RESEARCH ARTICLE

Clinicopathological Evaluation of Gastric Signet Ring Cell Carcinoma: Our Experience

Sevgi B Altay[1], Gökhan Akkurt[2], Nisbet Yılmaz[3], Nuriye Özdemir[4]

Abstract

Aim: Gastric cancer is one of the most common cancers worldwide. In Turkey, stomach cancer is ranked 5th among men and 8th among women in all cancers and is located in the forefront in cancer-related deaths. Signet ring cell adenocarcinoma, which is the histopathological subtype of gastric cancer, has a poor prognosis. The incidence of signet ring cell adenocarcinoma is rising. In the present study, we aimed to describe the clinicopathologic features of signet ring cell adenocarcinoma.

Materials and Methods: A total of 79 patients with 30 being female (38%) and 49 male (62%) who were diagnosed with gastric signet ring cell adenocarcinoma in the Medical Oncology Department of Ankara Numune Training and Research Hospital between January 2004 and October 2015 were retrospectively evaluated.

Results: The baseline demographic characteristics of the patients, such as tumor localization, tumor stage, preoperative serum tumor markers, and treatment type (surgery and chemotherapy regimen), and the effects of these variables on survival and mortality were evaluated. Total surgery, stage III disease, moderate to poor grade, preoperative serum CA 19-9 and CEA levels were found as independent predictors of progression risk ($p < 0.05$). Each 1 ng/mL increase in preoperative serum CEA level was found to increase the risk of progression by 1.20 folds. Again, each 1 U/mL in preoperative serum CA 19-9 level was found to increase the risk of progression and mortality by 1.06 folds.

Conclusion: The clinicopathologic features of signet ring cell stomach cancer were described. Tumor localization and disease, CA 19-9 and CEA levels, and treatment type (surgery and chemotherapy regimen) were effective on survival and mortality. However, further studies with larger patient groups are needed on this issue.

Keywords: Clinicopathologic features, Early gastric cancer, Signet ring cell adenocarcinoma.

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Introduction

Gastric cancer is the second cause of cancer-related death in the world.[1] There are five histopathological subtypes of gastric adenocancer, including tubular, papillary, mucinous, poorly cohesive (including signet ring cell carcinoma), and rare variants according to the World Health Organization (WHO) classification.[2] Signet ring cell carcinoma (SRCC) differs from other gastric adenocarcinoma subtypes, because it contains intracytoplasmic mucin and more than 50% gastric cancer cells.[3] Epidemiologically, the risk factors for SRCC may differ from the general risk factors of gastric cancer. The classic risk factors of gastric cancer such as *Helicobacter pylori (H. pylori)* infection, smoking, salty food consumption, autoimmune gastritis, and obesity may not be risk factors for SRCC.[4] The incidence of gastric cancer worldwide declined after effective treatment of *H. pylori*, which is the definitive risk factor for gastric cancer.[5] In contrast, *H. pylori* infection may not be a risk factor for SRCC.[4] Therefore, while the incidence of gastric cancer decreases with the increase of *H. pylori* treatment, the incidence of SRCC subtype increases proportionally.[6]

SRCC has two forms as early and advanced cancer according to gastric wall invasion.[7] The presence of SRCC subtype is an independent risk factor for a poor prognosis, and early SRCC has a good prognosis more than advanced gastric cancer.[7] Therefore, it has become more important to diagnose the disease in an early stage and to define clinicopathological features of SRCC.

The aim of this study was to investigate basal demographic features of patients with SRCC and the effects of clinicopathological features on disease-free survival (DFS) and overall survival (OS).

[1]Department of Internal Medicine, Gaziantep 25 Aralık State Hospital, Gaziantep, Turkey

[2]Department of General Surgery, Kecioren Training and Research Hospital, Ankara, Turkey

[3]Department of Internal Medicine, Ankara City Hospital, Ankara, Turkey

[4]Oncology Department, Gazi University, Ankara, Turkey

Corresponding Author: Gökhan Akkurt, Department of General Surgery, Kecioren Training and Research Hospital, Ankara, Turkey, Phone: +90 3123569000, e-mail: drakkurt06@gmail.com

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Materials and Methods

This present study was approved by the local IRB. Patients with gastric adenocarcinoma were evaluated retrospectively from the hospital patient records between 2004 and 2015. DFS was determined as the time from surgery to disease relapse. The date of disease relapse in patients who died before the follow-up was determined as the date of death. OS was determined as the time from surgery to death. OS was noted based on the last date of follow-up in the patients who were still alive at the end of this study. The effects

of patient demographics, tumor and laboratory parameters, surgery type on DFS and OS were investigated.

Patient Demographics

Patients with gastric adenocarcinoma were examined as follows: a. patients without metastasis (M0) at the time of diagnosis and b. the medical records of patients who underwent surgical resection.

A total of 777 patients were found to meet these two criteria. Patients with gastric adenocarcinoma with more than 50% signet ring cell in the tumor tissue in histopathological examination were considered as SRCC according to World Health Organization (WHO) classification.[6] The exclusion criteria were defined as follows: (1) presence of metastasis at the time of diagnosis, (2) patients without curative surgery, and (3) presence of tumor cells in surgical margins. The sample of this present study consisted of non-metastatic patients who underwent curative surgery due to SRCC subtype of gastric adenocarcinoma. Baseline demographic characteristics of the patients such as age, gender, smoking, comorbid diseases, and Eastern Cooperative Oncology Group Performance Status (ECOG-PS)[8] were noted, separately.

Tumor and Laboratory Parameters

Tumor location, tumor size, lymph node involvement, tumor grade (gland-forming differentiation, WHO graduation G1, G2, G3), tumor stage, and pathologic features were examined. TNM staging system AJCC/UICC 8th edition staging system[9] was used in all patients. All resected lymph nodes were examined histopathologically, and lymph nodes with malignant cells were noted. Lymph node ratio (LNR) was obtained as the ratio of the metastatic lymph node to all resected lymph nodes. Lymph node ratio was formulated as the number of metastatic lymph nodes divided by the number of total resected lymph nodes. Preoperative serum CEA, CA19-9, hemoglobin, and albumin levels were evaluated. Type of surgery, total gastrectomy, or subtotal gastrectomy was noted in all patients.

Statistics

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL) program. The normally distributed data were evaluated by the Kolmogorov–Smirnov test. The numerical variables with normal distribution were shown as mean ± standard deviation, and the numerical variables without normal distribution were shown as median (min–max). Categorical variables were expressed as numbers and percentages. T-test (numerical variables with normal distribution) and Mann–Whitney U test (numerical variables without normal distribution) were used to determine the factors associated with two categories of risk groups. Chi-square test and Fisher's exact Chi-square test were used to compare the categorical data. Multivariable Cox regression analysis was used to determine the independent risk factors affecting disease relapse and mortality. $p < 0.05$ values were considered statistically significant.

Results

Patient Features

This retrospective study included a total of 79 non-metastatic SRCC patients with 30 being female (38%) and 49 male (62%). The mean age of patients diagnosed with SRCC was 55.3 ± 12.8 years. The most common symptoms were stomach pain ($n = 41$, 51.9%), weight loss ($n = 14$, 17.7%), vomiting ($n = 13$, 16.5%), difficulty in swallowing ($n = 4$, 5.1%), and gastrointestinal bleeding ($n = 4$, 5.1%), while 3 patients (3.8%) were asymptomatic. The basic demographic characteristics of the patients are shown in Table 1.

Surgical and Pathological Features

The surgical and pathological features are shown in Table 2. The mean tumor diameter was 7 cm (min–max: 2–16 cm). Total gastrectomy was performed in 63.3% and subtotal gastrectomy in 36.7% of the patients. The mean number of resected lymph nodes was 22 (min–max: 2–51). The mean number of lymph node involvement was 9 (min–max: 0–44).

Preoperative Serum CA 19-9 and CEA Levels

The mean preoperative CA19-9 level was 12.2 U/mL (min 0.6–max 534 U/mL), while 27.8% ($n = 22$) of the patients had high serum CA19-9. The mean preoperative CEA level was 1.9 ng/mL (min 0.1–max 397 ng/mL), and 24.1% ($n = 19$) of the patients had high serum CEA.

Disease-free Survival (DFS)

Disease relapse was detected in 58.2% of the patients, and the median DFS from the time of diagnosis was 81 months. The possible

Table 1: Basal demographic characteristics

Variables	*Patients n (%)*
Gender	
Female	30 (38.0)
Male	49 (62.0)
Age (± SD year)	55.3 ± 12.8
Smoking	36 (45.6)
Pack years (min–max)	36 (3–80)
Gastric cancer family history	
None	69 (87.3)
First-degree relatives	10 (12.7)
Comorbidity	24 (32.9)
Diabetes mellitus	6 (7.6)
Hypertension	12 (15.2)
Coronary artery disease	2 (2.5)
Other	6 (7.6)
None	55 (67.1)
Tumor localization	
Proximal tumor	63 (79.8)
Gastric cardia	13 (16.5)
Fundus	23 (29.1)
Corpus	27 (34.2)
Distal (antropyloric)	16 (20.3)
ECOG (0–4)	
0	15 (19.0)
1	40 (50.6)
2	21 (26.6)
3	3 (3.8)

ECOG-PS, Eastern Cooperative Oncology Group (ECOG) Performance Status; SD, standard deviation

Table 2: Surgical and pathological features

Stage (AJCC TNM)	*n = 79 (%)*
I	11 (13.9)
A	7 (8.9)
B	4 (5.1)
II	20 (25.3)
A	8 (10.1)
B	12 (15.2)
III	48 (60.8)
A	6 (7.6)
B	31 (39.2)
C	11 (13.9)
T stage	
T1	10 (12.7)
T2	7 (8.9)
T3	49 (62.0)
T4	13 (16.5)
N stage	
N0	15 (19.0)
N1	11 (13.9)
N2	6 (7.6)
N3	47 (59.5)
M stage	
M0	79 (100.0)
Tumor differentiation grade	
Grade 1	16 (20.3)
Grade 2	21 (26.6)
Grade 3	42 (53.2)

risk factors on DFS after the diagnosis are shown in Table 3. Total surgery (HR = 1.96; $p = 0.043$), stage III disease (HR = 5.41; $p = 0.021$), grade 2 differentiation (HR = 3.67; $p = 0.017$), grade 3 differentiation (HR = 4.07; $p = 0.014$), preoperative serum CA 19-9 level (HR = 1.06; $p = 0.020$), and preoperative serum CEA level (HR = 1.20; $p = 0.035$) were independent predictors of disease relapse. The odds of disease relapse in patients with total gastrectomy was 1.96 folds higher than in patients with subtotal gastrectomy (HR = 1.96, log rank $p = 0.022$) (Fig. 1A).

The disease relapse odds in patients with stage III disease was 5.41 folds higher than in patients with stage I disease (HR = 5.41, log rank $p = 0.017$). But in patients with stage II disease, DFS rates were longer than in patients with stage III disease, although not statistically significant (Fig. 1B). The risk of disease relapse was increased in parallel with the grade of tumor differentiation. The highest risk was determined in the highest tumor grade. Patients with grade 3 had 4.07 folds relapse odds (HR = 4.07, log rank $p = 0.026$), and patients with grade 2 had a 3.67 folds relapse odds (HR = 3.67, log rank $p = 0.026$) compared to patients with grade 1 (Fig. 1C).

Preoperative serum CA 19-9 levels above 14.4 U/mL predicted the relapse risk of the disease with 60.9% sensitivity and 90.9% specificity (AUC ± SE = 0.692 ± 0.061; $p = 0.001$). Patients with serum CA 19-9 levels above 14.4 U/mL had a 4.38 folds higher risk of relapse than the patients with 14.4 U/mL or lower (HR = 4.38; log rank $p < 0.001$) (Fig. 1D).

Preoperative serum CEA levels above 1 ng/mL predicted the relapse risk of the disease with 80.4% sensitivity and 61.6% specificity (AUC ± SE = 0.708 ± 0.058; $p < 0.001$). Patients with serum CEA levels above 1 ng/mL had a 2.80 folds higher risk of relapse than patients with 1 ng/mL or lower (HR = 2.80; log rank = 0.003) (Fig. 1E). It was found that the rising of 1 ng/mL of serum CEA level increased the risk of the disease relapse by 1.20 folds and the rising of 1 U/mL of serum CA 19-9 level increased the risk of the disease relapse by 1.06 folds.

Overall Survival

Median OS was 84 months, and 55.7% of the patients were exitus. The effects of possible risk factors on mortality after diagnosis are shown in Table 4. In our study, lymph node ratio (LNR, HR = 2.65; $p = 0.027$) was obtained by the ratio of metastatic lymph nodes (HR = 1.04; $p = 0.013$) with all resected lymph nodes (HR = 1.02; $p = 0.173$). LNI was determined as a possible risk factor for mortality ($p = 0.027$).

Total surgery (HR = 2.25; $p = 0.020$), stage III disease (HR = 5.18; $p = 0.15$), grade 2 differentiation (HR = 3.50; $p = 0.021$), grade 3 differentiation (HR = 3.93; $p = 0.018$), preoperative serum CA 19-9 level (HR = 1.06; $p = 0.027$), and preoperative serum CEA level (HR = 1.18; $p=0.035$) were independent predictors of mortality. The odds of mortality in patients with total gastrectomy was 2.25 folds higher than in patients with subtotal gastrectomy (HR = 2.25, log rank $p = 0.013$) (Fig. 2A). The mortality odds in patients with stage III disease was 5.18 folds higher than in patients with stage I disease (HR = 5.18, log rank $p = 0.016$). But in patients with stage II disease, OS rates were longer than in patients with stage III disease, although not statistically significant (Fig. 2B).

The risk of mortality was increased in parallel with the grade of tumor differentiation. The highest risk was determined in the highest tumor grade. Patients with grade 3 had 3.93 folds mortality odds (HR = 3.93, log rank $p = 0.033$), and patients with grade 2 had 3.50 folds mortality odds (HR = 3.5, log rank $p = 0.033$) compared to patients with grade 1 (Fig. 2C).

Preoperative serum CA 19-9 levels above 14.6 U/mL predicted the mortality risk of the disease with 68.2% sensitivity and 94.3% specificity (AUC ± SE = 0.824 ± 0.048; $p < 0.001$). Patients with serum CA 19-9 levels above 14.6 U/mL had a 6.30 folds higher risk of mortality than patients with 14.6 U/mL or lower (HR = 6.30; log rank $p < 0.001$) (Fig. 2D).

Preoperative serum CEA levels above 1.1 ng/mL predicted the mortality risk of the disease with 81.8% sensitivity and 71.4% specificity (AUC ± SE=0.824 ± 0.046; $p < 0.001$). Patients with serum CEA levels above 1.1 ng/mL had a 6.58 folds higher risk of mortality than patients with 1.1 ng/mL or lower (HR = 6.58; log rank $p < 0.001$) (Fig. 2E). It was found that the rising of 1 ng/mL of serum CEA level increased the risk of mortality by 1.18 folds and the rising of 1 U/mL of serum CA 19-9 level increased the risk of mortality by 1.06 folds.

Discussion

The results of this study indicate that the possible risk factors for DFS and OS are (a) total surgery, (b) stage III disease, (c) middle and poor grade, (d) lymph node ratio, and (e) preoperative serum CA 19-9 and

Table 3: Effect of patient and tumor characteristics on DFS

			Univariable analysis		*Multivariable analysis*	
Variables	*DFS (mth.)*	*DFS 5 years (%)*	*HR (95% CI)*	*p*	*HR (95% CI)*	*p*
Gender						
Female	36	33%	Ref.		–	–
Male	39	38%	0.91 (0.51–1.65)	0.757	–	–
Age			0.99 (0.97–1.01)	0.406		
Smoking						
Yes	46	48%	Ref.	0.08	–	–
No	29	20%	1.68 (0.94–3.01)			
Tumor local.						
Gastric cardia	32	35%	Ref.			
Fundus	36	39%	0.92 (0.38–2.19)	0.847	–	–
Corpus	65	42%	0.78 (0.32–1.87)	0.571	–	–
Antropyloric	28	21%	1.27 (0.51–3.18)	0.609	–	–
Subtotal gastrectomy	67	56%	Ref.		Ref.	
Total gastrectomy	29	31%	2.08 (1.09–3.98)	0.026*	1.96 (1.02–3.78)	0.043*
Stage						
I	110	78%	Ref.		Ref.	
II	51	40%	4.18 (0.93–18.92)	0.063	3.82 (0.84–17.32)	0.082
III	29	25%	6.01 (1.44–25.14)	0.014*	5.40 (1.29–22.71)	0.021*
Tumor diff. grade						
Grade 1	116	67%	Ref.		Ref.	
Grade 2	30	31%	3.56 (1.17–10.83)	0.025*	3.67 (1.27–10.65)	0.017*
Grade 3	29	28%	3.79 (1.32–10.83)	0.013*	4.07 (1.32–12.52)	0.014*
Lymph node (LN)						
Resected LN	–	–	1.02 (0.99–1.04)	0.024*	–	–
Metastatic LN			1.03 (1.01–1.05)	0.024*		
LNR			2.36 (1.02–5.47)	0.045*		
Preop. CEA			1.18 (1.01–1.35)	0.037*	1.20 (1.01–1.40)	0.035*
Preop. CA 19-9			1.05 (1.01–1.09)	0.019*	1.06 (1.01–1.11)	0.020*

Multivariable regression model: −2 log-likelihood = 328.6; $p < 0.05$ * is significant; DFS, disease-free survival time (months); OS, overall survival rate; HR, hazard ratio; CI, confidence interval; LNR, lymph node ratio; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9

CEA levels. SRCC occurs in 4 to 17% of the other subtypes of gastric cancer.[10] Gastric cancer is more common in men than in women.[11] As a hypothesis, sex hormones can affect the development of gastric cancer.[12,13] Endogenous or exogenous estrogen may have a protective effect against gastric cancer.[14] Interestingly, the likelihood of gastric cancer increases in men with frontal baldness pattern.[15] In contrast to other gastric cancer subtypes, SRCC has been reported to be more common in women.[16] But there was a male dominance in our study. This may be because of our study patients selected from non-metastatic (M0) patients. However, this contradictory situation can provide additional information; that is why, SRCC is diagnosed before metastasis in men. Already, it is known that sex hormones have effects on metastasis processes in lung cancer, breast cancer, and prostate cancer.[17,18] Sex hormones may affect metastasis process of SRCC, and further investigations are needed. Kwon et al.[7] reported that gender is not a prognostic factor in 51 patients with SRCC. In our study, we found that gender had no effect on DFS and OS and it was not a prognostic factor. Smoking is considered to be an important behavioral risk factor for gastric cancer, and the risk of gastric cancer decreases with smoking cessation.[19] There is a strong correlation between both cardia and non-cardia gastric adenocarcinoma and smoking.[20,21] In our study, the most common location of SRCC in both smokers and nonsmokers was gastric cardia and there was remarkably no correlation between SRCC and smoking habit in terms of tumor localization. However, we determined negative effects of smoking habits on DFS and OS. DFS and OS were shorter in smokers than in nonsmokers.

The effect of tumor localization on DFS and OS is controversial in the management and treatment of gastric cancer. There are

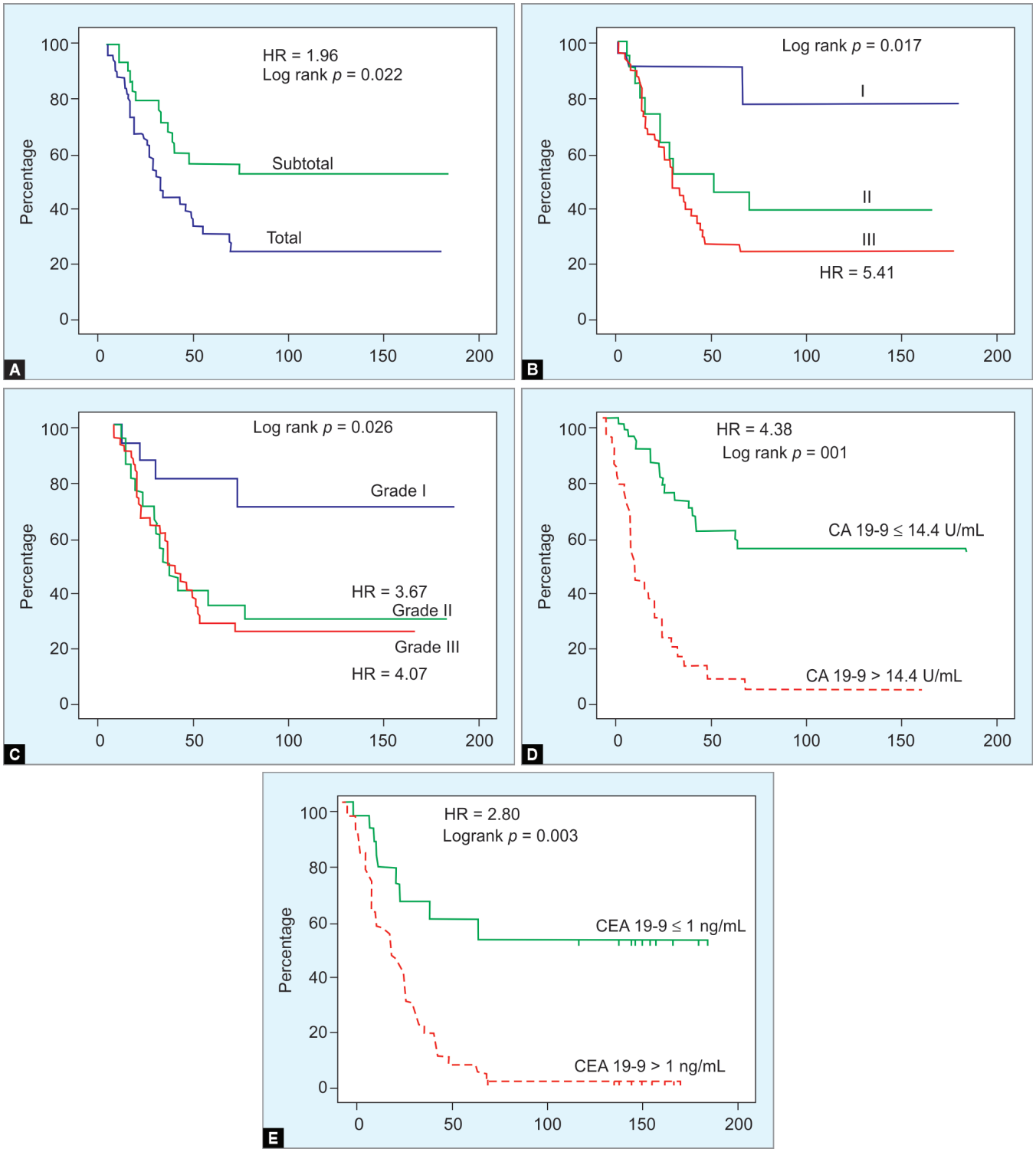

Fig. 1: (A) Odds of disease relapse in patients, (B) RFS rates in patients, (C) Log rank compared to patients with grade, (D) Comparison of serum CA 19-9 with patient relapse, (E) Comparison of serum CEA with patient relapse

some publications indicating that tumor localization has no effect on disease prognosis, but some publications claim otherwise.[22–24] Piessen et al.[25] classified tumor localization as antropyloric (distal) and non-antropyloric (proximal) in SRCC. Large tumor diameter, wall penetration, vascular invasion, lymph node metastasis, and advanced stage tumor are more common in non-antropyloric located tumors, and these decrease DFS and OS.[23,24] In our study, a large proportion of the tumors were located in the non-antropyloric region and there was no significant relationship between tumor localization and DFS and OS. Proximal localization has a poor prognosis because of the delayed diagnosis of proximal tumors and the progression of the disease to the advanced stage. Our study

Table 4: Effect of patient and tumor characteristics on OS

			Univariable analysis		*Multivariable analysis*	
Variables	*OS (mth.)*	*OS 5 years (%)*	*HR (95% CI)*	*p*	*HR (95% CI)*	*p*
Gender						
Female	45	37%	Ref.		–	–
Male	46	38%	1.05 (0.57–1.95)	0.873	–	–
Age			0.99 (0.97–1.01)	0.419		
Smoking						
Yes	46	50%	Ref.		–	–
No	33	21%	1.69 (0.93–3.07)	0.084		
Tumor local.						
Gastric cardia	50	40%	Ref.			
Fundus	36	39%	1.10 (0.45–2.74)	0.831	–	–
Corpus	65	45%	0.85 (0.33–2.16)	0.731	–	–
Antropyloric	31	21%	1.54 (0.59–4.00)	0.380	–	–
Subtotal gastrectomy	110	60%	Ref.		Ref.	
Total gastrectomy	30	27%	2.28 (1.16–4.45)	0.016*	2.25 (1.14–4.44)	0.020*
Stage						
I	119	78%	Ref.		Ref.	
II	52	40%	3.73 (0.82–17.05)	0.089	3.37 (0.74–15.47)	0.118
III	33	25%	5.84 (1.39–24.47)	0.016*	5.18 (1.23–21.80)	0.025*
Tumor diff. grade						
Grade 1	116	67%	Ref.		Ref.	
Grade 2	36	34%	3.34 (1.09–10.25)	0.035*	3.50 (1.21–10.13)	0.021*
Grade 3	30	30%	3.67 (1.28–10.51)	0.016*	3.93 (1.26–12.23)	0.018*
Lymph node (LN)						
Resected LN	–	–	1.02 (0.99–1.04)	0.173	–	–
Metastatic LN			1.04 (1.01–1.06)	0.027*		
LNR			2.65 (1.12–6.29)	0.027*		
Preop. CEA			1.19 (1.01–1.41)	0.038*	1.18 (1.01–1.37)	0.035*
Preop. CA 19-9			1.05 (1.01–1.10)	0.028*	1.06 (1.01–1.11)	0.027*

Multivariable regression model: −2 log-likelihood = 328.6; *($p < 0.05$) is significant; OS, overall survival rate; HR, hazard ratio; CI, confidence interval; LNR, lymph node ratio; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9

consisted of patients who were not in an advanced stage (M0), and therefore, tumor localization was not found to be a predictive factor. Tumor size is considered a prognostic factor in gastric cancer. Im et al.[26] reported 1,657 patients with gastric cancer in which tumor size was an independent risk factor in patients with advanced gastric cancer, but not in early gastric cancer. Yokato et al.[27] stated that tumor size is a clinical predictive factor in patients with gastric cancer, but not an independent risk factor. Tumor size affects TNM staging, the type of surgery (total, subtotal), and the resectability of the tumor. The tumor size was not an independent risk factor affecting DFS and OS in our study.

Tumor stage has an effect on the prognosis of gastric cancer as in other cancers. Mucosal limited early-stage SRCC has a better prognosis than other early gastric adenocarcinoma subtypes, irrespective of submucosal lymph node involvement.[28,29] Advanced SRCC has a poor prognosis than the other advanced gastric adenocarcinoma subtypes due to the low tumor-free resection rate in advanced SRCC.[30] In our study, stage III disease had significantly low DFS and OS rates and a higher high risk of disease relapse, compared to early-stage disease. Stage III disease was an independent predictor of low DFS and OS rates according to our study results.

In our study, patients with grade 3 differentiation in predicting disease relapse were compared with patients with grade 2 differentiation and grade 1 differentiation and were found to be statistically significantly at the borderline and it was determined as a possible risk factor in univariable analysis ($p < 0.05$), but not as an independent predictor. However, grade was found to be an important independent predictor of mortality. As the grade progressed from good to poor (from grade 1 to grade 3) (good

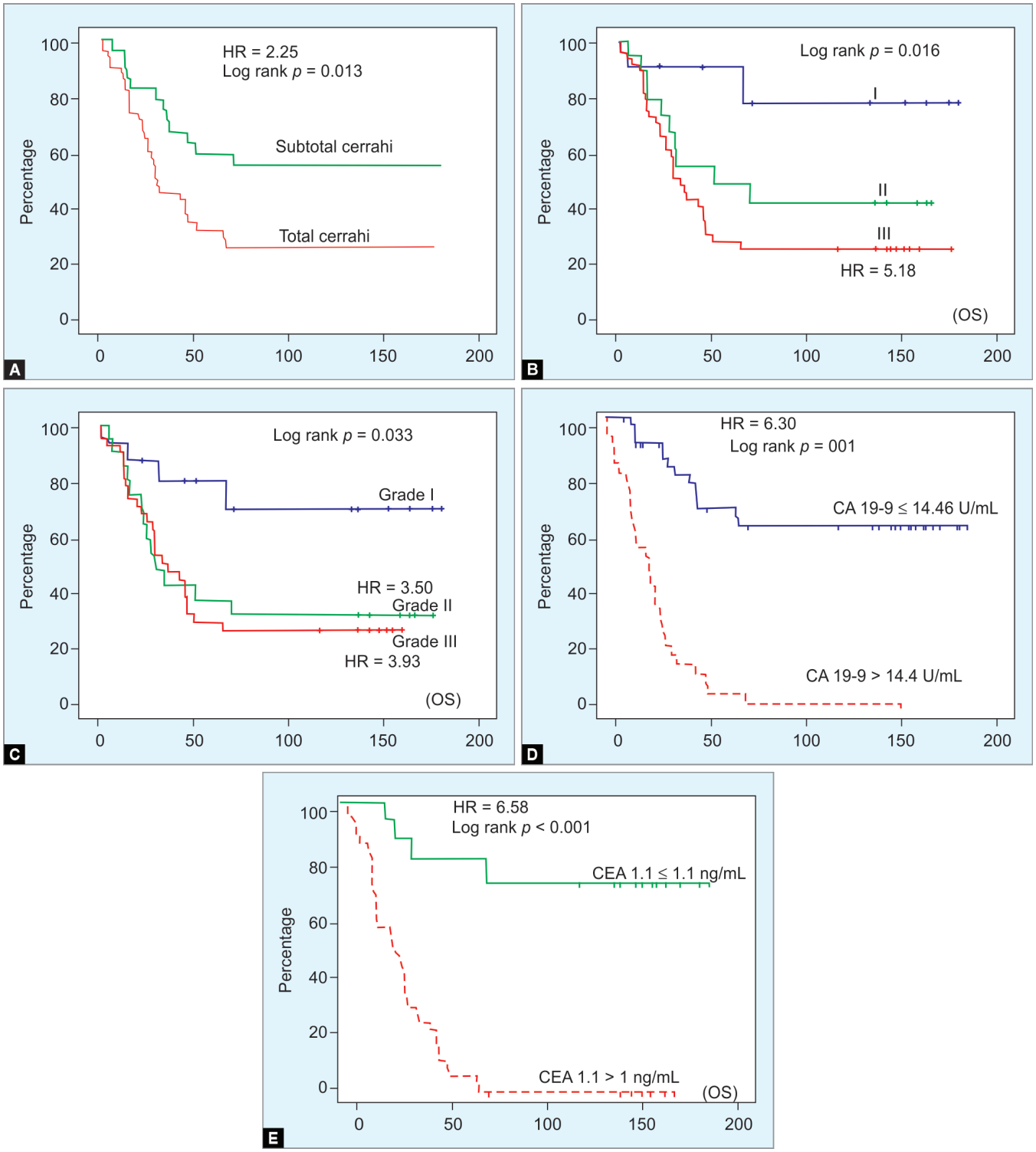

Fig. 2: (A) Odds of mortality in patients, (B) Comparison of stage with OS (C) Comparison of grade with OS (D) Comparison of serum CA 19-9 with OS (E) Comparison of serum CEA with OS

grade of 116 months, poor grade of 30 months), OS decreased. Our findings suggest that tumor differentiation grades can be used for a personalized follow-up chart for the patient's survival, because they are a possible predictor of disease relapse and a significant indicator of mortality. The curative treatment of gastric cancer is surgery.[2] Surgical options include total, subtotal gastrectomy, and recently laparoscopic-assisted distal gastrectomy.[31] Kong et al.[32] reported that there was no difference between total and subtotal gastrectomy in terms of mortality rates, complication rates, and five-year survival rates. But, Lin et al.[33] noted that five-year OS rate is lower in patients with total gastrectomy compared to subtotal gastrectomy. However, the surgical method of treatment

of SRCC is controversial. The surgical method is determined according to the location of SRCC and the stage of the disease. Total gastrectomy is considered as a treatment option because of increased tumor spread in advanced SRCC.[34] In our study, DFS and OS were lower in patients with total gastrectomy compared to subtotal gastrectomy. In addition, we found that the probability of disease relapse (1.96 folds) and mortality (2.25 folds) was higher in patients with total gastrectomy than in subtotal gastrectomy. The cause of low DFS and OS rates in total gastrectomy may not be about the type of surgery. It may be caused by total gastrectomy indication because total gastrectomy was performed in advanced stage disease.

Lymph node metastasis is an important factor for prognosis, because it affects TNM stage and it is more important in SRCC compared to other types of stomach cancer.[35] Lymph node metastasis in mucosal SRCC is not an appropriate prognostic factor, but lymph node metastasis is a prognostic factor in submucosal SRCC.[35] The difficulty of classifying the commonly used AJCC TNM is that at least 15 lymph nodes have to be removed in order to clearly determine N stage. Inadequate lymph node dissection leads to inappropriate staging in patients.[36] In recent years, there is evidence that LNR may be a more meaningful marker for survival than N stage.[36–38] LNR is better than the AJCC system in inadequate lymph node resection.[38] In our study, LNR was determined as a possible risk factor for mortality in SRCC patients ($p = 0.027$). Mortality rates were also high in patients with high LNR. As LNR got closer to 1, survival was also markedly deteriorated. LNR can be used to predict OS in patients with SRCC.

Multiple serum tumor markers such as CEA, CA19-9, and CA72-4 can be used in the diagnosis of gastric cancer.[39] There is no specific serum tumor marker for the diagnosis of gastric cancer, yet. However, CEA and CA 19-9 levels can be used to predict the prognosis of gastric cancer. CEA level had a positive correlation with the poor prognosis in early gastric cancer.[40] In addition, Kaya et al.[41]reported that CEA and CA19-9 levels increase, but are not diagnostic factors in SRCC. We investigated the effects of preoperative CEA and CA 19-9 levels on DFS and OS. There was a positive correlation between DFS and OS with preoperative serum CEA and CA 19-9 levels in our study. The patients with higher serum CEA and CA 19-9 levels had more frequently disease relapse and mortality. High preoperative serum CEA and CA 19-9 levels were associated with low DFS and OS rates.

The 1 ng/mL increase of preoperative serum CEA was found to increase the risk of disease relapse by 1.20 folds with high sensitivity and relatively low specificity. Preoperative serum CA19-9 level above 14.4 U/mL predicted the risk of disease relapse with relatively low sensitivity and high specificity ($p < 0.001$). In addition, preoperative CEA level above 1.1 ng/mL increased the mortality by 6.58 folds ($p < 0.001$). The 1 U/mL increase of preoperative serum CA 19-9 was found to increase the risk of mortality by 1.06 folds.

In our study, we determined the preoperative serum CA 19-9 levels as an independent predictor of DFS and OS. However, Dilege et al.[42] reported that CA 19-9 levels were correlated with lymph node metastasis and reported that CA 19-9 levels had no effect on OS in patients with non-metastatic operable gastric cancer. Duraker et al.[43] noted that serum CA 19-9 was effective in determining the disease level in resectable gastric cancer, but not as an independent predictor. This contradiction may be related to the patient population. All of our patient population consisted of the SRCC subtype of gastric cancer. CA 19-9 levels were not reported as independent predictors in all subtypes of gastric adenocarcinoma in their studies, whereas we found high serum CA19-9 level as an independent predictor in SRCC. Further studies are needed on this subject with a larger patient population.

In conclusion, the type of surgery, tumor differentiation grade, tumor stage, preoperative CA 19-9 and CEA serum levels were found as independent predictors of DFS and OS in patients with SRCC according to our study results. In patients with inadequate lymph node dissection, we recommend LNR as a valuable parameter in predicting OS.

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