RESEARCH ARTICLE

Goseki Grade and Tumour Location Influence Survival of Patients with Gastric Cancer

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Abstract

Background: Owing to the variability of histopathological features and biological behaviour in gastric carcinoma, a great number of categorisation methods such as classical histopathologic grading, Lauren classification, the TNM staging system and the newly presented Goseki grading method are used by pathologists and other scientists. In our study, we aimed to investigate whether Goseki grade and tumour location have an effects on survival of gastric cancer cases. Materials and Methods: Eighty-four patients with gastric adenocarcinoma were covered in the investigation. The importance of Goseki grading system and tumour location were analysed in addition to the TNM staging and other conventional prognostic parameters. Results: The median survival time in our patients was 35 months (minimum: 5, maximum: 116). According to our findings, there was no relation between survival and tumour size (p=0.192) or classical histological type (p=0.270). In contrast, the Goseki grade and tumour location significantly correlated with survival (p=0.007 and p<0.001, respectively). Additionally, tumours of the intestinal type had a longer median survival time (60.0 months) than diffuse tumours (24.0 months). Conclusions: In addition to the TNM staging system, tumour location and the Goseki grading system may be used as significant prognostic parameters in patients with gastric cancer.

Keywords: Gastric cancer - Goseki grade - tumour location - survival - Turkey

Asian Pac J Cancer Prev, **15 (3)**, 1429-1434

Introduction

Despite a rapid decline in the global incidence of gastric cancer (GC) over the last 20-30 years, GC is the second most common cancer resulting in morbidity and mortality globally (Lee et al., 2013; Song et al., 2013; Yu et al., 2013). Gastric cancer is commonly encountered in Japan, China, Chile and Eastern Europe. Conversely, its prevalence is low in the United States and the United Kingdom (Nagini, 2012; Saha et al., 2013). GC incidence is roughly 7.8/100.000 in the worldwide (Lee et al., 2013). In Turkey, the Turkish Ministry of Health stated that the rough ratio of GC in 2005 was 7.18/100,000 in males and 3.75/100,000 in females. According to this data, the general ratio was 5.48 per 100.000 (Yalcin, 2009).

The two main tumour sites of gastric adenocarcinoma (GAC) are proximal (cardia) and distal (non-cardia). Distal GC has decreased in recent years. On the contrary, cases in the proximal stomach have been rising in incidence since the 1970s, particularly amongst males in the Western world (Talaiezadeh et al., 2013; Grunnet, 2013). GC, which occurs in the cardia, has dissimilar features compared with cancers that are in other areas of the stomach. Proximal cancers are more common in men than in women. Family history in these patients is rare, and there are suggestive signs that link smoking and use of alcohol to GC (Holster et al., 2013). Moreover, cardia carcinomas tend to penetrate deeper into the wall of the stomach. Lymph node metastasis is more common, and these tumours have a worse prognosis than those in other locations (Bittoni et al., 2013; Ito et al., 2013).

Histologically, GCs are highly heterogeneous tumours in terms of structural or cytological features. Throughout the last fifty years, the histologic classification of GC has continued mostly with reference to Lauren design, in which diffuse and intestinal carcinoma are the two main histologic sub-groups in addition to uncommon variants such as 'indeterminate type' (Hu et al., 2012; Fontana et al., 2003; Qiu et al., 2013).

On the other hand, in 2010, the World Health Organisation (WHO) presented four major histologic sequences of GC: adenocarcinoma with tubular morphology, papillary morphology, mucinous and poorly differentiated morphology (involved signet ring cell carcinoma) and other rare morphologic variations (Hu et al., 2012). For a long time, a traditional grading system was used to assess differentiation of GC. Recently, Goseki et al. proposed a novel grading system as a prognostic parameter. This grading system is based on the evaluation of both the mucin contents of tumour cells and the degree

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of glandular differentiation (Goseki et al., 1992; Dixon et al., 1994, Ghosh et al., 2010). Goseki presented four groups according to their histologic characteristics: if the tumour consists of well-differentiated glands and is mucin-poor, it is grade I; if the tumour consists of well-differentiated glands and is mucin-rich, it is grade II; if the tumour consists of poor-differentiated glands and is mucin-poor, it is grade III; if the tumour consists of poor-differentiated glands and is mucin-rich, it is grade IV. Many other researchers have confirmed that this grading system is highly reliable (Songun et al., 1999; Mills et al., 2006). Some outcomes have shown that Goseki et al.'s histological grading system may be helpful in predicting survival time in patients with GC, but others have not (Fontana et al., 2003).

In the present investigation, we will research whether the Goseki grade and tumour location have an effect on surviving gastric cancer. In addition, we have tried to figure out whether these factors, which have recently gained importance, are associated with other prognostic factors.

Materials and Methods

Patients and materials

Our study consisted of 84 patients who were diagnosed with GC and underwent curative surgery at the Hospital of Medical Faculty, Atatürk University, Turkey between 2003 and 2008. Our patients comprised 59 males and 25 females, with an average age of 58.9 years (minimum: 32, maximum: 86).

Pathological review

The pathologic specimens were fixed by way of a 10% formaldehyde solution. Then, the fixed pathologic tissue was embedded in paraffin via the usual procedures. The preparations were painted with haematoxylin and eosin and were investigated by a practiced pathologist. Their histological type has been classified based on Lauren criteria and the WHO's histopathologic classification. The histological grade of the tumours were investigated according to Goseki's histological grading system and a conventional grading system (Goseki et al., 1992; Hu et al., 2012). To assess the spread of the tumour, we used the American Joint Committee on Cancer's (AJCC) TNM staging system (Washington, 2010).

Survival analysis

The survival times of the patients were evaluated by considering the period from the day of surgery to death or the end of the study. The survival graphs of patients and statistical data were obtained using the Kaplan-Meier method.

Statistical analysis

The interrelations between the cases' clinicopathological features and the Goseki grade or tumour location were evaluated by the Kruskal-Wallis test, the chi-squared test, the Mann-Whitney test or ANOVA. The survival curves were plotted using the Kaplan-Meier method, and statistical differences were assessed via Breslow and Log-rank tests. SPSS 15.0 software was used for these statistical tests. Again, p values less than 0.05 were considered statistically significant.

Results

Clinicopathological findings

Amongst the 84 gastric cancer patients, 70.2% were male and 29.8% were female. Also, the mean age of the patients was 58.9 (range: 32-86). Three of the patients (3.6%) were under the age of 40, 14 (16.7%) were 40-49, 25 (29.8%) were 50-59, 24 (28.6%) were 60-69, 16 (19.0%) were 70-79 and 2 (2.4%) were over the age of 80. Tumor size were <5 cm in 32 (38.1%) of 84 patients, and were ≥5 cm in 52 (61.9%) of 84 patients. From 84 tumours, 22 (26.2%) were located in the cardia, 19 (22.6%) in the antrum, 16 (19.0%) in the fundus and 23 (27.4%) in the corpus. Linitis plastica was only seen in 4 (4.8%) cases. In the histopathologic examination, 37 (44%) cases were intestinal type and 47 (23%) were diffuse type. According to WHO, 62 (73.8%) of 84 patients were tubular carcinoma, 11 (13.1%) were mucinous carcinoma and 11 (13.1%) were signet cell carcinoma. Regarding the classic grading system, 7 (8.3%) were grade 1 (well-differentiated), 33 (39.3%) were grade 2 (moderately differentiated) and 44 (52.4%) were grade 3 (poorly differentiated). According to Goseki's classification, 29 (34.5%) cases were grade I, 6 (7.1%) were grade II, 41 (48.8%) were grade III and 8 (9.5%) were grade IV (Figure 1A, B, C, D). There were a statistically significant relationship between histological type and Goseki grade (p=0.001). Besides, there were distinct correlation between Lauren and classical or

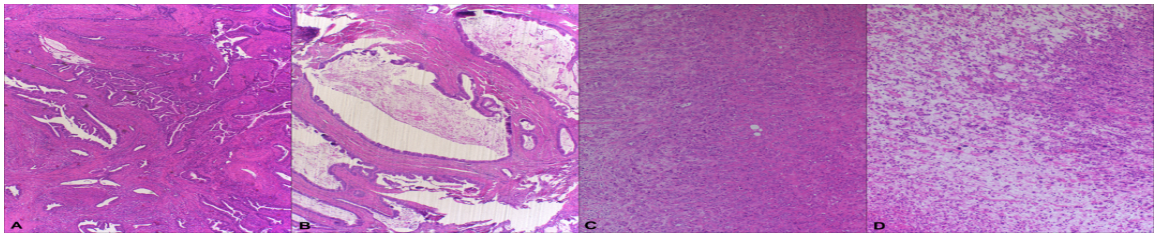

Figure 1. Illustrations with Grade 1-4 According to Goseki Histologic Grade in Gastric Carcinomas. A) Well-differantiated and mucin-poor tubules in grade 1; **B)** Well-differantiated and mucin-rich areas in grade 2; **C)** Poor-differantiated and mucin-poor areas of tumor in grade 3; **D)** poor-differantiated and mucin-rich areas of tumor in grade 3. Original magnification A, C, B and D×200

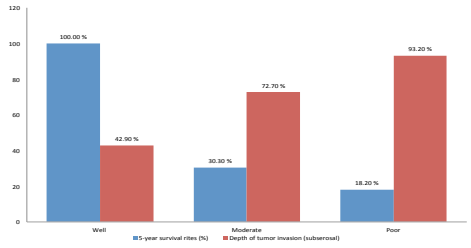

Figure 2. The Tumour Depth Invasion and 5-year Survival Times in Gastric Cancer Patients According to Classical Histological Grade. When the tumor differentiation decreased, the depth of tumour invasion increased. And thus, the 5-year survival times were low in gastric cancer patients with advenced histological grade

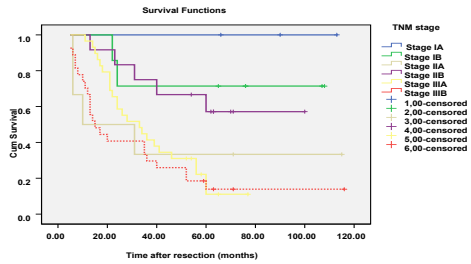

Figure 3. Survival Curves According to TNM Stage. Prominent Difference between Stage IA and IIIB is Observed

Goseki histologic grade (p=0.001). In contrast, there were no statistically correlation between histological type of WHO and classical histological grade (p=0.339).

Lymph nodes were positive for metastasis in 71 (84.5%) cases (1-2 metastasis: 11%, 3-6 metastasis: 35.7%, 7 and above metastasis: 35.7%) and 13 (15.5%) cases were lymph node negative. There was insignificant relationship between lymph node metastasis and Goseki grade or classical histologic grade (p=0.618, p=0.369, respectively). When the cases were assessed in terms of their tumour depth invasion, three (3.6%) of the cases were limited to the mucosa or submucosa, 13 (15.5%) of cases were invaded muscularis propria, 68 (81.0%) of cases were within subserosal layer. According to our findings, there were significant relationship between classical histological grade and depth of tumour invasion (p<0.001) (Figure 2). According to TNM stage, 3 (3.6%) of the cases were in stage IA, 7 (8.3%) were in stage IB, 6 (7.1%) were in stage IIA, 12 (14.3%) were in stage IIB, 29 (34.5%) were in stage IIIA and 26 (32.1%) were in stage IIIB. According to the chi-square test, lymph node metastases and tumour depth invasion were highly correlated with TNM stage (p<0.001). But, There were no any correlation between TNM stage and Goseki grade or tumor location (p=0.781, p=0.195, respectively).

Correlation between survival times and clinicopathologic parameters

The follow-up was completed on July 1, 2012. Fifty-eight (61%) patients died within this period. Twenty-six (30.9%) of our patients were still living when the follow-up period concluded. We determined that after surgical treatment, 20 of these patients would live for a minimum of five years. According to our data, patients had a median survival of 35 months (minimum: 5 months, maximum: 116 months). Survival rates were higher in females than in males, but there was no statistical correlation between gender and survival time (log rank, p=0.934). Additionally, tumour size and histological type (WHO) did not correlate with survival (p=0.192 and p=0.270, respectively). When survival time was evaluated according to Lauren method, it was found that cancers with intestinal morphology had a longer median survival time (60.0 months) than those with diffuse morphology (24.0 months). In comparison with the WHO's histological type, Lauren classification system correlated with survival (log rank, p=0.012).

Table 1. Distribution of Patients with Gastric Cancer (n=84) According to Various Clinicopathological Parameters and 5-year Survival Rate (%)

Parameter		n	5-year survival rites %	p value
Sex	Male	59	30.50	0.914
	Famale	25	28.00	
Age	<40	3	0.00	0.001
	40-49	14	14.30	
	50-59	25	48.00	
	60-69	24	33.30	
	70-79	16	18.80	
	80.00	2	0.00	
Tumor size	<5	32	43.80	0.192
	≥5	52	21.20	
Tumor location	Cardia	22	22.70	0.0001
	Antrum	19	0.00	
	Fundus	16	68.80	
	Corpus	23	34.80	
Diffuse involvement		4	25.00	
Histological type	Tubular	62	33.9	0.270
	Mucinous	11	18.20	
	Signet cell	11	18.20	
Lauren's	Intestinal	37	43.20	0.012
	Diffuse	47	19.10	
Goseki grade	I	29	51.70	0.007
	II	6	33.30	
	III	41	19.50	
	IV	8	0.00	
Histologic grade	Well	7	100.00	0.002
	Moderate	33	30.30	
	Poor	44	18.20	
TNM stage	IA	3	100.00	0.001
	IB	7	71.40	
	IIA	6	33.30	
	IIB	12	58.30	
	IIIA	29	13.80	
	IIIB	27	14.80	

Table 1 indicates relations between patients' basic features and survival. Most of the tumours had diffuse morphology in Lauren classification. Contrarily, tumours with tubular histology were common in terms of the WHO's classification system. Again, most of the tumours were grade 2 or grade 3 (considering the conventional grading system), and a lot of the tumours were Goseki grade I or III. Regarding TNM, most of the cases were in the terminal stage. Contrary to this, very few patients were in the early stage (IA or IB). As seen in Table 1, five-year survival times of patients had important alterations in accordance with TNM classification (from 71.4% in stage IB to 14.8% in stage IIIB) and conventional histologic

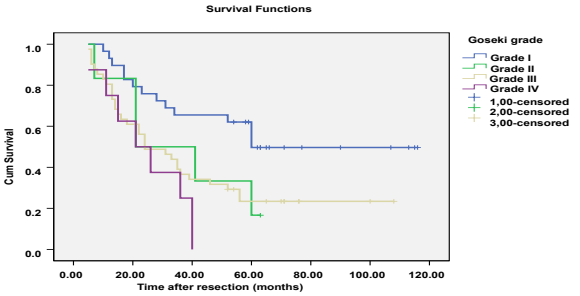

Figure 4. Survival Curves using the Kaplan-Meier Method. Patients with Goseki grade III and grade IV had a poor prognosis compared with patients with grade I and grade II (p=0.007)

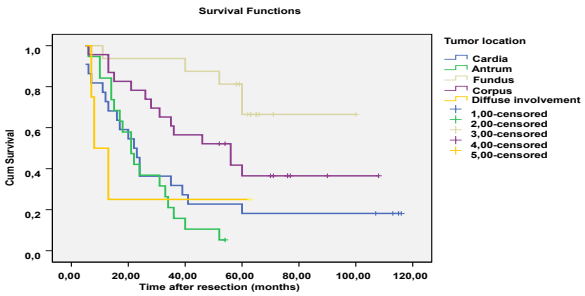

Figure 5. Survival Curves Using the Kaplan-Meier Method. Survival curves showed that patients who had proximal (cardia and antrum) carcinoma had an unfavourable prognosis compared with patients who had distal carcinoma (p=0.001)

Table 2. The Influence of Goseki's Grading System On Mean Survival Time After Potentially Curative Resection for Gastric Carcinoma

Goseki Grade	Mean survival time (month)	p value
Grade I	73,910±8,279	0.007
Grade II	35,500±8,530	0.007
Grade III	43,151±6,034	0.007
Grade IV	24,250±4,780	0.007

Table 3. According to Tumour Location, Mean Survival Time of Gastric Cancer Patients

Tumor location	Mean survival time (month)	p value
Cardia	38,364±8,276	0.0001
Antrum	24,842±3,071	0.0001
Fundus	81,778±7,087	0.0001
Corpus	60,157±8,248	0.0001
Diffuse involvement	22,750±11,675	0.0001

grade (from 100.0% in grade 1 to 13.1% in grade 3). According to the Kaplan-Meier method (p=0.001), there was a highly significant correlation between TNM stage and survival (Figure 3). Likewise, there were considerable relationships between histological grade and follow-up (Breslow, p=0.001) (Figure 2).

Both the depth of the tumour invasion and the presence of lymph node metastasis had a significant value in prognosis. The survival findings show that tumours with limited mucosa or submucosa had longer survival times than tumours that spread to the serosa (p=0.040). Similarly, while 76.9% of patients without lymph node metastasis had a long survival time, it was determined that only 13.3% of the patients with 7 or more lymph node metastases survived for 5 years after surgical treatment (log rank test: p<0.001).

When we investigated the survival rate of Goseki's grading system in GC patients, we determined that the survival of patients with different degrees of Goseki grade were quite different from one another (p=0.007) (Figure 4). While the median survival of patients with grade I was 60.0 months, this value for patients with grade II and grade IV was 21.0 months (Table 2).

We also assessed the interaction between tumour location and survival. According to our data, the most common tumour location was cardia (22 patients, or 26.2%) and corpus (23 patients, or 27.4%). The 5-year overall survival rate of patients with cardia cancers was 22.7%, whereas the patients with fundus tumours had a higher ratio (68.8%). When we evaluated the survival rates according to other tumour locations, we found that the rate was 0.0% in patients with antral tumours, 34.8% in patients with corpus tumours and 25.0% in patients with diffuse cancers. We found a pronounced relationship between tumour location and survival time (log rank, p<0.001) (Figure 5). According to our data, distal tumours had a higher survival rate than proximal tumours (Table 3).

Discussion

If bronchogenic cancers are excluded, it can be said that GC is the most common cancer in the world. The number of new cases reported annually is 870,000, and 650,000 of patients die from this disease. In Turkey, the incidence of GC is between the incidence in the West and the East. The mean age of patients with GC is around 56 years (Yalcin, 2009). In accordance with the literature, the mean age of the patients in our study was 58.9, and the male-female ratio was roughly 2:4.

Mortality from GC is higher than in other common tumours such as prostate, colon and breast cancer. The 5-year survival rate of patients with GC is only 20% (Nagini, 2012). The reason for this is usually due to presentation in the terminal period and the restricted scope of cure alternatives (Carl-McGrath et al., 2007). In this study, we found that the survival rate of our cases was 28.9%. Although most of our patients were in the advanced stage, this slight elevation in the rate of survival perhaps can be explained by genetic differences between ethnic groups.

Many prognostic factors such as Lauren classification, the WHO's classification, histological grade, TNM stage and tumour depth invasion are used to determine the prognosis for GC. However, few of them can provide important clinical needs including estimation of prognosis and determination of curative surgery. Thus, many researchers are still striving to find a different classification system that has prognostic importance. One of them is Goseki's grading system (Dixon et al., 1994, songun et al., 1999; Ghosh et al., 2010). In the present study, we have investigated Goseki's classification system and tumour location.

In the 1970s and earlier, most GC cases were in the distal parts of the stomach. These were well-differentiated tumours with intestinal morphology. From 1976 onward, the incidence of tumour-localised cardia and gastro-esophageal junction (GEJ) has consistently increased. Moreover, these tumours are usually poorly differentiated and diffusely infiltrative. The causes for this quick rise in offensive proximal tumours are still ambiguous (Dolan et al., 1999). In our study, tumours in the cardia constituted 22 (26.2%) of the events. This data is compatible with the latest findings in which the incidence of tumours located in the proximal stomach ranges from 25-40%. Michelassi et al. indicated a significant decrease in the survival time of GC patients with tumours located beneath the GEJ and cardia (Michelassi et al., 1994). Likewise, Sanchez-Bueno et al. stated that patients with proximal tumours had lower survival rates than those with distal tumours (Sanchez-Bueno et al., 1998). Harrison et al. handled this issue in a new report comparing the survival of patients with proximal GC to that of patients with distal tumours (Harrison et al., 1997). Whilst the 5-year survival rate was 42% in the patients with proximal tumours and the median survival was 47 months, the 5-year survival rate was 61% in patients with distal tumours and the median survival was 106 months. Moreover, when the location of the tumour shifted toward proximal, the prognosis worsened (the location of the primary lesion appeared to influence survival). Depending on the tumour's location, the survival rate was 62% in antral tumours, 59% in corpus tumours and 22% for tumours in the GEJ. Similarly, our investigation showed that the location of the primary cancer was highly affective on survival (log rank, p<0.001). In our study, the 5-year survival of patients with cardia cancers was 22.7%, whereas the 5-year survival of patients with fundus was 68.8%.

The TNM staging system has been created considering the main and important parameters, including metastasis to lymph nodes and depth invasion of tumour, which affect the survival of patients with GC. It is commonly used and highly appreciated because of its briefness, credibility and clinical applicability. For this reason, it is used as a guide for treatment and the estimation of survival time (Wang et al., 2010). As in previous research, in our study there were highly remarkable relations between survival and TNM stage (log rank, p=0.001). According to our data, the 5-year survival times of patients with GC relative to stages IA, IB, IIA, IIB, IIIA and IIIB were 100.0%, 71.4%, 33.3%, 58.3%, 17.2% and 14.8%, respectively.

On the other hand, there were apparent discrepancies between our investigation and various studies that investigated the relation between other basic pathological features and survival. For example, Deng et al. (2010) stated that the traditional histological grading system did not affect the survival of GC patients, yet our investigation demonstrated that traditional histological grade was related to survival (Breslow, p=0.001). The patients with grade 1 and grade 2 carcinomas had longer survival times than those with grade 3 carcinomas.

Even though some scientists have advised determining cases for adjuvant chemotherapy after curative surgery in GC considering the Goseki method, the prognostic importance of this grading method has been reviewed in very few investigations and has had conflicting results (Fontana et al, 2003). The median survival or survival rates were different according to Goseki histologic grades in distinct manners in the two investigations: Martin et al. (1994) determined longer survival in Goseki grade III patients than in grade IV patients, whereas the opposite results were found by Songun et al. (1999). According to Songun et al. (1999), the relationship between Goseki's grading system and the survival status of patients with GC was insignificant. In the present study, the survival rates after surgical treatment of grade I, II, III and IV tumours were 51.7%, 33.3%, 12.2% and 0%, respectively. According to log rank, there was a significant relationship between Goseki grade and survival (p=0.007). Additionally, with respect to our data, there was a relationship between Goseki grade, Lauren classification and the conventional grading system (Kruskal-Wallis, p=0.001). Moreover, the interrelation between Goseki grade and histological type was rather remarkable (chi-square, p=0.001).

In conclusion, GC is a common malignancy in Turkey as well as worldwide. In spite of improvements in diagnosis and therapy, the 5-year survival rate of this cancer is only 20%. Many basic prognostic parameters such as conventional histological grading and the TNM staging system (including lymph node involvement, the depth-invasion level of the tumour and distant metastasis) are used to foresee the prognosis of GC. Indeed, TNM staging is one of the most significant predictors of survivability in patients with GC, according to our data. In addition to this, tumour location and Goseki's grading system may be used as an important prognostic parameter in these patients. In our opinion, while the pathology reports are being written by pathologists for gastrectomy materials as well as classical parameters, Goseki's histological grade must be indicated.

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