Table 1 Patient characteristics

Number of patients	1,017
Age (years)	62.9±11.7 (range, 26–91)
Gender	
Male/female	658/359
Body mass index (kg/m^2)	21.7±3.2 (range, 13.1–37.5)
Glasgow prognostic score	
0/1/2	904/92/21
Modified Glasgow prognostic score (mGPS)	
0/1/2	956/40/21
Comorbidity (ASA class)[a]	
1/2/3	743/240/34
Tumor location[b]	
Upper	255
Middle	445
Lower	317
Surgical procedure (laparoscopy-assisted surgery)	
Total gastrectomy	239 (52)
Distal gastrectomy	735 (432)
Proximal gastrectomy	43 (29)
Operation time (min)	231.6±69.1 (range, 103–709)
Blood loss (ml)	181.3±265.9 (range, 0–2,440)
Blood transfusion	
No/yes	991/26
Maximun tumor diameter (cm)	4.5±2.9 (range, 0.3–210)
Differentiation	
Differentiated	447
Undifferentiated	550
Tumor depth (T)[b]	
1/2/3/4	596/126/149/146
Lymph node metastasis (N)[b]	
0/1/2/3	685/182/106/90
Pathological stage[b]	
I/II/III	648/182/187
Complication[c]	163 (16.0 %)

[a]According to the ASA risk classification system

[b]According to the 7th UICC-TNM classification

[c]≥ grade 2 of the Clavien–Dindo classification

Results

Demographics

Table 1 details the characteristics of our study patients with curable gastric cancer (n=1017). The majority of patients were male, had no severe comorbidity, and had normal GPS and mGPS. Fifty-two patients with GPS 1 were included in mGPS 0 because patients with hypoalbuminemia with absence of an elevated CRP concentration were allocated mGPS 0. A remarkable feature of this series was that more than half of the patients were T1N0 and pathological stage (pStage) I and underwent laparoscopic surgery for early gastric cancer. There was no patient with pStage IV gastric cancer in this study because patients with non-curative surgery or with distant metastasis were excluded. One hundred sixty-three patients (16.0 %) had postoperative complications of ≥ grade 2 according to the Clavien–Dindo classification.

Risk Factors for Postoperative Complications

Univariate analysis found no relationship between GPS and postoperative complications (P=0.9289; Table 2). Table 3

Table 2 The relationship between GPS and postoperative complication

	GPS (number of patients)			
	0 (n=904)	1 (n=92)	2 (n=21)	P value
Complications (%)[a]	144 (15.9)	15 (16.3)	4 (19.1)	0.9289

[a]≥ grade 2 of Clavien–Dindo classification

Table 3 Multivariate logistic regression analysis for postoperative complication

Variables	Odds ratio	95 % CI	*P* value
Gender			0.0063
Male	1.73	1.16–2.62	
Female	1.00		
Body mass index (kg/m^2)			0.0259
< 25	1.00		
≥ 25	1.64	1.06–2.50	
Tumor location[a]			0.0002
U	2.07	1.42–2.99	
M/L	1.00		
Blood transfusion			0.0147
No	1.00		
Yes	3.06	1.26–7.26	
Tumor depth[a]			0.0048
pT1/2	1.00		
pT3/4	1.74	1.19–2.54	
Comorbidity (ASA class)[b]			0.0081
1	1.00		
≥ 2	1.66	1.14–2.40	

CI confidence interval

[a] According to the 7th UICC-TNM classification

[b] According to the ASA risk classification system

lists the statistically significant variables by multivariate logistic regression analysis, which revealed a strong correlation between the incidence of postoperative complications and male gender, body mass index (BMI) ≥ 25 kg/m^2, tumor in the upper third of the stomach, blood transfusion, and comorbidity (≥ ASA class 2). Gender, BMI, and comorbidity therefore seem to be more important than GPS as preoperative patient-related risk factors of complications.

Prognostic Factors

The median follow-up time was 35.9 months (range 0.4–69.8 months). The 3-year OS and CS rates among all patients were 91.0 and 93.5 %, respectively. Figure 1 shows the survival curves that represent the relationship between GPS or mGPS and OS ($P<0.0001$) or CS ($P<0.0001$). When we compared the influence of systemic inflammatory response on OS or CS between GPS and mGPS, there were some differences in survival among GPS 0, 1, and 2 patients (Fig. 1a, b), whereas the survival curves of mGPS 0 and 1 overlapped (Fig. 1c, d), suggesting that GPS was reflecting survival more accurately than mGPS in the prognosis of patients with gastric cancer surgery. Consequently, we used GPS for all subsequent analyses. The relationship between clinicopathological characteristics and survival rates is presented in Table 4. Univariate analysis of OS identified the following significant risk factors: age ($P=0.0035$), BMI ($P=0.0009$), and GPS ($P<0.0001$) as preoperative patient-related factors; tumor location ($P=0.0049$), maximum tumor diameter ($P<0.0001$), tumor depth ($P<0.0001$), and lymph node metastasis ($P<0.0001$) as tumor-related factors; and surgical procedure ($P<0.0001$), operation time ($P=$

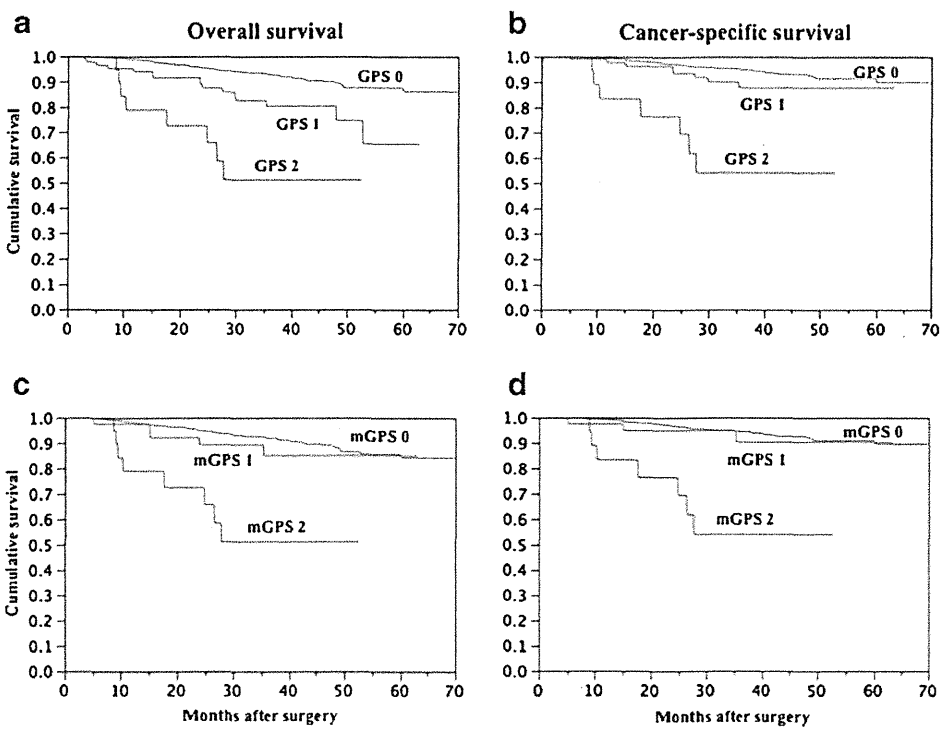

Fig. 1 The relationship between inflammation-based Glasgow prognostic scores (**a**, **b** GPS; **c**, **d** modified GPS) and survivals (**a**, **c** overall survival; **b**, **d** cancer-specific survival) in patients with curable gastric cancer surgery. Survival analysis was performed using the Kaplan–Meier method with the log rank test

Table 4 Univariate analysis of prognostic factors for overall and cancer-specific survival

Variables	*n*	Overall survival		Cancer-specific survival	
		3-y OS	*P* value	3-y CS	*P* value
Age (years)			0.0035		0.2762
< 75	705	92.4		94.0	
≥ 75	312	83.4		90.2	
Gender			0.0900		0.3174
Male	658	89.8		92.8	
Female	359	93.3		94.7	
Body mass index (kg/m^2)			0.0009		0.0131
< 25	838	91.1		92.7	
≥ 25	179	96.7		97.1	
Glasgow prognostic score			< 0.0001		< 0.0001
0	904	92.8		94.8	
1	92	80.5		87.8	
2	21	51.2		54.0	
Comorbidity (ASA class)[a]			0.6791		0.9775
1	743	92.1		93.6	
≥ 2	274	90.1		93.2	
Tumor location			0.0049		0.0048
Upper	255	88.9		89.0	
Middle/lower	762	93.0		94.9	
Maximum tumor diameter (cm)[b]			< 0.0001		< 0.0001
< 4	496	97.0		98.3	
≥ 4, < 8	382	90.4		92.1	
≥ 8	127	76.1		77.4	
Differentiation			0.1924		0.0219
Differentiated	455	93.3		95.6	
Undifferentiated	562	90.8		91.9	
Tumor depth (T)[c]			< 0.0001		< 0.0001
T1/2	772	96.8		98.4	
T3/4	295	79.8		81.0	
Lymph node metastasis (N)[c]			< 0.0001		< 0.0001
N0/1	821	95.9		97.6	
N2/3	196	79.8		75.8	
Surgical procedure			< 0.0001		< 0.0001
Total gastrectomy	239	82.5		84.5	
Distal gastrectomy	735	93.3		96.0	
Proximal gastrectomy	43	95.0		95.0	
Operation time (min)			0.0003		0.0006
< 240	636	94.1		96.0	
≥ 240	381	86.0		89.4	
Blood loss (ml)			< 0.0001		< 0.0001
< 250	788	94.3		96.6	
≥ 250	229	79.8		82.4	
Blood transfusion			< 0.0001		< 0.0001
No	991	92.9		94.1	
Yes	26	57.6		67.6	
Complication			0.0001		0.0007
No	854	92.4		94.6	
Yes[d]	163	83.4		87.3	

3-y OS 3-year overall survival rate, *3-y CS* 3-year cancer-specific survival rate

[a]According to the ASA risk classification system

[b]The data of maximum tumor diameter was missing in the case of 12 patients

[c]According to the 7th UICC-TNM classification

[d]≥ grade 2 of the Clavien–Dindo classification

0.0003), blood loss ($P<0.0001$), blood transfusion ($P<0.0001$), and postoperative complication ($P=0.0001$) as surgical factors. Although most factors with a significant difference on univariate analysis were the same for CS and OS, only the age factor disappeared.

Multivariate analysis revealed that age ≥ 75 years (HR 2.21, $P=0.0029$), GPS 2 (HR 5.23, $P=0.0003$ as compared to GPS 0), tumor in the upper third of the stomach (HR 1.71, $P=0.0172$), lymph node metastasis ≥ pN2 (HR 5.75, $P<0.0001$), and postoperative complication (HR 1.66, $P=0.0370$) were independently associated with OS, whereas GPS 2 (HR 5.07, $P=0.0018$ as compared to GPS 0), tumor in the upper third of the stomach (HR 1.93, $P=0.0137$), and lymph node metastasis ≥ pN2 (HR 11.69, $P<0.0001$) were independently associated with CS (Table 5). GPS 2 was therefore a highly significant predictor for both OS and CS.

Discussion

In the present study, we investigated the impact of a systemic inflammatory response, reflected in GPS, on the prediction of both short- and long-term outcomes after curative resection of gastric cancer. The results showed that GPS predicted both OS and CS independently of other tumor-related factors. On the other hand, GPS was not an appropriate predictor of postoperative complications. BMI and comorbidity, as preoperative patient-related factors, instead better reflected the incidence of complications in curable gastric cancer surgery.

Since Forrest and colleagues [18] first published a scoring system based on the combination of CRP and albumin in patients with inoperable non-small cell lung cancer, there is now increasing evidence for a role of the systemic inflammatory response in predicting survival in various cancers, independent of tumor stage.[25, 29, 30] In gastric cancer, Crumley et al. [13] reported that the GPS predicted CS, independent of tumor stage and treatment received, in patients with inoperable gastro-esophageal cancer. Also, Nozoe et al.[31] demonstrated GPS and tumor stage to be independent prognostic indicators for worse prognosis in patients with curatively resected gastric cancer. The results of our study are consistent with these previous works. However, no reports have fully discussed the significance of GPS in predicting outcome after curable gastric cancer surgery, especially with respect to short-term outcomes. Some studies have related poor nutritional status and elevated CRP to an increased incidence of postoperative complications in esophagogastric cancer patients.[21–23] In addition, Moyes et al. [32] recently reported that, in 455 patients undergoing colorectal cancer surgery, preoperative mGPS was independently associated with an increased risk of developing postoperative infectious complications. One hypothesis, therefore, is that preoperative systemic inflammatory response and the associated malnutrition, reflected by hypoalbuminemia, naturally has a strong influence on the incidence of postoperative complications. Unexpectedly, however, the GPS was not shown to be a risk factor of postoperative complications in our study. In addition, neither component of the GPS, CRP ($P=0.7938$) nor albumin ($P=0.6645$), was associated with the incidence of complications. Dutta et al.[23] compared the

Table 5 Multivariate analysis for overall survival and cancer-specific survival

Variables	Overall survival			Cancer-specific survival		
	HR	95 % CI	*P* value	HR	95 % CI	*P* value
Age (years)						
< 75	1.00					
≥ 75	2.21	1.33–3.55	0.0029			
Glasgow prognostic score						
0	1.00			1.00		
1	1.82	1.00–3.11	0.0499	1.26	0.54–2.56	0.5702
2	5.23	2.30–10.37	0.0003	5.07	1.94–11.41	0.0018
Tumor location[a]						
Upper	1.71	1.10–2.59	0.0172	1.93	1.15–3.18	0.0137
Middle/lower	1.00			1.00		
Lymph node metastasis[a]						
pN0/1	1.00			1.00		
pN2/3	5.75	3.79–8.75	< 0.0001	11.69	6.82–20.87	< 0.0001
Complication			0.0370			
No	1.00					
Yes[b]	1.66	1.03–2.60				

HR hazard ratio, *CI* confidence interval

[a]According to the 7th UICC-TNM classification

[b]≥ grade 2 of the Clavien–Dindo classification

GPS and POSSUM physiology score for predicting postoperative outcomes in patients undergoing curative resection of esophago-gastric cancer and suggested that systemic inflammatory response, as opposed to patient physiology, was a major factor in determining long-term survival, while patient physiology had superior value in predicting postoperative complications. Similar trends were reported in patients with colorectal cancer.[30] Therefore, the results of the present study indicating that BMI and co-morbidity, but not the GPS, remain as significant risk factors of postoperative complications are in agreement with their studies.

It is of interest that GPS reflected the prognosis of patients with curable gastric cancer more accurately than mGPS. The decisive difference between GPS and mGPS is the inclusion of patients with hypoalbuminemia in the absence of an elevated CRP concentration. However, in this study, only 49 (4.8 %) patients had hypoalbuminemia in the absence of an elevated CRP concentration, and this is consistent with the concept that the development of hypoalbuminemia is often secondary to an ongoing systemic inflammatory response.[10, 33] On the other hand, the minor population of GPS 1 patients, who had hypoalbuminemia in the absence of an elevated CRP, suggested that these patients had hypoalbuminemia due to malnutrition, which is a common feature of advanced cancer, so-called cachexia, and has been identified as an independent prognostic factor in patients with gastric cancer.[11, 12, 14] In the present study, indeed the univariate analysis associated both albumin and CRP with OS and CS. However, when we replace GPS with CRP or albumin on the multivariate analysis, only albumin alone was independently associated with both OS (HR 2.36, 95 % CI 1.28–4.15, P=0.0071) and CS (HR 2.22, 95 % CI 1.04–4.33, P=0.0392), and CRP alone did not remain as an independent prognostic factor (data not shown). Therefore, the GPS, which comprises the serum concentrations of CRP and albumin, may enable a better appreciation of the effects of the tumor on both ongoing systemic inflammation and malnutrition.

Our ultimate goal is to improve long-term survival in patients with curable gastric cancer, and, for this purpose, we sought to identify preoperative patient-related factors relevant to the GPS. In this study, we showed that the simply derived inflammation-based GPS is a useful tool for predicting long-term survival in patients with curable gastric cancer surgery. Thus, because the presence of a systemic inflammatory response clearly underlies the recognized relationship between poor nutritional status and poor prognosis, nutritional intervention before surgery should be considered for patients with an elevated GPS due to a state of malnutrition. Furthermore, our finding that postoperative complications were an independent prognostic factor would suggest that controlling the significant risk factors of complications, such as BMI and comorbidity, in addition to nutritional status, has the potential to improve long-term survival in these patients with curable gastric cancer.

Acknowledgments We gratefully acknowledge Shogo Nomura, a biostatistician, M.Sc. (Research Center for Innovative Oncology, National Cancer Center Hospital East, Chiba, Japan), for providing advice on our statistical analysis.

Conflict of interest The authors declare no conflict of interest.

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Phase II Study of Preoperative Chemotherapy With S-1 and Cisplatin Followed by Gastrectomy for Clinically Resectable Type 4 and Large Type 3 Gastric Cancers (JCOG0210)

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Background and Objectives: We conducted a phase II study to evaluate the safety and efficacy of preoperative chemotherapy with S-1 + cisplatin followed by gastrectomy in patients with linitis plastica (type 4) or large ulcero-invasive-type (type 3) gastric cancer.
Methods: Eligibility criteria included histologically proven adenocarcinoma of the stomach; clinically resectable gastric cancer of type 4 or type 3. Patients received two 28-day courses of preoperative chemotherapy of S-1 (80–120 mg/body, p.o., days 1–21) and cisplatin (CDDP; 60 mg/m^2, i.v., day 8). Primary endpoints were completion of protocol treatment and incidence of treatment-related death (TRD).
Results: Among the 49 eligible patients with the median age of 61 years, 36 completed the protocol treatment comprising two courses of preoperative chemotherapy and R0/1 resection (73.5% completion, 80% CI, 63.7–81.7%). One TRD was observed during the first course of chemotherapy. Median survival and 3-year overall survival were 17.3 months and 24.5%, respectively.
Conclusions: Preoperative chemotherapy with S-1 + CDDP followed by gastrectomy is a safe and promising treatment for type 4 and large type 3 gastric cancers. Based on the results of this study, we are now conducting a phase III study (JCOG0501) to confirm the superiority of this treatment.
J. Surg. Oncol. © 2013 Wiley Periodicals, Inc.

KEY WORDS: **gastric cancer; preoperative chemotherapy; type 4 gastric cancer; linitis plastica; type 3 gastric cancer**

INTRODUCTION

Gastric cancer is the second most frequent cause of cancer-related deaths in Japan. Although the incidence of gastric cancer in Japan has decreased in recent years as noted in Western countries, it still has the highest incidence among cancers in Japan [1]. The prognosis of patients with a special type of gastric cancer known as linitis plastica (or Borrmann type 4) is extremely poor. Patients with type 4 are generally excluded from clinical trials due to a much poorer prognosis than other types of gastric cancer [2,3]. The large (<8 cm) ulcero-invasive-type (type 3) gastric cancer has the same biological characteristics as type 4 gastric cancer [4]. Surgery with systematic node dissection and postoperative adjuvant chemotherapy using S-1 is the standard treatment for potentially curable advanced gastric cancer in Japan. However, even extended surgical procedures and postoperative adjuvant chemotherapies have not considerably improved the survival of patients with this subgroup of gastric cancer. Recently, preoperative chemotherapy combined with postoperative chemotherapy in patients with localized gastric or gastroesophageal adenocarcinoma has significantly prolonged survival compared with surgery alone [5]. The combined chemotherapy with S-1 + cisplatin (CDDP) is an attractive regimen for preoperative chemotherapy. In a phase II study using this regimen in patients with metastatic gastric cancer, a high response rate of 76.0% and acceptable toxicities were reported [6]. These results were confirmed in a phase III study for advanced or metastatic gastric cancer where S-1 + CDDP showed a much higher response rate of 54.0% than S-1 monotherapy, which had a 31.1% response rate [7].

To evaluate the efficacy and safety of the preoperative chemotherapy with S-1 + CDDP followed by gastrectomy with D2/3 lymph node dissection for type 4 and large type 3 gastric cancers, the Gastric Cancer Surgical Study Group of the Japan Clinical Oncology Group (GCSSG/JCOG) initiated a multi-institutional phase II study in 2003 (JCOG0210). We hereby present our final results.

Grant sponsor: Ministry of Health, Labour and Welfare of Japan; Grant numbers: 14S-3, 14S-4, H13-Gan-014.

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Received 26 April 2012; Accepted 12 November 2012

DOI 10.1002/jso.23301

Published online in Wiley Online Library (wileyonlinelibrary.com).

PATIENTS AND METHODS

Eligibility Criteria

The eligibility criteria included (i) histologically proven and clinically resectable gastric adenocarcinoma (cN0-2, cM0); (ii) macroscopically, type 3 of ≥8 cm or type 4 (linitis plastica); (iii) esophageal invasion of 3 cm or less; (iv) 20–75 years of age; (v) ECOG performance status 0–1; (vi) no prior chemotherapy, radiation therapy or operation for gastric cancer; (vii) adequate oral intake without any active bleeding or intestinal obstruction; (viii) sufficient organ function (white blood cell [WBC] count ≥3,000 and ≤12,000/mm^3; hemoglobin ≥9.0 g/dl; platelet [PLT] count ≥100,000/mm^3; GOT and GPT less than or equal to two-and-a-half times of the upper limit of the normal range; total bilirubin ≤2.0 mg/dl; creatinine ≤1.5 mg/dl; creatinine clearance ≥60 ml/min); and (ix) written informed consent. The exclusion criteria included (i) synchronous or metachronous (within 5 years) malignancy other than carcinoma in situ; (ii) pregnancy or lactation; (iii) undergoing treatment with a major tranquilizer; (iv) undergoing long-term treatment with steroids; (v) undergoing treatment with flucytosine, phenytoin, or warfarin; and (vi) lung fibrosis, interstitial pneumonitis, bowel obstruction, or ischemic heart disease that requires therapy.

Preoperative Chemotherapy

In this treatment, S-1 was given orally twice daily for the first 3 weeks of a 4-week course. The dose of S-1 administered each time was calculated according to the patient's body surface area as follows: less than 1.25 m^2, 40 mg; 1.25 or greater but less than 1.5 m^2, 50 mg; and 1.5 m^2 or greater, 60 mg. CDDP was given as an intravenous infusion of 60 mg/m^2 on day 8 of each course.

Fourteen to 20 days after the second course of chemotherapy, tumor resectability was assessed.

Surgery

The resection criteria were as follows: (i) R0 resection was possible by gastrectomy with D2/3 lymph node dissection where resectability was assessed comprehensively with CT scan, upper gastroenterological endoscopy and barium meal study, and (ii) sufficient organ function (WBC >3,000/mm^3, PLT count >100,000/mm^3, arterial oxygen pressure in room air >60 torr). Patients who fulfilled those criteria were subjected to surgery between 21 and 34 days after the last administration of chemotherapy. When R0 resection was achieved, no additional treatment was prescribed until the tumor recurred.

Objectives, Evaluation, and Statistical Hypothesis

Primary endpoints were percent completion of protocol treatment and incidence of treatment-related death (TRD). Secondary endpoints were overall survival (OS), response rate, toxicities, and postoperative morbidity and mortality.

The percent completion of protocol treatment was defined as the number of patients in all eligible patients who completed the two courses of preoperative chemotherapy and the R0/1 resection by gastrectomy with extended removal of regional lymph nodes (D2) specified in the Japanese classification of gastric cancer (JCGC) or D2 plus para-aortic nodal dissection (D3). The definition of peritoneal lavage cytology (CY) was also specified in the JCGC. CY is diagnosed from either ascites or peritoneal lavage and was classified as CY1 (positive) and CY0 (negative). R1 resection due to CY1 was included in the numerator of percent completion, but R1 resection due to other causes was excluded. OS was defined as the time from the date of registration to the date of death regardless of cause, and was censored cases at the date of the last follow-up for surviving patients.

As the Response Evaluation Criteria in Solid Tumors cannot be used to evaluate the efficacy on the primary tumor, response evaluation was performed using the upper gastroenterological barium meal study according to the Japanese Gastric Cancer Association (JGCA) classification in this study (Japanese Classification of Gastric Carcinoma) [8].

The pathological response of the primary tumor was assessed and divided into five categories of Grades 0–3, according to the criteria defined by JGCA [8]. Surgical specimens were pathologically evaluated and graded according to the proportion of the tumor affected by degeneration or necrosis, as follows: Grade 0, none of the tumor affected; Grade 1a, <1/3 affected; Grade 1b, ≥1/3 and <2/3 affected; Grade 2, ≥2/3 affected; and Grade 3, no residual tumor. Adverse events during chemotherapy were evaluated by National Cancer Institute—Common Toxicity Criteria Version 2.0 [9].

The planned sample size was 50 patients, which was calculated by SWOG's two-stage design based on the expected percent completion of protocol treatment of 60% and a threshold of 45%, with a one-sided alpha of 10%. Three-year OS was one of the secondary endpoints, which was expected to exceed 15%. The survival curve was estimated using the Kaplan–Meier method and 95% CI of yearly survival was calculated with Greenwood's formula. The number of TRD was monitored regularly and the treatment was considered to be safe if point estimates of TRD did not exceed 5%. Statistical analysis was done with SAS version 9.1 (SAS Institute, Cary, NC).

This phase II study was approved by the JCOG Clinical Trial Review Committee and the institutional review board of each institution involved. Twenty-five institutions of the GCSSG of the JCOG participated in the study.

RESULTS

Between March 2003 and December 2003, 50 patients were enrolled into this study. All patients except 1 were eligible and were followed up for more than 3 years after registration. One patient was judged as TRD by the JCOG Data and Safety Monitoring Committee. Flow diagram of 50 enrolled patients shows in Figure 1. Table I shows patient demographics and tumor characteristics.

Preoperative Chemotherapy and Clinical Response

Of the 49 eligible patients, 43 completed the two courses of chemotherapy defined by the protocol. One patient refused to receive any protocol treatment and five patients did not complete the preoperative chemotherapy due to disease progression in 2, adverse events in 2, and TRD in 1.

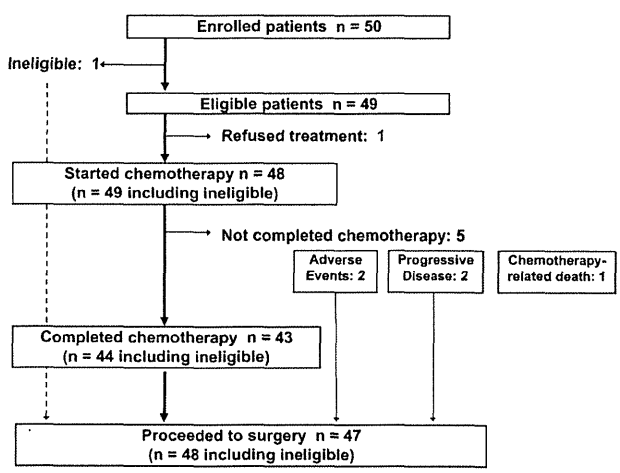

Fig. 1. Flow diagram of 50 enrolled patients.

TABLE I. Patient Demographics and Tumor Characteristics (n = 50)

Age (median, range)	61, 32–75
Sex (male/female)	29/21
PS (0/1)	45/5
Location of the tumor	
Upper third	12
Middle third	26
Lower third	10
Unknown	2
Macroscopic type	
Type 3	20
Type 4	30
Histology (Lauren's)	
Intestinal	9
Diffuse	41

Among the 49 eligible patients, clinical responses by upper gastrointestinal barium meal study were centrally reviewed in 41. Of the 41 patients, 25 were responders, including no complete response and 25 partial responses; 13 had stable disease; and 3 had progressive disease. Thus, the clinical response rate in all the 49 eligible patients was 51.0% (95% CI, 36.3–65.6%).

Surgical Findings and Surgical Pathology

All the 43 patients who completed chemotherapy underwent surgery. Of the five patients who did not complete chemotherapy, four underwent surgery and one did not due to TRD. In total, 47 patients underwent surgery attempting R0 resection.

Of these 47 patients, R0 resection was performed in 31, R1 in 6 due to positive peritoneal cytology (CY1), and R2 in 10 due to unresectable tumors (Table II). Thus, the proportion of R0/1 resections in all the 49 eligible patients was 75.5% (95% CI, 61.1–86.7%).

TABLE II. Pathological Findings in All Resected Patients (n = 47)

Depth of tumor invasion[a]	
T1	4
T2	11
T3	18
T4	7
Unknown	1[b]
JGCA-nodal status[a]	
N0	8
N1	10
N2	16
N3	7
Curability	
R0	31
R1	6
R2	10
JGCA-stage	
IA	3
IB	2
II	7
IIIA	5
IIIB	6
IV	24
JGCA-pathological response[a]	
Grade 0	9
Grade 1a	9
Grade 1b	10
Grade 2	12
Grade 3	1

[a]Six patients with bypass or probe laparotomy were not included.
[b]Not evaluable due to no residual cancer cells.

TABLE III. Surgical Findings in All Operated Patients (n = 47)

Depth of tumor invasion	
T1	0
T2	8
T3	30
T4	9
JGCA-nodal status	
N0	9
N1	11
N2	16
N3	8
NX	3
Peritoneal cytology	
Negative	33
Positive	14
Peritoneal dissemination	
Negative	38
Positive	9
Type of resection	
Total gastrectomy	38
Distal gastrectomy	3
Bypass	1
Probe laparotomy	5
Lymph node dissection[a]	
D2	30
D3	7
Other	4
Number of nodes dissected[b]	
Median, range	67; 24–157
Resection of adjacent organs	
No	11
Yes	36
Resected organs (multiple choices allowed)	
Spleen	30
Gallbladder	23
Pancreas	7
Colon	7
Others	5

[a]Six patients with bypass or probe laparotomy were not included.
[b]Six patients with bypass or probe laparotomy were not included. One patient had no available data.

Among the 43 patients who completed the two courses of preoperative chemotherapy, 36 underwent the R0/1 resection. Therefore, the percentage completion of protocol treatment was 73.5% (80% CI, 63.7–81.7%), which rejected the null hypothesis ($P < 0.0001$).

The surgical findings are shown in Table III. Among the 10 patients who underwent R2 resection, 5 underwent exploratory laparotomy due to peritoneal metastases and 1 underwent gastro-jejunostomy as a palliative measure.

The pathological findings are shown in Table III. The pathological response rate in all the eligible patients, defined by the degeneration/necrosis area $\geq$1/3 (Grades 1b, 2, and 3), was 46.9% (23/49).

Adverse Events During the Chemotherapy

Safety analysis of the chemotherapy was performed in all the treated patients including the ineligible patient. Adverse events during the chemotherapy are shown in Table IV. One patient died due to uncontrollable hemorrhage from the primary tumor. Thus, the proportion of chemotherapy-related mortality was 2.0% (1/49).

Surgical Complications

Surgical complications were assessed in all the operated patients including the ineligible patient, and the results are shown in Table V. Grade 4 pneumonia was observed in two patients. Overall, there was neither surgical mortality nor reoperation.

TABLE IV. Adverse Events During the Chemotherapy in All Eligible Patients (n = 49)

	Grade 1	Grade 2	Grade 3	Grade 4	% Grade 3/4
Laboratory findings					
Leukocyte	15	11	3	0	6
Neutrophil	11	11	7	0	14
Hemoglobin	14	13	5	0	10
Platelet	2	3	0	0	0
Hypoalbuminemia	32	3	0	–	0
Total bilirubin	10	2	0	0	0
AST	7	0	0	0	0
ALT	7	1	0	0	0
Creatinine	3	1	0	0	0
Hyponatremia	19	–	3	0	6
Hypokalemia	8	–	2	0	4
Febrile neutropenia	–	–	0	0	0
Hemorrhage (with Grade 3 or 4 thrombocytopenia)	0	–	1	0	2
Infection (with Grade 3 or 4 neutrophils)	–	–	1	0	2
Objective findings					
Fatigue	14	4	1	0	2
Anorexia	21	9	7	0	14
Diarrhea	5	4	0	0	0
Nausea	20	6	3	0	6
Vomiting	7	2	0	0	0
Stomatitis	8	2	0	0	0

Overall Survival

Survival was examined in the 49 eligible patients. The OS curve is shown in Figure 2. The percentage of 3-year survival was 24.5% (95% CI, 13.6–37.1%) and thus, the lower limit of the 95% CI was slightly lower than the prespecified threshold (15%). Median survival time was 17.3 months (95% CI, 15.1–23.8 months).

The OS curves according to macroscopic type (type 4 and large type 3) are shown in Figure 3, where survival curves are not much different (hazard ratio, 1.20; 95% CI, 0.62–2.32).

DISCUSSION

This phase II study demonstrated that excellent percentage of completion of protocol treatment could be achieved by preoperative chemotherapy with S-1 + CDDP. The completion of protocol treatment of both R0/1 gastrectomy and preoperative chemotherapy was 73.5%, which was much higher than the threshold of 45% and even the expected proportion of 60%. In addition, the proportion of TRD is 2.0% in our study. From the results of the present study, preoperative chemotherapy with S-1 + CDDP followed by gastrectomy was considered to be safe and feasible enough to be followed by a subsequent phase III study for type 4 and large type 3 gastric cancers.

Despite recent advances in chemotherapy and radical surgery, the prognosis of advanced gastric cancer is still unsatisfactory. There is a significant difference in prognosis based upon the Borrmann's macroscopic classification of gastric cancers [10]. The prognoses of patients with large tumors of types 3 and 4 were significantly worse than those of patients with tumors of types 1 and 2. This is not only due to high rate of M1 diseases at the time of surgery but also the high recurrent rate even after curative resection. To treat large type 3 or type 4 gastric cancer, the spleen or the pancreas is often involved by the primary tumor, which would necessitate organ resection; even without involvement, splenectomy is often carried out considering the high frequency of nodal metastasis to the splenic hilum. The recovery from such surgery is often prolonged, and delay or cancellation of adjuvant therapy is not rare. Therefore, a new strategy, such as preoperative or perioperative chemotherapy, is warranted.

A recent randomized controlled trial shows that perioperative chemotherapy with epirubicin, CDDP, and fluorouracil improves OS and progression-free survival in patients with resectable gastric cancer, as compared with surgery alone [4]. However, OS was still unsatisfactory considering the tumor stages of the registered patients.

S-1 is a promising drug for advanced gastric cancer. Recently, it was proven that adjuvant chemotherapy with S-1 monotherapy can significantly improve OS of patients with pathological stages 2 and 3 gastric cancer who underwent R0 resection with D2 lymphadenectomy [11]. Previously, we conducted a phase II study to evaluate the safety and efficacy of preoperative chemotherapy with S-1 monotherapy followed by radical surgery in patients with type 4 gastric cancer

TABLE V. Surgical Complications in All Operated Patients (n = 48)

	No. of patients (%)
Leakage	0 (0)
Pancreatic fistula	4 (8.3)
Cholecystitis	1 (2.1)
Peritoneal abscess	3 (6.3)
Pneumonia	2 (4.2)
Atelectasis	1 (2.1)
Wound infection	3 (6.3)
Stomal stenosis	0 (0)

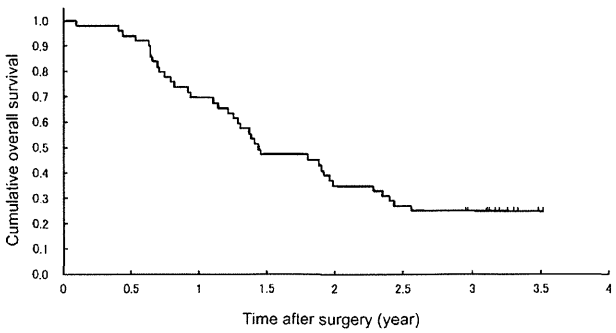

Fig. 2. Kaplan–Meier overall survival curve for the 49 eligible patients.

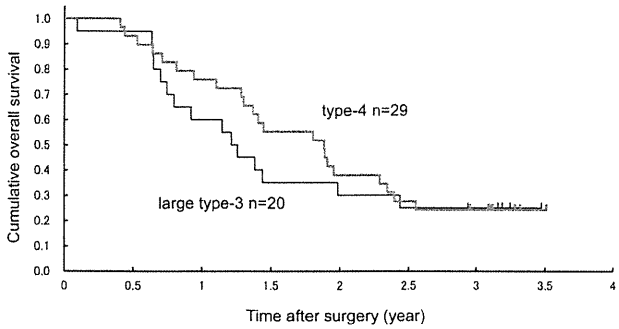

Fig. 3. Kaplan–Meier overall survival curve according to macroscopic type (type 4 and large type 3) for the 49 eligible patients.

(JCOG0002) [12]. JCOG0002 revealed that the response rate was as low as 32.6%, although the toxicity of the chemotherapy and the surgical complications were acceptable. The 2-year survival was better than that of the historical controls, but did not reach the expected survival. Therefore, other combination chemotherapies are considered to be more promising than S-1 monotherapy for preoperative chemotherapy against type 4 or large type 3 gastric cancer.

From the viewpoint of chemotherapeutic effects, S-1 + CDDP showed much better effects than S-1 monotherapy. One patient showed complete response. Unlike breast cancer, complete response is relatively rare and the evaluation of the therapeutic effect is carried out by determining the proportion of the primary tumor area showing fibrosis or degeneration. However, whether or not such an evaluation method can predict prognosis is still controversial [13,14].

CPT-11 is another promising drug for advanced gastric cancer. In a JCOG0001 phase II study of preoperative chemotherapy with CPT-11 + CDDP for locally advanced gastric cancer with extensive lymph node metastasis, the toxicities were not very high but the mortality was more than 5% [15]. In the present study, one TRD occurred during the preoperative chemotherapy but the overall mortality was 2.0%, which was lower than that of the JCOG0001 study. In addition, Grade 4 pneumonia was observed postoperatively in two patients, but both were manageable. Compared with CPT-11 + CDDP, S-1 + CDDP showed a much better safety profile and operative morbidity was as low as that in the pure surgical study, JCOG9501 [16].

In the present study, this multimodality treatment achieved a favorable percentage of 3-year survival of 24.5% (95% CI, 13.6–37.1%) for patients with type 4 or large type 3 gastric cancer. Compared to patients with these tumors who were treated with surgery alone even after curative resection, the point estimate of the 3-year survival was high, although the inferior border of the 95% CI was not higher than expected. This might be due to more patients with peritoneal seedings than that estimated before this study.

As a result, 14 of the 47 patients (29.8%) were revealed to have positive peritoneal cytology. Because of the difficulty in excluding patients with peritoneal dissemination by conventional diagnostic imaging procedures, such as CT and the use of barium enema, staging laparoscopy is useful to estimate advanced gastric cancer [17]. As our main objective was to confirm the safety of this preoperative treatment and the high percentage R0 resection, we did not include laparoscopically confirmed M0 in our eligibility criteria. In the ongoing phase III study, however, we apply laparoscopic examination to exclude patients with macroscopic peritoneal seedings.

As the results of this study met our expectations in terms of the primary endpoints, we have started a phase III study (JCOG0501) on large type 3 or type 4 gastric cancer, comparing this preoperative chemotherapy followed by D2 surgery with surgery alone, both of which are followed by postoperative S-1 adjuvant chemotherapy for 1 year. The results of the ongoing phase III study are awaited.

ACKNOWLEDGMENTS

We thank members of the JCOG Data Center and Operations Office for support in data management (Ms. Aya Kimura), helpful comments for manuscript preparation (Dr. Hiroshi Katayama and Mr. Junki Mizusawa), and overseeing the study (Dr. Haruhiko Fukuda).

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特集 傍大動脈リンパ節郭清の意義：婦人科，消化器外科，泌尿器科における意義と課題

進行胃癌に対する傍大動脈郭清の意義と課題

梨本　篤*1　藪崎　裕*1　松木　淳*1

The Significance and Problem of the Abdominal Para-aortic Lymph Node (PAN) Dissection for Advanced Gastric Carcinoma: Nashimoto A*1, Yabusaki H*1 and Matsuki A*1 (*1Department of Surgery, Niigata Cancer Center Hospital)

The clinical significance of the 806 patients who underwent gastrectomy with D2+PAN dissection from 1969 to 2010 was studied. The median operative time was 255 minutes, bleeding volume was 268 g and the median retrieved lymph nodes were 57. The number of patients with positive PAN was 224 (27.8%), and 125 patients (55.8%) were performed R0 operation, whose 5-year survival rate was 13.4% and the median survival time (MST) was 457 days. There were 17 patients who survived more than 5 year and the number of their positive PAN was mostly one or two. The positive rate of each field of PAN was 20.3% in a2-inter region, 28.2% in a2-latero region, and 24.1% in b1-inter region, and 34.4% in b1-latero region, and its 5-year survival rate was 2.1%, 8.7%, 7.5%, 5.5%, respectively.

The clinical significance of 22 patients who underwent recurrent PAN concentrated dissection from 1990 to 2006 was also studied. The number of the positive and retrieved number of PAN was 9 (ranged 1～30), and 16 (ranged 4～31), respectively. An average interval period was 24.5 months from the first surgery to the second surgery and the MST was 24.8 months from the second surgery. After the second surgery, 4 patients survived more than five years, but patients died around 1 year after second surgery. The criteria for dissection of PAN should be strict.

The result of JCOG-9501 denied the prophylactic dissection of PAN. But the dissection of positive PAN after preoperative chemotherapy or dissection of recurrent PAN may be selected as one of the multimodality therapy, when there are other non-curative factors.

Key words: Dissection of abdominal para-aortic lymph node (PAN), Gastric cancer, Recurrence, Survival
Jpn J Cancer Clin **58**(1): 17～24, 2012

はじめに

日本では胃癌に対するリンパ節郭清はD2郭清が標準治療となっている[1]．全国胃癌登録によるとD2郭清による術死率は2%以下であり[2]，専門施設では1%以下であった[3]．1976年にD2+傍大動脈リンパ節（No. 16）郭清の5年生存例が報告され[4]，これを系統的に郭清する手技が確立されていった．専門施設を中心に積極的に拡大郭清が施行されるようになり，その有効性や[5～6]，転移状況や転移陽性症例の予後，郭清に起因した合併症などが検討された[7～8]．No. 16郭清は手術時間，出血量，血圧低下期間，入院期間などを延長させる負の部分があるが，手術関連死亡の増加は認められなかった．同部の転移率は20～35%[9,10]であり，No. 16転移陽性例の5年生存率は11.5～23.1%[5,9,11～13]と報告されている．

JCOG9501（大動脈周囲リンパ節郭清の臨床的意義に関する研究）は深達度がT2（SS）以深で根治切除が可能な進行胃癌に対し標準的D2郭清

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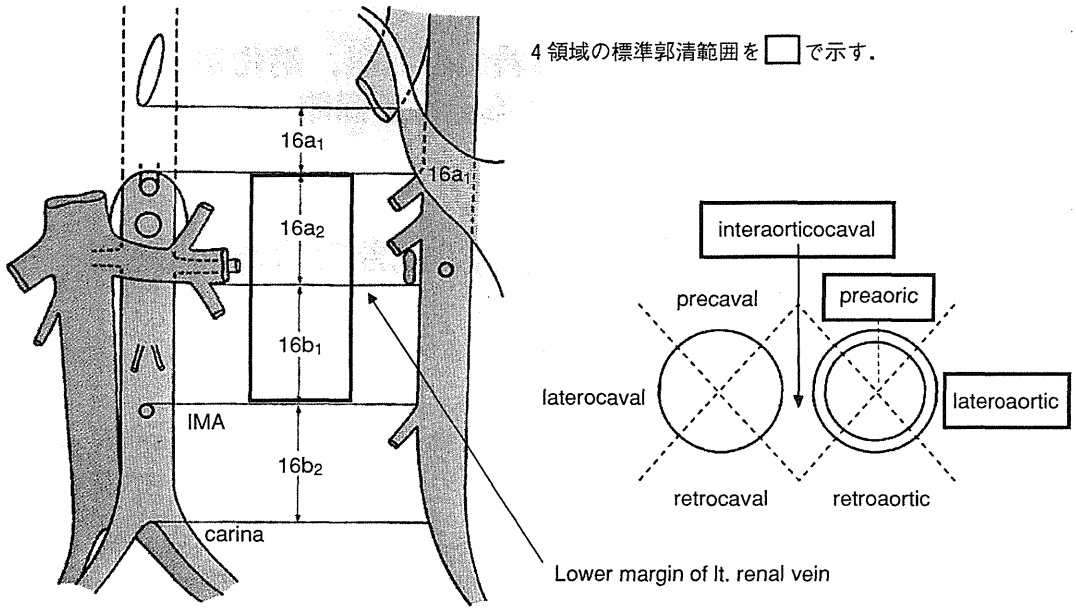

胃癌取扱い規約 第13版より引用

図1　腹部傍大動脈リンパ節郭清範囲

にNo. 16郭清を加えることの是非を問うた無作為比較臨床試験である[14]．その結果，No. 16郭清を加えた拡大リンパ節郭清群は標準郭清群に比べ手術侵襲が大きいものの術後合併症に差がなかった．一方，5年生存率や再発形式にも全く差を認めなかった[15]．これより，進行胃癌に対する予防的No. 16郭清は否定され，ガイドライン[16]でもD2郭清が標準となった．

当院では以前より進行胃癌に対し積極的にNo. 16郭清（**図1**）（原則的にはNo. 16a2/b1）を施行してきたので，その臨床的意義と問題点について検討するとともに若干の文献的考察を加えた．

1 No. 16郭清例

1 対象と方法

1969～2010年末までにcT3/cT4, cN1/cN2胃癌を中心に818例に対し4領域郭清を標準としNo. 16郭清を施行してきた[6,11,17]．No. 16郭清症例が最も多かったのは1989年(61例)であるが，最近は次第に減少してきている（**図2**）．No. 16郭清を伴う胃切除は806例に施行された．

2 成　績

1）臨床病理学的因子

臨床病理学的諸因子を検討すると（**表1**），男女比は521例/285例，年齢中央値62歳，腫瘍最大径7.0 cmであり，局在（U/M/L/UML）は235例/153例/291例/127例，術式は胃全摘453例（56%），幽門側胃切除355例であった．sT因子（T2/T3, T4）は166例/640例（79%），pT因子（T2/T3, T4）は274例/532例（66%）とpT3, pT4が10%以上減少しており，sN因子（sN0/sN1/sN2－）は88例（11%）/177例/541例（67%），pN因子（pN0/pN1/pN2－）は175例（22%）/147例/484例（60%）とpN0が2倍に増加した．肉眼型は限局型42%，浸潤型58%，組織型は分化型43%，未分化型57%であり，割合はほぼ同様であった．手術時間は中央値255分，出血量は268 gであり，郭清リンパ節個数は中央値57個であった．

2）No. 16転移陽性症例

No. 16陽性症例は224例（27.8%）であり，そのうちR0手術を施行できたのは125例（55.8%）であった．その5年生存率は13.4%，MSTは457日であった（**図3**）．

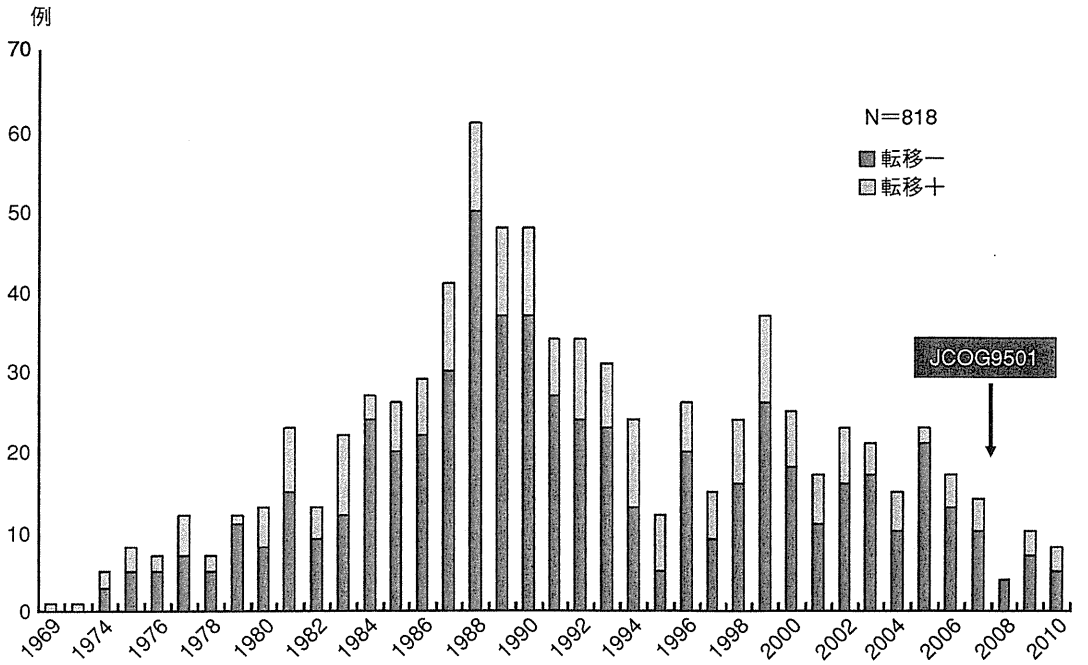

図2　当院における No. 16 郭清例の推移

3）No. 16 領域別転移状況と遠隔成績

No. 16 の領域別転移状況をみると a2-inter 20.3%（47/231），a2-latero 28.2%（116/412），b1-inter 24.1%（12/446），b1-latero 34.4%（19/346）であった．b2-inter 17.1%，b2-latero 28.6%と b2 にも転移例を認めたが，郭清症例数は少なかった（図 4）．主な 4 領域別に No. 16 陽性例の 5 年生存率をみると a2-inter 2.1%，a2-latero 8.7%，b1-inter 7.5%，b1-latero 5.5%であり，a2-inter の成績が最も不良であったが，他の 3 領域にはほとんど差が見られなかった（図 5）．

一方，術前，術中は転移なしと判定したにもかかわらず，組織学的に転移陽性であった割合は a2-inter 4.1%，a2-latero 7.5%，b1-inter 7.1%，b1-latero 8.3%，b2-inter 2.2%，b2-latero 3.1%であった（図 6）．

4）5 年生存例

5 年以上生存した 17 例の詳細を示す（図 7）．最も転移個数が多かったのは手術時 54 歳の女性で，26 個の転移を有していた．再発はなかったが，10 年 7 カ月後に心不全で他病死した．23 個の No. 16 転移を有していた 33 歳の女性は術後 5 年経ってから腹膜再発をきたし，5 年 9 カ月で原病死した．しかし，大多数の 5 年以上生存例は転移個数が 1〜2 個であった．

2 No. 16 再発郭清例

胃癌術後の No. 16 再発に対しては主に化学療法が施行されるが，No. 16 以外に遠隔転移がなく切除可能と判断した症例に限り選択的 No. 16 郭清を施行してきた．

1 対象と方法

1990 年〜2006 年末までの根治術後 No. 16 再発し，化学療法を主体として集学的治療を行った 59 例のうち開腹手術を施行した 22 例を対象とした．No. 16 郭清は標準的な 4 領域郭清ではなく No. 16 の重点的郭清であったが，状況に応じて No. 16b2 より下方のリンパ節も郭清した．根治術後 No. 16 再発の判定基準は CT でリンパ節長径 1.5 cm 以上の No. 16 出現としたが，1.0 cm でもモザイク様構造が確認された場合は再発と判定した[18]．

表1　Clinicopathological characteristics
N=806

Characteristic		No. of cases (%)
Sex	male	521例(65%)
	female	285例(35%)
Age	median (range)	62歳(21～88)
Location	U	235例(29%)
	M	153例(19%)
	L	291例(36%)
	LMU	127例(16%)
Tumor size	median(range)	7.0 cm(2～25)
Gross type	expansive (0,1,2)	341例(42%)
	invasive (3, 4, 5)	465例(58%)
sT-factor	T2	166例(21%)
	T3, 4	640例(79%)
sN-factor	N0	88例(11%)
	N1	177例(22%)
	N2-	541例(67%)
pT-factor	pT 1, 2	274例(34%)
	pT 3, 4	532例(66%)
pN-factor	pN0	175例(22%)
	pN 1	147例(18%)
	pN 2	192例(24%)
	pN 3	292例(36%)
Surgical resection	total	453例(56%)
	distal	355例(44%)
Curability	CA	171例(21%)
	CB	492例(61%)
	CC	143例(18%)
Ope. Time	median(range)	255分(70～720)
Blood loss	median(range)	268 mL (30～2,600)
No. of retrieved nodes	median(range)	57個(6～162)
Hist.	diff.	347例(43%)
	undiff.	459例(57%)

caudal pancreatectomy 287 (36%), splenectomy 407 (51%)

2）成　績

1）初回手術時の臨床病理学的諸因子

男性17例，女性5例であり，年齢中央値は57歳（38～76歳）であった（表2）．肉眼型は浸潤型が45%であり，肝転移，腹膜播種が1例ずつ存在していたが同時に合併切除した．リンパ節郭清度はD1:2例，D2:14例（64%），D3:6例と多くの症例でD2以上の郭清がなされており，術式は胃全摘10例，幽門側胃切除12例であった．

2）No. 16再発時の転移状況

再手術時のNo. 16郭清リンパ節個数は16個（4～31個）であり，No. 16転移リンパ節は9個（1～30個）であった．再手術時大動脈または上腸間膜動脈への直接浸潤のため単開腹に終わった2症例を経験した．また，1例は下腸間膜動脈より足側のNo. 16b2および総腸骨動脈周囲の転移を郭清した．肝転移を伴っていた症例が3例，副腎転移2例であり，再手術の延べ術式はリンパ節郭清20例，肝切除3例，副腎摘出2例，試験開腹2例であった．

3）遠隔成績

手術を施行した22例の初回手術から再手術まで（平均介在期間24.5カ月），および再手術からの経過（平均生存期間24.8カ月）を図8に示す．再手術後5年以上生存が確認できた症例は4例であり，5年生存率22.7%，MSTは38.6カ月であった．最長生存例については既に報告済みであるが[19]，再手術後17年10カ月までは無再発生存であったことを確認している．しかし，死亡例の大半は再手術後1年前後に死亡しており，No. 16再郭清を施行する際の適応は厳格にすべきである．

3　考　察

日本ではD2＋No. 16郭清も積極的に行われ，良好な成績が報告されてきた[5,8,11]．D2郭清群よりもNo.16郭清を追加した群の予後が良好であった理由として，stage migrationやNo. 16に存在した微小転移の除去などが推測される．また，しかし，予防的No. 16郭清の是非が問われたJCOG 9501により進行胃癌の治癒切除例に対するD2＋予防的No. 16郭清は否定された．しかし，JCOG9501では拡大群における組織学的No. 16リンパ節転移陽性例は8.8%（23/260）と少なく，No. 16陽性例に対する郭清効果の検討はできていない．全国アンケート調査[20]によるとNo. 16転移陽性で5年生存した53例では，転移個数が3個以下で腫瘍径が小さな2型症例が多い傾向が示唆された．また，JCOG9501による

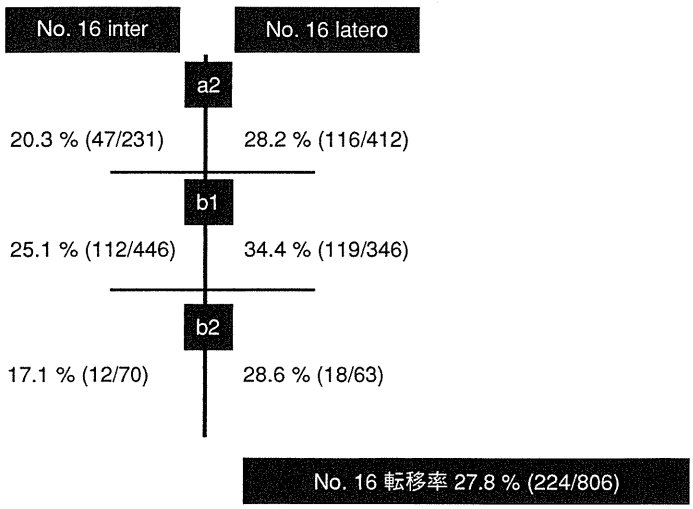

図3　No. 16 部位別転移状況

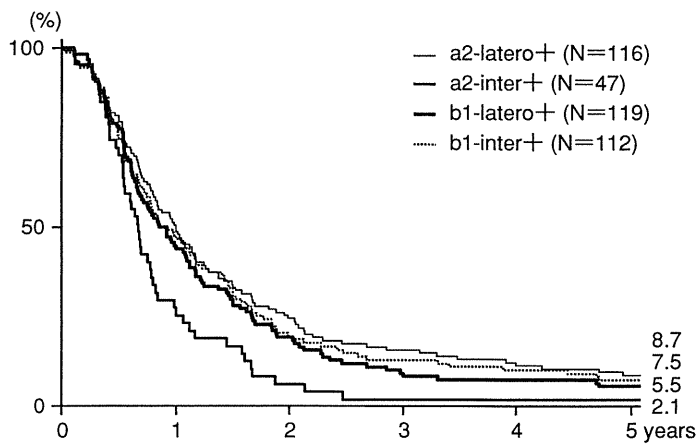

図4　領域別 No. 16 転移陽性症例の生存曲線

QOL の検討にて，D2＋No. 16 郭清による手術後の症状悪化と体重減少は比較的限定されており，若干の延命効果が期待されるサブグループに対しては D2＋No. 16 郭清を行う余地がある[21]．われわれの検討では No. 16 転移陽性例に対する No. 16 郭清にて 35.8％と良好な 5 年生存率が得られており，a2-latero, b1-inter ではそれぞれ 30％を超える郭清効果が認められた[22]．

INT-0116 study により放射線化学療法が D0/D1 郭清による治癒切除後の局所コントロールには有効であることが証明された[23]．わが国でも No. 16 再発が限局している場合に放射線療法が選択されることもある．リニアック照射により CR や good PR などの良好な局所効果が認められたとの報告[24]もみられる．しかし，照射範囲に腎門部が含まれている場合には遅発性の腎障害が認められることもあり，照射野を決める際には充分な注意が必要である．

No. 16 再発に対する郭清の是非についてはいまだエビデンスがないが，No. 16 再発リンパ節を郭清し長期生存が得られたとの報告はみられる[25]．われわれも No. 16 再発に対するリンパ節郭清により 4 例の再手術後 5 年生存例を経験している．再発例に対する No. 16 郭清の適応をさ

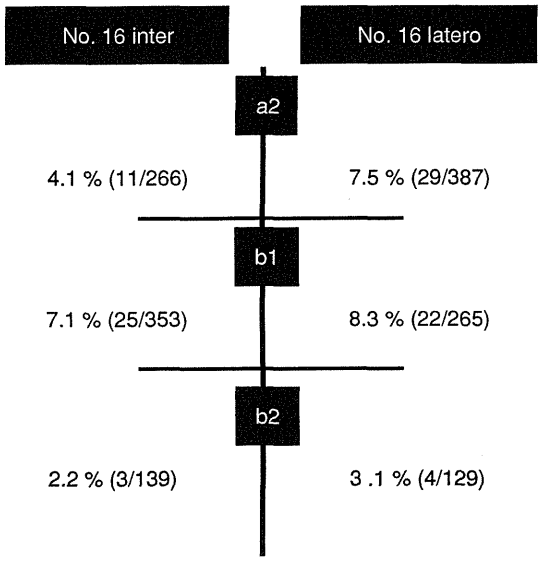

図5　肉眼的転移陰性症例における No. 16 領域別転移状況（No. 16LN 転移率：Surgical　0.0％，Pathological 8.3％）

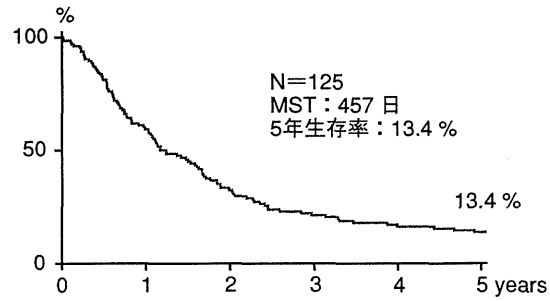

図6　No. 16 転移陽性 R0 症例の生存曲線

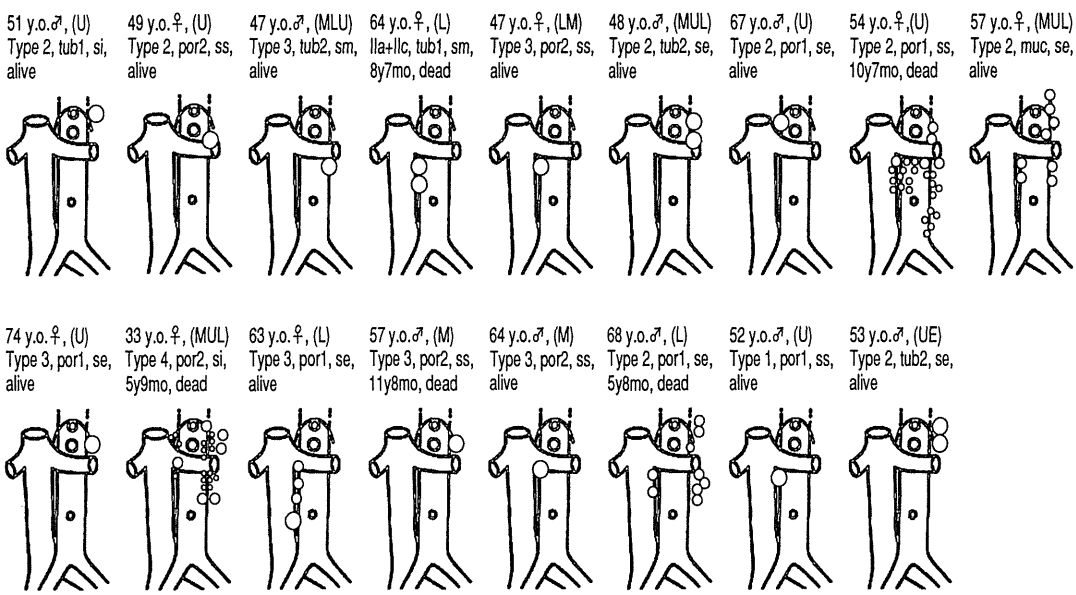

図7　5-YEAR SURVIVORS AFTER GASTRECTOMY with No. 16 LN dissection (17 Cases)

らに厳密にする必要はあるが，他に非治癒因子がない場合は No. 16 郭清が適応となると考えている．従って，No. 16 転移が疑われる症例に対しては，まず診断的腹腔鏡検査を行い，腹膜播種がない場合，術前化学療法後に D2＋No. 16 郭清手術を行っている．術前化学療法として TS-1＋CDDP 療法を原則として 2 コース行っているが，奏効例や治癒切除例では延命効果が認められている[26]．

しかし，一般的には根治手術不能胃癌や No. 16 再発をきたした場合の第一選択はやはり化学療法であろう．最近の化学療法は奏効率が向上

表2　No. 16再発に対する切除（郭清）例
初回手術時の背景因子　(N＝22)

Characteristics		No. of patients
Sex	male/female	17/5
Age		median 57y.o. (38～76)
Location	L/M/U/LMU	10/3/7/2
sT	sT2/sT3/sT4	4/16/2
P	P0/P（+）	21/1
H	H0/H（+）	21/1
sN	sN0/sN1, sN2/sN3	4/12/6
Gross	0/1, 2/3, 4	2/10/10
D	D1/D2/D3	2/14/6
Tumor size		median 8.4 cm (3.3～13.5)
Surg.	Total Gr./Distal Gr.	10/12
Depth	mp, ss/se/si	8/12/2
pN	pN0/pN1, N2/pN3	2/13/7
Curability	A/B	3/19
Hist.	diff./undiff	10/12

し，まれではあるがS-1, S-1＋CDDPやDCS療法などによってNo. 16再発巣が完全に消失したとの報告が散見される[27,28]．しかし，CR率はまだまだ満足できるものではない．切除可能なNo. 16再発は切除すべきか，化学療法のみで治療すべきかを決定するには臨床試験が必要となるが，症例数も少なく実施することは非常に困難である．

おわりに

JCOG9501の結果，予防的なNo. 16郭清効果は否定された．術前診断で既にNo. 16転移と診断された場合，化学療法を先行した後No. 16郭清を施行してきたが，その是非に関してはいまだcontroversialである．また，No. 16単独再発に対するNo. 16郭清により長期生存例も存在しており，他に非治癒因子がない場合はNo. 16郭清も集学的治療の一選択肢としたい．

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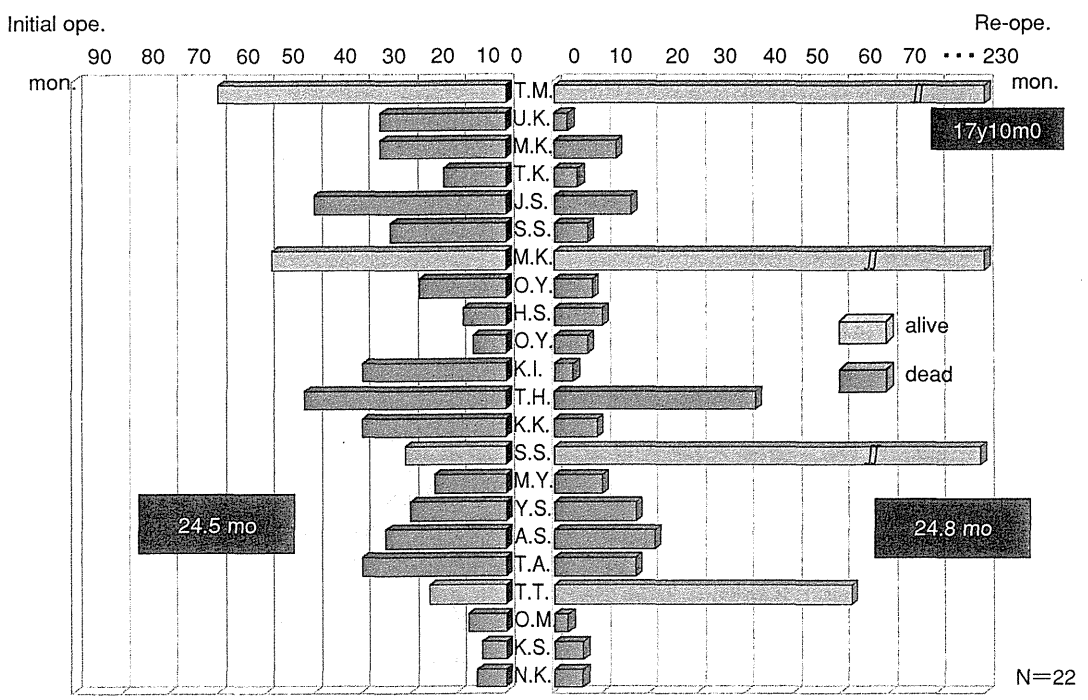

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Hindawi Publishing Corporation
International Journal of Surgical Oncology
Volume 2012, Article ID 301530, 7 pages
doi:10.1155/2012/301530

Clinical Study

The Significance of Splenectomy for Advanced Proximal Gastric Cancer

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Received 13 January 2012; Accepted 11 March 2012

Academic Editor: Marco Bernini

Objectives. The significance of splenectomy in advanced proximal gastric cancer is examined retrospectively. *Methods.* From 1994 to 2004, 505 patients with advanced proximal gastric cancer underwent curative total gastrectomy with preserving spleen (T) for 264 patients and total gastrectomy with splenectomy (ST) for 241 patients. *Results.* Patients who underwent splenectomy showed more advanced lesions. The metastatic rate of lymph node (LN) in the splenic hilus (No. 10) in ST was 18.3%. As for the incidence of surgical complications, there was not statistically difference except for pancreatic fistula. The index of estimated benefit of (No. 10) LN was 4.2, which was similar to that of (No. 9), (No. 11p), (No. 11d), and (No. 16) LNs. 5-year survival rate of (No. 10) positive group was 22.2%. 5-year survival rates of pSE and pN2 in T group were better than that of pSE and pN2 in ST, respectively. The superiority of ST was not confirmed even in Stage II, IIIA, and IIIB. *Conclusion.* Splenectomy was not effective for patients with (No. 10) metastasis in long-term survival. Spleen-preserving total gastrectomy will be feasible and be enough to accomplish radical surgery for locally advanced proximal gastric cancer.

1. Introduction

Although it is well known that lymph node (LN) metastasis is an important factor in the prognosis of gastric cancer, the optical extent of LN dissection remains controversial. Splenectomy has been indicated to remove the LNs surrounding the splenic artery (No. 11) and splenic hilum (No. 10). Previous reports suggested that gastrectomy with splenectomy resulted in better survival than gastrectomy alone in gastric cancer patients [1]. The Japanese retrospective studies revealed that the frequency of LN metastasis to No. 10 in proximal gastric cancer was 15–20%, and the 5-year survival rate was 20–25% [2, 3]. Total gastrectomy with splenectomy is considered to be a standard procedure for proximal advanced gastric cancer in gastric cancer treatment guidelines [4]. But two large prospective randomized trials in western countries reported that splenectomy was a risk factor for morbidity and mortality [5, 6]. Preservation of the spleen during extended lymphadenectomy decreases complications with no clear evidence of improvement or detriment to overall survival [7]. Then modified D2 lymphadenectomy avoiding splenectomy is now accepted as a standard procedure in the west countries. Our retrospective study was designed to investigate the significance of splenectomy by evaluating postoperative morbidity, frequency of the each LN metastasis, and long-term surgical outcomes of locally advanced proximal gastric cancer patients who underwent total gastrectomy with R0 resection.

2. Patients and Methods

2.1. Pathological Examination of Lymph Nodes. All regional LNs were separated immediately after gastrectomy by the operators. Node numbers were recorded using a LN map (Figure 1). Nodes were assigned to the appropriate anatomical stations according to Japanese Classification of Gastric Carcinoma (JCGC) of the 2nd English edition [8]. Nodes found at each station were labeled and immediately sent for histological examination.