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## ORIGINAL PAPER

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# Survival Time in Treatment Modalities of Gastric Carcinoma at King Khalid Hospital- Jeddah Saudi Arabia: a Retrospective Cohort Study

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## ABSTRACT

**Background:** Gastric cancer (GC) is the fifth most common cancer worldwide and is responsible for 10% of annual cancer deaths. Gastric cancer treatment requires a multimodality approach involving surgery, adjuvant chemotherapy (AC), and neoadjuvant chemotherapy (NAC) for locally advanced tumors. Surgical removal of the tumor is the most common and effective curative approach with a more promising survival rate. **Objectives:** Due to the scarcity of studies in the kingdom of Saudi Arabia, this study aims to provide an epidemiological background on the subject and compare multiple treatments and their survival outcomes in a tertiary hospital in the western region. **Methods:** After obtaining the IB approval, data was collected from medical files of all histologically confirmed GC patients (101) between the years 2000-2015. In this study, patients' demographics, tumor characteristics, treatment types, and patients' vital status (deceased or alive) were collected. Survival analysis between treatment modalities subgroups was carried out using the Kaplan-Meier test and Cox regression model. **Results:** Out of 101 patients with GC, 65.35% were males with a mean age of 64.9±19 years and 61.71±17.83 years for female patients. Most patients had a stage IV tumor 47 (74.6%). The adjuvant chemotherapy group had a median survival time of 140 months (95% CI 33.72-246.29), while the neoadjuvant chemotherapy was 69 months. Patients who only underwent surgery had a median survival time of 28 months (95% CI 0-56.14), whereas patients who received no intervention had a median survival time of 8 months (95% CI 1.47-14.53) (log-rank = 0.002). The median

overall survival time for all patients was 28 months (95%CI 0-77.68) with an overall five-year survival rate of 19.6%. Cox regression model revealed that treatment type and tumor stage were significant predictors of survival with p values of 0.001 and 0.009, respectively. **Conclusion:** Adjuvant, neoadjuvant, and palliative chemotherapy constitute the paramount treatment modalities of GC with adjuvant treatment having the highest survival time. However, these modalities necessitate further understanding as to whether other factors play a role in the selection of one treatment with the preferable outcome.

**Keywords:** Stomach Neoplasms, Neoadjuvant therapy, Adjuvant therapy, Survival.

## 1. INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer worldwide with approximately 990,000 people diagnosed annually, of whom about 738,000 die from this disease, making it the second deadliest cancer (1). Of all the different forms of cancer, GC is responsible for 8% of total cancer cases and 10% of annual cancer deaths worldwide (2). Gastric cancer is considered one of the highest cancer burdens measured by disability-adjusted life years lost (1). The global incidence of GC estimated in 2011, was more frequent among men and was subsequently ranked the fourth most common cancer with 640,000 cases following lung cancer, and fifth most common in women with an incidence of 350,000 cases (2). In addition to gender, age is an essential demographic factor that is strongly

associated with an increased prevalence of GC. In the United States, approximately 1% of cases were diagnosed between the ages of 20 and 34 years during the period between 2005 and 2009, whereas 29% of cases diagnosed between the ages of 75 and 84 years (1).

Gastric cancer treatment requires a multimodality approach involving surgery, adjuvant chemotherapy (AC), and neoadjuvant chemotherapy (NAC) for locally advanced tumors. Surgical removal of the tumor is the most common and effective curative approach with a more promising survival rate (3). A retrospective study conducted in Iran estimated a 5-year survival rate increase from 47% to 54% in patients who underwent resection alone (4). While resection is the initial curative step, a well-known standard approach implements the use of AC after surgery, which can increase overall survival in comparison to surgery alone (5). On the other hand, recent studies advocated the effectiveness of NAC, especially when it is associated with a high resection rate (6). Both AC and NAC have been progressively applied to improve the prognosis of localized advanced GC, particularly in the East (7).

In Saudi Arabia, gastric cancer accounts for 2.9% of all diagnosed cancers. According to the Saudi Cancer Registry, 291 cases of GC were diagnosed in 2010 which suggests a slight increase in the incidence over the last decade in both genders (8). A hospital-based study was conducted at King Faisal Specialist Hospital to measure the incidence of GC in 76 patients. Out of the 76 patients enrolled in the study, only 2 patients underwent NAC, 7 patients underwent AC, and 13 patients underwent surgery alone. The remaining 54 patients were excluded from the study due to a lack of follow-up, death, or palliative care. The findings suggest that patients who underwent surgery alone had a lower overall survival rate than those who underwent neoadjuvant or adjuvant chemotherapy (9). The study did not specify certain criteria for choosing one treatment over another, nor did it directly compare the prognosis or survival rate in patients treated with AC and NAC. For further evaluation of available treatment modalities, this study aims to propose which treatment modality is associated with a better prognosis in GC patients and provide epidemiological background at Princess Norah Oncology Center in Jeddah.

## 2. OBJECTIVES

Due to the scarcity of studies in the kingdom of Saudi Arabia, this study aims to provide an epidemiological background on the subject and compare multiple treatments and their survival outcomes in a tertiary hospital in the western region.

## 3. MATERIAL AND METHODS

After obtaining the Institutional Review Board approval from King Abdullah International Medical Research Center (KAIMRC) to conduct this retrospective study in Princess Norah Oncology Center located in King Khalid Hospital in the western region of Saudi Arabia, 103 medical files were selected for all patients diagnosed with GC between the years 2000 and 2015. The data extracted from files with confirmed histopathological features of GC included age, gender, date of diagnosis and last contact, types of treat-

ment, the pathological features, site of the tumor, the clinical outcome, and stage of the tumor at the time of diagnosis based on the criteria of the American Joint Committee on Cancer (AJCC) 7th edition guidelines (10). We excluded patients with a pathologic diagnosis of esophageal cancer or treated with more than one treatment modality. Further exclusion criteria included patients diagnosed outside of our center and patients who were diagnosed at our center but preferred to seek treatment at another center.

Included patients were retrospectively followed-up until the end of the year 2019, and vital status information (deceased or alive) was extracted from digital files or directly contacted patients with inactive digital records beyond the year 2015. The duration of survival time was defined as the period from the date of histopathological diagnosis of GC to the date of death, or to the end of 2019 for patients who survived. Intervention plans for each patient involved a multidisciplinary team (MDT) whose role consisted of frequent meetings to provide an individualized interventional approach for each patient. The MDT is comprised of multispecialty personnel from multiple departments including medical and radiation oncology, pathology, radiology, gastrointestinal surgeons, and general surgeons with other subspecialties. The assessment of each patient depends on the stage of cancer and how well the recommended treatment modality can be tolerated. Patients who had localized gastric cancer (stage I to III) were evaluated for the potential of resection, and those who had advanced or metastatic disease (stage IV) were treated with palliative chemotherapy or referred to palliative care as determined by the MDT.

### Statistical analysis

Statistical analyses were carried out using SPSS ver. 23.0 software (IBM Corp., Armonk, NY). For nominal data (gender, type of treatment modality, tumor site, and stage of the tumor), all values were presented as percentages. For normally distributed numerical data (age), values were expressed as mean and standard deviation (SD), and median and range for not normally distributed numerical data (months survived since diagnosis). Kaplan-Meier curve was performed to demonstrate survival curves in patients who underwent adjuvant and neoadjuvant chemotherapy, palliative chemotherapy, surgery, and no intervention. Median survival time was reported for each treatment subgroup with a 95% confidence interval as well as a five-year survival rate. Moreover, to assess the significance of distribution differences among the former treatment subgroups, a log-rank test was performed. The Cox regression model was used to test independent prognostic factors of overall survival between treatment modalities. All statistical analyses were 2-sided, and differences were considered statistically significant at a  $p$ -value  $< 0.05$ .

## 4. RESULTS

### 4.1. Baseline Characteristics

During 2000-2015, a total of 103 patients were diagnosed with gastric cancer in princess Norah Oncology Center located in King Khalid hospital. Two out of 103 patients were excluded from the study due to having undergone both adjuvant and neoadjuvant chemotherapy. Table 1

Characteristics		
		N (%)
Gender	Male	66 (65.35)
	Female	35 (34.7)
Cases per year	2000	2 (1.9)
	2002	3 (2.9)
	2003	5 (4.95)
	2004	6 (5.9)
	2005	17 (16.8)
	2006	27 (26.7)
	2007	8 (7.9)
	2008	13 (12.9)
	2009	2 (1.9)
	2010	2 (1.9)
	2013	6 (5.9)
2014	6 (5.9)	
2015	4 (3.9)	

Table 1. Patients characteristics

Characteristics		
		N (%)
Tumor site	Gastroesophageal junction	19 (32.2)
	Antrum	14 (23.7)
	Body	11 (18.6)
	Multiple sites	8 (13.6)
	Fundus	7 (11.9)
AJCC staging	Stage I	1 (1.6)
	Stage II	3 (4.8)
	Stage III	12 (19.05)
	Stage IV	47 (74.6)
Histological type	Adenocarcinoma	32 (60.4)
	Adenocarcinoma (Signet cell)	11 (20.8)
	GIST	3 (5.7)
	Linitis plastica	2 (3.8)
	Gastric neuroendocrine tumor	1 (1.9)
	kaposie sarcoma	1 (1.9)
	Small cell carcinoma	1 (1.9)
	Squamous cell carcinoma	1 (1.9)
	Stromal cell sarcoma / Liyomiosarcoma	1 (1.9)

Table 2. Tumor characteristics. AJCC: the American Joint Committee on Cancer; GIST: gastrointestinal stromal tumor

summarizes patients' characteristics and the number of cases where the highest was 27 (26.7%) cases diagnosed in 2006, while the lowest were two cases (1.9%) diagnosed in 2000, 2009, 2010 and 2013. The overall age range for patients was 17 to 102 years, and most patients were males (65.35%) with a mean age of 64.58±19.84 years, while female patients

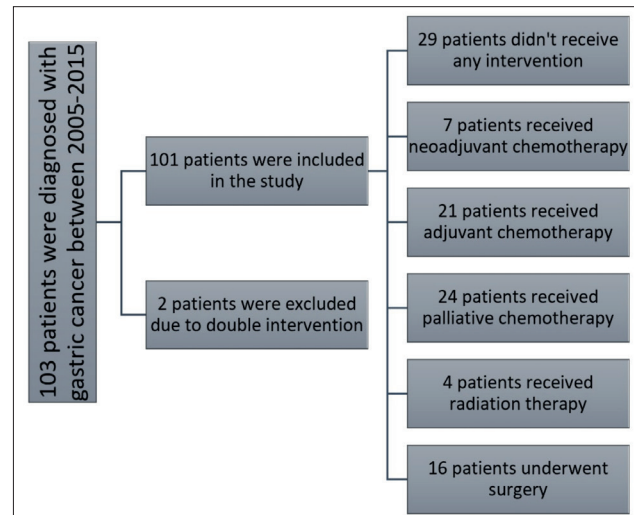


Figure 1. Study flowchart

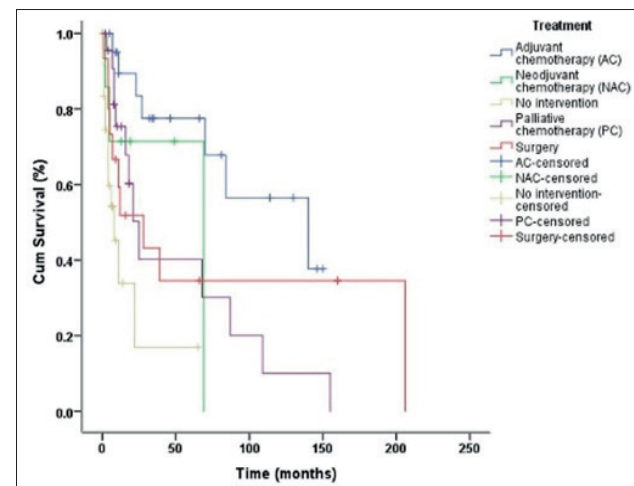


Figure 2. Kaplan-Meier curve showing survival time of gastric cancer patients in all treatment modalities

had a mean age of 61.71±17.83 years. Table 2 summarizes tumor characteristics where the most common tumor site was the gastroesophageal junction which occurred in 19 patients (32.2%) and the least common site was the stomach fundus 7 (11.9%). Almost half of all patients (47) presented with stage IV tumor (74.6%) with histological features of adenocarcinoma (60.4%) and signet ring (20.8%) features. The adenocarcinoma histological type presented in 16 patients diagnosed with stage IV. Other histological types occurred in fewer cases as demonstrated in Table 2.

#### 4.2. Treatment Modalities and Median Survival

Figure 1 depicts the grouping of patients according to the treatment modality they received. Most patients (44) underwent surgery, and out of those 44, 21 patients underwent NAC, and 7 patients underwent AC. Only 16 patients had surgery alone, while 24 patients had palliative chemotherapy and 4 patients had radiation therapy. Moreover, the AC group demonstrated the highest survival with a 5-year survival rate of 42.9% with a median survival time of 140 months (Table 3). The long-rank value (p-value=0.002) calculated for the treatment subgroups signifies statistical significance on survival. Figure 2 depicts survival curves for each treatment modality.

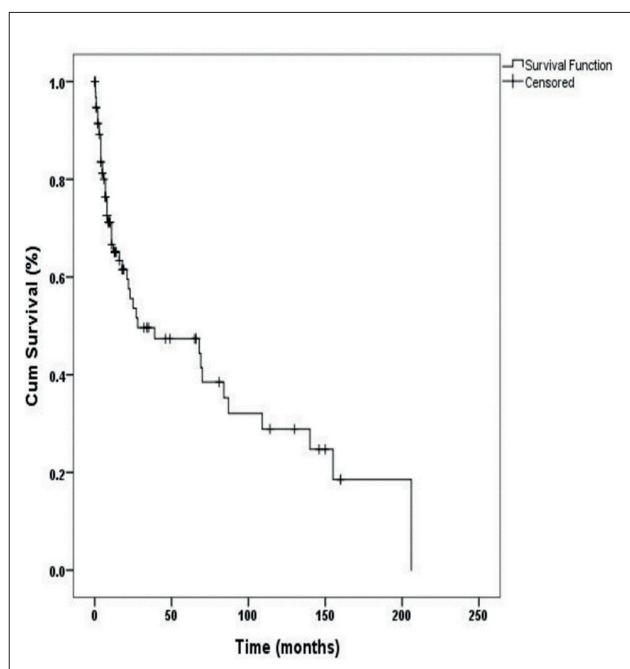


Figure 3. Kaplan-Meier curve showing overall survival time of gastric cancer patients

Treatment modality	Median survival time in months (95% CI)	Five-year survival rate
Adjuvant chemotherapy	140 (33.72-246.29)	42.9%
Neoadjuvant chemotherapy	69	14.3%
Surgery	28 (0-56.14)	26.7%
Palliative chemotherapy	25 (15.31-34.69)	17.4%
No intervention	8 (1.47-14.53)	3.7%

Table 3. Comparison of survival time in treatment modalities. CI: confidence interval

Many patients presented with advanced stage, albeit the MDT decided no intervention was needed, and a total of 13 patients out of 27 had died with a median survival time of 8 months and a 5-year survival rate of 3.7% (Table 3). For the patients who had taken radiation therapy, no survival time was reported in their medical files and all of them were lost to follow up. For all combined former five treatment groups, the median overall survival was 28 months (95%CI 0-77.68) with a 5-year survival rate of 19.6% as demonstrated on the Kaplan-Meier graph in Figure 3. Moreover, the Cox regression model was used to measure survival's associative significance to treatment type, cancer stage, age, and gender (Table 4). Only treatment type and cancer stage showed statistically significant values (p-value <0.05) of 0.001 and 0.009, respectively emphasizing their substantial impact on survival. The Cox regression test further demonstrated that AC subgroup was associated with a higher survival time, while the no intervention subgroup was independently associated with a higher risk of mortality as well as for stage IV disease.

### 5. DISCUSSION

Globally, it was estimated a total of 951,000 cases occurred in 2012 making gastric cancer the fifth most common malignancy in the world (11). In 2015, the National Cancer

Variables	p-value	Exp(B) 95% CI
	0.001	
Treatment	Adjuvant chemotherapy	0.04 0.31 (0.1-0.94)
	Neoadjuvant chemotherapy	0.55 0.65 (0.16-2.68)
	Surgery	0.71 1.50 (0.18-12.64)
	Palliative chemotherapy	0.11 0.46 (0.1-1.19)
	No intervention	0.02 3.42 (1.17-9.97)
	0.009	
Stage	I	0.99 0.00
	II	0.97 0.00
	III	0.46 0.55 (0.11-2.71)
	IV	0.002 3.38 (1.55-7.38)
Age	0.82 0.99 (0.98-1.02)	
Gender	0.30 1.38 (0.75-2.56)	

Table 4. Analysis of factors affecting survival time of gastric cancer using Cox regression model. Exp(B): the exponentiation of the B coefficient; CI: confidence interval

Registry of Saudi Arabia reported a total of 315 GC cases diagnosed in the Kingdom of Saudi Arabia. Around 184 cases (3.7%) were reported in males, while females had 131 (2.1%) newly diagnosed cases (9). The five Saudi regions with the highest incidence in 2015 were Najran region with an incidence of 5%, Madinah region (3.8%), Jazan region (3.3%), Jouf region (3.3%), and Asir region (2.9%). Gastric cancer is the eleventh most common cancer in Saudi Arabia and accounts for 2.9% of all diagnosed cancers with a median age of diagnosis at 65 years for males (range 4-94 years), and 60 years for females (range 23-100 years) (8). This study reported a similar age of patients at the time of diagnosis where males presented at the mean age of 64.58 years and females at 61.71 years. The overall Age-Standardized Incidence Rate (ASR) reportedly was 2.7 per 100,000 where males had a value of 3.1 per 100,000 and 2.3 per 100,000 for females. Comparing the ASR to other countries, Saudi Arabia ranked the seventh-lowest nation worldwide falling behind Eastern Asian countries such as the Republic of Korea and Japan with ASRs of 58.6 per 100,000 and 41.0 per 100,000, respectively (12).

In advanced carcinomas (stage III and IV), the prognosis for linitis plastica is commonly poor because it is considered as a transmural tumor with lymph node metastasis at the time of diagnosis. Nevertheless, linitis plastica is a rare variant of gastric cancer found globally in 7-14 % of cases and reported in only 3.8% of all histological types in our study (13). The most common tumor site reported in this study was the gastroesophageal junction and the least common site was the fundus. Additionally, most of the patients in the study presented with stage IV tumors with the histological features of adenocarcinoma (60.4%) and signet ring cell carcinoma (20.8%).

Furthermore, Eom et al. reported that tumor locations varied from the Eastern and the Western parts of the world (14). In older studies, most of the reported tumors were located in the distal part of the stomach in the East, while the



West reported tumors in the proximal part of the stomach. Moreover, they showed that there was a change in this trend where the percentage of cardia tumors was increasing in two large cohort studies in Japan and Korea (14). In Saudi Arabia, a study published in 1994 showed that stomach antrum was the most common tumor site (47%) while the cardia was only 15% (15). Two single-center based studies, published in 2016 and 2017 in Saudi Arabia, reported that the body of the stomach was the most common tumor site with measured percentages of 53% and 44.5% (9,16). On the other hand, our study showed that gastroesophageal junction was the predominant site (32.3%). This difference can be attributed to the fact that our center is a tertiary care center that treats National Guard employees and their family members. Non-cardia GC is associated with *H. pylori* infection, smoking, and high dietary salt intake, while cardia GC is associated with obesity (17). According to a prospective cohort study conducted by Hasosah et al. in our center, the prevalence of *H. pylori* infection in children was 49.8% in Jeddah and Riyadh (18). The high prevalence was associated with a crowded environment and poor living conditions. On the other hand, the World Health Organization (WHO) (19) recently reported that the prevalence of obesity has been increasing in the kingdom over the past decade affecting a third of the population. Moreover, the overall smoking prevalence is 12.1% with a wide gap between genders, 23.7% among males and 1.5% among females (20). Whether these factors could explain the location differences between our study and the former two studies remains unknown, but it could explain the steady increase of GC incidence in Saudi Arabia.

In this study, there were different treatment types reviewed, and multiple stages showed commonality in some treatment types more than others. On the other hand, there was only one stage I patient and 3 patients who were at stage II of the disease; the patients who were stage II of the disease underwent AC with a 5-year survival rate of 42.9% and median survival time of 140 months. Al-Batran et al. conducted a clinical trial where 716 patients were randomly assigned to AC treatment in 38 German hospitals, the median overall survival was 50 months significantly lower than this study's survival time due to the difference in sample size (21). A randomized trial that again showed a significant improvement in overall and progression-free survival in patients who underwent NAC compared to those who underwent surgery with 5-year survival around 20%, which does not differ greatly from the current study value of 14.3% (22). The World Journal of Gastroenterology reported in 2014 that the 5-year overall survival rate was 14% in patients that had undergone NAC (23).

Neoadjuvant chemotherapy is generally offered for patients with stage II or III disease and for patients with stage IV as a palliative treatment (22). Moreover, in this study, stage III patients were mostly treated with AC; while, stage IV patients mostly underwent palliative therapy. Most of the patients that underwent surgery alone were at stage IV; however, the addition of chemotherapy to surgical resection has shown a drastic improvement in survival time. The 3-year overall survival reported in one study among patients who had tumor resection with stage I was 97.9 %,

92.5% for stage II, 69.5% for stage III, and 20% for stage IV (24). The current study had an overall 5-year survival rate of 26.7% not accounting for the stage of cancer factor in the surgery group. Consequently, the Cox regression model was used to predict the impact of variations in treatment modality, stage, age, and gender on the cumulative survival of GC patients (Table 2). The findings of the variants showed that gender does not vitally contribute to survival (p-value of 0.3), and so does age with a p-value of 0.8. However, stage and treatment modality seemed to have a significant relationship with survival with p values of 0.009 and 0.001, respectively. Jaberi et al. conducted a study on GC patients in Iran that used the Cox model to study the effect of variables such as age, gender, and stage on survival, and similarly reported that the patients' survival rate was statistically significant concerning the stage of cancer (25).

## 6. CONCLUSION

Our study design was a retrospective cohort that only included a single center; thus, the total sample was relatively small. Another limitation was that the study's selected period predates the introduction of the BESTCare system that was recently implemented in 2016, which replaced hard copy files for digital files. As a result, a few reviewed files were worn out and had missing data, especially information about the site and stage of tumors. The last limitation was the scarcity of previous studies on gastric cancer in Saudi Arabia; nonetheless, this study analyzed data with a wide range of patient and disease demographics from a tertiary care center and profusely investigated survival time in several offered treatment modalities for GC, hoping to provide adequate knowledge suitable for the management of GC in the Saudi Arabian population. In conclusion, surgery remains the mainstay of treatment but this alone may not achieve the desired outcome in survival, as demonstrated in this study. Adjuvant, neoadjuvant, and palliative chemotherapy constitute the paramount treatment modalities of gastric cancer with adjuvant treatment having the highest survival time. However, the treatment modalities aforementioned necessitate further understanding as to whether other factors such as stage, histological type, and age play a role in the selection of one treatment with the preferable outcome. There is a crucial need for further studies to demonstrate the effect of different gastric cancer treatment modalities in a larger population and to investigate why the majority of patients present with advanced stage. Our study has described cases of GC in a tertiary care hospital in the western region of Saudi Arabia with predominant advanced stage disease which may warrant early diagnosis and screening in improving survival time as applied in high-risk populations worldwide.

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tutional Review Board (IRB SP18/355/J) at King Abdullah International Medical Research Center (KAIMRC) in Jeddah, Saudi Arabia.

- **Authors contribution:** S.A, F.B gave substantial contribution to the conception and design of the work. S.A, F.B, M.B, A.H, and E.J participated in the acquisition, analysis and interpretation of data for the work. SFZ supervised the whole project as principal investigator. Each author had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- **Conflict of interest:** There is no conflict of interest to declare.
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