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Exploratory Analysis to Find Unfavorable Subset of Stage II Gastric Cancer for Which Surgery Alone Is the Standard Treatment; Another Target for Adjuvant Chemotherapy

Toru Aoyama[1], Takaki Yoshikawa[1], Hirohito Fujikawa[1], Tsutomu Hayashi[1], Takashi Ogata[1], Haruhiko Cho[1], Takanobu Yamada[2], Shinichi Hasegawa[2], Kazuhito Tsuchida[2], Norio Yukawa[2], Takashi Oshima[2], Yasushi Rino[2], Munetaka Masuda[2]

[1]*Department of Gastrointestinal Surgery, Kanagawa Cancer Center, 1-1-2 Nakao, Asahi-ku, Yokohama 241-0815, Japan*

[2]*Department of Surgery, Yokohama City University, Yokohama, Japan*

The aim of the present study was to explore the unfavorable subset of patients with Stage II gastric cancer for whom surgery alone is the standard treatment (T1N2M0, T1N3M0, and T3N0M0). Recurrence-free survival rates were examined in 52 patients with stage T1N2-3M0 and stage T3N0M0 gastric cancer between January 2000 and March 2010. Univariate and multivariate analyses were performed to identify risk factors using a Cox proportional hazards model. The recurrence-free survival (RFS) rates of the patients with stages T1N2, T1N3, and T3N0 cancer were 80.0, 76.4, and 100% at 5 years, respectively. The only significant prognostic factor for the survival rates of the patients with stage pT1N2-3 cancer measured by univariate and multivariate analyses was pathological tumor diameter. The 5-year RFS rates of the patients with stage pT1N2-3 cancer were 60.0%, when the tumor diameters measured $<$30 mm, and 88.9% when the tumor diameters measured $>$30 mm ($P = 0.0248$). These data may suggest that pathological tumor diameter is associated with poor survival in patients with small T1N2-3 tumors. Because our study was a retrospective single-center study with a small sample size, a prospective multicenter study is necessary to confirm whether small tumors are risk factor for the RFS in T1N2-3 disease.

Key words: Gastric cancer – Stage II – Adjuvant chemotherapy

Correspondence author: Takaki Yoshikawa, Department of Gastrointestinal Surgery, Kanagawa Cancer Center, 1-1-2 Nakao, Asahi-ku, Yokohama 241-0815, Japan.
Tel.: 045-391-5761; Fax: 045-361-4692; E-mail: yoshikawat@kcch.jp

Every year, more than 934,000 people develop gastric cancer worldwide. After lung cancer, gastric cancer is the second most frequent cancer-related cause of death.[1] Complete resection is essential to cure gastric cancer. Patients with stage II or stage III gastric cancer often develop tumor recurrence, even after complete curative resections.

In 2007, the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) phase III trial demonstrated that S-1 is effective as adjuvant chemotherapy in Japanese patients who have undergone curative D2 gastrectomy for advanced gastric cancer.[2] In general, patients eligible for ACTS-GC were those diagnosed with pathological stages II and III. However, patients classified with pathological (p) stages T1N2M0, T1N3M0, and T3N0M0—which are classified as part of stage II—were excluded from the ACTS-GC trial. Because in the prior phase III studies comparing surgery alone and adjuvant chemotherapy, patients with stages T1N+ and T2-3/N0 cancer had excellent prognoses with 5-year overall survival (OS) rates of more than 80% from surgery alone,[3,4] these patients were excluded from receiving adjuvant chemotherapy. Japanese Gastric Cancer Association (JGCA) guidelines clearly state that the standard treatment for these patients is surgery alone.[5]

Therefore, patients with stage II gastric cancer have been divided into two groups: one for whom the standard treatment is surgery alone, and the other for whom the standard treatment is surgery and adjuvant chemotherapy with S-1. Before the advent of ACTS-GC, survival rates were poorer in the latter group than in the former. However, treatment with adjuvant chemotherapy with S-1 has reversed this trend. Now, patients in the latter group receiving S-1 adjuvant chemotherapy have 5-year OS rates of 84.2%.[6] Therefore, it may be old rationale that dictates that patients in the former group should be excluded from receiving adjuvant chemotherapy, because the 5-year OS rates are now more than 80% by S-1 adjuvant chemotherapy in the latter group. Five-year OS rates of 80% would not be obtained by surgery alone. Among those patients with stage II gastric cancer assigned to the surgery alone group, some may have a poor prognosis and be good candidates for adjuvant chemotherapy. The aim of the present study was to explore the unfavorable subset of patients among those with stage II gastric cancer for whom surgery alone is the standard treatment (T1N2M0, T1N3M0, and T3N0M0).

Patients and Methods

Patients

The patients were selected from the prospective database of the Kanagawa Cancer Center, Department of Gastrointestinal Surgery, Yokohama, Japan, according to the following criteria: (1) the patients had a diagnosis of histologically proven gastric adenocarcinoma, (2) the patients underwent curative resection for gastric cancer as a primary treatment between January 2000 and March 2010, (3) the patients with stages T1N2M0, T1N3M0, and T3N0M0 disease were diagnosed pathologically according to the third English edition of the Japanese classification of gastric carcinoma published by JGCA,[7] and (4) the patients did not receive any other adjuvant chemotherapy after surgery.

Surgery and follow-up

All patients underwent total or distal gastrectomy with lymph node dissection to the D1+ or D2 level in accordance with the Japanese gastric cancer treatment guidelines published in 2010 (ver. 3).[5] In distal gastrectomy, D1+ resects the lymph nodes of Nos. 1, 3, 4sb, 4d, 5, 6, 7, 8a, 9; D2 resects the lymph nodes of D1+ and 11p, 12a. In total gastrectomy, D1+ resects the lymph nodes of Nos. 1, 2, 3, 4sa, 4sb, 4d, 5, 6, 7, 8a, 9, 11p; D2 resects the lymph nodes of D1+ and 10, 11d, 12a. In principal, D1+ lymphadenectomy was indicated for patients with cT1N0 tumors other than those for whom endoscopic mucosal resection or endoscopic submucosal dissection were recommend. D2 lymphadenectomy was indicated for patients with potentially curable T2-T4 tumors, as well as for those with cT1N+ tumors.

The patients received follow-up visits at outpatient clinics. Hematological tests and physical examinations were performed at least every 3 months for 5 years after surgery. CEA and CA19-9 tumor marker levels were checked at least every 3 months for 5 years. The patients underwent a CT examination every 6 months during the first 3 years after surgery, and then every year until 5 years after surgery.

Evaluation and statistical analyses

The staging and clinicopathological characteristics are based on the third English edition of the Japanese classification of gastric carcinoma.[7]

The recurrence free survival (RFS) was defined as the period between the surgery and the occurrence

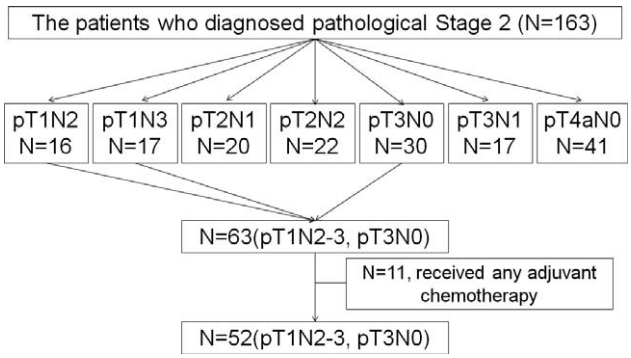

Fig. 1 Flow diagrams and the details of the 163 patients diagnosed with stage II cancer according to the third English edition of the Japanese classification of gastric cancer.

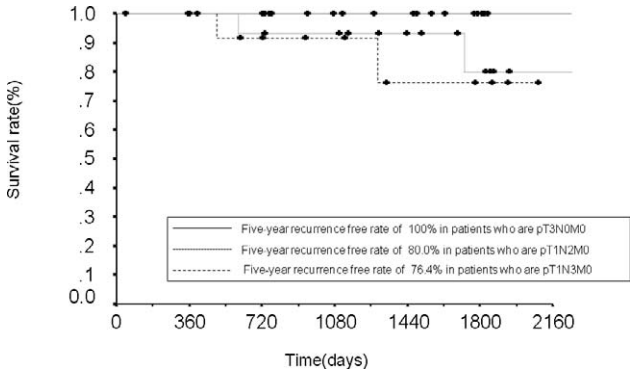

Fig. 2 The RFS curves in patients with stage T1N2-3M0 and stage T3N0M0 cancer.

of an event, any recurrence, or death, whichever came first. The data for the patients who did not experience an event were treated as censored cases on the date of the final observation.

The RFS curves were calculated using the Kaplan-Meier method and compared by the log-rank test. Cox's proportional hazard model was used to perform univariate and multivariate analyses. The survival data were obtained from hospital records or from the city registry system. A P value of <0.05 was defined to be statistically significant. A commercial statistical software package (SPSS v11.0J Win; SPSS, Chicago, IL) was used for all statistical analyses.

Table 1 Comparison of patients' characteristics between pT1N2-3M0 group and pT3N0M0 group

Characteristics	pT1N2-3M0 group (n = 28)	pT3N0M0 group (n = 24)
Age, y		
≤70	21	21
≥70	7	3
Performance status (ECOG)		
0	27	22
1	1	2
Site of tumor		
Upper third	4	6
Middle third	16	11
Lower third	8	7
Maximal tumor diameter, mm		
<30	9	11
≥30 to <50	10	7
≥50	9	6
Tumor invasion		
Mucosa	2	0
Submucosa	26	0
Sub serosa	0	24
Histological type		
Differentiated	13	12
Undifferentiated	15	12
Lymphatic invasion		
Negative	13	18
Positive	15	6
Vascular invasion		
Negative	19	14
Positive	9	10

Results

Between January 2000 and March 2010, a total of 163 patients underwent surgical resection and were diagnosed with pathological stage II gastric cancer. The details of the stage II patients are shown in Fig. 1. Among these patients, 52 were eligible for the present study. The patients' median age was 64 years (range: 37–80 years). Thirty-two patients were male and 20 were female. The pathological stage was classified to be T1N2 in 15 patients, T1N3 in 13 patients, and T3N0 in 24 patients. The backgrounds of the 52 patients are shown in Table 1. The median follow-up period was 47.8 months (range: 1–99.4 months). Recurrence was observed in 4 patients; lymph node in 2 (from T1N2M0 and T1N3M0 in each); liver in 1 (from T1N2M0); and bone in 1 (from T1N3M0).

The RFS rates of the patients with T1N2, T1N3, and T3N0 cancer were 93.3, 91.7, and 100% at 3 years, respectively, and 80.0, 76.4, and 100% at 5 years, respectively (Fig. 2). Because the patients with stage T3N0 cancer had excellent survival rates and there is no significant difference in RFS between T1N2M0 group and T1N3M0 group, we are grouping the patients with N2 and N3 together. Thus, further prognostic analyses were focused on the patients with stage T1N2-3 cancer. When the RFS rates were stratified according to each clinical factor,

Table 2 Comparison of RFS rate by patient's characteristics

Characteristics	Patients, n	3-year rate, %	5-year rate, %	*P* value
Age, y				
≤70	21	95.0	88.2	0.2487
≥70	7	85.7	57.1	
Pathological tumor diameter, mm				
≤30	9	75.0	60.0	0.0449
≥30 to ≤50	10	100	100	
≥50	9	100	80.0	
Histological type				
Differentiated	13	100	83.3	0.3250
Undifferentiated	15	86.7	77.0	
Lymph node metastasis				
pN2	15	93.3	80.0	0.6189
pN3	13	91.7	76.4	
Tumor invasion				
Mucosa	2	100	100	0.5682
Submucosa	26	92.0	77.6	
Lymphatic invasion				
Absent	13	92.3	66.5	0.7087
Minimum	4	—	—	
Moderate	8	85.7	85.7	
Severe	3	—	—	
Vascular invasion				
Absent	19	94.7	72.4	0.5570
Minimum	5	—	—	
Moderate	4	66.7	66.7	
Severe	0	—	—	

a significant difference was observed in the diameters of the pathological tumors (Table 2). A pathological tumor diameter of 30 mm and age of 70 years were regarded to be the optimal critical point of classification, considering the 3-year and 5-year survival rates. Each clinicopathological factor was categorized as shown in Table 3 and analyzed for prognostic significance. Both univariate and multivariate analyses of the RFS rates demonstrated that pathological tumor diameter was the only significant prognostic factor (Table 3). The RFS rates of the patients with stage T1N2-3 cancer were 75.0% at 3 years and 60.0% at 5 years when the pathological tumor diameter was <30 mm, and were 100% at 3 years and 88.9% at 5 years when the pathological tumor diameter was >30 mm ($P = 0.0248$; Fig. 3). When examining the clinicopathological differences in the patients with T1N2-3 tumors, both lymph-vascular invasion was significantly more frequently observed in the small tumors (3/9, 33.3%) than in the large tumors (1/19, 5.3%; $P = 0.047$). However, there is no relation between tumor size and other factors such as age, sex, tumor site, macroscopic tumor appearance, depth of tumor invasion, number of lymph node metastasis, lymphatic invasion, vascular invasion, and histological type (Table 4).

Discussion

The present study explored the unfavorable subset of patients with stage II gastric cancer for whom the standard treatment is surgery alone. We reported that the patients with stage T3N0 cancer had excellent outcomes; however, the patients with stage T1N2-3 cancer had relatively poor survival rates, suggesting that the T3N0 category is homogeneous in survival rates, while the T1N2-3 category consists of subpopulations with different survival rates. Therefore, we further analyzed the prognostic factors by focusing on the patients with stage T1N2-3 cancer, and found that only pathological tumor diameter was an independent significant prognostic factor in these patients. The survival rates of the patients with stage T1N2-3 cancer were clearly associated with the diameters of the pathological tumors. The RFS rate was only 60% at 5 years when the tumor diameter was less than 30 mm. These data may suggest that pathological tumor diameter is associated with poor survival in patients with small T1N2-3 tumors, although because our study was a retrospective single-center study with a small sample size, a prospective multicenter study is necessary to confirm whether small tumors are risk factor for the RFS in T1N2-3 disease.

In our institution, 6 patients with T1N2-3M0 tumors received the adjuvant chemotherapy. When comparing RFS between the surgery alone and adjuvant chemotherapy, 5-year RFS was 77.5% in the surgery alone and 83.3% in the adjuvant chemotherapy. Although there is some selection bias in the adjuvant chemotherapy, adjuvant chemotherapy might improve the survival of the patients with T1N2-3M0 tumors. Because the survival difference was small, it would be valuable to identify unfavorable subset of T1N2-3.

Why did the patients with small T1N2-3 tumors show poor prognoses in this study? First possibility is by chance. Our study is a single-center study with small sample size. Moreover, number of the event observed in this group was only 4. Second possibility is that our finding is true. Indeed, lymph-vascular invasion was more frequently observed in the small tumors than in the large tumors in this study, although the number was small and *P* value

Table 3 Uni- and multivariate Cox proportional hazards analysis of clinicopathological factors

		Univariate			Multivariate		
Characteristics	N	OR	95% CI	*P* value	OR	95% CI	*P* value
Age, y							
≤70	21	1.000		0.272	1.000		0.055
≥70	7	3.028	0.420–21.848		12.283	0.949–159.013	
Pathological tumor diameter, mm							
≥30	19	1.000		0.045	1.000		0.019
≤30	9	11.073	1.059–115.775		34.504	1.800–661.450	
Histological type							
Differentiated	13	1.000		0.348			
Undifferentiated	15	2.978	0.305–29.063				
Lymph node metastasis							
pN2	15	1.000		0.622			
pN3	13	1.643	0.228–11.837				
Lymphatic invasion							
Negative	13	1.000		0.353			
Positive	15	0.341	0.035–3.302				
Vascular invasion							
Negative	19	1.000		0.750			
Positive	9	1.446	0.149–14.022				

CI, confidence interval.

was 0.047. However, we do not know the exact mechanism of why smaller tumors have a worse prognosis. Generally, the large tumors metastasize to lymph nodes more often than the small tumors, because the chances to encounter the lymph-vascular vessels may be greater in the large tumors than in the small tumors if invading potential is not different regardless of the tumor size. However, all patients had T1N2 or T1N3 disease in the present analyses regardless of the size of tumors. Are large or small tumors more biologically malignant in this situation? The small T1 tumors should have less chance to encounter the lymph-vascular vessels than the large tumors. Nevertheless, the small T1 tumors had N2/N3 in the present study. Thus, the small T1 tumors have a greater potential of invading lymph-vascular vessels. On the other hand, large T1 tumors have a greater chance of encountering lymph-vascular vessels because the tumor volume is large. The large T1 tumors may invade lymph-vascular vessels even though the invading potential is low. Indeed, lymph-vascular invasion was more frequently observed in the small tumors than in the large tumors in this study, although the number was small and *P* value was 0.047. The small size may represent the invading potential when the tumors are limited to T1N2-N3. Although there were no basic and clinical papers to support our hypothesis in gastric cancer, there is one clinical paper in colon cancer. Previously, Mitomi *et al* examined prognostic factors which associated with metastasis in 211 patients with colorectal cancer. They found that a small tumor was one of the risk factors for lymph node and/or liver metastasis in patients with colorectal cancer.[8] Further molecular analyses would clarify the exact mechanisms underlying these observations.

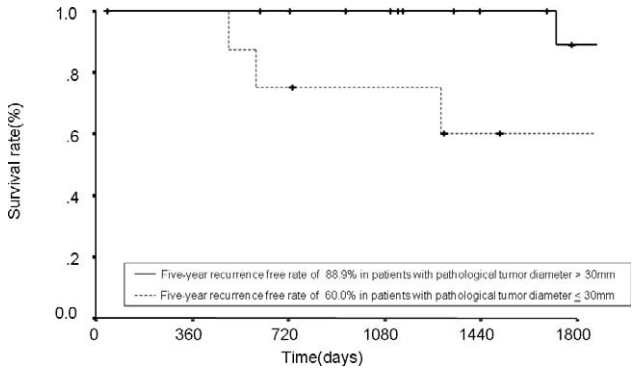

Fig. 3 The RFS curves in patients with pathological tumors with diameters >30 mm and <30 mm.

On the other hand, patients with stage T1N2-3 cancer had relatively low survival rates in this study. Ahn *et al* also reported similar survival rates in patients with stage T1N2-3 cancer.[9] Why were the

Table 4 Comparison of the clinicopathological characteristics between the stage T1N2-3 patients who had tumor diameter <30 mm and those who had tumor diameter > 30 mm

Characteristics	Tumor diameter <30 mm group (n = 9)	Tumor diameter >30 mm group (n = 19)	*P* value
Age, y			
≤70	8	13	0.243
≥70	1	6	
Gender			
Male	4	10	0.686
Female	5	9	
Tumor size			
11–20 mm	4	0	—
21–30 mm	5	0	
31–40 mm	0	5	
41–50 mm	0	7	
≥51 mm	0	7	
Median (range, mm)	25 (17–30)	50 (32–97)	
Site of tumor			
Upper third	1	3	0.903
Middle third	5	11	
Lower third	3	5	
Macroscopic tumor appearance			
0–1	0	3	0.288
0-2a	1	1	
0-2c	6	12	
1	0	2	
2	1	0	
3	1	0	
4	0	0	
5	0	1	
Tumor invasion			
Mucosa	0	2	0.312
Submucosa	9	17	
Number of lymph node metastasis			
3–6	5	10	0.885
7 or more	4	9	
Histological type			
Differentiated	4	9	0.885
Undifferentiated	5	10	
Lymphatic invasion			
0	4	9	0.441
1	1	3	
2	4	4	
3	0	3	
Vascular invasion			
0	5	14	0.135
1	1	4	
2	3	1	
3	0	0	
Both lymph-vascular invasion			
Negative	6	18	0.047
Positive	3	1	

survival rates of patients with stage T1N2-3 cancer worse in spite of the detection of early disease? Some authors have reported on the significance of lymph node metastasis. Folli *et al* examined 584 patients with early gastric cancer and reported that the patients with 3 or fewer positive lymph nodes presented with superior 5-year prognoses (83%) compared with those with more than 3 positive lymph nodes (48%; $P = 0.0001$).[10] As previously described, lymph node metastasis is reportedly an independent predictive factor in patients with serosa-negative gastric cancer.[11] Other researchers have also reported that lymph node metastasis is one of the most important risk factors for early or serosa-negative gastric cancer and that the N stage correlates with survival and recurrence rates.[12–14] N2 to N3 stage T1 tumors would have a more prognostic impact than T3 tumors without nodal metastases.

However, there are some limitations in this study. First, this was a retrospective single-center study with a small sample size. The number of the patients may be too small to lead to a definite conclusion. However, this is the first study to try to explore the unfavorable subset of stage II, and we found that tumor size was a significant risk factor. Before conducting a multicenter study, basic data is necessary. It is difficult to come to a definite conclusion without a multicenter study for the following reasons. First, T1N2M0, T1N3M0, and T3N0M0 are rare—especially, T1N2 and T1N3, which are quite rare. Ahn *et al* examined stage migration of 9998 gastric cancer patients between 1986 and 2006, and reported that the incidence of T1N2M0 was 1.2% (121/9998); T1N3M0 was 0.45% (45/9998); and T3N0M0 was 6.6% (662/9998), respectively.[11] We had only 52 patients who were classified with these categories and did not receive adjuvant chemotherapy during 2000 and 2010. Moreover, only 28 patients were classified with pT1N2-3 tumors. Second, before 1999, many patients had received adjuvant chemotherapy such as UFT or 5-FU, which was a community standard in most Japanese hospitals in the older period. Although we limited this study to the period between 2000 and 2010, 11 out of 63 patients (17.5%) received adjuvant chemotherapy. The survival would not be accurate if such patients were included. Thus, it is difficult to increase the number of patients of this category even though we searched for candidates before 1999. The situation would be similar in other Japanese hospitals. Thus, the only way to draw definite conclusion is to collect recent data from

many hospitals. Without our data, no one knows which parameters should be included in the future study. Second, the optimal cutoff value was unknown. When we examined prognosticators by selecting several different cutoff values, the age of 70 years was most valuable and tumor diameter of 30 mm was only significantly different by considering the *P* value (dates were not shown). Therefore, we set cutoff value at age of 70 years and tumor diameter of 30 mm in this study. However, appropriate cutoff value should be determined in the other validation studies. Third, we used disease-free survival as the primary endpoint because the follow-up period is not enough and the occurrence of events was small. When we analyze overall survival by Cox's proportional hazard model, the results were similar to the present results. Considering these factors, a multi-institutional study is necessary to confirm our results in the future.

In conclusion, we tried to explore the unfavorable subset of stage II gastric cancer for which surgery alone is the standard treatment, and found that a pathological tumor diameter was associated with poor survival in patients with small T1N2-3 tumors. Because our study was a retrospective single-center study with a small sample size, a prospective multicenter study is necessary to confirm whether small tumors are risk factor for the RFS in T1N2-3 disease.

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Conflict of Interest Statement

None declared

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