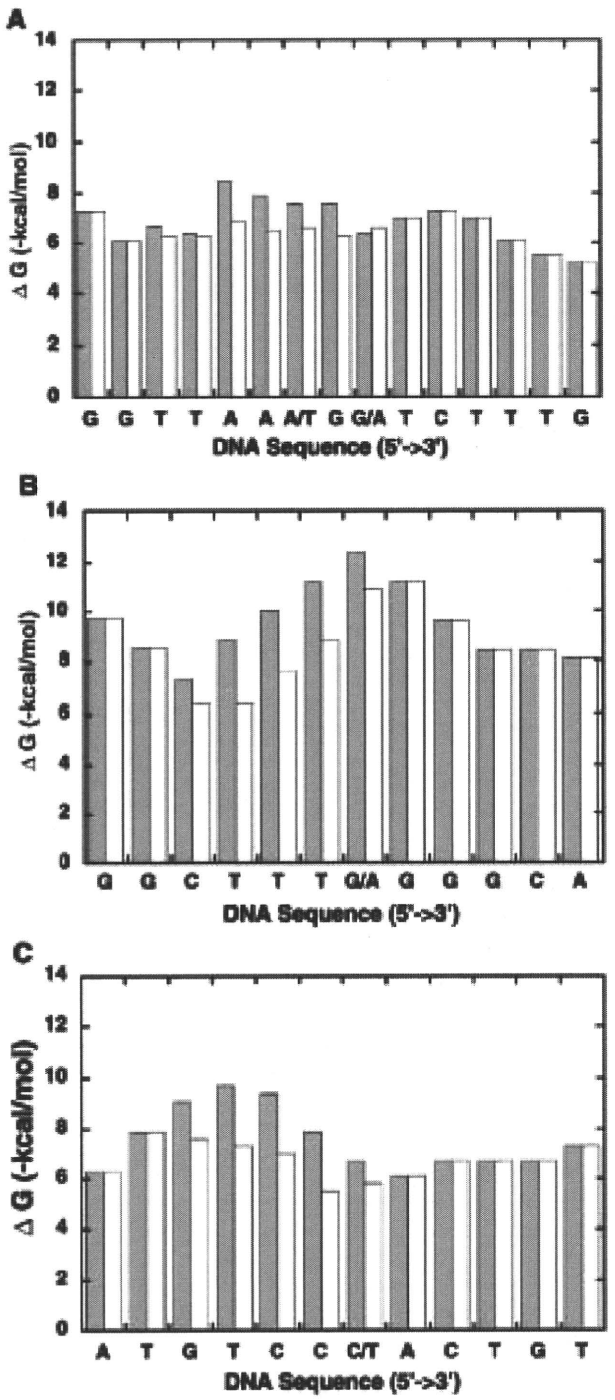

FIG. 4. Free energy of each probe around the mutation site. (A) The free energy of each BCP probe. Black bars and white bars show the free energy values of the Cy5-CPR1 probe (wild-type) and the Cy5-CPR2 probe (mutant), respectively. (B) The free energy of each PC probe. Black bars and white bars show the free energy values for the Cy5-PC2 probe (wild-type) and the Cy5-PC3 probe (mutant), respectively. (C) The free energy of each nt1858 probe. Black bars and white bars show the free energy values for the Cy5-GA5 probe (T-1858) and the Cy5-GA3 probe (C-1858), respectively.

mutants in a heterogeneous mixture (20). Real-time PCR, like that used in the TaqMan assay, is a very sensitive and reliable method for quantifying genes, but there may be some difficulties with sequences containing only a single base mutation. Shin et al. reported that annealing curve analysis was necessary for detecting YMDD mutants after real-time PCR (26). Our method is robust enough to detect a variety of mutations, and little time is needed to adjust the experimental conditions because of the simple probe designs. We have also determined the percent abundance of other HBV mutation sites (including L528M and YMDD (5)) using ASOCH (manuscript in preparation).

The Handy Bio-Strand system can simultaneously analyze 17–34 patient DNA samples using Cy5-labeled oligonucleotide probes. As shown in our previous report (22), Bio-Strands can be reused 2–3 times by washing out the bound Cy5 probes with hot water. Since the three targeted sites (BCP, PC and nt1858) used in this study are located on the same DNA fragments (304 bp) (Supplementary data), repeated automatic hybridization can semi-quantitatively determine the percent abundance of all three species, thereby reducing the time needed to prepare the Bio-Strand Tip.

Amplification bias during nested PCR either does not occur or does not pose a significant problem as repeated experiments were carried out changing the template amount and PCR cycles without effect on the hybridization patterns.

Since real-time PCR is the best method for estimating HBV load in copies/ml, we propose the following method. First, the HBV load in a patient's serum should be precisely determined by real-time PCR. Second, the percent abundance of each HBV mutant site should be determined using ASOH or ASOCH with the Handy Bio-Strand system. Semi-quantitative mutant populations may then be calculated from these two parameters. We believe that these data provide an important new approach to the diagnosis of HBV and the design of HBV-specific treatments in future clinical studies.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jbiosc.2009.06.023.

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Original article

Functional outcomes after extended surgery for gastric cancer

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Background: Extended gastrectomy with para-aortic nodal dissection (PAND) or thorough dissection of mediastinal nodes using a left thoracoabdominal (LTA) approach is an alternative to D2 lymphadenectomy, with variable postoperative results.

Methods: Two randomized controlled trials have been conducted to compare D2 lymphadenectomy alone (263 patients) *versus* D2 lymphadenectomy plus PAND (260), and the abdominal–transhiatal (TH) approach (82) *versus* the LTA approach (85), in patients with gastric cancer. Prospectively registered secondary endpoints bodyweight, symptom scores and respiratory function were evaluated in the present study.

Results: Bodyweight was comparable after D2 and D2 plus PAND, but higher after TH than after LTA procedures at 1 and 3 years. At 1- and 3-year follow-up symptom scores were comparable between D2 and D2 plus PAND. A LTA approach resulted in significantly worse scores than a TH approach in terms of meal volume, return to work, incisional pain and dyspnoea up to 1 year. The decrease in vital capacity was significantly greater after LTA than TH procedures up to 6 months.

Conclusion: Bodyweight and postoperative symptoms were not affected by adding PAND to a D2 procedure. A LTA approach aggravated weight loss, symptoms and respiratory functions compared with a TH approach. Registration numbers: NCT00149279, NCT00149266 (http://www.clinicaltrials.gov).

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Introduction

Radical gastrectomy with D2 lymphadenectomy is the standard treatment for patients with curable gastric cancer in east Asia[1]. To improve survival further, more extensive surgery has been attempted in specialized centres. Two multicentre randomized controlled trials have evaluated extended gastric surgery. In the Japan Clinical Oncology Group (JCOG) 9501 trial, D2 plus para-aortic nodal dissection (PAND) was compared with D2 lymphadenectomy for tumour category (T) 2b to T4 potentially curable gastric cancer[2,3]. In the JCOG9502 trial, a left thoracoabdominal (LTA) approach accompanied by thorough lower mediastinal lymphadenectomy was compared with an abdominal–transhiatal (TH) approach for proximal gastric cancer invading the oesophagus[4].

Contrary to expectations, there was no survival benefit from these extended procedures. D2 plus PAND or a LTA approach resulted in a longer duration of operation than D2 or a TH procedure. The morbidity was also worse after these extended procedures than after the standard operations. This has led to the conclusion that they should not be employed as prophylactic lymphadenectomy for curable gastric cancer[2,4]. Apart from survival and short-term morbidity, postoperative evaluation of symptom, bodyweight and respiratory function outcomes after extended surgery permits proper decision-making regarding surgical treatment for gastric cancer. In the present study, changes in the secondary endpoints bodyweight, various symptom-related scores and respiratory function in these two trials were assessed prospectively.

Methods

Japan Clinical Oncology Group 9501 trial

Patients younger than 75 years of age with histologically proven gastric adenocarcinoma considered potentially curable were enrolled in the JCOG9501 trial[2,3]. Additional eligibility criteria derived from intraoperative findings were T2b or higher, no gross metastases to para-aortic nodes, and negative cytology by peritoneal lavage. The surgeon confirmed the eligibility criteria during surgery and telephoned the JCOG Data Centre to register patients. Patients were then randomized to either standard D2 or extended D2 plus PAND using the minimization method according to clinical T category, Borrmann macroscopic type and institution. The surgeon then performed the allocated operation as described in the protocol.

The surgical procedures used in each group have been described previously[2,3]. In short, in the D2 group gastrectomy with D2 lymphadenectomy was carried out according to the 12th edition of the Japanese Classification of Gastric Carcinoma[5]. In the D2 plus PAND group the para-aortic lymph nodes were also dissected. The spleen was removed in patients having total or proximal subtotal gastrectomy. Pancreatectomy was confined to patients in whom the pancreas was involved by tumour. The reconstruction method was not prespecified. Adjuvant or neoadjuvant therapy was not allowed. This study was registered with ClinicalTrials.gov (no. NCT00149279).

Japan Clinical Oncology Group 9502 trial

The eligibility criteria for the JCOG9502 trial were: histologically proven adenocarcinoma of the gastric cardia or body with oesophageal invasion of 3 cm or less, clinically T2–4, patient no more than 75 years old, no distant metastasis, and no bulky node category (N) 3 or N4 metastasis[1]. Patients were randomized to either standard TH or extended LTA treatment using the minimization method according to clinical T stage, Borrmann macroscopic type and institution.

The surgical procedures used in each group have been described previously[4]. In short, a total gastrectomy with D2 and additional dissection of the left upper para-aortic nodes was performed in the TH group. The lower mediastinum was accessed through the oesophageal hiatus extended by a longitudinal incision of the median part of the diaphragm. In the LTA group a long oblique incision over the seventh intercostal space was extended into the right abdomen. In the abdominal cavity, the same procedure as that performed in the TH group was carried out and thorough mediastinal lymph node dissection below the inferior pulmonary vein was performed. The reconstruction method was not prespecified. Adjuvant or neoadjuvant therapy was not allowed. This study was registered with ClinicalTrials.gov (no. NCT00149266).

Subjective symptom-related scores

The primary endpoint of these trials was overall survival. Postoperative changes in bodyweight and symptoms (JCOG 9501 and 9502) and also in respiratory function (JCOG9502 only) were assessed prospectively as secondary endpoints. Bodyweight was measured before surgery, and at 6 months, 1 year and 3 years after operation.

Surgeons evaluated patient symptoms during outpatient clinic visits at 6 months, 1 year and 3 years after surgery, without being blinded to the procedure performed. Symptoms included appetite, meal volume, bowel habit, sleep and occurrence of pneumonia (JCOG 9501 and 9502), and also incisional pain and dyspnoea for JCOG9502. As a surrogate for total physical strength, the proportion of patients who were able regularly to leave their homes to perform daily activities and those who returned to their former work were evaluated. All items were dichotomized, and scoring was performed as shown in *Table 1*.

Respiratory function, including vital capacity, forced expiratory volume in 1 s (FEV1) and arterial partial pressure of oxygen (PaO_2) in room air, were also measured before, and at 1 and 6 months after surgery.

Statistical analysis

The group means of bodyweight, vital capacity, FEV1 and PaO_2 were determined using a mixed-effect model with pretreatment value, treatment arms, time and treatment–time interaction as co-variables. Items related to symptoms and respiratory function were dichotomized

Table 1 Nine symptom items evaluated in this study

	Score 0	Score 1
Appetite	Poor	Good
Meal volume	$< \frac{1}{2}$ preoperative amount	$\geq \frac{1}{2}$ preoperative amount
Bowel habit	Irregular, diarrhoea	Daily, normal
Sleep	Disturbed	Good
Leaving home	Seldom	Regularly
Return to work	No	Yes
Pneumonia	Experienced	Never
Incisional pain*	Always, often	Seldom, none
Dyspnoea*	Yes	No

*These parameters were evaluated only in the Japan Clinical Oncology Group 9502 trial.

and these group means were evaluated by marginal models fit via generalized estimating equations (GEEs), with treatment arms, time and treatment–time interaction as co-variables. All group means were compared at each time point between two groups. According to these models, point estimates with least-squares means, their confidence intervals and *P* value were calculated and compared at each time point between two groups. GEE is used to take into account the within-patient correlation that is inevitable when outcomes are measured repeatedly from the same patients[6].

Measurements were missing for those who were still in hospital as a result of major complications and those who developed recurrence, and these data points were excluded from the analysis. Because of the exploratory nature of between-group comparisons, the test results are reported with two-sided *P* values without multiplicity adjustment of type I error.

All statistical analyses were carried out with SAS® software release 9.1 (SAS Institute, Cary, North Carolina, USA).

Results

In the JCOG9501 trial, 523 patients were assigned randomly to either the D2 group (263 patients) or the D2 plus PAND group (260) in 24 Japanese hospitals between July 1995 and April 2001 (*Fig. S1*, supporting information). Patient characteristics have been published previously[3]. Total gastrectomy was performed in 102 patients (38·8 per cent) in the D2 group and 97 (37·3 per cent) in the D2 plus PAND group. The most common method of reconstruction was the Roux-en-Y procedure in both groups (D2, 59·7 per cent; D2 plus PAND, 60·8 per cent). Splenectomy was performed in 98 (37·3 per cent) and 93 (35·8 per cent) patients in the D2 and D2 plus PAND groups respectively; only nine (3·4 per cent) and 12 (4·6 per cent) patients respectively underwent distal pancreatectomy.

In the JCOG9502 trial, 167 patients were randomly assigned to either the TH (82 patients) or LTA (85) approach in 27 Japanese hospitals between July 1995 and December 2003 (*Fig. S1*, supporting information). Details of patient and tumour characteristics have already been published[4]. Most patients in both TH and LTA groups underwent total gastrectomy with splenectomy. Distal pancreatectomy was performed in 22 patients (27 per cent) in the TH group and 13 (15 per cent) in the LTA group.

Table 2 Postoperative change in bodyweight between groups in Japan Clinical Oncology Group 9501 and 9502 trials

	Group	No. of patients	Bodyweight (kg)*	*P*
JCOG9501				
Before operation	D2	263	57·5 (56·3, 58·7)	—
	D2 + PAND	259	56·9 (55·7, 58·2)	
After 6 months	D2	256	51·1 (50·6, 51·6)	0·030†
	D2 + PAND	252	50·3 (49·8, 50·8)	
After 1 year	D2	242	51·1 (50·5, 51·7)	0·241†
	D2 + PAND	233	50·6 (49·9, 51·2)	
After 3 years	D2	192	51·1 (50·4, 51·8)	0·381†
	D2 + PAND	190	50·7 (50·0, 51·4)	
JCOG9502				
Before operation	TH	82	58·5 (56·4, 60·5)	—
	LTA	82	57·6 (55·6, 59·7)	
After 6 months	TH	75	49·7 (48·7, 50·6)	0·115‡
	LTA	71	48·6 (47·6, 49·6)	
After 1 year	TH	68	50·0 (49·0, 51·0)	0·031‡
	LTA	66	48·2 (47·0, 49·5)	
After 3 years	TH	47	50·7 (49·7, 51·7)	0·046‡
	LTA	40	49·0 (47·6, 50·3)	

*Values are mean (95 per cent confidence interval), crude mean for preoperative values and least-squares mean for the others. JCOG, Japan Clinical Oncology Group; PAND, para-aortic nodal dissection; TH, abdominal–transhiatal; LTA, left thoracoabdominal. †*Versus* D2 + PAND, ‡*versus* LTA (mixed-effect model).

Table 3 Postoperative change in respiratory function between abdominal–transhiatal and left thoracoabdominal groups

	Group	No. of patients	Mean	*P**
Vital capacity (ml)				
Before operation	TH	82	3573 (3416, 3731)	—
	LTA	82	3421 (3225, 3617)	
After 1 month	TH	80	2944 (2855, 3034)	< 0·001
	LTA	74	2427 (2327, 2528)	
After 6 months	TH	73	3193 (3088, 3297)	< 0·001
	LTA	68	2658 (2552, 2764)	
FEV1 (%)				
Before operation	TH	82	80·2 (78·3, 82·1)	—
	LTA	82	80·4 (78·3, 82·5)	
After 1 month	TH	80	84·4 (82·7, 86·2)	0·416
	LTA	74	83·3 (81·1, 85·4)	
After 6 months	TH	73	84·7 (82·6, 86·7)	0·985
	LTA	68	84·7 (81·8, 87·6)	
Pa_{O_2} in room air (mmHg)				
Before operation	TH	80	86·6 (84·5, 88·8)	—
	LTA	81	87·1 (85·1, 89·1)	
After 1 month	TH	72	87·6 (85·5, 89·8)	0·004
	LTA	69	82·8 (80·3, 85·2)	
After 6 months	TH	73	90·3 (87·9, 92·8)	0·057
	LTA	68	87·0 (84·7, 89·4)	

Values in parentheses are 95 per cent confidence intervals. TH, abdominal–transhiatal; LTA, left thoracoabdominal; FEV1, forced expiratory volume in 1 s; Pa_{O_2}, arterial partial pressure of oxygen. **Versus* LTA (mixed-effect model).

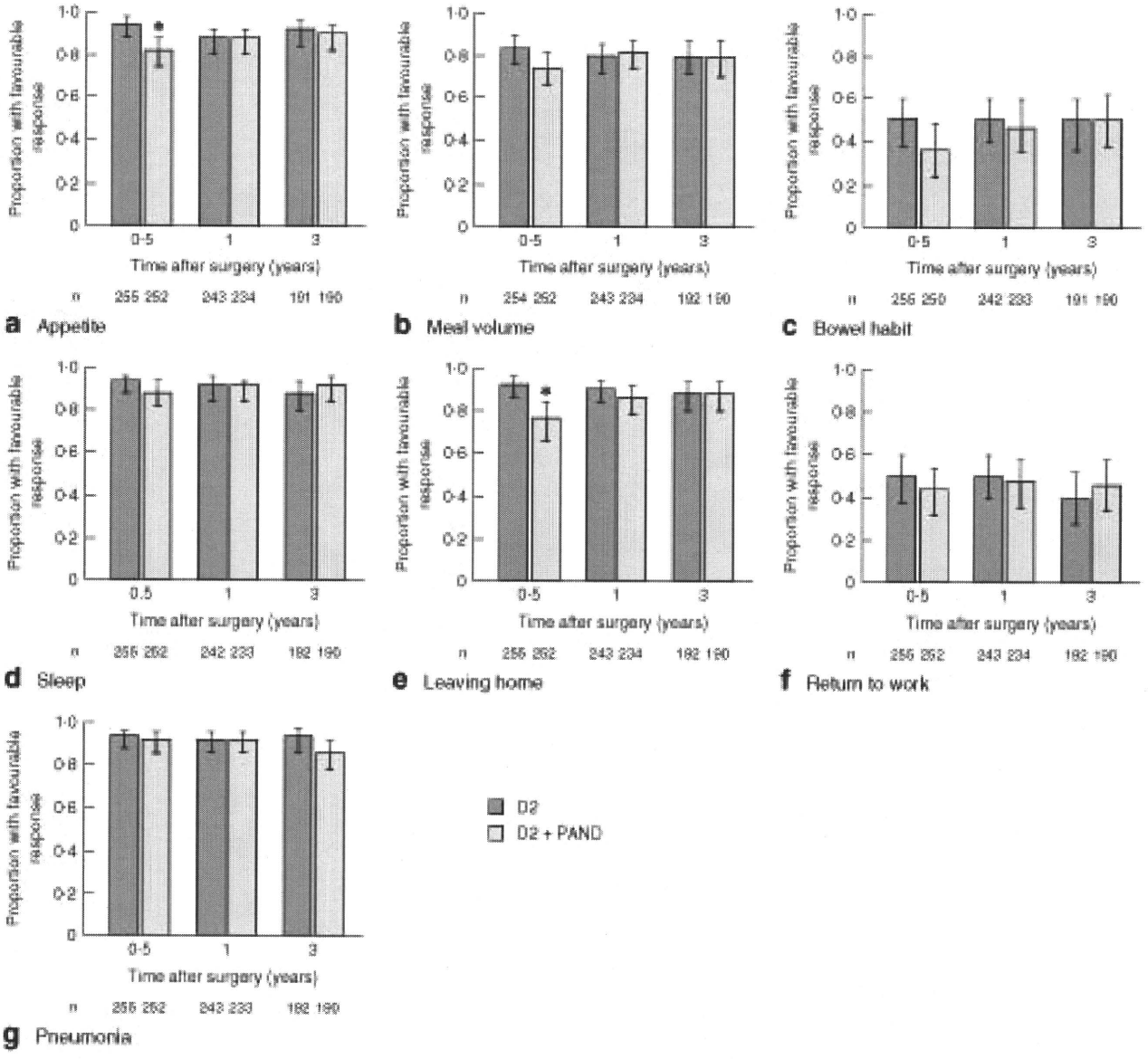

Fig. 1 Comparison of proportion of patients with a favourable response regarding seven symptoms between D2 and D2 + para-aortic nodal dissection (PAND) groups: **a** appetite, **b** meal volume, **c** bowel habit, **d** sleep, **e** leaving home, **f** return to work and **g** pneumonia. Group means are shown with 95 per cent confidence intervals. *$P < 0.050$ *versus* D2 (generalized estimating equations model)

Bodyweight

In the JCOG9501 trial, the decrease in mean bodyweight at 6 months was 6·4 kg in the D2 group and 6·6 kg in the D2 plus PAND group (*Table 2*). Postoperative bodyweight remained unchanged thereafter in both groups. Bodyweights were comparable between groups at 1 and 3 years' follow-up.

In the JCOG9502 trial, the decrease in mean bodyweight was 8·8 kg in the TH group and 9·1 kg in the LTA group at 6 months after surgery (*Table 2*). At 1 and 3 years' follow-up mean bodyweight was higher after a TH than a LTA procedure ($P = 0.031$ and $P = 0.046$ respectively).

Postoperative symptoms

Symptom scores after surgery are shown in *Figs 1* and *2*. In the JCOG9501 trial, appetite and the proportion of patients able to leave their home almost every day were significantly higher in the D2 group than in the D2

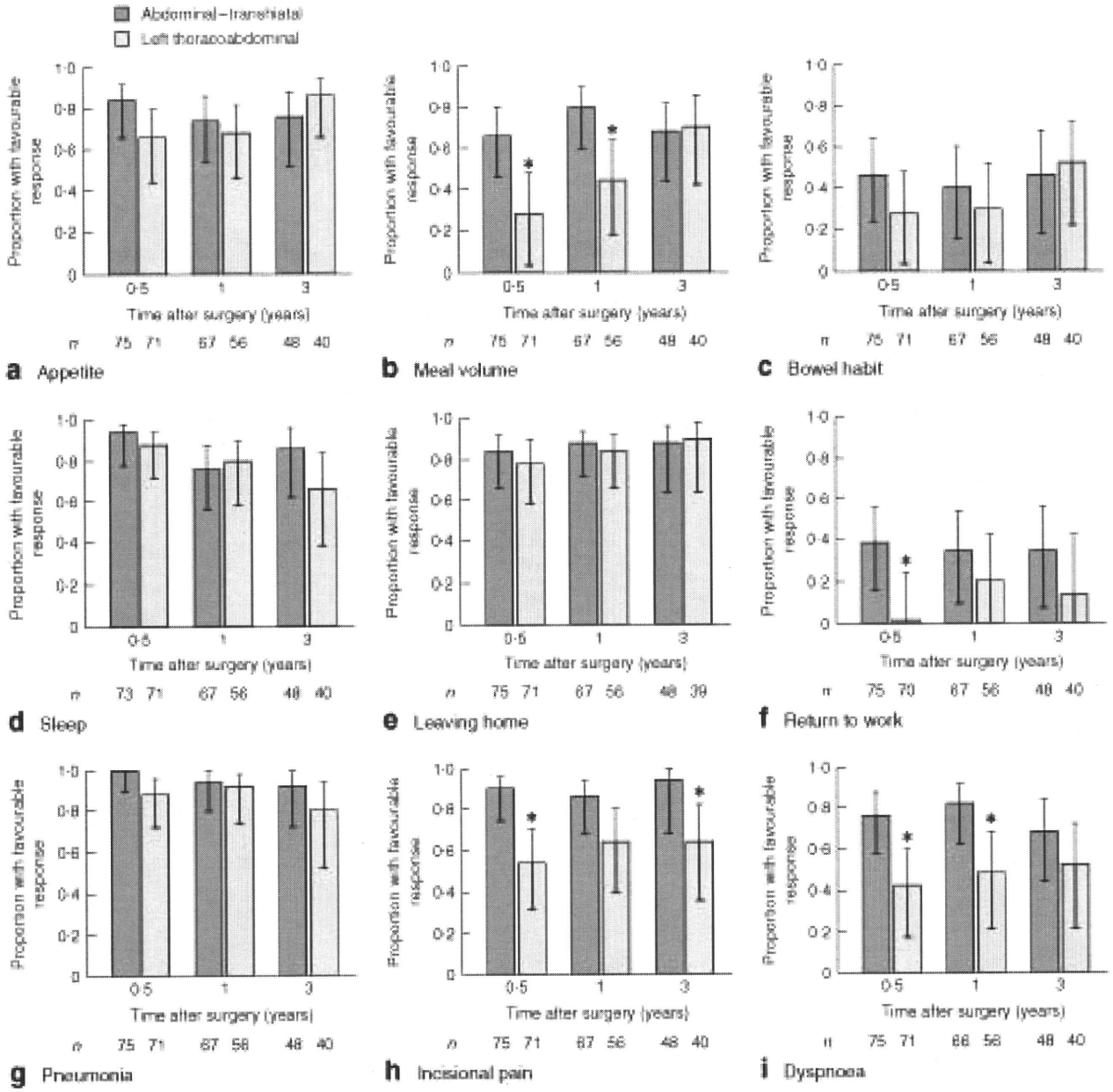

Fig. 2 Comparison of proportion of patients with a favourable response regarding nine symptoms between abdominal–transhiatal (TH) and left thoracoabdominal (LTA) groups: **a** appetite, **b** meal volume, **c** bowel habit, **d** sleep, **e** leaving home, **f** return to work, **g** pneumonia, **h** incisional pain and **i** dyspnoea. Group means are shown with 95 per cent confidence intervals. *$P < 0{\cdot}050$ *versus* TH (generalized estimating equations model)

plus PAND group at 6 months. At 1- and 3-year follow-up symptom scores were comparable between the two groups.

In the JCOG9502 trial, meal volume and respiratory status (dyspnoea) were better in the TH group than in the LTA group up to 1 year after surgery. The proportion of patients with incisional pain was significantly higher in the LTA group than in the TH group until the end of follow-up at 3 years.

Respiratory function in Japan Clinical Oncology Group 9502 trial

The LTA group showed a significantly greater decrease in vital capacity than the TH group at 1 and 6 months after

surgery (*Table 3*). There was no deterioration in FEV1 after surgery in either group. PaO_2 in the TH group did not change in the 6 months after surgery, whereas there was a transient decrease in the LTA group.

Discussion

The first randomized controlled trial compared two types of lymphadenectomy within the same surgical approach for gastric cancer, whereas the second trial compared two completely different surgical approaches, namely with and without thoracotomy. In the present study, secondary outcomes of patients without recurrence after gastrectomy were evaluated. Bodyweight was comparable after D2 and D2 plus PAND, whereas the difference in bodyweight between the TH and the LTA groups widened gradually owing to recovery in the TH group. This means that bodyweight change after gastrectomy is more dependent on surgical approach than on the extent of lymphadenectomy. Some of the clinical symptoms were particularly negatively affected by a LTA compared with a TH approach, whereas D2 and D2 plus PAND had comparable scores. The decrease in vital capacity was significantly greater after a LTA than a TH procedure.

Clinical symptoms in the D2 plus PAND group were limited to a short time after operation, and mostly related to changes in bowel habit. This may be due either to autonomic nerve damage or to lymphoedema of the jejunum caused by PAND. However, limited autonomic nerve dissection in PAND may not cause long-term impairment of intestinal function. A small-scale randomized controlled trial of PAND in patients with pancreatic cancer showed that dissection of such nodes frequently caused diarrhoea for up to 4 months after surgery[7]. Although changes in bowel habit may be the biggest disadvantage of PAND, these negative effects were limited to the early postoperative period and seemed to be acceptable clinically. Wu *et al.*[8] compared postoperative symptoms between D1 alone and D2 plus retropancreatic lymph node dissection in a single-institution randomized controlled trial[9]. They reported no significant difference in symptoms between the two groups and concluded that postoperative changes in symptoms were related largely to the scope of gastric resection, disease status and combined resection of the pancreas or spleen rather than the extent of lymph node dissection.

Pain and dyspnoea are well known sequelae of intercostal thoracotomy[9,10]. The negative impact of the thoracotomy procedure on symptoms within the first year agreed with the results of previous studies[11,12]. The difference in meal volume might arise from the location of the anastomosis, in the open thoracic cavity in LTA procedures *versus* the mediastinum in TH operations.

Although quality of life and symptoms are distinct entities, symptoms usually affect patients' quality of life quite strongly. Quality of life is usually assessed by questionnaire and is evaluated by the patients themselves to minimize information bias[13,14]. However, the Japanese versions of validated questionnaires such as the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) or the Functional Assessment of Cancer Therapy – General (FACT-G) were not available when these randomized controlled trials were conducted[14,15]. In the present study, the Gastric Cancer Surgical Study Group/JCOG Symptom Questionnaire, which consisted of only seven or nine queries, was used, because the more complicated the survey, the lower the compliance would have been. Moreover, this questionnaire evaluating patient-centred outcome such as symptom scores was completed by the doctor not the patient, which might have introduced observer bias.

The decrease in bodyweight and worsening of post-operative symptom scores following PAND was limited compared with D2 without PAND. Therefore, D2 plus PAND might be one option when R0 resection is impossible without dissection of such nodes. The LTA approach worsened both symptoms and respiratory function to a greater extent than the TH approach. Surgeons are advised to avoid the LTA approach based not only on previously published survival-related evidence but also on other parameters such as those evaluated in this study.

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Supporting information

Additional supporting information may be found in the online version of this article.

Fig. S1 CONSORT diagrams for **a** Japan Clinical Oncology Group (JCOG) 9501 and **b** JCOG9502 trials. PAND, para-aortic nodal dissection; TH, abdominal–transhiatal; LTA, left thoracoabdominal (Word file)

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Influence of Bursectomy on Operative Morbidity and Mortality After Radical Gastrectomy for Gastric Cancer: Results of a Randomized Controlled Trial

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Abstract

Background Bursectomy, a procedure dissecting the peritoneal lining covering the pancreas and the anterior plane of the transverse mesocolon, has been commonly performed with radical gastrectomy for gastric cancer patients. Although possibly improving the prognosis of gastric cancers, adverse events related to bursectomy should be evaluated in prospective studies.

Methods This prospective randomized controlled trial was conducted by experienced surgeons in 11 Japanese institutions. Patients with T2 or T3 gastric adenocarcinoma were intraoperatively randomized to radical gastrectomy plus D2 lymphadenectomy either with or without bursectomy. Postoperative morbidity and mortality were compared between the two groups.

Results A total of 210 patients were assigned to the bursectomy group (104 patients) and the nonbursectomy group (106 patients) between July 2002 and January 2007. Background characteristics were well balanced. Intraoperative blood loss was greater in the bursectomy group than in the nonbursectomy group (median 475 vs. 350 ml, $p = 0.047$), whereas other surgical factors did not vary significantly. The overall morbidity rate was 14.3% (30 patients), the same for the two groups. Likewise, the incidence of major postoperative complications, including pancreatic fistula, anastomotic leakage, abdominal abscess, bowel obstruction, hemorrhage, and pneumonia, were not significantly different between the two groups. The medians of the amylase level of the drainage fluid on postoperative day 1 were similar for the two groups (median 282 vs. 314 IU/L, $p = 0.543$). The hospital mortality rate was 0.95%: one patient per group.

Conclusions Experienced surgeons could safely perform a D2 gastrectomy with an additional bursectomy without increased major surgical complications.

Introduction

More than half of the new cases of gastric cancer occur in eastern Asia [1]. The surgical intervention for gastric cancers has rapidly developed in Japan. An extended radical lymphadenectomy, which is almost identical to the present D2 dissection, along with bursectomy was established as the standard treatment for advanced gastric cancers during the early 1960s [2, 3]. Bursectomy is a traditional surgical procedure to dissect the peritoneal lining covering the pancreas and the anterior plane of the transverse mesocolon with an omentectomy [4, 5]. This procedure is recommended in the Japanese Gastric Cancer Treatment Guidelines as part of the radical surgery for gastric cancer to remove micrometastases disseminated into the bursa omentalis [6]. As gastric cancer in the posterior wall sometimes shows peritoneal dissemination only in the bursa omentalis, its resection may improve survival [7].

On the other hand, a bursectomy causes some surgical stress when performed in addition to a D2 lymph node

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dissection. Therefore, the possible increase in the incidence of postoperative complications, including pancreatic fistula formation, intestinal obstruction, and hemorrhage, may be concerning. As the safety of a D2 lymph node dissection is still controversial in Western countries [8, 9], we should also carefully evaluate the safety of bursectomy. To elucidate the safety and usefulness of the bursectomy, we conducted a multiinstitutional randomized controlled trial. We hereby present our operative morbidity and mortality data, the secondary endpoints of this trial. The final analysis of survival data is scheduled to take place in 2012.

Patients and methods

Patients

Patient eligibility criteria for this study were as follows: (1) histologically proven primary adenocarcinoma of the stomach; (2) a preoperative and intraoperative classification of T2N0, T3N0, T2N1, or T3N1 according to 13th edition of the Japanese Classification of Gastric Carcinoma [10]; (3) a lack of noncurative surgical factors except for positive lavage cytology; (4) no Borrmann type 4 (linitis plastica) cases; (5) no prior chemotherapy or radiation therapy; (6) ages 20 to 80 years with a performance status of 0 to 2 according to the Eastern Cooperative Oncology Group (ECOG) scale; (7) no history of gastrectomy or other malignancy during the last 5 years. All patients gave written informed consent before undergoing randomization.

When the surgeon confirmed the above eligibility criteria immediately after the initial laparotomy, patients were then intraoperatively randomized to the bursectomy group (a D2 gastrectomy with bursectomy) or the nonbursectomy group (without bursectomy). Randomizations were made by the minimization method according to sex, clinical T stage (cT2 vs. cT3), and gastrectomy (total vs. distal subtotal gastrectomy).

Surgery

In both the bursectomy and nonbursectomy groups, the surgeon performed a total or distal subtotal gastrectomy and D2 lymph node dissection as a standard treatment for advanced gastric cancers [10]. With total gastrectomy for T2 or deeper tumors in the proximal third of the stomach, the spleen was removed in principle for splenic hilar lymphadenectomy. Pancreatectomy was confined to those patients whose pancreas was involved by tumor.

An omentectomy was performed for both groups in this study. In the bursectomy group, the peritoneal lining of the bursa omentalis was removed en bloc as much as possible from the anterior plane of the transverse mesocolon and the pancreas. In the caudal area of the bursa omentalis, the anterior lesion was removed with the minor omentum at the edge of the left lobe of the liver. The posterior and right-sided lesions were removed with lymph node dissection along the common hepatic artery (no. 8a), the splenic artery (no. 11p/d), the left gastric artery (no. 7), and in the hepatoduodenal ligament (no. 12a). As complete removal of the left side of the bursa omentalis did not allow a distal subtotal gastrectomy, pancreatic serosa was removed up to the proximal half of the splenic artery (no. 11p). For the transverse colon mesentery, the peritoneum was removed up to the left gastroepiploic artery (no. 4sb). In the nonbursectomy group, the right anterior surface of the transverse colon mesentery was partially removed around the root of the right gastroepiploic artery (no. 6). Only a small amount of peritoneum could be removed for lymph node dissection. Thus, the bursa omentalis peritoneal lining was preserved as much as possible in the nonbursectomy group. The type of reconstruction and the indication of prophylactic cholecystectomy were not specified in the protocol.

Patients were enrolled from 11 hospitals belonging to the Osaka University Clinical Research Group for Gastroenterological Surgery. More than 50 gastrectomies were performed each year in these 11 hospitals. All operations were performed or supervised by senior surgeons who were members of the Japanese Gastric Cancer Association. During the planning of the study, all participating surgeons reached an agreement concerning the technical details of bursectomy.

Postoperative evaluation

Operative methods and pathology results were recorded according to the 13th edition of the Japanese Classification of Gastric Carcinoma [10]. The number of dissected lymph nodes was measured by pathology. Drainage fluid was collected via an operatively placed drain on postoperative day (POD) 1 for measuring the amylase level. The six Representative data for the six major morbidities—pancreatic fistula, anastomotic leakage, abdominal abscess, bowel obstruction, hemorrhage, pneumonia—were prospectively collected. A pancreatic fistula was defined by a drainage output on or after POD 5 with an amylase content more than three times the upper normal serum value. Pneumonia, anastomotic leakage, abdominal abscess, and bowel obstruction were diagnosed radiologically or clinically. Postoperative hemorrhage requiring a transfusion was recorded as morbidity. Any other complications requiring pharmacologic or surgical treatment were recorded on a free format. Operative morbidity until 3 months after surgery was also analyzed in this study. Operating time, blood loss, duration of hospital stay after surgery, and reoperation details were also recorded. Hospital mortality

was defined as postoperative death of any cause within 30 days or death during the same hospitalization.

Patients were followed every 3 months until 5 years after the operation. Adjuvant therapy was not permitted before a recurrence of cancer.

Statistical Analysis

The primary endpoint was overall survival (OS). Secondary endpoints were recurrence-free survival, operative morbidity, and POD 1 drainage amylase levels. We planned initially to recruit 200 patients, with an alpha error of 0.1 and statistical power of 80%. This allowed detection of a 10% margin of noninferiority for the nonbursectomy group under the estimation of a 60% 5-year OS in the bursectomy group. The projected accrual period and follow-up period were 3 years and 5 years, respectively. After registration of 204 patients, we amended the sample size and analysis to correct the estimation of the 5-year OS in the bursectomy group as 75% and to reduce alpha error. The amended sample size was 464, with an alpha error of 0.05 and statistical power of 80%, with an 8-year accrual period (total) and 5-year follow-up.

In January 2007, the positive result of a large-scale randomized controlled trial to evaluate adjuvant S-1 chemotherapy for stage II/III gastric cancer patients was reported [11, 12]. Since then, adjuvant S-1 chemotherapy has been a new standard treatment for stage II/III gastric cancer patients in Japan. However, because any adjuvant treatment including S-1 was not allowed after surgery in our study, we decided to close the accrual of our study in January 2007.

The operative morbidity and mortality rates were based on the proportion of the number of cases divided by all registered patients based on the intention-to-treat principle. The differences in proportion between the two groups were evaluated using Fisher's exact test or chi-squared test. The differences of continuous variables, including age, body mass index, tumor size, operating time, blood loss, and the number of dissected lymph nodes for the two groups were tested with a Mann-Whitney U-test. All p values were two-sided, and statistical analysis was done using SPSS Statistics software, version 17.0 (SPSS, Chicago, IL, USA).

Results

Patients and surgery

Between July 2002 and January 2007, a total of 210 patients were randomly divided into 104 in the bursectomy group and 106 in the nonbursectomy group (Fig. 1). One patient in the bursectomy group did not undergo bursectomy, and one in the nonbursectomy group underwent

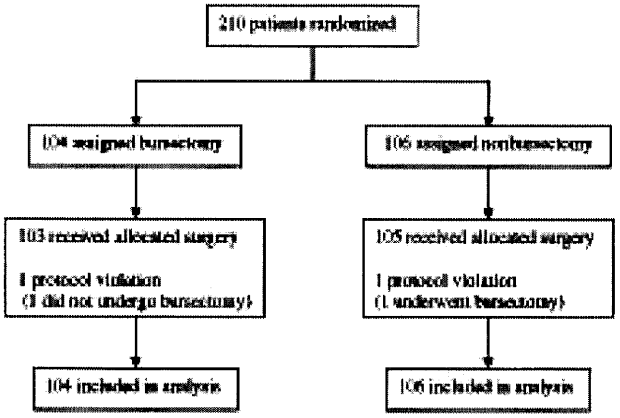

Fig. 1 CONSORT flowchart for patients

bursectomy. Most of the baseline characteristics were well balanced (Table 1). The bursectomy group had slightly older patients than the nonbursectomy group (median 65 vs. 63 years, $p = 0.099$). The number of patients with pathologically positive nodes was slightly higher in the bursectomy group than in the nonbursectomy group (52.9% vs. 43.4%, $p = 0.214$).

The operative details are shown in Table 2. A total gastrectomy was performed on 22 (21.2%) patients in the bursectomy group and on 27 (25.5%) patients in the nonbursectomy group. About one-half of patients in each of the two groups underwent a Roux-en-Y reconstruction procedure. A combined resection of other organs was performed for 103 patients in total. The resected organs were the gallbladder in 98 patients, spleen in 26 patients, part of the pancreas in 1 patient, the colon in 1 patient, the left adrenal gland in 1 patient, and the diaphragm in 1 patient. It was of note that although the difference was not statistically significant the number of patients with a combined resection was greater in the nonbursectomy group than in the bursectomy group (42.3 vs. 55.7%, $p = 0.055$). When we evaluated the operating time after dividing the patients into two subgroups, either with or without a combined resection of other organs, the bursectomy required a longer operating time (median 27 min in patients with a combined resection, 26 min in patients without a combined resection). The amount of blood loss significantly increased in the bursectomy group compared to the nonbursectomy group (median 475 vs. 350 ml, $p = 0.047$). There was no significant difference between the two groups regarding the number of dissected lymph nodes.

Operative morbidity and mortality

The overall operative morbidity rate was 14.3% (30 patients), which was the same in the two groups (Table 3). Prespecified complications, including pancreatic fistula, anastomotic leakage, abdominal abscess, bowel obstruction,

Table 1 Patient and tumor characteristics

Characteristic	Bursectomy ($n = 104$)	Nonbursectomy ($n = 106$)	p^*
Age (years)			0.099
Median	65	63	
Range	31–79	34–78	
Sex			0.761
Male	73	77	
Female	31	29	
Body mass index			0.653
Median	22.3	22.5	
Range	15.7–28.9	15.6–29.4	
Tumor size (cm)			0.311
Median	4.3	4.5	
Range	0.9–11.0	1.5–12.0	
Histological type			0.784
Differentiated	47	50	
Undifferentiated[a]	57	56	
Clinical T stage[b]			0.572
cT2	61	67	
cT3	43	39	
Clinical N stage[b]			1.000
cN0	59	61	
cN1	45	45	
Pathologic T stage[b]			0.902
pT1	17	19	
pT2	62	64	
pT3/4	25	23	
Pathologic N stage[b]			0.119
pN0	49	60	
pN1	37	24	
pN2/3	18	22	
Residual tumor			1.000
R0	101	102	
R1	3	4	

* The p values were calculated by Fisher's exact test for sex, histological type, clinical T stage, clinical N stage, and residual tumor; by the chi-squared test for pathologic T stage and pathologic N stage; and by the Mann–Whitney U-test for age, body mass index, and tumor size

[a] Undifferentiated type included one endocrine cell carcinoma case in the nonbursectomy group

[b] T stage and N stage were according to the 13th edition of the Japanese Classification of Gastric Carcinoma

Table 2 Profile of surgical treatment

Treatment	Bursectomy ($n = 104$)	Nonbursectomy ($n = 106$)	p^*
Gastrectomy			0.515
Total	22	27	
Distal subtotal	82	79	
Reconstruction method			0.705
Roux-en-Y	48	55	
Billroth I	54	49	
Other[a]	2	2	
Combined resection of other organs			0.055
Present	44	59	
Gallbladder	41	57	
Spleen	12	14	
Other[b]	1	2	
Absent	60	47	
Operating time (min)			0.368
Median	222	221	
Range	134–488	111–360	
Blood loss (ml)			0.047
Median	475	350	
Range	80–3970	55–2901	
No. of dissected lymph nodes			0.417
Median	38	37	
Range	11–98	7–97	

* p values were calculated by Fisher's exact test for gastrectomy and combined resection of other organs (present vs absent); by chi-squared test for the reconstruction method; and by the Mann–Whitney U-test for operating time, blood loss, and the number of dissected lymph nodes

[a] Others included one Billroth II method and one intestinal interposition method in the bursectomy group and two Billroth II methods in the nonbursectomy group

[b] Others included one adrenal gland in the bursectomy group and one pancreas and one diaphragm in the nonbursectomy group

Table 3 Postoperative morbidity

Morbidity	Bursectomy ($n = 104$)	Nonbursectomy ($n = 106$)	p^*
Any complication	15	15	1.000
Pancreatic fistula	3	7	0.332
Anastomotic leakage	4	3	0.720
Abdominal abscess	3	8	0.214
Bowel obstruction	2	1	0.620
Hemorrhage	1	0	0.495
Pneumonia	1	1	1.000

* The p values were calculated by Fisher's exact test

hemorrhage, and pneumonia, did not significantly differ between the two groups. Among the 10 patients with a pancreatic fistula, 6 underwent splenectomy, but no patients underwent pancreaticosplenectomy. Ten patients suffered from other complications, including two cases of chylous lymphorrhea, two of delayed gastric emptying without obstruction, and one case of afferent loop syndrome, acute cholecystitis, acute enteritis, arteriosclerosis obliterans of the leg, drug-induced hepatitis, and anastomotic stricture. The incidence of these miscellaneous complications tended

to be more frequent in the bursectomy group than in the nonbursectomy group (7.7 vs. 1.9%, $p = 0.057$). The median amylase levels in the drainage fluid on POD 1 were 282 IU/L in the bursectomy group and 314 IU/L in the nonbursectomy group ($p = 0.543$). Reoperation was required in four patients (1.9%): two for intestinal obstruction, one for afferent loop syndrome in the bursectomy group, and one for anastomotic leakage in the nonbursectomy group. The median hospital stay after surgery was 16 days in the bursectomy group and 15 days in the nonbursectomy group ($p = 0.744$).

There were two hospital deaths (0.95%). One patient in the bursectomy group and one patient in the nonbursectomy group died of sepsis after anastomotic leakage and pancreatic fistula formation, respectively. All other patients recovered from surgery and were discharged from the hospital.

Discussion

Two factors are necessary for bursectomy to be accepted as a standard treatment for advanced gastric cancers: safety and oncologic benefit. Only a randomized clinical trial can scientifically evaluate this proposition, and we are the first worldwide to conduct such a trial. This article is an early report of this trial with respect to operative safety. We found that overall morbidity and mortality were equivalent with and without bursectomy. Although the amount of surgical blood loss was significantly increased with bursectomy, overall we concluded that this procedure is safe and acceptable.

The safety of surgical treatments strongly depends on the surgeon's experience. Specific training is required to perform any surgical procedure, particularly when it is done for cancer treatment. There have been clinical trials studying the extent of lymph node dissection during gastric surgery. Two European randomized trials comparing D1 with D2 lymphadenectomy concluded that D2 was not acceptable as a standard treatment because D2 was associated with higher morbidity and mortality than D1 [8, 9]. On the other hand, two randomized trials comparing D1 with D2 and D2 with D3 lymphadenectomy in eastern Asia demonstrated that both D2 and D3 gastrectomy could be performed with low operative risk [13, 14]. This finding can be explained by the high volume of gastric cancer patients treated at that hospital and the high prevalence of gastric cancer in eastern Asia. In this study, all the patients were enrolled from an institution in which more than 50 gastrectomies were performed each year. In our trial the surgical procedures being performed by experienced surgeons accounted for the low mortality rates (0.95%) and low morbidity rates (14.3%).

Among various adverse events after surgery, we were concerned about the increased incidence of pancreatic fistulas after bursectomy because bursectomy requires resection of the capsule covering the pancreas [15]. However, we did not observe a significant increase in the incidence of pancreatic fistulas or inappropriate amylase levels in the postoperative drainage fluid, a surrogate marker of a pancreas fistula. This suggests that a pancreatic fistula is not caused by removal of a pancreatic capsule but may be caused by lymph node dissection adjacent to the pancreas parenchyma.

The next concern included the possibility of adhesion formation. Intestinal obstruction is the representative symptom of adhesion. In this study, two bursectomy patients and one nonbursectomy patient suffered from postoperative bowel obstruction, but there was no significant difference between the two groups. As 3 months' observation after surgery was not enough to evaluate the incidence of intestinal obstruction, a longer observation is necessary to draw a conclusion. Adhesion to the mesocolon and pancreas may cause specific local symptoms, such as delayed gastric emptying or afferent loop syndrome. It is of note that both delayed gastric emptying (two patients) and afferent loop syndrome (one patient) were observed only in the bursectomy group. Although this also did not reach statistical significance, careful observation is required in a larger cohort study.

In general, omentectomy and bursectomy are simultaneously performed for the same purpose, but their clinical pictures are somehow different. As the great omentum has numerous milky spots, which absorb ascites and actively incorporate cancer cells, peritoneal metastasis is frequently observed [16]. On the other hand, bursa omentalis, which is a semi-closed cavity, allows exfoliated cancer cells to remain. As for the surgical aspects, omentectomy is not difficult and does not increase the operating time or the blood loss. In contrast, the bursectomy technique is complicated and increases the operating time and bleeding. Considering the balance between the risk and benefit of each surgical procedure, we performed an omentectomy for all patients and randomly assigned each case to either with or without bursectomy. If we cannot find a benefit of bursectomy in this trial, we should elucidate the significance of omentectomy in the next step.

Conclusions

This study showed that experienced surgeons could safely perform a D2 gastrectomy with bursectomy. Although bursectomy resulted in more blood loss, the major operative complications and hospital deaths were not increased. Regarding the survival benefit of this procedure, we must

wait for the results of the final analysis when the data have matured sufficiently.

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Conflict of interest The authors declare no conflicts of interest.

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Survival Analysis of Patients With Duodenal Gastrointestinal Stromal Tumors

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Goals: To evaluate the survival characteristics of patients with duodenal gastrointestinal stromal tumors (GISTs).

Background: GISTs represent the most common mesenchymal neoplasms. However, duodenal GISTs are relatively rare, and few studies have been performed with a focus on duodenal GISTs.

Study: We collected the data of 41 GIST patients including 7 duodenal cases. Clinicopathologic findings and recurrence-free survival (RFS) of duodenal GIST patients were analyzed.

Results: The proportion of having any symptoms was 86% in duodenum, 32% in stomach, and 56% in other GISTs ($P = 0.034$), and the most common symptoms of duodenal GISTs were melena and anemia. The 2-year RFS rates were 51.4% in duodenal GISTs, 78.4% in stomach GISTs, and 100% in other GISTs, and duodenal GISTs showed poorer RFS than nonduodenal GISTs (hazard ratio, 5.2; log-rank $P = 0.019$). Particularly, in low-risk and intermediate-risk group, the hazard ratio of recurrence was 12.3 (log-rank $P = 0.010$). Multivariate Cox analysis showed symptom ($P = 0.007$), mitotic index ($P = 0.011$), and tumor location ($P = 0.043$) were significant prognostic factors of recurrence.

Conclusions: RFS of duodenal GISTs was worse than nonduodenal GISTs.

Key Words: duodenum, GIST, RFS, survival

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Gastrointestinal stromal tumors (GISTs) represent the most common mesenchymal neoplasms arising within the gastrointestinal tract. These tumors are thought to share a common progenitor cell with the interstitial cells of Cajal, and usually have activating mutations in either c-kit (75% to 80%) or platelet-derived growth factor receptor α (PDGFRA) (5% to 10%), 2 closely related receptor tyrosine kinases.[1] These mutations lead to ligand-independent activation and signal transduction mediated by constitutively activated KIT or PDGFRA. This theory was first proposed by Kindblom et al[2] and Hirota et al[3] revealed an association between the presence of c-kit mutation and tumor development.

GISTs can arise anywhere in the gastrointestinal tract, but their most frequent locations are the stomach (60%) and the small intestine (25%). Duodenal GISTs are relatively rare and comprise about 5% of surgically resected GIST cases.[4,5] Earlier studies have reported that duodenal GISTs were larger than stomach GISTs, and that their most frequent locations were the second and third portions of the duodenum.[4] Owing to the unique and complex anatomy of the duodenum, complete resection of duodenal GISTs sometimes requires wide resection methods such as pancreaticoduodenectomy,[5] which is rarely the case for GISTs in other locations. Only few reports about the characteristics of duodenal GISTs have been published earlier,[5–9] and few studies have been performed a survival analysis of patients with duodenal GISTs. From August 1993 to January 2008, we encountered 41 GIST cases of which 7 were duodenal GISTs. Here we conduct a retrospective cohort study to evaluate the survival characteristics of duodenal GISTs.

PATIENTS AND METHODS

Patients

We retrospectively reviewed the records of all patients with GISTs treated at the Osaka National Hospital between August 1993 and January 2008. The diagnosis of GISTs was conducted by histologic examination, immunohistochemical staining for KIT and CD34, and detection of c-kit or PDGFRA mutations.

Data on patients' age, sex, tumor location, symptoms, pathologic findings, c-kit and PDGFRA mutations, treatment, and survival outcome were collected. Tumor size was defined as the largest diameter of the primary tumor in any dimension. Pathologic data included mitotic index and results of immunohistochemical staining for KIT and CD34. Treatment data included type of resection and adjuvant treatment. Tumor size and mitotic index were used for risk classification according to the Fletcher score.[10] However, in this study, we combined low-risk and intermediate-risk patients in the survival analysis because "low-risk" has not been defined for duodenal GISTs.

Statistical Analysis

Associations between tumor location and clinicopathologic variables were analyzed using the χ^2 test. Recurrence-free survival (RFS) was defined as the time

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TABLE 1. Characteristics of 7 Patients With Duodenal GISTs

Age (y)	Sex	Clinical Symptom	Location of Duodenal GIST	Size (mm)	Operation	Adjuvant Therapy	KIT	CD34	Mitotic Index (per 50 HPF)	C-*Kit* Mutation	Risk Classification
64	F	Melena	Second part	60	Gastrojejunostomy	–	–	–	< 5	Exon 11	Intermediate
58	F	Melena	Second part	70	Pancreaticoduodenectomy	–	+	+	< 5	NA	Intermediate
70	F	Abdominal mass	Fourth part	150	Partial duodenal resection	+	+	+	< 5	Exon 13	High
67	F	Absent	First part	60	Partial duodenal resection	–	+	+	< 5	Exon 11	Intermediate
39	F	Melena	First part	120	Partial duodenal resection	–	+	+	5-10	Exon 11	High
65	M	Anemia	Second part	30	Partial duodenal resection	–	+	NA	5-10	Exon 9	Intermediate
75	F	Anemia	Second part	40	Pancreaticoduodenectomy	–	+	–	> 10	Exon 11	High

GISTs indicates gastrointestinal stromal tumors; HPF, high-power field; F, female; M, male; NA, not analyzed.

from surgery to either the first recurrence or death from any cause. RFS curves were estimated by the Kaplan-Meier method and compared using the log-rank test. Multivariate Cox regression analyses were performed to adjust for the potential confounding factors whose P values were under 0.2 in univariate analyses. All statistical analyses were performed with SPSS software, version 15.0J. P values less than 0.05 were considered statistically significant, and all tests were 2-sided.

RESULTS

Patient Characteristics

Forty-one patients with GISTs were admitted for treatment to Osaka National Hospital between August 1993 and January 2008, and of these 7 patients (17%) were diagnosed with duodenal GISTs (Table 1). Six of the 7 duodenal GIST patients were female. The second portion of the duodenum was most frequently affected, which is of significance because of the need for pancreaticoduodenectomy if the tumor is located on the same side of intestine as the Papilla Vater. For 1 duodenal GIST patient, we could not perform radical surgery because of severe patient's general condition, whereas the other duodenal GIST patients received complete gross resection. Postoperative complications occurred in 3 of 7 duodenal GIST patients. These complications included pancreatic fistula, and intra-abdominal abscess, but none of the patients died within 1 month after surgery. Only 1 patient received adjuvant chemotherapy after surgery. One patient showed immunohistochemical staining of neither c-kit nor CD34. Six cases had c-kit mutations; 4 for exon 11, 1 for exon 9, and 1 for exon 13. The numbers of intermediate-risk and high-risk patients were 4 (57%) and 3 (43%), respectively.

We compared patients with duodenal GISTs to those with stomach GISTs and other GISTs (Table 2). Among 9 patients with other GISTs, 4 were found in rectum and in small intestine, and 1 in omentum. There were no statistical differences in clinicopathologic factors except for clinical symptoms and CD34 positivity. With regard to immunohistochemical findings, the KIT-positive rate was similar in duodenal and other GISTs, whereas the CD34-positive rate was lower in duodenal GISTs ($P = 0.049$). Although over 30% patients with stomach GISTs were classified as low-risk, there were no low-risk patients among the duodenal and other GIST groups.

Of patients with duodenal GISTs, 86% had symptoms, whereas 32% of patients with stomach GISTs, and 56% of those with other GISTs were affected; this difference was statistically significant ($P = 0.034$). Five of 6 symptomatic patients with duodenal GISTs had melena or anemia, whereas a half of symptomatic patients with stomach GISTs complained of epigastralgia (Table 3).

TABLE 2. Comparison of Characteristics Among Duodenal GISTs, Stomach GISTs, and GISTs in Other Locations

	Duodenum (n = 7)	Stomach (n = 25)	Other (n = 9)	*P*
Age (y)				0.90
Median (range)	65 (39-75)	67 (48-82)	59 (45-86)	
Sex				0.10
Male	1 (14%)	13 (52%)	2 (22%)	
Female	6 (86%)	12 (48%)	7 (78%)	
Clinical Symptom				0.034
Absent	1 (14%)	17 (68%)	4 (44%)	
Present	6 (86%)	8 (32%)	5 (56%)	
Immunohistochemistry				
KIT				0.53
Positive	6 (86%)	22 (88%)	9 (100%)	
Negative	1 (14%)	3 (12%)	0 (0%)	
CD34*				0.049
Positive	4 (67%)	23 (96%)	6 (67%)	
Negative	2 (33%)	1 (4%)	3 (33%)	
Tumor size (cm)†				0.40
Median (range)	6.0 (3.0-15)	5.0 (1.7-24)	6.0 (2.5-12)	
Mitotic Index (per 50 HPF)				0.59
< 5	4 (57%)	16 (64%)	3 (33%)	
5-10	2 (29%)	5 (20%)	3 (33%)	
> 10	1 (14%)	4 (16%)	3 (33%)	
Risk Classification				0.13
Low	0 (0%)	8 (32%)	0 (0%)	
Intermediate	4 (57%)	7 (28%)	5 (56%)	
High	3 (43%)	10 (40%)	4 (44%)	
C-kit mutation‡				0.33
Exon 9	1 (17%)	0 (0%)	1 (50%)	
Exon 11	4 (66%)	17 (86%)	1 (50%)	
Exon 13	1 (17%)	1 (7%)	0 (0%)	
Exon 17	0 (0%)	1 (7%)	0 (0%)	

*One duodenal GIST case and 1 stomach GIST case were not analyzed.
†One stomach GIST case was not analyzed.
‡One duodenal GIST case, 15 stomach GIST cases, and 7 other GIST cases were not analyzed.
GISTs indicates gastrointestinal stromal tumors; HPF, high-power field.

TABLE 3. Symptoms Among Duodenal GISTs, Stomach GISTs, and GISTs in Other Locations

	Duodenum (n = 6)	Stomach (n = 8)	Other (n = 5)
Anemia	2 (33%)	2 (25%)	0
Melena	3 (50%)	0	1 (20%)
Epigastralgia	0	4 (50%)	0
Abdominal mass	1 (17%)	1 (13%)	1 (20%)
Nausea	0	1 (13%)	1 (20%)
Others	0	0	2 (40%)

GISTs indicates gastrointestinal stromal tumors.

Survival

In survival analysis of all GIST patients, the 2-year RFS rates of duodenal, stomach, and other GISTs were 51.4%, 78.4%, and 100%, respectively ($P = 0.058$) (Fig. 1A). As the survival curves of stomach and other GISTs were similar, we combined the stomach GISTs with other GISTs as a nonduodenal group, and compared RFS of duodenal GIST patients with those of nonduodenal GIST patients. As the result, the hazard ratio (HR) of recurrence was 5.1 [95% confidence interval (CI), 1.1-23.2] in the duodenal GIST patients, and the log-rank test showed statistical significance ($P = 0.019$) (Fig. 1B). In the low-risk and intermediate-risk groups specifically, the 2-year RFS rates of patients with duodenal and nonduodenal GISTs were 50% and 100%, respectively, showing a statistical difference (log-rank $P = 0.010$) and the HR of recurrence was 12.3 (95% CI, 1.1-142.9) (Fig. 2A). However, in the high-risk group there was no significant difference in RFS between duodenal GIST patients and nonduodenal GIST patients (log-rank $P = 0.60$) (Fig. 2B), and the HR of recurrence was 1.8 (95% CI, 0.19-17.9).

Univariate analyses revealed that symptom ($P = 0.009$), mitotic index ($P = 0.038$), and tumor location ($P = 0.035$) were the statistically significant prognostic factors of RFS (Table 4). These 3 factors were significantly associated with RFS even in multivariate analysis.

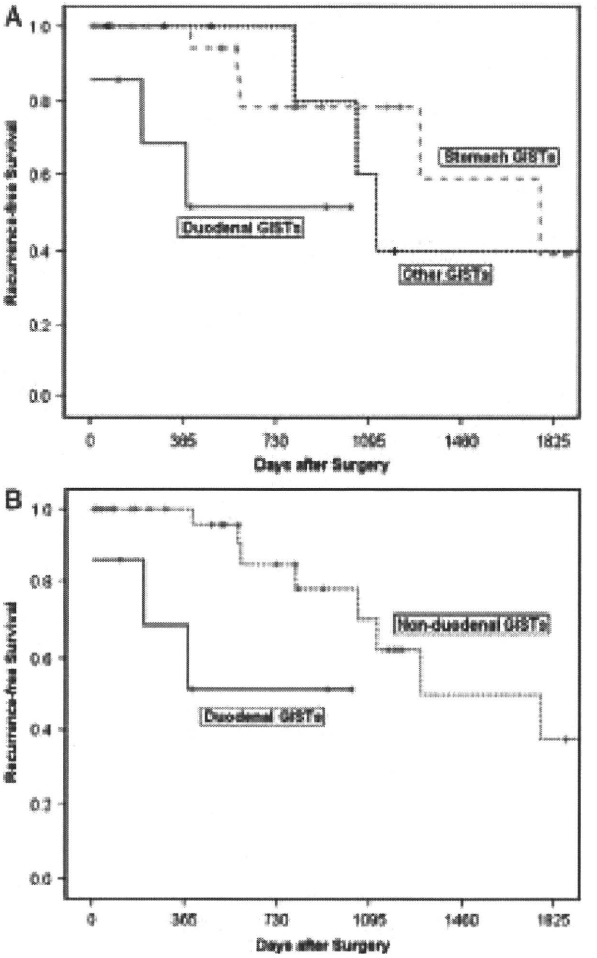

FIGURE 1. Recurrence-free survival of patients with gastrointestinal stromal tumors (GISTs) on the basis of tumor location. A, Duodenal versus stomach versus other GISTs. B, Duodenal versus nonduodenal GISTs.

DISCUSSION

GISTs are often discovered in the stomach and small intestine, but duodenal GISTs comprise only about 5% of these. Although 2 case series have studied duodenal GISTs,[7,8] neither conducted a survival analysis. This study showed that the RFS of duodenal GIST patients was worse than that of patients with stomach GISTs or GISTs in other locations, and the poor prognosis of duodenal GISTs was more remarkable in low-risk and intermediate-risk patient groups. Several earlier studies have reported that patients with GISTs of the small intestine have an unfavorable prognosis, compared with stomach GISTs.[11-13] In this study, we combined small intestine cases with stomach cases, because the survival curves of stomach and other GISTs were similar. Multivariate Cox analyses performed after adjusting for other prognostic factors revealed that tumor location was

TABLE 4. Association of Clinicopathological Factors With Recurrence-free Survival

	Univariate		Multivariate	
	Hazard Ratio (95% CI)	P	Hazard Ratio (95% CI)	P
Age (>65 y)	2.4 (0.64-9.2)	0.20	1.6 (0.34-7.3)	0.56
Sex (male)	1.4 (0.43-4.8)	0.55	—	—
Symptom (present)	17.4 (2.0-150.1)	0.009	158.1 (3.9-6374.0)	0.007
Tumor size (>5 cm)	1.6 (0.45-5.7)	0.47	—	—
Mitotic index (≥5/50 HPF)	5.1 (1.1-23.8)	0.038	37.0 (2.3-596.7)	0.011
Location (duodenum)	5.1 (1.1-23.3)	0.035	10.9 (1.1-111.1)	0.043

CI indicates confidence interval; HPF, high-power field.

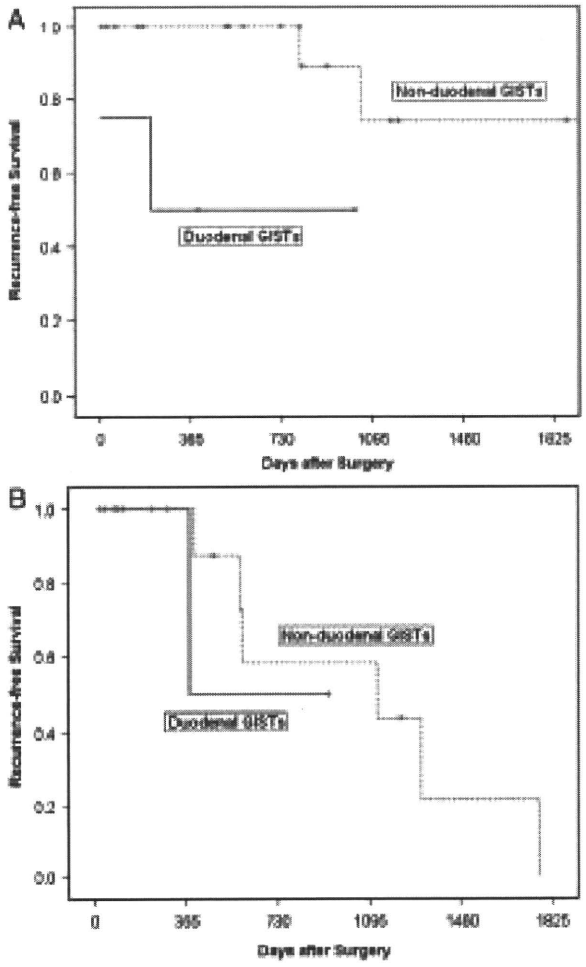

FIGURE 2. Recurrence-free survival of patients with duodenal gastrointestinal stromal tumors (GISTs) and nonduodenal GISTs in (A) low-risk and intermediate-risk group and (B) high-risk group.

an independent prognostic factor for GISTs. This result may indicate that the duodenal GISTs are biologically different from other GISTs.

Over the past several years, site-specific differences in appearance, morphology, and clinical outcome have been identified in GISTs. It has been reported that the proportion of CD34-positive tumors and the frequency of c-kit mutations are different depending on location.[14,15] An earlier study reported that CD34 positivity was more frequent in malignant tumors than in borderline or benign tumors.[16] Another study reported that CD34 positivity in patients with recurrence is higher than those without recurrence, although the difference was not statistically significant.[17] In this study, the proportion of CD34-positive patients with duodenal GISTs was even lower than that in patients with stomach GISTs. Thus, we cannot explain the poor survival of patients with duodenal GISTs by CD34 positivity alone. In contrast, earlier studies showed that mutations of exon 9 were more common in patients with small intestinal GISTs than in those with stomach GISTs.[18,19] GISTs with exon 9 mutations are often clinically and pathologically malignant, and this subgroup of patients is often resistant to imatinib. In our population, a duodenal GIST patient with an exon 9 mutation showed early metastases to the liver after surgery. The positivity rate of c-kit exon 9 mutations may contribute to the poor survival of patients with duodenal GISTs. In this study, however, we did not analyze c-kit mutation sites for about half of all GIST cases, so we could not evaluate the association between survival and the location of c-kit mutation.

In comparison of clinicopathologic characteristics among 3 location types of GISTs, clinical symptom was the most significant finding. Many duodenal GIST patients had symptomatic complaints that were mainly associated with bleeding from tumor, whereas the proportion of stomach GIST patients who had any clinical symptoms in diagnosis was low (28%). Most of asymptomatic patients with stomach GISTs were diagnosed in medical screening or follow-up of other diseases. In Japan, medical screening with upper gastrointestinal endoscopy or x-ray has been widespread because of high prevalence of gastric cancer, and it may contribute to early detection of asymptomatic stomach GISTs. These features may induce the survival difference between the duodenal and nonduodenal GISTs. However, the tumor location was an independent prognostic factor after adjusting for the presence of clinical symptoms in the multivariate Cox analyses.

Surgery remains the mainstay of treatment for patients with primary GISTs without distant metastasis. A recent retrospective study to compare the survivals of duodenal GIST patients after pancreaticoduodenectomy with those after limited resection reported that the disease-free survivals were similar between 2 surgical procedures.[6] In this study, both the 2 cases who received pancreaticoduodenectomy are alive without recurrence, whereas 2 of 4 patients who received limited duodenal resection had recurrence after surgery. Complete gross resection with an intact pseudocapsule may be the most important thing to treat duodenal GISTs, and so we should not hesitate to perform combined resection such as pancreaticoduodenectomy to achieve gross resection, even though the surgical procedure is highly invasive.

Limitations of this study include its retrospective design and small sample size. As survival analyses with small number of patients sometimes mislead the results, we should therefore be careful in evaluating its results. However, to our knowledge, this is the first study to focus on the survival of patients with duodenal GISTs, and the difference of RFS between duodenal and nonduodenal GISTs was remarkable. In the future, prospective studies using larger numbers of patients will be needed.

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