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Definitive Chemoradiation for Gastroesophageal Junction (GEJ) Adenocarcinomas: A Single-Institution Experience

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ABSTRACT

Background and Objectives: The non-surgical treatment outcome of gastroesophageal junction (GEJ) adenocarcinoma remains to be defined. We aimed to assess the outcomes of definitive chemoradiation (CRT) of GEJ tumors.
Methods: This retrospective cohort study was entirely carried out in the radiation oncology ward of Cancer Institute of Iran. We included patients with adenocarcinoma histology whose tumors had involved the gastro-esophageal junction and underwent chemoradiotherapy without surgery. In the final analysis, we evaluated 50 patients with non-metastatic adenocarcinoma of GEJ (Siewert's type I and II) from 2008 to 2017. The primary outcome was overall survival; secondary outcomes were progression-free survival and local and distal metastasis.
Results: The reasons for not undergoing surgery in order of frequency from highest to lowest were patient refusal or medical unfitness for surgery, tumor unresectability or progress at the time of operation and incident metastasis in pre-op restaging, and. The 1-year, 2-year, and 3-year overall survival rates were 53%, 26%, and 12%, respectively. The 1-year, 2-year, and 3-year progression-free survival rates were 44%, 18%, and 10%, respectively. In the multivariate analysis, the only independent predictor of survival was a distant failure (P=0.031).
Conclusion: Although the outcomes of non-surgical treatments are disappointing in GEJ adenocarcinomas, a few patients may experience long-term survival using definitive CRT. This option should be discussed with all patients who are not candidates for surgery.

Keywords: Esophagogastric Junction, Adenocarcinoma, Esophageal Neoplasms, Chemoradiotherapy, Survival Rate, Gastric Cancer

INTRODUCTION:

Worldwide, gastric and esophageal cancers are the fourth and seventh most common cancers, respectively [1]. In Iran, these cancers play a more substantial role in annual incidental cases of cancer. Based on national estimates, gastric and esophageal cancers are Iran's second and fourth most commonly diagnosed cancers [1]. Gastroesophageal junction (GEJ) cancers are a type of cancer sharing the clinicopathological characteristics of both esophageal and gastric cancers. Recently, there has been an increasing incidence of GEJ cancers, particularly in Western and Asian countries [2,3]. Unfortunately, most patients with GEJ cancers are diagnosed at an advanced stage with poor outcomes. Thus, only a minority of patients survive more than three years after surgical resection of their tumors [4].

According to Siewert's classification, GEJ adenocarcinomas (ADC) can be divided into three types. These include type 1 tumors with their epicenter located 1 to 5 cm above the anatomic GEJ, type 2, situated 1 cm above and 2 cm below the GEJ, and type 3, located between 2 to 5 cm below the GEJ [5]. According to recent guidelines, preoperative chemoradiation or chemotherapy followed by surgical resection are viable options for type 1 and 2 tumors (stage T1b and higher), although, the former method is preferred. For type 3 tumors, although perioperative chemotherapy is the standard of choice, surgery followed by adjuvant chemo/radiotherapy or even preoperative chemoradiation are other recommended options [6].

Despite advances in systemic therapies and radiation techniques, surgery is still the mainstay of treatment in esophageal and GEJ cancers. However, some patients are not candidates for surgical resection due to reasons such as inoperable tumors, comorbidities affecting medical fitness for anesthesia and surgery, and patient refusal. The clinical prognosis in these patients is poor, and the 5-year survival rate is around 20% [7,8]. Definitive chemoradiation (DCRT) is the treatment of choice in these patients. However, about 50% still experience loco-regional recurrence after DCRT [7,9].

According to recent trials, in patients with esophageal squamous cell carcinoma (SCC), we may opt for DCRT for treatment so that if a complete response occurs, one can forgo surgery. Nevertheless, there is a lack of data regarding the outcome of such an approach in ADC patients [10–13]. Besides, most studies investigating the role of DCRT did not exclusively evaluate patients with GEJ cancers; their population comprised both esophageal and GEJ tumors.

Our study aimed to assess the outcomes of patients with ADC of GEJ treated with DCRT in our institution.

Methods:

Study design, patients, and tumors characteristics

We performed a retrospective cohort study on 50 patients with biopsy-proven GEJ adenocarcinoma (evaluated with upper endoscopy, endo-ultrasonography (EUS), and computed tomography of chest and abdomen) who underwent concurrent chemoradiotherapy (CCRT) between August 2011 and October 2016 at Iran Cancer Institute. Patients without any post-treatment follow-up or those treated with either chemotherapy or radiotherapy were excluded. Moreover, patients with synchronous visceral, peritoneal, and non-regional lymphatic metastasis in primary diagnostic evaluations and those unable to receive concurrent chemotherapy were excluded from the study. The diagnostic staging laparoscopy was not mandatory before commencing chemoradiation. The study design was approved by the institutional review board (#94-03-207-30323).

The median age of the patients was 70 years (range: 46-85), and 36 (72%) patients were male (Table 1).

The most common clinical stage was IIIC. Only 12% of patients had stage II disease, while the remaining (88%) suffered from stage III disease (Table 2).

Treatment protocols

The patients were treated with external 3-dimensional conformal radiotherapy (mostly 18 Mega Voltage photon x-rays). The median interval between diagnosis and initiation of DCRT was 2.5 months. The median radiotherapy duration and dose were 38 days and

Table 1. Characteristics of Patients and treatments

Age		69±8.7
Male: Female		36:14 (72%:28%)
Grade	Well-differentiated	14 (28%)
	Moderately-differentiated	5 (10%)
	Poorly-differentiated	16 (32%)
	Non specified	15 (30%)
Clinical Stage	IIB	6 (12%)
	IIIA	13 (26%)
	III B	10 (20%)
	III C	21 (42%)
Induction Chemotherapy		16 (32.0%)
Concurrent Chemotherapy	5FU based	45 (90%)
	Taxane-based	5 (10%)
Biopsy to RT interval (months)		3.4±2.49
RT duration (days)		40±7.6
RT dose (Gray)		48±3.25

Table 2. Clinical tumor and node staging

		Clinical N stage				Total
	0	1	2	3		
Clinical T stage	2	-	1 (2.2%)	1 (2.2%)	-	2 (4.3%)
	3	5 (10.9%)	9 (19.6%)	8 (17.4%)	5 (10.9%)	27 (58.7%)
	4	1 (2.2%)	4 (8.7%)	11 (23.9%)	1 (2.2%)	17 (37.0%)
Total		6 (13.0%)	14 (30.4%)	20 (43.5%)	6 (13.0%)	46 (100.0%)

50 Gray, respectively. The most common concurrent chemotherapy regimen was oral daily capecitabine from day one to five/weekly (54%) followed by intravenous bolus 5-fluorouracil plus calcium folinate (5FU+LV) in the first and last week of radiotherapy (18%). Overall, 90% received 5FU-based regimens, and only 10% received a weekly intravenous carboplatin/paclitaxel combination. Due to the following reasons, none of our patients underwent surgery: 1) 70% were unfit for surgery or declined it, 2) 10% ended up having distant metastases after restaging evaluations, and 3) 20% were found to have peritoneal seeding or unresectable tumor at the time of laparotomy which resulted in abortion of surgery without gastrectomy.

Assessment and follow up

Our follow-up visits consisted of history and physical examinations performed every three months. Upper gastrointestinal endoscopy and/or chest and abdominal computed tomography (CT) scans were requested in patients with new complaints or abnormal physical exams. Routine response assessment to therapy was

not performed for all our patients. Metastatic patients received systemic chemotherapy and were evaluated with appropriate imaging studies for response rate.

Outcomes and analysis

Overall survival (OS) was considered the time from the end of radiation treatment to death due to any cause. Disease-free survival (DFS) was the time from the end of radiation therapy to local or distant metastasis or death due to any cause.

Data were analyzed using SPSS v.21 statistical software (IBM, Chicago, IL, USA). We used the Kaplan-Meier and Cox proportional hazards tests to assess disease-free survival and overall survival and their predictors. A p-value less than 0.05 was considered statistically significant.

Ethics

This study was designed and performed in agreement with the declaration of Helsinki and was approved by our institutional review board. All patients provided written informed consent regarding permission to extract data from their medical records for research purposes.

Results:

Treatment outcomes

The median follow-up duration was 42 months (reverse Kaplan-Meyer method). During follow-up, 24% of patients experienced local disease progression requiring intervention. Forty-two percent (21 patients) of subjects experienced distant metastasis during the follow-up period. The most common first site of distant failure was the peritoneum (seven patients), followed by the liver (four patients). Nine patients had a second metastatic site during follow-up. Thirty-seven patients died from their diseases during the follow-up period. The 1-year, 2-year, and 3-year overall survival rates were 53%, 26%, and 12%, respectively (Figure 1). The median OS time

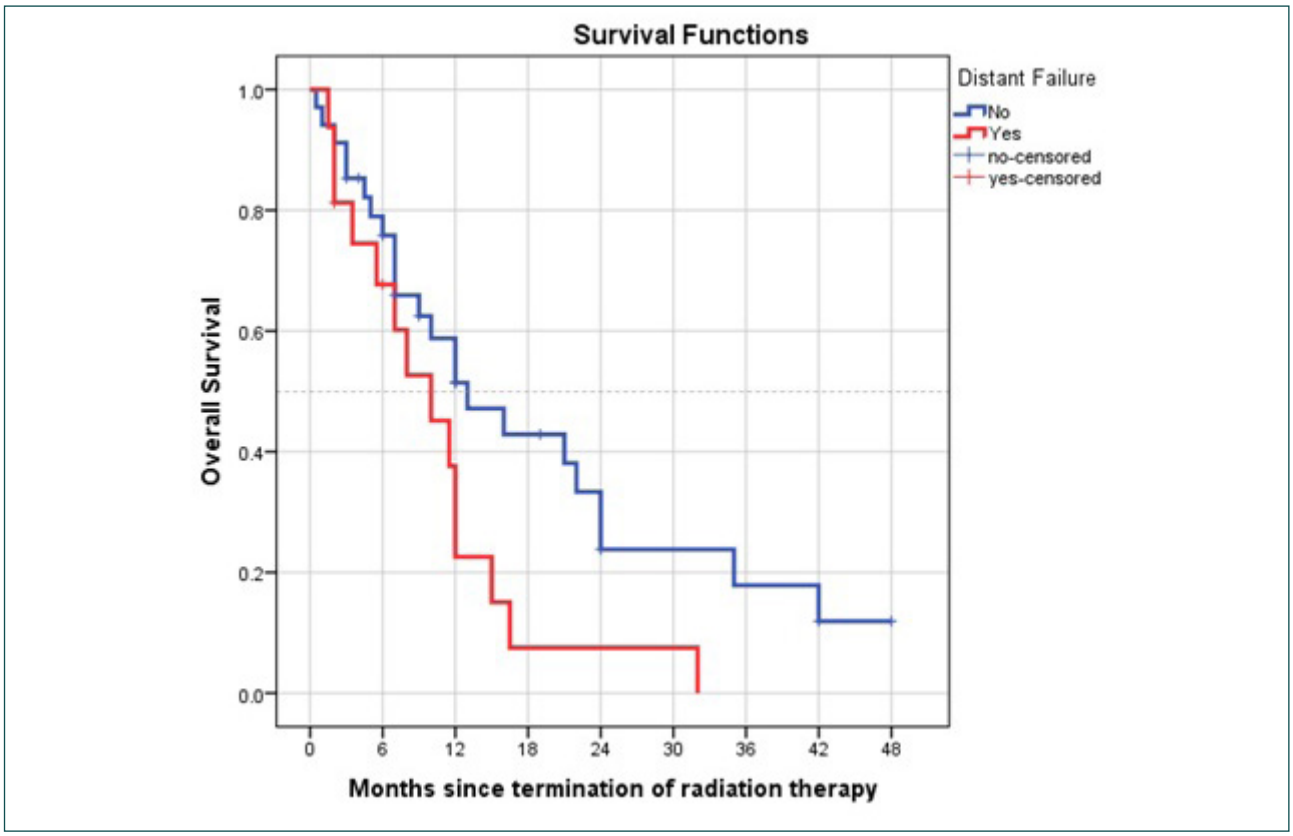

Figure 1. Figure 1. Overall survival in all patients

was 13.1 months. We observed a plateau in the survival curve for around 10% of our patients that seem to have long-term survival with dCRT.

The 1-year, 2-year, and 3-year progression-free survival rates were 44%, 18%, and 10%, respectively. The median PFS time was 10.7 months (Figure 2).

Predictors of overall survival

In the univariate Cox regression analysis (Table 3), age group, the reason for not having surgery, histologic grade, RT duration, and distant metastatsis were associated with overall survival with P values below 0.1. Every one-day increase in RT duration correlated with 1.04 times the risk of death (P=0.094). However, in multivariate analysis, the only independent predictor of survival was a distant failure (P=0.031).

The overall survival based on distant failure is demonstrated in Figure 3.

Discussion:

Surgery is the cornerstone of treatment in esophageal and GEJ adenocarcinomas. However, there are subsets of patients who are unsuitable for surgery (due to unresectability or comorbidities) or decline it. The next best treatment choice for these patients is considered to be definitive chemoradiotherapy, although systemic therapy alone would be another option. Thus far, most of the data for DCRT have been in esophageal cancer

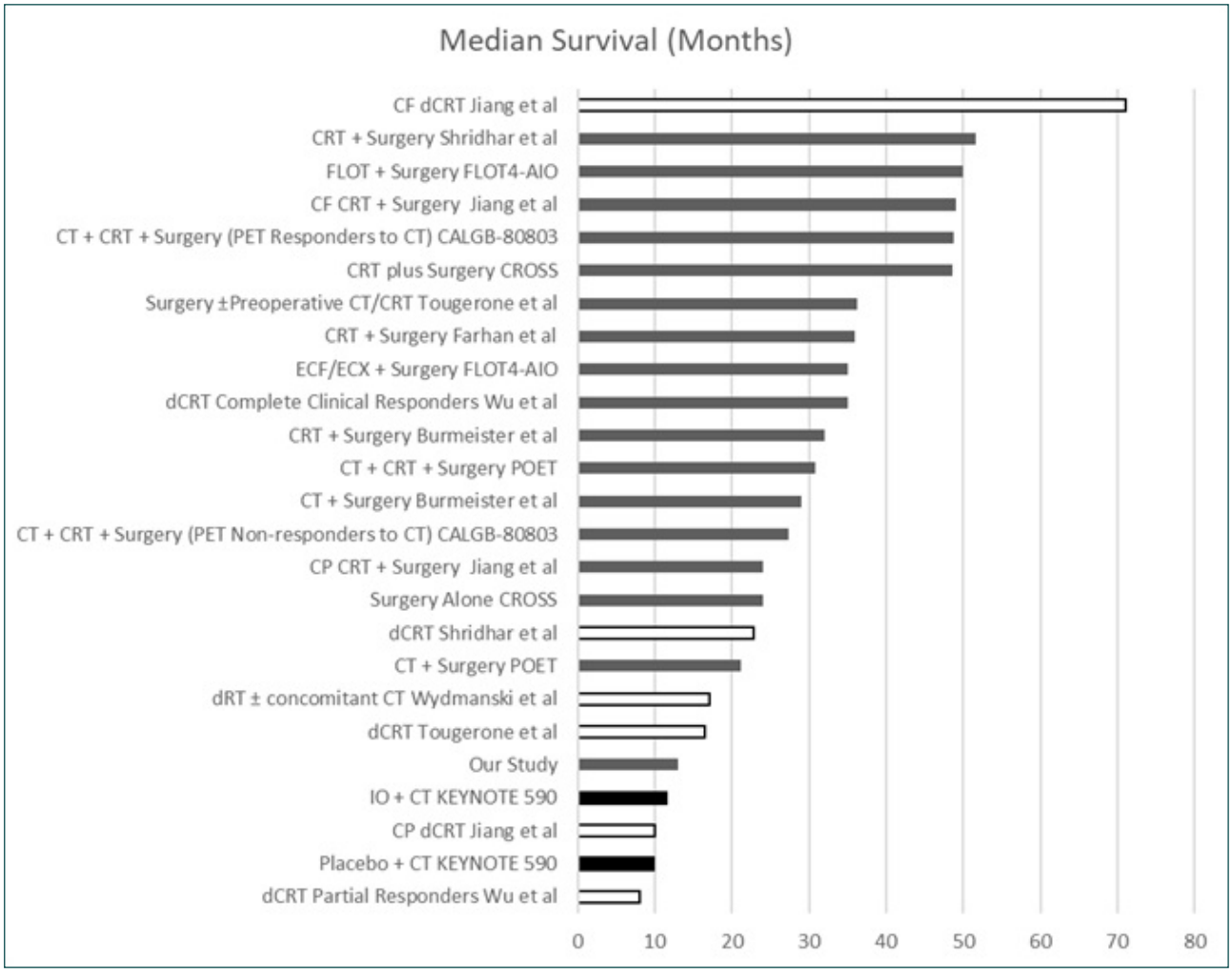

Figure 2. Progression-free survival in all patients

Table 3. Predictors of Median Overall Survival (Univariate and Multivariate Analysis)

Variable	Group	Median OS (months)	Hazard Ratio Univariate (95% CI)	P for Univariate Cox	Hazard Ratio Multivariate (95% CI)	P for Multivariate Cox
Age Group	65 year or less	6	Reference		Reference	
	Over 65 years	15	0.39 (0.20-0.77)	0.004	0.76 (0.31-1.83)	0.542
Sex	Male	13	Reference			
	Female	8	1.55 (0.73-3.29)	0.235		
Histological Grade	Well to Moderate	15	Reference		Reference	
	Poor	9	2.04 (0.92-4.53)	0.078	1.62 (0.69-3.77)	0.259
Clinical T	T2	12	Reference			
	T3	12	0.45 (0.10-1.99)	0.294		
	T4	7	0.66 (0.15-2.94)	0.590		
Clinical N	N0	12	Reference			
	N1	12	1.13 (0.39-3.30)	0.810		
	N2	7	1.38 (0.49-3.83)	0.536		
	N3	5	3.22 (0.89-11.60)	0.074		
Induction Chemo	Yes	16	Reference			
	No	11.5	1.5 (0.75-3.05)	0.246		
Concurrent Chemo Regimen	5FU based	12	Reference			
	Taxane-based	6	0.6 (.14-2.57)	0.482		
Radiotherapy Duration	Six weeks or less	12	Reference		Reference	
	More than Six weeks	10	1.87 (0.88-3.95)	0.102	1.4 (0.23-2.26)	0.577
Reason for not having the surgery	Medically Unfit/ Patient's Refusal	12	Reference		Reference	
	Met/Seeding/ Unresectable	7	2.04 (0.993-4.22)	0.052	1.7 (0.65-4.53)	0.275
Treatment-related Toxicity	Lower than Grade 3	12	Reference			
	Grade 3 or higher	8	1.03 (0.47-2.27)	0.932		
Distant Metastasis	No	13	Reference		Reference	
	Yes	10	2.00 (1.01-3.98)	0.048	3.4 (1.12-10.23)	0.031

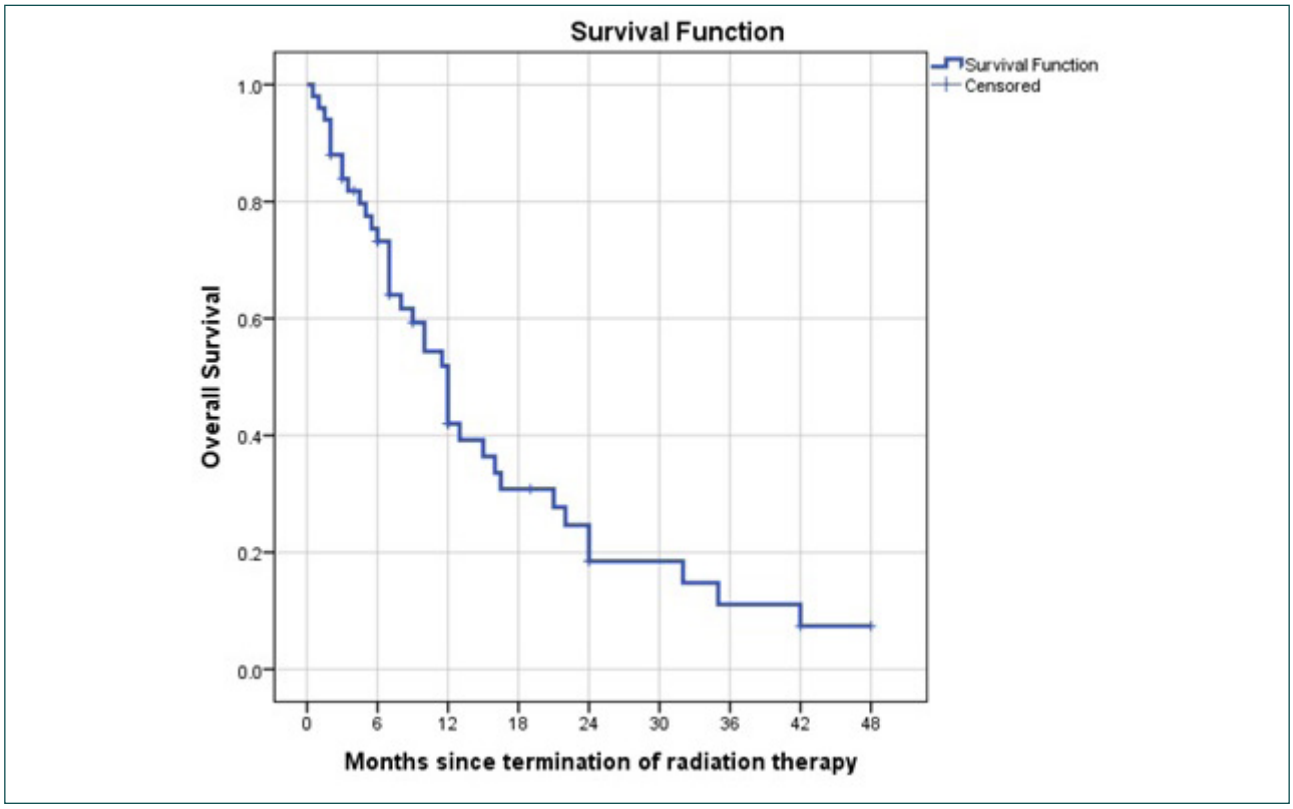

Figure 3. Overall survival based on distant failure

without focusing on a specific histology or GEJ site of the tumor. Our study is among the few that investigated the outcome of DCRT in patients with ADC of GEJ.

Most of our patients (~ 90%) presented at an advanced stage (stage 3). Seventy percent of them did not undergo gastrectomy due to comorbidities or declining the surgery. The remaining were found to have distant metastases, peritoneal seeding, or locally advanced unresectable tumors during surgery or presurgical restaging workup. During our follow-up time, 24% of our patients experienced local progression, while the rate is around 50% in the literature [14].

There are studies comparing trimodality (radiation + chemotherapy + surgery) treatment with DCRT in patients with ADC of the esophagus. Tougeron et al. compared the treatment results of patients with esophageal ADC in two groups, retrospectively: the surgery group (+/- preoperative treatment) versus the DCRT group (p=0.02). They concluded that DCRT was not an alternative to surgery in esophageal ADC treatment and that this method should be reserved for patients with significant operative risks [15]. In 2014, Shridhar et al. performed a retrospective comparison between DCRT and adding surgery to neoadjuvant chemoradiation in 154 patients with ADC of the esophagus. Median and 5-year OS for surgical patients were 4.1 years and 43.6% versus 1.9 years and 35.6% for non-surgical patients (p=0.007). They concluded that esophagectomy after CRT was associated with improved survival and that this approach should remain the standard of care for esophageal ADC [16].

Recently, a prospective trial has investigated the role of DCRT in patients with GEJ tumors. Takata et al. published their results of preoperative CRT in 61 patients suffering from GEJ tumors who declined surgery after pre-op CRT. All of their patients had acquired complete clinical response (CR), and 65% of patients had ADC histology. The 5-year OS and RFS

rates were 58.1±8.4% and 35.3±7.6%, respectively. They concluded that although the outcome in this patient group was reasonable, surgery must be encouraged for all trimodality-eligible patients [17].

In addition to the above studies, numerous studies addressed the outcome of various interventions in GEJ ADCa patients [18-28]. To have a better picture, Figure 4 is developed to see the median OS based on the study and the intervention in major clinical trials and retrospective studies in a manner almost similar to ours. As seen, studies incorporating surgery after neoadjuvant therapy reported superior outcomes. Among interventions excluding surgery, the results have been highly heterogonous, and rates have been reported between 8 months to 71 months. As seen, a subset of patients may benefit from long-term survival rates by dCRT, as seen in Jiang et al.'s study in its most prominent way [18].

As for our results, we observed one- and two-year OS of 53% and 26%, respectively, with a median OS time of 13.1 months. It seems that our patients' inferior OS, compared with some studies, is due to several limitations. Compared to other studies, our patients' median age was higher, which could have a detrimental effect on the outcome. Most of our patients did not undergo a thorough staging evaluation, and a few were staged using abdominal laparoscopy, making it possible that a subgroup of our patients had occult peritoneal metastases at presentation. Also, particular attention must be paid to the nutritional status of GEJ cancer patients. The majority of our patients did not have proper nutritional access, such as jejunostomy. Therefore, some of them could not go through the whole treatment plan in the appropriate duration. Lastly, we had a heterogeneous group of patients with a considerable fraction who had distant metastases during the presurgical evaluation but were not excluded from the study.

Nonetheless, our results are still superior to the outcome of patients receiving the best supportive care, with studies reporting that these patients' median OS is around five months [29]. At the same time, we observed a 15.9-month median OS time in our study. Although the outcome of DCRT in patients with ADC of GEJ is not

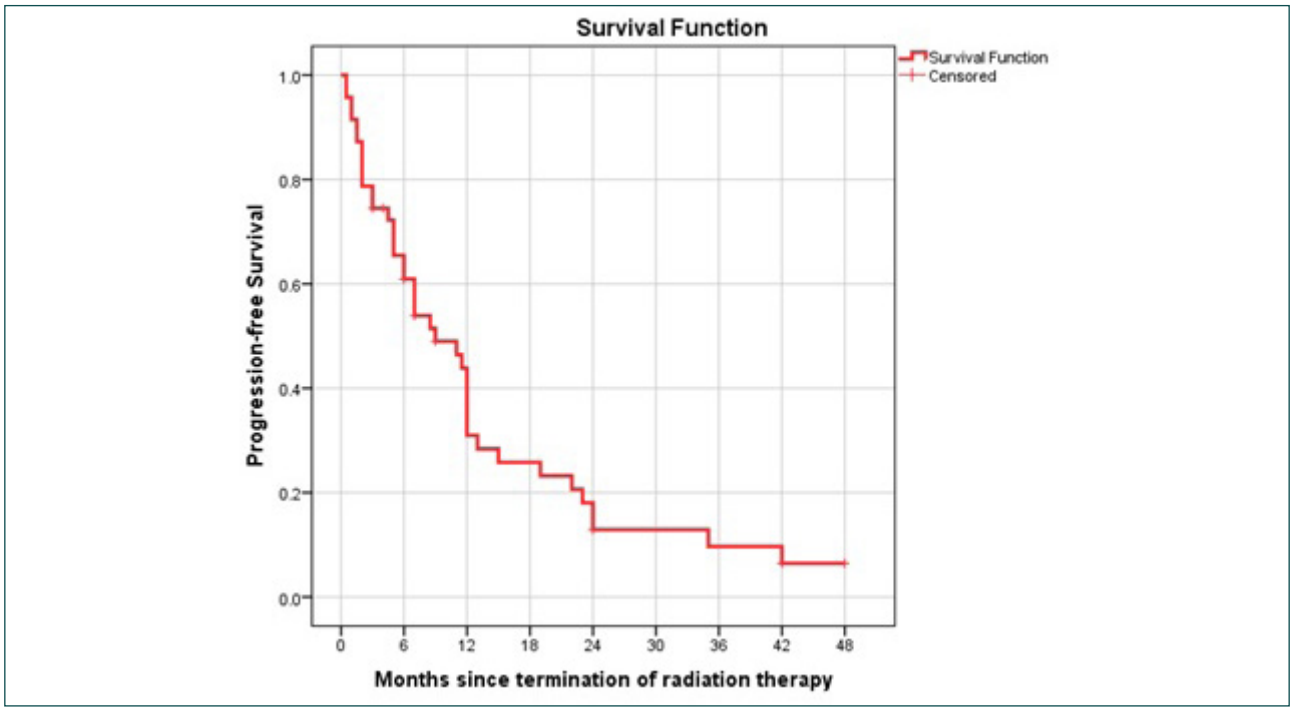

Figure 4. Median survival of studies in esophageal and esophagogastric adenocarcinomas. CF: Cisplatin and 5FU; CRT: Chemoradiation; CT: Chemotherapy;dCRT:definitivechemoradiotherapy;IO:Immunotherapy

as promising as trimodality therapy, this approach yields a much better outcome than the best supportive care in non-resected locally advanced or metastatic patients, making it a viable option for selected patients.

Conclusion:

Our results showed that definitive chemoradiation could be a viable option for patients who are not surgical candidates, and a small subset of patients may experience long-term survival. Further efforts should be made to first identify the long-term survivors and then improve outcomes in other subsets of patients, including providing secure nutritional access, performing staging laparoscopy, and encouraging patients to undergo surgery following chemoradiation in the medically fit group. Also, it would be important to compare the results of patients who undergo surgery after chemoradiotherapy with those who undergo chemoradiotherapy or chemotherapy alone in one population. Another direction is to evaluate the outcomes based on the molecular and genetic predictors to know which subgroup of patients benefits the most from chemoradiotherapy compared to other treatments.

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Conflict of Interests:

None declared.

Financial disclosures:

None declared.

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