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Extended versus peripancreatic lymph node dissection for the treatment of left-sided pancreatic cancer

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Purpose: The pathways of lymphatic metastases differ according to the tumor location in pancreatic cancer patients. However, it is unclear whether extended lymph node dissection (LND) is essential for all left-sided pancreatic cancer. The aim of this study is to evaluate the survival outcomes according to the extent of LND and tumor location in patients with left-sided pancreatic cancer.
Methods: January 2005 to December 2013, we retrospectively identified 107 patients who underwent curative intent surgery for left-sided pancreatic cancer. The left-sided pancreatic cancer was defined as a tumor located in pancreatic body or tail. The extent of LND was divided into 2 groups: extended LND and peripancreatic LND. The extended LND group included celiac and superior mesenteric LNs.
Results: We included 107 patients with left-sided pancreatic cancer; 59 patients with pancreatic body cancer and 48 patients with pancreatic tail cancer. The median follow-up period was 17 months (range, 3–110 months). Fifty patients with pancreatic body cancer and 30 patients with pancreatic tail cancer underwent extended LND. In patients with pancreatic body cancer, extended LND was associated with improved disease-free survival (DFS) (P = 0.010) and overall survival (P = 0.014). However, extended LND was not associated with DFS in patients with pancreatic tail cancer.
Conclusion: Extended LND could improve survival in patients with pancreatic body cancer. However, extended LND had no survival benefit for the treatment of pancreatic tail cancer.
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Key Words: Pancreas, Neoplasms, Lymph node excision, Survival

INTRODUCTION

Lymphatic metastases are common in adenocarcinoma including pancreatic ductal adenocarcinoma. Therefore, lymph node dissection (LND) is essential for pancreatic cancer to achieve curative intent surgery. However, there are many different pathways of lymphatic metastases in left-sided pancreatic cancer. The lymphatics from the pancreatic body drain into celiac or superior mesenteric lymph nodes (LNs), although lymphatics from the pancreatic tail drain into splenic hilar or gastrosplenic LNs [1]. In 2003, Dr. Strasberg introduced radical antegrade modular pancreatosplenectomy (RAMPS) for the treatment of left-sided pancreatic cancer. The RAMPS procedure has 3 main concepts; N1 group LND, modular setting of the posterior plane, and right to left direction of dissection. Celiac LNs and superior mesenteric LNs were included in N1 LN group and recommended to be removed in all left-sided pancreatic cancers [1,2]. The notion was supported by recent studies that RAMPS is helpful in obtaining negative tangential margin and could enhance survival outcomes in patients with left-sided pancreatic cancer [3-7].

However, lymphatic drainages from the pancreatic tail rarely drain into celiac or superior mesenteric LNs. Therefore, extended LND including celiac and superior mesenteric LNs

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seem to be not associated with survival benefit but with surgical complication in patients with pancreatic tail cancer. There is still controversy as to whether celiac and superior mesenteric LND is always necessary if the tumor is located in the body of the pancreas. Moreover, it is still unclear whether extended LND is associated with survival benefit for the treatment of pancreatic cancer. Recent studies reported that there was no survival difference even though extended LND was performed for pancreatic head cancer compared with peripancreatic LND group. On the other hand, extended LND was associated with surgical complications [8]. There are very complicated nerve plexuses near the celiac axis and superior mesenteric artery, and most of the foregut and midgut are innervated through the nerve plexus [9,10].

Naturally, LND is essential for the treatment of adenocarcinoma. However, the optimal extent of LND for left-sided pancreatic cancer has not yet been established. Moreover, the tail of the pancreas should be distinguished from the body of the pancreas because of the lymphatic drainage system is different. The aim of this study is to investigate the perioperative complication rate and survival outcomes according to the extent of LND in each case of pancreatic body and tail cancer. We would like to identify the optimal extent of LND according to tumor location in patients with left-sided pancreatic cancer.

METHODS

This study was approved by the Institutional Review Board of Samsung Medical Center (approval number: 2015-11-001). From January 2005 to December 2013, we identified patients with left-sided pancreatic cancer who underwent curative intent surgery. The medical records were retrospectively reviewed. Exclusion criteria were palliative surgery, follow-up period less than 3 months, distant LN metastasis cases, and double primary cancer. Left-sided pancreatic cancer was defined as a tumor located in the body or tail of the pancreas, and laterally to the left border of the superior mesenteric vein. The location of pancreatic cancer was divided into the body and tail of the pancreas. We determined the pancreatic body cancer, of which the epicenter of the tumor was located within the medial half of the left pancreas. The other lateral half was defined as pancreas tail. When the tumor had invaded both of the body and tail of the pancreas, it was categorized into pancreatic body cancer group. To evaluate the extent of LND, we reviewed photos of the operation field. We routinely took pictures of the operation field from 2005. The extent of LND was divided into 2 categories; extended LND, and peripancreatic LND. Extended LND included common hepatic, left gastric, and celiac LNs with or without superior mesenteric LND. Peripancreatic LND included inferior pancreatic, splenic artery, gastrosplenic, and splenic hilar LNs. We analyzed recurrence patterns and survivals according to the extent of LND and the location of tumor.

One hundred thirty-seven patients underwent open left-sided pancreatectomy for pancreatic body or tail cancer. Thirty patients were excluded and 107 were investigated. There were 59 patients of pancreatic body cancer and 48 patients of pancreatic tail cancer. In pancreatic body cancer group, 50 of 59 patients underwent extended LND, and 9 patients underwent peripancreatic LND. In pancreatic tail cancer group, 30 patients underwent extended LND, and 18 patients underwent peripancreatic LND.

To prevent recurrence, we recommended adjuvant chemotherapy based on fluorouracil (5-FU), capecitabine, or gemcitabine. Postoperative surveillance for recurrence was performed every 3 months for the first 2 years and 6 months thereafter; this included physical examination, chest X-ray, and abdominal CT scanning. In addition to medical records, Roentgen images were reviewed retrospectively to identify recurrence patterns.

The LNs were isolated during operation according to the location and adjacent vessels. The pancreas was transected at the neck of pancreas level to reduce pancreatic fistula because the pancreas neck is the thinnest area. However, we preserved the pancreas body in selected patients if the thickness of the pancreas body was less than 15 mm without pancreatitis. The antegrade dissection was performed for left-sided pancreatic cancer to obtain secure resection margin from the retroperitoneum. The spleen was mobilized *en bloc* and removed in all patients. The left adrenal gland was also sacrificed if there was tumor invasion. Peripancreatic LND was routinely performed in all patients. Extended LND was routinely attempted for pancreatic body cancer. However, extended LND was not performed according to the surgeon's discretion, especially in patients with comorbidities. In patients with pancreatic tail cancer, we did not have standard guidelines for LND. We performed extended LND for pancreatic tail cancer according to surgeon preference without guidelines.

Various variables including sex, age, American Society of Anesthesiologists (ASA) physical status classification, CA 19-9, location and size of tumor, T stage, N stage, tumor cell differentiation, chemotherapy, radiation therapy, estimated blood loss, hospital duration, postoperative complications, recurrences, sites of recurrences, death, disease-free survival (DFS), and overall survival (OS) were investigated in each patient. The T and N stages were determined according to the 7th edition of the American Joint Committee on Cancer guidelines. We evaluated the extent of LND, operation periods, LN metastasis, histologic grade, and adjuvant chemotherapy as a prognostic factor. If the P-value of univariate analysis was less than 0.20, the variables were included in multivariate analysis.

The categorical variables are presented as number (percen-

tage). The continuous variables are presented as median (range). The categorical variables were compared using the chi-square test or Fisher exact test. The continuous variables were compared using the Mann Whitney U-test. Survival was calculated using the Kaplan-Meier method from the date of surgical treatment, and the differences in survival were examined using the log-rank test and Cox proportional hazard model. A P-value less than 0.05 was considered statistically significant.

RESULTS

A total of 137 patients underwent surgery for left-sided pancreatic cancer, and 107 patients were included in this study. According to the exclusion criteria, 15 patients who underwent palliative surgery, 2 patients with distant LN metastasis, and eight patients with double primary cancer were excluded. The follow-up period was less than 3 months in 5 patients, and they were regarded as follow-up loss cases and also excluded. The median age was 64 years (range, 42–83 years) and the median follow-up period was 17 months (range, 3–110 months).

Demographics

There were 59 patients of pancreatic body cancer and 48 patients of pancreatic tail cancer. In pancreatic body cancer group, 50 patients (85%) underwent extended LND. In pancreatic tail cancer group, 30 patients (63%) underwent extended LND. There were no significant differences in patients' characteristics including sex, age, operation period, ASA physical status classification, serum CA 19-9 level, tumor size, T stage, LN metastasis, poorly differentiated histologic type, and adjuvant chemotherapy (Table 1).

Perioperative outcomes

There was no postoperative mortality. There were in total 32 cases of postoperative complications. In pancreatic body cancer patients, the morbidity rate was 26% after extended LND, and it was 11% after peripancreatic LND (P = 0.67). Pancreatic fistula occurred in 4 patients (8%) after extended LND, and 1 patient (11%) after peripancreatic LND (P = 0.58). The median hospital duration was 9 days in both groups (P = 0.74). The median operation time was 182 minutes (range, 147–382 minutes) in peripancreatic LND group and 200 minutes (range, 121–432 minutes) in extended LND group (P = 0.35). The median estimated blood loss was 300 ml in both groups (P = 0.86).

In pancreatic tail cancer patients, the morbidity rate was 67% after extended LND and it was 39% after peripancreatic LND (P = 0.99). Pancreatic fistula occurred in 6 patients (20%) after extended LND and 1 patient (6%) after peripancreatic LND (P = 0.23). The median hospital duration were 9.5 days (range, 7–25 days) in peripancreatic LND group and 10 days (range, 7–181 days) in extended LND group (P = 0.84). The median operation

Table 1. Demographics

Variable	Pancreatic body cancer			Pancreatic tail cancer		
	Peripancreatic LND (n = 9)	Extended LND (n = 50)	P-value[a]	Peripancreatic LND (n = 18)	Extended LND (n = 30)	P-value[a]
Sex, male:female	7:2	26:24	0.27	10:8	17:13	0.99
Age (yr)	60 (47–76)	64 (42–83)	0.52	64.5 (52–77)	66.5 (51–79)	0.97
Operation year						
Period 1 (from 2005 to 2010)	7	20	0.071	10	10	0.13
Period 2 (from 2011 to 2013)	2	30		8	20	
ASA PS classification						
1	3	14	0.80	5	5	0.52
2	6	34		11	23	
3	0	2		2	2	
CA 19-9 (U/mL)	126 (3–722)	80 (5–9453)	0.83	291 (11–5009)	177 (1–10028)	0.27
Tumor size (cm)	4.0 (1.2–6.5)	2.5 (1.2–8.0)	0.089	3.9 (1.5–6.0)	3.8 (1.5–8.0)	0.77
T stage						
T1 or T2	0	3	0.99	0	1	0.99
T3	9	47		18	29	
LN metastasis	3	26	0.47	11	21	0.53
Poorly differentiated type	4	19	0.73	3	9	0.49
Adjuvant chemotherapy	5	32	0.72	13	16	0.20

Values are presented as number or median (range).
LND, lymph node dissection; ASA PS, American Society of Anesthesiologist physical status; LN, lymph node.
[a]Chi-square test, Fisher exact test for or Mann Whitney U-test.

time was 174 minutes (range, 81–241 minutes) in peripancreatic LND group and 200 minutes (range, 82–411 minutes) in extended LND group (P = 0.17). The median estimated blood loss was 300 mL (range, 50– 1,100 mL) in peripancreatic LND group and 275 mL in extended LND group (P = 0.86). Extended LND was not associated with postoperative complication, hospital duration, operation time, or estimated blood loss in both pancreatic body cancer group and tail cancer group (Table 2).

Lymph node metastasis

There were significant differences in extracted LN numbers according to the extent of LND. The average number of extracted LNs was 5.1 ± 4.8 after peripancreatic LND and 18.4 ± 10.6 after extended LND for pancreatic body cancer (P < 0.001). The average number of metastatic LNs was 0.6 ± 0.9 after peripancreatic LND and 1.5 ± 2.1 after extended LND. The average number of extracted LNs was 8.3 ± 4.3 after peripancreatic LND and 22.4 ± 12.2 after extended LND for pancreatic tail cancer (P < 0.001). The average number of metastatic LNs was 2.3 ± 3.0 after peripancreatic LND and 2.2 ± 3.1 after extended LND.

The overall LN metastasis rate was 38% in peripancreatic LND group, and the rate was 59% in extended LND group. In patients with pancreatic body cancer, the LN metastasis rate was 33% after peripancreatic LND and 52% after extended LND (P = 0.47). In patients with pancreatic tail cancer, the LN metastasis rate was 61% after peripancreatic LND, and it was 70% after extended LND (P = 0.53). The extended LNs metastases were detected in 4 cases (15%) of patients who underwent extended LND for pancreatic body cancer although there was only 1 case (5%) for pancreatic tail cancer.

Recurrence and survival

The median DFS was 6.8 months after peripancreatic LND, and it was 13.7 months after extended LND for pancreatic body cancer. Although the LN metastasis rate in peripancreatic LND group was lower than that of extended LND group, the patients who underwent peripancreatic LND experienced recurrence more frequently. The median DFS was 10.1 months after peripancreatic LND, and it was 12.7 months after extended LND for pancreatic tail cancer. The survival curve of extended LND group was superior to that of peripancreatic LND group for pancreatic body cancer (P = 0.010). However, there were no significant differences in pancreatic tail cancer group (P = 0.64).

The liver was the most common recurrence site in all subgroups. Thirteen patients (26%) who underwent extended LND and 5 patients (56%) who underwent peripancreatic LND for pancreatic body cancer experienced hepatic metastasis. For pancreatic tail cancer, 9 patients (30%) who underwent extended LND and 6 patients (33%) had experienced hepatic metastasis. The local recurrence rate was 8% after extended LND and 22% after peripancreatic LND for pancreatic body cancer. For pancreatic tail cancer, the local recurrence rate was 23% after extended LND and 28% after peripancreatic LND. In

Table 2. Postoperative outcomes

Variable	Pancreatic body cancer			Pancreatic tail cancer		
	Peripancreatic LND (n = 9)	Extended LND (n = 50)	P-value[a]	Peripancreatic LND (n = 18)	Extended LND (n = 30)	P-value[a]
Postoperative complications	1	13	0.67	7	11	0.99
Pancreatic fistula	1	4		1	6	
Pseudoaneurysm	0	1		1	0	
Ileus	0	4		1	1	
Wound dehiscence	0	1		0	1	
Bowel perforation	0	0		2	0	
Pleural effusion	0	0		1	0	
Ascites	0	1		0	2	
Glucose intolerance	0	1		1	0	
Delirium	0	2		0	0	
Stroke	0	1		0	0	
Urinary tract infection	0	0		0	1	
Hospital duration (day)	9 (8–16)	9 (6–23)	0.74	9.5 (7–25)	10 (7–181)	0.84
Operation time (min)	182 (147–382)	200 (121–432)	0.35	174 (81–241)	200 (82–411)	0.17
Estimated blood loss (mL)	300 (100–850)	300 (50–1,500)	0.86	300 (50–1,100)	275 (20–3,000)	0.86

Values are presented as number or median (range).
LND, lymph node dissection.
[a]Chi-square test, Fisher exact test for or Mann Whitney U-test.

the 5 patients with extended group LN metastasis, the lung was the most common recurrent site, and 3 patients (60%) experienced lung metastasis. There was 1 hepatic recurrence and 1 local recurrence. The median DFS was 4 months in the patients with extended group LN metastasis and the survival curves were significantly lower than those of the regional LN metastases (P = 0.001). Lung metastasis was detected on 3-month follow-up CT image after surgery in the patient with pancreatic tail cancer with extended group LN metastasis. However, the number of LN metastases was not associated with DFS (P = 0.72) (Fig. 1).

The median OS was 17.7 months and 1-year survival rate was 67% after peripancreatic LND; they were 37.9 months and 93% after extended LND for pancreatic body cancer, respectively. For pancreatic tail cancer, the median OS was 24.3 months and the 1-year survival rate was 88% after peripancreatic LND; they were 36.9 months and 87% after extended LND, respectively. The OS curve of extended LND group was also superior to that of peripancreatic LND group in patients with pancreatic body cancer (P = 0.014). However, there were no significant differences in patients with pancreatic tail cancer (P = 0.80) (Fig. 2).

The extent of LND, operation period, LN metastasis, histologic grade, and adjuvant chemotherapy were evaluated by cox proportional hazard model. In pancreatic body cancer patients, the P-value of extended LND, operation period, LN metastasis, and poorly differentiated type were less than 0.2 and validated by multivariate analysis. In multivariate analysis, extended LND was the only significant prognostic factor of DFS. The hazard ratio (HR) was 0.37 (range, 0.16–0.85) (P = 0.019). In pancreatic tail cancer patients, the P-value of poorly differentiated type, and adjuvant chemotherapy, were less than 0.2. The extent of LND and those factors were validated by multivariate analysis. However, there were no statistically significant prognostic factors for DFS. The HR of extent of LND was 0.96 (range, 0.44–2.08) in pancreatic tail cancer patients (P = 0.92) (Table 3).

DISCUSSION

We found that the extended LND could improve survival significantly in the patients with pancreatic body cancer. However, it was not associated with survival in pancreatic tail cancer patients. Regional LND is thought to be an essential component for adenocarcinoma because of LN metastasis being very common. However, the lymphatic drainage pathways are different between the body and tail of the pancreas. The celiac LNs and superior mesenteric LNs are closely located to the body of the pancreas; however, the distance from the tail of the pancreas to celiac and superior mesenteric LNs is relatively long. Moreover, the greater part of lymphatics from the tail of the pancreas drainage pathway is not medially but laterally through splenic hilar or gastrosplenic LNs [2,11,12].

The liver was the most common recurrent site in left-sided pancreatic cancer. However, the hepatic recurrence rate was reduced with extended LND in patients with pancreatic body cancer. Moreover, the local recurrence rate was lower in extended LND group than peripancreatic LND group. Celiac LNs are the pathway of lymphatic drainage to the liver. Therefore, hepatic recurrence might be reduced by celiac LND. However, the recurrence pattern was similar according to the extent of LND in the patients with pancreatic tail cancer. In this study, splenectomy was routinely performed and splenic hilar LNs were removed simultaneously in pancreatic tail cancer. Therefore, peripancreatic LNs of pancreatic tail cancer were mostly removed in both extended LND group and peripancreatic LND group. There were five cases of extended

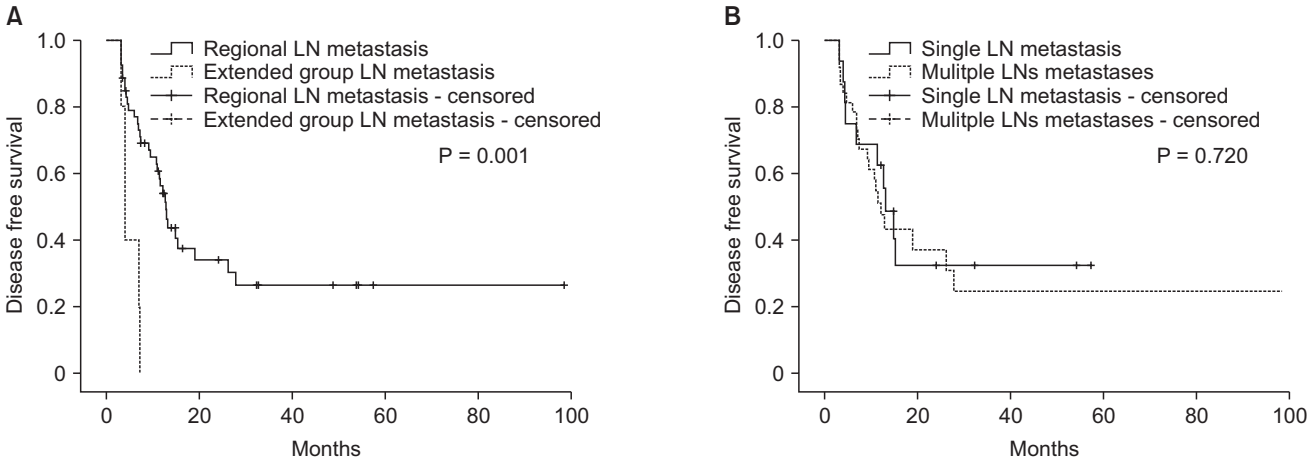

Fig. 1. Disease free survival (DFS) curves according to the location and number of lymph node (LN) metastasis. Extended group LNs include celiac LNs and superior mesenteric LNs. (A) DFS curves according to the location of LN metastasis. (B) DFS curves according to the number of LN metastasis.

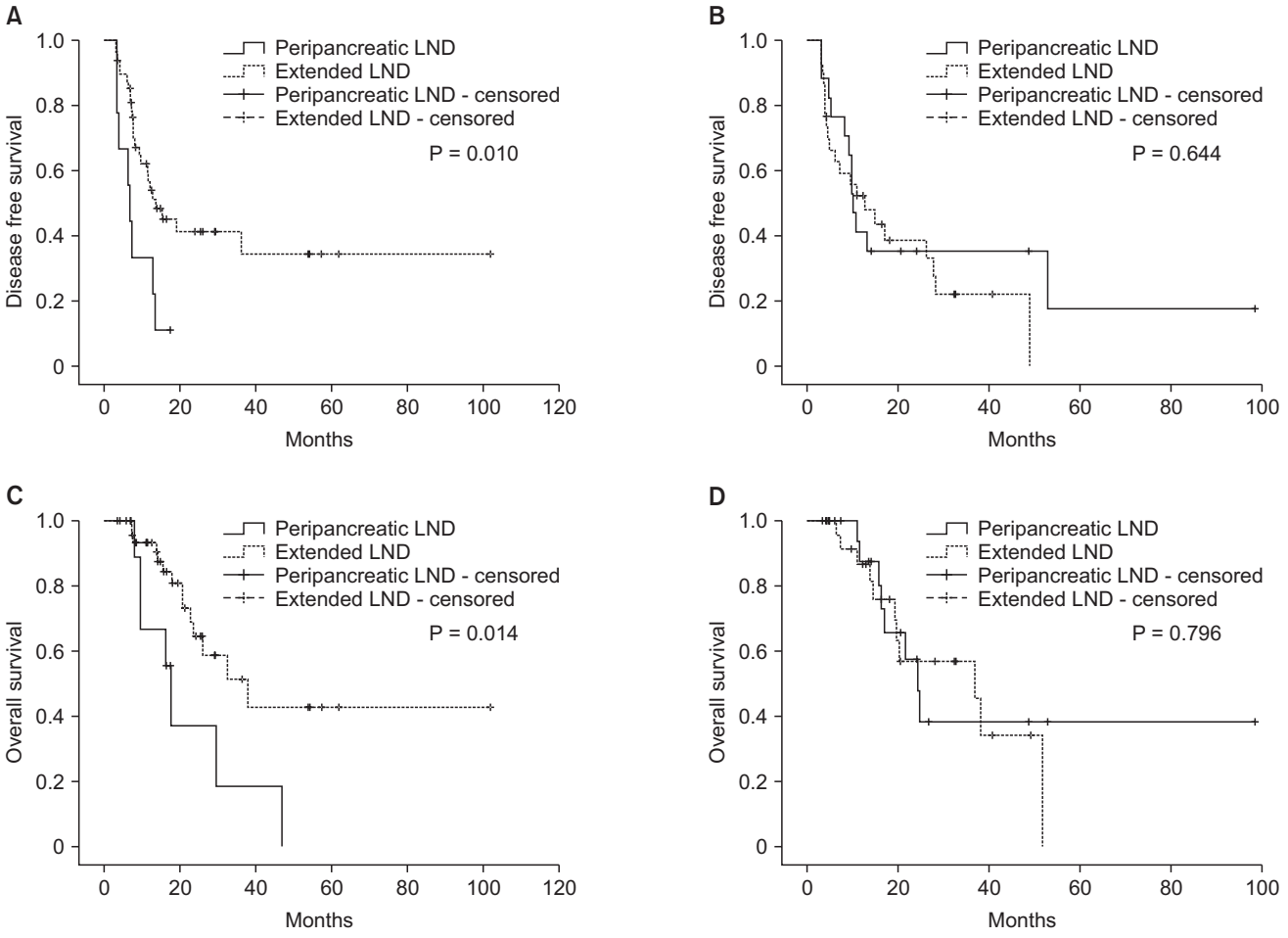

Fig. 2. Disease free survival (DFS) and overall survival (OS) curves according to the extent of lymph node dissection (LND) and tumor location (A) DFS curves in patients with pancreatic body cancer, (B) DFS curves in patients with pancreatic tail cancer, (C) OS curves in patients with pancreatic body cancer, (D) OS curves in patients with pancreatic tail cancer.

Table 3. Multivariate analysis for disease free survival in patients with pancreatic tail cancer

Variable	Pancreatic body cancer				Pancreatic tail cancer			
	Univariate analysis	Multivariate analysis			Univariate analysis	Multivariate analysis		
	P-value	HR	95% CI	P-value[a]	P-value	HR	95% CI	P-value[a]
Extended LND	0.013	0.37	0.16–0.85	0.019	0.65	0.96	0.44–2.08	0.92
Operation period 2	0.15	0.61	0.30–1.22	0.16	0.69	-	-	-
LN metastasis	0.11	1.52	0.76–3.04	0.24	0.95	-	-	-
Poorly differentiated type	0.098	1.89	0.93–3.83	0.078	0.071	1.88	0.85–4.12	0.12
Adjuvant chemotherapy	0.67	-	-	-	0.083	0.55	0.26–1.19	0.13

HR, hazard ratio; CI, confidence interval; LND, lymph node dissection.
[a]Cox regression analysis

group LN metastasis and the recurrence pattern of patients with extended group LN metastasis was different from the patients with peripancreatic LN metastasis. The lung was the most common recurrent site in patients with extended group LN metastasis although the liver was the most common recurrent site in patients with peripancreatic LN metastasis.

For the treatment of gastric cancer, the LNs are categorized into D1 and D2 groups according to the location of the tumor

and the distance from the tumor. A recent study reported that the survival is different between D1 LND and D2 LND in patients with T3 or T4 gastric cancer [13]. In pancreatic cancer, there is no consensus of LN group. In this study, the survival curve of the extended LN metastasis group was significantly lower than that of the peripancreatic LN metastasis group. Therefore, the distance from pancreatic cancer is thought to be important to determine survival outcome.

LN metastasis is a significant prognostic factor of pancreatic cancer [14,15]. The extent of LND was evaluated in recent studies for the treatment of pancreatic head cancer. The extended LND did not provide a significant survival benefit compared with standard LND in pancreatic head cancer in a prospective randomized controlled study [9,16]. Extended LND might be not necessary for all pancreatic cancer patients. Because the survival outcome of pancreatic cancer is very poor, a greater number of patients have systemic disease at the time of diagnosis. However, adequate LND is also important in determining the N stage precisely. A recent study recommended that the minimum total number of LN examined be 15, and para-aortic LND was regarded as a standard LND [10,17].

There might be a reasonable extent of LND for pancreatic cancer. However, it seems be difficult to determine the optimal extent of LND because extended LND could increase postoperative morbidity [8]. In this study, the pancreatic fistula rate was slightly higher in extended LND group as well. However, it is still unclear whether LND is associated with pancreatic fistula [9]. For the treatment of pancreatic head cancer, hepatic artery LND is the standard LND although hepatic artery LN metastasis is associated with poor survival [18]. For the treatment of left-sided pancreatic cancer, there is no standard guideline of the extent of LND. Strasberg et al. [2] reported that celiac and superior mesenteric LND is essential for left-sided pancreatic cancer. However, a recent study recommended that splenic hilar, splenic artery, and inferior pancreatic border LND be the standard LND for left-sided pancreatic cancer [19]. In this study, there was survival benefit with extended LND including celiac and superior mesenteric LND for pancreatic body cancer. Moreover, the location of LN metastasis was more important than the number of LN metastases. If there is extended group LN metastasis, the survival outcome is very poor; extended LND should be considered in patients with pancreatic body cancer.

The left-sided pancreas could be divided into the body and tail of the pancreas. However, there are no landmark structures between the body and tail of the pancreas. In the past, the left border of the aorta was used to distinguish the body of the pancreas from the tail. However, recent reviews of pancreas anatomy describe the pancreas tail as the lateral termination of the pancreas, ranging from 1.5 to 3.5 cm in length in adults [12]. The distance from the neck of the pancreas to the left border of the aorta is too short and the range of 1.5 to 3.5 cm is inaccurate. Therefore, we adopted the Japanese classification that indicates the medial half is classified into the body, and the lateral part is regarded as the tail of the pancreas.

Minimally invasive surgery is attempted for the treatment of left-sided pancreatic cancer. In selected patients, laparoscopic surgery was technically feasible and oncologically safe for left-sided pancreatic cancer [20,21]. However, celiac and superior LND is technically difficult to do. In this study, extended LND could improve survival in patients with pancreatic body cancer but there was no survival benefit for pancreatic tail cancer. Therefore, minimally invasive surgery might be feasible if the tumor is located in the tail of the pancreas without extrapancreatic invasion.

Previous studies reported that adjuvant chemotherapy with gemcitabine, fluorouracil, and S-1 could enhance survival [22-24]. However, adjuvant chemotherapy was not associated with survival outcome in the results. We recommended adjuvant chemotherapy for all patients who underwent curative intent surgery. However, the general condition is important in receiving chemotherapy. Therefore, there might be a selection bias for adjuvant chemotherapy.

This study is the first study on the optimal extent of LND according to the location of left-sided pancreatic cancer, as far as we know. However, this study is a retrospective and nonrandomized controlled trial. There was a relatively small number of patients in the peripancreatic LND for pancreatic body cancer group. Therefore, this is not conclusive data affirming the superiority of extended LND to the standard LND in patients with pancreatic body cancers. A larger-scale future study may be necessary to validate our findings.

In conclusion, extended LND may improve survival outcomes. However, the survival was not different for pancreatic tail cancer. The location of LN metastasis is a significant prognostic factor in patients with left-sided pancreatic cancer. This result should be validated by further investigation.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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