

# The Outcomes of Esophageal and Gastric Cancer Treatments in a Retrospective Study, Single Center Experience

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## ABSTRACT

**Introduction:** Esophageal and gastric cancers are among the most common cancers in Iran. Usually survival of these cases is poor despite of treatment. Here we studied outcome of these cases in our center to have an estimation of general prognosis of patients.

**Methods:** In this retrospective study, we reviewed the data of patient's files before treatment, including cancer stage at diagnosis, types of treatments and outcomes. We studied 368 patients treated between 1995 and 2011.

**Results:** The study included 368 patients (248 [67.4%] males and 120 [32.6%] females) with a median age of 58 (range: 23 - 94). Sixty nine patients (18.8%) had esophageal cancer with a median age of 58.5 years (range: 33 - 84), and 47.8% (33/69) of whom were male. Sixty five (17.7%) were reported to have gastro-esophageal junction (GEJ) with a median age of 62.0 (range: 32 - 94), among them 72.3% (47/65) of whom were male and finally Two hundred thirty four (63.6%) had gastric cancer with a median age of 57.0 (range: 23 - 82), which 71.8% (168/234) of whom were male. The Median follow-up was 10 months. The majority of patients were diagnosed at an advanced stage of disease. Stage III or IV was observed in 65.0% (39/60) of patients with esophageal cancer, 75.0% (33/44) with GEJ cancer and 65.4% (121/185) with gastric cancer. In this study, 58% of patients with esophageal cancer, 50.8% with GEJ and gastric cancers had unresectable disease or metastases at presentation. One-year EFS was 51.8% (95% CI: 39.8 - 67.3%), 32.8% (95% CI: 22.1 - 48.7%), and 56.7% (95% CI: 50.1 - 64.3%) in patients with esophageal, GEJ and gastric cancers, respectively ( $p=0.002$ ). The 1-year OS was 54.5% (95% CI: 42.6 - 69.8%), 39.5% (95% CI: 28.1 - 55.5%), and 68.2% (95% CI: 61.8 - 75.3%), respectively ( $p<0.001$ ).

**Conclusion:** Cancers of the upper gastrointestinal (GI) tract contribute to the high mortality and morbidity rates because they are more likely to be diagnosed at late or advanced stages of disease. Cancer of the GEJ has a poor prognosis compared to esophageal and gastric cancers. Moreover, treatment protocols may need improvement to achieve better results.

**KEYWORDS:** Esophageal cancer, Gastric cancer, Survival analysis

## INTRODUCTION

Esophageal and gastric cancers are among the most common cancers in Iran (according to report

of ministry of health of Iran). As they are typically diagnosed at more advanced stages, chemotherapy and invasive surgery are usually necessary. Gastric

cancer is the second leading cause of cancer-related death that Approximately 700,000 people succumbed to this malignancy in the world in 2000.<sup>1</sup> Despite declining rates of gastric cancer in western countries and Japan, unfortunately Iran still have a high incidence, particularly in the north and northwest of the country, both men and women.<sup>2,3</sup>

Esophageal and gastric cancer are multi-factorial diseases and different risk factors such as genetic factors, male gender, lifestyle, nutrition (salted and low levels of antioxidants), alcohol, smoking, infection, and H.pylori bacteria have been associated with the development of them.<sup>4,5</sup> Race and ethnicity can also be independent risk factors for esophagus and gastric cancers.

Majority of Iranian patients present at an advanced stage of disease.<sup>6</sup> To improve results of their treatment needs, we need to study patient's outcome in our country and compare results with others to know possible pitfalls.

Surgery has an important role in treatment of the esophagus and stomach cancers. Different extensions of surgery applied in different parts of the world. In case of gastric cancer, D2 surgery recommended by experts as preferred type of surgery and lymph node dissection but this type of surgery is popular in limited number of centers with high expertise in dealing with gastric or GEJ cancers. Chemotherapy and radiotherapy can improve results of treatment and usually added to treatment protocols.<sup>7-9</sup>

In this retrospective study we studied the outcomes of different treatment modalities applied in our center to have an estimation of general outcome of these diseases.

## MATERIALS AND METHODS

In this retrospective study, we analyzed the data of 368 patients that were treated in our center between 1995 and 2011. We studied patient's files and extract data according to our designed data gathering sheet. This questionnaire included demographic data of patients, type of histology according to pathology reports, stage of disease (according to AJCC classification), and type of surgery.

Also, we studied patient's outcomes from time of diagnosis to endpoints (death, and disease progress

or death in case of non metastatic or non-locally advance disease).

Survival curves were calculated using Kaplan-Meier estimators and 95% confidence intervals (CI) were computed using log-transformed method. Cox proportional hazards (PH) model was used to estimate the effect of variables on event-free survival (EFS) and overall survival (OS). The estimated effects were reported through hazards ratio (HR) with 95% confidence interval (CI). Variables which were associated with EFS and OS with p-values less than 0.2 were candidate to enter the final model. To find the multiple predictors of EFS and OS, Cox PH model with backward elimination method was applied. The PH assumption was tested using the chi-square test of correlation coefficient between transformed survival times and Schoenfeld residuals. The "survival" package in R software version 3.0.0 was used to conduct the analyses.

## RESULTS

Demographic data of 368 patients are presented in Table 1. Sixty nine patients (18.8%) had esophageal cancer with a median age of 58.5 (range: 33 – 84), and 33 (47.8%) were male. Sixty five (17.7%) were reported to have GEJ with a median age of 62 (range: 32 – 94), and 47 (72.3%) were male. Two hundred thirty four (63.6%) had gastric cancer with a median age of 57 (range: 23 - 82), and 168 (71.8%) were male patients (Table 1).

The Radiologic type of lesion in patients with esophageal, GEJ, and gastric cancer were ulcerative in 16 (23.2%), 22 (33.8%), and 70 (29.9%), polypoid-fungating in 9 (13.0%), 2 (3.1%), and 24 (10.3%), and infiltrative in 5 (7.2%), 9 (13.8%), and 32 (13.7%), respectively.

Histopathological type of cancer in esophageal, GEJ, and gastric cancer were adenocarcinoma in 15 (21.7%), 51 (78.5%), and 208 (88.9%), and were squamous cell carcinoma in 44 (63.8%), 7 (10.8%), and 1 (0.4%), respectively. The remaining patients had other histopathologic types of cancer.

Median follow-up of survivors was 10 months. One-year EFS in adenocarcinoma patients was 52.4% (95% CI: 46.1 – 59.5%) and in squamous cell carcinoma patients was 51.0%, (95% CI: 37.5 – 69.3%; p = 0.679). One-year OS in adenocarcinoma

was 61.6%, (95% CI: 55.4 – 68.5%), and in squamous cell carcinoma was 56.3% (95% CI: 42.6 – 74.2%;  $p = 0.710$ ).

Comorbidities (including heart disease, major cardiovascular diseases, pulmonary disease, etc.) were observed in 10 (14.5%), 8 (12.3%), and 20 (8.5%) of patients with esophageal, GEJ and gastric cancer. Also, 4 (5.8%), 2 (3.1%), and 15 (6.4%) of patients had a positive family history of gastric cancer at the time of diagnosis.

Overall staging at the time of diagnosis, were operable in 28 (40.6%), 28 (43.1%), and 122 (52.1%), and were locally advanced disease in 17 (24.6%), 10 (15.4%), and 23 (9.8%), and were metastatic disease in 21 (30.4%), 16 (24.6%), and 71 (30.3%) in esophageal, GEJ and the gastric cancer, respectively.

Stage of disease at diagnosis for cancer of the esophagus, GEJ, and gastric were respectively 8.3% (5/60), 6.8% (3/44), and 3.8% (7/185) in stage I; 26.7% (16/60), 18.2% (8/44), and 30.8% (57/185) in stage II; 28.3% (17/60), 40.9% (18/44), and 24.9% (46/185) in stage III; and were 36.7% (22/60), 34.1% (15/44), and 40.5% (75/185) in stage IV.

Only 30 (12.8%) patients with gastric cancer received neoadjuvant treatment. most patients were referred to this center after surgery.

The median proportion of positive lymph nodes of totally removed lymph nodes in patients undergoing surgery was 42.9% (range: 0 to 100%),

which is correlated with disease stage (Spearman's  $\rho = 47.4\%$ ). The hazard ratio of EFS per 10 percent increase in proportion of positive lymph nodes was 1.09 (95% CI 1.02 – 1.15;  $p = 0.006$ ) and the hazard ratio of death per 10 percent increase in proportion of positive lymph nodes was 1.04 (95% CI 0.98 – 1.11;  $p = 0.221$ ).

The histological grades of all patients were 20.8% (49/236) of grade I, 34.3% (81/236) of grade II, and 44.9% (106/236) of grades III or IV. One-year EFS of histological grades were 59.3% (95% CI: 45.5 – 77.2%), 55.3% (95% CI: 4.3 – 69.1%), and 48.7% (95% CI: 39.2 – 60.4%) in grades I, II, and III or IV, respectively ( $p=0.031$ ). One-year OS of histological grades was 63.5% (95% CI: 50.1 – 80.5%) in grade I, 64.2% (95% CI: 53.3 – 77.3%) in grade II, and 59.1% (95% CI: 49.4 – 70.6%) in grade III or IV ( $p=0.052$ ).

Seven (10.1%) of patients with esophageal cancer, 2 (3.1%) of GEJ cancer, and 2 (0.9%) of gastric cancer patients underwent to dilatation as a palliative treatment.

One-year EFS in stages I/II, III, and IV were 69.0% (95% CI: 59.4 – 80.3%), 55.2% (95% CI: 44.7 – 68.2%), and 35.1% (95% CI: 25.8 – 47.9%), respectively ( $p<0.001$ ; Figure 1a). Likewise, one-year OS was 77.6% (95% CI: 68.9 – 87.4%) in stage I/II, 66.1% (95% CI: 55.8 – 78.2%) in stage III, and 47.6% (95% CI: 37.4 – 60.7%) in stage IV ( $p<0.001$ ; Figure 1b).

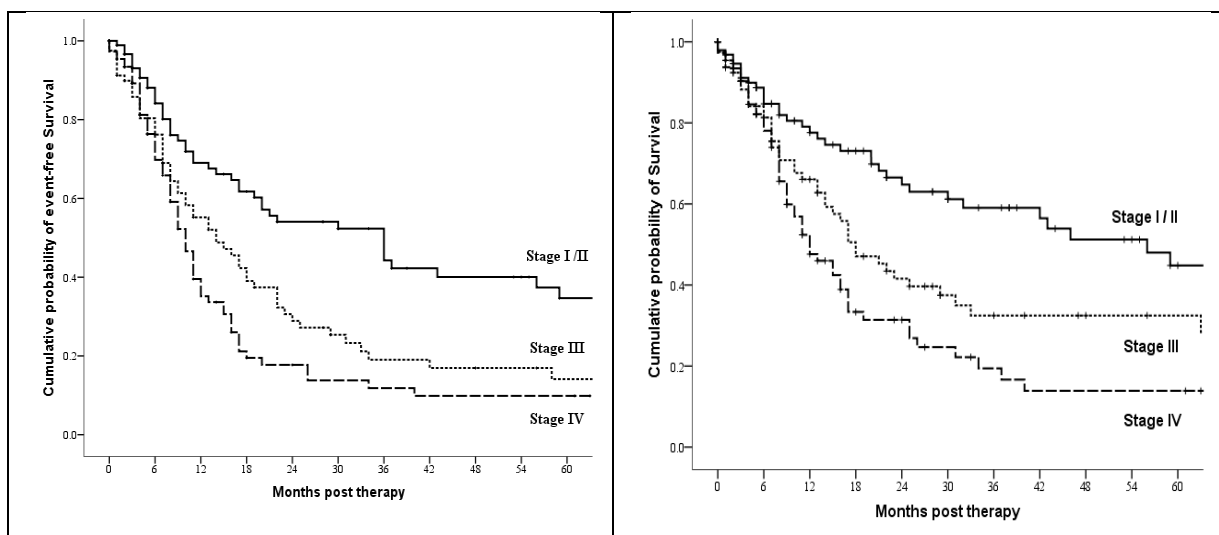


Figure 1. a: EFS, b: OS according to Stage of Disease

**Table 1. Patient and treatment characteristics**

		Esophageal (n=69)	GEJ (n=65)	Stomach (n=234)
Age at Dx.	Median (range)	58.5 (33 - 84)	62 (32 - 94)	57 (23 - 82)
Gender	Male	33 (47.8%)	47 (72.3%)	168 (71.8%)
	Female	36 (52.2%)	18 (27.7%)	66 (28.2%)
Stage of disease	I / II	21/60 (35.0%)	11/44 (25.0%)	64/185 (34.6%)
	III	17/60 (28.3%)	18/44 (40.9%)	46/185 (24.9%)
	IV	22/60 (36.7%)	15/44 (34.1%)	75/185 (40.5%)
Radiologic type	Ulcerative	16 (23.2%)	22 (33.8%)	70 (29.9%)
	Polypoid fungating	9 (13.0%)	2 (3.1%)	24 (10.3%)
	Infiltrative	5 (7.2%)	9 (13.8%)	32 (13.7%)
Histopathologic type	Adenocarcinoma	15 (21.7%)	51 (78.5%)	208 (88.9%)
	Squamous cell carcinoma	44 (63.8%)	7 (10.8%)	1 (0.4%)
	Other types	10 (14.5%)	7 (10.8%)	25 (10.7%)
Comorbidities		10 (14.5%)	8 (12.3%)	20 (8.5%)
Positive family history		4 (5.8%)	2 (3.1%)	15 (6.4%)
Overall staging	Operable	28 (40.6%)	28 (43.1%)	122 (52.1%)
	Locally advanced	17 (24.6%)	10 (15.4%)	23 (9.8%)
	Metastatic	21 (30.4%)	16 (24.6%)	71 (30.3%)
LN+/TLN proportion <sup>1</sup>	Median (range)	7.7% (0 - 100%)	35.4% (0 - 100%)	50% (0 - 100%)
Histological grade	I	14/38 (36.8%)	15/49 (30.6%)	20/149 (13.4%)
	II	11/38 (28.9%)	15/49 (30.6%)	55/149 (36.9%)
	III/IV	13/38 (34.2%)	19/49 (38.8%)	74/149 (49.7%)

<sup>1</sup>LN+/TLN proportion, The proportion of positive lymph nodes of totally removed lymph nodes.

One-year EFS, in esophageal cancer, GEJ, and gastric cancer was 51.8% (95% CI: 39.8 – 67.3%), 32.8% (95% CI: 22.1 – 48.7%) and 56.7% (95% CI: 50.1 – 64.3%), respectively (p=0.002) while one-year OS was 54.5% (95% CI: 42.6 – 69.8%), 39.5% (95% CI: 28.1 – 55.5%), and 68.2% (95% CI: 61.8 – 75.3%; p<0.001), respectively. Although, after adjustment for stage of disease, there was no statistically significant difference between the three types of cancer with EFS (p=0.253). After adjust for disease stage, the hazard ratio of EFS in GEJ versus esophageal cancer was 1.46 (95% CI: 0.88, 2.43; p=0.142), and the hazard ratio of EFS in stomach cancer versus esophageal cancer was 1.05 (95% CI: 0.71, 1.55; p=0.806).

Using multivariable analyses, the only important predictor of EFS was stage of disease while the multiple predictors of OS were found as stage of disease, age at diagnosis, and neoadjuvant therapy (Table 2).

**Table 2. Multiple predictors of EFS and OS**

		HR	95% CI	p
EFS	Stage of disease			
	I/II	1	---	<0.001
	III	1.89	1.28 - 2.80	0.001
	IV	2.43	1.65 - 3.58	<0.001
OS <sup>1</sup>	Age at diagnosis	1.02	1.01 - 1.04	0.003
	Neo-adjuvant	1.85	1.07 - 3.22	0.029
	Stage of disease			
	I/II	1	---	0.001
	III	1.77	1.14 - 2.75	0.011
	IV	2.3	1.49 - 3.55	<0.001

<sup>1</sup> The proportional hazards assumption was confirmed (p=0.693).

## DISCUSSION

Despite the problems of a retrospective study, our study represents an estimate of the survival in

patients who are referred to us in different stages of disease. In gastric cancers generally D1 resection is most common in Iran. So, our study is more comparable with western studies than Japan and Southeast Asian Studies.<sup>7-10</sup>

In Kunz study the 3-year survival of gastric cancer patients reported 20%.<sup>10</sup> In this study, only 34.5% of patients were with localized stage that corresponded with our conditions. Generally prognosis for gastric cancer is poorer in our country than western countries according to our results and previous reports.<sup>6, 11, 12</sup>

In total, improvements in outcomes of treatment may need to develop clear guidelines and use of more effective surgery and better methods of chemotherapy and radiotherapy. Also, appropriate supportive therapy may improve outcome.

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