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Original Research Article

Factors affecting prognosis in signet ring cell gastric cancers with expanded lymph node dissection; high volume centre experience

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ABSTRACT

Background: Signet ring cell gastric cancer differs from gastric adenocarcinoma in terms of demographic and clinical features, age, gender, tumour grade and stage. In this study, we aimed to evaluate the clinical features and overall survival of gastric signet ring cell carcinoma and the prognostic factors affecting survival.
Methods: We analysed 138 patients who were operated on with the diagnosis of signet ring cell gastric cancer. The univariant and multivariate hazard ratios of these parameters were analysed and the factors affecting the long-term average survival outcomes were investigated.
Results: We performed Cox regression univariate analysis to investigate the effects of clinicopathological factors on mean survival follow-up in signet ring cell gastric cancer. As age increases, the mean survival follow-up period decreases. This relationship is also statistically significant. Mean survival follow-up for the open technique was lower than for laparoscopic procedures. The mean survival follow-up time of patients with positive perineural invasion (PNI) and lymphovascular invasion (LVI) is lower than patients with negative LVI and PNI. We did not find a significant relationship between the hazard ratios (HRs) of tumour markers and systemic inflammatory response parameters. However, we found a significant relationship between the increase in fibrinogen value and HR.
Conclusions: We investigated the clinicopathological features of nonmetastatic signet ring cell gastric carcinomas and identified predictors of long survival. Age, lymphovascular and perineural invasion, open surgery, higher tumor infiltration, and lymph node involvement were independent predictors of shorter survival times in nonmetastatic signet ring cell gastric cancers.

Keywords: Gastric cancer, Signet ring cell carcinoma, Gastrectomy

INTRODUCTION

Although gastric cancer survival outcomes have improved significantly in recent years, it is one of the most common causes of cancer-related deaths worldwide.[1] Histopathologically, the most common type is adenocarcinoma.[2] The 2019 World Health Organization (WHO) classification has divided gastric adenocarcinomas into five main groups: tubular, papillary, mucinous, poorly cohesive, and mixed adenocarcinoma. The incidence of signet ring cell carcinoma, which is a subtype of poorly cohesive carcinomas and accounts for 16.8% of gastric cancer cases, has been increasing in recent years.[3] It is a rare histological type with a poor prognosis due to rapid tumor growth and infiltration into surrounding tissues.[4] With the developments in treatment modalities, its prognosis tends to improve in recent years.[5]

Signet ring cell carcinoma is a histological diagnosis characterized by prominent cytoplasmic mucin expression and a nucleus pushed to the periphery.[6] It exhibits different tumorigenic properties and epidemiological distribution compared to other types of gastric cancer.[7] It differs from

gastric adenocarcinoma in terms of demographic and clinical features, age, gender, tumor grade, and stage.[3]

Although there are studies on the prognostic values of various factors in gastric cancer in the literature, data on prognostic factors in signet ring cell cancers are limited.[4] Today, the American Joint Cancer Committee (AJCC) staging system is used to evaluate gastric cancer prognosis and treatment plan.[8] However, since the AJCC staging system does not take into account some important clinicopathological features such as age, gender, and treatment method when patients are evaluated individually, it may not be sufficient to predict survival.[9]

However, due to their rarity, data on optimal treatment management are limited. Therefore, investigating the specific characteristics of patients can provide the necessary information to improve the clinical management of these patients. In this study, we aimed to evaluate the clinical features and overall survival of gastric signet ring cell carcinoma and the prognostic factors affecting survival.

METHODS

We retrospectively analysed 138 patients who were operated on with the diagnosis of signet ring cell gastric cancer in the department of surgical oncology, Faculty of Medicine, Ankara University, between 2006 and 2018. Because the study was retrospective, ethical approval was not obtained.

To be considered signet ring cell (SRC), more than 50% mucin and cohesive variants in the pathology reports were found. Patients with >50% mucin and a component containing cohesive variants in their endoscopic pathology or final pathology and without distant metastases in their preoperative imaging were included in the study. Patients with distant metastases, synchronous tumors, and signet ring component <50% were excluded from the study. 2 patients with recurrence, 4 patients with peritoneal involvement, and 4 patients with missing parameters in the file examination were excluded from the study. A total of 128 patients were included in the study. Since the factors affecting the mean survival of signet ring cell gastric cancer were investigated in our study, no grouping was made. We aimed to evaluate the effect of demographic characteristics, histopathological type, tumour location, type of operation, neoadjuvant therapy, presence of lymph node metastasis, the ratio of metastatic lymph node number to lymph node dissection number, N stage, T stage, presence of lymphovascular (LVI) and/or perineural invasion (PNI), tumour grade and the level of tumour markers and inflammatory parameters (platelet/ lymphocyte ratio, lymphocyte/monocyte ratio, neutrophil/ lymphocyte ratio, fibrinogen) on mean survival time by Kaplan-Meier. The univariant and multivariate hazard ratios of these parameters were analysed and the factors affecting the long-term average survival outcomes were investigated.

Statistical analysis

Data were analysed by using statistical package for the social sciences (SPSS) version 22.00. Univariate and multivariate death hazard ratios (HRs) were calculated by the Cox regression hazard model. Kaplan Meier test was used to calculate the mean survival curves. $P<0.05$ was deemed statistically significant.

RESULTS

Demographic clinicopathologic characteristics

128 patients included in the study were analysed retrospectively. 70 of the patients were male and 58 were female. The mean age is 57.70 years and the youngest patient is 24 years old. The tumour was mostly located in the antrum (38.3%) and corpus (39.1%), and a total gastrectomy was performed in 69 patients (53.9%). The operation was completed laparoscopically in 25 of the patients. Lymph node metastasis was present in 103 patients, with a mean lymph node metastasis of 1.51. The ratio of the number of metastatic lymph nodes to the number of lymph nodes dissected is 0.40 on average. 48.4% of the patients are in N3, and 75% of them are in the T4 stage. LVI is present in 67 patients and 92 patients are high grade. The mean value of carcino-embryogenic antigen (CEA) of the patients included in our study was 11.38 ng/ml, and the mean value of carcipher antigen 19-9 (Ca 19-9) was 44.51 ng/ml. In the distribution of inflammatory parameters, the platelet/lymphocyte ratio (PLR) average is 215.69, the lymphocyte/monocyte ratio (LMR) average is 4.34, the neutrophil/lymphocyte ratio (NLR) average is 5.74, and the fibrinogen value is 5.18 (Table 1).

Univariate and multivariate analysis

We performed Cox regression univariate analysis to investigate the effects of clinicopathological factors on mean survival follow-up in signet ring cell gastric cancer. First, we examined the hazard ratios of demographic parameters. As age increases, the mean survival follow-up period decreases. This relationship is also statistically significant ($p=0.011$). But HR is 1.021. Although it is statistically significant, the HR coefficient is very close to 1. In other words, although the increase in age statistically affects the mean survival follow-up period, this rate is quite low. This ratio loses its statistical value when the age of 65 is used as a basis for the WHO to distinguish between the elderly and young population (HR=1.414, 95% CI: 0.94-2.127, $p\leq0.097$). In other words, there is no significant relationship between the mean survival time of patients over and under 65 years of age. Again, there was no statistically significant difference in the effect of gender HR, and the p-value was 0.658. In the relationship between tumour localization and HR, the mean survival time of patients with only linitis plastica was significantly lower (HR=4.173, $p=0.021$) when antral tumours were considered the reference. When we compare other

localizations with the antrum, there is no significant difference. There is a significant difference between the mean survival and follow-up times of the surgeries performed with the laparoscopic or open technique. Mean survival follow-up for the open technique was lower than for laparoscopic procedures (HR=1.821, 95% CI: 1.03-3.129, p=0.039). There is a significant difference between the mean survival follow-up times of the patients according to the presence of LVI and PNI. The mean survival follow-up time of patients with positive LVI and PNI is lower than patients with negative LVI and PNI (HR=3.620, 95% CI: 2.306-5.684, p<0.001 and HR=2.058, 95% CI: 1.369-3.093, p=0.001). Lymph node metastasis is also an important variable that increases HR. The mean survival time of patients with lymph node metastases was significantly lower than those without lymph node metastasis (HR=3.945, 95% CI: 2.041-7.627, p<0.001). We confirmed this relationship with the analysis of the N phases. When we accepted N0 as a reference, we found that the mean survival and follow-up times of n2 and n3 patients were significantly lower. (HR=2.551 for N2, 95% CI: 1.167-5.578, p=0.019 and HR=8.062 for N3, 95% CI: 4.024-16.150, p<0.001). In the analysis of tumour T stages, when we accept the T1 stage as the reference value, the mean survival follow-up time of only T4 patients is significantly lower (HR=4.496, 95% CI: 1.943-10,404, p<0.001). There is no significant difference in the mean survival follow-up times of other T stages compared to T1. We did not find a significant relationship between the HRs of tumour markers and systemic inflammatory response parameters. However, we found a significant relationship between the increase in fibrinogen value and HR. Accordingly, an increase in the fibrinogen value leads to a significant decrease in the mean survival follow-up period of the patients (HR=1.312, 95% CI: 1.214-1.418, p<0.001). When we group the fibrinogen as high and normal according to the reference range, this rate increases even more. The mean survival time of patients with fibrinogen values above the reference value was 4.394 times lower than patients in the normal range (HR=4.394, 95% CI: 2.686-7.189, p<0.001). In the multivariate analysis, we found that no variable except fibrinogen made a significant contribution to the model. Although HR slightly decreased, fibrinogen also affected the mean survival follow-up in multivariate analysis (HR=2.286, 95% CI: 1.145-4.568, p<0.019) (Table 2).

Survival analysis

We studied the mean survival analyses of the parameters whose HRs were found to be significant in Cox regression using the Kaplan Meier test. We found a significant correlation between the mean survival curves of tumour localization. The mean survival of patients with antrum localization was 56.61 months, while patients with linitis plastica were 6.33 months (p=0.03). There is a significant relationship between the mean survival curves of PNI and LVI. The mean survival of patients with PNI (+) and LVI (+) was lower than the patients with negative (31.88 versus 69.14 months, p<0.001 and 18.16 versus 86.42 months, p<0.001). The increase in the N stage and T stage is one of the important parameters affecting the average survival. Accordingly, the mean survival of patients with N3 is 15.65 months and 33.85 months for T4 patients. There is a significant difference in the mean survival analysis of fibrinogen, which contributes significantly to HR in both univariant and multivariate analyses.

The mean survival for patients with fibrinogen values above the reference range was 22.69 months, and the mean survival for patients within the normal reference range was 101.76 months (p<0.001). The mean survival curves of the variables and analysis results are detailed in Figures 1-3.

Table 1: Demographic and histopathological distribution of the patient.

Variables	Mean±SD, n (%)
Age (years)	57.70±14.11 (24-87)
Gender	
Male	70 (54.7)
Female	58 (45.3)
Location	
Antrum	49 (38.3)
Corpus	50 (39.1)
Fundus	3 (2.3)
Cardia	23 (18)
Linitis plastica	3 (2.3)
Neoadjuvant therapy	
Absent	115 (89.8)
Present	13 (10.2)
Laparoscopic-open	
Laparoscopic	25 (19.5)
Open	103 (8.5)
Operation	
Subtotal	59 (46.1)

Continued.

Variables	Mean±SD, n (%)
Total	69 (53.9)
Metastatic lymph node status	
Absent	25 (19.5)
Present	103 (80.5)
Metastatic node	1.51±1.04 (0-6)
Metastatic lymph node ratio	0.40±0.37 (0-1.65)
N stage	
N0	25 (19.5)
N1	17 (13.3)
N2	24 (18.8)
N3	62 (48.4)
T stage	
T1	16 (12.5)
T2	5 (3.9)
T3	11 (8.6)
T4	96 (75)
LVI	
Absent	61 (47.7)
Present	67 (52.3)
PNI	
Absent	73 (57)
Present	55 (43)
Grade	
Low	20 (15.6)
Middle	16 (12.5)
High	92 (71.9)
Carcinoembryonic antigen (ng/ml)	11.38±50.27 (0-438.62)
Carbohydrate antigen 19-9 (ng/ml)	44.51±107.36 (0.6-949.9)
Platelet/lymphocyte ratio (PLR)	215.69±185.29 (4.2-1670)
Lymphocyte/monocytes ratio (LMR)	4.34±8.69 (0.26-82.8)
Neutrophil/lymphocyte ratio (NLR)	5.74±8.65 (0.07-67)
Fibrinogen (mg/dl)	5.18±2.53 (1.14-13.60)
Length of hospital stay (days)	15.17±14.30 (5-160)
Length of intensive care stay (days)	2.48±12.83 (0-146)
Follow-up time (months)	37.89±44.47 (0-179)
Survival	
Live	31 (24.2)
Death	97 (75.8)

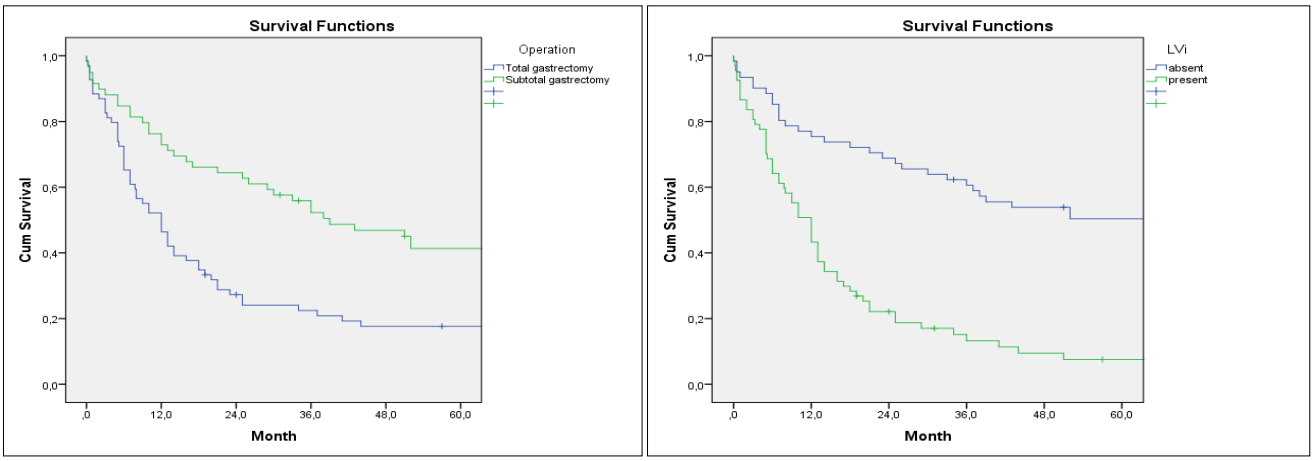

Figure 1: The mean survival curves of the variables.

Table 2: Univariate and multivariate analysis of signet ring cell gastric carcinoma for overall survival.

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% Cl)	P value	HR (95% Cl)	P value
Age	1.021 (1.005-1.037)	0.011		
Age (years)				
<65				
>65	1.414 (0.94-2.127)	0.097		
Gender				
Male				
Female	1.110 (0.744-1.657)	0.608		
Location				
Antrum				
Corpus	1.45 (0,927-2,282)	0.103		
Fundus	2.70 (0.816-8.946)	0.104		
Cardia	0.915 (0,492-1,701)	0.778		
Linitis plastica	4.173 (1.239-14.052)	0.021		
Neoadjuvant therapy				
Absent	1.241 (0.660-2.2334)	0.503		
Present				
Laparoscopic/open				
Laparoscopic				
Open	1.821 (1.03-3,219)	0.039		
Operation				
Total	0.504 (0.334-0.762)	0.001		
Subtotal				
LVI				
Absent	3.620 (2.306-5.684)	<0.001		
Present				
PNI				
Absent	2.058 (1.369-3.093)	0.001		
Present				
Grade				
Low				
Middle	1.756 (0.712-4.326)	0,221		
High	3.210 (1.601-6.435)	0.001		
Metastatic node status				
Absent	3.945 (2.041-7.627)	<0.001		
Present				
N stage				
n0				
n1	1.507 (0.612-3.711)	0.372		
n2	2.551 (1.167-5.578)	0.019		
n3	8.062 (4.024-16.150)	<0.001		
T stage				
T1				
T2	0.529 (0.064-4.398)	0.556		
T3	2.714 (0.935-7.878)	0.066		
T4	4.496 (1.943-10.404)	<0.001		
Metastatic lymph node ratio	7.594 (4.517-12.765)	<0.001		
Carcinoembryonic antigen	1.003 (1.00-1.006)	0.073		
Carbohydrate antigen 19-9	1.001 (1.00-1.002)	0.086		
Platelet/lymphocyte ratio	1.00 (0.999-1.002)	0.391		
Lymphocyte/monocyte ratio	1.011 (0.987-1.036)	0.373		
Neutrophil/lymphocyte ratio	0.997 (0.973-1.021)	0.781		
Fibrinogen	1.312 (1.214-1.418)	<0.001		

Continued.

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% Cl)	P value	HR (95% Cl)	P value
Fibrinogen				
Normal				
High	4.394 (2.686-7.189)	<0.001	2.286 (1.145-4.568)	0.019

Table 3: Mean overall survival time of LVI, operation type according to log rank analysis.

Operation	Mean overall survival (month)	%95 Cl		Log rank, p value
		Lower bound	Upper bound	
TG	34,903	21,973	47,833	0.001
SG	71,257	52,703	89,811	
LVI				<0.001
Absent	86,429	67,082	105,775	
Present	18,168	12,676	23,660	

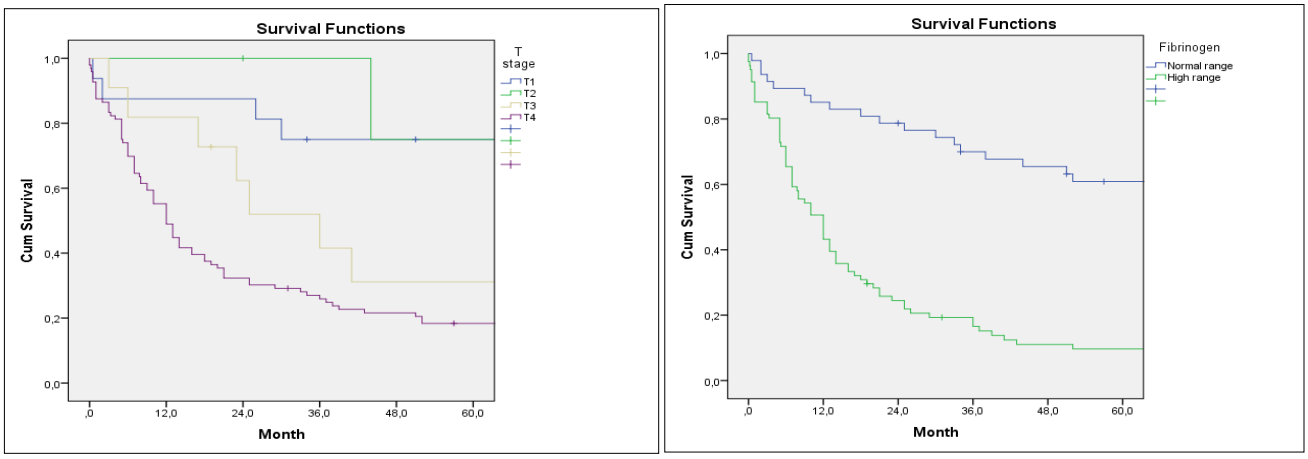

Figure 2: The mean survival curves of the variables.

Table 4: Mean overall survival time of T stage according to log rank analysis.

T stage	Mean overall survival (month)	%95 Cl		LogRank P value	Fibri-nogen	Mean overall survival (month)	%95 Cl	Log rank	P value
		Lower bound	Upper bound			Lower bound	Upper bound		
T 1	120,323	83,858	156,788	Normal	101,762	79,657	123,866	<0.001	<0.001
T 2	145,250	87,962	202,538	High	22,691	14,910	30,471		
T 3	50,260	21,119	79,400						
T 4	33,850	24,278	43,422						

Table 5: Mean overall survival time of PNI and grade according to log rank analysis.

Parameters	Mean overall survival (month)	%95 Cl		Log rank p value
		Lower bound	Upper bound	
PNI				<0.001
Absent	69,147	52,165	86,130	
Present	31,886	16,911	46,861	
Grade				0.001
Low	105,830	71,321	140,339	
Middle	67,817	34,600	101,035	
High	38,456	26,601	50,311	

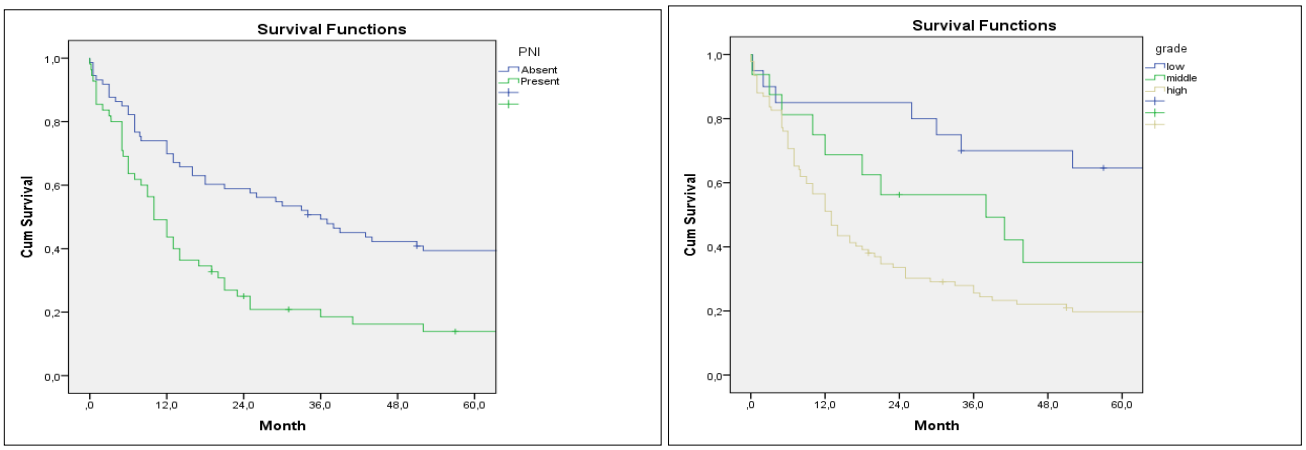

Figure 3: The mean survival curves of the variables.

Table 6: Mean overall survival time of N stage.

Parameters	Mean overall survival (month)	%95 CI		Log rank p value
		Lower bound	Upper bound	
N stage				
N 0	99,782	75,546	124,018	<0.001
N 1	95,887	58,623	133,150	
N 2	63,896	34,995	92,797	
N 3	15,658	9,095	22,221	
Metastatic node status				
Absent	99,782	75,546	124,018	<0.001
Present	39,120	27,595	50,646	

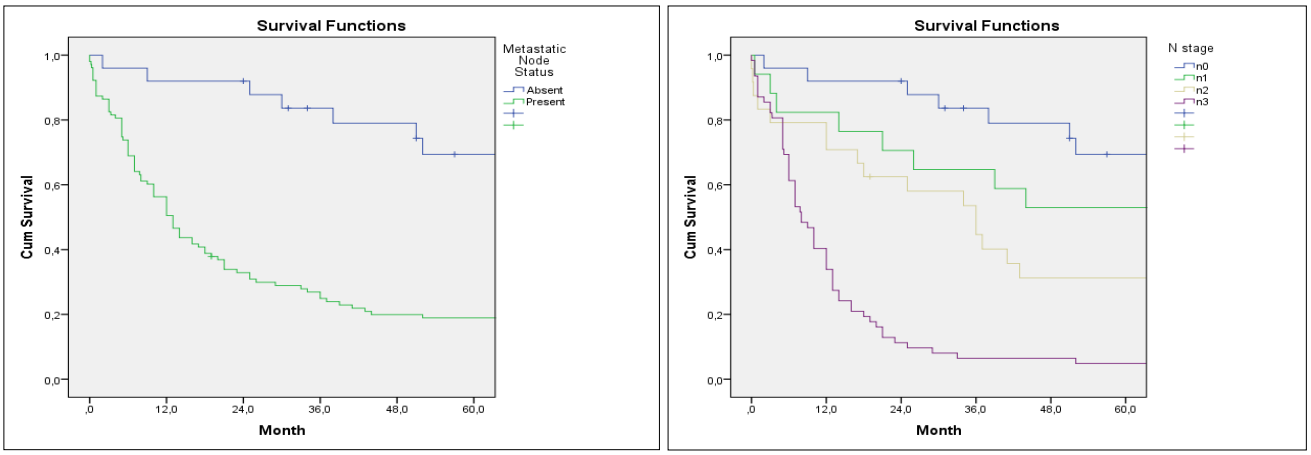

Figure 4: The mean survival curves of the variables.

DISCUSSION

Signet ring cell gastric carcinomas are a rare type of histological gastric cancer and are associated with poor overall survival compared to adenocarcinoma. Studies are reporting that it is a poor prognostic marker except for early-stage gastric cancer.[10] Its incidence has been increasing in recent years and continues to be an important health problem for patients.[3] However, there is a need to determine the optimal treatment strategy by avoiding unnecessary morbidity and mortality. Therefore, it is important to evaluate the clinicopathological features of signet-ring cell gastric carcinomas. In studies conducted in Asian and Western countries, it has been shown that signet ring cell gastric carcinomas are more common in young people, women, diffuse type, corpus, and distal stomach.[11] Although studies evaluating prognostic factors in gastric cancer are widespread, the prognostic predictors of signet ring cell gastric carcinomas are largely undefined. The effect of age on prognosis is controversial. It has been reported that the prognosis is better in younger patients with low-grade signet-ring cell gastric carcinomas who

underwent radical surgery.[12] In a population-based study based in China, age and advanced stage were reported to be poor prognostic risk factors for signet ring cell gastric cancer.[13] Poor tolerance to radical surgery and chemotherapy due to poor performance status and comorbidities in elderly patients may be the reason for this.[14] In our study, we observed that the mean survival time decreased with increasing age in signet-ring cell gastric cancers (HR=95%, p=0.011). However, when the patients were divided into two groups old (≥65 years) and young (<65 years) according to the WHO data, we could not find a significant relationship between the age of 65 and the mean survival time.

In addition, in our study, gender does not seem to be valuable in predicting the prognosis of signet ring cell gastric carcinomas, consistent with the findings of Chon et al.[15] Contrary to studies showing that proximal gastric cancer has a worse prognosis than distally located ones, no statistically significant difference in survival was observed between tumors of the antrum and other regions in our study.[16] The mean survival of patients with only linitis plastica Borrman type IV was significantly lower (HR=4.173, p=0.021). In our study, the mean survival follow-up times were found to be longer in patients who underwent subtotal gastrectomy than in patients who underwent total gastrectomy (HR=0.504). We think that this is due to the higher incidence of complications due to total gastrectomy and delays in adjuvant treatment.

Signet ring cell gastric carcinoma has a similar prognosis to adenocarcinoma in advanced stages, while it is associated with a better survival rate in early gastric cancer.[17] However, it has similar features to adenocarcinoma in terms of long-term survival in advanced stages.[3] In addition, the histological grade is one of the other poor prognostic factors in gastric cancer. However, there are also studies reporting that histological grade is not a prognostic factor in signet-ring cell gastric carcinomas.[18] In our study, we observed that high histological grade, depth of infiltration, and lymph node metastasis adversely affected the mean survival.

In general, lymphovascular and perineural invasion in gastric cancer is an unfavorable prognostic indicator independent of the stage.[19] Although specific studies for signet ring cell gastric carcinomas are insufficient in the literature, lymphovascular and perineural invasion are unquestionably poor prognostic factors for this histological subtype. In our study, the mean survival of patients with positive lymphovascular and perineural invasion was found to be significantly lower.

When we examined the effects of tumor markers, inflammatory response parameters, and hematological parameters that we routinely studied preoperatively, as well as the prognostic factors we could obtain with postoperative pathological results, we observed an inverse relationship between preoperative plasma fibrinogen levels and mean survival follow-up time. Considering the studies reporting that high plasma fibrinogen levels are associated with adjacent organ involvement, lymph node metastasis, liver metastasis, and poor overall survival in gastric cancer, this result was a significant finding for our study.[20]

The benefit of neoadjuvant chemotherapy in signet ring cell gastric cancer is controversial. Although the advantages of chemotherapy in gastric cancer were emphasized in the MAGIC study, the benefits of neoadjuvant chemotherapy in signet-ring cell gastric cancers are controversial.[21] In a retrospective study evaluating 924 signet ring cell gastric cancers, it was reported that perioperative chemotherapy did not affect survival, and neoadjuvant chemotherapy was associated with shorter survival compared to surgery alone.[22] Similar results were obtained in different neoadjuvant chemotherapy studies.[23] Conversely, there are studies indicating that neoadjuvant chemotherapy is associated with better outcomes in signet ring cell gastric cancer.[24] The negative effects of neoadjuvant therapy on survival may be due to postoperative morbidity due to drug toxicity. However, there is a risk of tumor progression during treatment.[22,25]

In our study, we observed that neoadjuvant chemotherapy did not affect survival (HR=1.24.1 p=0.503). Despite conflicting data in the literature, advanced signet ring cell gastric cancers can be treated with neoadjuvant chemotherapy or direct surgery. More studies are needed to evaluate the effectiveness of these two approaches. Advanced signet ring cell gastric carcinoma has a worse prognosis than other histological types.[26] Metastases to lymph nodes and peritoneum are common at the time of diagnosis.[27] There is no consensus in the literature on the preferred surgical method and the extent of lymph node dissection. In a recent study by Morkavuk et al, they compared D1 and D1+ lymph node dissection in signet-ring cell gastric cancers and did not report a significant difference in survival between the two methods.[28] However, it is widely accepted that survival rates increase with D2 lymphadenectomy.[26] Since we applied D2 dissection to all patients in our study, we could not find the opportunity to compare D1 and D2 lymphadenectomy. However, we observed that the mean survival follow-up times were shorter in N1 and N2 patients. We think that standard D2 lymphadenectomy may improve prognosis in signet-ring cell gastric cancers, reduce the risk of tumor recurrence and metastasis, and prolong survival.

Radical gastrectomy is the gold standard in the treatment of gastric cancer, and the current literature supports minimally invasive surgery.[29] On the other hand, in advanced stage signet ring cell gastric cancer, the data in the literature are conflicting and there is no consensus on the surgical method. In the CLASS-01 study, in which 15% of the laparoscopic group consisted of signet-ring cell gastric cancers, similar results were obtained in terms of 3-year disease-free survival between the laparoscopic and open groups in patients who underwent distal gastrectomy

and D2 lymph node dissection.[30] In our study, the average survival time was found to be longer in patients who underwent laparoscopic surgery compared to conventional surgery. The reason for this may be that we preferred laparoscopy in the selected patient group with a low clinical stage when we started laparoscopic surgery. With the increase in our experience in laparoscopic surgery and technological developments in minimally invasive surgery, we now prefer laparoscopy in our current practice, also in locally advanced stages.

Our study has some limitations that may affect the results. First of all, the most important limitations of our study are that it is retrospective, single-centered, and the number of patients is small. Since patients with distant metastases were not included in the study, our knowledge of all signet ring cell gastric cancers is limited. In addition, the inhomogeneity of the adjuvant treatments of the patients, the lack of data on tumor size, distant metastasis, and recurrence time can be counted among the limitations. However, we think that this study is valuable, given the lack of data in the literature on prognostic factors in signet-ring cell gastric cancers.

CONCLUSION

In conclusion, we investigated the clinicopathological features of nonmetastatic signet ring cell gastric carcinomas and identified predictors of long survival. Age, lymphovascular and perineural invasion, open surgery, higher tumor infiltration, and lymph node involvement were independent predictors of shorter survival times in nonmetastatic signet ring cell gastric cancers. Our study has important implications for the clinical management of signet ring cell gastric carcinomas. In the future, more studies are needed to develop individual strategies for the treatment and management of signet ring cell gastric cancers.

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