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ORIGINAL ARTICLE

Clinicopathological features of gastric cancer in young patients

Yukiko Takatsu · Naoki Hiki · Souya Nunobe · Manabu Ohashi · Michitaka Honda · Toshiharu Yamaguchi · Toshifusa Nakajima · Takeshi Sano

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Abstract
Background Early-onset gastric cancer is relatively rare. To evaluate the clinicopathological features and surgical outcome of young patients with gastric cancer, this retrospective comparative study was conducted.
Methods From 2000 to 2010, 4882 patients underwent surgery for gastric adenocarcinoma in our institution. A total of 136 patients under 40 years old were enrolled as the young group, and a total of 1435 patients aged between 60 and 69 were identified as the control group for this study. The patient's characteristics, pathological findings, surgical and clinical outcomes were reviewed, and the risk factors of recurrence were compared between the two groups.
Results Among the young group, patients had significantly fewer comorbidities and postoperative complications. The patient proportion having 7 or more lymph node metastases was higher in the young group (25 %) than in the control group (16 %). The presence of lymph node metastasis was identified as a strong risk factor for recurrence (odds ratio = 4.31) in the young group according to the results of the step-wise logistic regression analysis. Although the disease-specific survival at stage II was relatively better in the young group ($p = 0.0439$) than in the control group, there were no significant differences in overall survival for all stages.
Conclusion Early-onset gastric cancer is likely to present lymph node metastases. The survival rate of gastric cancer in young patients was equivalent to that in patients in their 60s, which is the typical age at onset.

Keywords Gastric cancer · Young patients · Gastrectomy · Risk factor

Introduction

In recent years there have been many advances in the treatment of gastric cancer, including the establishment of surgical techniques for tumor resection and lymph node dissection. Together with progress in adjuvant chemotherapy and molecular-targeted therapy, patient outcome has greatly improved. To maximize the efficacy of treatment, however, it is important to establish the prognosis of individual patients and to apply treatment strategies that are suitable for them. One factor that has been cited as an indicator of poor prognosis of gastric cancer is early onset, i.e., that occurring in patients who are comparatively young [1–4]. Gastric cancer usually occurs in individuals aged 50–70 years [2, 5, 6] and is rare in the young [7–9]. Factors that contribute to the poor prognosis of gastric cancer in the young include delayed detection, resulting in an advanced stage at presentation, diffuse infiltration of the tumor and a poorly differentiated histology [1, 4, 10]. On the other hand, recent studies have indicated that prognosis in young patients is equivalent to [7, 11, 12] or better than that in middle-aged patients with cancers at the same stage [8, 9, 13, 14]. Thus, the concept of gastric cancer having a poorer prognosis in relatively young

Y. Takatsu · N. Hiki · S. Nunobe · M. Ohashi · M. Honda · T. Yamaguchi · T. Nakajima · T. Sano
Department of Gastroenterological Surgery, Cancer Institute Ariake Hospital of JFCR, Tokyo, Japan

N. Hiki (✉)
Department of Gastroenterological Surgery, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-10-6 Ariake, Koto-ku, Tokyo 135-8550, Japan
e-mail: naoki.hiki@jfcr.or.jp

patients remains controversial. However, the results of previous studies focusing on young patients with gastric cancer have not been convincing because of the small number of patients and lack of recent data. Moreover, the definition of "early onset" has varied among studies (e.g., disease occurrence at less than 30, 35, 40 or 45 years of age [3, 10, 13, 14]). In addition, few studies have compared young and middle-aged patients epidemiologically or focused specifically on the clinicopathological characteristics of younger patients.

Against this background, we performed the present study to identify the specific clinicopathological characteristics and prognosis of young patients with gastric cancer. For this purpose, we provided a clear rationale for the definition of gastric cancer in young patients and compared their prognosis with that of patients representative of the typical age in relation to the disease stage. For this case-controlled study, we selected patients younger than 40 years of age (136 individuals) and patients aged 60–69 years (1435 individuals) from among those with gastric cancer treated at our institution since 2000. This population of young patients was relatively large in comparison with those used in recent studies.

Patients and methods

Definition of "young" gastric cancer patients

In this study, "young" patients were defined as those within the bottom fifth percentile in the age histogram for gastric cancer patients, and "middle-aged" patients were defined as those within the 10-year range around the second quartile point in the histogram for comparison with young patients. Figure 1a shows the histogram for the 4358 patients with gastric cancer who underwent surgical resection at our institution between 2000 and 2010. The fifth percentile represented patients under 41 years old, and the second quartile point for age was 65 years. Accordingly, 136 patients less than 40 years old were identified as the young group, and patients aged 60–69 years were isolated as the middle-aged group (control group) from the database of the Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan. As a reference, the age distribution of patients who underwent surgical intervention for gastric cancer listed in the database of the Japanese Gastric Cancer Association [6] is shown in Fig. 1b. There were no significant differences in the age distribution compared with patients seen at our hospital.

Data collection

This was a single-center, retrospective, observational study. We reviewed the demographics of the patients, histopathological characteristics of the tumors and data pertaining to surgery and follow-up.

Data on patient demographics included age, gender, American Society of Anesthesiologists physical status (ASA-PS) and body mass index. Tumor characteristics included size, location, macroscopic type, histological type, depth of invasion, lymph node metastases and distant metastases. Surgical data included the procedure employed, operation time, blood loss and postoperative complications. Follow-up data included survival time, pattern of recurrence and the overall and disease-specific survival rates.

Statistical analysis

Statistical analysis was conducted to evaluate age-related differences in specific patient background factors, histopathological factors or prognosis. Continuous variables were evaluated as means (standard deviation) using the *t* test, and interval values are presented as medians.

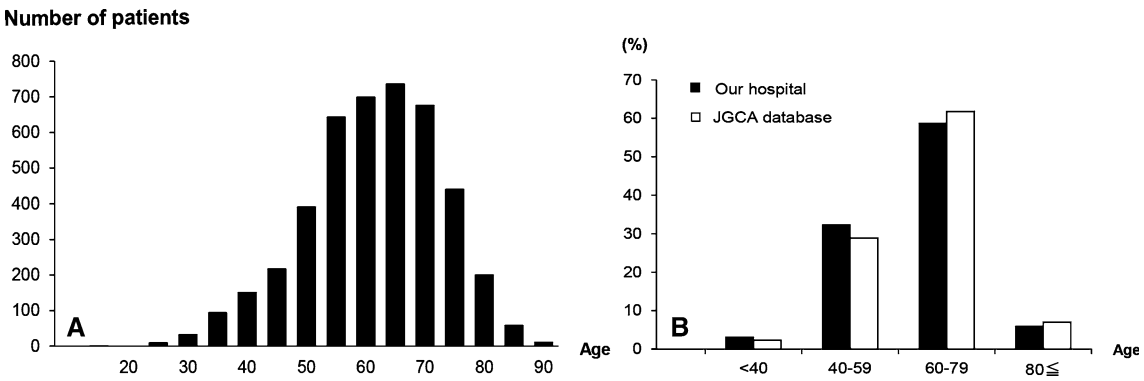

Fig. 1 **a** Age histogram for all patients with gastric cancer treated at our institution. Fifth percentile age value was under 41 years old. The second quartile age point was 65 years old. **b** Age histogram showing comparison with the database of the Japanese Gastric Cancer Association (JGCA)

Differences in proportions between the groups were evaluated using the chi-squared test. When considering outcome, multivariate analysis was performed to investigate risk factors for recurrence, followed by stepwise logistic regression analysis. Overall and disease-specific survival rates were determined using the Kaplan-Meier method. The difference between survival curves was assessed using the log-lank test. The accepted level of statistical significance was $p < 0.05$.

Results

Patient characteristics

The patient characteristics of two groups are shown in Table 1. The median age in the young group was 36 (range 16–39) years, and this group contained a higher proportion of female patients (47.1 %) than the middle-aged group (28.6 %). ASA scores were significantly lower in the young group than in the middle-aged group. The primary tumor most commonly involved the middle third of the stomach in the young group (51.5 %). The proportion of lesions located in the upper third was slightly higher in the middle-aged group (26.8 %) than in the young group (18.4 %). Diffusely infiltrative cancer was more common in the young group, and histologically undifferentiated tumors were significantly more frequent in the young group (90.4 %) than in the middle-aged group (53.9 %). No significant inter-group differences in T-factor were evident, but the proportion of patients who had seven or more lymph node metastases (N3) was higher in the young group (25 %) than in the middle-aged group (16 %).

Surgical procedures and outcomes

The types of surgical procedures and their outcomes are shown in Table 2. Curative resection was performed in 83.8 % of patients in the young group and 86.5 % in the middle-aged group. There were no significant differences in the median number of lymph nodes harvested. The amount of blood loss and incidence of postoperative complications in the middle-aged group were higher than those in the young group.

Outcome

In the young group and the middle-aged group, the median observation periods were 48.8 (range 1–161) and 46.6 (1–147) months, respectively. The overall 5-year survival rate was 80.6 and 74.8 %, and the disease-specific survival rate was 80.6 and 79.5 %, respectively. The survival curves for each stage are shown in Figs. 2 and 3. Disease-specific survival at stage II was relatively better in the young group ($p = 0.0439$) than in the middle-aged group, although there was no significant difference in overall survival for stages overall.

Recurrence patterns and risk factors

Thirteen (11.4 %) patients in the young group and 139 (11.2 %) in the middle-aged group suffered recurrence after curative resection. The patterns of recurrence are shown in Table 3. The results of stepwise logistic regression analysis of risk factors for recurrence are shown in Table 4. The T, N and M factors, tumor size, histological type and location were isolated as predictive variables by univariate analysis. The T and N factors and tumor location (upper stomach) were identified as significant predictive factors for recurrence (odds ratio: 3.95, 2.20, 2.17) in the middle-aged group. In the young group, only N was a significant predictive factor (odds ratio: 4.31).

Discussion

In the present study, the incidences of comorbidity and postoperative complications were significantly lower in young patients than in control patients. Furthermore, the outcome of young patients was equivalent to that of control patients in terms of both overall and disease-specific survival. One of the reasons for the relatively better prognosis in young patients might be that such patients rarely have comorbidities, have better performance status that gives them better tolerance to surgery or chemotherapy and have fewer potentially fatal accompanying diseases [15]. Because the incidence of postoperative complications is reportedly an indicator of poor prognosis [16, 17], the rarity of such complications likely confers a survival advantage on young patients.

Histologically, most young patients had undifferentiated carcinoma, and advanced lymph node metastasis was frequent in this group. Diffusely infiltrative tumors were also more common in young patients. As indicated in previous studies [7, 9, 10], well-differentiated, intestinal-type gastric cancer usually originates from intestinal metaplastic mucosa, whereas undifferentiated gastric cancer usually originates from gastric fundus glands. Therefore, undifferentiated rather than well-differentiated gastric cancer might be more likely to occur in young patients in whom atrophy of the gastric mucosa is uncommon. In addition, because undifferentiated gastric cancer infiltrates more prominently in a vertical direction and frequently shows lymph node involvement, then presumably Borrmann types 3 and 4 would be more common in young patients, thus conferring a high risk of lymph node metastasis. In fact,

Table 1 Patient characteristics

	Young ($n = 136$, %)	Middle aged ($n = 1435$, %)	P value
Age			
(Range)	36 (16–39)	65 (60–69)	
Sex			
Male	72 (52.9)	1024 (71.4)	<0.0001
Female	64 (47.1)	411 (28.6)	
BMI			
Mean (SD)	21.4 kg/m^2 (3.5)	22.1 kg/m^2 (3.2)	<0.0008
ASA-PS			
1	135 (99.0)	1297 (90.4)	0.0009
2	1 (0.1)	138 (9.6)	
3	0	0	
Location			
Upper	25 (18.4)	385 (26.8)	0.0540
Middle	70 (51.5)	581 (40.5)	
Lower	35 (25.7)	416 (29.0)	
Entire	6 (4.4)	53 (3.7)	
Gross type			
0	77 (56.6)	817 (57.0)	
1	0	23 (1.6)	<0.0001
2	4 (2.9)	179 (12.5)	
3	33 (24.3)	323 (22.5)	
4	21 (15.5)	88 (6.1)	
5	1 (0.7)	5 (0.3)	
Histological type			
Differentiated	13 (9.6)	662 (46.1)	<0.0001
Undifferentiated	123 (90.4)	773 (53.9)	
T			
1	60 (44.1)	727 (50.7)	0.2780
2	15 (11.0)	157 (10.9)	
3	22 (16.2)	165 (11.5)	
4	39 (28.7)	386 (26.9)	
N			
0	69 (50.8)	839 (58.5)	
1	17 (12.5)	182 (12.7)	
2	15 (11.0)	153 (10.7)	
3	34 (25.0)	230 (16.0)	0.0100
Unknown	1 (0.7)	31 (2.1)	
M			
0	114 (83.8)	1245 (86.8)	0.4090
1	22 (16.2)	190 (13.2)	
Stage			
I	65 (47.8)	786 (54.8)	0.4540
II	21 (15.4)	206 (14.4)	
III	28 (20.6)	253 (17.6)	
IV	22 (16.2)	190 (13.2)	

BMI body mass index, *ASA-PS* American Society of Anesthesiology performance status

our present study showed that lymphatic recurrence was the second most frequent mode of recurrence after peritoneal dissemination. Logistic regression analysis of risk factors for recurrence indicated that lymph node metastasis, with a higher odds ratio than invasion depth, was particularly important, suggesting that early-onset gastric

Table 2 Surgical procedures and outcomes

	Young (n = 136, %)	Middle aged (n = 1435, %)	P value
Approach			
Laparotomy	91 (66.9)	1039 (72.4)	0.2060
Laparoscopy	45 (33.1)	396 (27.6)	
Resection			
Distal gastrectomy	75 (55.2)	732 (51.0)	0.0540
Proximal gastrectomy	3 (2.2)	54 (3.7)	
Total gastrectomy	32 (23.5)	445 (31.0)	
Pylorus preserving gastrectomy	23 (16.9)	142 (9.9)	
Partial resection	2 (1.5)	31 (2.2)	
Unresectable	1 (0.7)	31 (2.2)	
Residual tumor			
R0	114 (83.8)	1241 (86.5)	0.4650
R1	5 (3.7)	100 (7.0)	
R2	17 (12.5)	94 (6.5)	
Operation time (min) (SD)	228 (72.0)	231 (81.1)	0.6690
Blood loss (ml) (SD)	211 (272)	274 (387)	0.0330
Harvested lymph nodes (range)	36 (16–101)	37 (12–109)	
Postoperative complication*	14 (10.3)	276 (19.2)	0.0100

* Grade 2 or greater (Clavien-Dindo classification)

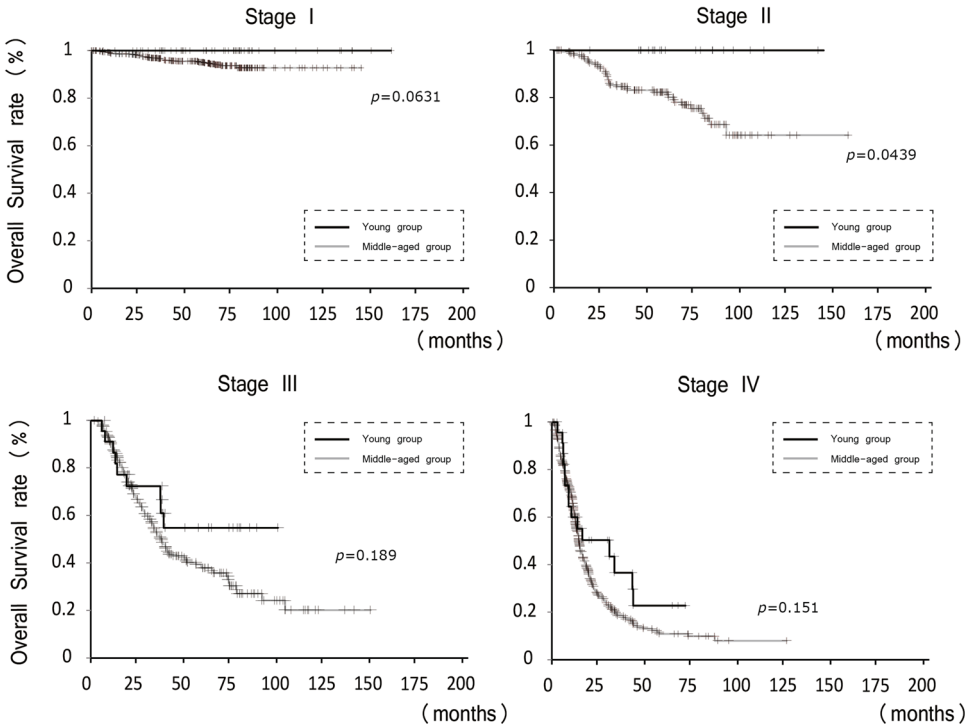

Fig. 2 Overall 5-year survival rate

cancer characteristically tends to spread via the lymphatic system. In the light of these findings, lymph node dissection may have particularly important significance in the surgical treatment of gastric cancer in young patients. In addition, possible metastasis and recurrence in extra-regional lymph nodes should be considered during post-operative follow-up.

R0 resection was performed slightly less frequently in young patients than in control patients because, in some patients with advanced tumor invasion and lymph node

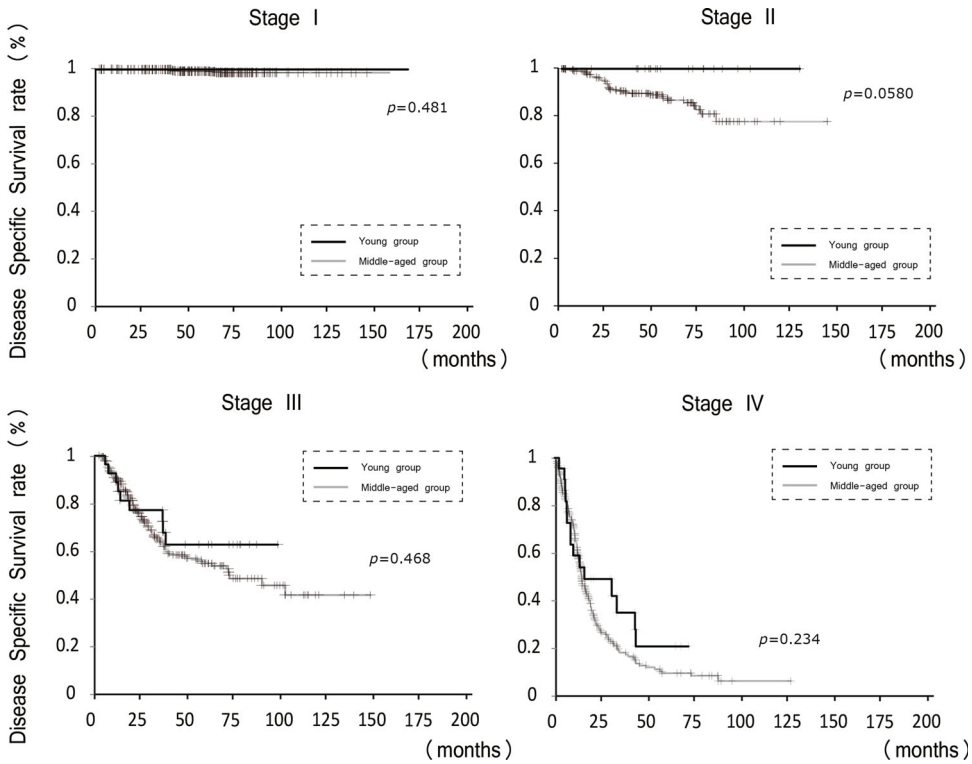

Fig. 3 Disease-specific 5-year survival rate

Table 3 Recurrence patterns after R0 resection

Recurrence pattern	Young ($n = 13$, %)	Middle age ($n = 139$, %)
Peritoneal	6 (46.1)	58 (41.7)
Lymph node	2 (15.4)	20 (14.4)
Distant metastasis		
Liver	1	33
Lung	1	9
Bone	2	4
Adrenal	0	1
Others	1	1
Local	0	13

metastasis, radical resection was precluded. Recent studies have demonstrated the diagnostic usefulness of staging laparoscopy [18–20], which allows more accurate assessment of resectability. It has been shown that multidisciplinary strategies involving chemotherapy followed by surgical resection, rather than palliative resection as an initial approach, achieve better results in patients with peritoneal dissemination, positive ascites cytology or bulky lymph node metastasis. The use of such strategies may represent an important option in the treatment of advanced gastric cancer in young patients.

Because the objectives included some old cases in this study, it was impossible to investigate the profile of

Table 4 Risk factors of recurrence

	Young		Middle aged	
	OR	(95 % CI)	OR	(95 % CI)
T (T3 ≤)	1.24	(0.127–12.1)	3.95*	(2.22–7.02)
N	4.31*	(1.87–9.94)	2.20*	(1.79–2.72)
Location (compared with middle)				
Upper	1.61	(0.285–9.08)	2.17*	(1.30–3.61)
Lower	0.228	(0.0201–2.58)	1.29	(0.759–2.20)
Histological type	–		1.01	(0.650–1.57)
Tumor size (40 mm ≤)	1.17	(0.142–9.72)	1.33	(0.956–1.85)
BMI	0.582	(0.139–2.43)	0.953	(0.623–1.46)

OR Odds ratio, *CI* confidence interval, *BMI* body mass index

* Significant difference

genetics among young gastric cancer patients. Indeed, recent studies have shown the specific gene has a strong relationship to early-onset or diffuse type gastric cancer [21]; a survey of E-cadherin (CDH1) germline or RhoA germline mutations might be relevant to the risk assessment of young gastric cancer patients [22, 23]. Further studies will be needed to investigate these genetic characteristics among early-onset gastric cancer patients.

Conclusion

Our present series of young patients with gastric cancer had a lower incidence of comorbidities and incidence of postoperative complications than middle-aged control patients. On the other hand, early-onset gastric cancer usually exhibits poor histologic differentiation and is likely to metastasize to lymph nodes. The outcome of gastric cancer in young patients was equivalent to that in patients in their 60s, which is the typical age at onset.

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