first-line chemotherapy for gastric cancer. Shitara [6] reported the median OS was only 9.1 months with S-1-containing chemotherapy and 10.1 months with a non-S-1-containing regimen. These results suggest that, in patients who have recurrence after adjuvant S-1 chemotherapy, the disease may have to be treated as refractory to S-1.

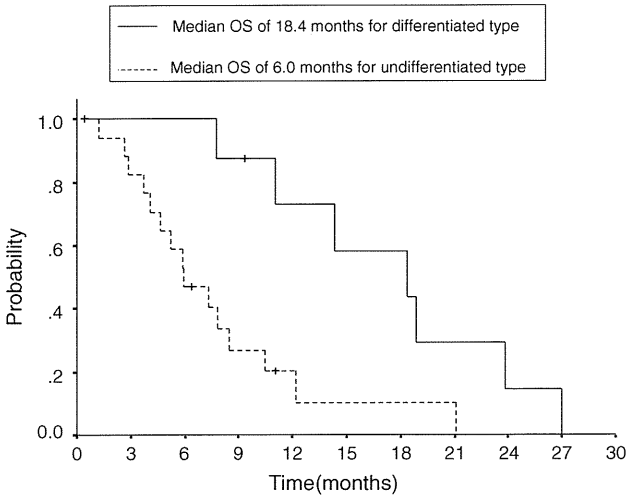

Fig. 2 Kaplan–Meier curves for overall survival (*OS*) showed a significant difference between patients with the differentiated type (*solid line*) and those with the undifferentiated type (*broken line*; $P = 0.009$)

Table 3 Stepwise multivariate Cox proportional hazards analysis of clinicopathologic factors

Factor (category)	No. of patients	*P* value	Hazard ratio	95% CI
Histological type (Differentiated versus undifferentiated)	9 and 17	0.009	4.117	1.420–11.931

Histological type is not known as a prognosticator in first-line chemotherapy for gastric cancer. The present study is the first to demonstrate that histological type was the only significant prognosticator by univariate and multivariate analyses in patients with recurrence after adjuvant S-1. On the other hand, some authors have reported the significance of the histological type in the survival of preoperative patients or in sensitivity to chemotherapy. Adachi et al. [7] evaluated 504 preoperative patients with gastric cancer that was classified as well-differentiated and poorly differentiated types. They found the 5-year survival rate to be higher in patients with well-differentiated gastric carcinoma than that in patients with poorly differentiated gastric carcinoma. Futatsuki et al. [8] reported a late phase II study of CPT-11 in advanced gastric cancer that found that the response rate was higher in patients with differentiated types than those with undifferentiated types (30.0 vs. 14.3%). On the other hand, Mai et al. [9] reported a late phase II study of docetaxel in advanced gastric cancer and found that the response rate was similar in patients with differentiated-type cancer and those with undifferentiated type (20.0 vs. 26.3%). In addition, two phase II studies of paclitaxel in advanced gastric cancer showed that the response rates for diffuse- and intestinal-types were 29 and 17%, and 36 and 24%, respectively [10, 11]. These reports may suggest that the histological type is important for chemosensitivity. which determines survival especially in S-1-refractory tumors. Patients with a differentiated type may have a greater chance of responding to both taxanes and CPT-11

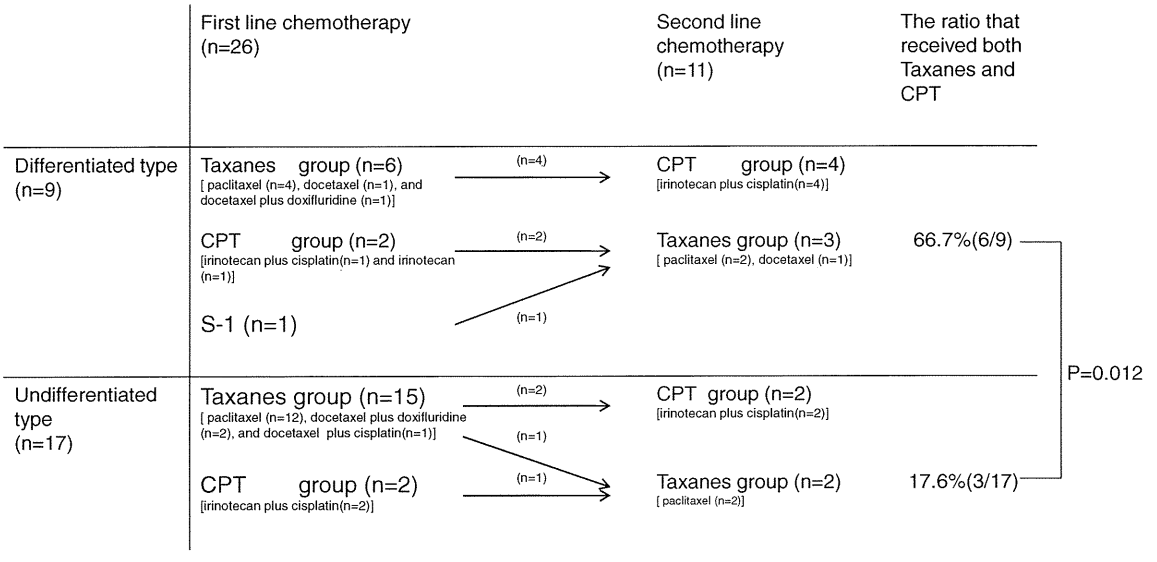

Fig. 3 Details of the first line- and second-line chemotherapy regimens in 9 patients with the differentiated type and 17 with the undifferentiated type

in comparison to those with an undifferentiated type, which would thereby contribute to the survival.

The present study found that 66.7% of patients with the differentiated type received both taxanes and CPT-11, in comparison to 17.6% of those with the undifferentiated type. This difference may have affected the difference in the survival between the two types. In particular, only 2 patients received CPT-11 as second-line chemotherapy among 15 patients with the undifferentiated type who had received taxanes as first-line chemotherapy, which decreased the rate of the entry into the second-line chemotherapy and may have shortened the survival. However, the undifferentiated type has more chance of responding to taxanes than CPT-11, as mentioned above. It is unclear whether or not the survival of the undifferentiated type is improved by selecting CPT-11 as the first-line chemotherapy.

Of note, the duration of the S-1 adjuvant chemotherapy did not have a significant prognostic impact in our study. Although a group who received S-1 for 3 months or longer tended to have a lower risk of recurrence compared with a group who received S-1 for <3 months, the difference did not reach statistical significance. Moreover, multivariate analysis identified the histological type as the only independent significant prognostic factor. Nevertheless, the duration of S-1 chemotherapy could, in theory, be relevant, and there is a possibility that the small number of patients analyzed might have adversely affected our results. The reasons for discontinuation of S-1 should also be taken into consideration when discussing the prognostic impact of the treatment duration. Again, given the small sample size, it was not practical at this time to analyze survival by further subdividing the patients into those who discontinued treatment due to toxicity and those whose treatment was terminated due to recurrence. In addition to the issue of sample size, the retrospective nature of the study and diversity of the drugs used after S-1 failure are weaknesses that need to be borne in mind when interpreting results from the present study.

In summary, the present study revealed that survival after failing the standard adjuvant chemotherapy did not reach the expected 12 months as observed in recent phase III trials for untreated advanced/metastatic gastric cancer. Undifferentiated phenotype was a significant indicator of poor prognosis in these patients.

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Conflict of interest None declared.

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ORIGINAL ARTICLE

Evaluation of Postoperative Pancreatic Fistula After Total Gastrectomy with D2 Lymphadenectomy by ISGPF Classification

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Abstract
Introduction Postoperative pancreatic fistula (POPF) is a serious complication of total gastrectomy (TG) with D2 lymphadenectomy (D2). However, the actual incidence and risk factors are not yet completely understood, due in part to the absence of the widely accepted criteria for POPF following gastrectomy.
Patients and methods One hundred and four patients who underwent TG with D2 between March 2007 and December 2009 were included in this study. The incidence and severity of POPF were evaluated according to the International Study Group on Pancreatic Fistula (ISGPF) classification. In addition, risk factors for POPF of ISGPF grade B or higher were investigated.
Results POPFs of ISGPF grade B or higher were observed in 23 patients (22.1%). Univariate analysis found that sex, body mass index, and amylase concentration of drainage fluid (D-AMY) on the first postoperative day (1POD) were significant predictors of POPF grade B or higher. The appropriate cutoff level of D-AMY on 1POD was calculated as 3398 IU/l. Multivariate analysis showed that D-AMY ≥3,398 IU/l on 1POD was the only independent risk factor.
Conclusions High D-AMY on 1POD (≥3,398 IU/l) can predict a grade B or higher POPF, and this value may be useful in the early detection of POPF following TG with D2.

Keywords POPF · Total gastrectomy · D2 lymphadenectomy · ISGPF

Introduction

At present, surgical resection is the mainstay of the treatment for gastric cancer.[1] For advanced gastric cancer located in the upper third of the stomach, total gastrectomy (TG) with D2 lymphadenectomy, which generally includes splenectomy, is a standard treatment in Japan. However, it has been shown that splenectomy in TG is associated with high morbidity rates.[2–7]

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Among such morbidities, postoperative pancreatic fistula (POPF) is one of the serious complications after TG, and it is sometimes life-threatening. Although POPF following TG has been investigated before, the incidence and risk factors are not completely understood, due in part to the absence of widely accepted criteria for POPF. Accordingly, different definitions of POPF have been used, resulting in highly variable reported rates of POPF, ranging from 5.3% to 49.7%,[8–16] thus making it impossible to even accurately estimate the incidence of POPF.

In 2005, the International Study Group on Pancreatic Fistula (ISGPF) formulated an objective definition of POPF.[17] Although this classification has been well accepted for pancreatic surgery, its validation for POPF following gastrectomy is yet to be fully investigated and still remains unclear.

Therefore, the aim of this retrospective study was to clarify the actual incidence of POPF after TG with D2 lymphadenectomy using the ISGPF classification. Risk factors for POPF, including the appropriate cutoff level for

Table 1 International Study Group on Pancreatic Fistula classification with examples[14]

No POPF	D-AMY on or after 3POD is not three times more than the upper normal serum amylase level.
Grade A	No specific treatment is required, although D-AMY on or after 3POD is three times more than the upper normal serum amylase level.
Grade B	Requires a change in management or adjustment of the clinical pathway. For example, antibiotics, total parenteral nutrition or enteral nutrition, and repositioning of drainage tubes are included in this grade.
Grade C	Requires a major change in the clinical pathway. Clinical intervention is aggressive, and often in the ICU setting.

POPF postoperative pancreatic fistula, *D-AMY* drainage amylase level, *3POD* third postoperative day, *ICU* intensive care unit

the amylase concentration of the drainage fluid (D-AMY) to predict POPF, were also investigated.

Methods

Patients

Between March 2007 and December 2009, 256 patients underwent TG at the Shizuoka Cancer Center, Shizuoka, Japan. Patients were excluded if they met any of the following criteria: (1) patients who underwent combined resection of pancreas, (2) patients who received neoadjuvant chemotherapy, (3) patients who underwent non-curative surgery, and (4) patients with remnant gastric cancer. Among the remaining 194 patients, 110 patients underwent TG with D2 lymphadenectomy. Six patients, in whom D-AMY was not examined on or after the third postoperative day (3POD), were excluded from the analysis; thus, the remaining 104 gastric cancer patients were included in the present study. The patients' clinical, surgical, and pathological records were collected from the database of our hospital.

In this retrospective study, the pathological data were recorded according to the 7th edition of the TNM Classification.[18] Macroscopic type, histologic type, and the number of lymph node stations were determined according to the Japanese Gastric Cancer Association classification (2nd English edition).[19]

Definition of D2 Lymphadenectomy for Upper Third Gastric Cancer

If the primary lesion is located only in the upper third part, the perigastric lymph nodes, suprapancreatic lymph nodes [along the celiac axis (station 9), the common hepatic artery (station 8a), the left gastric artery (station 7), and the splenic artery (station 11)], and splenic hilar lymph nodes should be dissected for D2 lymphadenectomy. If the primary lesion invaded the middle third part, lymph nodes along the proper hepatic artery (station 12a) should be dissected. For the patients with invasion of primary lesion to lower third part, lymph nodes along the superior mesenteric vein (station 14v) should be dissected additionally.

Amylase Concentration of Drainage Fluid

During surgery, one to four drainage tubes were placed. Each drain was connected to a bag through an extension tube. The amylase concentration of the fluid from each drain was evaluated on the first postoperative day (1POD) and on or after 3POD in all patients. In patients with two or more drains, the highest amylase value was taken as the representative value on that day.

Definition and Severity of POPF

In this study, we defined and classified POPF using the ISGPF criteria. The grades of POPF severity, determined by the ISGPF classification, are summarized in Table 1.

Table 2 Clavien–Dindo classification with examples[21]

Grade 0	No complications
Grade I	Deviation from normal hospital course, no need for medication or intervention. Allowed therapeutic regimens are drugs such as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy
Grade II	Requires pharmacological treatment with drugs other than those allowed for grade I complications. For example, antibiotics, blood transfusions, and total parenteral infusion are included in this grade.
Grade IIIa	Requires intervention not under general anesthesia. For example, exchange of drainage tube or insertion of a new drainage tube is included in this grade.
Grade IIIb	Requires intervention under general anesthesia
Grade IVa	Readmission to ICU—single organ dysfunction (including dialysis)
Grade IVb	Readmission to ICU—multiorgan dysfunction
Grade V	Postoperative mortality

ICU intensive care unit

Using the ISGPF criteria, patients with D-AMY on or after 3POD of three times more than the upper normal serum amylase level were defined as having POPF. We classified patients as grade A when no specific treatment was needed. Grade B required a change in management or adjustment in the clinical pathway, for example, repositioning of drainage tubes or administration of antibiotics. In grade C, a major change in clinical management was required. Patients in this grade were managed in the intensive care unit because of sepsis or organ dysfunction.

In patients with POPF of ISGPF grade B or higher, we also classified their POPF severity by the Clavien–Dindo classification to obtain a more precise grading. This classification also consists of therapy-oriented objective criteria and contains seven severity grades (Table 2). ISGPF grade B or higher is equivalent to Clavien–Dindo grade II or higher, and this condition is considered potentially fatal. In this study, therefore, we focused on POPF with an ISGPF grade of B or higher (Clavien–Dindo classification of grade II or higher).

Statistical Analysis

In order to identify clinicopathological variables that affect the development of POPF, variables were compared between patients with and without POPF of ISGPF grade B or higher. The chi-square test was used for categorical variables, and the Student's *t* test or Wilcoxon test was used for numerical variables as appropriate.

A multivariate logistic regression model was used to adjust for potential confounding factors. Variables achieving a probability value <0.05 in the univariate analysis were subsequently introduced in a multivariate analysis.

The receiver operating characteristic (ROC) curve of D-AMY on 1POD was used to identify an appropriate cutoff level to detect grade B or higher POPF.

All statistical analyses were performed with JMP software, version 8.0 (SAS Institute, Cary, NC). Values of *P* values <0.05 were considered statistically significant, and all tests were two-sided.

This study was approved by the Human Ethics Review Committee of the Shizuoka Cancer Center.

Results

Patient Characteristics

The clinicopathological features of the 104 patients included in the study are summarized in Table 3. Over two thirds of cases were male, and the mean age was 65.8 years.

Table 3 Clinicopathological characteristics of all eligible patients

	No. of patients (n = 104)
Age (years)[a]	65.8 (9.0)
BMI[a]	21.7 (3.6)
Total protein (g/dl)[a]	6.9 (0.8)
Sex	
Male	76 (73.1)
Female	28 (26.9)
Blood loss (ml)[b]	547.5 (70–2,103)
Operation time (min)[b]	239 (153–399)
Macroscopic type	
0	25 (24.0)
1	11 (10.6)
2	24 (23.1)
3	33 (31.7)
4	11 (10.6)
Histological type	
Undifferentiated	55 (52.9)
Differentiated	49 (47.1)
pT	
1	8 (7.7)
2	17 (16.3)
3	39 (37.5)
4a	36 (34.6)
4b	4 (3.8)
pN	
0	30 (28.8)
1	26 (25.0)
2	15 (14.4)
3a	12 (11.5)
3b	21 (20.2)
pStage	
IA	6 (5.8)
IB	11 (10.6)
IIA	17 (16.3)
IIB	21 (20.2)
IIIA	4 (3.8)
IIIB	21 (20.2)
IIIC	24 (23.1)
IV	0 (0)

Values in parentheses are percentages unless indicated otherwise

BMI body mass index

[a] Values are mean (standard deviation)

[b] Values are median (range)

The proportion of patients with early gastric cancer (pT1) was 7.7%. Nodal metastasis was detected in 74 patients (72.2%). The median operation time was 239 min (range, 153–399 min), and median blood loss was 547.5 ml (range, 70–2,103 ml).

Incidence and Severity of POPF

The overall incidence of POPF was 55.8% by the ISGPF criteria. ISGPF grade A and B POPF were observed in 33.7% and 22.1% of patients, respectively. No patient was classified as ISGPF grade C. Perioperative mortality was not seen. The median postoperative hospital stay for patients with no POPF, grade A POPF, and grade B POPF was 16, 14, and 25 days, respectively (Table 4).

Patients with grade A do not need any specific treatment and resolved. All 23 patients, who were classified as grade B POPF, received antibiotics. Of these patients, 16 patients underwent repositioning of drainage tubes, one patient underwent insertion of a new drainage tube, and another patient underwent both repositioning and insertion of a new drainage tube. All 23 patients with grade B resolved after these treatments. Fistulography was performed in 18 patients of grade B, and communication with the main pancreatic duct was not confirmed in any of these patients.

Using the Clavien–Dindo classification, five patients who only received antibiotics were classified as grade II POPF. Eighteen patients who underwent repositioning of a drainage tube or insertion of a new one, in addition to the administration of antibiotics, were classified as grade IIIa. The median postoperative hospital stay for patients with grade II and grade IIIa POPF was 16 and 28 days, respectively (Table 4).

Appropriate Cutoff Level of D-AMY on 1POD

The median D-AMY on 1POD was 1,755 IU/l (range, 124–133,380 IU/l). In order to identify the appropriate cutoff level of D-AMY on 1POD for detecting POPF of ISGPF grade B or higher, we used a ROC curve (Fig. 1). This analysis revealed that 3,398 IU/l on 1POD was the best cutoff value. The sensitivity, specificity, and positive predictive value of the amylase concentration for POPF of ISGPF grade B or higher were 72.7%, 76.7%, and 54.3%, respectively.

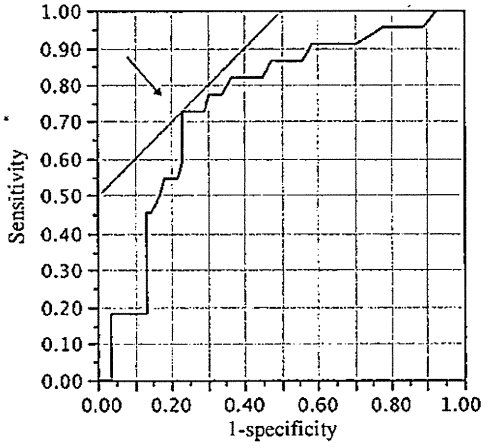

Fig. 1 ROC curve of drainage amylase levels on the first postoperative day, for distinguishing postoperative pancreatic fistula of grade B or higher, based on the International Study Group on Pancreatic Fistula classification. The *arrow* shows the best cutoff point. The area under the curve was 0.75

Risk Factors of POPF

Univariate analysis identified several factors which were highly associated with POPF of ISGPF grade B or higher (Table 5). The preoperative factors, sex (male, $P=0.021$) and increasing body mass index ($P=0.036$) had a strong association with the development of grade B or higher POPF. Moreover, the perioperative factor, D-AMY on 1POD (≥3,398 IU/l, $P<0.001$) was also significantly associated with the development of POPF of grade B or higher. However, no pathological factors were associated with the development of grade B or higher POPF.

Multivariate analysis showed that D-AMY on 1POD≥ 3,398 IU/l was the only significant independent risk factor for POPF of ISGPF grade B or higher ($P=0.001$; Table 6), and the odds ratio was 6.03 (95% CI, 2.14–18.44).

Table 4 Incidence and severity of postoperative pancreatic fistula according to the International Study Group on Pancreatic Fistula and Clavien–Dindo classifications

ISGPF classification	No. of patients	Postoperative hospital stay (days)[a]	Clavien–Dindo classification	No. of patients	Postoperative hospital stay (days)[a]
No POPF	46 (44.2)	16 (10–27)			
Grade A	35 (33.7)	14 (10–27)			
Grade B	23 (22.1)	25 (13–87)	Grade II	5 (4.8)	16 (13–33)
			Grade IIIa	18 (17.3)	28 (15–87)
Grade C	0 (0)				

Postoperative hospital stay is shown with respect to each POPF grading. Values in parentheses are percentages unless indicated otherwise

ISGPF International Study Group on Pancreatic Fistula, *POPF* postoperative pancreatic fistula

[a] Values are median (range)

Table 5 Association between patient characteristics and pancreatic fistula severity according to the International Study Group on Pancreatic Fistula classification

Parameters	Pancreatic fistula (no. of patients)		
	No POPF, grade A	Grade B	*P* value
Preoperative factors			
Sex			0.021
Male	56 (73.7)	20 (26.3)	
Female	26 (92.9)	2 (7.1)	
Age (years)[a]	65.3	67.7	0.276
BMI[a]	21.2	23.3	0.036
Total protein (g/dl)[a]	6.9	7.1	0.181
Perioperative factors			
Blood loss (ml)[b]	524	629	0.479
Operation time (min)[b]	238.5	248	0.796
Amylase concentration			<0.001
<3,398 (IU/l)	63 (90.0)	7 (10.0)	
≥3,398 (IU/l)	19 (55.9)	15 (44.1)	
Pathological factors			
Macroscopic type			0.881
0, 1, 2	47 (78.3)	13 (21.7)	
3, 4	35 (79.6)	9 (20.4)	
pT			0.692
T1, T2	19 (76.0)	6 (24.0)	
T3, T4	63 (79.7)	16 (20.3)	
pN			0.577
N0, N1	43 (76.8)	13 (23.2)	
N2, N3	39 (81.2)	9 (18.8)	
pStage			0.510
I, II	42 (76.4)	13 (23.6)	
III, IV	40 (81.6)	9 (18.4)	
Histological type			0.252
Differentiated	41 (74.6)	14 (25.4)	
Undifferentiated	41 (83.7)	8 (16.3)	

Values in parentheses are percentages unless indicated otherwise

POPF postoperative pancreatic fistula, *BMI* body mass index

[a] Values are mean

[b] Values are median

Discussion

The overall incidence of POPF grade B or higher after TG with D2 lymphadenectomy was 22.1%. In addition, we revealed that a high value for D-AMY on 1POD (≥3,398 IU/l) was the only independent predictor of grade B or higher POPF.

Table 6 Multivariate analysis of association between patient characteristics and postoperative pancreatic fistula of grade B or higher, classified by the International Study Group on Pancreatic Fistula definitions

Variables	Odds Ratio (95% CI)	*P* value
Sex (male)	3.73 (0.90–25.64)	0.072
BMI	5.90 (0.31–135.14)	0.240
D-AMY on 1POD (≥3,398 IU/l)	6.03 (2.14–18.44)	0.001

CI confidence interval, *BMI* body mass index, *D-AMY on 1POD* drainage amylase concentration on the first postoperative day

The extent of lymphadenectomy in gastric cancer surgery remains controversial, and D2 lymphadenectomy has not been performed routinely in Western countries. However, the Dutch Gastric Cancer Study Group recently showed that D2 lymphadenectomy is associated with low locoregional recurrence and gastric cancer-related death rates than D1 surgery after a median follow-up of 15 years.[20] Furthermore, clinical guidelines of the European Society of Medical Oncology referred to D2 lymphadenectomy as the standard treatment for advanced gastric cancer in 2010.[21] D2 lymphadenectomy is considered to be an important role for the local control of advanced gastric cancer, and it may be performed more widely in Western countries. Thus, it is important to comprehend complications after D2. In such complications, intra-abdominal infection which is often induced by POPF is potentially fatal, and so early detection of POPF and appropriate management is essential after D2. This is why we

investigated the risk factors of POPF for early detection in this study.

In the past, there have been some reports concerning pancreatic-associated complications after gastrectomy.[8,15,16,22–24] In these reports, however, the authors developed their own definition of POPF, and POPF after TG has rarely been analyzed using a set of widely accepted objective criteria. Sano et al.[8] defined POPF as a condition in which D-AMY was more than three times the normal serum amylase concentration for more than 7 days. On the other hand, the report of Katai et al.[22] describes pancreas-related abscesses, which they diagnosed when purulent fluid containing turbid necrotic debris drained from the peripancreatic area for more than 7 days. There have also been other definitions of POPF in previous studies.[15,16] To solve this problem, we used the ISGPF classification which is a therapy-oriented objective classification. It was first proposed for pancreatic surgery and has been validated in this situation and has become widely accepted in recent times.[17,25] However, validation of this classification after gastrectomy has not been fully investigated to date. Recently, Obama et al.[23] reported POPF after laparoscopic gastrectomy using the ISGPF classification. However, in their report, they used an additional definition of POPF to allow for missing data for D-AMY on 3POD, which was not the original ISGPF definition. As far as we know, our present study is the first study in which POPF after TG with D2 lymphadenectomy was evaluated by the original ISGPF classification as the objective criteria.

The ISGPF definition of POPF is objective and prevents down-rating because it is based on data that are usually well documented and easily verified. This kind of standardized and reproducible method allows comparison among different centers. However, this classification consists of only three severity groups. Thus, grades B and C may include a very wide range of patients' medical conditions. Accordingly, we also classified patients with grade B or higher POPF by the Clavien–Dindo classification for further investigation. The Clavien–Dindo classification allows the identification of most complications, and it also has gained widespread acceptance.[26–29] This classification consists of seven severity grades, including two subgroups for grades III and IV. In the current study, ISGPF grade B was divided into Clavien–Dindo grades II and IIIa, and more detailed grading could be performed. Anyhow, we considered a complication which needed some sort of intervention as potentially life-threatening. Thus, we analyzed the risk factors for POPF of ISGPF grade B or higher (Clavien–Dindo grade II or higher).

In our study, over half of the patients were diagnosed as POPF: 33.7% and 22.1% of all patients were classified with POPF of ISGPF grades A and B, respectively. It must be noted that total POPF rate after TG with D2 by ISGPF classification becomes high. These rates are higher than those reported after pancreatic surgery.[25] This can be explained by the soft quality of the pancreas in patients with gastric cancer. In fact, soft pancreas density was reported to be a significant risk factor for POPF in pancreatic surgery. Furthermore, resection of pancreatic capsule in D2 may be associated with POPF.

It is true that the frequency of POPF (55.8%) seems to be high, but 33.7% of all patients were ISGPF grade A. We consider that ISGPF grade A is not clinically important because they have only abnormal data and do not need any treatment. Additionally, the origin of high D-AMY cannot be specified exactly, and this amylase-rich fluid in grade A may be from disrupted lymphatic vessels, not from the damaged pancreas itself. This is why we focused on ISGPF grade B or higher as a potentially fatal condition in this study. We compared our incidence of POPF with past some reports (Table 7). Most of the definitions in past reports may approximately correspond

Table 7 Summary of the literatures about POPF after total gastrectomy

First author	Year	No. of patients	Extent of lymph node dissection	Incidence of POPF (%)	Definitions of POPF
Sano	1997	102	D0–D3	14	D-AMY>3 times more than s-AMY for≥7 days
Furukawa	2000	110	D2 (with vs. without pancreatectomy)	16 vs. 13	D-AMY>500 IU/l for 2 weeks
Ichikawa	2004	258	D1–D3	5.8	D-AMY>1,000 IU/l for ≥7 days
Okabayashi	2005	317	Not described	9.5	D-AMY and D-lipase >3 times more than s-AMY and s-lipase, drainage volume >10 ml/day
Kunisaki	2006	147	D2–D3 (with pancreatosplenectomy)	49.7	Dirty appearance, skin redness, D-AMY>1,000 IU/l, bacterial infection, and enhancement of abscess cavity
Nobuoka	2008	740	D1–D3	18	Purulent discharge for ≥7 days
Tanaka	2009	191	D1–D2	19.4	d-AMY between POD1 and POD3>3 times more than s-AMY, drain tube≥2 weeks, no evidence of anastomotic leakage

d-AMY amylase concentration of drainage tube, *s-AMY* serum amylase concentration, *s-lipase* serum lipase concentration, *POD* postoperative day

to ISGPF grade B or higher, and the incidence of POPF in those past reports were about 10–20%. Accordingly, our incidence of ISGPF grade B (22.1%) is not so high rate, considering that the extent of lymph node dissection was specified to D2 in our study.

The results of this study showed that high D-AMY on 1POD (≥3,398 IU/l) was the only statistically significant predictor of POPF, graded B or higher. This is meaningful as this cutoff value can be used in clinical practice. For example, this value can be used as a reference for the early removal of drains, or early preventive management for infection. In their previous report, Sano et al.[8] described that D-AMY on 1POD>4,000 IU/l was the best cutoff value. However, they did not use objective therapy-oriented criteria. Furthermore, the extent of lymphadenectomy was not specified in their study. In fact, standard D2 lymphadenectomy was performed in about half the patients, and the rest of the patients underwent D1 or D3 lymphadenectomy in their report. Thus, we consider D-AMY of approximately 3,000 IU/l on 1POD as a more appropriate cutoff value after TG with D2 lymphadenectomy. At present, there is no definite clinical guideline for the treatment of POPF. We consider that early preventive management by antibiotics or drainage tube placement for the long term may be beneficial for patients whose D-AMY on 1POD is higher than 3,000 IU/l.

In conclusion, the incidence of grade B or higher POPF after TG with D2 lymphadenectomy was 22.1% according to the ISGPF classification. A high D-AMY on 1POD (≥3,398 IU/l) was the only significant predictor of POPF grade B or higher. This cutoff value may be useful in the early detection of patients likely to develop POPF after TG with D2 lymphadenectomy, allowing for the appropriate management of these patients in a timely fashion.

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ORIGINAL ARTICLE

Intra-abdominal infectious complications following gastrectomy in patients with excessive visceral fat

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Abstract
Background Excessive visceral fat may be a better predictor of the development of postoperative morbidity after gastrectomy than body mass index (BMI). The aim of the present study was to clarify the most appropriate fat parameter to predict pancreas-related infection and anastomotic leakage following gastrectomy.
Methods The study was performed in 206 patients who underwent curative gastrectomy at the Shizuoka Cancer Center between April 2008 and March 2009. Relationships between fat parameters, including visceral fat area (VFA), and early surgical outcomes were investigated. The risk factors for pancreas-related infection and anastomotic leakage were identified using univariate and multivariate analyses.
Results There was no strong association between any of the fat parameters and operating time, intraoperative blood loss, the number of lymph nodes retrieved, or the duration of the postoperative hospital stay. Pancreas-related infection occurred in 18 patients (8.7%), whereas anastomotic leakage was observed in 10 patients (4.9%). Of all the fat parameters, only VFA was found to be an independent risk factor for both pancreas-related infection and anastomotic leakage, with odds ratios (95% confidence intervals) of 1.015 (1.005–1.025) and 1.010 (1.000–1.021), respectively.
Conclusions Excessive visceral fat, represented by the VFA, was found to be an independent risk factor for both pancreas-related infection and anastomotic leakage following gastrectomy.

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Keywords Gastric cancer · Gastrectomy · Visceral fat · Postoperative complication

Introduction

Surgery is the only treatment strategy that offers the hope of a cure for gastric cancer patients. In Japan, in which the rates of gastric cancer are greater than those in Western countries, gastrectomy with D2 lymph node dissection is a well-established and widely accepted procedure [1, 2]. Although two large randomized controlled trials in Europe failed to demonstrate the efficacy of this procedure, due, in part, to increased postoperative morbidity and mortality [3, 4], recent reports suggest that gastrectomy with D2 lymph node dissection may be beneficial in certain patients [3–6]. One of the reasons for the unfavorable outcomes of gastrectomy with D2 lymph node dissection in the European studies may have been the higher proportion of obese patients in those studies.

Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify obesity. In Japan, the median BMI of gastric cancer patients, as well as that of the general population, has increased in recent years [7]. Although a relationship between BMI and postoperative morbidity has been reported previously, it remains contentious whether a high BMI is really associated with an increased rate of postoperative morbidity [8–12]. Recently, several reports have suggested that visceral fat area (VFA) is more strongly associated with postoperative intra-abdominal infectious complications, including pancreas-related infection and anastomotic leakage, than BMI [13, 14]. However, this issue is also contentious.

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Therefore, in the present study we investigated the relationships between various fat parameters, including VFA, and early surgical outcomes following gastrectomy to clarify the most appropriate fat parameter to predict the development of pancreas-related infection and anastomotic leakage.

Methods

Patients

Between April 2008 and March 2009, a total of 217 patients underwent open distal or total gastrectomy with curative intent for primary gastric cancer at Shizuoka Cancer Center, Shizuoka, Japan. Patients who underwent splenectomy, distal pancreatic resection, and cholecystectomy were included in the study, whereas seven patients who underwent combined resection of other organs (liver, colon, and adrenal gland) and four patients who had synchronous cancer in other organs (colon, rectum, and kidney) were excluded from the study. Therefore, data from 206 patients were analyzed in the present study.

Lymph node station number, the degree of lymph node dissection, and pathological stage were determined on the basis of the *Japanese classification of gastric carcinoma* [15] and the *Gastric cancer treatment guidelines in Japan* [16]. Gastrectomy with D2 lymph node dissection was performed in patients with advanced gastric cancer, whereas D1 plus beta lymph node dissection (i.e., D1 + numbers 7, 8a, 9) was performed in patients with early gastric cancer.

Fat measurement

Multidetector computed tomography (MDCT) was performed in all patients prior to surgery. Patients were examined while in the supine position, with their arms stretched above their heads, at the end of inspiration, using a CT scanner (Aquilion; Toshiba Medical Systems, Tokyo, Japan). Parameters for scanning were: tube voltage, 120 kVp; scan time, 0.5 s; and reconstruction slice thickness, 2 mm. The tube current was determined automatically by the CT automatic exposure control system. The images obtained were transferred to a Ziostation workstation (Ziosoft, Tokyo, Japan), which was used to quantify the total fat area (TFA), subcutaneous fat area (SFA), and VFA at the level of the umbilicus. In the present study, relationships between early surgical outcomes following gastrectomy and TFA, VFA, SFA, and BMI, as the fat parameters, were investigated.

Definition of early surgical outcomes

Operating time, intraoperative blood loss, the number of lymph nodes retrieved, postoperative morbidity and mortality, and the duration of the postoperative hospital stay were investigated as early surgical outcomes.

Patients with Grade II or greater complications based on the Clavien-Dindo classification were defined as having postoperative morbidity [17]. In the present study, pancreas-related infection was diagnosed on the basis of the definitions of the International Study Group on Pancreatic Fistula (ISGPF) [18]. Diagnosis of anastomotic leakage was confirmed by radiological examination using contrast media. Postoperative mortality was defined as any death within 30 postoperative days (PODs).

Statistical analysis

Spearman's rank correlation coefficient was used to evaluate relationships between individual fat parameters (BMI, TFA, SFA, and VFA) and early surgical outcomes (operating time, intraoperative blood loss, number of lymph nodes retrieved, postoperative hospital stay). Relationships between individual fat parameters and the categorical variables of pancreas-related infection and anastomotic leakage were evaluated using logistic regression.

To identify independent risk factors for each of the intra-abdominal infectious complications, a multivariate logistic regression model with forward selection was used, with BMI, TFA, SFA, VFA, age, sex, operating time, intraoperative blood loss, number of lymph nodes retrieved, surgical procedure (total or distal gastrectomy), type of lymph node dissection (D2 or D1 plus beta), and splenectomy (yes or no) included as covariates.

All statistical analyses were performed using SPSS version 13.0 (SPSS, Chicago, IL, USA). All continuous data are presented as medians (ranges). $P < 0.05$ was considered significant.

Results

Patients' characteristics

The patients' characteristics are given in Table 1. Total gastrectomy was performed in 48 patients, 29 of whom also underwent splenectomy for the removal of splenic hilar lymph nodes. Additional pancreatosplenectomy was performed in 2 of the 48 patients. The remaining 158 patients underwent distal gastrectomy. D2 lymph node dissection was performed in 111 patients, whereas 95 patients underwent D1 plus beta lymph node dissection.

Table 2 lists the early surgical outcomes of all patients. Postoperative complications were observed in 55 patients (26.7%). The incidence of pancreas-related infection and anastomotic leakage was 8.7% and 4.9%, respectively. Five patients had both pancreas-related infection and

Table 1 Clinocopathological characteristics of patients

Age (years)	65.9 (39–89)
Sex (male/female)	146/60
Diabetes mellitus (*n*)	17
Individual fat parameter	
BMI (kg/m^2)	23 (16.0–32.3)
TFA (cm^2)	198 (6.9–505.8)
SFA (cm^2)	107.4 (3.0–266.9)
VFA (cm^2)	90.5 (3.6–262.5)
Surgical procedure (*n*)	
Total gastrectomy	48
Distal gastrectomy	158
Lymph node dissection (*n*)	
D2	111
D1 plus beta	95
Splenectomy (*n*)	
Yes	29
No	177
Pathological stage (*n*)	
IA	88
IB	48
II	44
IIIA	15
IIIB	9
IV	2

Unless indicated otherwise, values are means, with ranges given in parentheses

BMI body mass index, *TFA* total fat area, *SFA* subcutaneous fat area, *VFA* visceral fat area

Table 2 Early surgical outcomes of 206 patients

Operating time (min)	194 (103–489)
Intraoperative blood loss (mL)	265 (13–2606)
No. of lymph nodes retrieved	37 (8–109)
Postoperative complications	55 (26.7%)
Pancreas-related infection	18 (8.7%)
Anastomotic leakage	10 (4.9%)
Postoperative hospital deaths	1 (0.5%)
Duration of postoperative hospital stay (days)	11 (7–87)

Values are presented as either median with ranges in parentheses or as the number of patients in each group, with percentages in parentheses

anastomotic leakage. Both of the two patients who underwent distal pancreatectomy had pancreas-related infection. Postoperative mortality was observed in one patient (0.5%). This patient had undergone distal gastrectomy with D2 lymph node dissection, and anastomotic leakage developed on POD 7. This patient died suddenly on POD 9 due to a pulmonary embolism.

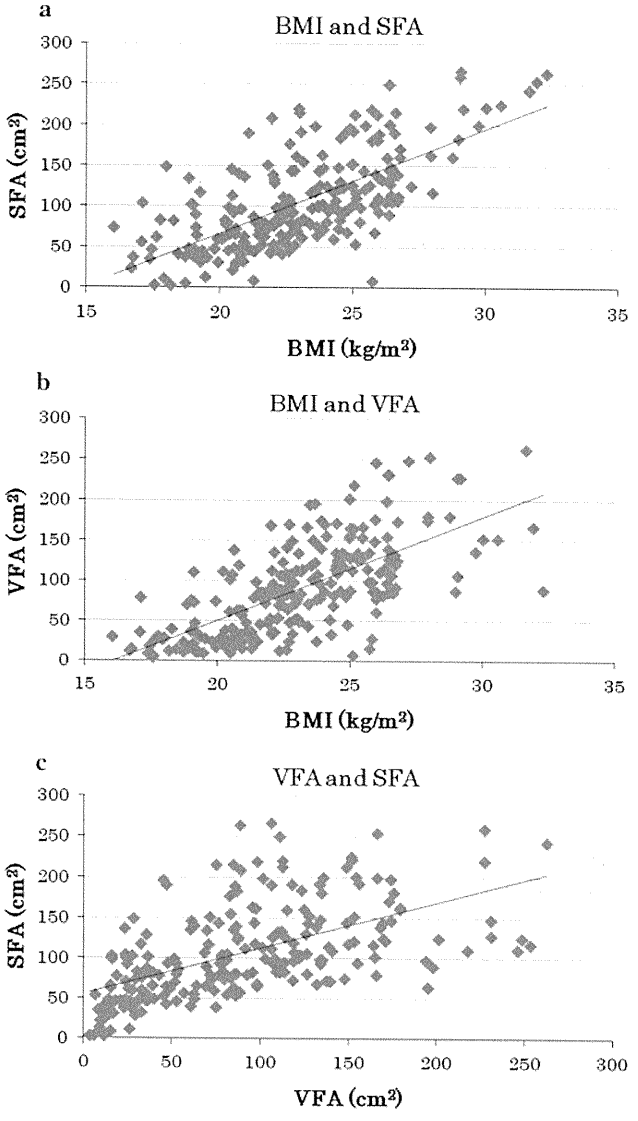

Fig. 1 Correlations between **a** superficial fat area (*SFA*) and body mass index (*BMI*); $R = 0.672$, $P < 0.001$, **b** visceral fat area (*VFA*) and BMI; $R = 0.683$, $P < 0.001$, and **c** SFA and VFA; $R = 0.555$, $P < 0.001$. Significant associations were observed for all comparisons

Relationships between fat parameters and early surgical outcomes

Figure 1 shows the correlations between SFA, VFA, and BMI. Significant correlations were found between SFA and both BMI and VFA, as well as between VFA and BMI. Correlation coefficients for each of the fat parameters and operating time, intraoperative blood loss, number of lymph nodes retrieved, and postoperative hospital stay are given in Table 3. Although VFA was weakly associated with prolonged operating time (correlation coefficient 0.304) and increased intraoperative blood loss (correlation coefficient 0.371), no significant relationships were observed for any of the fat parameters and operation time,

Table 3 Relationship between fat parameters and early surgical outcome data

	Intraoperative blood loss	Operating time	No. of lymph nodes retrieved	Postoperative hospital stay
BMI	0.295 (<0.001)	0.235 (0.001)	−0.196 (0.005)	0.011 (0.872)
TFA	0.322 (<0.001)	0.250 (<0.001)	−0.134 (0.055)	0.103 (0.139)
SFA	0.199 (0.004)	0.153 (0.028)	−0.022 (0.756)	0.025 (0.726)
VFA	0.371 (<0.001)	0.304 (<0.001)	−0.197 (0.005)	0.155 (0.026)

Values are the correlation coefficients, with *P* values given in parentheses

BMI body mass index, *TFA* total fat area, *SFA* subcutaneous fat area, *VFA* visceral fat area

Table 4 Identification of risk factors for the development of pancreas-related infection and anastomotic leakage, determined using univariate analysis

	Pancreas-related infection			Anastomotic leakage		
	Odds ratio	95% CI	*P*	Odds ratio	95% CI	*P*
BMI (kg/m^2)	1.318	1.121–1.548	0.001	1.156	0.946–1.411	0.156
TFA (cm^2)	1.009	1.004–1.014	0.001	1.003	0.997–1.009	0.291
SFA (cm^2)	1.008	1.001–1.016	0.035	0.999	0.987–1.010	0.802
VFA (cm^2)	1.016	1.008–1.025	0.001	1.010	1.000–1.021	0.042
Age (years)	0.978	0.934–1.023	0.332	0.997	0.937–1.061	0.923
Sex (male or female)	2.335	0.655–8.323	0.191	1.681	0.346–8.158	0.519
Intraoperative blood loss (mL)	1.002	1.001–1.003	0.001	1.001	1.000–1.002	0.227
Operating time (min)	1.010	1.003–1.018	0.007	1.006	0.996–1.016	0.234
No. of lymph nodes retrieved	0.987	0.954–1.021	0.458	0.961	0.912–1.012	0.133
Surgical procedure (total or distal)	5.574	2.094–14.841	0.001	2.303	0.622–8.526	0.212
Lymph node dissection (D2 or D1)	3.555	1.137–11.110	0.029	1.300	0.356–4.751	0.692
Splenectomy (yes or no)	7.515	2.729–20.694	0.001	0.667	0.081–5.468	0.706

CI confidence interval, *BMI* body mass index, *TFA* total fat area, *SFA* subcutaneous fat area, *VFA* visceral fat area

intraoperative blood loss, the number of lymph nodes retrieved, or the duration of the postoperative hospital stay.

Risk factors for intra-abdominal infectious complications

Tables 4 and 5 list the results of univariate and multivariate analyses used to identify risk factors for intra-abdominal infectious complications. On the basis of the univariate analysis, all fat parameters, operating time, intraoperative blood loss, surgical procedure, type of lymph node dissection, and splenectomy affected the development of pancreas-related infection. Multivariate analysis revealed that VFA, intraoperative blood loss, and splenectomy were independent risk factors for pancreas-related infection, with odds ratios (95% confidence intervals) of 1.015 (1.005–1.025), 1.001 (1.000–1.003), and 7.125 (2.083–24.372), respectively. With regard to anastomotic leakage, both univariate and multivariate analyses revealed VFA as a risk factor for the development of anastomotic leakage, with an odds ratio (95% confidence interval) on multivariate analysis of 1.010 (1.000–1.021).

Table 5 Multivariate analysis identification of independent risk factors for the development of pancreas-related infection

	Odds ratio	95% CI	*P*
VFA (cm^2)	1.015	1.005–1.025	0.004
Intraoperative blood loss (mL)	1.001	1.000–1.003	0.009
Splenectomy (yes or no)	7.125	2.083–24.372	0.002

CI confidence interval, *VFA* visceral fat area

In order to justify the use of correlation analysis to find risk factors for the surgical complications, it was mandatory to prove that the fat components did not relate to outcomes in binomial fashion. To do so, we divided the patients into 4 groups according to the VFA (<35.8, 35.8–85.6, 85.6–126.5, and >126.5 cm^2), and looked at the incidence of surgical complications in each group. Pancreas-related complications were observed in 0, 2, 8, and 8 patients, respectively, in these 4 groups, showing that the relationship between VFA and surgical complications was not binomial.

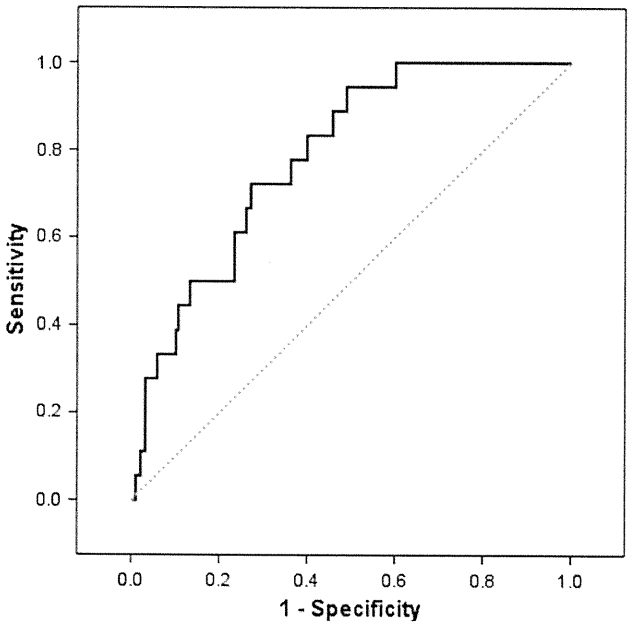

Fig. 2 Receiver operating characteristic (ROC) curve to identify the appropriate cut-off value of VFA to predict pancreas-related infection. The area under the curve (AUC) was 0.787 and the threshold of VFA was 113.6 cm^3 with sensitivity of 72.2% and specificity of 62.9%

The cut-off value for VFA as an indicator of pancreas-related infection

Figure 2 shows the receiver operating characteristic (ROC) curve used to identify the appropriate cut-off value of VFA to predict pancreas-related infection. The area under the curve (AUC) was 0.787 and the threshold of VFA was 113.6 cm^2 with sensitivity of 72.2% and specificity of 62.9%.

Discussion

The incidence of postoperative morbidity following gastrectomy with lymph node dissection (D2 or more) has been reported to be 17–21% in eastern Asia [19, 20] and 21–46% in Europe [3, 4, 21–25]. Previous studies of the risk factors for postoperative morbidity indicate that obesity, defined as BMI > 25 kg/m^2, is one of the most important [8–10]. The recent development of specific computer software has enabled the easy calculation of the amount of visceral fat, and some authors have suggested that the VFA may be a better predictor of the development of postoperative morbidity than the BMI [13, 14].

Of all morbidities, intra-abdominal infectious complications, including pancreas-related infection and anastomotic leakage, are potentially fatal complications; thus, in the present study, we investigated independent risk factors for both of these complications. Although Tokunaga et al. [13] have reported that excessive visceral fat is a risk factor for postoperative intra-abdominal infectious complications and Tanaka et al. [14] have reported that the amount of visceral fat affects the development of pancreas-related infection, independent risk factors for both complications had not been investigated simultaneously in previous studies. In the present study, we determined the factors affecting the development of both pancreas-related infection and anastomotic leakage.

The results of the present study indicate that a high VFA is associated with the development of both pancreas-related infection and anastomotic leakage following gastrectomy. To date, the risk factors for anastomotic leakage after gastrectomy have not been completely clarified [26]. Both Ser et al. [27] and Kang et al. [28] have reported that anastomotic leakage may occur in cases in which there is excess tension and pressure on the anastomotic site and that these conditions are more frequently observed in patients with excessive visceral fat because the thick mesentery creates tension on the anastomosis. In addition, a deeper surgical field in these patients, and preoperative comorbidities, such as cardiovascular disease or diabetes mellitus, which are frequently seen in obese patients, may affect the development of anastomotic leakage [29–31].

In the present study, pancreas-related infections were observed in 18 patients (8.7%), with splenectomy, intraoperative blood loss, and VFA identified as independent risk factors. Splenectomy is a well-known and widely accepted risk factor, because manipulation of the tail of the pancreas during the procedure increases the risk of pancreas-related infection [6, 14, 31]. In Europe, the final results of the Dutch D1D2 trial recommended D2 gastrectomy. However, they also recommended that the spleen should be preserved, because of increased morbidity and mortality after splenectomy [32]. In Japan, though the current standard treatment for upper-third gastric cancer is a total gastrectomy with splenectomy, a recent randomized controlled trial revealed a high incidence of postoperative complications after splenectomy [33]. We should await final survival analysis of this study before we conclude whether or not the spleen has to be preserved. Distal pancreatectomy has been thought to be correlated with pancreas-related complications. In the present study, actually, both of the two patients with pancreatectomy had this complication. However, the number was so small that further analysis could not be done.

In the present study, excessive visceral fat also increased the incidence of pancreas-related infection. It has been proposed that excessive visceral fat makes it difficult to find the border between the pancreas and lymph nodes, which may result in intraoperative pancreatic injury [13, 14]. Our ROC analysis revealed that a VFA of 113.6 cm^2

was an appropriate cut-off value. Careful surgery will be required particularly in these patients having a VFA of 113.6 cm^2 or more.

Although the present study identified a significant relationship between intraoperative blood loss and pancreas-related infection, others have reported that increased bleeding does not affect the incidence of pancreas-related infection [34, 35]. We believe that increased bleeding may have created difficulties in identifying the border between the pancreas and lymph nodes, as occurs in patients with excessive visceral fat, thus contributing to an increased incidence of pancreas-related infection.

Preoperative co-morbidities have also been considered to affect the incidence of postoperative complications. Also, poor nutritional status due to advanced primary gastric cancer may be associated with a high incidence of postoperative complications. However, in the present study, the patients' preoperative nutritional status (performance status, serum albumin level) and co-morbidities (diabetes mellitus, hypertension) were not associated with the incidence of intra-abdominal infectious complications (data not shown).

In conclusion, excessive visceral fat, represented by the VFA, was found to be an independent risk factor for both pancreas-related infection and anastomotic leakage following gastrectomy. Greater diligence during surgery is necessary for patients with excessive visceral fat, particularly if splenectomy has to be performed simultaneously.

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胃癌の外科治療に関する臨床試験

Problem and perspective of surgical clinical trials for gastric cancer in Japan

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【ポイント】
◆ 胃癌に対するリンパ節郭清のRCTの結果，欧米ではD1が標準，アジアではD2が標準となった．
◆ わが国において現在進行中の3つの大規模RCT（脾摘，網嚢切除，腹腔鏡下手術）の結果が待たれている．
◆ 手術の臨床試験の成功には，JCOGのような組織による試験の質と手術手技の質の管理が不可欠である．

臨外　66(5)：582～586，2011

胃癌手術における長年の課題

1881年にTheodor Billrothが胃癌に対する幽門側胃切除術を世界ではじめて成功させて以来，徐々に胃癌手術の短期成績は向上してきた．術後の長期成績を向上させるためには，胃と一緒にリンパ節を郭清することが重要であることが認識されるようになり，より広範囲のリンパ節まで郭清する拡大手術がわが国を中心に広まっていった．近年までの長い歴史の間，どの範囲のリンパ節まで郭清すればよいのかというのは最も重要な課題であったが，経験豊富な外科医の経験論，あるいは限られた過去のデータのなかから治療成績を検討するといった「後向き研究」によって，郭清範囲が決定されることがほとんどであった．

しかし，これらの方法は「バイアス」といわれるような様々な因子の影響が入るために好ましくないということが認識されるようになり，正しいエビデンスに基づいた医療の実践が望まれるようになった．正しいエビデンスを得るためには「前向き研究」，なかでもランダム化比較試験（randomized controlled trial：RCT）という無作為に治療方法を分けて比較する研究が必要であり，適切な統計手法を用いた解析が不可欠である．1990年代からは手術法同士を比較するRCTが徐々に世界中で実施されるようになり，最も適切な手術法，すなわち標準手術といわれる手技が確立されるようになってきた．

欧米での標準的リンパ節郭清

胃のすぐ近傍にあるリンパ節のみを郭清するD1手術に比べて，胃の基幹動脈の周囲にあるリンパ節まで郭清するD2手術を適切に行うためには，より高い技術の習得が必要である（図1a）．

胃癌患者が非常に少ない英国とオランダでD1とD2を比較する2つのRCTが1980年代から1990年代前半にかけて行われた．その結果，英国の試験ではD1の5年生存率が35%，D2が33%，オランダの試験ではD1の5年生存率が45%，D2が47%と，両試験ともにD2の優越性を示すことができなかったばかりか，両試験ともに術後合併症や在院死の割合がきわめて高いことが問題視された（表1）[1,2]．D2手術手技の教育がほとんど行われることなく実施された英国の試験では，D2の術後合併症発生割合が46%，在院死割合が13%に達し，最低限のD2手術手技の教育が行われたオランダの試験においても，D2の術後合併症発生割合が43%，在院死割合が10%であった．これらのRCTの結果から，欧州における胃癌の標準手術はD1であり，D2は臨床試験を除いて通常は行うべきではない

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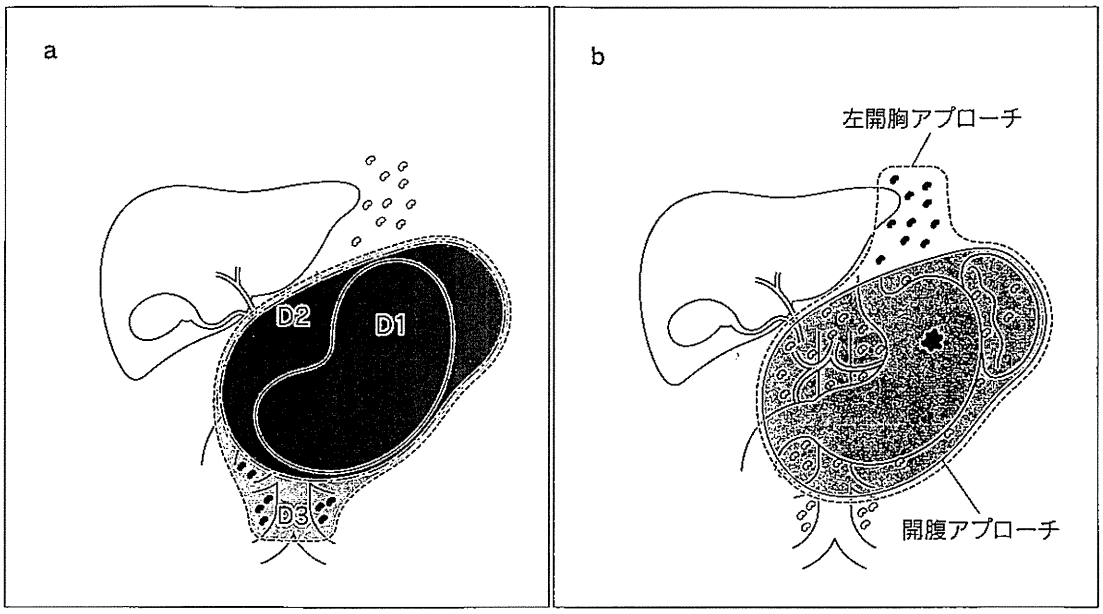

図1　胃癌手術におけるD1/D2/D3のリンパ節郭清範囲（a）と，食道浸潤胃癌に対する開腹アプローチと左開胸アプローチのリンパ節郭清範囲（b）

表1　胃癌リンパ節郭清に関するRCTの成績

	英国	オランダ	台湾	日本
群	D1 vs. D2	D1 vs. D2	D1 vs. D2	D2 vs. D3
総患者数	400	711	221	523
合併症発生割合	D1：28% D2：46%	D1：25% D2：43%	D1：7% D2：17%	D2：21% D3：28%
在院死割合	D1：7% D2：13%	D1：4% D2：10%	D1：0% D2：0%	D2：0.8% D3：0.8%
5年生存率	D1：35% D2：33%	D1：45% D2：47%	D1：54% D2：60%	D2：69% D3：70%

という結論に至った．

また，米国では胃癌術後の補助化学放射線療法の有無に関するRCTが実施され（INT0116），根治切除後に45 Gyの放射線治療と5-FU＋ロイコボリンによる化学療法を受けた群では，手術単独群に比べて有意に生存率の改善効果が認められるという結果が得られた[3]．驚くべきことに，この試験の登録患者の54%が胃のすぐ近傍にあるリンパ節すらも十分に郭清しない手術（D0）を受けており，D1とD2の手術を受けた割合はそれぞれ36%，10%であった．郭清度のサブグループ別に生存曲線を比較すると，D0とD1のサブグループでは両群間の差が大きかったのに対し，D2では両群間の差はまったく認められなかった．全登録患者の85%で病理学的リンパ節転移陽性だったことから，D0やD1の手術しか受けなかった場合には多くの症例で局所リンパ節転移が遺残したため，術後の化学放射線療法によって生存率の改善が得られたと考えられる．

以上から，進行胃癌に対する局所制御が不十分なD0やD1の手術しか実施されない米国では術後の化学放射線療法が不可欠であることが証明された．

アジアでの標準的リンパ節郭清

胃癌の罹患率が欧米よりも極端に高い日本においては，1970年頃からD2が標準的なリンパ節郭清となっていた．日本と同じく胃癌罹患率の高い台湾において，欧州の試験と同様にD1とD2（「胃癌取扱い規約」（第12版）[4]におけるD3に相当する）を比較するRCTが実施された．この試験では1993年から1999年の間に221例の胃癌患者が登録され，D2手術の経験が豊富な3人の外科医によって実施された．その結果，術後合併症発生割合はD1が7%，D2が17%，在院死は両群

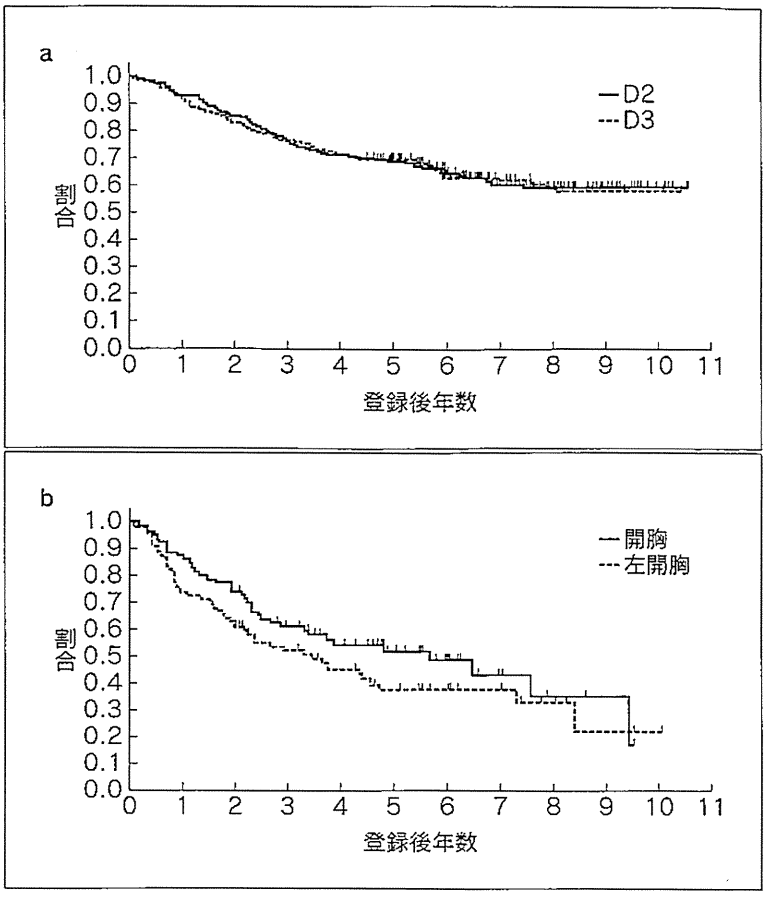

図2　D2群とD3群の全生存曲線（a：JCOG9501）と，開腹群と左開胸群の全生存曲線（b：JCOG9502）

ともに0であり，D2手術に慣れた外科医が行えば安全にできることが確認された（表1）[5]．さらに，5年生存率はD1が54%であったのに対しD2は60%であり，統計学的有意差（p=0.04）をもってD2の生存率改善効果が証明された．つまり，胃癌手術の技術および術後管理の優れた施設においては，標準手術はあくまでもD2であると証明されたわけである．

一方わが国では，1980年代に入って通常のD2よりもさらにリンパ節郭清範囲を広げる試みがなされるようになった．たとえば，胃の漿膜下層以深にまで浸潤したような胃癌の場合には，腹部大動脈周囲のリンパ節に転移する可能性が高くなるため，予防的な大動脈周囲リンパ節郭清（本稿ではD3と定義する）が行われるようになっていたのである（図1a）．そこで，日本臨床腫瘍研究グループ（JCOG）において，標準手術であるD2と拡大手術であるD3とを比較するRCT（JCOG9501）が1995年から実施され，2001年までに523例の胃癌患者が登録された．この試験では，100例以上のD2手術の経験のある外科医，もしくは年間80例以上の胃切除症例を有する24施設のみで実施され，定期的に手術ビデオの供覧を行って手術手技の統一化がはかられた．その結果，D2とD3の合併症発生割合はそれぞれ21%と28%，在院死割合は両群ともに0.8%という比較的良好な成績を示すことができたものの（表1），D3の5年生存率は70%と，D2の69%と比べてほぼ同等であり（図2a），統計学的有意差を認めなかった（p=0.85）[6]．以上から，漿膜下層以深に浸潤した胃癌に対する予防的D3の臨床的意義は否定され，標準手術は引き続きD2であることが確認された．

JCOG9501以外にリンパ節郭清範囲を広げる手術の有用性を調べたRCTとしては，食道に浸潤した胃癌に対して左開胸による下縦隔リンパ節郭清を行うべきか否かを調べたRCT（JCOG9502）がある．標準手術である開腹からのアプローチに比べて，左開胸からのアプローチを行うことは侵襲的ではあるものの，下縦隔のリンパ節を十分に郭清することで生存率が改善することが期待された（図1b）．1995年から2003年までに167例の胃癌患者が登録され，2003年に第1回目の中間解析が実施されたが，拡大手術である左開胸群