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ORIGINAL ARTICLE

Optimal Extent of Superior Mesenteric Artery Dissection during Pancreaticoduodenectomy for Pancreatic Cancer: Balancing Surgical and Oncological Safety

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Abstract

Background We describe the short- and long-term outcomes for PDAC patients after tailored mesopancreas dissection using supracolic artery-first approach followed by adjuvant therapy.

Methods This study analyzed 233 consecutive patients who underwent artery-first pancreaticoduodenectomy for PDAC. Dissection extent for the superior mesenteric artery (SMA) was categorized into three levels: level 2 (LV2) including regional lymph nodes, level 3 (LV3) with hemicircumferential nerve plexus dissection, and extended-level 3 (E-LV3) including borderline resectable cases for the SMA. All clinical, pathological, and survival outcomes were reviewed.

Results LV2/3/E-LV3 dissection was performed in 77/115/41 patients. The short-term outcomes were similar among groups without mortality. Although postoperative diarrhea requiring opioids was significantly more frequent in the E-LV3 group (76%) than other groups (vs. LV2 (21%), $P < .0001$; vs. LV3 (34%), $P < .0001$; LV2 vs. LV3, $P = 0.20$), most cases of diarrhea were well controlled. Adjuvant chemotherapy was introduced similarly among groups (LV2, 76%; LV3, 81%; E-LV3, 88%, $P = 0.29$). The 3- and 5-year overall survival rates in the LV2/3/E-LV3 groups were 42/33/42% and 27/22/26%, respectively, showing no significant difference among groups.

Discussion Our tailored dissection and preemptive use of opioid antidiarrheal effectively prevents intractable diarrhea, increasing the success of adjuvant chemotherapy.

Keywords Pancreaticoduodenectomy · Artery first · Superior mesenteric artery · Diarrhea · Adjuvant therapy

Abbreviations

PD	pancreaticoduodenectomy
SMA	superior mesenteric artery
PDAC	pancreatic ductal adenocarcinoma
plSMA	the nerve plexus around the SMA
LN	lymph node
LV2	level 2
LV3	level 3
BR	borderline resectable
E-LV3	extended-level 3
AC	adjuvant chemotherapy
PV	portal vein
HA	hepatic artery
POPF	postoperative pancreatic fistula
DGE	delayed gastric emptying

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Introduction

Pancreaticoduodenectomy (PD) is considered a standard technique for curative resection of periampullary tumors.[1] The past decade has seen enthusiastic discussions and active proposals emerge for new approaches to dissecting around the superior mesenteric artery (SMA) during PD for pancreatic cancers.[2–4] The artery-first technique seems to facilitate safe and precise dissection of the nerve plexus around the SMA, and we previously proposed to tailor the extent of SMA dissection during this technique by using three different levels according to the patients' disease.[5,6]

Invasive pancreatic ductal adenocarcinoma (PDAC), which has dismal prognosis, has the unique characteristic wherein it favors invasion into the nerve plexus around the pancreas such as the first and second nerve plexus of the pancreas head (so-called mesopancreas), and the nerve plexus around the SMA (plSMA).[7–9] Therefore, extended resection of plSMA is sometimes necessary to achieve R0 resection, particularly for patients with borderline resectable PDAC, however, such extended resections can cause severe diarrhea, which is a common cause of failure with adjuvant therapy.[9,10] Thus, we have to find a balance between the extent of SMA dissection for R0 resection and sufficient preservation of plSMA to avoid intractable postoperative diarrhea.

We previously described our systematic mesopancreas dissection during PD with three different levels of dissection around the SMA.[5,6] We hypothesized that such a tailored operation with adjustable levels of SMA dissection according to the preoperative imaging for patients with PDAC could reduce the risk of postoperative neurogenic diarrhea and improve the outcomes for patients undergoing pancreatic resection by increasing the induction rate for adjuvant therapy. Here, we reviewed our experience of more than 200 patients with PDAC who were managed with this approach.

Methods

Concept and Surgical Technique of Dissection Around the SMA for PDACs

A level 1 (LV1) dissection comprises simple resection of the pancreas head, duodenum, and biliary system without dissection of lymph nodes (LNs) or the nerve plexus. A level 2 (LV2) dissection includes the central vascular ligation technique,[6] whereby the inferior pancreaticoduodenal artery (often forming the common trunk with jejunal arteries) is ligated at its root, leading to systematic resection of the corresponding LNs and mesopancreas while preserving the entire plSMA. A level 3 (LV3) dissection encompasses the hemicircle of the plSMA en bloc with the tumor to obtain cancer-free margins from cancer invasion via perineural spread.

The level 1 dissection without oncological resection is not indicated for PDACs and thus was not used in this study.[5] LV2 was selected for patients whose tumor was located far from the SMA or whose systemic status including age, nutrition, and performance status was insufficient for a more extensive surgical burden (Fig. 1a–c); this approach involved en bloc resection of anterior and posterior pancreaticoduodenal nodes (no. 17a, 17b, 13a, and 13b), nodes in the hepatoduodenal ligament (no. 12a, 12b, 12p, 12c), nodes along the superior mesenteric artery (no. 14p, 14d), pyloric nodes (no. 5, 6), and nodes along the common hepatic artery (no. 8a and 8p; nomenclature for nodal stations was based on the General Rules for Surgical and Pathological Studies on Cancer of the Pancreas[11]). For resectable PDACs showing suspected invasion into the mesopancreas without abutment to the SMA, LV3 dissection was conducted anatomically with hemicircumferential resection of plSMA in addition to dissection of LNs (Fig. 1a, d, e). For borderline resectable PDACs abutting the SMA (BR-SMA) up to 180°, plSMA resection would often need to be extended more than 180° to secure horizontal margins, although total circumferential resection was strictly avoided and defined as extended-LV3 (E-LV3) in this study (Fig. 1a, f, g). Therefore, dissections around the SMA for PDACs could be divided into three groups: LV2, LV3, and E-LV3. The SMV was resected even in cases showing minimal tumor abutment and reconstructed by end-to-end anastomosis. Para-aortic LN dissection was not routinely performed, but sampling was used in some cases to rule out contraindications such as bulky or multiple para-aortic LNs metastasis.

Management of Postoperative Nutrition and Diarrhea

On the first postoperative day, enteral nutrition was initiated using a feeding tube applied into the jejunum during surgery together with administration of compound digestive enzymes (excelase, 6 g per day, Meiji Seika Pharma, Tokyo, Japan). On postoperative day 6, an oral diet was introduced with tapering of the enteral nutrition. The extent of diarrhea was estimated based on the frequency of defecation and status of feces. If a patient suffered watery defecation more than five times a day without evidence of bacterial enteritis, non-opioid antidiarrheal agents (albumin tannate 3–6 g/day, and natural aluminum silicate 3–6 g/day) were first administered. An opioid antidiarrheal drug (opium tincture) was used if the non-opioid versions could not relieve the symptoms. We used opium tincture of 0.9 mg per day as an initial dose before each meal, then modified the dose according to the symptom with the aim of achieving solid or soft stool three or less times a day. After discharge, the administration of antidiarrheal drugs was maintained at the outpatient clinic, and in cases showing improved diarrhea, the drug was de-escalated or discontinued. “Intractable diarrhea” was defined as that which could not be controlled even with opioids and which hampered the postoperative chemotherapy.

Adjuvant Chemotherapy and Follow-up

Adjuvant chemotherapy (AC) was administered after confirming sufficient patient recovery for outpatient chemotherapy based on oral intake, performance status, and absence of intractable diarrhea. Until March in 2013, gemcitabine (intravenous injection at a dose of 1000 mg/m^2 over 30 min on days 1, 8, and 15, followed by a 1-week rest period) was

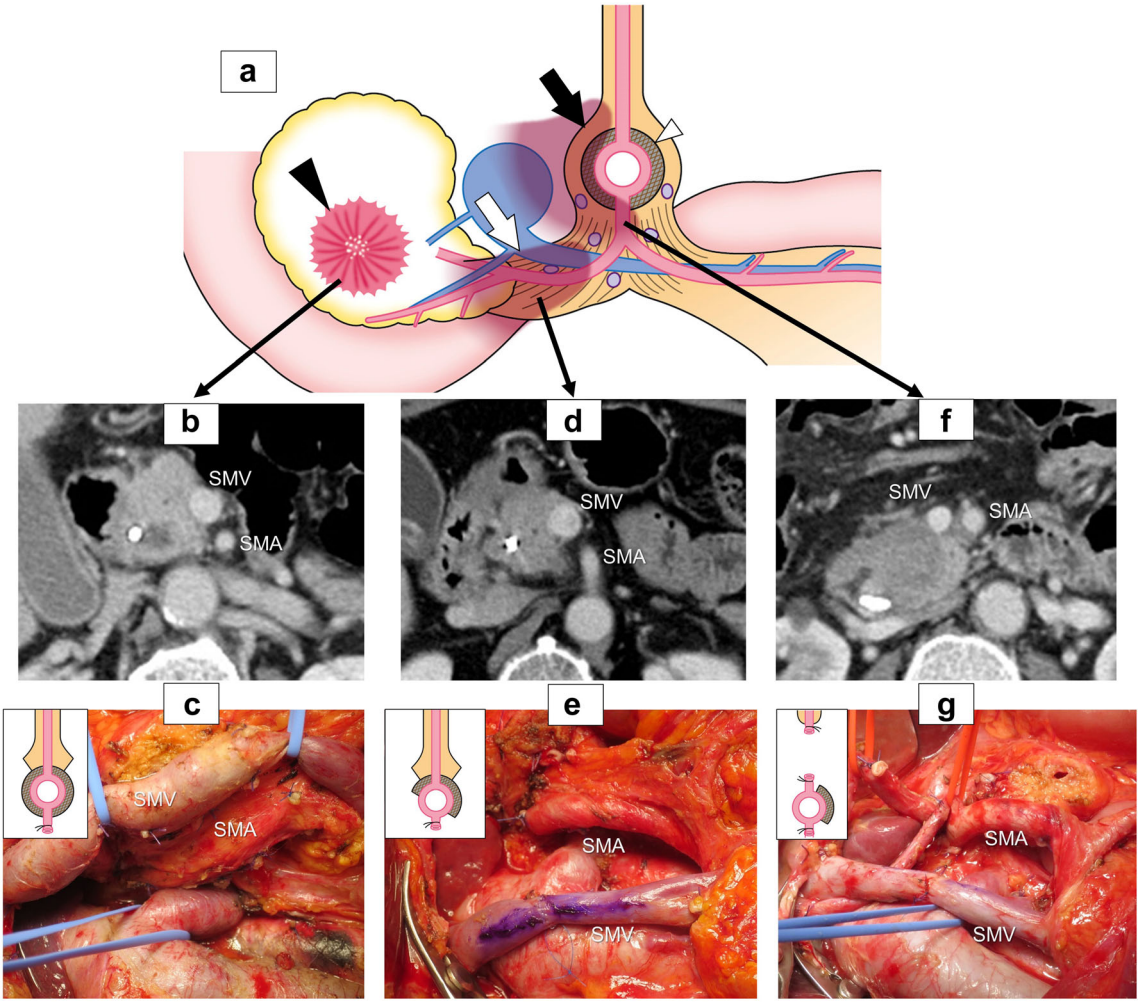

Fig. 1 Conceptual schema of incremental dissections. **a** Transverse view of dissection depth toward the superior mesenteric artery (SMA). White arrowhead indicates the nerve plexus around the SMA (plSMA). Black arrowhead indicates cancer located in the pancreatic head without perineural invasion. White arrow indicates cancer invasion into the mesopancreas or the second nerve plexus of the pancreatic head. Black arrow indicates cancer invasion up to plSMA. **b** Preoperative CT image of a pancreatic head cancer without perineural invasion. SMV superior mesenteric vein. **c** Intraoperative view and schema after level 2 dissection. The plSMA was totally preserved. **d** Preoperative CT image of a pancreatic head cancer with invasion into the mesopancreas. **e** Intraoperative view and schema after level 3 dissection. The plSMA was hemicircumferentially resected to gain a vertical margin from the cancer invasion to the mesopancreas. **f** Preoperative CT image of a pancreatic head cancer with invasion up to plSMA. **g** Intraoperative view and schema after extended-level 3 dissection. A hemicircumferential dissection of the plSMA was not sufficient to gain a horizontal margin from tumor abutment to the artery

used as a standard regimen and was replaced by S-1 (oral dose of 40 mg for body surface area less than 1.25 m^2, 50 mg for body surface area of 1.25 m^2 or more but less than 1.5 m^2, or 60 mg for body surface area of 1.5 m^2 or more, twice per day for 28 consecutive days followed by a 14-day rest).[12] The duration of AC was usually set as 6 months, with some exceptional cases wherein a patient participated in a clinical trial or underwent R1 resection. In patients who suffered early recurrence before initiation of AC, palliative chemotherapy was administered. If recurrence occurred during the AC period, the regimen was changed to an alternative therapy. As postoperative follow-up, we performed contrast-enhanced CT every 3 months until 2 years after resection, and thereafter every 6 months until 5 years after resection. CA19-9 and CEA levels were checked monthly during adjuvant therapy and every 3 months after that.

Patients

Between January 2008 and June 2015, 249 consecutive patients with PDAC underwent PD with tailored mesopancreas dissection. Among them, 4 patients were excluded due to lost follow-up or incomplete clinical data and 12 were excluded due to pathology other than ductal adenocarcinoma. As a result, 233 patients were the subjects of this retrospective study. We conducted upfront surgery for every case with one exception wherein a patient had undergone preoperative chemotherapy in another hospital before referral. Evaluation of tumor

resectability and elimination of contraindications were conducted using preoperative dynamic CT or MRI, and then resectability was divided into three groups, i.e., resectable PDAC, BR-portal vein (PV), and BR-A (abutment for the hepatic artery (HA) or the SMA) according to which vessel had the most prominent interface to the tumor invasion according to guidelines of the National Comprehensive Cancer Network.[13] The dissection extent (LV2, LV3, or E-LV3) was determined based on these preoperative findings, with modification if necessary based on intraoperative findings. In all operations, the specimen was macroscopically explored, and the regional lymph nodes were identified, numbered, and isolated by the attending surgeon. The LNs surrounding the main tumor were left untouched, and simply noted. Surfaces of the SMV groove and SMA margin were inked respectively. Specimen dissection was conducted by axial slicing, and pathological R0 resection was defined by the revised R0 criteria (distance to resection margin more than 1 mm).[14]

The final diagnosis was confirmed by the pathological findings. All clinical, surgical, and pathological data were obtained from prospectively accumulated databases. Postoperative pancreatic fistula (POPF) and delayed gastric emptying (DGE) were defined based on international studies.[15,16] Other postoperative complications were defined according to the Clavien-Dindo classification.[17] The institutional review board of the Cancer Institute Hospital approved this retrospective study with waived informed consent. Local recurrence was defined as one from soft tissue around the pancreas bed or one in the remnant pancreas. Other recurrences were defined as distant metastasis.

Statistics

All continuous data were expressed as median values with range. Categorized variables were compared using Fisher's exact test. All differences among the means of three groups were compared using the Tukey-Kramer honest significant difference test. Survival curves were determined using the Kaplan-Meier method and compared using a log-rank test. Factors found to be significant on univariate analysis were subjected to multivariate analysis using a Cox proportional hazards model. P values < 0.05 were considered as statistically significant. Statistical analysis was performed using JMP software (version 13; SAS Institute Inc., Cary, NC).

Results

Patients Demographics and Surgical Outcomes

Table 1 shows the baseline characteristics of 233 patients; 157 patients were deemed resectable, 20 had BR-PV, 14 had BR-HA, and 42 had BR-SMA. LV2, LV3, and E-LV3 dissections were performed in 77, 115, and 41 patients, respectively. The LV2 group contained significantly older patients compared with the other two groups (LV2 vs. LV3, $P = 0.0039$; LV2 vs. E-LV3, $P = 0.001$). All patients except one in the E-LV3 group were BR-SMA patients. Tumor size on preoperative imaging findings was significantly larger in patients of the E-LV3 group than those in LV2 (4.0 vs. 3.1 cm, $P = 0.039$).

Surgical duration was significantly shorter in the LV2 group than the E-LV3 (492 vs. 544 min, $P = 0.0016$). Amount of blood loss and incidence of blood transfusion was not significantly different among groups. The incidence of SMV-PV resection was significantly higher in the LV3 and E-LV3 group compared to the LV2 patients. Incidence of postoperative complications greater than C–D grade 2, POPF ≧ grade B, DGE, and length of postoperative hospital stay was not significantly different among groups. Postoperative intraabdominal bleeding occurred at the stump of the gastroduodenal artery in 2 patients, the peripheral branch of omentum in 2, the small branch of the right hepatic artery in 1, and the dorsal pancreatic artery in 1 patient. Four patients recovered after relaparotomy, and two after radiologic interventional hemostasis. There was no 90-day mortality.

Pathological Results

Pathological examination (Table 2) showed a higher incidence of venous invasion in the E-LV3 (46%) and LV3 (34%) groups compared with the LV2 (14%) group (LV2 vs. E-LV3, $P = .0002$; LV2 vs. LV3, $P = .0013$; LV3 vs. E-LV3, $P = 0.19$). Perineural invasion was significantly more frequent in the E-LV3 group (83%) compared with LV2 (36%) or LV3 (49%) groups (E-LV3 vs. LV2, $P < .0001$; E-LV3 vs. LV3, $P = .0005$; LV2 vs. LV3, $P = 0.07$). The E-LV3 group (37%) had a significantly higher positive rate of pathological resection margin of the SMA aspect than the other groups (E-LV3 vs. LV2 (11%), $P = .0014$; E-LV3 vs. LV3 (13%), $P = .0008$; LV2 vs. LV3, $P = 0.82$). Incidences of positive margin at other sites were similar among groups. Incidence of positive LNs, LN yields, and LN ratios (positive LNs/resected LNs) were similar among groups.

Postoperative Diarrhea According to Dissection Levels

Although postoperative diarrhea requiring opioids was significantly more common in the E-LV3 group (76%) than other groups (E-LV3 vs. LV2 (21%), $P < .0001$; E-LV3 vs. LV3 (34%), $P < .0001$; LV2 vs. LV3, $P = 0.20$), most cases of diarrhea were well controlled (Table 1). Opioid-based antidiarrheal medication was administered in 86 patients, at a similar required dose and rate of discontinuation among the groups, and these 86 patients had a similar incidence of DGE (28%) to the 147 patients not administered opioids (18%, $P = 0.25$). No patient developed opioid dependence requiring treatment.

Table 1 Baseline characteristics and the short-term outcomes of each group

	Level 2 75	Level 3 117	Extended-level 3 41	*P* value
Age (years)	69 (42–86)	67 (36–80)	63 (47–77)	0.0004
Sex (M/F)	41/34	61/56	19/22	0.69
Resectability (resectable/borderline resectable)	66/9	90/27	1/40	< 0.0001
Type of borderline resectable				
Superior mesenteric artery	0	3	39	
Celiac or hepatic artery	4	10	0	
Portal vein	5	14	1	
Preoperative therapy (present/absent)	1/74	2/115	6/35	0.0004
Body mass index	21.6 (16.5–29.9)	21.1 (15.7–46.5)	21.2 (16.4–28)	0.65
Diabetes	20 (27%)	29 (25%)	12 (29%)	0.85
Symptoms	50 (67%)	80 (68%)	28 (68%)	0.97
CEA (ng/ml)	2.9 (0.6–44.5)	2.7 (0.5–44)	3.0 (0.7–24)	0.84
CA19-9 (U/ml)	222.5 (2–50,000)	163.5 (2–18,798)	120.6 (2–50,000)	0.14
Size (cm)	3.1 (1.5–8.5)	3.5 (1.3–7.5)	4.0 (0.5–6.5)	0.035
Operation time (min)	492 (318–768)	516 (341–953)	544 (370–989)	0.0021
Blood loss (ml)	500 (85–2600)	620 (50–1810)	630 (120–2400)	0.16
Blood transfusion	8 (11%)	14 (12%)	6 (15%)	0.82
SMV/PV resection	27 (36%)	73 (62%)	30 (73%)	< 0.0001
Postoperative complication				
Postoperative pancreatic fistula	15 (20%)	12 (10%)	8 (20%)	0.12
Grade B/C	14/1	11/1	5/3	
Cause of grade C				
Intraabdominal bleeding	1	0	2	
Intraabdominal abscess	0	1	1	
Delayed gastric emptying	15 (20%)	21 (18%)	14 (34%)	0.36
Grade (A/B/C)	6/6/3	9/6/6	4/5/5	
Diarrhea				< 0.0001
Absent	49 (65%)	57 (50%)	6 (15%)	
Present	26 (35%)	57 (50%)	35 (85%)	
Non-opioid antidiarrheal	10 (13%)	18 (16%)	4 (10%)	
Opioid antidiarrheal	16 (21%)	39 (34%)	31 (76%)	
Required dose (ml/day)	1.65 (0.6–4.8)	1.5 (0.2–6.0)	1.55 (0.4–7.2)	0.73
Tapered and discontinued	4	9	3	
Intractable diarrhea	0	3 (2.6%)	3 (7.3%)	
Clavien-Dindo scale	0.33			
Grade 0–2	67	109	34	
Grade 3	9	7	6	
Cause of intervention	1	0	0	
Intraabdominal bleeding	4	0	2	
Intraabdominal abscess	3	4	2	
Major bile leak	0	1	1	
Bowel obstruction	1	1	0	
Ascites	0	1	1	
Pleural effusion	1	0	0	
Grade 4	1	0		
Sepsis	1	0	0	
Grade 5	0	0	0	
Postoperative stay (days)	27 (12–111)	25 (16–75)	32 (17–87)	0.07

Continuous data are shown as median and range

Postoperative Chemotherapy and the Long-Term Outcomes

Postoperative chemotherapy was conducted in the majority of cases with similar frequency (Table 3). The intervals from resection were similar among groups, and reasons for delayed starting were mainly due to poor recovery of performance status or oral intake. In 188 patients who successfully started AC, completion rate was similar among groups (LV2, 76%; LV3, 70%; E-LV3, 65%, $P = 0.46$), and most AC discontinuations were attributable to conversion of therapy due to recurrence.

The long-term survival analysis revealed shorter overall survival in the extended-LV3 group (3-/5-year overall survival, 42%/26%; MST, 18.5 months) compared to the LV2 (42%/27%; MST, 28.7 months; $P = 0.40$) or LV3 (33%/22%; MST, 21.1 months, $P = 0.78$) group, but the difference was not statistically significant (Fig. 2a). Recurrence-free survival rates

Table 2 Pathological outcomes and recurrences

	Level 2 75	Level 3 117	Extended-level 3 41	*P* value
Pathology (pap well/mod/por)	23/46/6	29/71/17	13/26/2	0.53
Pathological margin status				
R0	63 (84%)	93 (79%)	24 (59%)	0.0054
R1	11	24	17	
R2	1	0	0	
Site of positive margin*				
Margin around the SMA	8 (11%)	15 (13%)	15 (37%)	0.0005
Posterior margin	2 (3%)	2 (2%)	2 (5%)	
Margin around the hepatic artery	2 (3%)	4 (3%)	0	
Pancreatic stump	1 (1%)	3 (3%)	2 (5%)	
Bile duct stump	0	1 (1%)	0	
Microscopic venous invasion	11 (14%)	39 (34%)	19 (46%)	0.0003
Microscopic perineural invasion	28 (36%)	56 (49%)	34 (83%)	< 0.0001
Lymph node metastasis	54 (70%)	85 (74%)	33 (80%)	0.48
Number of lymph nodes harvested	33 (13–68)	35 (11–87)	37 (12–67)	0.32
Lymph nodes ratio	0.064 (0–0.42)	0.067 (0–0.47)	0.071 (0–0.53)	0.74
Recurrence	54 (72%)	85 (74%)	30 (73%)	0.82
Local recurrence	13 (17%)	24 (21%)	6 (15%)	0.63
Soft tissue	9 (12%)	20 (17%)	6 (15%)	
Remnant pancreas	4 (5%)	4 (3%)	0	
Distant metastasis**	42 (55%)	65 (57%)	25 (61%)	0.83
Liver	25 (33%)	37 (32%)	12 (29%)	
Mesenteric lymph nodes	5 (7%)	3 (3%)	1 (2%)	
Peritoneal dissemination	7 (9%)	17 (15%)	7 (17%)	
Others	14 (19%)	12 (10%)	6 (15%)	

*Includes patients with duplicated positive sites

**Includes duplicated recurrence sites or patients with concomitant local recurrence

SMA, superior mesenteric artery

Continuous data are shown as median and range

were similar among groups (Fig. 2b). More than 70% of patients suffered recurrence without difference among groups, showing dominancy of distant metastasis as a first recurrence site (Table 3). Uni- and multivariate analysis identified CA19-9 levels > 200 U/ml, LN ratio > 0.1, and absence of postoperative chemotherapy as significant prognostic factors (Table 4).

Discussion

In this report, we described our approach to achieving maximal chance of R0 resection and minimal negative impact with postoperative recovery for patients undergoing PD for PDAC. Dissection extent around the SMA was categorized into three degrees, selected according to pre- and intraoperative findings.[5,6] This is the first report of the short- and long-term outcomes after different dissection extents of plSMA in the era of the artery-first approach, and we also propose a promising management regimen of postoperative diarrhea to achieve a high rate of successful adjuvant chemotherapy.

Because of high local recurrence rates after conventional R0 resections with 0 mm rules, a revised standard of R0 resection with a margin clearance of > 1 mm has been proposed and validated by several groups.[18–22] Moreover, several recent reports advocated wider margins of 1.5 or 2 mm as a convincing prognostic factor.[19,23] These trends indicate the importance of maximizing the resection margin length. To improve the prognosis, negative margins toward the SMV and the SMA are often reported as the most difficult to achieve.[18] Based on our principle, SMV margins could be cleared by aggressive, preemptive co-resection even in cases with minimal abutment of tumor to the vein. As a result, most patients in our LV3 (62.4%) and E-LV3 (73.2%) groups underwent SMV resection. For the SMA margin, we attempted to maximize the vertical distance from the tumor by co-resecting the plSMA at the tumor side, hemicircumferentially in cases with suspicious

Table 3 Postoperative chemotherapy

	Level 2 77	Level 3 115	Extended-level 3 41	*P* value
Postoperative chemotherapy	63 (84%)	103 (88%)	38 (93%)	0.38
Interval from resection (weeks)	8.6 (4.7–24.9)	8.3 (5.1–24.1)	8.4 (4.2–29.4)	0.82
Number of patients with interval ≦ 12 weeks	56 (75%)	94 (80%)	30 (73%)	0.52
Number of patients with > 12 weeks or abandon	21	21	11	
Reasons				
Poor PS recovery	2	1	1	
Intractable diarrhea	0	3	1	
Recurrent ascites	0	1	0	
Other complication	3	3	6	
Poor oral intake	7	8	1	
Active other cancer	1	0	0	
High age	5	0	0	
Patient's will	1	1	1	
BSC for early recurrence	2	4	1	
Setting				
Adjuvant	57 (76%)	95 (81%)	36 (88%)	0.29
Palliative therapy for early recurrence	6 (8%)	8 (7%)	2 (5%)	
Agents				0.24
S1	26	49	16	
Gemcitabine	35	48	17	
Others	2	6	5	
Adjuvant chemotherapy	57 (76%)	95 (81%)	36 (88%)	
Duration (months)	6 (1–12)	6 (0.5–14)	6 (0.5–12)	0.75
Duration ≧ 6 months	69	25	0.46	
Reasons < 6 months	8	25	11	
Early recurrence	10	13	9	
Poor PS	0	3	0	
Intractable diarrhea	0	1	1	
Complication during chemotherapy	2	7	1	
Mental disorder	0	1	0	

PS, performance status; *BSC*, best supportive care

Continuous data are shown as median and range

invasion to the second nerve plexus of the pancreas head. The BR-SMA cases required more than a hemicircumferential dissection of the plSMA to gain a horizontal margin from the tumor abutting the artery. Of note, circumferential plSMA dissection was strictly avoided based on previous RCTs including one trial that documented significantly higher incidences of watery diarrhea even 3 months after resection in extended dissection groups.[10,24–26] Using incremental dissections as described herein, an acceptable R0 (> 1 mm) resection rate was achieved in all three groups and the incidence of local recurrence was comparable to or lower than those cited in previous reports[27–29]; in addition, most neurological diarrhea was controlled enough to receive adequate AC. These systematic adjustments of dissection were safely performed using the supracolic anterior artery-first approach without SMA injury or postoperative SMA aneurysm, both of which are potentially fatal complications.

Extended lymphadenectomy including para-aortic LNs during PD is also discouraged based on negative results of previous RCTs.[10,24–26] For example, routine para-aortic LNs dissection has caused recurrent ascites, leading to insufficient recovery for AC. Based on these results, it was considered that routine extensive dissection of distant LNs should be restricted. In our principle, sampling of no. 16 b2 inter-LNs only was sufficient to confirm operability, and resection was abandoned if a patient had multiple metastases in the sampled LNs. Wide and accurate resection of regional LNs during PD has also been advocated by several groups to ensure precise disease staging and guaranteed resection quality.[30–32] In the three groups presented in this report, dissection width was set at

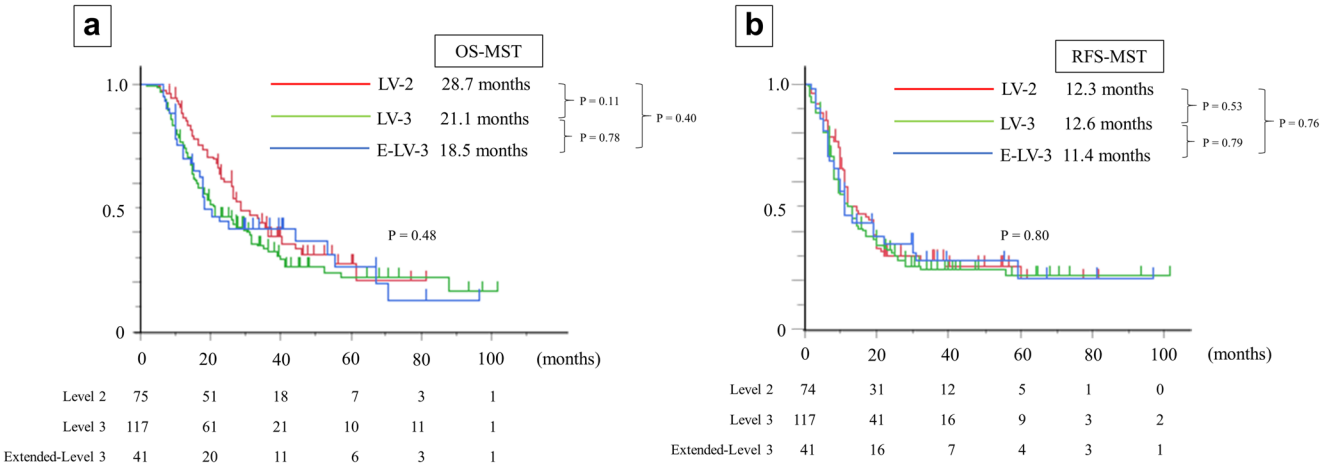

Fig. 2 Survival among the three groups. No significant difference was observed among groups in either overall survival (**a**, $P = 0.48$) or recurrence-free survival (**b**, $P = 0.80$). Numbers below the x-axis indicate the number of patients at risk. OS, overall survival; MST, median survival time; RFS, recurrence-free survival

regional LNs according to general rules for the study of pancreas cancer and international consensus.[11,33] As a result, LN yields were similar among groups as shown in Table 3, and the incidence of recurrent ascites hampering patient recovery was rare.

Another important aspect of our approach was aggressive control of postoperative diarrhea. As was confirmed by several RCTs, adequate AC is essential to maximize survival length after curative resection.[12,34–36] PlSMA dissection has generally been regarded as a surgical risk or obstruction for AC, and recent reports suggested that dissection of plSMA should be avoided if possible due to intractable diarrhea leading to failure of AC.[37,38] However, this discussion also has long been lacking systematic criteria of dissection extent described above and an optimal method of diarrhea control. In the current series, most of patients, even those with the E-LV3 dissection had well-controlled diarrhea, and postoperative chemotherapy was successfully introduced in a high proportion of patients (nearly 90%) compared to previous clinical reports,[39–42] and most shortenings of AC were attributable to early recurrence due to invisible micrometastasis or aggressive tumor biology. Our strategy wherein the dose of antidiarrheal drug was determined based on the frequency of watery diarrhea was simple, comprehensible, and achieved a stable postoperative recovery with minimal abandoning of AC regardless of dissection extent.

Adequate selection of dissection extent with subsequent AC supported by strict diarrhea control could have contributed to the incidence of local recurrence being seemingly lower than those previously reported.[27,29] The R1 resection rate in the E-LV 3 group was significantly higher than that in the LV 2 or LV 3 group, although multivariate analysis revealed that borderline resectability and R1 resection (< 1 mm) had no significant negative impact under our strategy. These results indicate that our adjustment of SMA dissection using the anterior artery-first approach could have minimized the risk of incomplete local resection in pancreatic head cancers. We also note that the incidence of local recurrence in our LV2 and LV3 patients with theoretically optimized resection margins was similar to that of the E-LV3 patients. Thus, surgically maximizing the length of cancer-free margin seems to reach a limit in improving the incidence rates of local recurrence, and as proposed previously,[43] further improvement of local control might require preoperative therapy including new drugs and/or chemoradiotherapy.

Survival outcomes retrieved from our strategy showed acceptable, but not sufficient, results. Especially the long-term (e.g., 5 years) survival was similarly depressed in all groups, likely determined by the presence of systemic metastasis as indicated by the high incidence of distant metastasis shown in Table 3. Accordingly, multivariate analysis identified significant prognostic factors that were representative of aggressive tumor biology or potential distant metastasis, regardless of local control. Therefore, besides adequate local control, stricter patient selection is warranted using preoperative therapy as an observation window. Recently several trials have been conducted to investigate the efficacy of neo-adjuvant therapy for BR- or resectable PDACs.[43–47] Although robust evidence has not been established, these trends would facilitate more selective surgery for patients with locally limited PDAC, and in such selected cohorts, certainty of local control would be prerequisite.

This report has several limitations. First, although dissection extent was determined from three degrees and recorded prospectively, the real dissection extent might have been influenced by each surgeon's skill, patient anatomy, and/or amount of visceral fat, leading to a risk of intergroup migration. Second, the majority of our patients underwent upfront resection regardless of the extent of disease because this was the standard strategy in Japan until 2014. With the emergence

Table 4 Univariate and multivariate analysis

		Univariate analysis			Multivariate analysis	
		n	MST (months)	*P* value	Hazard ratio	*P* value
Age (years)	≥ 67	125	22.3	0.65		
	< 67	108	26.6			
Sex	Male	121	27.3	0.21		
	Female	112	19.2			
Symptoms	Present	158	21.2	0.1		
	Absent	75	35			
Diabetes	Present	61	25.8	0.62		
	Absent	172	25.2			
Size (cm)	≥ 3.6	107	18.8	0.0006	1.41	0.062
	< 3.6	126	33.7		1	
CEA (ng/ml)	≥ 3.1	104	18.1	0.0006	1.34	0.051
	< 3.0	129	31.7		1	
CA19-9 (U/ml)	≥ 201	114	18.3	0.0004	1.59	0.015
	< 201	119	31.9		1	
Borderline resectable	Yes	75	18.1	0.13		
	No	158	26.6			
Blood loss (ml)	≥ 600	107	21.5	0.13		
	< 600	126	28.7			
Operation duration (min)	≥ 520	110	26	0.89		
	< 520	123	23			
Portal vein resection	Yes	130	20.6	0.0011		
	No	103	31.4			
Pathology	Pap/well	65	31.9	0.2		
	Mod/por	168	21.5			
Lymph node metastasis	Present	172	21.1	0.0027	1.31	0.22
	Absent	61	41.1		1	
Lymph node ratio	≧ 0.1	73	16.7	< 0.0001	1.96	0.0004
	< 0.1	160	31.7		1	
Margin status 1 mm	R1/2	53	18.5	0.014	1.31	0.17
	R0	180	28.7		1	
PV invasion	Present	69	20.2	0.013	1.28	0.18
	Absent	164	29.6		1	
Perineural invasion	Present	118	21.2	0.064		
	Absent	115	26.7			
Pancreatic fistula B/C	Yes	35	35	0.45		
	No	198	23			
Delayed gastric emptying B/C	Yes	31	26	0.64		
	No	202	25.2			
Diarrhea treated by Opioid	Present	86	26.9	0.96		
	Absent	147	22.3			
Postoperative complication	≥ C–D 3	23	15.2	0.098		
	< C–D 3	210	26.3			
Postoperative hospital stay	≥ 29	99	20.6	0.19		
	< 29	134	26.7			
Postoperative chemotherapy	Present	204	26.6	0.019	1	0.014
	Absent	29	16.8		1.84	

of more effective chemotherapeutic regimens such as FOLFIRINOX[48] and gemcitabine with nab-paclitaxel,[49] neo-adjuvant therapy has gradually been adopted as standard therapy for patients with BR-PDAC.[43,47] Accordingly, we have now converted our strategy to neo-adjuvant gemcitabine with nab-paclitaxel for BR-PDAC patients from the beginning of 2015; however, it should be noted that imaging showing tumor abutment toward the major visceral arteries usually remains and down staging is rare.[50] To maintain a high R0 rate after NAC, radical resection would therefore still be justified. Third, our study involved exclusively Japanese patients, who tend to have a lower BMI. Although Japanese people have genetically different fat distribution characterized by higher amounts of visceral fat compared with people in other regions, extremely obese patients are rare in Japanese society. Therefore, the feasibility and efficacy of our approach remain unclear in patients with a high BMI or obesity in western countries, although we hope that our approach will be carefully considered and evaluated by surgeons elsewhere in the world who have an interest in our method. Finally, although postoperative recovery would be better assessed based on postoperative quality of life, our retrospective study lacks

prospective quantitative measurement of this aspect. Instead, we used rate of successful introduction and endurance of adjuvant therapy as a surrogate for favorable postoperative recovery. Further investigation by large-scale, prospective trial is warranted to confirm the best rationale of nerve plexus resection using standardized resection extent criteria and method of diarrhea control, comparing both oncological benefit and quality of life.

In conclusion, we have detailed the short- and long-term outcomes after PD with incremental dissection extents for patients with PDACs. Strict adjustment of dissection according to pre-and intraoperative findings and systematic usage of opioid antidiarrheal agents facilitated successful AC, together leading to acceptable survival even in borderline resectable cases.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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