research was so specific).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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