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ORIGINAL ARTICLE

Practical significance of pancreatectomy with lymphadenectomy around the superior mesenteric artery for pancreatic cancer: comparison of prognosis after adjusting for major prognostic factors

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Abstract

Introduction Although pancreatectomy with lymph node (LN) and nerve plexus dissection has usually been performed for pancreatic cancer, recent randomized controlled trials have questioned its survival benefits. However, superior mesenteric artery (SMA) LN dissection has still been included in standard treatment guidelines.

Methods A total of 94 patients who underwent pancreaticoduodenectomy for resectable pancreatic cancer without LN enlargement around the SMA on imaging were identified between 2008 and 2017. Disease-free survival (DFS), overall survival (OS), and complications were compared between those with LN and hemicircumferential nerve plexus dissection around the SMA (SMA ly+) and those without thorough LN and nerve plexus dissection around the SMA (SMA ly−) after adjusting for major prognostic factors.

Results A total of 78 and 16 patients with SMA ly+ and SMA ly− were identified, respectively. Our data demonstrated no difference in DFS and OS rates between both groups ($P = 0.18$ and 0.83, respectively). Patients with SMA ly+ had significantly more complications, particularly severe diarrhea, compared to those with SMA ly− ($P = 0.001$).

Conclusion LN and nerve plexus dissection around the SMA did not prolong survival and significantly increased the frequency of severe diarrhea, suggesting that performing in all cases carries less practical significance.

Keywords Pancreatic cancer · Superior mesenteric artery · Lymphadenectomy · Pancreaticoduodenectomy

Introduction

In 2019, approximately 56,770 and 45,750 new cases and deaths from pancreatic ductal carcinoma (PC), respectively, had been recorded in the USA [1]. PC has continued to be an aggressive global health problem. Moreover, it has caused approximately 34,900 estimated deaths, making it the fourth deadliest malignancy throughout Japan in 2018 [2]. Furthermore, the 5-year relative survival rate from PC remained at 9.3% from 2009 to 2015 [3]. Currently, although new chemotherapeutic regimens have gradually improved survival, surgical resection has remained the only curative treatment [4, 5]. Pancreatectomy with extended lymph node and nerve plexus dissection has routinely been performed for resectable pancreatic cancer considering some data showing improved prognosis in Japan [6, 7]. However, recent randomized controlled trials (RCTs) found that extended lymphedenectomy has no significant survival benefit over standard dissection [8, 9]. Moreover, the lack of survival benefit from pancreatectomy with radical extended lymphadenectomy was further confirmed following RCTs comparing standard resection and pancreatectomy with radical extended lymphadenectomy in Japan and Korea [10–12]. Acknowledging the aforementioned studies, the 2019 version of the Pancreatic Cancer Practice Guidelines suggested that extended lymph node and nerve plexus dissection for all patients with pancreatic cancer did not improve survival rate and recommended against its uniform performance [13]. However, lymphadenectomy around the superior mesenteric artery (SMA) has still been included in standard treatment protocols in Japan despite no common consensus regarding whether lymphadenectomy with hemicircumferential

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nerve plexus dissection or nerve plexus preservation without lymphadenectomy should be actively performed.

The use of adjuvant chemotherapy has obviously resulted in increased overall survival (OS) and disease-free survival (DFS) [14–16]. Moreover, early initiation of adjuvant chemotherapy has been an independent prognostic factor after pancreatectomy for patients with PC [17], while postoperative complications following pancreatectomy have been associated with adjuvant chemotherapy omission and delays [18]. Physiological dissection of the nerve plexus around the SMA has been shown to induce severe diarrhea due to sympathetic nerve dissection. Pancreatectomy with lymphadenectomy involving only hemicircumferential dissection of the nerve plexus might also induce severe diarrhea and increase other complications. However, proper dissection of all lymph nodes around the SMA is practically difficult for all patients with PC unless not only the lymph nodes around the SMA but also the nerve plexus are dissected.

We hypothesized that patients with resectable PC who underwent lymph node and hemicircumferential nerve plexus dissection around the SMA would experience increased complications without any survival benefit.

Materials and methods

Patient selection

We pooled 153 patients with resectable pancreatic adenocarcinoma from our prospectively collected database who underwent elective pancreatic resection at the Department of Surgery, Jikei University School of Medicine between 2008 and 2017. Among them, four with incomplete clinical data and 45 who underwent distal pancreatectomy were excluded. Ultimately, 94 patients who underwent pancreaticoduodenectomy for resectable pancreatic cancer without lymph node enlargement around the SMA on imaging were analyzed. Pathological staging was done through the Union for International Cancer Control (UICC) the 7th edition. This analysis was approved by the Jikei University School of Medicine Review Board. Medical records were retrospectively analyzed for age, gender, American Society of Anesthesiologists Physical Status Classification System (ASA-PS), comorbidities, operative time, intraoperative blood loss, postoperative hospital stay, complications, re-operation, adjuvant chemotherapy, staging (UICC), tumor size, nodal involvement, tumor grade, extra-pancreatic invasion, and positive pancreatic transection margin. As shown in Fig. 1, patients were divided into two groups: those with lymph node and hemicircumferential nerve plexus dissection around the SMA (SMA ly+) and those without thorough lymph node and nerve plexus dissection around the SMA (SMA ly−). Patients with intraductal mucinous cyst adenocarcinoma, stage 4 PC, and borderline resectable PC, as well as those who underwent other procedures, were excluded. Patients whose tumors suspected of being in contact with SMA, infiltrated by SMA or lymph nodes around the SMA, were swollen on preoperative imaging were also excluded. Severe diarrhea was defined as that which was difficult to control with probiotics alone and required antidiarrheals and opiates for control until discharge. The degree of lymph node and nerve plexus dissection around the SMA was based on not only descriptions from surgical records but also imaging analysis by two or more board-certified instructors or board-certified HBP surgeons.

Treatment

Patients with resectable pancreatic cancer underwent pancreaticoduodenectomy with or without thorough lymph node and hemicircumferential nerve plexus dissection around the SMA. The 6th edition of Classification of Pancreatic Cancer (the 3rd edition of the English version) shows seven categories for the nerve plexus around pancreas: PLphI, pancreatic head nerve plexusI; PLsma, superior mesenteric nerve plexus; PLhdl, hepatoduodenal ligament nerve plexus; PLce, celiac plexus; PLphII, pancreatic head nerve plexusII; PLcha, common hepatic artery nerve plexus; and PLspa, splenic artery nerve plexus [19]. PLphI and PLphII were dissected with lymph nodes to performed pancreaticoduodenectomy in all patients. Patients underwent pancreaticoduodenectomy with thorough lymph node and hemicircumferential PLsma on dissection line 1. Those without thorough lymph node and PLsma dissected on dissection line 2 (Fig. 2). Our strategy involved avoiding thorough lymph node and nerve plexus dissection around the SMA among elderly patients with any complication or low ASA-PS. Adjuvant chemotherapy, which consisted of gemcitabine or TS-1 continued for 6 months as tolerated, was initiated 12 weeks after pancreatectomy. Decisions regarding therapy were made during the multidisciplinary conference.

Surveillance

Patients underwent imaging study and blood tests every 3 months for 5 years. Recurrence of PC was defined as newly detected local or distant metastases on imaging study with or without increase in serum carcinoembryonic antigen or carbohydrate antigen 19-9.

Statistical methods

Differences in continuous data were compared using Student's *t*-test, while differences between other characteristics between SMA ly+ and SMA ly− groups were determined using chi-square tests or Fisher's exact tests as needed for small sample sizes. OS and DFS were estimated using the Kaplan–Meier method and compared using the log-rank test. Hazard ratios (HRs) with 95% confidence intervals (CIs) for

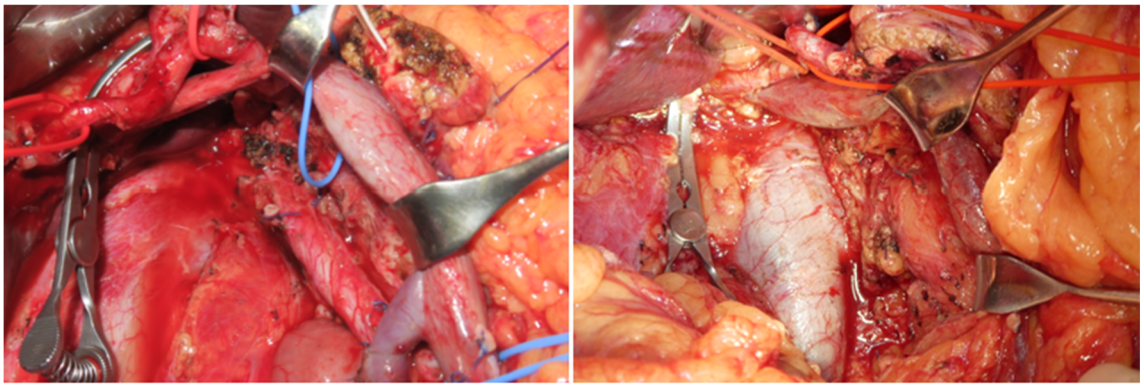

Fig. 1 The representative intraoperative picture about SMA ly− and SMA ly+

DFS and OS were calculated using Cox proportional hazard models with and without adjustment for age, ASA-PS, comorbidities, positive pancreatic transection margin, complications, adjuvant chemotherapy, UICC stage, tumor grade, and SMA ly±. All statistical analyses were performed using SAS version 9.4 software (SAS Institute, Cary, NC, USA) with *P* values less than 0.05 being considered statistically significant.

Results

Patient characteristics

Table 1 summarizes the patient characteristics. Majority of the patients were men (52.1%) and had a PS score of 2 (58.5%). About location of tumor, head/uncinate process ratios were 15:1 in the ly- group and 74:4 in the ly+ group. There were no statistical differences between two groups ($P = 0.722$). The SMA ly− group were more likely to have cardiovascular disease ($P = 0.002$), hypertension, ($P = 0.017$), and diabetes mellitus ($P = 0.061$) compared to the SMA ly+ group. As shown in Table 2, which details all perioperative factors, the mean operative time was 559.0 (SD 105.7) min, while the mean intraoperative blood loss was 1054.9 (SD 834.4) ml. Moreover, 76.6% of the patients received adjuvant chemotherapy, while mean postoperative hospital stay was 29.3 (SD 22.7) days. While operative time and intraoperative blood loss was almost similar between both groups, significantly more patients in the SMA ly+ group received adjuvant chemotherapy after surgery ($P = 0.01$). Some patients developed complications, such as pancreatic fistula (8.5%), bile leakage (4%), delay gastric empty (13%), hemorrhage (3.2%), pseudoaneurysm (5.3%), abscess (5.3%), SSI (13.8%), and severe diarrhea (35.1%), as indicated in Table 2, with the SMA ly+ group having significantly more complications, particularly severe diarrhea, after surgery compared to the SMA

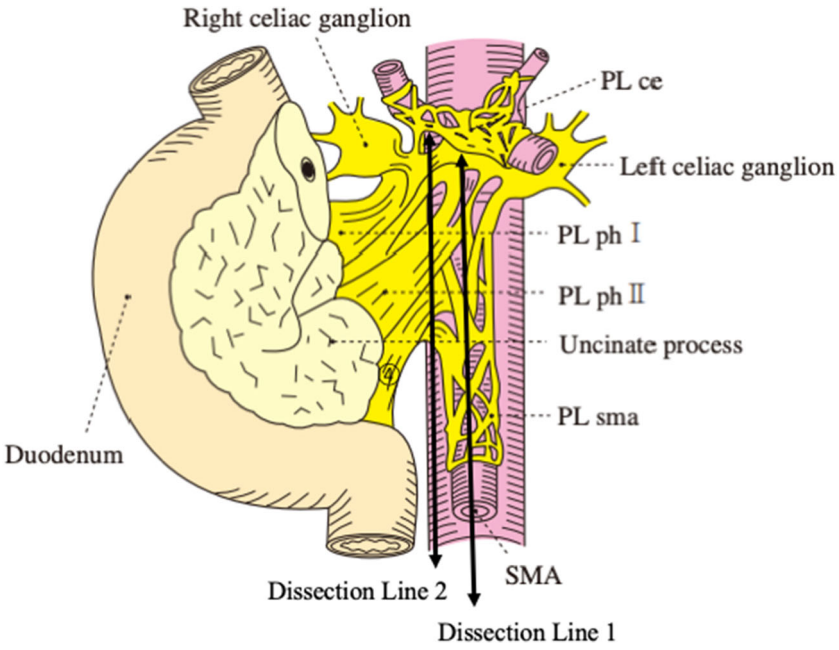

Fig. 2 The structure of the nerve and fibrous tissue around the SMA (ref.19). The shema is reprinted by courtesy of Japan Pancreas Society

Table 1 Patient characteristics

N		All		SMA ly−		SMA ly+		*P*
		94		16		78		
Age	Mean (SD)	68.1 (10.2)		73.4 (4.6)		67.1 (10.7)		<0.001
Gender	Male	49	52.1%	9	56.3%	40	51.3%	0.717
	Female	45	47.9%	7	43.8%	38	48.7%	
ASA-PS	1	36	38.3%	4	25.0%	32	41.0%	0.406
	2	55	58.5%	11	68.8%	44	56.4%	
	3	3	3.2%	1	6.3%	2	2.6%	
Location of tumor	Head	89	94.7%	15	93.8%	71	91.0%	0.722
	Uncinate process	5	5.3%	1	6.3%	7	9.0%	
CVD		18	19.1%	8	50.0%	10	12.8%	0.002
Hypertension		45	47.9%	12	75.0%	33	42.3%	0.017
DM		39	41.5%	10	62.5%	29	37.2%	0.061
COPD		2	2.1%	0	0.0%	2	2.6%	1.000

SMA ly+, lymph node and hemicircumferential nerve plexus dissection around the superior mesenteric artery; SMA ly−, without thorough lymph node and nerve plexus dissection around the superior mesenteric artery; *N* number of patients, *ASA-PS* American Society of Anesthesiologists Physical Status, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus

ly− group ($P < 0.001$). There were 3 cases of hemorrhage and 5 cases of pseudoaneurysm in SMA ly+ group. Re-operation was required for 1 case with hemorrhage from the pseudoaneurysm located on the stump of gastroduodenal artery and another case with hemorrhage for which the bleeding site was not detected. Percutaneous coil embolization was performed for 1 case with hemorrhage and pseudoaneurysm which bleed from the site of ligation of the gastroduodenal artery and 1 case of pseudoaneurysm at the site of periphery of the left gastric artery and 1 case of pseudoaneurysm at the site of ligation of the gastroduodenal artery. One case of small pseudoaneurysm at the stump of the gastroduodenal artery was closely followed up. Only one patient in SMA ly+ group died after reoperation due to postoperative hemorrhage from the pseudoaneurysm at the stump of the gastroduodenal artery. All of patients with severe diarrhea had long-lasting symptoms after discharge although the medication dose could be reduced in some patients. The incidence time peak of diarrhea was 3–5 days after surgery when oral intake was resumed. Three cases (1 pancreatic duct and 2 retroperitoneal margin) in SMA ly− group and 30 cases (11 pancreatic duct and 19 retroperitoneal margin) in SMA ly+ group were diagnosed as positive, respectively. No positive pancreatic transection margin around SMA nor nerve plexus was observed. Regarding the status of the surgical margin, we do not follow the "1-mm" rule. In other words, the locations of positive pancreatic transection margin are all cut-off edges and not near the SMA with no significant difference among two groups. Pathological findings were similar between the SMA ly+ and SMA ly− groups. Locations of the positive LNs were also No. 8, 12, and around pancreas in both groups. There were no positive LN at No. 14 station in the SMA ly+ group.

Disease-free survival and overall survival

The median follow-up duration was 1.48 (IQR 2.38) years. Among the 94 included patients, 74 (78.7%) died and 20 (21.3%) survived upon the writing of this study. The median DFS and OS was 0.95 and 1.84 years, respectively. Figures 3 and 4 present the DFS and OS in the SMA ly± groups. Accordingly, the SMA ly+ and SMA ly− group had a median DFS of 0.79 and 1.24 years ($P = 0.180$) and a median OS of 1.78 and 2.18 years ($P = 0.833$), respectively. The SMA ly+ group tended to have worse DFS and OS than the SMA ly− group, though the difference was not significant.

Table 3 shows the DFS and OS according to patient characteristics, perioperative factors, and pathological factors. Accordingly, univariate analysis showed that low UICC stage, nodal involvement, tumor grade, and extra-pancreatic invasion were significantly associated with longer DFS and OS. Table 4 presents the results of multivariate analysis for DFS and OS after adjusting for age, ASA-PS, and comorbidities along with all other factors. Accordingly, multivariate analysis revealed that UICC stage and tumor grade remained significantly associated with DFS, while UICC stage, tumor grade, positive pancreatic transection margin, and adjuvant chemotherapy remained significantly associated with OS. However, DFS and OS were similar between the SMA ly+ and SMA ly− groups.

Table 2 Perioperative and pathological factors

N		All		SMA ly−		SMA ly+		*P*
		94		16		78		
Perioperative factors								
Operative time	Mean (SD)	559.0 (105.7)		554.3 (95.9)		557.9 (108.2)		0.826
Blood loss	Mean (SD)	1054.9 (834.4)		1193.1 (609.0)		1026.6 (874.0)		0.470
Hospital stay	Mean (SD)	29.3 (22.7)		30.2 (12.0)		29.1 (24.4)		0.791
Positive pancreatic transection margin		33	35.1%	3	18.8%	30	38.5%	0.132
Complications	Any	52	55.3%	5	31.3%	47	60.3%	0.034
	Panc fistula	8	8.5%	2	12.5%	6	7.7%	0.620
	Bile leakage	4	4.3%	1	6.3%	3	3.8%	0.532
	DGE	13	13.8%	1	6.3%	12	15.4%	0.456
	Hemorrhage	3	3.2%	0	0.0%	3	3.8%	1.000
	Pseudoaneurysm	5	5.3%	0	0.0%	5	6.4%	0.584
	Abscess	5	5.3%	2	12.5%	3	3.8%	0.200
	SSI	13	13.8%	3	18.8%	10	12.8%	0.690
	Diarrhea	33	35.1%	0	0.0%	33	42.3%	0.001
Re-operation		3	3.2%	0	0.0%	3	3.8%	1.000
Adjuvant Chemo		72	76.6%	8	50.0%	64	82.1%	0.010
Pathological factors								
T stage	1	9	9.6%	2	12.5%	7	9.0%	0.897
	2	53	56.4%	9	56.2%	44	56.4%	
	3	32	34.0%	5	31.3%	27	34.6%	
N stage	0	36	38.3%	8	50.0%	28	35.9%	0.514
	1	39	41.5%	6	37.5%	33	42.3%	
	2	19	20.2%	2	12.5%	17	21.8%	
UICC stage	1	28	29.8%	7	43.8%	21	26.9%	f[0.372
	2	47	50.0%	7	43.8%	40	51.3%	
	3	19	20.2%	2	12.5%	17	21.8%	
Tumor size	≤2.0 cm	6	6.4%	1	6.3%	5	6.4%	0.976
	2.1–4.0 cm	55	58.5%	9	56.3%	46	59.0%	
	4.1 ≤ cm	33	35.1%	6	37.5%	27	34.6%	
Nodal involvement		60	63.8%	9	56.3%	51	65.4%	0.489
Tumor grade	Well	29	30.9%	6	37.5%	23	29.5%	0.786
	Moderate	60	63.8%	9	56.3%	51	65.4%	
	Poor	5	5.3%	1	6.3%	4	5.1%	
Extra-panc invasion		78	83.0%	13	81.3%	65	83.3%	1.000

SMA ly+, lymph node and hemicircumferential nerve plexus dissection around the superior mesenteric artery; SMA ly−, without thorough lymph node and nerve plexus dissection around the superior mesenteric artery; *N* number of patients, *DGE* delayed gastric emptying, *SSI* surgical site infection; *Chemo* chemotherapy, *Extra-panc invasion* extra-pancreatic invasion

Discussion

In the present study on resectable PC, elderly patients with any comorbidity underwent lymphadenectomy with hemicircumferential nerve plexus dissection around the SMA for less invasiveness. Moreover, initiating adjuvant chemotherapy among such patients remained difficult due to their vulnerability and frailty. Therefore, adjusting for patient characteristics and other prognostic factors was important for evaluating independent predictors of DFS and OS. Studies have already identified UICC stage and tumor grade as prognostic factors [20, 21]. Furthermore, adjuvant chemotherapy has been shown to improve prognosis and has been considered a standard treatment for PC following tumor resection [14–16]. Other studies have also found that positive pancreatic transection margin was associated with poor prognosis [22].

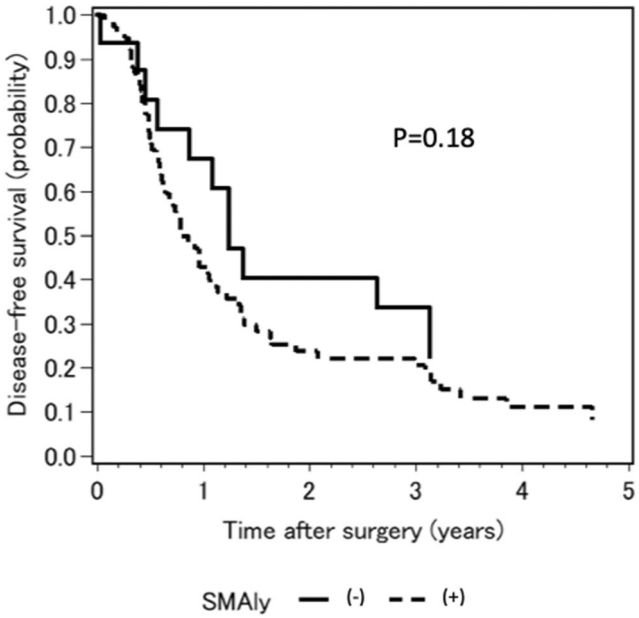

Fig. 3 Kaplan–Meier survival curve for disease-free survival

Similarly, our data showed that the aforementioned factors were significantly associated with OS during multivariate analysis after adjusting for age, ASA-PS, comorbidities, and other prognostic factors. The lack of a significant association between adjuvant chemotherapy, as well as positive pancreatic transection margin, and DFS was thought to have been cause by the small number of patients and the generally short DFS from pancreatic cancer. The SMA ly− and SMA ly+ groups had similar DFS and OS after adjusting for age, ASA-PS, comorbidities, and other prognostic factors, suggesting that lymphadenectomy with hemicircumferential nerve plexus dissection around the SMA had no prognostic

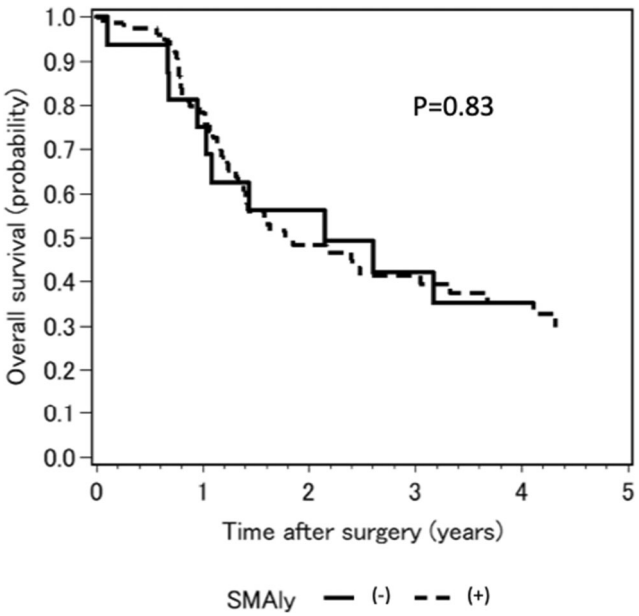

Fig. 4 Kaplan–Meier survival curve for overall survival

significance. Though patients with SMA ly− received less adjuvant chemotherapy, they have the same DFS and OS of patients with SMA ly+. This outcome, despite the fact that adjuvant chemotherapy is one of prognostic factors from the multivariate analysis, is thought to be due to the large surgical invasiveness. It could be thought that excessive lymph node dissection increased complications and the invasiveness was due to prognosis.

The operative time is same between the two groups probably because we usually do not need to do the additional procedure for SMA nerve plexus dissection. We only need to change the dissection level (layer) around the SMA nerve plexus; it could be the explanation of the similar operation time between dissection and non-dissection groups. According to the lymphadenectomy, we tried to dissect the same levels of lymph nodes regardless of the levels of SMA nerve plexus dissection, so that there was no difference in the operation time between two groups.

Patients with SMA ly+ exhibited significantly higher rates of severe diarrhea than those with SMA ly−. Moreover, over complication rates were significantly higher among patients with SMA ly+ perhaps due to the higher rates of severe diarrhea. Several reports have shown that diarrhea due to nerve plexus dissection around the SMA has been one of the risk factors for adjuvant chemotherapy failure [11], while other studies have revealed that introducing adjuvant chemotherapy has remained difficult for almost all patients with PC [23, 24]. Furthermore, severe diarrhea has been shown to cause malnutrition. Therefore, worsening of prognosis could be possible with late initiation of feeding and non-improvement of nutritional status [25]. However, studies have shown that early countermeasures for various complications were important [8–12], with one recent study showing that severe diarrhea could be managed early using antidiarrheals to avoid delaying or failure of adjuvant chemotherapy [26]. Considering that we also administrated antidiarrheals early for patients with SMA ly+, we believed that none of the complications, including severe diarrhea, contributed to DFS and OS, though multivariate analysis showed that adjuvant chemotherapy was associated with OS related. Although severe diarrhea can be controlled through pharmacotherapy and interventions, nerve plexus dissection around the SMA should be avoided from the viewpoint of quality of life when it provides no apparent survival benefits. Unnecessary lymphadenectomy around blood vessels should be avoided considering the risk for complications.

Studies have already revealed that R0 resection and early adjuvant chemotherapy administration improve OS among patients with PC [17, 22]. As such, performing the necessary lymphadenectomy and early introduction of adjuvant chemotherapy have both been considered imperative. Given that drastic extended lymphadenectomy considerably increases complications, early adjuvant chemotherapy introduction

Table 3 Univariate analysis for disease-free and overall survival

		DFS			OS		
		HR	95% CI	*P*	HR	95% CI	*P*
Age	Per year	0.98	0.96–1.00	0.063	0.99	0.97–1.03	0.908
ASA-PS	1	1.00	Ref	0.422	1.00	Ref	0.610
	2	1.10	0.69–1.78		1.25	0.72–2.22	
	3	0.48	0.08–1.60		0.76	0.12–2.62	
CVD		0.99	0.54–1.69	0.960	1.60	0.86–2.83	0.134
Hypertension		0.57	0.35–0.90	0.015	0.74	0.43–1.25	0.263
DM		0.87	0.54–1.39	0.567	1.02	0.59–1.74	0.932
COPD		1.05	0.17–3.34	0.952	1.47	0.24–4.75	0.612
SMA ly	(+)	1.00	Ref	0.163	1.00	Ref	0.834
	(−)	1.55	0.85–3.10		0.93	0.50–1.90	
Hospital days	Per 1 day	1.00	0.99–1.01	0.344	1.01	0.99–1.02	0.192
Positive pancreatic transection margin		1.41	0.87–2.24	0.165	1.22	0.70–2.09	0.470
Complication	Any	1.09	0.68–1.74	0.729	0.71	0.42–1.21	0.208
	Panc fistula	0.60	0.21–1.35	0.239	0.96	0.33–2.18	0.927
	Bile leakage	0.76	0.19–2.06	0.636	0.32	0.02–1.45	0.168
	DGE	0.61	0.28–1.17	0.142	0.46	0.16–1.05	0.068
	Hemorrhage	0.79	0.13–2.52	0.729	0.47	0.03–2.14	0.396
	Pseudoaneurysm	0.99	0.30–2.38	0.980	0.62	0.10–1.99	0.473
	Abscess	1.60	0.56–3.63	0.346	1.37	0.41–3.39	0.563
	SSI	1.38	0.68–2.51	0.351	1.38	0.65–2.62	0.377
	Diarrhea	1.50	0.92–2.40	0.101	0.84	0.46–1.47	0.550
Re-operation		3.25	0.53–10.69	0.169	0.81	0.05–3.71	0.833
Adjuvant chemo		1.31	0.74–2.50	0.363	0.66	0.37–1.23	0.183
UICC stage	1	1.00	Ref	<0.001	1.00	Ref	0.006
	2	2.92	1.67–5.33		2.77	1.45–5.65	
	3	3.16	1.59–6.30		2.29	1.03–5.13	
Tumor size	≤2.0cm	1.00	Ref	0.305	1.00	Ref	0.416
	2.1–4.0cm	1.66	0.61–6.86		1.11	0.40–4.61	
	4.1≤cm	2.18	0.76–9.14		1.59	0.55–6.75	
Nodal involvement		2.88	1.73–5.02	<0.001	2.12	1.19–3.99	0.010
Tumor grade	Well	1.00	Ref	0.003	1.00	Ref	0.018
	Moderate	1.99	1.18–3.54		1.74	0.96–3.34	
	Poor	6.87	1.92–19.48		5.78	1.61–16.51	
Extra-panc invasion		2.09	1.09–4.53	0.024	2.22	1.03–5.80	0.042

SMA ly+, lymph node and hemicircumferential nerve plexus dissection around the superior mesenteric artery; SMA ly−, without thorough lymph node and nerve plexus dissection around the superior mesenteric artery; *N* number of patients, *ASA-PS* American Society of Anesthesiologists Physical Status, *COPD* chronic obstructive pulmonary disease, *DM* diabetes mellitus, *DGE* delayed gastric emptying, *SSI* surgical site infection, *Chemo* chemotherapy, *Extra-panc invasion* extra-pancreatic invasion

Table 4 Multivariate analysis for disease-free and overall survival

		DFS			OS		
		HR	95% CI	*P*	HR	95% CI	*P*
SMA ly	(+)	1.00	Ref		1.00	Ref	
	(−)	1.19	0.52–2.93	0.697	0.96	0.40–2.45	0.927
Positive pancreatic transection margin		1.69	0.96–2.97	0.066	2.42	1.22–4.80	0.011
Complication		0.97	0.53–1.76	0.916	0.57	0.28–1.13	0.112
Adjuvant Chemo		0.53	0.24–1.19	0.117	0.35	0.15–0.82	0.015
UICC stage	1	1.00	Ref		1.00	Ref	
	2	3.20	1.68–6.37	<0.001	2.48	1.20–5.44	0.018
	3	3.00	1.39–6.55	0.005	2.54	1.05–6.25	0.039
Tumor grade	Well	1.00	Ref		1.00	Ref	
	Moderate	2.55	1.33–5.13	0.007	2.48	1.20–5.46	0.019
	Poor	5.75	1.46–19.13	0.007	7.34	1.77–26.39	0.003

Hazard ratios (HR) and 95% confidence intervals (CI) were calculated with adjustment for age, ASA-PS, and comorbidities along with all the factors listed in the table; SMA ly+, lymph node and hemicircumferential nerve plexus dissection around the superior mesenteric artery; SMA ly−, without thorough lymph node and nerve plexus dissection around the superior mesenteric artery; *Chemo* chemotherapy

should be done without lymphadenectomy, which does not contribute to DFS and OS. Our findings seem to suggest the importance of a balance between lymphadenectomy and early adjuvant chemotherapy introduction. Moreover, the present study found that lymphadenectomy with hemicircumferential nerve plexus dissection around the SMA increased complications without providing any survival benefits. Accordingly, thorough lymph node and hemicircumferential nerve plexus dissect around the SMA for prophylaxis would be meaningless. However, lymphadenectomy with nerve plexus dissection should be performed without hesitation among those suspected of lymph node metastasis or direct invasion around the SMA considering that R0 resection is an independent prognostic factor [22].

The limitations of the current study include its retrospective single-center design and the relatively small sample size. However, some strengths of our study do need to be noted: (1) our data can be considered credible given that OS-related factors were determined after adjusting for confounding variables and (2) this has been the first report on the subject matter.

In conclusion, our data showed that SMA ly+ provided no survival nor oncological benefit while increasing rates of severe diarrhea, suggesting that pancreatectomy with lymphadenectomy and hemicircumferential nerve plexus dissection around the SMA may carry no practical significance for pancreatic cancer.

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Availability of data and material The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request. A copy of the written consent is available for review upon requests.

Declarations

Ethics approval The study protocol was approved by the ethics committee of the Jikei University School of Medicine (27-177(8062)), and the written informed consent was obtained from each patients.

Consent to participate and consent for publication Written informed consents were obtained from all subjects for participate and publication of this study.

Conflict of interest The authors declare no competing interests.

References

1. Siegel RL, Miller KD, Jemal A (2019) Cancer statistics, 2019. CA Cancer J Clin 69:7–34. https://doi.org/10.3322/caac.21551
2. Cancer statistics in Japan '18 Cancer information Service, National Cancer Center Japan (2019). https://ganjoho.jp/en/professional/statistics/brochure/2018_en.html. Accessed 26 September 2020
3. National Cancer Institute (2017) Cancer of the Pancreas - SEER Stat Fact Sheets. Surveillance, Epidemiol. End Results Progr. http://seer.cancer.gov/statfacts/html/pancreas.html. Accessed 26 September 2020
4. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y et al (2011) Folfirinox versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 365:768–769. https://doi.org/10.1056/nejmoa1011923
5. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M et al (2013) Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 369:1691–1703. https://doi.org/10.1056/nejmoa1304369
6. Manabe T, Ohshio G, Baba N, Miyashita T, Asano N, Tamura K, Yamaki K, Nonaka A, Tobe T (1989) Radical pancreatectomy for ductal cell carcinoma of the head of the pancreas. Cancer. 64:1132–1137. https://doi.org/10.1002/1097-0142(19890901)64:5<1132::AID-CNCR2820640528>3.0.CO;2-V
7. Nagakawa T, Nagamori M, Futakami F, Tsukioka Y, Kayahara M, Ohta T, Ueno K, Miyazaki I (1996) Results of extensive surgery for pancreatic carcinoma. Cancer. 77:640–645. https://doi.org/10.1002/(SICI)1097-0142(19960215)77:4<640::AID-CNCR9>3.0.CO;2-K
8. Yeo CJ, Cameron JL, Lillemoe KD, Sohn TA, Campbell KA, Sauter PK, Coleman JA, Abrams RA, Hruban RH (2002) Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, Part 2. Ann Surg 236:355–368. https://doi.org/10.1097/00000658-200209000-00012
9. Farnell MB, Pearson RK, Sarr MG, DiMagno EP, Burgart LJ, Dahl TR et al (2005) A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surgery. 138:618–628. https://doi.org/10.1016/j.surg.2005.06.044
10. Nimura Y, Nagino M, Takao S, Takada T, Miyazaki K, Kawarada Y, Miyagawa S, Yamaguchi A, Ishiyama S, Takeda Y, Sakoda K, Kinoshita T, Yasui K, Shimada H, Katoh H (2012) Standard versus extended lymphadenectomy in radical pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas. J Hepatobiliary Pancreat Sci 19:230–241. https://doi.org/10.1007/s00534-011-0466-6
11. Jang J-Y, Kang MJ, Heo JS, Choi SH, Choi DW, Park SJ, Han SS, Yoon DS, Yu HC, Kang KJ, Kim SG, Kim SW (2014) A prospective randomized controlled study comparing outcomes of standard resection and extended resection, including dissection of the nerve plexus and various lymph nodes, in patients with pancreatic head cancer. Ann Surg 259:656–664. https://doi.org/10.1097/sla.0000000000000384
12. Jang J-Y, Kang JS, Han Y, Heo JS, Choi SH, Choi DW, Park SJ, Han SS, Yoon DS, Park JS, Yu HC, Kang KJ, Kim SG, Lee H, Kwon W, Yoon YS, Han HS, Kim SW (2017) Long-term outcomes and recurrence patterns of standard versus extended pancreatectomy for pancreatic head cancer: a multicenter prospective randomized controlled study. J Hepatobiliary Pancreat Sci 24:426–433. https://doi.org/10.1002/jhbp.465
13. Okusaka T, Nakamura M, Shimizu K, Furuse J, Ito Y, Hanada K et al (2020) Clinical practice guidelines for pancreatic cancer 2019

from the Japan Pancreas Society: a synopsis. Pancreas. 49:326–335. https://doi.org/10.1097/mpa.0000000000001513

14. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, Niedergethmann M, Zülke C, Fahlke J, Arning MB, Sinn M, Hinke A, Riess H (2013) Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. J Am Med Assoc 310:1473–1481. https://doi.org/10.1001/jama.2013.279201
15. Ueno H, Kosuge T, Matsuyama Y, Yamamoto J, Nakao A, Egawa S, Doi R, Monden M, Hatori T, Tanaka M, Shimada M, Kanemitsu K (2009) A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer. Br J Cancer 101:908–915. https://doi.org/10.1038/sj.bjc.6605256
16. Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, Kaneoka Y, Shimizu Y, Nakamori S, Sakamoto H, Morinaga S, Kainuma O, Imai K, Sata N, Hishinuma S, Ojima H, Yamaguchi R, Hirano S, Sudo T, Ohashi Y (2016) Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet. 388:248–257. https://doi.org/10.1016/s0140-6736(16)30583-9
17. Valle JW, Palmer D, Jackson R, Cox T, Neoptolemos JP, Ghaneh P, Rawcliffe CL, Bassi C, Stocken DD, Cunningham D, O'Reilly D, Goldstein D, Robinson BA, Karapetis C, Scarfe A, Lacaine F, Sand J, Izbicki JR, Mayerle J, Dervenis C, Oláh A, Butturini G, Lind PA, Middleton MR, Anthoney A, Sumpter K, Carter R, Büchler MW (2014) Optimal duration and timing of adjuvant chemotherapy after definitive surgery for ductal adenocarcinoma of the pancreas: Ongoing lessons from the ESPAC-3 study. J Clin Oncol 32:504–512. https://doi.org/10.1200/jco.2013.50.7657
18. Merkow RP, Bilimoria KY, Tomlinson JS, Paruch JL, Fleming JB, Talamonti MS, Ko CY, Bentrem DJ (2014) Postoperative complications reduce adjuvant chemotherapy use in resectable pancreatic cancer. Ann Surg 260:372–377. https://doi.org/10.1097/sla.0000000000000378
19. Japan Pancreas Society (2011) Classification of Pancreatic Carcinoma, Third English edn. Kanehara & Co., Ltd, Tokyo
20. Rochefort MM, Ankeny JS, Kadera BE, Donald GW, Isacoff W, Wainberg ZA, Hines OJ, Donahue TR, Reber HA, Tomlinson JS (2013) Impact of tumor grade on pancreatic cancer prognosis: validation of a novel TNMG staging system. Ann Surg Oncol 20:4322–4329. https://doi.org/10.1245/s10434-013-3159-3
21. Hlavsa J, Cecka F, Zaruba P, Zajak J, Gurlich R, Strnad R et al (2018) Tumor grade as significant prognostic factor in pancreatic cancer: validation of a novel TNMG staging system. Neoplasma. 65:637–643. https://doi.org/10.4149/neo_2018_171012n650
22. Kato K, Yamada S, Sugimoto H, Kanazumi N, Nomoto S, Takeda S, Kodera Y, Morita S, Nakao A (2009) Prognostic factors for survival after extended pancreatectomy for pancreatic head cancer: influence of resection margin status on survival. Pancreas. 38:605–612. https://doi.org/10.1097/mpa.0b013e3181a4891d
23. Mayo SC, Austin DF, Sheppard BC, Mori M, Shipley DK, Billingsley KG (2010) Adjuvant therapy and survival after resection of pancreatic adenocarcinoma. Cancer. 116:2932–2940. https://doi.org/10.1002/cncr.25082
24. Croome KP, Farnell MB, Que FG, Reid-Lombardo KM, Truty MJ, Nagorney DM, Kendrick ML (2014) Total laparoscopic pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: oncologic advantages over open approaches? Ann Surg 260:633–638; discussion 638–40. https://doi.org/10.1097/sla.0000000000000937
25. Watanabe J, Otani S, Sakamoto T, Arai Y, Hanaki T, Amisaki M, Tokuyasu N, Honjo S, Ikeguchi M (2016) Prognostic indicators based on inflammatory and nutritional factors after pancreaticoduodenectomy for pancreatic cancer. Surg Today 46:1258–1267. https://doi.org/10.1007/s00595-016-1308-6
26. Inoue Y, Saiura A, Oba A, Kawakatsu S, Ono Y, Sato T, Mise Y, Ishizawa T, Takahashi Y, Ito H (2019) Optimal extent of superior mesenteric artery dissection during pancreaticoduodenectomy for pancreatic cancer: balancing surgical and oncological safety. J Gastrointest Surg 23:1373–1383. https://doi.org/10.1007/s11605-018-3995-3