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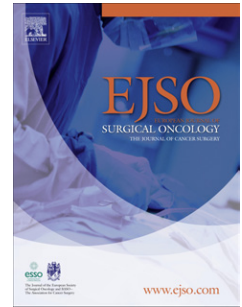
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**Palliative gastrectomy and other factors affecting overall survival in stage IV gastric adenocarcinoma patients receiving chemotherapy: A retrospective analysis**

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**Running header:** Gastric cancer prognostic factors

**Key words:** prognostic factors, gastric carcinoma, palliative surgery, chemotherapy, survival

**Abstract**

**Objective:** Most patients with gastric cancer present with locally advanced or metastatic disease and usually receive palliative therapy. We sought to identify factors influencing overall survival in patients with stage IV gastric cancer receiving palliative chemotherapy.

**Patients and Methods:** The records of 311 patients with histological diagnosis of gastric adenocarcinoma were retrospectively reviewed and 17 clinicopathological and therapeutic parameters were evaluated for their influence on overall survival.

**Results:** In multivariate analysis 9 factors were found to independently influence survival: no previous palliative gastrectomy [Hazard ratio (HR, 12; CI 7.969-18.099)], single agent chemotherapy instead of combination chemotherapy (HR, 1.35; CI 1.068- 1.721), histological grade III (HR, 1.39; 95% CI 1.098-1.782), the presence of hepatic (HR, 1.6; 95% CI 1.246-2.073) and abdominal metastasis (HR, 1.33; 95% CI 1.039-1.715), CA 72-4 >7 U/L (HR, 1.39; 95% CI 1.026-1.887), LDH > 225 U/L (HR, 1.72; 95% CI 1.336-2.236], need for blood transfusions (HR, 1.58; 95% CI 1.213-2.082), and weight loss > 5% (HR, 1.96; 95% CI 1.352-2.853) at the time of initial diagnosis. Patients were stratified as low (0-2 factors), intermediate (3-6 factors) and high (7-9 factors) risk and the median survival was 76, 40 and 11 weeks, respectively.

**Conclusion:** Nine clinical and laboratory factors that adversely affect survival in patients with stage IV gastric cancer who receive chemotherapy were identified. Their concurrent presence seems to have an additive effect as patients with seven to nine factors have the worse prognosis. Palliative gastrectomy and combination chemotherapy appear to be associated with improved survival.

## Introduction

Gastric cancer is an aggressive tumour, posing the second leading cause of cancer specific mortality worldwide. Disease prevalence is higher in countries of northeast Asia (Japan, Korea, China), intermediate in Europe, South America and lower in North America, Australia and New Zealand. Overall survival in the United States, Europe and China is 20-25%, however reported survival in Japan is better (52%) which could be attributed to early detection through nationwide implementation of screening programs and optimized management[1]. In Greece, mortality rates from gastric cancer have been reported to be 10,9 and 5,8 / 10<sup>5</sup> for men and women, respectively[2].

Surgery is considered to be the most appropriate treatment for gastric cancer.

However, the majority of gastric cancer patients present with locally advanced or metastatic disease, despite the progress in diagnostic modalities and curative resection is feasible in only 36% of cases; moreover, even patients with presumed resectable disease have relapse rates of 40-60%[3]. Evidently, palliative treatment evolves as the primary management strategy for many gastric cancer patients. A number of trials have justified the use of palliative chemotherapy as compared to best supportive care to improve patient survival [4]. On the contrary, there is still insufficient evidence to recommend palliative gastrectomy in terms of survival benefit and therefore, the decision for surgery in current practice is individualized based on patient's clinical status and local surgical expertise, aiming at symptom relief and maintenance of patient's independence and function.

Given that chemotherapy and/or surgery could be associated with significant complications, there is a need to identify prognostic factors which may determine treatment response and survival in stage IV gastric cancer patients. Such an approach could refine palliative management according to the likelihood of clinical benefit. The aim of this study was to evaluate factors affecting survival in patients with stage IV gastric adenocarcinoma receiving palliative chemotherapy.

## Patients and Methods

### *Patients and data sources*

The medical records of 311 patients who received chemotherapy for histopathologically diagnosed stage IV gastric cancer between February 1997 and

October 2007 were retrospectively reviewed. All were consecutive non-selected cases from a single Oncology Center and all patients were treated outside of clinical trials. Stage IV gastric cancer was defined based on American Joint Committee on Cancer (AJCC, 6<sup>th</sup> edition) as M<sub>1</sub> or T<sub>4</sub>N<sub>1-3</sub>M<sub>0</sub>[5]. Patients with Gastro-Esophageal junction tumors, lymphoma and squamous cell carcinoma were excluded. All patients included in the study had histological diagnosis of gastric adenocarcinoma and all demographic, clinical, imaging, laboratory and follow-up data were available. Metastatic disease was diagnosed by applying various imaging modalities, including chest X-ray, ultrasonography and computed tomography. Tissue specimens were obtained by gastroscopy, surgery, or fine-needle aspiration biopsy from liver lesions. 218 (70%) had previously undergone palliative surgery (subtotal or total gastrectomy) at six different tertiary Greek hospitals where primary evaluation and surgical treatment was performed and further referral to the oncology centre initiated. The indications for palliative gastrectomy were judged individually by attending surgeons based on patients' general health, performance status, symptoms, extent of disease and feasibility of resection. Single-agent chemotherapy regimens were based on leucovorin modulated 5-Fluorouracil (5-FU, n= 135). Combination chemotherapy regimens included combination treatments based on Irinotecan, Oxaliplatin and Capecitabine according to established protocols (n=176)[4,6]. These protocols evolved over time in accordance to internationally accepted standards and guidelines with respect to stage IV gastric cancer. The primary end point of the study was Overall Survival (OS). The study was approved by the Ethical Committee for Research Projects of Laiko Hospital, Athens, Greece.

### ***Prognostic variables***

17 putative clinicopathological and therapeutic prognostic variables were selected, based on factors identified by previous studies, as well as our own clinical experience[7-15]. Patient-related factors included age ( $\leq 60$  years or  $>60$  years), gender, and pre-treatment performance status (PS) according to the Karnofsky Performance Status Scale Index. Tumor-related factors included symptoms including pain (yes vs. no), weight loss (no, 0 - 5%,  $>5\%$ ), and necessity for blood transfusions (yes vs. no); location of primary tumor (body vs. antrum), histological grading according the World Health Organisation (WHO) system, location of

metastasis: Local invasion, lymph nodes, liver, lung, ovaries, bone abdomen/peritoneum; and biochemical parameters. For the latter, group categorizations were used: for carcinoembryonic antigen (CEA): normal  $\leq 5$  ng/dl vs. elevated  $>5$  ng/dL; for cancer antigen 19-9 (CA 19-9): values  $\leq 30$  U/ml vs.  $>30$  U/ml; for cancer antigen CA 72-4 (CA 72-4): normal  $\leq 7$  U/ml vs. elevated  $>7$ U/ml; for C-reactive protein (CRP): normal  $<5$  mg/dl vs. elevated  $>5$  mg/dl; for Albumin normal  $>3.4$  g/dL vs. decreased  $<3.4$  g/dL; and for Lactate Dehydrogenase (LDH): normal  $<225$  U/L vs. elevated  $>225$  U/L. Factors related to therapy included palliative gastrectomy (yes vs. no) and chemotherapy (single agent vs. combination chemotherapy).

### Statistical analysis

Descriptive statistics were calculated with the use of mean, median and standard deviation for quantitative measurements and counts/percentages for discrete factors. Survival data were studied with the use of Kaplan-Meier method. Changes in survival between groups were recorded with the log-rank test. Prognostic models were established by searching all variables that significantly related OS at a level of  $P$  values  $\leq 0.05$  in the univariate analysis. Multivariate analysis was subsequently carried out using stepwise Cox proportional hazards modeling for OS. Best model selection for the factors that significantly affected OS factors were based on automated techniques. Results of regression analyses were displayed in the form of regression estimates tables. Hazard ratios (HRs) of outcomes under study were calculated for each parameter estimate as well as 95% confidence intervals. All categorical variables were compared using a baseline category as reference. All analyses were conducted at a 5% significant level using SPSS v12.0 statistical package.

## Results

### Patients

311 patients with Stage IV gastric cancer were included in this analysis. The median age was 62 years (range: 30-74) and the frequencies of the clinicopathological variables are shown in Table 1. Palliative surgery was performed in 70% of patients. All patients received chemotherapy; single agent and combination chemotherapy were administered in 43.5% and 56.5% of patients, respectively.

### Overall Survival

Survival data were collected for all patients. No patient was alive by the time of this analysis. The 1-year overall survival rate was 36%. Based on the Kaplan-Meier method, the median survival time (MST) was recorded at 39 weeks (95% CI 34- 44 weeks) (Figure 1).

### Univariate Analysis

In univariate analysis the following parameters were found to adversely relate to survival (Table 2): Single agent chemotherapy (P= 0.011), PS 60-70 (P<0.001), histology Grade III (P= 0,033), presence of hepatic (P< 0.001) and peritoneal/abdominal metastasis (P= 0.009) , need for blood transfusions (P< 0.001), weight loss > 5% (P< 0.001), no previous palliative gastrectomy (P< 0.001), albumin < 3.4 g/dL (P< 0.001), LDH > 225 U/L (P< 0.001), CRP >5 mg/dL (P< 0.001), presence of pain (P< 0.001), CA 19-9 >30U/ml (P= 0.009) and CA 72-4 >7 U/ml (P= 0.007).

### Multivariate Analysis

Factors that were found to be significantly related to OS were included in the multivariate analysis which is presented in Table 3.

#### *Hazard Ratios of Risk Factors*

9 prognostic factors were found to independently affect survival. 2 factors had a positive influence on survival including palliative gastrectomy and combination chemotherapy. In particular patients who had undergone palliative gastrectomy had 12 times lower probability of death compared with those who had no surgery and patients who had received combination chemotherapy had 1.35 lower probability of death compared to those received single agent chemotherapy. 7 factors were found to adversely affect survival including the presence of hepatic, abdominal/peritoneal metastasis (HRs 1.60 and 1.30 respectively), Grade III histology (HR, 1.40), CA 72-4 >7 U/L (HR, 1.39), LDH> 225 U/L (HR, 1.72), weight loss > 5% (HR, 1.96), and the need for blood transfusions at presentation (HR, 1.58).



### **Prognostic Grouping**

A prognostic grouping of the 311 patients was carried out according to the following criteria; low risk group: zero to two factors, intermediate risk group: three to six factors, high risk group: seven to nine factors and the corresponding survival curves are depicted in Figure 2. One year survival rates for low, intermediate and high risk patients were calculated at 71%, 33% and 0%, respectively (Figure 2).

### **Discussion**

We retrospectively analyzed data from 311 patients with Stage IV gastric adenocarcinoma who had undergone palliative chemotherapy. Our analysis demonstrated that factors associated with disease burden had a negative effect on survival. These included the presence of hepatic and abdominal/peritoneal metastasis, histological grade III, elevated CA 72-4 levels, elevated LDH levels and poor functional status at the time of initial presentation as indicated by weight loss > 5% and anemia necessitating blood transfusions.

#### **Prognostic significance of hepatic and abdominal/peritoneal metastasis**

Hepatic and abdominal/peritoneal metastasis have been shown previously to adversely affect survival in a multivariate analysis of a large cohort of patients with locally advanced and metastatic esophago-gastric cancer with an estimated hazard ratio of 1.41 and 1.33 respectively[7]; similar results were subsequently reported by others[9,15].

#### **Prognostic significance of histological grading**

The various histological indexes commonly used for grading gastric cancer have been extensively investigated with regards to their prognostic potential with conflicting results[16,17]. The main difficulty in the histological classification of gastric cancer is the great variability of architectural and cytological features that may be present within the same tumor, hence, the prognostic significance of the various commonly used indexes for grading gastric cancer is rather controversial[18]. Nevertheless, our study supports the prognostic significance of the WHO histological staging as histology grades I, II and III were associated with progressively decreasing survival time (MST 50, 42 and 34 weeks respectively).

**Prognostic significance of CA 72.4**

Tumor markers can be used clinically for monitoring of tumor recurrence as well as prognostic factors. Our results conform to previously published reports on the prognostic significance of CA 72-4 in Stage IV gastric cancer. Preoperative CA72-4 levels have been shown previously to be more frequently elevated in patients with gastric cancer and lymph node (P=0.01), peritoneal (P=0.03) and liver involvement (P=0.001), being associated with a 3.8-fold higher risk of death by multivariate analysis[19]. The prognostic significance of CA 72-4 has been further highlighted by a sub- group analysis of patients with advanced gastric cancer (stages III and IV) in the study published by Louhimo *et al.*, (HR, 1.2)[12].

**Prognostic significance of LDH**

Our study reinforces the prognostic significance of elevated LDH levels, a well established prognostic indicator in terminally ill cancer patients [20].

**Prognostic significance of weight loss**

The etiology of weight loss at presentation in patients with gastric cancer is complex and poorly characterized and implies a physical wasting process, in excess of the degree of nutritional deficit. Decreased intake due to the anatomical location of tumor and cytokine induced anorexia may further aggravate the problem. The association of weight loss with poor survival, as well as with higher toxicity and lower chemotherapy response rates has already been described among patients with gastric cancer[21,22], similarly to the results presented in our study.

**Prognostic significance of blood transfusions**

The relationship between blood transfusions and survival in gastric cancer remains controversial. A previous study by Kampschoer *et al.* [23] showed no difference between 5-years survival rates in transfused and non-transfused patients grouped by stage and similar results were reported by others [24]. On the contrary, other reports, including an analysis of 1,710 patients with Stage III and IV gastric cancer by Hyung *et al.* showed that survival in transfused patients was clearly poorer than in nontransfused patients [25], which is in accordance to our findings.

**Prognostic significance of palliative gastrectomy**

Our study highlights the importance of palliative gastrectomy as a modality associated with improved survival. The value of palliative operations, including gastrectomy, in patients presenting with metastatic gastric cancer is still unsettled, since palliative gastrectomy was associated in some early studies with significant postoperative

morbidity, prolonged hospital stay and poor quality of life[13]. Moreover, the indications and the type of the appropriate palliative surgical treatment in such patients are rather based on clinical judgment, local surgical expertise and patient's arguments than on data from controlled trials[26]. The rationale for offering palliative gastrectomy to patients with locally advanced or metastatic gastric cancer is to avoid tumor bleeding, perforation, obstruction, or complicated ascites and to possibly improve the outcome by reducing tumor burden, rendering the patients more responsive to adjuvant modalities. It has been postulated that tumor volume reduction diminishes the hypercatabolic state and may also confer immunological benefit by reducing the production of tumor derived immunosuppressive cytokines[14,27]. Although limited by a small number of patients Saidi *et al.* demonstrated a significantly better survival in gastrectomised patients who received adjuvant chemotherapy as compared with a chemotherapy only group (P= 0.01; mean survival 16.3 months versus 5.9 months). In their study the mortality and morbidity of palliative gastrectomy was 8.7% and 33.3% respectively, which was not statistically different from the mortality and morbidity following curative gastrectomy [14]. Similar results were obtained from subsequent analysis of larger cohorts demonstrating improved survival in patients with advanced gastric adenocarcinoma after palliative gastric resection, as compared to those who did not undergo the procedure[8-10]. In the current study, patients with previous palliative gastrectomy had clearly more favorable clinical course compared with those without gastrectomy (MST 53 vs. 16 weeks).

### **Prognostic significance of combination chemotherapy**

Single agents used in the first line setting achieve only modest responses and are preferred for patients who are unable to tolerate combination chemotherapy[28]. Combination regimens are able to achieve better response rates at the expense of increased toxicity and are therefore preferred in appropriately selected patients. A meta-analysis comparing trials of systemic mono-therapy with those of multi-agent therapy, showed a significant increase in response with multi-agent therapy, with a hazard ratio of 0,83 (95% CI 0,74-0,93) and improvement in overall survival by about 1 month[4]. Nevertheless, no chemotherapy combination has been accepted as the gold standard in Stage IV gastric cancer. Both CF [cisplatin(CDDP/5)- 5-fluorouracil (5-FU)] and ECF (epirubicin-CDDP/5-FU) are seen as regimens of reference, but the median survival time (MST) does not exceed 7-10 months[29]. Options have

expanded as it has been shown that capecitabine is at least as good as 5-FU and that oxaliplatin at least as good as cisplatin in these combinations[6]. In our study, 135 patients were treated with single agent chemotherapy (leucovorin modulated 5-FU while 176 patients had received combination chemotherapy and on multivariate analysis combination chemotherapy evolved as an independent prognostic factor for survival as compared to single agent chemotherapy (MST was 29 weeks for the single agent chemotherapy group and 45 weeks for the combination chemotherapy group, while 1- year survival was 29.6% and 45%, respectively). These results further add to the accumulation of data from other studies suggesting a clear survival benefit when palliative gastrectomy is combined with postoperative chemotherapy [11,14]. In particular, Lin *et al.* have shown that the 1-year, 3-year and 5-year survival rate of stage IV gastric cancer patients who were treated with palliative gastrectomy and postoperative chemotherapy were 85.7%, 32.1%, and 8.9%, which were far better for those who were not; moreover, survival benefits were also apparent in patients with liver metastasis, peritoneal dissemination, and/or N3 lymph node metastasis if treated with this multimodality approach.

#### **Prognostic scoring system**

Prognostic scoring systems have been defined in several cancer types and are being increasingly used in clinics to stratify patients into different risk groups. The nine factors found by our analysis to independently affect survival in Stage IV gastric cancer were further evolved into a prognostic model which separates patients into three groups with distinct prognosis with 1-year survival rates for low, intermediate and high risk patients at 71%, 33% and 0%, respectively.

#### **Study limitations**

The limitations of this analysis are the retrospective setting and the involvement of surgical teams from six different tertiary Greek hospitals in the surgical management of patients. Nevertheless, all surgeons were affiliated with the Medical School of the National and Kapodistrian University of Athens, practiced in hospitals with adequate case volume and, more importantly, applied similar therapeutic protocols/algorithms [30]. In addition, all patients were consecutive, non-selected cases, received chemotherapy treatment outside clinical trials, and were followed up by a single Oncology Center under the supervision the same oncology team which further addresses a real life situation.

## Conclusions

A number of factors may independently influence survival in stage IV gastric cancer patients. Factors associated with the severity of the disease such as the presence of hepatic and abdominal/peritoneal metastasis, histological grade III, elevated CA 72-4, elevated LDH and poor functional status at time of initial diagnosis as indicated by weight loss > 5% and anemia necessitating blood transfusions have a detrimental effect on survival. Therapeutic modalities such as palliative gastrectomy and combination chemotherapy appear to favor survival, although interpretation of data is restricted by the retrospective nature of the study and possible variability in the quality and the modality of the surgical procedures performed. In addition, it is anticipated that the prognostic model based on the above parameters will facilitate individual risk stratification and assist in the design of future prospective studies.

## Conflict of interest statement

No conflicts of interest.

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**Table 1.** Patient Characteristics

		(n=311)	(%)
Age	≤60	137	44.2
	>60	173	55.8
Gender	Male	209	67.2
	Female	102	32.8
PS	60-70	117	37.6
	80	107	34.4
	90-100	87	28.0
Pain	No	176	56.6
	Yes	135	43.4
Weight Loss	No	73	23.5
	0-5%	148	47.6
	> 5%	90	28.9
Blood Transfusion	No	183	58.8
	Yes	128	41.2
Tumor Location	Body	179	57.6
	Antrum	132	42.4
Histological Grade	I	14	4.5
	II	179	57.6
	III	118	37.9
Metastasis	Local invasion	163	52.4
	Lymph nodes	247	79.4
	Liver	162	52.1
	Lung	26	8.4
	Ovaries	29	9.3
	Bone	12	3.9
	Abdomen/Peritoneum	151	48.6
CEA	≤ 5 ng/ml	158	50.8
	> 5 ng/ml	153	49.2
CA 19-9	≤30 U/ml	118	37.9
	> 30 U/ml	193	62.1
CA 72-4	≤7 U/ml	59	19.0
	> 7 U/ml	251	81.0
CRP	≤ 5 mg/dL	165	53.1
	>5 mg/dL	146	46.9
Albumin	>3.4 g/dL	171	55.0
	< 3.4 g/dL	140	45.0
LDH	<225 U/L	137	44.2
	> 225 U/L	173	55.8
Palliative gastrectomy	No	93	29.9
	Yes	218	70.1
Chemotherapy	single agent chemotherapy	135	43.5
	combination chemotherapy	176	56.5
	chemotherapy		

PS: performance status, CEA: Carcinoembryonic Antigen, CA 19-9: Cancer Antigen 19-9, CA 72-4: Cancer Antigen 72-4, CRP: C-Reactive Protein, LDH: Lactate Dehydrogenase.



**Table 2.** Univariate Analysis for Survival

Variable		MST	1-year survival %	P-value	
Age	≤ 60	39	37.2	0.536	
	>60	40	34.1		
Gender	Male	40	35.4	0.728	
	Female	36	32.4		
Chemotherapy	single agent	29	29.6	0.011	
	combination chemotherapy	45	45.0		
PS	60-70	21	16.2	<0.001	
	80	48	44.9		
	90-100	55	50.6		
Histological Grade	I	50	35.7	0.033	
	II	42	39.1		
	III	34	29.7		
<b>Metastasis</b>	Local	No	41	0.409	
		Yes	33		34.4
	Lymph nodes	No	36	0.110	
		Yes	40		39.7
	Liver	No	50	<0.001	
		Yes	28		24.7
	Lung	No	40	0.155	
		Yes	30		23.1
	Ovaries	No	39	0.715	
		Yes	40		34.5
	Bone	No	40	0.078	
		Yes	17		25.0
	Abdomen/Peritoneum	No	42	0.009	
		Yes	33		27.8
Blood Transfusion	No	53	50.3	<0.001	
	Yes	21	15.6		
Weight Loss	No	51	48.0	<0.001	
	0-5%	48	45.3		
	> 5%	12	8.9		
Palliative gastrectomy	Yes	53	51.4	<0.001	
	No	16	0.0		
Albumin	>3.4 g/dL	50	46.2	<0.001	
	< 3.4 g/dL	21	22.1		
LDH	<225 U/L	57	51.8	<0.001	
	> 225 U/L	30	22.0		
CRP	≤ 5 mg/dL	48	44.9	<0.001	
	>5 mg/dL	24	25.3		
Pain	No	45	43.2	<0.001	
	Yes	22	25.9		
CA 19-9	≤30 U/ml	48	42.4	0.009	
	> 30 U/ml	38	31.6		
CA 72-4	≤7 U/ml	50	44.1	0.007	
	> 7 U/ml	38	33.5		
CEA	≤ 5 ng/ml	40	32.3	0.359	
	> 5 ng/ml	37	39.2		
Location	Body	No	40	34.9	0.454

	Yes	38	34.1	
Antrum	No	40	34.1	
	Yes	38	34.9	0.454

MST: median survival time, PS: performance status, LDH: Lactate Dehydrogenase, CRP: C-Reactive Protein, CA 19-9: Cancer Antigen 19-9, CA 72-4: Cancer Antigen 72-4, CEA: Carcinoembryonic Antigen

**Table 3.** Multivariate Analysis of Survival

		P-Values	HR	95.0% CI	
				Low	High
<b>Palliative Gastrectomy</b>					
No vs. Yes		0.000	12	7.969	18.099
<b>Chemotherapy</b>					
single agent vs. combination		0.013	1.35	1.068	1.721
<b>Liver metastasis</b>					
Yes vs. No		0.000	1.60	1.246	2.073
<b>Abdominal/Peritoneal metastasis</b>					
Yes vs. No		0.024	1.33	1.039	1.715
<b>Histological Grade</b>					
Grade III vs. Grade I		0.007	1.39	1.098	1.782
Grade II vs. Grade I		0.889	0.95	0.528	1.741
<b>CA72-4</b>					
>7 vs. ≤7		0.034	1.39	1.026	1.887
<b>LDH</b>					
Yes vs. No		0.000	1.72	1.336	2.236
<b>Weight Loss</b>					
> 5% vs. 0-5%		0.599	0.92	0.685	1.244
> 5% vs. No		0.000	1.96	1.352	2.853
<b>Blood Transfusions</b>					
Yes vs. No		0.001	1.58	1.213	2.082

HR: Hazard Ratio, CI: Confidence Interval, CA 72-4: Cancer Antigen 72-4, LDH: Lactate Dehydrogenase.

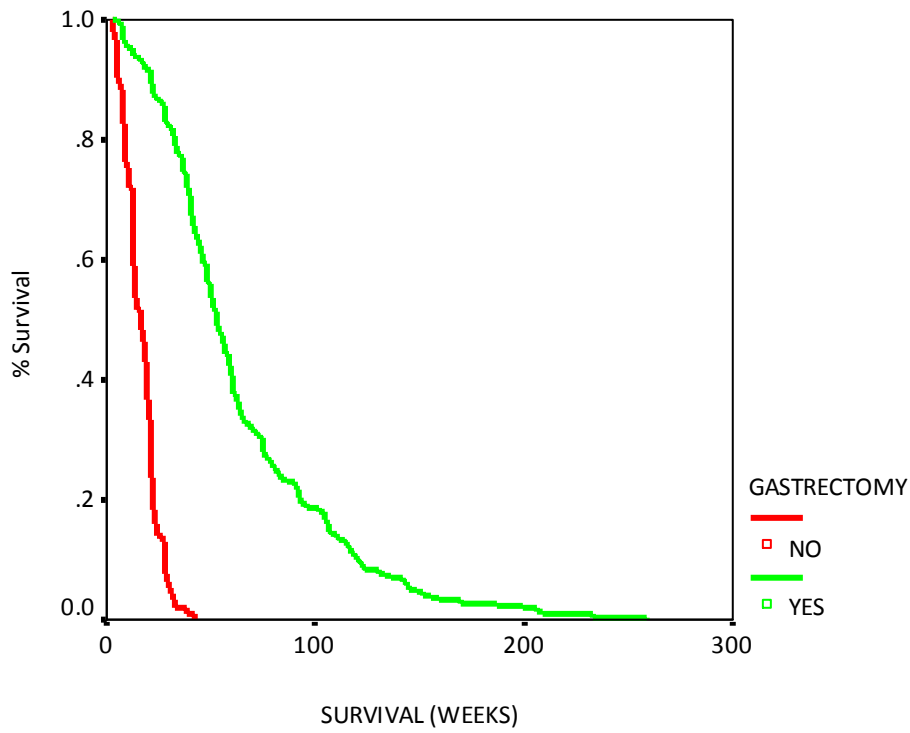
**Figure 1.** Overall Survival (Patients with gastrectomy vs patients without gastrectomy)

Figure 2.

