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Evaluation of Factors Affecting Survival and Chemotherapy Regimens in Patients with Gastric Cancer

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ABSTRACT

Methods: This retrospective cohort study analyzed patients diagnosed with gastric cancer at our institution between 2009 to 2013. We examined demographic characteristics of the patients, the presence of Helicobacter pylori (HP), and survival outcomes, including disease-free survival and overall survival, according to different treatment protocols.

Results: The study included 122 patients (37 female and 85 male) with a mean age of 58.6 ± 10.3 years. Among them, 41% received 5-fluouracil, leukoverine chemotherapy (MAYO regimen), 26.2% received docetaxel, cisplatin and fluorouracil combination (DCF regimen), 10.7% received epirubicin, cisplatin and fluorouracil (ECF regimen), and 6.6% received cisplatin-xeloda regimen. The average disease-free survival was 14.7 ± 11.1 months, and the average overall survival time was 16.5 ± 11.4 months. The MAYO regimen group showed significantly longer diesease-free survival and overall survival compared to the other chemotherapy combination groups ($p < 0.001$). In multivariate analysis, metastasis and TNM stage were identified as independent negative prognostic factors for both disease-free survival and overall survival.

Conclusion: Our study demonstrated that disease-free and overall survival rates are markedly low in patients with advanced gastric tumors and those with metastases at diagnosis, underscoring the limited efficacy of chemoterapy in these cases. However, the MAYO regimen was associated with better survival outcomes compared to other treatment protocols.

Keywords: Chemotherapy, Gastric cancer, Survival

ÖZET

Amaç: Çalışmamızın amacı mide kanserinin prognozunu etkileyen faktörleri incelemek ve farklı kemoterapi rejimlerinin hastalıksız sağkalım ve genel sağkalım üzerine etkisini değerlendirmektir.

Yöntem: Bu kohort çalışmada, 2009-2013 yılları arasında kurumumuzda mide kanseri tanısı alan hastalar retrospektif olarak incelendi. Hastaların demografik özellikleri, Helicobacter pylori (HP) varlığı ve hastaların tedavi protokollerine göre hastalıksız ve genel sağkalımları incelendi.

Bulgular: Ortalama yaşı 58,6 ± 10,3 yıl olan 33 kadın ve 85 erkek çalışmaya dahil edildi. Hastaların %41'i 5-fluourasil, lökoverin kemoterapisi (MAYO rejimi), %26,2'si dosetaksel, sisplatin ve fluorourasil kombinasyonu (DCF rejimi), %10,7'si Epirubisin, sisplatin ve Fluorourasil (ECF rejimi) ve %6,6'sı Sisplatin-Xeloda rejimi aldı. Ortalama hastalıksız sağkalım süresi 14,7 ± 11,1 ay, genel sağkalım süresi ise 16,5 ± 11,4 aydı. MAYO rejimi grubunda hastalıksız sağkalım ve genel sağkalım kombinasyon kemoterapisi gruplarına kıyasla daha uzundu ($p < 0,001$). Çok değişkenli analizde, metastaz ve TNM evresi hastalıksız ve genel sağkalım için bağımsız negatif prognostik faktörlerdi.

Sonuç: Çalışmamız ilerlemiş tümörlerde ve tanı anında metastazı olan hastalarda hastalıksız ve genel sağkalım oranlarının oldukça düşük olduğunu göstermiş ve özellikle bu grup hastalarda kemoterapi protokollerinin sınırlı etkisini ortaya koymuştur. Bununla birlikte, MAYO rejimi diğer tedavi protokollerine göre daha üstündü.

Anahtar Kelimeler: Kemoterapi, Mide kanseri, Sağkalım

Gastric cancer is one of the most common cancers worldwide and the second most common cause of cancer-related deaths (1). In addition to environmental, genetic and familial factors, Helicobacter pylori (HP) infection plays a significant role in the development of gastric cancer. The incidence of gastric cancer is associated with socioeconomic status, with higher rates observed in developing countries (2,3). HP infection has been linked to condition such as gastritis, peptic ulcer disease and gastric malignancies. It has been a central focus of many clinical and microbiological studies, especially in recent years. The location of gastric cancer within the stomach can vary depending on etiological factors. For instance, HP infection and dietary factors are more closely associated with distal gastric cancer, whereas gastroesophageal reflux disease (GERD) and obesity are more strongly linked to the development of proximal and gastroesophageal cancers (4).

Surgery can be curative in early-stage gastric cancer, while adjuvant chemotherapy (CT) and radiotherapy (RT) have been shown to improve survival outcomes. However, survival rates decline significantly in advanced stages of the disease. Currently, postoperative chemotherapy is the standard of care for patients with early-stage gastric cancer. 5-fluorouracil and leucovorin chemotherapy (MAYO regimen) is the most commonly used CT protocol. For metastatic gastric cancer, the most effective results have been achieved using combinations of platinium and fluorouracil- based therapies. The combination of epirubicin, cisplatin and fluorouracil (ECF) is one of the standard chemotherapy combinations for metastatic gastric cancer (5-6).

One of the most favorable survival outcomes in treating metastatic gastric cancer has been achieved with the combination of docetaxel, cisplatin and fluorouracil (DCF) (7). In Asia, where gastric cancer has the highest prevalence, the cisplatin and Xeloda (capecitabine) regimen is a standard treatment protocols for patients with metastatic and unresectable gastric cancer.

Our study aimed to investigate the demographic characteristics of 122 gastric cancer patients treated in the Oncology Department of Istanbul Training and Research Hospital, assess their association with HP infection, and evaluate the impact of various treatment options on disease-free and overall survival.

Material And Method

Our study retrospectively analyzed 122 patients diagnosed with gastric cancer who were followed in the medical oncology and radiation oncology departments between 2009 and 2013. At the time of analysis, the median follow-up period was 16 months.

We analyzed the patients' demographic characteristics and disease-related parameters, including sex, age, histological grade, stage, tumor location, chemotherapy regimen, chemotherapy response, and presence of Helicobacter pylori (HP) infection. Tumor localization and prognosis were also evaluated. Patients with metastatic disease at the time of diagnosis were compared with those who initially had no metastases but later developed metastases, in term of survival. Additionally, disease-free survival and overall survival were compared based on factors such as stage at diagnosis, HP status (HP +/-), histological subtype and CT regimen in metastatic patients. Patients with insufficient data or no follow-up were excluded from the study. Overall survival was defined as the time from the start of treatment to death, while disease-free survival was defined as the time from the end of treatment to disease progression. Patients were staged according to the WHO 2000 classification. Chemotherapy protocols were used according to the NCCN guideline for gastric cancer, version 2.2013.

Statistical Analyses

Mean, standard deviation, ratio and frequency values were used in the descriptive statistics of the data. Kaplan Meier (Log-rank / Mental Cox) and Cox-Regression analyzes were used for survival analysis. SPSS (IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) program was used in the analyzes. A p value of less than 0.005 was considered significant.

Results

Of the 122 patients, 30.3% were female, 69.7% were male, with a mean age of 58.6 ± 10.3 years. Overall survival ranged from 1 to 96 months, with a mean of 16.5 ± 11.1 months. The most common tumor location was the antrum, present in 61.5% of cases (n=75). At diagnosis, the 57.4% of patients (n=70) had stage IV disease, and adenocarcinoma was the most prevalent histological type, accounting for 75.4% of cases (n=92). HP test results were available for 46 patients (37.7%), of whom 24 (52.1%) tested positive.

Table 1. Demographic and treatment characteristics of the patients

Parameter	n	%
Age	58.64	10.3
Gender		
Female	37	30.3
Male	85	69.7
Localization of Tumor		
Antrum	75	61.5
Fundus	6	4.9
Cardia	19	15.6
Corpus	13	10.7
Other	9	7.4
Histopathological Subtype		
Adeno carcinoma	92	75.4
Undifferentiated carcinoma	1	0.8
Malignant epithelial carcinoma	1	0.8
Neuroendocrine carcinoma	2	1.6
Signet-ring cell carcinoma	24	19.7
Stage		
I	18	14.8
II	8	6.6
III	26	21.3
IV	70	57.4
Helicobacter Pylori +	24	19.7
Chemotherapy protocol	107	87.7
Cisplatin-Xeloda	*8*	*6.6*
*DCF**	*32*	*26.2*
ECF†	*13*	*10.7*
MAYO‡	*50*	*41*
Other	*4*	*3.3*
Number of Chemotherapy, mean (min-max)	4 (1-6)	1.5
Radiotherapy	90	73.8
Chemotherapy+ Radiotherapy	76	62.3
Surgery	117	95.9
Metastasis	53	43.4
Number of patients with progression	36	29.5
Time Without Progression (month)	14.7	11.1
Second Chemotherapy	19	15.6
Last Status		
Alive	68	55.7
Deceased	54	44.3
Survival Time (month)	16.5	11.4

DCF: Docetaxel, Capecitabine, 5-Flourourasil;
ECF: Epirubicin, Cisplatin and Fluorouracil;
MAYO: 5-Flourourasil+ leukoverine

Following diagnosis, 95.9% of patients underwent surgery (n=117), 87.7% received chemotherapy (n=107), 73.8% received RT (n=90), and 62.3% received CRT (n= 76). Metastases were present in 43.4% of patients (n=53) at the time of diagnosis.

The chemotherapy regimens used included the MAYO protocol in 41% of patients (n=50), the DCF protocol in 26.2% (n= 32), the ECF protocol in 10.7% (n=13), the cisplatin-Xeloda protocol in 6.6% (n=8), and other protocols (cisplatin-etoposide, DC) in 3.3% (n=4).

The mean duration of chemotherapy was 4.76 ± 1.49 months. The mean disease-free survival during follow-up was 14.7 ± 11.1 months. Disease progression was observed in 36 patients (29.5%). A second chemotherapy regimen was administered to 19 (15.6%) of these patients. The median survival was 16.5 ± 11.4 months (Table 1).

There was no significant difference between the HP (+) and HP (-) groups in terms of predicted disease-free (p=0,025) time and predicted survival (p=0.505).

In our study, when the survival rates of patients receiving chemotherapy were examined according to stage, the predicted progression-free period in the stage IV group [18.08 months (14.00-22.16)] was significantly ($p < 0.001$) shorter than that in the stage I group [29.40 months (23.41-35.59)], stage II [33.70 months (25.58-41.81)], and stage III [36.71 months (31.73-41.69)] (Table 2)

Table 2. Survival According to Stage

				%95 Confidence Interval		
		n	Predict	Min	Max	*p*
Progression-free time (month)						
Stage	I	18	61.46	51.94	70.98	**< 0.001**
	II	8	33.70	25.58	41.81	
	III	26	35.61	30.42	40.81	
	IV	70	18.08	14.00	22.16	
Survival time (month)						
Stage	I	18	48.70	29.89	67.51	**< 0.001**
	II	8	30.10	20.33	39.88	
	III	26	33.12	27.51	38.74	
	IV	70	16.68	13.35	20.01	

Predicted progression-free time (p<0.001) and predicted survival (p=0.002) were significantly longer in the MAYO group than in the Cisplatin-Xeloda and DCF group. However, there was no significant difference between the groups receiving cisplatin-Xeloda, DCF and ECF (p=0.036) (Table 3).

Table 3. Survival According to Chemotherapy Type

				%95 Confidence Interval		
		n	Predict	Min	Max	*p*
Progression-free time (month)						
Type of Chemotherapy	Cisplatin-Xeloda	8	10.52	6.66	14.38	**< 0.001**
	DCF	32	18.76	12.56	24.95	
	ECF	13	25.38	16.98	33.78	
	Mayo	48	31.09	27.51	34.67	
Survival time (month)						
Type of Chemotherapy	Cisplatin-Xeloda	8	16.49	11.04	21.95	***0.002***
	DCF	32	17.93	12.59	23.27	
	ECF	13	25.34	17.58	33.11	
	Mayo	48	31.77	27.65	35.88	

In univariate analysis for overall survival stage (p <0.001), KT type (p=0.001), metastasis (p <0.001) and presence of progression (p=0.002) were found to be factors affecting survival. On multivariate analysis, metastasis (p=0.006) and stage (p=0.031) were found to be independent factors (Table 4).

Table 4. Univariate and multivariate analysis of factors affecting overall survival time

	Univariate Model			Multivariate Model		
	OR	%95CI	*p*	OR	%95CI	*p*
Metastasis	4.84	2.66-8.79	**<0.001**	2.77	1.35-5.69	***0.006***
Grade (I/ II/ III/ IV)	2.84	1.56-3.51	***<0.001***	1.63	1.05-2.55	***0.003***
Histopathological Subtype	0.92	0.45-1.89	0.83			
Chemotherapy	0.57	0.27-1.21	0.141			
Chemotherapy Type	0.61	0.46-0.81	**0.001**			
H. Pylori	0.70	0.25-1.98	*0.508*			
Progression	2.37	1.39-4.05	**0.002**			

In univariate analysis for disease-free survival stage (p <0.001), KT type (p <0.001), metastasis (p <0.001) and HP pylori presence (p=0.043) were found to be factors affecting survival. After multivariate analysis, metastasis (p=0.037) and stage (p=0.039) were found to be independent factors (Table 5).

Table 5. Univariate and multivariate analysis of factors affecting progression-free time

	Univariate Model			Multivariate Model		
	OR	%95CI	*p*	OR	%95CI	*p*
Metastasis	4.97	2.45-10.07	***<0.001***	2.47	1.06-5.77	***0.003***
Stage	2.63	1.56-4.42	***<0.001***	1.80	1.03-3.14	***0.003***
Histopathological Subtype	0.69	0.27-1.78	0.438			
Operation	0.35	0.13-0.96	***0.042***			
Chemotherapy	3.88	0.53-23.38	0.181			
Chemotherapy Type	1.51	0.37-0.71	**<0.001**			
H. Pylori	0.20	0.04-0.95	***0.043***			

Discussion

Gastric cancer, one of the leading causes of cancer-related mortality worldwide, presents a set of challenges in diagnosis and treatment. It is 2-4 times more common in men than in women. Its incidence increases between the ages of 60 and 80. Several studies have established between HP infection and conditions such as gastritis, peptic ulcer and gastric cancer. Gastric cancer is typically diagnosed at an advanced stage (Stage III-IV) (2-4).

In our study, we present epidemiological and clinicopathological characteristics, survival times and progression-free survival times of patients with gastric cancer. The demographic data of our cohort align with previous studies, showing that gastric cancer is more common in men than in women, with the mean age of diagnosis between 55 and 60 years. The majority of tumors were located in the antrum, and 75% of cases were adenocarcinomas. It is also observed that most patients are diagnosed at an advanced stage.

The mean age of diagnosis of gastric cancer is typically reported as 56 years (8), with its incidence rising between the ages of 60 and 80. It is rarely observed before the age of 30 (9). In our study, the average age of patients was 58.64 ± 10.32 years.

One study found that 36% of gastric cancers were located in the antrum, 36% in the corpus, 20% in the cardia and 8% diffusely (10). In our study, 61.5% of cases were located in the antrum, 15.6% in the cardia, 4.9% in the fundus and 7.4% in other locations (e.g, pylorus, diffuse), which is similar to previously reported results.

The relationship between HP and conditions such as gastritis, peptic ulcers and gastric cancer has been explored in numerous studies. Although different studies using varying methods have yielded mixed results, the most optimistic estimates suggest that HP infection accounts for approximately one-third of gastric cancers (11). Recently, a decline in the incidence of gastric cancer in the antrum and corpus has coincided with a reduction in the prevalence of HP infection (12,13).

In our study, HP results were available for 46 patients (37.7%), with 24 of these patients (52.17%) testing positive for HP. The results are positive in more than half of the patients whose results we can reach, which is higher than the general literature data. This result confirms the information that HP is more common in developing countries with inadequate socioeconomic conditions, such as our country (14).

We found no significant difference in overall (p=0.505) or disease-free survival time (p=0.025) between the HP (+) and (-) groups. This lack of difference may be attributed to the limited number of patients with available HP results and the advanced stage of disease in the majority of patients.

Surgical resection remains the primary curative treatment for gastric cancer (15). After curative surgery, the 5-year survival rate for tumors confined to the gastric mucosa ranges from 85-90%, while for T4 and lymph node positivity, the local and regional failure rate is 50-60% and the 5-year survival rate is 15-20% (16).

While radical surgery alone is preferred for early-stage disease, the addition of radiotherapy and/or chemotherapy is considered essential for improving local regional control and survival in patients with locally advanced disease (17,18).

The optimal combination and sequence of chemotherapy in the treatment algorithm for gastric cancer is currently under extensive investigation. The MAYO regimen has shown promising results in terms of progression-free and overall survival compared to other chemotherapy regimens, particularly in early-stage patients (19). However, the optimal treatment strategy remains a subject of ongoing research, with a focus on tailoring therapies based on individual patient characteristics and tumor biology (19, 20). Currently, perioperative chemotherapy, particularly for T3/T4a has gained prominence, particularly for T3/T4a tumors and/or those with regional lymph node involvement, is becoming more widely used. Furthermore, neoadjuvant chemotherapy has been associated with higher rates of pathological complete response (21).

In our study, the predicted progression-free survival for patients receiving the MAYO regimen [31.09 (27.51-34.67)] was significantly longer compared to those receiving the Cisplatin-Xeloda regimen [10.52 (6.66-14.38)] and the DCF regimen [18.76 (12.56) -24.95)] (p< 0.001). No significant difference in progression-free survival was observed between the Cisplatin-Xeloda, DCF, and ECF groups (p= 0.036) (Table 3).

Similarly, the predicted overall survival in the MAYO regimen [31.09 (27.51-34.67)] group was significantly longer compared to those receiving Cisplatin-Xeloda [10.52 (6.66-14.38)] and DCF [18.76 (12.56-24.95)] regimens (p<0.001). No significant difference in overall survival was observed between the Cisplatin-Xeloda, DCF, and ECF groups (p=0.038) (Table 3).

The observed longer progression-free survival and overall survival in the MAYO regimen group compared to the combination chemotherapy groups can be attributed to the fact that the MAYO regimen was primarily administered to patients with early- stage disease, while combination chemotherapy regimens were less effective due to severe side effects and patient intolerance.

A review on the effectiveness of chemotherapy versus supportive care, found that chemotherapy improved survival outcomes compared to supportive care alone. Consequently, systemic chemotherapy remains the mainstay of treatment for advanced gastric cancer. However, uncertainty persists regarding the optimal regimen. (22).

In the univariate analysis of factors affecting overall survival; stage and metastasis (p<0.001), chemotherapy type (p=0.001) and progression (p=0.002) were identified as significant factors. Multivariate analysis showed that stage and metastasis were independently of survival (p=0.031, p<0.006, respectively) (Table 4).

In the univariate model, it was observed that metastasis, stage and chemotherapy type (p<0.001) and H.P (p=0.043) affected the patient's progression-free time. In multivariate analysis, metastasis and stage were found to be effective in predicting disease-free survival (p=0.003) (Table 5).

In conclusion, there are numerous treatment options available for gastric cancer. Surgical resection should be considered for appropriate patients, followed by chemotherapy and/or radiotherapy. In cases where surgery is not feasible, one of the available chemotherapy regimens should be used in combination with radiotherapy.

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Conflict of interest:

The authors declare no competing interests.

Ethics Approval:

This study was approved by the Istanbul Education and Research Hospital Ethical Committee. (Date 24.05.2013 and number: 258)

Availability of Data and Material:

Available.

Authors' Contributions:

All authors have made substantial contributions to this article being submitted for publications. All authors critically reviewed the manuscript and approved the final form.

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