

Comparison of Clinicopathological Characteristics and Prognostic Factors of Gastric Cancer in Patients Aged 50 Years and Younger and in the Elderly

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ABSTRACT

Aim: The present study examines the clinicopathological characteristics and prognostic factors of young-age patients with gastric cancer and makes a comparison with those of older patients with gastric cancer.

Materials and Methods: The data of 262 patients who underwent curative gastrectomy at our clinic between November 2006 and December 2018 was reviewed retrospectively. A comparison was made between the 46 patients (17.6%) aged 50 years and younger and the 216 patients (82.4%) aged more than 50 years.

Results: Young-age gastric cancer was found to be more common in the male respondents (63%). The Lauren diffuse histological type was more common, the number of removed lymph nodes was higher and the length of hospital stay was shorter in patients with young-age gastric cancer ($p < 0.05$). The Lauren diffuse histological subtype, large tumor diameter and distal tumor localization ($p < 0.05$) were identified as prognostic factors in the young patient group, whereas small tumor diameter, proximal tumor localization and the number of removed lymph nodes ($p < 0.05$) were identified as prognostic factors in the elderly patient group, although there was no significant difference between the two groups in overall survival.

Conclusion: Despite the lack of a significant difference in overall survival between the young-age patients and elderly patients with gastric cancer, the prognostic factors were significantly different, including large tumor diameter, distal tumor localization and Lauren histological subtype.

Introduction

Despite a decrease in the incidence of gastric cancer, it still ranks fifth among other cancer types and it is encountered as one of the important causes of cancer-related morbidity and mortality [1]. Gastric cancer is often encountered between the ages of 50 and 70 years, although there has been an increase in the rate of gastric cancer in recent years in the young-age group, with a prevalence rate of young-age gastric cancer reported to be in the range of 2–8% [2]. Young-age gastric cancer is associated with such prognostic factors as a poorly differentiated histology and advanced disease

stage [3,4]. Consequently, some studies have reported a poorer prognosis in young-age gastric cancer due to delays in diagnosis and the presence of poor prognostic factors [5]. Other studies, however, have reported similar or even better prognosis in young-age gastric cancer cases than in elderly patients with gastric cancer [6].

Although studies to date have identified the clinicopathological characteristics of young-age patients and the patients in the other age groups, none have addressed prognostic factors for survival in the elderly patient group, nor the effects of these prognostic

factors in the young-age patient group. The present study identifies prognostic factors in the young-age patients and determines whether these prognostic factors have an effect in the other age group. The study similarly evaluates whether the prognostic factors in the other age group affect the young-age patients.

Materials and Method

The data of a total of 320 patients who underwent a total or subtotal gastrectomy and D2 lymph node dissection due to the presence of gastric adenocarcinoma in the Gastroenterological Surgery clinic of XXX Hospital between November 2006 and December 2015 were analyzed retrospectively. The cut-off date for the survival analysis was December 31, 2018. D2 dissections were performed in accordance with the principles of the Japanese Research Society for the Study of Gastric Cancer (JRSG) [7]. The Tumor, Node, Metastasis (TNM) classification system of the American Joint Committee on Cancer (AJCC) (7th edn 2010) was used in the study. The data was obtained from the follow-up forms stored in our clinical database, and pathology results were recorded. Patients diagnosed with distant organ metastasis at the time of surgery (8 patients), patients with a positive peritoneal cytology (12 patients), patients who received neoadjuvant chemoradiotherapy (34 patients) and those who had positive surgical margins (4 patients) were excluded from the study, even if they underwent a gastric resection. A total of 262 patients were included in the study. Complications occurring within 30 days of surgery were defined as surgery-related complications, and were recorded.

Statistical Analysis

A Chi-square test, a Fisher's exact test, and a Mann-Whitney U test were used to analyze the differences in the study variables in the comparison of patients aged 50 years and younger and those

aged older than 50 years. A Kaplan-Meier test was used to compare the survival of patients aged 50 years and younger and patients older than 50 years, and a log rank test was used to evaluate the differences between the survival curves. Univariate and multivariate analyses were performed with a stepwise Cox regression in order to identify prognostic factors for survival in patients aged 50 years and younger and in those older than 50 years. The variables included gender, Lauren histological subtype, tumor localization, tumor diameter, total number of removed lymph nodes, stage, vascular invasion, perineural invasion and presence of complications. The SPSS version 21 software package was used for the study and the level of statistical significance was set at an alpha of <0.05.

Results

Of the patients, 17.6% (n=46) were aged 50 years and younger and 82.4% (n=216) were older than 50 years. A comparison of clinicopathological characteristics between the two groups revealed no significant difference in terms of gender, gastrectomy type, tumor localization, T stage, N stage, TNM stage, vascular invasion, perineural invasion, tumor diameter and number of positive lymph nodes (Table 1). A significant difference was noted in the Lauren histological subtype between the two groups ($p<0.05$); and 80.4% in the young-age group and 65.3% in the elderly group had diffuse histology. The median total number of removed lymph nodes was 27 (10-73) in the young-age group and 23 (6-74) in the elderly group, showing a statistically significant difference between the two groups ($p<0.05$). The rate of postoperative complications was numerically higher in patients older than 50 years (15.2% versus 27.8%); and while close, the difference was not statistically significant ($p=0.076$). There was a statistically significant difference in the length of hospital stay, which was median 9 days in the young-age group and 10 days in the elderly group ($p<0.05$).

Table 1: Clinicopathological characteristics and surgical outcomes.

	≤50		>50		p
	n	%	n	%	
Gender					
Male	29	63.00%	150	69.40%	0.397
Female	17	37.00%	66	30.60%	
Gastrectomy					
Subtotal	27	58.70%	107	49.50%	0.259
Total	19	41.30%	109	50.50%	
Lauren histological type					
Intestinal	9	19.60%	75	34.70%	0.046*
Diffuse	37	80.40%	141	65.30%	
Location					
Proximal	6	13.00%	52	24.10%	0.239
Middle	13	28.30%	59	27.30%	
Distal	27	58.70%	105	48.60%	

Depth of invasion					
T1	4	8.70%	21	9.70%	0.577
T2	6	13.00%	21	9.70%	
T3	16	34.80%	97	44.90%	
T4	20	43.50%	77	35.60%	
Lymph node metastasis					
N0	16	34.80%	71	32.90%	0.525
N1	5	10.90%	43	19.90%	
N2	8	17.40%	36	16.70%	
N3	17	37.00%	66	30.60%	
TNM Stage					
1A	4	8.70%	20	9.30%	0.947
1B	2	4.30%	13	6.00%	
2A	8	17.40%	34	15.70%	
2B	6	13.00%	28	13.00%	
3A	6	13.00%	37	17.10%	
3B	9	19.60%	29	13.40%	
3C	11	23.90%	55	25.50%	
Vascular invasion					
Negative	17	37.00%	81	37.70%	0.927
Positive	29	63.00%	134	62.30%	
Perineural invasion					
Negative	16	34.80%	69	32.20%	0.739
Positive	30	65.20%	145	67.80%	
Complication					
No	39	84.80%	156	72.20%	0.076
Yes	7	15.20%	60	27.80%	
Tm Diameter (cm)	Median	Min-Max	Median	Min-Max	
Total number of lymph nodes	4	11-Jan	5	0.4-18	0.442
Number of positive lymph nodes	27	Oct-73	23	Jun-74	0.052
Length of hospital stay	4	0-29	2	0-48	0.37
	9	Jun-35	10	0-158	0.048*

Note: *p<0.05

No significant difference in survival was noted between the patients aged 50 years and younger and those older than 50 years ($p>0.05$), with 50% ($n=23$) of the patients aged 50 years and younger and 53.7% ($n=116$) of the patients older than 50 years surviving (Figure 1), (Table 2). The prognostic factors for survival in patients aged 50 years and younger and in patients older than 50 years were analyzed using a Cox regression analysis. The Lauren

diffuse histological subtype, distal tumor localization, total number of removed lymph nodes and tumor diameter larger than 4cm were identified as prognostic factors affecting the risk of mortality in a univariate analysis. Middle tumor localization, tumor diameter larger than 4cm and total number of removed lymph nodes were identified as prognostic factors affecting the risk of mortality in a multivariate analysis (Table 3).

Table 2: Comparison of survival according to age using Kaplan-Meier test.

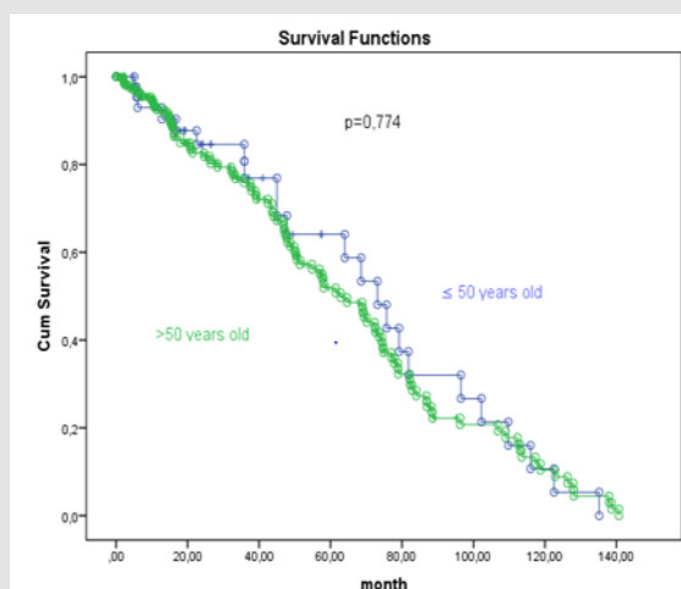
Log-rank test					
	Non-survivors	Survivors	Estimate (mean)±SE	95% CI	p value
≤50	23 (50%)	23 (50%)	73.133±7.686	(58.069-88.197)	0.774
>50	100 (46.3%)	116 (53.7%)	62.833±5.734	(51.595-74.072)	
Overall	123 (46.9%)	139 (53.1%)	68.567±5.794	(57.211-79.922)	

Note: CI: Confidence Interval

Table 3: Univariate and multivariate analyses in patients with gastric cancer aged 50 years and younger.

	Univarite Analysis		Multivarite Analysis	
	OR (95% CI)	p	OR (95% CI)	p
Gender				
Male	1.584	0.31	1.636	0.534
Female	(.652-3.850)		(.347-7.715)	
Lauren histological type				
Intestinal	3.717	0.027*	0.426	0.33
Diffuse	(1.159-11.917)		(.076-2.372)	
Location				
Upper	0.922 (.255-3.340)	0.025*	11.706 1.129-121.413	0.017*
Middle	5.44 (1.561-18.958)	0.902	1.09 (.163-7.310)	0.039*
Lower		0.008*		0.929
Tumor diameter				
≤4 cm	3.913 (1.276-12.002)	0.017*	6.855 (1.097-42.813)	0.039*
>4 cm	1.037 1.037 (1.003-1.071)	0.033*	1.054 (1.002-1.109)	0.041*
Total number of lymph nodes Stage				
I	0.61 (.196-1.900)	0.465	269 (.042-1.735)	0.287
II	1.138 (.377-3.435)	0.394	0.439 (.025-7.680)	0.168
III		0.819		0.573
Vascular invasion	1.342 .564-3.191	0.506	0.764 (.184-3.177)	0.711
Perineural invasion	1.302 (.529-3.202)	0.566	0.634 (.126-3.199)	0.581
Complication	0.21 (.037-1.182)	0.077	0.385 (.038-3.843)	0.416

Note: OR: Ods Ratio, CI: Confidence Interval, *p<0.05

**Figure 1:** Overall survival comparison of age-related.

In a univariate analysis of the patients aged older than 50 years, proximal tumor localization, total number of removed lymph nodes and tumor diameter smaller than 4cm were identified as prognostic factors affecting the risk of mortality. Tumor diameter smaller than 4cm and total number of removed lymph nodes were identified as prognostic factors affecting the risk of mortality in a multivariate analysis (Table 4). The prognostic factors in patients aged 50 years and younger were partially different to those in patients older than 50 years. Although the total number of removed

lymph nodes was identified as a prognostic factor in both groups in a stepwise Cox regression analysis, distal tumor localization and large tumor diameter were significant prognostic factors in the young-age group, whereas proximal tumor localization and small tumor diameter were significant in the elderly patients. The Lauren diffuse histological subtype was found to be significant in a univariate analysis of the young-age patient group, but insignificant in the elderly patient group.

Table 4: Univariate and multivariate analyses in patients with gastric cancer aged older than 50 years.

	Univariate Analysis		Multivariate Analysis	
	OR (95.0% CI)	p	OR (95.0% CI)	p
Gender				
Male	1.002	0.991	0.988	0.966
Female	(.660-1.522)		(.570-1.712)	
Lauren histological type				
Intestinal	0.995	0.979	1.034	0.891
Diffuse	(.659-1.502)	0.037*	(.641-1.668)	0.305
Location				
Upper	0.99	0.971	0.776	0.478
Middle	(.573-1.710)		(.386-1.563)	
Lower	0.591		0.646	
	(.369-.945)	0.028*	(.368-1.135)	0.128
Tumor diameter				
≤4 cm	0.605 (.403-.908)	0.015*	0.538 (.341-.848)	0.008*
>4 cm	1.028 (1.011-1.046)	0.001*	1.022 (1.002-1.042)	0.030*
Total number of lymph nodes Stage				
I	1.285	0.611	1.742	0.196
II	(.783-2.108)		(.953-3.183)	
III	1.156		1.555	
	(.687-1.942)	0.585	(.737-3.278)	0.246
Vascular invasion	1.106	0.623	0.828	0.486
Perineural invasion	(.739-1.656)		(.486-1.409)	
Complication	0.841		0.648	
	(.563-1.258)	0.399	(.382-1.102)	0.109
	1.409	0.128	0.814	0.409
	(.907-2.188)		(.500-1.326)	

Note: OR: Ods Ratio, CI: Confidence Interval, *p<0.05

Discussion

Gastric cancer is often more common in the 50–70 years age group, with a higher prevalence in males than in females in this age group, with a male-to-female ratio of 2:1 [8]. Gastric cancer is less prevalent in the young-age group, with a reported prevalence of 2–9% in literature [9]. Although various studies have reported different results, young-age gastric cancer is associated with poor prognosis; the incidence is higher in females; and the disease often occurs in the proximal section of the stomach and manifests in the

advanced stage with a Lauren diffuse histology, and particularly with a signet ring histology [10]. Sex hormones or analogues have been identified as occurring more often in females [11]. Although the present study found no difference between the two groups in terms of prognosis, there was a male predominance in all age groups and in the young patients with gastric cancer.

Furthermore, the number of removed lymph nodes was significantly lower and the length of hospital stay was significantly shorter in young patients with gastric cancer. The rate of

encountering a Lauren diffuse-type histology in gastric cancer is around 30% and is more frequent in young-age gastric cancer cases and in females [12]. In a Lauren diffuse-type histology, cells appear scattered in the stroma or as a cluster of cells rather than having tubular or glandular appearance due to loss of cellular adhesion [13]. Gastric cancers with a Lauren diffuse-type histology are associated with poorer prognosis due to the more aggressive tumor behavior with advanced T stage and N stage [14]. In our study, the patients with a Lauren diffuse-type histology were mostly in the young-age patient group, and the Lauren diffuse histology was identified as a prognostic factor in a univariate analysis, but not in a multivariate analysis.

The rate of complications related to surgery was lower and the length of hospital stay was shorter in young patients who were operated on for gastric cancer. The present study produced similar results. Large tumor size is one of the poor prognostic factors in gastric cancer (Zhou et al. 2019). The likelihood of lymph node involvement and peritoneal involvement increases with increasing tumor size, and patients with gastric cancer present with early recurrence, and for this reason, more aggressive treatment options are required as the tumor size increases [15]. The 5-year survival rate of patients with a tumor diameter less than 5 cm is 45.5%, whereas 5-year survival is 24.8% in patients with a tumor diameter greater than 5cm [16]. A lower cut-off level was used for the tumor diameter in the present study, with a tumor diameter greater than 4cm identified as a prognostic factor in young patients with gastric cancer. Different from other studies, tumor diameter smaller than 4cm was identified as a prognostic factor in patients with gastric cancer who were aged older than 50 years.

There has been an increase in the prevalence of proximal gastric cancer and a decrease in the prevalence of distal gastric cancer since the 1970s, and epidemiological studies suggest different etiologies and biological behaviors for these two tumor localizations [17]. Proximal gastric cancer is associated with a poorer prognosis due to the more frequent occurrence in the elderly patients with advanced stage and a poor histological subtype [18]. Aside from tumor localization, the location of the tumor within the stomach is another prognostic factor, in that tumors located in the greater curvature are associated with poorer prognosis than those located in the lesser curvature [19]. Young-age gastric cancer is often located in the middle and distal stomach, though the prognostic value of this localization is controversial [20]. In the present study, young-age gastric cancers were mostly localized to the middle-distal stomach, the localization being of no prognostic value.

Proximal gastric cancer was more common in the elderly patients, and the localization had a prognostic value. National Comprehensive Cancer Network (NCCN) guidelines state that a minimum 15 lymph nodes must be removed in order to accurately determine the number of positive lymph nodes [21]. The status of

the lymph nodes is related entirely to prognosis and recurrence, and the removal of 22 or more lymph nodes increases overall survival, particular in patients with advanced T stage [22,23]. The number of removed lymph nodes was also found to have an effect on prognosis in the present study.

Conclusion

young patients with gastric cancer have different clinicopathological characteristics to elderly patients with gastric cancer. Furthermore, different to elderly patients, a Lauren diffuse-type histology and a large tumor diameter appear to be significant prognostic factors in young-age patients with gastric cancer. The Lauren histological subtype is of no prognostic significance in elderly patients with gastric cancer, in whom small tumor diameter appears to be an important prognostic factor.

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