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Prognostic Differences of Tumor Localization in Gastric Cancer Patients Undergoing Curative Resection

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Abstract

Background: Gastric cancer is the fifth most frequent cancer worldwide and the third major cause of cancer-related fatalities

Objectives: The current study aims to investigate whether there is a relationship between tumor location and various prognostic factors in patients who underwent curative resection for gastric cancer.

Methods: A total of 293 patients who underwent curative surgical resection for gastric cancer were analysed retrospectively. Siewert type II and III tumours were defined as proximal gastric cancer (PGC). More distally located tumours were defined as distal gastric cancer (DGC). Siewert type I tumours were excluded.

Results: Out of 293 patients, 78 were diagnosed with PGC and 215 had DGC. There was a significant relationship between preoperative/postoperative chemotherapy administration, gastrectomy type, presence of lymphatic metastasis, Tumour-Node-Metastasis stage, and tumour localization ($P < 0.05$). There was no significant difference between PGC and DGC in terms of length of hospital stay ($P = 0.137$). Five-year survival rates for PGC and DGC were 48.4% and 45.8%, respectively ($P = 0.863$). pT stage, preoperative and postoperative chemotherapy were determined as independent risk factors ($P < 0.05$). The location of the tumour and the type of surgical resection did not affect the prognosis ($P > 0.05$).

Conclusion: Tumour localization is not a prognostic factor in gastric cancer. When safe surgical margins were provided in DGC, total gastrectomy for DGC had no effect on the survival rate.

Keywords: Gastric cancer, Gastrectomy, Prognosis, Survival

1. Background

Gastric cancer is the fifth most frequent cancer worldwide and the third major cause of cancer-related fatalities (1). Recent studies suggest that the incidence of proximal gastric cancer (PGC) has increased despite a decrease in distal involvement (2). Since gastric tumours in different anatomical locations have different biological and clinicopathological features, their prognosis may also vary (3). Some authors have reported that the prognosis for PGC is worse than for distal gastric cancer (DGC) because of various prognostic factors, such as age, gender, tumour size, lymphatic metastasis, and Tumour-Node-Metastasis (TNM) stage (4). On the contrary, the relationship between tumour location and prognosis could not be demonstrated in a study involving 16,119 patients by Zhao et al. (5). According to the results of one of the recent meta-analyses, the concept of subtotal gastrectomy versus total gastrectomy is still controversial, although there is evidence in favour of subtotal gastrectomy in tumours located in the distal third (6). Based on these data, there is still no consensus on the prognostic value of the tumour location in gastric cancer, and the debate on this issue is still ongoing. Consequently, verifications are required in this context.

2. Objectives

The current study aims to investigate whether there is a relationship between tumor location and various prognostic factors in patients who underwent curative resection for gastric cancer.

3. Methods

The institutional review board of XXX Hospital approved the study protocol, and ethics committee approval was obtained from the same hospital. (Ref. No:2019.7/52-268). This committee waived the need for informed consent from all eligible patients.

Data obtained from 324 patients who underwent surgery for gastric cancer at XXX hospital between November 2006 and November 2019 was reviewed. Eighteen of them were excluded from the study due to emergency surgery, palliative surgery, and missing data. In addition, 13 out of 306 patients who underwent curative surgical resection were excluded because they could not complete the adjuvant treatment for various reasons. The data of the remaining 293 patients over the age of 18, diagnosed with gastric adenocarcinoma and underwent curative

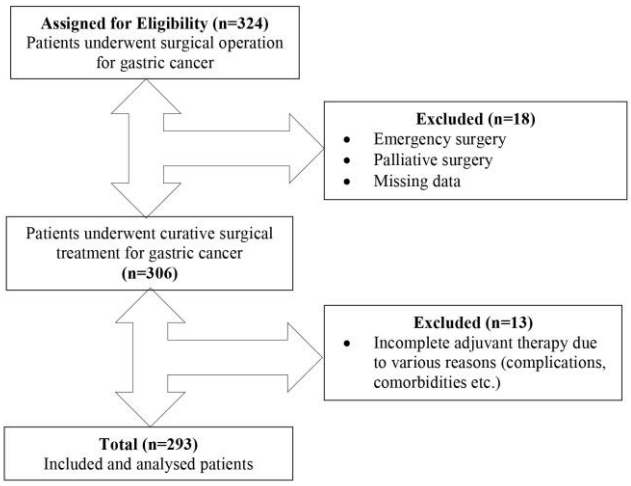

Figure 1. Flowchart of the research design and patient data enrolment

(R0) surgical resection were analysed retrospectively (Figure 1).

As part of preoperative (neoadjuvant) chemotherapy, docetaxel, cisplatin, fluorouracil (DCF) or fluorouracil, leucovorin, oxaliplatin, docetaxel (FLOD) regimens were administered to the patients. Postoperative (adjuvant) chemotherapy was given to patients as either a continuation of preoperative chemotherapy or as a fluorouracil-based or capecitabine plus oxaliplatin (XELOX) regimen. Since a limited number of patients received radiotherapy (RT) as neoadjuvant or adjuvant therapy, RT data of the patients was not mentioned.

The data of the patients were analysed according to the following variables which were among the prognostic factors: age (over/under 65 years), gender, Charlson Comorbidity Index (CCI), body mass index (BMI), neoadjuvant/adjuvant chemotherapy, tumour location, type of surgical resection, TNM stage (according to American Joint Committee on Cancer, Cancer Staging Manual 8th Edition) (7), pT stage, the total number of lymph nodes evaluated, number of metastatic lymph nodes, lymphovascular invasion (LVI), perineural invasion (PNI), tumour grade (well-, moderately-, and poorly-differentiated), and primary tumour size (<5 cm, 5 cm).

The PGC was defined as Siewert type II, which is considered to be a true gastric cardia tumour with the centre located between 1 cm above and 2 cm below the esophagogastric junction, and Siewert type III, which is considered to be subcardial gastric cancer located between 2-5 cm below the esophagogastric junction (8). More distally located gastric tumours were accepted as DGC. Siewert type I cancers were excluded. Total gastrectomy was performed for surgical margins in large gastric tumours located in the corpus and distal gastric tumours located in the small curvature.

The surgical complications were classified according to the Clavien–Dindo classification system (9).

3.1. Statistical Analysis

Statistical analysis was performed using SPSS software (version 22.0) (Released 2013. IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.). Kolmogorov Smirnov test was used to determine whether numerical variables followed a normal distribution. Qualitative data were presented as frequency and percentage. Quantitative data were presented as mean ± standard deviation (SD) if normally distributed, and as median (minimum-maximum) if not. Chi-Square *and Fisher's exact tests* were used to compare categorical data. Independent samples t-test was used to compare numerical data according to the tumour localization. The effect of proximal and distal localization on overall survival was analysed with the Kaplan-Meier method. Prognostic variables affecting mortality considering survival were determined using multivariate Cox regression analysis. A P-value of < 0.05 was considered statistically significant.

4. Results

Out of 293 patients included in the study, 78 (26.7%) and 215 (73.3%) had PGC and DGC, respectively. Furthermore, the median follow-up period was 26.5 (10.6-60.7) and 24.3 (11.8-66.9) months for PGC and DGC, respectively.

There was no significant difference in terms of age and gender between the PGC and DGC patient groups ($P = 0.149$ and 0.117, respectively). Although the CCI score was higher in patients with proximal tumours, there was no significant difference between PGC and DGC patients ($P = 0.091$). In addition, no significant difference was observed between PGC and DGC patients in terms of BMI ($P = 0.419$) (Table 1).

Neoadjuvant therapy rate was significantly higher in PGC patients. While 38% of all patients received neoadjuvant therapy regardless of tumour location,

Table 1. Demographic and clinicopathologic characteristics of patients

Variables		Proximal n=78	Distal n=215	*P*
		n (%)	n (%)	
Age, years	<65	54 (69.2%)	129 (60.0%)	0.149
	≥65	24 (30.8%)	86 (40.0%)	
Sex	Male	61 (78.2%)	148 (68.8%)	0.117
	Female	17 (21.8%)	67 (31.2%)	
CCI	0-2	49 (62.8%)	157 (73.0%)	0.091
	≥3	29 (37.2%)	58 (27.0%)	
BMI	<18.5	3 (3.8%)	4 (1.9%)	0.419
	18.5-24.9	29 (37.2%)	94 (43.7%)	
	≥25.0	46 (59.0%)	117 (54.4%)	
Neoadjuvant	Yes	38 (48.7%)	62 (28.8%)	0.002
	No	40 (51.3%)	153 (71.2%)	
Type of gastrectomy	Total	78 (100.0%)	69 (32.1%)	<0.001
	Subtotal	0 (0.0%)	146 (67.9%)	
pT stage	pT1-pT2	14 (17.9%)	57 (26.5%)	0.131
	pT3-pT4	64 (82.1%)	158 (73.5%)	
No of nodes examined	0-15 nodes	10 (12.8%)	44 (20.5%)	0.136
	> 15 nodes	68 (87.2%)	171 (79.5%)	
Nodal metastasis	Yes	57 (73.1%)	130 (60.5%)	0.047
	No	21 (26.9%)	85 (39.5%)	
Distant metastasis	Yes	10 (12.8%)	14 (6.5%)	0.082
	No	68 (87.2%)	201(93.5%)	
LVI	Yes	50 (64.1%)	125 (58.1%)	0.358
	No	28 (35.9%)	90 (41.9%)	
PNI	Yes	54 (69.2%)	134 (62.3%)	0.276
	No	24 (30.8%)	81 (37.7%)	
Tumor grade	Well	5 (6.4%)	20 (9.3%)	0.525
	Moderately	29 (37.2%)	67 (31.2%)	
	Poorly	44 (56.4%)	128 (59.5%)	
TNM stage	I-II	22 (28.2%)	90 (41.9%)	0.034
	III-IV	56 (71.8%)	125 (58.1%)	
Tumor size	<5cm	40 (51.3%)	102 (47.4%)	0.561
	≥5cm	38 (48.7%)	113 (52.6%)	
Complication	No or Minor	71 (91.0%)	191 (88.8%)	0.590
	Major	7 (9.0%)	24 (11.2%)	
Adjuvant	Yes	63 (80.8%)	139 (64.7%)	0.008
	No	15 (19.2%)	76 (35.3%)	
		Mean ± SD (95% CI)		
Length of stay, days		11.5 ± 5.5 (-0.467-3.395)	10.1 ± 7.9 (-0.173-3.102)	0.137

BMI: Body Mass Index; CCI: Charlson Comorbidity Index; CI: Confidence Interval; LVI: Lymphovascular Invasion; PNI: Perineural Invasion; TNM: Tumour-Node-Metastasis

48.7% of patients with PGC and only 28.8% of patients with DGC were given neoadjuvant therapy (P = 0.002). According to tumour location, total gastrectomy was surgical resection type of choice for all patients with PGC (n = 78, 100.0%), whereas only one third (n = 69, 32.0%) of patients with DGC underwent total gastrectomy (P < 0.001) (Table 1).

There was no significant relationship between tumour localization and either the pT stage or the number of lymph nodes examined (P > 0.05). On the other hand, 130 (69.5%) of 187 patients with lymph node metastasis had DGC and this relationship was statistically significant (P = 0.047). There was no significant relationship in terms of distant metastasis presence, LVI, PNI, histological grade and primary tumour size (P > 0.05). When TNM stages were examined according to tumour localization, there were 181 patients defined as TNM stage III or IV. Moreover, 56 of these patients had PGC (71.8% of PGC patients), whereas 125 had DGC (58.1% of DGC patients) (P = 0.034). In parallel with this, the adjuvant therapy rate was found to have a significant relationship with tumour localization. Adjuvant therapy was given to 63 (80.8%) of 78 patients with PGC and 139 (64.7%) of 215 patients with DGC (P = 0.008) (Table 1).

Duration of hospital stay showed no significant difference between PGC and DGC. The mean

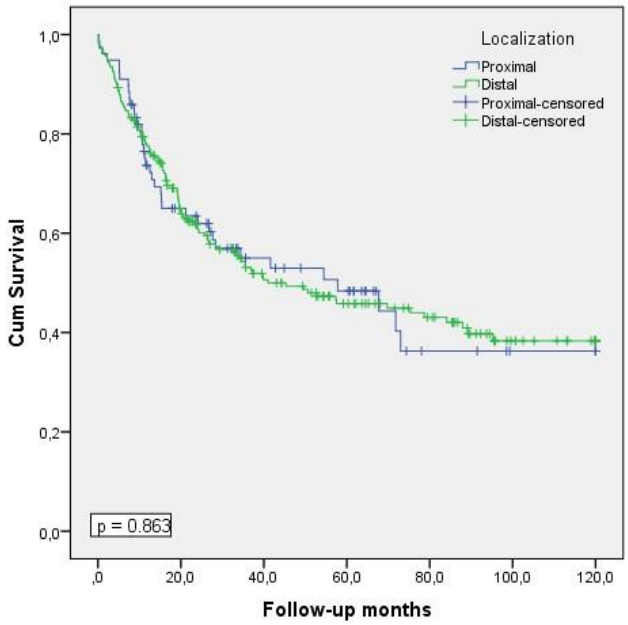

Figure 2. Overall survival analysis in patients with proximal gastric cancer and distal gastric cancer, according to the Kaplan-Meier method

postoperative stay was 11.5 ± 5.5 and 10.1 ± 7.9 days in patients with PGC and DGC, respectively (P = 0.137) (Table 1).

Five-year overall survival rates were 48.4% in PGC and 45.8% in DGC. Although cumulative survival rates were higher in patients with DGC, this was not statistically significant (P = 0.863) (Figure 2). Cox regression analysis examining variables with potential impact on mortality showed that localization had no prognostic effect (P = 0.301). In contrast, pT stage, neoadjuvant and adjuvant therapy rates appeared to be the only significant independent prognostic factors. Advanced pT stage (pT3-pT4) was found to increase mortality by 2.1 times compared to early pT stages (pT1-pT2) (P = 0.035). The mortality rate was 2.6 times lower in patients who received neoadjuvant therapy than those who did not (P < 0.001), whereas mortality was 2.5 times higher in those receiving adjuvant therapy (P = 0.004) (Table 2).

Table 2. Prognostic factors for mortality, identified by multivariate Cox regression analysis

Prognostic factors		OR	95% CI		*P*
Age, ≥65 years		1.358	0.970	1.903	0.075
Sex, female		1.190	0.812	1.744	0.372
Localization, distal		1.284	0.799	2.062	0.301
Neoadjuvant, yes		0.378	0.258	0.553	<0.001
Adjuvant, yes		2.593	1.366	4.922	0.004
No of nodes examined, >16		0.840	0.558	1.263	0.401
Nodal metastatis, yes		0.492	0.185	1.310	0.156
LVI, yes		0.952	0.598	1.515	0.835
PNI, yes		0.736	0.453	1.194	0.214
Grade	well	1			
	moderately	0.659	0.254	1.713	0.392
	poorly	0.635	0.243	1.665	0.356
Tumor size ≥5cm		1.128	0.789	1.613	0.510
Type of gastrectomy, subtotal		0.824	0.539	1.259	0.371
CCI ≥3		1.045	0.720	1.516	0.818
BMI	<18.5	1			
	18.5-24.9	0.867	0.204	3.676	0.846
	≥25.0	0.997	0.237	4.190	0.997
pT stage, pT3-pT4		2.112	1.056	4.223	0.035
TNM stage, III-IV		2.449	0.849	7.064	0.097

BMI: Body Mass Index; CCI: Charlson Comorbidity Index;
CI: Confidence Interval; OR: Odds Ratio; LVI: Lymphovascular Invasion;
PNI: Perineural Invasion; TNM: Tumour-Node-Metastasis

5. Discussion

This retrospective study with a sample of 293 patients was conducted to determine whether tumour localization in gastric cancer is associated with various prognostic factors or not.

Based on the findings of the present study, the location of gastric tumours showed a significant relationship with the neoadjuvant and adjuvant therapy rates, preferred gastrectomy type, metastatic involvement in lymph nodes and TNM stage. In other words, these prognostic factors showed significant differences according to tumour location. In addition to these results, it was determined that pT stage, neoadjuvant and adjuvant therapy were independent variables in determining the prognosis of the patients and may predict a worse outcome.

After neoadjuvant therapy has been shown to increase survival outcomes in studies conducted by Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) and La Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC)-Fédération Francophone de Cancérologie Digestive (FFCD), it has become increasingly used in cases with locally advanced gastric adenocarcinoma and is recommended by several guidelines (10, 11). According to our data analysis in the current study, it was determined that neoadjuvant therapy was mostly indicated in patients with PGC and in patients with advanced TNM stage. In addition, better outcome results, such as 2.6 fold decrease in mortality rates, were detected in patients who received neoadjuvant therapy compared to those who did not receive neoadjuvant therapy. This positive effect of neoadjuvant therapy on prognosis may be due to its ability to increase the resectability of the tumour (12). Based on this finding, neoadjuvant therapy for patients with advanced gastric cancer may provide better survival outcomes as an independent prognostic factor.

While all the patients with PGC in this study had undergone total gastrectomy as expected, this rate was only 32.1% for patients with DGC. Bozzetti et al. (13) investigated the prognostic significance of this relationship in their study involving 315 patients undergoing total gastrectomy and 303 patients subtotal gastrectomy. The authors reported five-year overall survival rates for PGC and DGC as 62.4% and 65.3%, respectively. They further stated that total gastrectomy had no contribution to the survival rates. Kong et al. (14) presented similar results in their meta-analysis. In the present study, the five-year overall survival rate of patients undergoing total gastrectomy was 64.5%, whereas this rate was 68.4% in patients undergoing subtotal gastrectomy. Our Cox regression analysis showed that total gastrectomy had no significant role in prognosis compared to subtotal gastrectomy. This result supports the claim made by Bozzetti et al. (13) that subtotal gastrectomy has no disadvantage in survival when a safe proximal margin is provided for DGC.

In the present study, the pT stage, another prognostic factor, showed no significant difference according to the tumour site. Various results have been reported by previous studies about the relationship between the pT stage and localization. Stages pT3 and pT4 have been reported to be more common in PGC (15), however, there are conflicting reports suggesting that advanced disease is more common in DGC (16). In this retrospective analysis, stages pT3 and pT4 have been observed to increase mortality by 2.1 times compared to stages pT1 and pT2. The advanced pT stage was found to be an independent prognostic factor, compatible with previous reports.

Unlike the pT stage, the presence of nodal metastasis was found to be associated with tumour localization. The data about the relationship between lymph node involvement and tumour localization also varies like conflicting reports about pT stages as mentioned above. Some studies have reported that the rate of lymph node involvement is higher in DGC (17). In contrast, contradicting reports available that lymph node metastasis is more common in PGC (16, 18). Lymph node metastasis is an accepted prognostic factor and predicts poor overall survival outcomes (19, 20). However, our results could not confirm lymphatic metastasis as an independent prognostic factor.

Adjuvant therapy following gastrectomy has become a standard option for patients with advanced cancer by having favourable effects on recurrence rates and prognosis (21). On the other hand, there are also available studies suggesting results against favourable effects of adjuvant therapy (17, 22). Based on our findings from the data analysis, 80.8% of patients with PGC received adjuvant therapy, while this rate was 64.7% of patients with DGC. This situation may be attributed to the more advanced TNM stage of PGC patients at the time of diagnosis. Over seventy percent of patients with PGC included in this study were diagnosed as TNM stage III-IV, and this rate was significantly higher than the proportion of advanced-stage patients among DGC patients. While studies suggest different and contradictory results about a relationship between tumour location and disease stage, the predominant opinion is that patients with advanced disease at the time of diagnosis are more likely to have PGC, which is confirmed by our data as well (3, 17, 22). In addition, the mortality rate is higher in those receiving adjuvant therapies in our study. This situation may be interpreted as that the advanced diseases for which adjuvant treatment is received are associated with reduced survival rates. Despite all these logical explanatory efforts, this impact of adjuvant therapy on the prognosis could not be representative of this study.

The debate over whether there is a difference in survival rates between PGC and DGC continues. Wang et al. (3) reported a significant difference between DGC and PGC in favour of PGC in terms of three-year survival rates. Yu et al. (4) reported the five-year

survival rates for PGC and DGC as 28.0% and 51.0%, respectively ($P < 0.001$). Zhao et al. (5) reported five-year survival rates as 36.3% and 32.3% for PGC and DGC, respectively. According to Costa et al. (17), five-year overall survival outcomes were reported to be 35.0% for PGC and 32.0% for DGC, and the authors found no significant difference in this regard. Finally, according to the current meta-analysis results of Petrelli and colleagues (23), the location of the primary GC in the upper third of the stomach is related to the all-cause of mortality. The Kaplan-Meier analysis performed in the present study has revealed the five-year survival rates as 48.4% for PGC and 45.6% for DGC, showing that the location of gastric cancer does not differ between the two localizations.

The primary purpose of this study was to cover nearly all the factors that may affect prognosis in patients undergoing elective curative surgery. Contrary to many reports available, PGC was found not to be associated with a poor survival rate compared to DGC.

This study has limitations as follows: It is based on retrospective data and only overall survival rates have been addressed. Data analysis does not include the RT data, and no information about recurrence is presented.

6. Conclusion

Based on the findings of the present study, there is no significant difference between PGC and DGC in terms of overall survival rates. Unlike most studies, the proximal or distal location of the tumour has been found not to be a prognostic factor. It has been further observed that total gastrectomy does not provide an advantage for survival if safe surgical margins are provided in DGC. Randomized controlled trials with larger volumes are required to validate these findings.

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Footnotes

Conflicts of Interest: All authors declare that there are no conflicts of interest.

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