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ORIGINAL ARTICLE – HEPATOBILIARY AND PANCREATIC TUMORS

Therapeutic Value of Lymph Node Dissection in Advanced Gastric Cancer with Macroscopic Duodenum Invasion: Is the Posterior Pancreatic Head Lymph Node Dissection Beneficial?

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ABSTRACT

Background. In advanced gastric cancer (AGC) with duodenum invasion, the posterior pancreatic lymph nodes are susceptible to metastasis because of their proximity to the duodenum. The therapeutic value of lymph node dissection in this area for AGC with macroscopic duodenum invasion remains unclear.

Methods. Patients who had undergone curative gastrectomy for lower-third AGC from 1970 to 2004 at the Cancer Institute Hospital were recruited for this study. Clinicopathological data were collected retrospectively, and compared between cases of AGC with duodenum invasion (AGC-DI group) and AGC without duodenum invasion (AGC-nDI group). In the AGC-DI group, the therapeutic value of lymph node dissection was evaluated using a therapeutic index (multiplication of the frequency of metastasis to the station by the 5-year survival rate of patients with metastasis to that station).

Results. The AGC-DI group generally had tumors of higher pathological stage, which might account for the poorer 5-year survival rate compared with that of the AGC-nDI group (50.1% versus 68.5%; $P = 0.0002$). The incidence of lymph node metastasis was higher in the AGC-DI group than that in the AGC-nDI group, including nodes in the posterior pancreatic head (23.9% versus 7.0%, $P < 0.0001$). In the AGC-DI group, posterior pancreatic head lymph node dissection was of therapeutic value (4.19) equivalent to dissection of second-tier lymph nodes.

Conclusions. The dissection of posterior pancreatic head lymph nodes might be effective in AGC with macroscopic duodenum invasion since this has therapeutic value equivalent to that of second-tier lymph node dissection and might improve patients' long-term outcomes.

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Advanced gastric cancer (AGC) carries a high postoperative morbidity and mortality rate. Although a number of large randomized trials in Europe have failed to prove the efficacy of D2 lymph node dissection for AGC, gastrectomy with this lymph node dissection is performed widely and safely in Japan.[1–7] Therefore, the Gastric cancer treatment guideline established by Japanese Gastric Cancer Association (JGCA) recommends dissection of all second-tier lymph nodes with gastrectomy as standard therapy for AGC in Japan.[8,9]

The JGCA guidelines generally classify perigastric lymph nodes as first-tier lymph nodes, while extraperigastric lymph nodes are classified as second- or third-tier nodes, depending on the tumor location. In lower-third gastric cancer, stations 7, 8a, 9, 11p, 12a, and 14v (located along the left gastric artery, common hepatic artery, celiac axis, proximal half of the splenic artery, proper hepatic artery, and superior mesenteric vein at the lower border of pancreas, respectively) are classified as second-tier lymph nodes and therefore should be dissected during surgery for AGC.[8,9]

Advanced gastric cancers in the lower third of the stomach occasionally invade into the duodenum and are associated with poor prognosis.[10,11] This may be due to different clinicopathological features, including additional sites susceptible to lymph node metastasis such as the posterior pancreatic head (station 13 lymph node). This aspect of AGC remains unclear, as does the therapeutic

value of lymph node dissection at each station in cases with duodenum invasion. Currently the JGCA designates station 13 lymph nodes as third tier and thus does not recommend dissection of these nodes during standard D2 lymph node dissection despite of this station's proximity to the duodenum and possible susceptibility for metastases with duodenal invasion.[8,9]

The present study sought to clarify the distinct clinicopathological characteristics of lower-third AGC with macroscopic duodenum invasion. Site susceptibility for lymph node metastasis and the therapeutic value of dissection at each lymph node station, especially those in the posterior pancreatic head, were also investigated.

PATIENTS AND METHODS

Patients with lower-third AGC with and without duodenum invasion who were treated by gastrectomy at the Cancer Institute Hospital from 1970 to 2004 were recruited in this study. Only patients who underwent curative resection were included. Cases with invasion involving the middle or upper third of the stomach and those with multiple gastric cancer were also excluded from the present study.

Clinicopathological features collected retrospectively from the institute database were as follows: gender, age, surgical procedure, histological type, macroscopic type, size, tumor depth, degree and number of lymph nodes metastases, and pathological stage.

Definition of Duodenum Invasion

Resected specimens were cut at the greater curvature side for inspection by the surgeon immediately after surgery. Tumor invasion directly into the duodenal wall was assigned as AGC with duodenum invasion. The border between gastric wall and duodenum wall was taken as the top of the pyloric ring, according to the Japanese Classification of Gastric Carcinoma (JCGC) 12th edition.

Lymph Node Station Number

Lymph node station number was classified according to the JCGC.[9] In cases of lower-third gastric cancer, stations 3, 4d, 5, and 6 lymph nodes were first-tier lymph nodes, with all located in the perigastric area. Station 1 (right paracardial) was classified as a second-tier lymph node, despite also being in the perigastric area. Stations 7, 8a, 9, 11p, and 12a lymph nodes were second-tier lymph nodes located along the left gastric artery, the common hepatic artery, the celiac axis, the proximal half of the splenic artery, and the proper hepatic artery, respectively. Station 14v lymph nodes were also classified as second-tier nodes and were located along the superior mesenteric vein at the lower border of the pancreas (Fig. 1).

Comparison of Clinicopathological Features and Incidence of Lymph Node Metastasis

Clinicopathological features were compared between AGC with duodenum invasion (AGC-DI group) and AGC without duodenum invasion (AGC-nDI group) to clarify the characteristics of AGC with duodenum invasion.

The incidence of lymph node metastasis for each station was also investigated and compared between the two groups. This parameter was calculated by dividing the number of patients with metastasis at the given station by the number of patients in whom that station was dissected.

Therapeutic Value of Lymph Node Dissection in AGC with Duodenum Invasion

The therapeutic value of lymph node dissection in the AGC-DI group was evaluated by multiplying the frequency

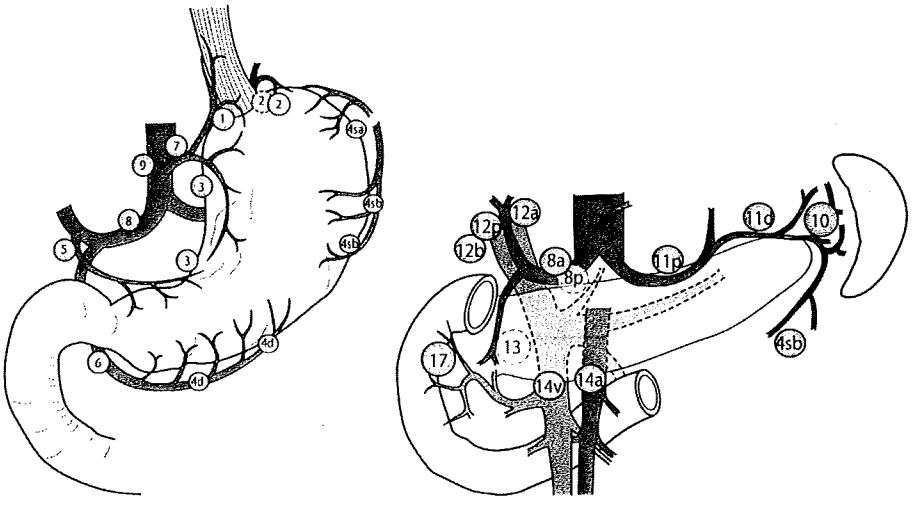

FIG. 1 Number of lymph node station according to the JGCA classification (lower-third gastric cancer). First-tier lymph node stations 3,.4d, 5, 6; second-tier lymph node stations 1, 7, 8a, 9, 11p, 12a, and 14v; third-tier lymph node stations 4sb, 8p, 12p/b, and 13. Para-aortic lymph node (station 16) was also classified as third-tier lymph node (not illustrated)

of metastasis to the station by the 5-year survival rate of patients with metastasis to that station, as proposed by Sasako et al.[12] The cumulative 5-year survival rate for patients with lymph node metastasis was calculated for each nodal station, irrespective of metastasis to other lymph node stations. All postoperative deaths were included in the survival analysis, including from the surgery and due to causes other than cancer.

Statistical Analysis

All continuous data are presented as mean ± standard error. Statistical analysis was conducted using the chi-square and Student's *t*-test. Five-year survival rates were calculated using the life-table method and statistically analyzed using the log-rank test. All statistical analysis was performed using the SAS program system version 9.1.3. Statistical significance was defined as $P < 0.05$.

RESULTS

From 1970 to 2004, 9,133 patients underwent gastrectomy for gastric cancer at the Cancer Institute Hospital. Of these, 1,369 patients had gastric cancer restricted to the lower third of the stomach and duodenum. Patients not able to undergo curative resection (100 patients), those with early gastric cancer (834 patients), and those with synchronous multiple gastric cancer (40 patients) were excluded from the study. The remaining 395 patients were recruited for analysis: 131 patients had AGC with duodenum invasion (AGC-DI group; $n = 131$) and the remainder had AGC without duodenum invasion (AGC-nDI group; $n = 264$) (Fig. 2).

Table 1 illustrates patient background and operative procedure for both groups. There was no difference in gender or age between groups. Pancreaticoduodenectomy was performed as a curative surgery in 5% of patients from the AGC-DI group (six cases) and in 2% of the AGC-nDI group (five cases).

Table 2 describes the patients' pathological profile. There was no difference in histological type between the groups. Tumors were generally larger and deeper in the AGC-DI group, which also showed a higher N-stage according to both the JCGC and International Union against Cancer (UICC) classifications. Thus, the AGC-DI group comprised patients with more advanced-stage cancer compared with the AGC-nDI group.

The 5-year survival rates were 50.1% for the AGC-DI group and 68.5% for the AGC-nDI group (Fig. 3; $P = 0.0002$).

The frequency of lymph node metastasis for each station is described in Fig. 4. In general, each lymph node station showed a significantly higher incidence of metastasis in the AGC-DI group compared with the AGC-nDI group. There was statistically significant difference in station 5 (19.2% versus 11.5%, $P = 0.0482$), station 6 (72.7% versus 57.4%, $P = 0.0035$), station 7 (20.2% versus 1.8%, $P = 0.0278$), station 8a (40.6% versus 27.5%, $P = 0.0090$), station 13 (23.9% versus 7.0%, $P < 0.0001$), and station14v (22.7% versus 4.0%, $P < 0.0001$).

Table 3 details the therapeutic value of lymph node dissection in the AGC-DI group, based on the calculated therapeutic index. This concept of the therapeutic value of lymph node dissection proposed by Sasako et al. was cited in

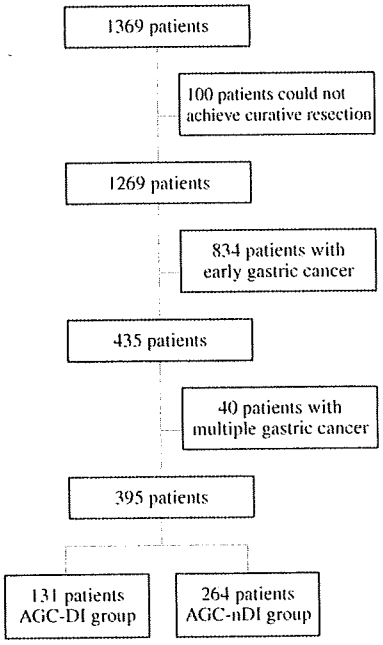

FIG. 2 Patient allocation in the present study. Patients with noncurative resection ($n = 100$), early gastric cancer ($n = 834$) or multiple gastric cancer ($n = 40$) were excluded

TABLE 1 Patient characteristics and operative procedure

	AGC-DI group	AGC-nDI group	*P*-value
Number (*n*)	131	264	
Gender			
Male/female	95/36	203/61	0.3416
Age (years)			
Mean	60.2 ± 1.0	60.8 ± 0.7	
Range	31–85	29–85	0.6575
Performed operation			
Distal gastrectomy	110 (84)	254 (96)	
Total gastrectomy	15 (11)	5 (2)	
Pancreaticoduodenectomy	6 (5)	5 (2)	<0.0001
Mean observation period (months)	74.1 ± 6.6	80.7 ± 4.7	0.4120

TABLE 2 Pathological characteristics of patients

	AGC-DI group (n = 131)	AGC-nDI group (n = 264)	P-value
Histologic type, n (%)			
Differentiated	95 (73)	203 (77)	
Undifferentiated	36 (27)	61 (23)	0.3416
Macroscopic type, n (%)			
0	5 (4)	27 (10)	
1	1 (1)	7 (3)	
2	42 (32)	72 (27)	
3	74 (56)	132 (50)	
4	4 (3)	8 (3)	
5	5 (4)	18 (7)	0.1199
Tumor size (mm), n (%)			
–39	23 (18)	100 (38)	
40–79	93 (71)	143 (54)	
80–	15 (11)	21 (8)	0.0002
Tumor depth, n (%)			
MP	33 (25)	106 (40)	
SS	30 (23)	81 (31)	
SE	59 (45)	76 (29)	
SI	9 (7)	1 (0)	<0.0001
Number of metastasized lymph nodes, n (%)			
0	27 (21)	74 (28)	
1–6	64 (49)	131 (50)	
7–15	25 (19)	48 (18)	
16+	15 (11)	11 (4)	0.0290
Degree of lymph nodes metastasis, n (%)			
N0	27 (21)	74 (28)	
N1	32 (24)	85 (32)	
N2	35 (27)	79 (30)	
N3	37 (28)	26 (10)	<0.0001
Pathological stage (UICC), n (%)			
IB	16 (12)	68 (26)	
II	47 (36)	100 (38)	
IIIA	27 (21)	52 (20)	
IIIB	14 (11)	25 (9)	
IV	27 (21)	19 (7)	0.0003
Pathological stage (JGCA), n (%)			
IB	16 (12)	68 (26)	
II	26 (20)	67 (25)	
IIIA	29 (22)	65 (25)	
IIIB	16 (12)	29 (11)	
IV	44 (34)	35 (13)	<0.0001

the latest edition of JCGC and has been widely accepted among specialists inside and outside Japan.[9,12–14] Lymph node on the posterior surface of the pancreatic head was dissected in 110 of 131 patients (84.0%), and 25 of these were found to have metastasis (23.9%). Five-year survival rate of these 25 patients was 17.5%. From these data, the therapeutic index of station 13 lymph node was 4.19, being of greater therapeutic value than dissection of station 7 (1.01), 9 (3.70), 11p (3.65) or 12a (0) lymph nodes, but of lower value than dissection of station 8a (12.59) or 14v (5.39).

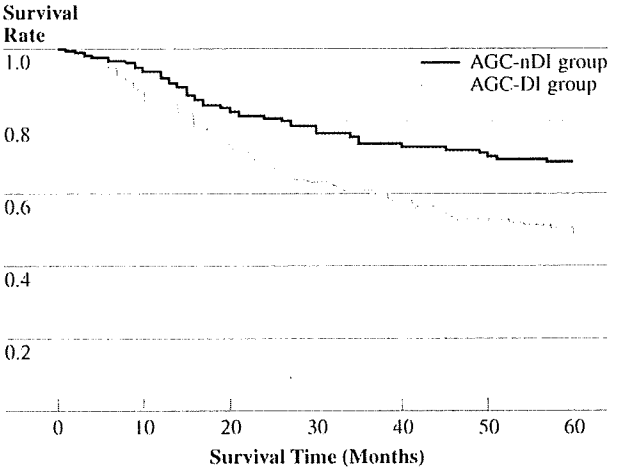

FIG. 3 Five-year survival rates of patients in both groups: AGC-DI group and AGC-nDI group

In the AGC-DI group, 5-year survival rate was better in patients who underwent lymph node dissection of the posterior pancreatic head (52.7%) than in those who did not (47.5%), although the difference was not statistically significant (P = 0.605).

DISCUSSION

In Japan, gastrectomy with D2 lymph node dissection is often performed as a safe and standard surgery for advanced gastric cancer, despite reports of high postoperative morbidity and mortality rates in large European trials.[1–7] According to JGCA guidelines, all first- and second-tier lymph nodes should be dissected during a D2 lymph node dissection.[8,9] For lower-third gastric cancer, second-tier lymph nodes include stations 1, 7, 8a, 9, 11p, 12a, and 14v lymph nodes irrespective of duodenum invasion, and these lymph nodes should be dissected.

The reported incidence of duodenum invasion is 11–25% in surgically resected specimen and 68.5% in autopsy cases.[10,11,15–17] Kekeji et al. reported that AGC with duodenum invasion is often infiltrative and advanced, with invasion into the serosa, and lymph node metastasis was frequently observed compared with AGC without duodenum invasion.[10,11] They also reported poorer 5-year survival rates in AGC with duodenum invasion. Perng et al. also reported that higher stage and larger tumors were frequently observed in AGC with duodenum invasion compared with AGC without duodenum invasion, while macroscopic type 3 and 4 gastric cancer frequently infiltrated the duodenum directly.[18]

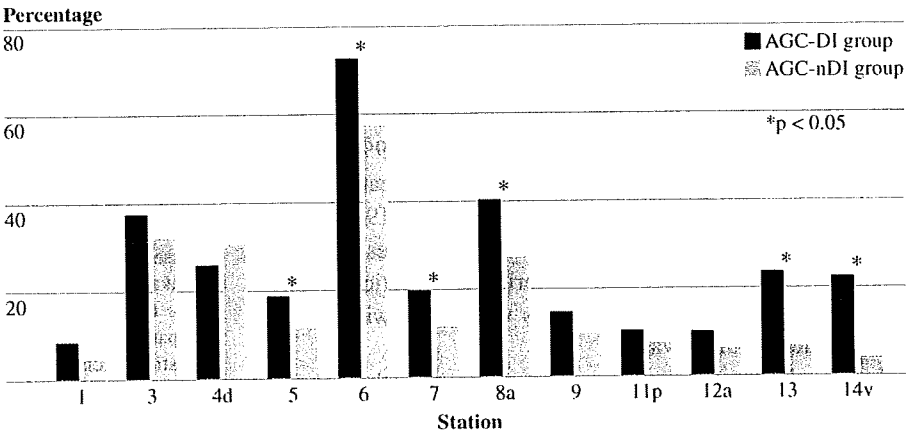

FIG. 4 Frequency of lymph nodes metastasis for each station: AGC-DI group and AGC-nDI group; * $P < 0.05$

TABLE 3 Therapeutic index (multiplication of frequency of lymph nodes metastasis by 5-year survival rate) of each lymph node station

Lymph node station	AGC-DI group		
	Frequency of LN meta (%)	5-Year survival rate (%)	Therapeutic index
1**	8.7	9.1	0.79
3*	37.7	34.2	12.89
4d*	26.4	32.5	8.58
5*	19.2	30.9	5.93
6*	72.7	42.5	30.90
7**	20.2	5.0	1.01
8a**	40.6	31.0	12.59
9**	14.8	24.9	3.70
11p**	10.7	34.2	3.65
12a**	10.5	0	0
13***	23.9	17.5	4.19
14v**	22.7	23.7	5.39

* First-tier lymph node

** Second-tier lymph node

*** Third-tier lymph node

Although the efficacy of systemic lymph node dissection was occasionally evaluated in previous studies, the therapeutic efficacy of lymph node dissection of each station was rarely investigated.[19,20] Sasako et al. proposed a simple index to determine the actual benefit of node dissection, which could circumvent the stage migration phenomenon by calculating the therapeutic efficacy of each station irrespective of other nodal status.[12] Theoretically, the ideal lymph node dissection includes stations with a higher predicted incidence of metastasis. Moreover, lymph node dissection of positive nodes should improve the patient's long-term survival. Therefore, a therapeutic index in their study was calculated by multiplying the frequency of metastasis to the station by the 5-year survival rate of patients with metastasis to that station.

The latest edition of JCGC, which adopts anatomical-based N-staging, was released subsequent to Sasako's report.[12] The JCGC cites the therapeutic index as an effective mean of categorizing each nodal station (N0, N1, N2, N3).[13,14] This latest edition of JCGC and the concept of the therapeutic index are now widely accepted among specialists inside and outside of Japan. We thus adopted this therapeutic index for use in the current study to evaluate the therapeutic efficacy of lymph node dissection of each station.

In the present study, 5-year survival rates were significantly lower in the AGC-DI group than that in the AGC-nDI group. As previously reported, the higher incidence of advanced-stage tumors in the AGC-DI group might account for these lower rates.[11,12,16] The results therefore suggested that an appropriate treatment strategy for AGC with duodenum invasion should be initiated, including effective lymph node dissection, to improve this poor 5-year survival rate. Understanding the relative susceptibility of a nodal area for metastasis might also improve long-term outcomes for these patients.

Different incidences of lymph node metastasis were observed in this study for stations 5, 6, 7, 8a, 13, and 14v between the AGC-DI and AGC-nDI groups. Although this might be due to the higher stage observed in the AGC-DI group, the differences in tumor location between groups might be associated with the difference. Except station 7, all stations in which the incidence of lymph node metastasis was different between the groups were close to the duodenum wall. On the other hand, the incidence of lymph node metastasis did not differ significantly among other lymph nodes (stations 1, 3, 4d, 9, and 11p), which were distant from the duodenum. Therefore, duodenum invasion itself might be associated with the higher incidence of some lymph node metastasis in the AGC-DI group.

Sasako et al. reported a 5-year survival rate of 0% for cases of lower-third AGC with posterior pancreatic head lymph node metastasis. They therefore discounted any

therapeutic value in posterior pancreatic head lymph node dissection.[12] However, 5-year survival rate of the present patients with posterior pancreatic head lymph node metastases in the AGC-DI group was 17.5%, and the frequency of this lymph node metastasis was 23.9%. As a result, the therapeutic index for posterior pancreatic head lymph node dissection in AGC-DI cases was 4.19, equivalent to that for most second-tier lymph nodes. These results therefore suggest that posterior pancreatic lymph node should be dissected in patients with AGC with macroscopic duodenum invasion.

In conclusion, there were many clinicopathological differences for patients with lower-third AGC between those with and without duodenum invasion, especially in areas susceptible for lymph node metastasis. Dissection of posterior pancreatic head lymph nodes might be effective in AGC with macroscopic duodenum invasion, particularly if curative surgery is possible, to improve patients' long-term outcomes.

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Original article

Phase II trial of S-1 for neoadjuvant chemotherapy against scirrhous gastric cancer (JCOG 0002)

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Abstract

Background. **The prognosis of scirrhous gastric cancer remains poor despite extended surgery or adjuvant or neoadjuvant chemotherapy. A pilot study of S-1 (TS-1; Taiho Pharmaceutical, Tokyo, Japan), an oral 5-fluorouracil derivative, for neoadjuvant chemotherapy unexpectedly showed good response and a promising effect on survival. Therefore, the Japan Clinical Oncology Group conducted a phase II trial to confirm the efficacy of S-1 for neoadjuvant chemotherapy against resectable scirrhous gastric cancer.**

Methods. **Patients were eligible if they had typical scirrhous gastric cancer invading more than half of the stomach, and resectable disease confirmed by laparoscopic staging. The treatment schedule consisted of two courses (each, 4-week administration and 2-week withdrawal) of S-1 (100–120 mg/body per day), followed by radical surgery.**

Results. **Fifty-five eligible patients were registered. Three completed only one course of the neoadjuvant chemotherapy, whereas 52 completed two courses. Toxicity was acceptable, with a few grade 3 (5.5%) events, but no grade 4 adverse events. The response rate was 32.6% in 43 evaluable patients. Of the 55 patients, 2 refused operation, 1 developed lung metastasis, and 52 underwent laparotomy. The curative resection rate was 80.8%, with acceptable morbidity and no mortality. The survival curve at 2 years' follow up showed a better survival rate than that of the historical controls, but did not reach the expected survival rate.**

Conclusion. **S-1 neoadjuvant chemotherapy appeared feasible and showed positive effects against scirrhous gastric cancer; however, the survival rate with S-1 did not reach the expected rate required when selecting an agent for a phase III trial to confirm the effectiveness of neoadjuvant chemotherapy against scirrhous gastric cancer.**

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Key words Scirrhous gastric cancer · Neoadjuvant chemotherapy · S-1

Introduction

Scirrhous gastric cancer, also known as linitis plastica or Borrmann type 4, is a special type of stomach cancer known for its very poor prognosis. It is very difficult to identify this cancer in its early stage, and even aggressive surgical procedures and adjuvant chemotherapies have not considerably improved the survival rate in patients with this neoplasia. Owing to its low incidence, only a few drug trials against this neoplasia have been conducted thus far. On the other hand, several studies of neoadjuvant chemotherapy against scirrhous gastric cancer have suggested the efficacy of such treatment [1–4]. However, all these studies involved a small sample size and they usually did not determine the survival benefits of such treatment. Furthermore, a phase II trial of sequential high-dose methotrexate and fluorouracil combined with doxorubicin (FAMTX) for neoadjuvant chemotherapy has shown moderate toxicity and no survival benefits [5]. Interestingly, S-1, which is a dihydropyrimidine dehydrogenase (DPD)-inhibitory fluoropyrimidine, has shown the highest response rate among many oral anticancer agents against unresectable advanced gastric cancer in early and late phase II trials [6–8]. In these late phase II trials, S-1 showed a 33% response rate against scirrhous gastric cancer. Because of the reported promising effects of S-1 for neoadjuvant chemotherapy against scirrhous gastric cancer in a previous pilot study [9], the Japan Clinical Oncology Group

(JCOG) decided to conduct a phase II trial to determine survival benefits of S-1 treatment.

Patients, materials and methods

Patient eligibility

Patient eligibility required the fulfillment of the following criteria: histologically confirmed gastric adenocarcinoma; potentially resectable laparoscopy-confirmed typical scirrhous gastric cancer (without definitive ulceration) that invaded more than half of the stomach; received no prior treatment; 70 years or younger; Eastern Cooperative Oncology Group performance status of 0 or 1; and oral intake possible. Patients also had to have adequate organ functions (creatinine clearance, ≥50 ml/min; blood urea creatinine, within the institutional limit; GOT and GPT, within twice the institutional limit; leukocytes, 3500/mm^3≤ leukocyte <12000/mm^3; hemoglobin, ≥9.0 g/dl; thrombocytes, ≥1000000/mm^3; total bilirubin, within twice the institutional limit; and normal electrocardiogram).

Diagnostic and staging procedures included physical examination, barium gastrography, endoscopy, chest X-ray, abdominal computed tomography (CT) scan, and laparoscopy with cytological examination of peritoneal washing of the Douglas pouch. Patients with positive cytology on peritoneal washing and potentially resectable disease without visible peritoneal dissemination were also included in the study.

This study was approved by the Institutional Review Board, and written informed consent was obtained from all patients.

Treatment schedule

Chemotherapy consisted of two courses (4-week administration and 2-week withdrawal) of S-1 at 100–120 mg/body per day. After two courses of neoadjuvant chemotherapy, patients were reevaluated for the presence of potentially resectable disease and those who were positive underwent laparotomy. Because two patients underwent endoscopic examination after one course of chemotherapy and stopped chemotherapy due to progressive disease, the treatment protocol was revised such that the evaluation of the effect of neoadjuvant chemotherapy should be carried out only after two courses and only by fluoroscopic examination. If indicated, patients received curative or palliative resection or exploratory laparotomy within 14 days after completing the second course of adjuvant chemotherapy. Patients with curative resection were followed up without any adjuvant chemotherapy every 3 months until cancer relapse.

Evaluation of response and toxicity

Potentially resectable scirrhous gastric cancer usually shows no measurable lesions, except for primary foci. We decided to evaluate the response of only primary foci following chemotherapy. Because it is very difficult to evaluate the response of the primary foci using the Response Evaluation Criteria in Solid Tumors criteria, we used a National Institutes of Health (NIH) image to calculate the barium-filling area or whole stomach on a double-contrast fluoroscopic examination study, as well as to compare the area before and after chemotherapy. Responses were classified as partial response (PR), more than 50% increase in the area after chemotherapy; stable disease (SD), 0 to less than 50% increase in the area; and progressive disease (PD), any decrease in the area and the appearance of new lesions. National Cancer Institute Common Toxicity Criteria ver2.0 were employed for determining chemotherapy toxicity.

Pathological assessment was performed to evaluate disease extent, resection margins, and response to chemotherapy as evidenced by the presence of necrotic and cancer cells. The pathological response to chemotherapy was classified according to the following criteria provided by the Japanese Gastric Cancer Association [10]: grade 0, absence of necrosis or degeneration; grade 1a, necrosis or degeneration is observed in less than one-third of the tumor; grade 1b, less than two-thirds and more than one-third of the tumor show necrosis or degeneration; grade 2, more than two-thirds of the tumor shows necrosis or degeneration; grade 3, all tumors show necrosis or degeneration.

Historical controls

Because we applied laparoscopic staging to exclude patients with visible peritoneal dissemination, it was very difficult to find good historical controls. Laparoscopic staging had gained popularity at the commencement of this trial; however, we had no identical historical controls. The historical controls consisted of 241 patients who had the same lesions as those described in the eligibility criteria for this study, and who had no visible peritoneal dissemination at laparotomy without laparoscopic staging, and had been treated at the participating institution during 1991–1993. Data for the historical controls were as follows: 2-year survival rate, 45%; curative resection rate, 90.3%; 30-day operative mortality rate, 1.2%; and in-hospital mortality rate, 3.5%.

Statistical considerations

The primary endpoint of this study was the 2-year survival rate. Fifty-five patients were required to be registered on the basis of the expectation that the 2-year survival rate of those receiving this neoadjuvant chemo-

therapy would be 60% (15% higher than that of the historical controls), allowing 10% of ineligible patients. Survival time was calculated from the initial date of the initiation of neoadjuvant chemotherapy to the date of death or the last follow-up date. Survival data were analyzed according to the method of Kaplan and Meier and then compared with the data of the historical controls.

Results

Patient accrual

From March 14, 2001, to February 4, 2003, 55 patients were enrolled in the study from 15 institutions. The mean age was 56 years (range, 31–70 years).

Neoadjuvant chemotherapy

The patients were composed of 26 male and 29 female patients. The scheduled two courses of neoadjuvant chemotherapy were performed in 52 patients. The remaining 3 patients received one course, because 2 of the 3 patients were judged to have PD by endoscopic evaluation after one course before the revision of the protocol, and 1 patient was found to have advanced bile duct carcinoma after one course of chemotherapy. These 3 patients received curative resection after one course of neoadjuvant chemotherapy. There was no chemotherapy-induced grade 4 adverse reaction in the cohort. Only 3 patients developed grade 3 adverse reactions (Table 1).

As mentioned earlier, the effect of adjuvant chemotherapy was evaluated from the change in the barium-filling area before and after the chemotherapy, as calculated from the NIH images. Among the 43 patients whose fluoroscopic films could be evaluated, 14 patients (32.6%) showed more than 1.5 times enlargement of the stomach (PR); 13 patients showed SD (30.2%), and 16 patients showed PD (37.2%).

Table 1. Adverse reactions

	Grade				%	
	0	1–2	3	4	Grade 4	Total
T. Bil	32	23	0	0	0	55
WBC	42	13	0	0	0	55
Neutrophils	42	12	1	0	0	55
ALT	43	11	2	0	0	55
AST	45	9	0	0	0	55
Hb	48	7	0	0	0	55
Nausea/vomiting	36	19	0	0	0	55
Pigmentation	44	11	0	0	0	55
Anorexia	45	10	0	0	0	55
Diarrhea	45	10	0	0	0	55
Stomatitis	45	10	0	0	0	55
General fatigue	46	9	0	0	0	55

Only three patients developed grade 3 adverse reactions, and they recovered by withdrawal of S-1

T. Bil, serum total bilirubin; WBC, white blood cell count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, hemoglobin

Operation

Among the 55 patients, 3 did not undergo operation, because of the refusal of 2 and because the other patient was found to have pulmonary metastases. Fifty-two patients underwent laparotomy, including the 3 patients who received one course of the neoadjuvant chemotherapy. Among the 52 patients, 6 patients did not undergo resection (5, peritoneal dissemination; 1, unresectable invasion of the duodenum and pancreatic head). Ten patients underwent palliative resection of the main tumor (2, peritoneal dissemination; 6, positive cytological examination of abdominal washing; 1, unresectable tumor with severe invasion to the retroperitoneum; 1, widespread lymph node metastases). The other 36 patients underwent curative total gastrectomy with various combined organ resections (25, spleen; 1, distal pancreas + spleen; 5, gallbladder; 2, left adrenal gland; 2, transverse colon; 1, pancreatic head and duodenum). Among the 36 patients, only 1 had D1 lymph node dissection and the remaining 35 had D2 or more lymph node dissection.

The mean operation time for curative resection was 214 min (range, 130–460 min) and that for noncurative resection was 295 min (range, 150–401 min). The mean blood loss for curative resection was 586 ml (range, 30–1815 ml) and that for noncurative resection was 872 ml (range, 230–2100 ml).

Among the 46 patients who underwent resection, postoperative complications were observed in 11 patients (23.9%). Overall, there was no mortality and there were no serious complications. The actual complications were as follows: wound infection, deep vein thrombosis, pancreatic fistula, anastomotic ulcer, pneumonia, pulmonary embolism, sepsis, abdominal abscess, liver function disorder, and mycotic uveitis.

Changes in the T, P, and CY (cytological examination of the abdominal washing) factors before and after neoadjuvant chemotherapy are shown in Tables 2 and 3. With regard to the T factor, a response was observed in 14 patients; however, cancer progression was observed in 8 patients. In regard to the P and CY factors, a response (PR) was observed in only 2 patients; however, 10 showed progressive disease (PD). The other 40 patients showed stable disease (SD).

The pathological therapeutic effects of neoadjuvant chemotherapy were evaluated according the grading described by the Japanese classification of gastric carci-

noma [10] general rules for gastric cancer study: grade 0, 12 patients (26.1%); grade 1a, 19 patients (41.3%); grade 1b, 4 patients (8.7%), and grade 2, 11 patients (23.9%).

At the time of the scheduled analyses (March 2005), 10 patients were still alive without recurrence, 13 were alive with recurrence, and 32 had already passed away. The modes of recurrence were as follows: peritoneal, 17 patients; retroperitoneal, 2 patients; local, 1 patient; lymph node, 1 patient.

Table 2. Changes in T factors before and after chemotherapy

Laparoscopic T		Pathological T
T2:7		T2:11
T3:39	Chemotherapy	T3:37
T4:5		T4:4
Tx:1		

Progression, 8 patients; downstage, 14 patients
Tx, T unknown

Table 3. Changes in P and CY factors before and after chemotherapy

No change or progression (SD and PD)	
P0, CY0→P0,CY0	37 (SD)
P0, CY0→P0, CY1	2 (PD)
P0, CY1→P0, CY1	3 (SD)
P0, CY0→P1	4 (PD)
P0, CY1→P1	4 (PD)
Downstage (PR)	
P0, CY1→P0, CY0	2 (PR)

The survival curves of all patients (n = 55) and the historical controls are shown in Fig. 1. The survival curve of the study arm was better than that of the historical controls; however, the survival rate did not reach the expected rate (2-year survival rate: 59% vs 60%).

With regard to the secondary endpoints, the response rate to the neoadjuvant chemotherapy was 32.6%. The rate of postoperative complications was 23.9%, as against 25.7% in the historical controls. The in-hospital mortality rate was 0% as against 3.5% in the historical controls. The curative resection rate was 80.8%, as against 90.3% in the historical controls.

Discussion

Despite recent advances in chemotherapy and extended surgery, the treatment outcomes of scirrhous gastric cancer, also known as diffuse gastric cancer, linitis plastica, or Borrmann type 4 in the West, have remained very poor because of the aggressive biological behavior of this tumor. Because of failure to improve survival even with aggressive postoperative chemotherapy, neoadjuvant chemotherapy has been applied to patients with resectable or unresectable scirrhous gastric cancer.

To date, the efficacy of neoadjuvant chemotherapy against scirrhous gastric cancer remains to be established because of the lack of well-validated phase II and phase III studies. The first phase II neoadjuvant chemotherapy trial was reported by Takahashi et al., using FAMTX [5]. In their trial, neoadjuvant chemotherapy was shown to be seemingly feasible against scirrhous

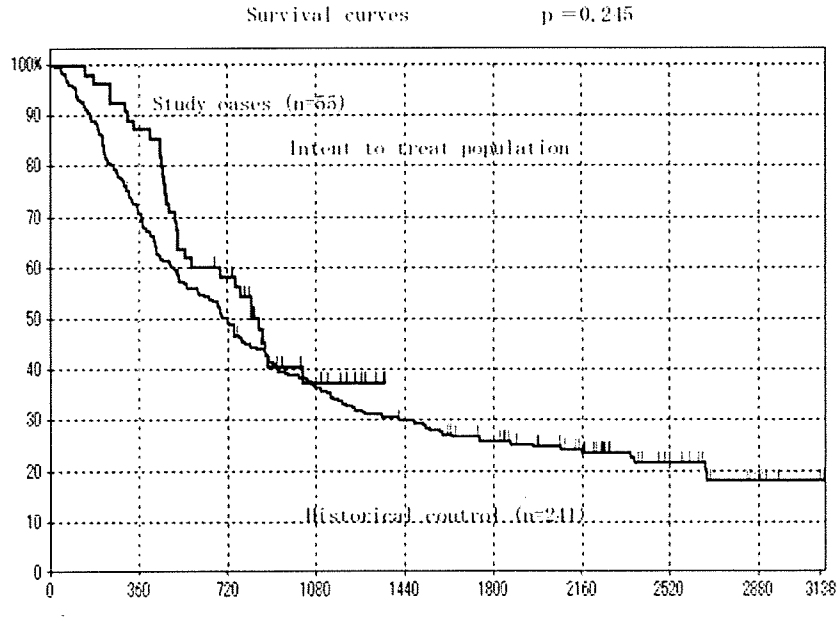

Fig. 1. Survival curves of all patients (n = 55) and the historical controls (n = 241)

gastric cancer, producing a higher resectability rate without any increase in morbidity rate. However, an interim analysis of the 2-year survival rate in 20 patients enrolled in the trial showed no improvement over the survival rate of the historical controls. Myelosuppression was the major cytotoxic effect of the FAMTX regimen, and grade 3 or 4 neutropenia was observed in 14 out of the 20 patients (70%). Eleven of these 14 patients required granulocyte colony-stimulating factor support. The overall response rate was 15% (3 PRs in 20 patients). Eighteen resected specimens showed only marginal histological effects (grades 0-Ib). For these reasons, Takahashi and co-workers discontinued the trial.

Because S-1 showed promising effects when used for neoadjuvant chemotherapy against scirrhous gastric cancer in a pilot study [9], we decided to conduct a phase II trial of S-1 to determine its beneficial effects on survival. Because of the difficulty in excluding patients with peritoneal dissemination by conventional diagnostic imaging procedures such as CT scan and the use of barium enema, we performed laparoscopic examination to identify and exclude patients with peritoneal dissemination.

At the time of starting the phase II trial, laparoscopic examination for cancer staging was still not a common procedure. Thus, we need to standardize this technique using a video for the quality control of the procedure. Regarding the historical controls, it was not possible to submit patients without peritoneal dissemination to laparoscopic examination, for the same reason. Data for previous patients with the same eligibility criteria and without peritoneal dissemination, confirmed by laparotomy, were collected from the participating institutions. Thus, in the present study, the control group was not identical to the study group.

Neoadjuvant chemotherapy using S-1 was safe and feasible when compared with other toxic combination chemotherapies. Only a few grade 3 and no grade 4 adverse reactions resulting from cytotoxicity were observed, and no specific morbidity and no increases in morbidity and mortality rates were seen when compared with the data in the historical controls.

Patients with positive cytological examination results were included in this phase II trial. This is the reason why we expected the S-1 neoadjuvant chemotherapy to produce negative cytological examination results. However, the results of the trial, in terms of cytological findings, were not very promising. Without considering the cytological examination results, it can be observed that although there was no significant difference in the curative resection rate between the study group and the historical control group, the curative resection rate in the study group was lower than the expected rate.

From the viewpoint of the pathological therapeutic effects of chemotherapy, S-1 neoadjuvant chemotherapy showed a much better therapeutic effect than FAMTX.

The survival rate of our study group showed a better curve than that of the historical controls; however, it did not reach the expected rate ($P = 0.245$). On the other hand, combination chemotherapy using S-1 and cisplatin (CDDP) showed a markedly high response rate (76%) in a phase II trial. Therefore, this combination can be considered more promising than S-1 monotherapy for neoadjuvant chemotherapy against scirrhous gastric cancer. The JCOG has also completed the accrual of patients evaluated in the phase II trial of neoadjuvant chemotherapy using the above S-1 and CDDP regimen for resectable scirrhous and more-than-8-cm giant type 3 gastric cancer. Because of the superiority of this regimen over S-1 monotherapy in terms of the response rate and pathological therapeutic effects, the JCOG group has already started a phase III trial to confirm the effectiveness of neoadjuvant chemotherapy using S-1 + CDDP as against extended surgery in patients with scirrhous or large type 3 gastric cancer.

In summary, neoadjuvant chemotherapy using S-1 against potentially resectable scirrhous gastric cancer appears feasible and effective; however, in the present phase II trial, the survival rate of the patients did not reach the expected rate. On the other hand, an S-1 + CDDP regimen is now being tested in a phase III trial by the JCOG group as a more promising neoadjuvant regimen.

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Clinical and Histopathological Features of Remnant Gastric Cancers, After Gastrectomy for Synchronous Multiple Gastric Cancers

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Background: Remnant gastric cancers have been extensively investigated; however, little has been unveiled the features of remnant gastric cancers with regard to the existence of synchronous multiple lesions. We evaluated the clinicopathological features of remnant gastric cancers, after initial gastrectomy for both single and multiple gastric cancers.

Methods: We retrospectively analyzed 3,042 patients diagnosed with gastric cancers who underwent gastrectomy. Of these, total gastrectomy cases were excluded, and remaining 2,120 cases were investigated.

Results: Among the 2,120 patients, 1,967 patients were histopathologically diagnosed with solitary lesion and 153 patients with multiple lesions. The incidence of remnant gastric cancers was higher in patients with multiple lesions at initial surgery than those with solitary lesion ($P < 0.05$). Moreover, remnant cancers developed within shorter duration of follow-up after treatment of synchronous multiple lesions compared to those that developed after treatment of solitary lesions ($P = 0.05$). Among the patients treated for synchronous multiple lesions, distance from the oral margin was a potential risk factor for the development of secondary cancers in the remnant stomach.

Conclusions: Patients with synchronous multiple gastric cancers are more susceptible to the development of secondary cancers in their remnant stomach. These patients need careful follow-up after initial gastrectomy.

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KEY WORDS: **remnant gastric cancer; multiple gastric cancer; gastrectomy**

INTRODUCTION

In the 1950s, Moertel et al. [1] reported that the incidence of synchronous multiple gastric cancers ranged from 0% to 3.4% in surgically resected specimens, thereafter, due to the advance in diagnostic strategy, series of reports demonstrated that multiple gastric cancers were found in ~4–7% of surgically resected cases [2]. In 1990, Kosaka [3] reported that synchronous multiple gastric cancers were observed in 5.8% of cases, and evaluation using serial sections of the whole stomach revealed that synchronous multiple gastric cancers were noticed in 13.2% of cases, thus, suggesting a higher incidence of latent lesions. Indeed, consistent with this report, Esaki [4] demonstrated the histological evaluation using serial sections of the whole stomach, and found that multiple gastric cancers were present in the resected stomach in 14.6% of cases. These observations suggested that although the incidence of multiple gastric cancers on macroscopic examination of the specimens was <10%, this figure would rise to ~14% if they were also studied using serial sections of the whole stomach.

Remnant gastric cancers are reported to be caused by multiple factors, and their incidence, pathological features, and potential mechanisms have been extensively investigated [5–7]. However, there have been few reports demonstrating the clinical and histopathological features of remnant gastric cancers with regard to the existence of synchronous multiple lesions.

In this study, we examined the clinical and pathological features of remnant gastric cancers after initial gastrectomy for synchronous multiple gastric lesions, and we discussed the potential optimal clinical approaches to the disease.

PATIENTS AND METHODS

Patients

Patients who underwent surgery for gastric cancers were analyzed retrospectively from the database of the Division of the Clinical Pathology in the National Cancer Center Hospital East, from October 1993 to July 2008, after approval from The Investigational Review Board in National Cancer Center. Preoperative diagnosis was based on preoperative imaging studies, including with upper gastrointestinal studies, endoscopy, and conventional cross-sectional imaging studies (computed tomography). Histological evaluation of endoscope-guided biopsy specimens was performed in all cases. Synchronous multiple gastric cancers were defined according to the criteria reported by Moertel et al. [1], which are as follows: (1) each lesion is histologically malignant, (2) each lesion is separated from another by the normal gastric tissue, and (3) each lesion is not the result of a local extension or metastasis of another lesion. If the depth of cancer infiltrations is the same in two or more lesions, the one extending over the greatest area is regarded as the main lesion, and the other lesions are regarded as accessory lesions. In this study, remnant gastric cancers were defined as either of the following two types: (1) cancer in the remnant stomach detected 10 years or more after the initial gastric surgery, and (2) cancer in the remnant stomach that could be identified as a new development not related to the primary lesions [8,9].

Additional Supporting Information may be found in the online version of this article.

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The patients' medical records were reviewed for the preclinical stage of the disease, surgical procedures, histopathological findings of the lesions, incidence of remnant gastric cancers, and the outcome.

Histopathological and Immunohistochemical Analysis

The resected stomachs were processed in the usual manner. Briefly, resected stomachs were opened along the greater curvature, placed on a wooden board with the mucosa facing up, and fixed with a 10% formalin solution for at least 24 hr. Several portions, including the distal and proximal stump as well as both main and sub-lesions, were sliced to a thickness of 5 mm and histologically examined. For exploration of multiple lesions, resected specimens were macroscopically evaluated before and after fixation, along with preoperative evaluation, using endoscopy and upper gastrointestinal studies. Furthermore, these examination methods were performed to identify suspected sub-lesions. For the histopathological evaluation, at least two specialized pathologists evaluated all stained slides of the lesions.

The gastric cancers were evaluated according to the General Rules for the Gastric Cancer Study of the Japanese Research Society for Gastric Cancer [10]. A macroscopic pattern of early gastric cancers was classified, according to the Japanese Society for Gastroenterology Endoscopic Criteria, as type I (protruded), type IIa (elevated), type IIb (flat), type IIc (depressed), and type III (excavated). In this study, the histological pattern of gastric cancers were classified into two types; well and moderately differentiated carcinoma were recorded as differentiated type, whereas poorly differentiated or undifferentiated carcinoma were recorded as undifferentiated type [11].

Statistical Analysis

Statistical differences between the two groups were analyzed using the Chi-square test and the Mann–Whitney *U*-test. Univariate and multivariate analyses were performed to evaluate the significance of the clinical and histopathological parameters. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Incidence and Clinicopathological Features of Multifocal Gastric Cancers

From October 1993 to June 2008, 3,042 patients with gastric cancers underwent gastrectomy at the National Cancer Center Hospital East. Of these, 2,776 patients (91.3%) were histologically diagnosed with a solitary lesion, whereas the remaining 266 patients (8.7%) were diagnosed with synchronous multiple gastric cancers in which more than two gastric cancer lesions were found in the resected stomach. Among the 2,776 patients who were histologically diagnosed with a solitary lesion, 809 patients (29.1%) underwent total gastrectomy. On the other hand, among 266 patients who were histologically diagnosed with synchronous multiple cancers, 113 patients (42.4%) underwent total gastrectomy. For the evaluation of the remnant gastric cancers in this study, we excluded the patients who underwent total gastrectomy, and focused on the remaining 1,967 patients with a solitary lesion and 153 patients with multiple lesions. Clinical and histopathological features of the 153 patients with synchronous multiple cancers are shown in Table I. In patients with multiple gastric cancers, the mean age at diagnosis of initial lesions was 63.2 years and significantly older than those with solitary lesion (57.6 years); 109 patients were men and 44 patients were women. The mean number of lesions was 2.23 per patient. The histological types of main lesions were consistent with those of the sub-lesions in 109 patients (71.2%). Of these, the differentiated type was present in 91 patients (59.4%), and the undifferentiated type was present in 18 patients (11.6%), and

TABLE I. Patients' Characteristics of the Initial Lesions in Patients With Gastric Cancers

	Solitary (n = 1,967)	Multiple (n = 153)	*P*-value
Age (mean, years)	57.6	63.2	<0.05
Gender (M:F)	2.1:1	2.5:1	n.s.
Mean no. of lesions	—	2.23/case	—
Consistency with histological type of the main lesion (total)	—	71.2%	—
Histological type			<0.01
Differentiated-type	43.7%	59.4%	
Undifferentiated-type	51.3%	11.6%	
Average distance between the lesions	—	28.5 mm	—
Location of main lesion			n.s.
The upper third of the stomach	13.5%	6.5%	
The middle third of the stomach	42.5%	51.0%	
The lower third of the stomach	38.6%	42.5%	

Differentiated-type, well- or moderately-differentiated adenocarcinoma; undifferentiated-type, poorly differentiated adenocarcinoma, undifferentiated carcinoma.
Statistical significance between both groups was analyzed by Chi-square test and Mann–Whitney *U*-test.

distribution of the histological types was significantly different compared with the cases with solitary lesion. The average distance between the main lesion and sub-lesions was 28.5 mm. Main lesions were located in the upper third of the stomach in 10 cases (6.5%), in the middle third of the stomach in 78 cases (51.0%), and in the lower third of the stomach in 65 cases (42.5%).

Supplemental Table I shows the comparison of the histopathological features of the initial lesions (main lesion vs. sub-lesion) among the patients who underwent gastrectomy for multiple lesions. The average tumor size of the main lesion and the sub-lesion was 37.9 and 13.8 mm, respectively ($P < 0.05$). Moreover, 30.7% of the main lesions were histologically diagnosed as undifferentiated carcinoma (poorly differentiated adenocarcinoma or undifferentiated carcinoma), whereas 19.1% of sub-lesions were undifferentiated carcinoma ($P = 0.13$). Furthermore, 73.4% of main lesions were histopathologically found to be mucosal or sub-mucosal lesions, whereas 96.7% of sub-lesions were mucosal or sub-mucosal lesions ($P < 0.05$). Finally, histological examination revealed that 23.7% of main lesions and 4.1% of sub-lesions showed lymph infiltrations ($P < 0.05$), 33.5% of main lesions and 6.9% of sub-lesions showed vascular invasion ($P < 0.05$), and 18.8% of main lesions and 1.3% of sub-lesions showed perineural invasions ($P < 0.05$).

Incidence and Histopathological Features of Remnant Gastric Cancers

Among 153 patients with synchronous multiple gastric cancers, 7 patients (4.5%) developed a secondary lesion in their remnant stomach, whereas 9 out of 1,967 patients (0.45%) developed a secondary lesion in their remnant stomach after initial gastrectomy for a solitary lesion. At initial gastrectomy, the incidence of remnant gastric cancers was significantly higher in patients with multiple cancers compared with those with solitary cancer at initial gastrectomy ($P < 0.05$; Fig. 1A).

As shown in Figure 1B, the average duration of follow-up for the detection of the remnant gastric cancers was 2.12 years in patients with multiple lesions and 3.93 years in patients with a solitary lesion ($P = 0.051$). Clinical and histopathological features of the initial lesions in patients who developed remnant gastric cancers during follow-up are shown in Table II. There were no significant differences between the solitary lesions and multiple lesions in terms of mean age

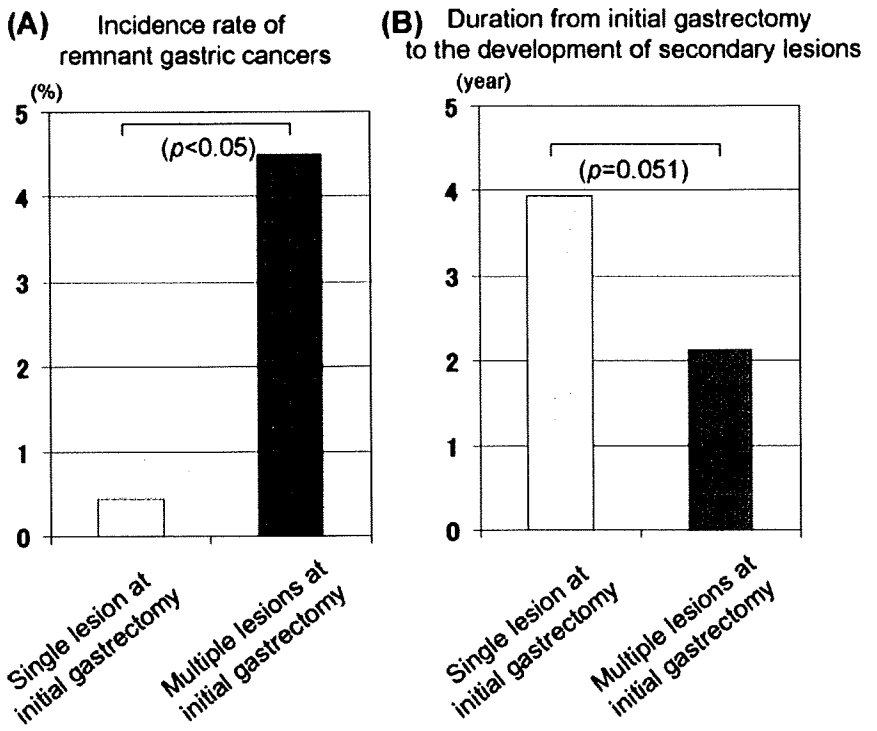


Fig. 1. Comparison of the incidence and interval of remnant gastric cancers after gastrectomy between patients with solitary and patients with synchronous multiple cancers as initial lesions. **A**: The incidence of remnant gastric cancers was significantly higher in patients with synchronous multiple gastric cancers compared to those with solitary lesions (Chi-square test). **B**: The average postoperative interval until detection of secondary cancers in the remnant stomach was shorter in patients with multiple gastric cancers (Chi-square test).

(61.8 years vs. 69.4 years; $P=0.11$), gender (6:3 vs. 6:1; $P=0.77$), population of the undifferentiated lesions (poorly differentiated carcinoma and undifferentiated carcinoma) (44.5% vs. 42.9%; $P=0.78$), histological depth of the invasion (sub-mucosal layer) (55.5% vs. 85.7%; $P=0.14$), mean tumor size (34.8 mm vs. 24.5 mm; $P=0.24$), lymph infiltration (37.5% vs. 15.7%; $P=0.32$), vascular invasion (44.5% vs. 15.3%; $P=0.34$), perineural invasion (22.2% vs. 7.9%; $P=0.53$), percentage of lymph node metastasis (11.1% vs. 0%; $P=0.89$), and location of the main lesions at initial surgery (85.7% vs. 92.3%; $P=0.68$). Table III shows the comparison of the histopathological features of secondary gastric cancer lesions in the remnant stomach. There were no significant differences between remnant gastric cancers that occurred after surgery for a solitary lesion and synchronous multiple lesions in terms of histological differentiation (55.6% vs. 14.3%; $P=0.14$), depth of tumor invasion (sub-mucosal layer) (44.4% vs. 85.7%; $P=0.14$), average size of the tumor (24.4 mm vs. 23.5 mm; $P=0.82$), and percentage of lymph node metastasis (22.2% vs. 0%; $P=0.56$). However, in patients who underwent initial gastrectomy for multiple lesions, a higher percentage of remnant gastric cancers were of the differentiated type and less deeply infiltrated the stomach wall, with no lymph node metastasis.

TABLE II. Comparison of the Clinicopathological Features of the Initial Lesions Which Developed Cancer in the Remnant Stomach During Follow-Up

Variables	Solitary lesion (n = 9)	Multiple lesions (n = 7)	*P*-value
Age (mean, years)	61.8	69.4	0.11
Gender (M:F)	6:3	6:1	0.77
Differentiation (undifferentiated-type)	44.5%	42.9%	0.78
Depth (m or sm)	55.5%	85.7%	0.14
Tumor size (mean)	34.8 mm	24.5 mm	0.24
Lymph infiltration	37.5%	15.3%	0.32
Vascular invasion	44.5%	15.3%	0.34
Perineural invasion	22.2%	7.69%	0.53
% of pN(+) case	11.1%	0%	0.89
Location (M, ML)	87.5%	92.3%	0.68

Undifferentiated-type, poorly differentiated adenocarcinoma, undifferentiated carcinoma; m or sm, mucosal or sub-mucosal layer of the stomach wall; M, the middle third of the stomach; ML, the lower two-thirds of the stomach.
Statistical significance between both groups was analyzed by Chi-square test and Mann–Whitney *U*-test.

TABLE III. Comparison of the Histopathological Features of the Secondary Cancers on the Remnant Stomach During Follow-Up

Variables	Solitary lesion (n = 9)	Multiple lesions (n = 7)	*P*-value
Differentiation (differentiated-type)	55.6%	14.3%	0.14
Depth of invasion (m or sm)	44.4%	85.7%	0.14
Tumor size (mean)	24.4 mm	23.5 mm	0.82
% of pN(+) case	22.2%	0%	0.56

Differentiated-type, well- and moderately-differentiated adenocarcinoma; m or sm, mucosa or sub-mucosal layer of the stomach wall.
Statistical significance between both groups was analyzed by Chi-square test and Mann–Whitney *U*-test.

Evaluation of Potential Risk Factors for the Development of Remnant Gastric Cancers After Gastrectomy for Multiple Lesions

Results of our study suggested that patients with multiple gastric cancers are more susceptible to the development of secondary gastric cancers in the remnant stomach (Fig. 1). Thus, to address the potential risk factors for the development of secondary lesions, we examined the differences in the clinical and histopathological features (differentiation of cancer, depth of invasion, size of the lesion, lymph infiltration, vascular invasion, perineural invasion, number of lymph nodes dissected, percentage of the cases with lymph node metastasis, macroscopic type, distance from the margin, location of tumors) of the primary lesions in patients with multiple gastric cancers at initial gastrectomy who developed remnant cancers and those who did not. As shown in Table IV, results of the univariate analysis revealed that there were no statistically significant differences in the percentage of poorly differentiated cancers, histopathological invasion of the lesion, size of the main lesion, percentage of lymph infiltration, percentage of vascular invasion, percentage of perineural invasion, and lymph node metastasis, between patients with and without development of secondary lesions. However, the margin to the oral side of stomach was significantly shorter in patients who developed secondary lesions (40.9 mm vs. 17.9 mm, $P = 0.03$). Furthermore, in patients who developed remnant gastric cancers, a higher percentage of lesions were located in the middle third of the stomach, and the location of the initial lesions (including main and sub-lesions) were significantly different compared to cases with no remnant gastric cancers ($P = 0.048$; Table IV, Fig. 2).

Multivariate analysis revealed that the margin to the oral side of the stomach at initial gastrectomy is a possible indicator for predicting the development of remnant gastric cancers after gastrectomy for synchronous multiple lesions ($P = 0.049$, 95% confidence interval (CI); 0.26–0.97).

DISCUSSION

The incidence of synchronous multiple gastric cancers is reported to be about 4–8%, using standard histopathological analysis of surgically resected specimens [3,12,13]. Several reports have indicated that the incidence of multiple gastric cancers has been increasing in recent years. In particular, studies that involved histopathological exploration of serial sections of the whole stomach showed a higher detection rate of multiple gastric cancers [3,4], which suggests a high frequency of coexistent latent lesions in surgically resected specimens. Detection of multiple gastric cancers could be influenced by several factors, including the method of histopathological analysis. Improvement in diagnostic devices is another important factor contributing to the current higher incidence in detection of multiple lesions.

Clinical and histopathological features of synchronous multiple gastric cancers have been reported sporadically [3,13,14], and it has been demonstrated that multiple gastric cancers are more frequently observed in elderly, predominantly male, patients [12,14]. Consistent with these observations, we found that patients with multiple gastric cancers were relatively old men compared to patients with a solitary lesion. Furthermore, in the present study, most of the lesions in patients with multiple gastric cancers were histopathologically confined to the mucosa or sub-mucosa, and did not infiltrate beyond the sub-mucosal layer of the stomach. These clinicopathological characters of multiple gastric cancers can be understood in several ways. Previous studies of histopathological examinations demonstrated possible associations for the initiation of multiple gastric cancers with intestinal metaplasia of the gastric mucosa [15]. Mai and Takagi [16] investigated the patterns of intestinal metaplasia and the histological type of stomach cancers, and demonstrated that synchronous multiple gastric cancers were frequently found as differentiated adenocarcinomas and were associated with the condition of a diffuse extensive type of intestinal metaplasia. Since a high incidence of intestinal metaplasia is usually observed in the stomach of elderly males [17–19], it is reasonable to assume that patients with multiple gastric cancers are most commonly found among this sub-group. The present study revealed that 71.2% of main lesions in synchronous multiple gastric cancers were consistent with the histological type of sub-lesions, which is compatible with previous observations [20]. This result shows that about 30% of sub-lesions have different histological type from that of main lesions, suggesting that several other factors are involved in the formation of sub-lesions although intestinal metaplasia may be important in the initiation of multiple cancers.

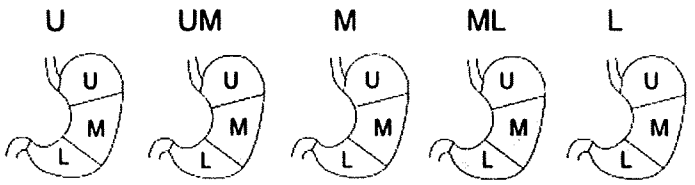
Cancer in the remnant stomach is the focus of much attention not only as a typical model of carcinogenesis, but also from the diagnostic aspect of the lesion. As a result of improvements in outcomes for gastric cancers, more attention to the possibility of formation of remnant gastric cancers is needed during follow-up after initial gastrectomy. Notably, together with advances in diagnostic modalities, the incidence of remnant gastric cancers is reported to be increasing, and the current incidence is ~0.5–1.7% [21–23]. On the other hand, few reports have demonstrated the occurrence rate or clinicopathological characters of remnant gastric cancers that developed after gastrectomy for multiple gastric cancers. Of these, the largest series

TABLE IV. Comparison of the Clinicopathological Features of the Initial Lesions Between the Cases With Or Without Remnant Gastric Cancers Among the Patients With Synchronous Multiple Lesions

Variables	Remnant cancer (−)	Remnant cancer (+)	*P*-value (univariate)	*P*-value (multivariate)
Undifferentiated-type	35.3%	53.8%	n.s.	—
Depth (m or sm)	85.8%	84.6%	n.s.	—
Size of the lesion	24.3 mm	24.6 mm	n.s.	—
Lymph infiltration	12.6%	15.4%	n.s.	—
Vascular invasion	18.8%	23.1%	n.s.	—
Perineural invasion	8.3%	7.7%	n.s.	—
No. dissected LNs	36.7	39.5	n.s.	—
% of pN(+) case	11.1	0.0	n.s.	—
Macroscopic type (type 0-IIc)	68.6%	76.9%	n.s.	—
Distance from margin (mean)	40.4 mm	17.9 mm	0.03	0.049 (0.26–0.97)
Location of the lesion on the middle two-thirds of stomach	37.6%	85.7%	0.048	n.s. (0.38–1.39)

Undifferentiated type, poorly differentiated adenocarcinoma, undifferentiated carcinoma; m or sm, mucosal or sub-mucosal layer of the stomach wall; type 0-IIc, early gastric cancer with depressed type of endoscopic finding.
Statistical significance between both groups was analyzed by Chi-square test and Mann–Whitney *U*-test.

Comparison of location of the initial lesions
between the cases with or without remnant gastric cancers
among the patients that underwent gastrectomy for multiple lesions



Area	U	UM	M	ML	L	*p*-value
No remnant Cancer	6(4.3%)	5(3.5%)	42(29.8%)	63(44.7%)	24(17.7%)	0.048
Remnant Cancer	0(0%)	0(0%)	6(85.7%)	1(14.3%)	0(0%)	

Fig. 2. Comparison of the location of initial lesions between patients with and without remnant gastric cancers, among the patients who underwent gastrectomy for multiple lesions. The distribution of initial lesions was significantly different in patients with and without remnant lesions (Chi-square test).

from a Japanese group showed that the incidence of remnant gastric cancers after gastrectomy for solitary gastric cancers was 1.7%, whereas that after surgery for synchronous multiple lesions was 4.7% [20]. Results of our study are consistent with this report; our results add to the previous literature because we demonstrated that the proximal surgical margin is a potential indicator to predict the formation of remnant gastric cancers after gastrectomy for multiple lesions. Furthermore, the present study found that in patients with remnant gastric cancers, the distribution of initial lesions was different from that of the initial lesions in patients without remnant cancers. More than 80% of the lesions in patients with remnant cancers were located in the middle third of the stomach, whereas 60% of lesions in patients without remnant cancers were found in the lower two-thirds of stomach. These results suggest that although no lesions were found in the upper third of the stomach, a higher percentage of multiple cancers tended to be present in the oral side of the stomach in patients with subsequent remnant lesions. This speculation, based on our results which showed a possible association between the oral margin and the potential risk of remnant gastric cancers, seems to be compatible with evidence from previous investigations into the clinical and histopathological aspects of remnant gastric cancers.

We did not examine the area of intestinal metaplasia, nor did we investigate the correlation between the fields of intestinal metaplasia. However, it is reasonable to assume that if the metaplastic area was diffusely extended in the oral direction of the stomach, the mucosa would be more susceptible to the development of a secondary lesion in the proximal area of the stomach. Therefore, there is a high possibility that these lesions would be close to the proximal margin of the stomach. Indeed, to support these speculations, several Japanese investigators have demonstrated that the diffuse type of intestinal metaplasia was found in about 80% of patients with synchronous multiple gastric cancers compared to 40–50% of patients with solitary cancers [15,16,18]. Since the concept of "field cancerization" has been postulated to explain the formation of multifocal gastric cancers [24–26], we should be more cautious in our approach to patients with synchronous multiple gastric cancers, particularly elderly males with diffuse type of intestinal metaplasia. The present study further indicated that although there were no significant differences, a higher percentage of remnant gastric cancers, in patients who underwent gastrectomy for multiple lesions, were of the differentiated type and less deeply infiltrated the stomach wall, with no lymph node metastasis. Thus, postoperative follow-up should be adequately planned to fully examine the remnant stomach, and endoscopic treatment should be considered as a useful option to resect secondary lesions in patients undergoing initial gastrectomy for multiple lesions.

Our study had several limitations. Some patients may have been excluded from analysis because of the lack of complete information about the postoperative findings of endoscopic examination. Endoscopy is the indispensable examination for the follow-up and occasionally the removal of secondary lesions in the remnant stomach; therefore, excluded information could have biased our observations. Moreover, we excluded the cases of total gastrectomy in this study. By excluding all patients that underwent total gastrectomy, the pathological contributions to the development of remnant gastric cancer could have biased. Furthermore, our study covered an almost 15-year period, during which preoperative diagnostic accuracy and postoperative follow-up regimens were different. However, histopathological explorations were consistently performed in the study, which may even be considered a strong point of the study.

In conclusion, the results of our study indicate the following: (1) Patients with synchronous multiple gastric cancers are at potential risk of developing secondary lesions in their remnant stomach after initial surgery. Furthermore, since a series of observations demonstrated that 20–30% of synchronous sub-lesions were detected during histopathological evaluation, we need to be more careful in the preoperative evaluation of these patients. (2) Moreover, in patients with multiple cancers, the supposed risk of secondary lesions is estimated to be around 3–4% in the remnant stomach. Therefore, intense postoperative follow-up is important, and total gastrectomy may be the alternative option in the case with adequate surgical margin cannot be obtained. (3) Since endoscopic exploration is the most reliable examination to detect these remnant lesions [22], patients with synchronous multiple gastric cancers, who are more susceptible to developing secondary gastric lesions in their remnant stomach, should be regularly checked by this technique. In this study, because remnant gastric cancers were detected 2.12 (mean, Fig. 1) years after initial gastrectomy, postoperative follow-up with intense endoscopic examination is required at least first couple of years after initial gastrectomy. Furthermore, given that most remnant gastric cancers after gastrectomy for multiple lesions are differentiated-type and do not infiltrate deep into the sub-mucosal layer of the stomach (Table III), the importance of endoscopic examination is noteworthy not only for detection but also for the subsequent treatment of these lesions on the remnant stomach.

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原 著

上部胃癌に対する噴門側胃切除の至適適応基準についての検討

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はじめに：我々の施設では過去の胃全摘後標本のリンパ節転移状況の検討から上部胃癌に対する根治術式として，術前評価が胃上部に限局する直径4cm以下の深達度MP以浅の症例を対象に脾温存の噴門側胃切除(以下，噴切)を施行してきた．今回，これらの症例をretrospectiveに検討し，特にリンパ節転移の観点から再評価し，上部胃癌への噴切の至適適応基準を再考することを目的とした．**方法**：1992年7月から2007年9月までに行われた上部胃癌術前深達度評価MP以浅の噴切症例206例を対象とし，その予後，再発様式について検討した．**結果**：病理組織学的検査での深達度はpM：49例，pSM：121例，pMP：28例，pSS：7例，pSE：1例であった．pN1をpSMに10例，pMPに9例，pSSに3例，pN2をpMに1例，pMPに2例認めた．総合所見fStage別の累積5年生存率(他病死含む)はIA：92.5%，IB：86.0%，II：61.5%であった．再発例は5例で縦隔リンパ節再発3例，肺転移1例，脾門部リンパ節再発2例であり，いずれも深達度pMP以深の症例であった．**考察**：今回の検討からリンパ節郭清範囲の十分な根治性を鑑みて，術前深達度評価がMP以深の上部進行胃癌の症例に対しては脾摘を含んだ胃切除を標準とし，縮小手術として脾温存される噴切の適応は術前評価が上部早期胃癌症例までに止めるべきである．

目 的

早期胃癌の割合は近年増加し，1990年以降その割合は55%に達している[1]．また，1980年代から内視鏡的粘膜切除術（endoscopic mucosal resection；以下，EMR)や内視鏡的粘膜下層剥離術(endoscopic submucosal dissection；以下，ESD)など内視鏡的切除術が普及し，その適応拡大に伴って，早期胃癌の手術適応は変化している[2)~6)]．一方で，噴門部および胃上部の早期胃癌については，EMRやESDの内視鏡操作が難しい症例や内視鏡的切除後遺残や脈管侵襲により追加切除が必要となり，外科的切除の適応となる症例も多い．これらの症例は噴門側胃切除（以下，噴切）のよい適応と考えられている．また，リンパ節転移の危険性の低い限局性の進行癌についても臓器機能温存の立場から噴切が施設によっては適用されているのが現状であり，特にこれらの症例に対する噴切の適応は施設間に差がある[7)~10)]．

噴切では，しばしば術後の愁訴や術後臓器機能が問題となるが，癌の手術における最も重要な問題は根治性であり，術前・術中のリンパ節転移診断に基づく至適郭清範囲を確保することである．

当院では開院当初（1992年）から術前評価で早期胃癌（cSM以浅）と診断された胃上部に限局する直径4cm以下の症例を対象として噴切を行ってきたが，2002年に過去の胃全摘症例を検討し，胃上部に限局した病理組織学的深達度MP以浅

Table 1 Patients characteristics

		n = 206
Gender	male/female	163/43
Age	(years；average±SD)	63.5±9.1
Splenectomy	+/−	10/196

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