Safety and efficacy of early drain removal and triple-drug therapy to prevent pancreatic fistula after distal pancreatectomy

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Running title: Early drain removal after distal pancreatectomy

Abstract

Objective: Prior studies suggested that early drain removal prevented the development of pancreatic fistula (PF) after pancreaticoduodenectomy (PD), but there has been no corresponding prospective trial for distal pancreatectomy (DP). The purpose of this study was to determine the safety and efficacy of early drain removal and triple-drug therapy (TDT) with gabexate mesilate, octreotide and carbapenem antibiotics to prevent PF after DP in patients at high-risk of developing PF.

Methods: A total 71 patients who underwent a DP were enrolled. We prospectively divided them into two groups: the late-removal group, in which the drain remained in place for at least for 5 days postoperatively (n=30) and the early-removal group in which the drain was removed on postoperative day1 (POD1) (n=41). For the patients with a high drain amylase level (≥ 10,000 IU/L) and patients with symptomatic intraperitoneal fluid collection, our original TDT was introduced. The primary endpoint was the safety and efficacy of this management, and the secondary endpoint was the incidence of PF.

Results: The incidence of clinical PF was significantly lower in the early-removal group (0% vs. the late removal 16%; $p<0.001$). In the early-removal group, TDT was administered to 12 patients (29%) and none of the patients needed additional treatment after TDT.

Conclusions: Postoperative management after DP with early drain removal and TDT was safe and effective for preventing PF.

INTRODUCTION

Distal pancreatectomy (DP) is generally performed for benign and malignant tumors of the left side of the pancreas. Several operative procedures for these tumors have been developed over the past 20 years, including the use of spleen preservation (1) and laparoscopic surgery (2). However, the incidence of the most common and most serious postoperative complication after DP, postoperative pancreatic fistula (PF), was not found to be improved in several clinical prospective trials (3–5). It is apparent that a radical change in postoperative management is necessary to prevent PF after DP.

Kawai et al. (6) reported the efficacy of early drain removal to prevent PF after pancreaticoduodenectomy (PD) for pancreas-head disease, and Bassi et al. (7) followed the early drain removal method and obtained the same results. Kawai et al. speculated that the reason for these favorable results is that there is a close association between infection via an inserted drain and subsequent PF development, and long-term drain insertion might cause intraperitoneal infections, including PF (6). In light of these results, it seems that prophylactic long-term drain insertion after PD is not ideal, and that it may be possible to prevent PF by early drain removal. However, to the best of our knowledge, prospective trials of early drain removal to prevent PF have not been conducted. The present prospective study was conducted to clarify whether PF after DP can be prevented by early drain removal.

Two groups reported that the incidence rate of PF after DP was higher than that after PD (8,9).

This finding implies that early drain removal could also be the cause of an increase of intraperitoneal abscess or intraperitoneal bleeding due to the rupture of a pseudoaneurysm. To reduce such an assumptive risk in the present study, we introduced an original triple-drug therapy (TDT) for high-risk patients whose drainage fluid had a high amylase level (i.e., a high drain amylase level) on postoperative day 1 (POD1) or any unusual symptom associated with intraperitoneal fluid collection after drain removal. The purpose of this study was to determine the safety and efficacy of the early drain removal and TDT to prevent PF after DP in high-risk PF patients.

PATIENTS AND METHODS

Patients

This was a prospective study conducted at the Department of Surgery, Nagasaki University Hospital. The study design and protocol were approved by the Institutional Review Board at our hospital. From June 2005 to April 2013, 79 DP procedures were performed in our department, and we divided the patients into two groups according to the day of drain removal as follows: the late-removal group, who underwent a DP in the period from June 2005 to September 2009, during which the drains were inserted for at least postoperative 5 days, and the early-removal group, who underwent a DP in the period from October 2009 to April 2013, during which the drain in all cases was removed on POD1 (Fig 1).

Of the 33 patients in the late-removal group, three patients were excluded from the present study

due to the combined resection of the remnant pancreas (one patient each because of pancreas head resection with a second portion of duodenectomy, duodenum-preserving pancreas head resection, and uncinectomy). Of the 46 patients in the early-removal group, five patients were excluded: combined with other-organ resection (one patient each for the colon and left kidney), one patient with uncinectomy of the remnant pancreas, and two patients because of postoperative intraperitoneal bleeding via the drain on the day of surgery. Thus a total of 30 patients in the late-removal group and 41 patients in the early-removal group were enrolled.

Operative procedure

Different types of DP procedures were performed in the study period. Spleen preservation and laparoscopic surgery were often performed for the low-grade malignant tumors such as intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN). For invasive ductal carcinoma, DP by means of laparotomy with splenectomy and lymph node dissection was always performed. For the pancreas stump closure, approx. one-half of the cases were transected by stapler (Endo GIA™ 60-mm Articulating Medium/Thick Reload with Tri-Staple™ Technology, Covidien, Mansfield, MA, USA) and the other half were closed by the fish mouse technique or gastric wall covering (10). A closed suction drain was always placed near the pancreas stump and pulled out from the patient’s left-side abdominal wall.

Postoperative management

On the day of surgery, all patients were controlled in the intensive-care unit and then moved to the general ward on POD1. Prophylactic antibiotics therapy by using the cefem was administered for three days including the day of surgery as a standard clinical practice. No other medicine which had the possibility to prevent PF was administered.

The drain amylase level was measured on POD1, 3, and 5 in the late-removal group, and on only POD1 in the early-removal group. In the late-removal group, the drain was removed unless clearly purulent fluid was drained on POD5, regardless of the drain amylase level or the amount of output. If purulent fluid was drained before POD5, drainage management was continued until the purulent output disappeared. In the early-removal group, the drain was always removed on POD1, regardless of the drain amylase level or amount of output.

TDT with gabexate mesilate (600 mg/day as a continuous intravenous injection [c.i.v.]), octreotide (300 μg/day c.i.v.) and antibiotic; carbapenem (0.5 g/day intravenous injection [i.v.]) antibiotics was administered to late-removal group patients with a high drain amylase level (≥ 10,000 IU/L) on POD1, 3, or 5 and to early-removal group patients with a high drain amylase level (≥ 10,000 IU/L) on POD1, and to patients who had developed any clinical symptoms (e.g., a fever ≥ 38°C, abdominal pain or fullness) with the intraperitoneal fluid collection after drain removal. According to

the antibiotic, carbapenem was employed for this study based on the results of the bacterial sensitivity of the drain tip culture after PD in our department (data not shown). Intraperitoneal fluid collection was confirmed by enhanced computed tomography (CT) or ultrasound (US). After the disappearance of clinical symptoms and a tendency for the patient's serum C-reactive protein (CRP) to decrease were confirmed, the patient's diet was restarted and the components of the TDT were discontinued one by one (Fig.2). If the patient's condition was not improved by the TDT, additional treatment such as drain re-insertion or relaparotomy was performed.

Date analysis and definition

As clinicopathologic variables for the evaluation in the present study, the following perioperative factors were recorded for each patient: age, gender, tumor characteristics, diabetes mellitus, preoperative white blood cells (WBC count), lymph cells (count and %), the serum levels of total protein, albumin, and amylase; pancreas texture, which was confirmed mainly by the time-intensity curve of magnetic resonance imaging (MRI) (11), operative procedure (laparotomy, hand-assisted, or pure laparoscopy), the presence of lymph node dissection and spleen preservation, the method of pancreas stump closure, the operative time, blood loss, the presence of blood transfusion, postoperative WBC (count), serum CRP and amylase on POD1, 3, and 7. The date of drain amylase level evaluation was described above.

We defined PF according to the criteria established by the International Study Group on

Pancreatic Fistula (ISGPF) (12), and grade B/C was considered PF in the present study; specifically, intraperitoneal drain re-insertion or over 20 days of drainage was considered PF grade B, and relaparotomy was considered PF grade C. Readmission was defined as admission due to a postoperative complication during the 3 months after the patient's initial discharge.

Study end points

The study's primary endpoints were the safety and efficacy of the present management (early drain removal and TDT for patients at high risk PF development), including indications of the necessity of additional invasive treatment. The secondary endpoint was the incidence of PF. We also performed a statistical analysis to detect risk factors of PF development.

Statistical analyses

Variables are described as either absolute numbers or median values and ranges. The Mann-Whitney U-test and Fisher's test were used for the comparative evaluation between the two patient groups. Quantitative variables were divided into two categories by the median value in the present multivariate analysis. *P*-values <0.05 were considered significant.

RESULTS

The clinical characteristics of the enrolled patients in both groups are summarized in Table 1. The serum

total protein level was significantly lower in the late-removal group (6.6 vs. 7.2 mg/dL, p=0.02), and both the operative procedure and the pancreas stump closure method (pancreas transection procedure) differed significantly between the two groups. The rates of blood loss and transfusion were significantly lower in the early-removal group.

Regarding the postoperative outcomes (Table 2), the drain amylase levels were not significantly different between the late- and early-removal groups (2,284 vs. 921 IU/L, p=0.15). Although TDT was introduced for 24% of the late-removal group, similarly to the early-removal group (29%, p=0.64), PF development was completely prevented in the early-removal group (0%), unlike the late-removal group (16%) (p<0.001). Understandably, the duration of the drain insertion differed between the groups (late removal, 5 days vs. early removal, 1 day, p<0.001), the duration of hospital stay was essentially the same (late, 17 days vs. early, 16.5 days).

From the every variables described in table 1 and 2, identified variables as the predictive factors for the development of PF by the univariate analysis are shown in Table 3. Although we divided the quantitative variables into two categories by the median value, each value of the patients with PF was so biased coincidentally that none of the predictive factors of PF were identified by the multivariate analysis. Therefore, based on the results of the univariate analysis, some variables — especially pancreas transection without a stapler and late removal of the drain— would strongly increase the risk of the development of PF after DP.

The cases of the patients who required additional treatment are summarized in Table 4. As shown, although five patients in the late-removal group received invasive additional treatment (one relaparotomy and four drain management), none of the patients in the early-removal group required any additional or invasive treatment. Eighteen patients in all were treated only with the TDT, and none of these 18 patients underwent additional treatment such as percutaneous drainage or relaparotomy. Moreover, all of the symptoms (i.e., fever up or abdominal fullness) which caused the introduction of the infusion therapy in patients in the early-removal group disappeared within 3 days after the introduction of TDT. As a result, there were no patients in the early-removal group who had to prolong the TDT over the protocol setting. There were no mortality in either group during the study period, but readmission was required for one of the patient in each group for varying reasons during the 3 months after their initial discharge.

DISCUSSION

In the present study, PF development after DP was prevented by means of early drain removal and TDT, especially for high-risk patients whose drain amylase level was high or who developed abdominal symptoms. Early drain removal was shown earlier to be effective to prevent PF after PD (7), and high drain amylase level ($\geq$ 4,000 IU/L) on POD1 was reported to be an independent prognostic factor for PF development (13). At our hospital, therefore, intensive TDT was introduced for the patients with high drain amylase levels since they had a potentially high risk of PF development and for patients showing

clinical symptoms that may be an early sign of PF development after early drain removal. In other words, the prevention of PF in the present patient population was achieved by the combination of these two strategies, early drain removal and TDT.

In regard to early drain removal after DP, it should be emphasized that early drain removal (i.e., on POD1) and initial no drain management — which has been reported after PD (14,15) and after PD/DP (16,17) — are intrinsically different protocols for safe postoperative management. We have found that the operative drain is useful as both an informative tool for intraperitoneal bleeding immediately after surgery, and to identify patients at high risk of PF development by the evaluation of the drain amylase level. In the present study, we had two cases of intraperitoneal bleeding immediately after surgery (these cases were excluded from this study), and the patients were safety treated because of the early detection of bloody drainage via the drain, Moreover, we suspect that the evaluation of the drain amylase level on POD1 itself can contribute to the prevention of PF.

As a cut-off value for the drain amylase level for the introduction of TDT, we used 10,000 IU/L in the present study. This value was determined based on the median drain amylase level on POD1 in the patients with PF development after PD in our hospital (data not shown). The drain amylase levels of 4,000 IU/L on POD1 with PD (13) and 5,000 IU/L on POD1 after PD or DP (18) were described as the cut-off value for the independent risk factor of PF development. The median drain amylase level on POD1 in the present study's patients who were eventually administered the TDT was not so high, approx.

3,000 IU/L, and thus the present 10,000 IU/L drain amylase cut-off seems to present a more risky disadvantage. However, in our early-removal group, no patients developed PF or suffered from a prolonged abdominal symptom due to intraperitoneal fluid collection. We therefore feel that 10,000 IU/L of drain amylase level is suitable as the cut-off value for the introduction of TDT.

Three types of medicine which are thought to help prevent PF were used simultaneously as the TDT in the present patient series. There have been no articles describing results of this combination therapy, but reports of the efficacy of each medicine to prevent PF after PD have been published. For example, concerning a proteolytic enzyme inhibitor that corresponds to the gabexate mesilate used in the present study, Uemura et al. described the efficacy of ulinastatin for preventing PF (19). There are more papers about octreotide, including some reviews describing negative conclusions (20–22). In the present study, three types of medicine were used simultaneously to make the treatment as effective as possible, the administration method of octreotide was changed (continuous venous injection, not subcutaneous injection), and the introduction of TDT was restricted to patients at high risk of PF development. These aspects of the TDT protocol were expected to lead to the successful and significant prevention of PF. However, further evaluations concerning the dose and duration of the TDT and the possibility of omitting one or more of the three drugs are needed.

It seems difficult to assess the precise time when fluid collection developed in the early-removal group, but an important finding of our study was that the intraperitoneal fluid collection with any

symptom could be controlled by the TDT without drainage management, even if it developed immediately after surgery or a few days later. We therefore recommend early drain removal and TDT, especially for symptomatic patients with intraperitoneal fluid collection after DP. However, the efficacy of this treatment protocol for patients with severe abdominal symptoms or massive fluid collection could not be evaluated in the present study. Careful observation of the patient during this TDT regimen and possible need for drainage or relaparotomy when a patient's status worsens are important.

We were not able to conduct a statistical examination of bacterial cultures using drainage fluid or an inserted drain tip because a culture examination was performed in only some of the patients. Positive culture findings and the development of PF were reported to be closely related (6,23), and early drain removal is thought to have contributed to the prevention of retrograde infection via the drain. Interestingly, among the 19 patients in the present early-removal group whose drain tip was evaluated by a bacterial culture examination, all three patients with positive findings eventually required the TDT after drain removal. We consider this an important result indicating the significance of the control of intraperitoneal infection (or colonization) to prevent PF, and we propose that further evaluations regarding infection prevention in the peritoneal cavity during the intraoperative period should be performed to prevent PF, even if the drain is removed on POD1.

A qualitative problem in the present study should be mentioned. In the group setting of this study, some clinical aspects of the patients such as pancreas transection procedure, blood loss or blood

transfusion were different between two groups. This is why the group setting was decided by the era in the study period. We should conduct the randomized controlled trial to clarify the efficacy of the early drain removal and TDT for preventing PF after DP.

In conclusion, we found that postoperative management after DP with early drain removal and TDT was safe and effectively prevented PF, and no invasive treatments were required in the early-removal group. However, randomized controlled trials of larger numbers of patients should be performed to obtain more precise data for the evaluation of early drain removal and TDT.

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FIGURE LEGEND

Fig. 1. Patients flow of this study. PHRSD: Pancreas head resection with segmental duodenectomy, DPPHR: Duodenum preserved pancreas head resection.

Fig. 2. TDT for high drain amylase levels (over 10,000 IU/L) in the early-removal group. TDT was introduced from POD1, and after confirmation of the absence of any clinical unusual symptom and the decrease of the patient's serum CRP level after POD7, the TDT components were omitted one by one. POD: postoperative day, c.i.v.: continuous intravenous injection, i.v.: intravenous injection.

Fig.1

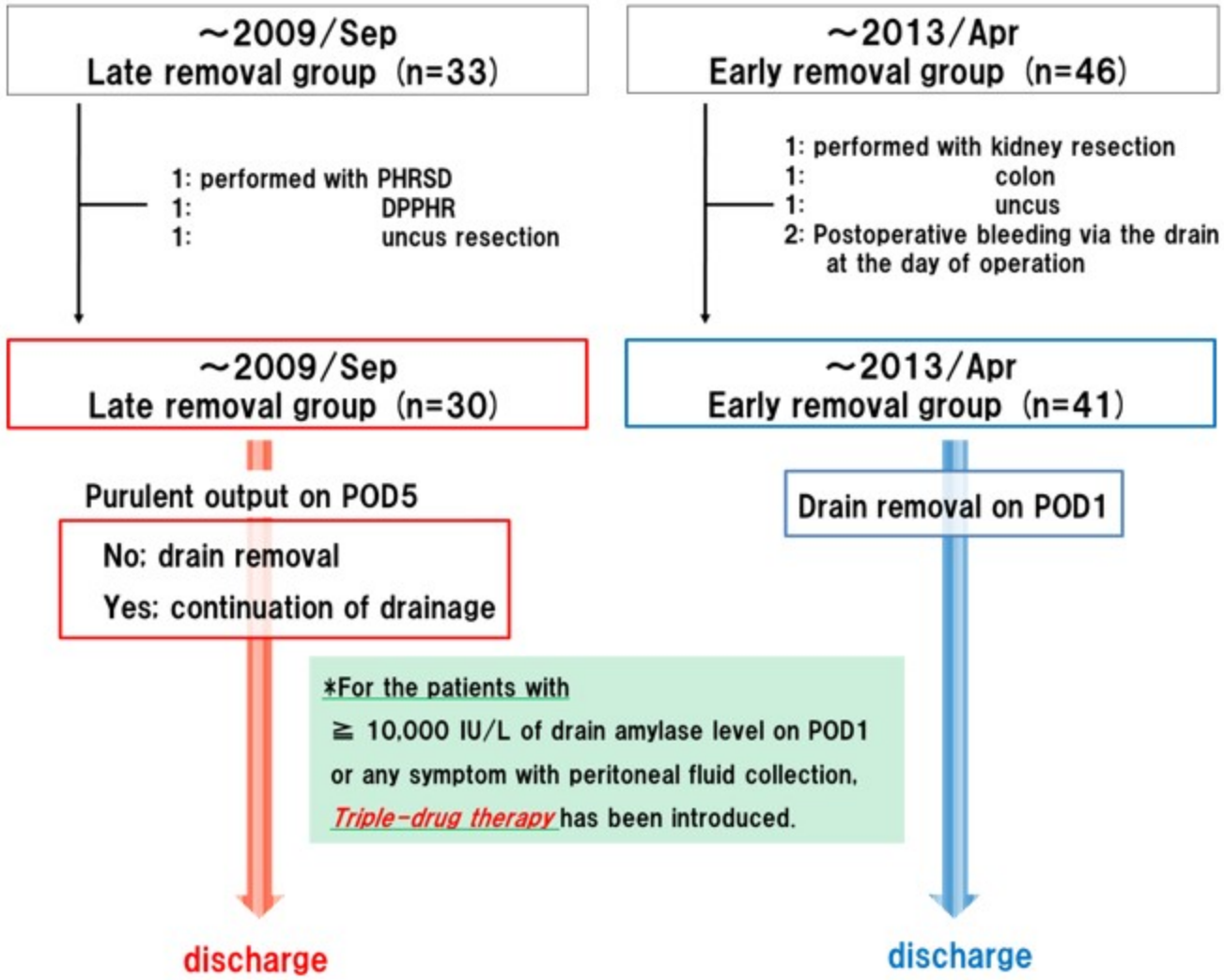
~2009/Sep
Late removal group (n=33)
1: performed with PHRSD
1: DPPHR
1: uncus resection
~2013/Apr
Early removal group (n=46)
1: performed with kidney resection
1: colon
1: uncus
2: Postoperative bleeding via the drain at the day of operation
~2009/Sep
Late removal group (n=30)
~2013/Apr
Early removal group (n=41)
Purulent output on POD5
No: drain removal
Yes: continuation of drainage
Drain removal on POD1
*For the patients with
≧ 10,000 IU/L of drain amylase level on POD1
or any symptom with peritoneal fluid collection,
Triple-drug therapy has been introduced.
discharge
discharge

Fig.2

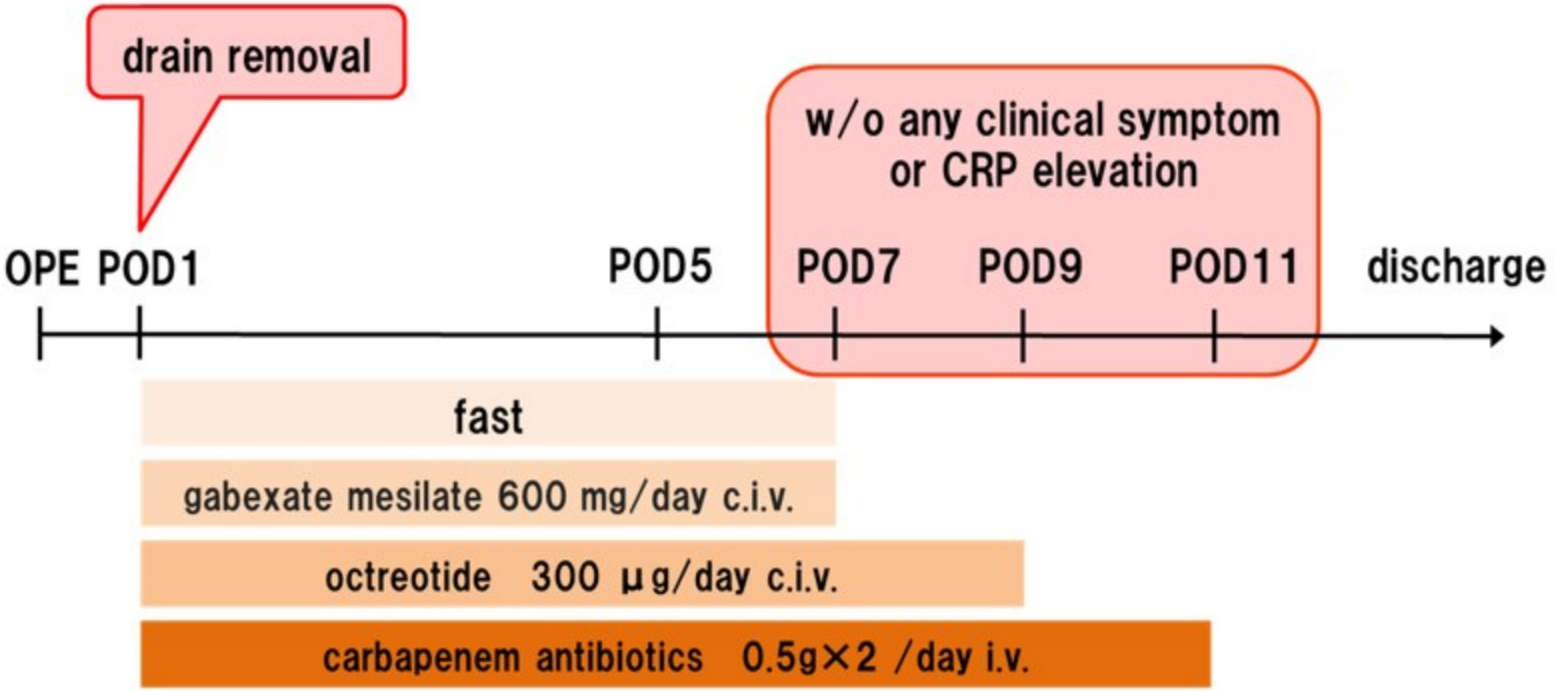
drain removal
w/o any clinical symptom
or CRP elevation
OPE POD1
POD5
POD7
POD9
POD11
discharge
fast
gabexate mesilate 600 mg/day c.i.v.
octreotide 300 μg/day c.i.v.
carbapenem antibiotics 0.5g×2 /day i.v.

Table 1. Preoperative and operative characteristics of the patients

Variable	late removal (n=30)	early removal (n=41)	*p*
gender (male/ female)	13/17	24/17	0.58
age (years)	67.5 (35–82)	64.0 (30–86)	0.20
invasive malignant tumor (%)	11/30 (37%)	11/41 (27%)	0.38
diabetes mellitus (%)	12/30 (40%)	8/41 (19%)	0.06
white blood cell ($\times 10^3$ mm^3)	5.0 (3.1–8.7)	5.7 (3.2–15.9)	0.22
lymph cells ($\times 10^3$ mm^3)	1.6 (0.4–3.8)	1.5 (0.5–3.1)	0.40
lymph cells (%)	0.35 (0.05–0.65)	0.27(0.07–0.53)	0.05
total protein (g/dL)	6.6 (5.5–7.9)	7.2 (5.7–8.0)	0.02
albumin (g/dL)	4.1 (2.5–5.0)	4.1 (2.2–4.9)	0.13
amylase (g/dL)	73 (21–238)	62 (8–243)	0.25
soft pancreas (%)	22/30 (73%)	36/41 (88%)	0.28
operative procedure (laparotomy/ HALS/ pure-LAP)	12/17/1	11/15/15	0.004
lymph node dissection (%)	13/30 (43%)	14/41 (34%)	0.43
spleen preservation (%)	8/30 (27%)	16/41 (39%)	0.28
pancreas transection by stapler	4/30 (13%)	34/41 (83%)	< 0.0001
operative time (min)	383 (168–623)	335 (148–578)	0.15
blood loss (mL)	790 (60–3400)	260 (5–3000)	0.007
blood transfusion (%)	11/30 (37%)	4/41 (10%)	0.006

HALS: hand-assisted laparoscopic surgery, LAP: laparoscopic surgery

Table 2. Comparison of the postoperative outcomes

Variable	late removal (n=30)	early removal (n=41)	*p*
White blood cell POD1 ($\times 10^3$ mm^3)	12.4 (7.400–18.9)	11.5 (4.0–24.1)	0.84
POD7	6.7 (3.8–13.2)	7.0 (2.8–13.2)	0.50
CRP POD1 (mg/dL)	10.0 (2.7–25.7)	9.1 (3.1–18.0)	0.03
POD7	3.6 (0.4–24.9)	5.0 (0.6–13.6)	0.11
amylase POD1 (g/dL)	132 (18–1795)	98 (12–204)	0.003
POD7	61 (12–213)	33 (7–110)	0.003
drain amylase level (IU/L) POD1	2284 (17–42570)	921 (112–87550)	0.15
POD3	876 (10–13626)	n/a	–
POD5	367 (7–6043)	n/a	–
TDT: triple-drug therapy (%)	6/25 (24%)	12/41 (29%)	0.64
PF: pancreas fistula(%)	5/30 (16%)	0/41 (0%)	< 0.001
duration of drain insertion (days)	5 (5–60)	1 (1–1)	< 0.001
Clavien-Dindo grade III a	PF: 4, cyle leak:1	0	0.006
III b	PF: 1	0	
IV a	pneumoniae: 1	ARDS: 1	
IV b/ V	0	0	
hospital stay (days)	17.5 (9–116)	16.0 (5–41)	0.25
readmission during 3 months after discharge (%)	1/30 (3%)	2/41 (5%)	0.75

n/a.: not applicable, ARDS: Acute respiratory distress symdrome

Table 3. Univariate analysis for predictive factors of PF

Variable		PF (−) (n=66)	PF (+) (n=5)	*p*
blood loss (mL)	<416 (n=35)	35	0	0.02
	416 ≤ (n=36)	31	5 (14%)	
lymph node dissection	no (n=44)	43	1 (2%)	0.045
	yes (n=27)	23	4 (15%)	
pancreas transection by stapler	no (n=33)	28	5 (15%)	0.01
	yes (n=38)	38	0	
White blood cell POD1 ($\times 10^3$ mm^3)	<9.3 (n=33)	33	0	0.03
	9.3 ≤ (n=38)	33	5(13%)	
CRP POD1 (mg/dL)	<9.54 (n=35)	35	0	0.02
	9.54 ≤ (n=36)	31	5(14%)	
amylase POD1 (IU/L)	<105 (n=35)	35	0	0.02
	105 ≤ (n=36)	31	5(14%)	
drain amylase level POD1 (IU/L)	<1254 (n=34)	34	0	0.03
	1254 ≤ (n=37)	32	5(14%)	
drain	late removal (n=30)	25	5(17%)	0.01
	early removal (n=41)	41	0	
duration of drain insertion (days)	1 (1–60)	1 (1–5)	20 (5–60)	< 0.001
hospital stay (days)	16 (5–116)	16 (5–74)	34 (25–116)	0.001

Table 4. Summary of the causes of additional treatment in each patient

Additional treatments	late-removal group (11/30: 37%)	early-removal group (12/41: 29%)
relaparotomy after drainage and TDT	duodenum perforation due to PF on POD90	
long-term drain insertion with TDT	drain removed on POD20	
	drain removed on POD28	
drain re-insertion after TDT	initial drain removed on POD5, re-insertion from POD9 to 20	
	initial drain removed on POD12, re-insertion from POD16 to 60	
TDT only	intraperitoneal fluid collection with fever up (POD 2)	intraperitoneal fluid collection with fever up (POD 2)
	intraperitoneal fluid collection with fever up (POD 6)	intraperitoneal fluid collection with fever up (POD 2)
	intraperitoneal fluid collection with fever up (POD 8)	intraperitoneal fluid collection with fever up (POD 3)
	intraperitoneal fluid collection with abdominal fullness (POD 6)	intraperitoneal fluid collection with fever up (POD 4)
	high drain amylase level (12605 IU/L) (POD 1)	intraperitoneal fluid collection with fever up (POD 5)
	high drain amylase level (13626 IU/L) (POD 3)	intraperitoneal fluid collection with fever up (POD 5)
		intraperitoneal fluid collection with fever up (POD 6)
		intraperitoneal fluid collection with fever up (POD 8)
		intraperitoneal fluid collection with fever up (POD 9)
		high drain amylase level (10639 IU/L) (POD1)
		high drain amylase level (35628 IU/L) (POD1)
		high drain amylase level (87550 IU/L) (POD1)
hospital stay (days)	23.5 (19–74)	23.5 (15–41)
readmission	unruptured pseudo aneurysm of splenic artery (1 day after discharge)	pseudocyst of the remnant pancreas (30 days after discharge)

TDT: triple drug therapy