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ORIGINAL ARTICLE

Reevaluation of regional lymph nodes in patients with pancreatic ductal adenocarcinoma in the pancreatic body and tail

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Abstract

Introduction: In patients with pancreatic ductal adenocarcinoma (PDAC) in the pancreatic body (Pb) and tail (Pt), the appropriate area for lymphadenectomy is controversial. This study aimed to reevaluate the extent of lymph node (LN) metastasis in Pb- and Pt-PDAC, and to define the optimal area of LN dissection.

Patients and methods: This single-center retrospective study evaluated patients with Pb- and Pt-PDAC who underwent distal pancreatectomy with extended lymphadenectomy between 2006 and 2020. LN metastasis in >3.0% of patients were defined as new regional LN.

Results: The study cohort included 135 patients with Pb-PDAC and 42 patients with Pt-PDAC. In patients with Pb-PDAC, LNs around the splenic artery (SPA) had the highest metastasis-positive rate (54.1%). LNs along the left gastric artery, common hepatic artery, celiac axis (CA), superior mesenteric artery (SMA), and splenic hilus were defined as new regional LNs. In patients with Pt-PDAC, LNs at the splenic hilum had the highest metastasis-positive rate (38.1%). The station and LN around the SPA were defined as new regional LNs in those with Pt-PDAC. Metastasis beyond the newly defined regional LNs was not associated with survival. The incidence of LN metastasis was lower in patients who received preoperative chemotherapy than in those who underwent upfront surgery in both Pb- and Pt-PDAC.

Conclusion: Although it needs to be verified in future multicenter studies, LN of both the CA and SMA systems should be dissected in patients with Pb-PDAC. However, only those around the SPA and splenic hilus should be dissected routinely in those with Pt-PDAC.

KEYWORDS
distal pancreatectomy, lymph node, lymph node metastasis, lymphadenectomy, pancreatic ductal adenocarcinoma

Yuki Matsui and Daisuke Hashimoto contributed equally to this paper.

1 | INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is difficult to cure. Currently, it is the fourth leading cause of cancer-related deaths in Japan.[1] Margin-negative resection remains the most important approach for cure, and recent advancements in multidisciplinary therapies, such as neoadjuvant therapy and adjuvant chemotherapy, have contributed to the improved survival of patients with PDAC.[2–5] However, the 5-y survival rate after PDAC resection remains low (15%–20%).[6]

Regional lymph node (LN) metastasis is one of the most important predictors of survival after pancreatectomy.[7–16] Moreover, a higher number of positive LN and an increased ratio of positive to total LN are strongly associated with decreased survival.[17] Although the importance of LN status has been well-described, the appropriate extent of lymphadenectomy remains controversial. Few studies have described the influence of LN involvement in the body or tail of the pancreas on the prognosis of patients with PDAC.

The seventh edition of the rules of the Japan Pancreas Society (JPS), was translated and published as the fourth edition of the English version,[18] and defines regional LN as shown in Table 1, and recommends lymphadenectomy along the left gastric artery (LGA, No. 7), common hepatic artery (CHA, No. 8), celiac axis (CA, No. 9), superior mesenteric artery (SMA, No. 14), splenic artery (SPA, No. 11), splenic hilus (No. 10), and inferior margin of the pancreas (No. 18) during distal pancreatectomy (DP) for both pancreatic body (Pb) and tail (Pt) PDAC. In contrast, the consensus statement by the International Study Group on Pancreatic Surgery (ISGPS)[19] recommends that lymphadenectomy around the CA should be performed only when Pb-PDAC is close to the CA. Moreover, lymphadenectomy along the CHA and SMA is not necessary for Pb- or Pt-PDAC in the ISGPS statement.[19] Thus, there is a difference in the recommended area of lymphadenectomy for PDAC between the JPS and ISGPS.

To understand the patterns of lymphatic spread and establish the appropriate extent of LN dissection, it is important to clarify the incidence of LN metastasis in regional LN and its impact on long-term survival.

The aim of this retrospective study was to reevaluate the regional LN of PDAC of Pb and Pt and to establish the optimal area of lymphadenectomy during DP.

2 | PATIENTS AND METHODS

2.1 | Study design

This retrospective, single-center, observational study was conducted at the Department of Surgery, Kansai Medical University, Osaka, Japan. Clinical and operative data and information on pathological findings and long-term outcomes of patients with PDAC in the Pb and Pt who underwent DP were collected from a prospective database. In accordance with the rules of the JPS,[18] Pb was defined as the area from the left margin of the superior mesenteric vein to the left margin of the aorta, and Pt was defined as the area to the left of the left margin of the aorta.

2.2 | Ethical issues

The study was reviewed and approved (No. 2020131) by the Institutional Review Board of Kansai Medical University, Japan, and complied according to the STROBE guidelines.[20] All the procedures in this study were performed in accordance with the guidelines of the Declaration of Helsinki. The records of patients who refused access to their data were excluded from the analysis.

2.3 | Patient selection

This study evaluated patients with histologically proven PDAC in the Pb and Pt who underwent DP with extended LN dissection (the area is described below) between January 1, 2006, and December 31, 2020, according to the seventh edition of the General Rules for the Study of Pancreatic Cancer by JPS.[18] In principle, preoperative therapy for resectable (R)/borderline resectable (BR) tumors was introduced in all cases in 2019. Until 2018, preoperative therapy for R/BR PDAC was planned and performed at the discretion of the attending surgeon. Patients who had unresectable (UR) PDAC due to distant metastasis or locally advanced unresectable PDAC[18] at their first visit and underwent surgery after chemotherapy and/or radiotherapy (conversion surgery) were included in this study. Preoperative chemotherapy was mainly performed with gemcitabine plus S1 for R/BR-V PDAC, and gemcitabine plus nab-paclitaxel for BR-A/UR PDAC.[3,21] Adjuvant chemotherapy was mainly performed with gemcitabine until 2012, and with S1 since 2013.[2]

2.4 | Pathological evaluation

The LN location was recorded and analyzed according to the seventh edition of the JPS rules[18] (Table 1). Before fixation, LN that were distant from the pancreatic tissue were picked up manually from the resected specimen and evaluated as distant LNs (Nos. 7, 8, 9, 12, 14, 15, 16, and 18). Subsequently, the resected specimens of the pancreas were fixed with formalin and sliced into 5-mm thick sections

TABLE 1 Regional lymph node defined in general rules for the study of pancreatic cancer by Japan Pancreas Society

No. 6	Infrapyloric lymph node
No. 7	Lymph nodes along the left gastric artery
No. 8	Lymph nodes along the common hepatic artery
No. 9	Lymph nodes along the celiac artery
No. 10	Lymph nodes at the splenic hilum
No. 11	Lymph nodes along the splenic artery
No. 12	Lymph nodes in the hepatoduodenal ligament
No. 13	Lymph nodes on the posterior surface of the pancreatic head
No. 14	Lymph nodes along the proximal superior mesenteric artery
No. 15	Lymph nodes along the middle colic artery
No. 16	Lymph nodes around the abdominal aorta
No. 17	Lymph nodes on the anterior surface of the pancreatic head
No. 18	Lymph nodes along the inferior margin of the pancreas

in all patients. The peripancreatic LN, defined as the LN surrounding the resected pancreatic tissues, were not picked up manually and fixed together with the pancreatic tissue (Nos. 10 and 11). The number of LNs involved were histologically reviewed.

R0 was defined as the microscopic absence of cancer cells at all resected margins, regardless of the tumor-free margin distance.[18]

2.5 | Definition of the regional LN

The seventh edition of the rules of the JPS[18] defines Nos. 7, 8, 9, 10, 11, 14, and 18 as the regional LN that should be resected during DP for both Pb- and panceatic tail PDAC (Table 1). Metastasis beyond regional LN is defined as M1 disease.[18] Metastasis in 1–3 LN was defined as N1a, and metastasis in in ≥4 LNs was defined as N1b.

LN dissection was performed according to the JPS rules of that era. In this article, the area of LN dissection was similar, regardless of the location and size of the tumor or the presence or absence of combined vessel resection. The paraaortic lymph nodes were sampled if they were found to be enlarged.

We planned to define the updated regional LN for Pb- and Pt-PDAC in accordance with the actual status of LN metastasis. LN with metastasis in >3.0% of patients were defined as new regional LNs, although there is no basis for this number to be determined.

2.6 | Statistical analysis

Descriptive data are presented as median (range) or number (percentage), as appropriate. Parameters were compared between patient subgroups using *t*-tests or Mann–Whitney *U* tests, and categorical data were evaluated using Fisher's exact or χ^2 tests. Overall survival (OS) was defined as the time between pancreatic resection and the final follow-up day (dead or alive). Disease-free survival (DFS) was defined as the time interval between pancreatic resection and disease recurrence. OS and DFS curves were constructed using the Kaplan–Meier method, and statistical significance was determined using the log-rank test. Multivariate analysis was performed using Cox proportional hazard survival regression to determine the effects of individual predictors. Statistical analysis was performed using EZR software (v. 1.41).[22] Differences were considered statistically significant at $P < .05$.

3 | RESULTS

3.1 | Clinicopathologic characteristics of the study cohort

During the study period, 177 patients who underwent DP for PDAC were included in this study (Table 2). When stratified by tumor location, the study cohort included 135 patients (76.3%) in the Pb group and 42 patients (23.7%) in the Pt group. The incidences of BR and UR-PDAC were significantly higher in the Pb group than in the Pt group ($P = .005$). Preoperative therapy was performed in 66 patients (48.9%) in the Pb group and in 15 patients (35.7%) in the Pt group ($P = .087$). The median carbohydrate antigen 19–9 (CA19-9) at the initial diagnosis was significantly higher in the Pt group ($P = .012$) than in the Pb group. The Pb group included 18 patients (13.3%) who underwent DP with celiac axis resection (DP-CAR), and the incidence of combined vessel resection was significantly higher in this group than in the Pt group ($P = .006$).

The median number of LNs evaluated was 33 (range, 10–74) in the Pb group and 24 (range, 10–54) in the Pt group ($P = .024$). That was 30 (range, 10–61) in the patients who underwent DP-CAR. There was no significant difference in the incidence of LN metastasis between both groups (60 patients (44.4%) in the N1a group and 24 (17.8%) in the N1b group in the Pb group vs 16 patients (38.1%) in the N1a group and 4 (9.5%) in the N1b group in the Pt group, $P = .301$). Moreover, the incidence of postoperative LN recurrence was similar in both groups (7.4% vs 9.5%, $P = .907$).

3.2 | Detailed incidence of LN metastasis of the study cohort

Table S1 shows the detailed incidence of total positive LN in the total LN dissected, the patients whose LN were resected, median (range) number of resected LN per patient, and incidence of patients with positive LN. Based on Table S1, the incidence of patients with positive LN is shown in Figure 1. In Pb-PDAC, No. 11 LN had the highest metastasis-positive rate (54.1%, Figure 1A). Nos. 7, 8, 9, 10, 11, and 14 were defined as new regional LN (3.0% or more) in Pb-PDAC. In Pt-PDAC, No. 10 had the highest metastasis-positivity rate (38.1%, Figure 1B). Similarly, Nos. 10 and 11 were defined as new regional LN in Pt-PDAC. All LN-positive patients had at least one metastasis to the new regional LN in both Pb- and Pt-PDAC. Only six patients (4.4%) with Pb-PDAC and two patients (4.8%) with Pt-PDAC had metastasis beyond the new regional LN.

3.3 | OS stratified with LN metastasis and factors involved

According to the status of LN metastasis, median OS was significantly worsened in both Pb (No: NA vs N1a: 30.3 mo vs N1b: 19.4 mo, $P = .001$, Figure 2A) and Pt -PDAC (No: 84.7 mo vs N1a: 24.8 mo vs N1b: 14.8 mo, $P = .038$, Figure 2B), respectively. In patients with N1 disease (n = 104), the median OS of the patients with the metastasis beyond the new regional LN (n = 8, 44.9 mo) was not worse compared with that of the patients without it (n = 96, 22.9 mo), and there was no significant difference ($P = .425$). Table 3 shows the results of the univariate and multivariate analyses for OS of the total study cohort. Preoperative chemotherapy (hazard ratio [HR] = 0.648, $P = .046$), CA19-9, ≥122.0 IU/mL (HR = 1.793, $P = .006$), postoperative complications (HR = 1.602, $P = .027$), tumor size ≥32 mm (HR = 2.292, $P < .001$), LN metastasis (HR = 2.335,

TABLE 2 Clinicopathologic characteristics of the study cohort

	Total (n = 177)	Pb (n = 135)	Pt (n = 42)	*P*-value (Pb vs Pt)
Male: Female, n (%)	94 (53.1): 83 (46.9)	68 (50.4): 67 (49.6)	26 (61.9): 16 (38.1)	.091
Median age (range), y	72 (44–87)	71 (45–86)	74.5 (44–87)	.050
Resectability at the initial diagnosis (R: BR: UR), n (%)	132 (74.6): 23 (13.0): 22 (12.4)	92 (68.1): 23 (17.0): 20 (14.8)	40 (95.2):0 (0): 2 (4.8)	.005
Median initial CA19-9 (range), IU/ml	121.7 (1.0–29 633.5)	101.1 (1.0–4171.1)	173.3 (4.0–29 633.5)	.012
Preoperative therapy, n (%)	81 (45.8)	66 (48.9)	15 (35.7)	.087
Surgical procedure, n (%)				
DP	159 (89.8)	117 (86.7)	42 (10.0)	.087
DP-CAR	18 (10.2)	18 (13.3)	0 (.0)	
Laparoscopic surgery, n (%)	3 (1.7)	1 (0.7)	2 (4.8)	.535
Combined vessel resection, n (%)	31 (17.5)	31 (23.0)	0 (.0)	.006
Combined organ resection, n (%)	51 (28.8)	35 (25.9)	16 (38.1)	.315
Median tumor size (range), mm	32 (9–115)	30 (9–115)	35 (10–65)	.537
Pathological stage (JPS), n (%)				
T1: T2: T3: T4	16 (9.0): 10 (5.6): 131 (74.0): 20 (11.3)	13 (9.6): 9 (6.7): 93 (68.9): 20 (14.8)	3 (7.1): 1 (2.4): 38 (90.5): 0 (.0)	.067
No: N1a: N1b	73 (41.2): 76 (42.9): 28 (15.8)	51 (37.8): 60 (44.4): 24 (17.8)	22 (52.4): 16 (38.1): 4 (9.5)	.301
M0: M1	176 (99.4): 1 (0.6)	134 (99.3): 1 (0.7)	42 (10.0): 0 (.0)	.536
Median number of lymph node evaluated (range)	32 (10–74)	33 (10–74)	24 (10–54)	.024
Margin status, R0: R1, n (%)	157 (88.7): 20 (11.3)	119 (88.1): 16 (11.9)	38 (90.5): 4 (9.5)	.891
Positive lavage cytology, n (%)	35 (19.8)	25 (18.5)	10 (23.8)	.596
Adjuvant chemotherapy, n (%)	140 (79.1)	108 (8.0)	32 (76.2)	.754
Recurrence, n (%)	108 (61.0)	79 (58.5)	29 (69.0)	.222
Site of recurrence, n (%)				
Liver	41 (23.2)	27 (2.0)	14 (33.3)	.074
Lung	26 (14.7)	19 (14.1)	7 (16.7)	.869
Local	20 (11.3)	16 (11.9)	4 (9.5)	.891
Peritoneum	19 (10.7)	15 (11.1)	4 (9.5)	.996
Lymph node	14 (7.9)	10 (7.4)	4 (9.5)	.907
Bone	1 (0.6)	0 (.0)	1 (2.4)	.538

Abbreviations: BR, borderline resectable; CA19-9, carbohydrate antigen 19–9; CAR, celiac axis resection; DP, distal pancreatectomy; JPS, Japan Pancreas Society; Pb, pancreatic body; Pt, pancreatic tail, R, resectable; UR, unresectable.

$P < .001$), positive lavage cytology (HR = 3.633, $P < .001$), and adjuvant chemotherapy (HR = 0.523, $P = .018$) were significant prognostic factors in the univariate analysis. Tumor size ≥32 mm (HR = 1.647, $P = .036$), LN metastasis (HR = 1.749, $P = .034$), positive lavage cytology (HR = 2.812, $P < .001$), and adjuvant chemotherapy (HR = 0.476, $P = .010$) were independent prognostic factors in the multivariate analysis. Metastasis beyond the new regional LN was not associated with OS.

Because positive lavage cytology was an independent prognostic factor in this cohort, the incidence of positive lymph nodes was compared between positive and negative lavage cytology. However, there were no significant differences in either Pb- nor Pt -PDAC.

3.4 | Impact of preoperative chemotherapy on lymph node metastasis

The incidence of LN metastasis (N1a and N1b) was significantly lower in patients who received preoperative chemotherapy (33/66 patients, 5.0%) than in those who underwent upfront surgery (51/69 patients, 72.5%) ($P = .004$) in Pb-PDAC. Although not significant,

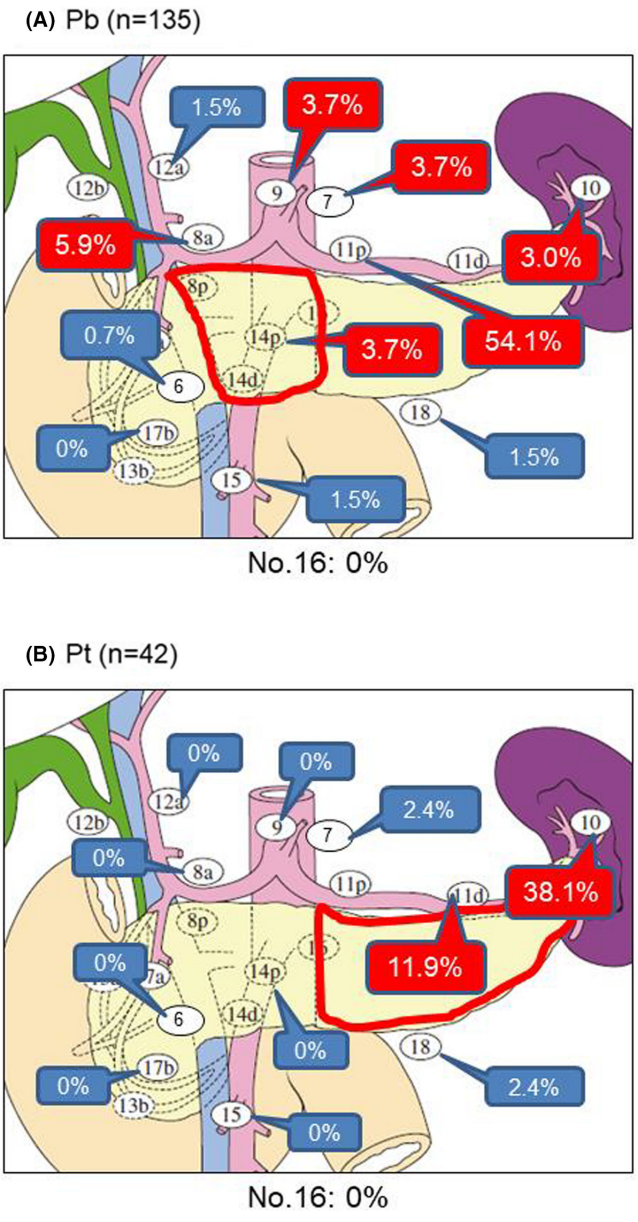

FIGURE 1 Incidence of positive LN in patients with pb- (A) and Pt- (B) PDAC. LNs with metastasis in >3.0% (red box) of patients were defined as new regional lymph nodes. The blue box indicates metastasis beyond the new regional lymph node

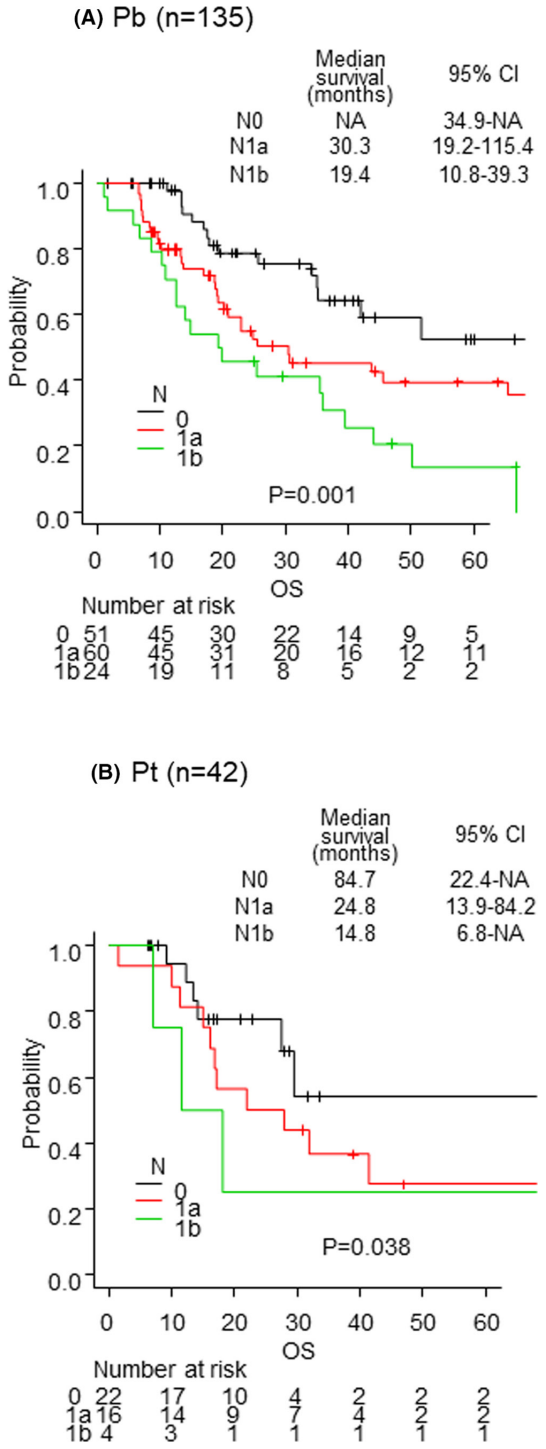

FIGURE 2 Overall survival stratified according to LN metastasis in pb (A) and Pt (B) PDAC. Metastasis in 1–3 LN is defined as N1a, and 4 or more is defines as N1b

the incidence of LN metastasis was similarly lower in patients who received preoperative chemotherapy (5/15 patients, 33.3%) than in patients who underwent upfront surgery (15/27 patients, 55.6%) ($P = .289$) in Pt-PDAC.

Detailed incidence of the total positive LNs in the total LNs dissected, patients whose LNs were resected, median (range) number of resected LNs per patient, and incidence of patients with positive LNs are shown in Table S2 (patients with preoperative therapy) and Table S3 (patients without preoperative therapy). Based on Tables S2 and S3, the incidence of patients with positive LN with or without preoperative chemotherapy is shown in Figure 3. In Pb-PDAC, it was decreased at almost all stations of the new regional LN, except for No. 10. In particular, it was significantly decreased in No. 11 (42.4% vs 65.2%, $P = .007$). Although there were no significant differences, it was decreased at all stations of the new regional LN in Pt-PDAC. In addition, the incidence of total positive LNs in patients who received preoperative chemotherapy was significantly lower in No. 11

TABLE 3 Univariate and multivariate analyses of overall survival in the study cohort (n = 177)

	Univariate				Multivariate			
	HR	95% CI		*P*-value	HR	95% CI		*P*-value
Sex, male	0.722	0.478	1.088	.012				
Age,72 y or more	1.374	0.904	2.089	.038				
Location, Pt	1.207	0.750	1.942	0.438				
Resectability, UR	1.350	.288	1.623	.231				
Preoperative chemotherapy	0.648	0.423	0.993	.046	0.766	0.489	1.201	.246
Preoperative radiotherapy	0.425	.034	1.351	.047				
CA19-9, 122.0 IU/mL or more	1.793	1.186	2.712	.006	1.413	0.890	2.220	.033
Procedure, DP-CAR	1.081	0.395	1.699	0.593				
Combined vessel resection	1.328	0.452	1.465	0.492				
Postoperative complication	1.602	1.055	2.433	.027	1.491	0.976	2.279	.065
Tumor size 32 mm or more	2.292	1.493	3.518	<.001	1.647	1.033	2.628	.036
LN metastasis (N1a and N1b)	2.335	1.444	3.775	<.001	1.749	1.044	2.930	.034
Metastasis beyond the regional LN	0.889	0.358	2.208	0.801				
Margin status, R1	1.278	0.695	2.350	0.431				
Positive lavage cytology	3.633	2.279	5.790	<.001	2.812	1.733	4.565	<.001
Adjuvant chemotherapy	0.523	0.305	0.895	.018	0.476	.270	0.840	.010

Abbreviations: CA19-9, carbohydrate antigen 19–9; CAR, celiac axis resection; DP, distal pancreatectomy; LN, lymph node; Pt, pancreatic tail, UR, unresectable.

in Pb-PDAC (5.8% vs 14.2%, $P < .001$) and No. 10 in Pt-PDAC (5.9% vs 1.0%, $P = .022$) than in those who underwent upfront surgery (Tables S2 and S3).

The OS of patients who received preoperative chemotherapy was better than that of patients who did not receive preoperative chemotherapy in both Pb- and Pt-PDAC (Figure 4A,B), although there were no significant differences.

According to the status of LN metastasis, the median OS was significantly worse in patients with ($P = .047$) or without ($P = .004$) preoperative chemotherapy (Figure 4C,D).

4 | DISCUSSION

In this retrospective single-center study, the incidence of LN metastasis at each station was evaluated for Pb- and Pt-PDAC. New regional LNs were defined as LNs with metastasis in >3.0% of patients. As a result, Nos. 7, 8, 9, 10, 11, and 14 in Pb-PDAC and Nos. 10 and 11 in Pt PDAC were defined as the new regional LN. The presence or number of LN metastases was an independent factor associated with OS in Pb- and Pt-PDAC. In patients undergoing preoperative chemotherapy, the incidence of LN metastasis was decreased in almost all stations in both Pb- and Pt-PDAC compared with upfront surgery.

As shown in the present study, LN status is well known to be a significant prognostic factor in patients with PDAC.[23–25] Lymphadenectomy during pancreatectomy is the standard procedure for the treatment of PDAC.[26] However, the optimal extent of lymphadenectomy remains controversial. Previous randomized controlled trials have reported that extended lymphadenectomy during pancreatoduodenectomy did not contribute to better survival for PDAC in the pancreatic head.[27,28] However, particularly for patients with Pb- and Pt-PDAC, few studies have focused on the significance of LN involvement in survival after pancreatectomy.

The seventh edition of the rules of the JPS requires the same LN stations during DP for both Pb- and Pt-PDAC.[18] This study demonstrated that there is a clear difference in LNs that should be dissected in Pb- and Pt-PDAC. In patients with Pb-PDAC, LNs around the LGA, CHA, CA, SMA, SPA, and splenic hilus were defined as new regional LNs. This is slightly different from the current JPS rule, which was vindicated for Pb-PDAC.[18] Pb-PDAC is located at the crossroads of complex lymphatic flow and may require dissection of LNs in both the CA and SMA systems. On the other hand, LNs only around the SPA and at the splenic hilus were proposed as new regional LNs for Pt-PDAC. This significantly differs from the current JPS rule.[18] Similar to our study, revaluation of regional LNs for Pb- and Pt-PDAC was performed. Single-center retrospective studies from Japan indicated that metastasis to LNs around the CHA (No. 8) and SMA (No. 14) was observed in patients with Pb-PDAC, and no patients with Pt-PDAC had metastasis to LNs around the CHA (No. 8).[29,30] These results support our own findings, and our study included the most cases compared to previous studies.

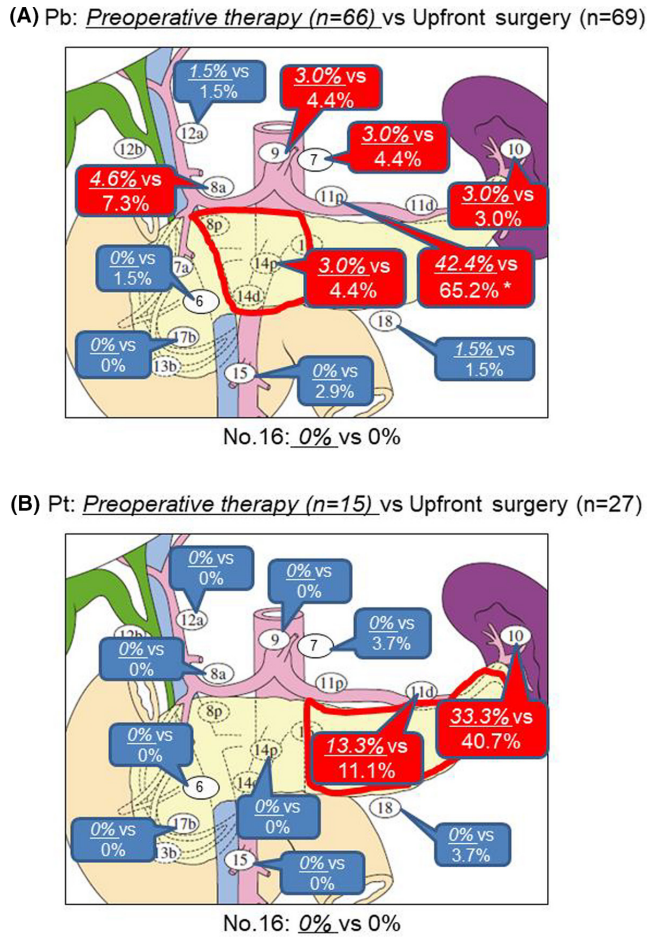

FIGURE 3 Incidence of patients with positive LN among patients who received preoperative chemotherapy with upfront surgery in pb (A) and Pt (B) PDAC. Italics with underline indicate patients who received preoperative chemotherapy. ※, $P < .05$

Moreover, metastasis beyond the newly defined regional LNs is rare. There was no significant difference in the survival of patients with LN metastasis stratified by the presence of metastasis beyond the new regional LN. Thus, the presence or absence of LN metastasis is more important than its location. Moreover, the number of metastatic nodes is important for LN metastasis. Based on these results, we propose that only new regional LNs sets in Pb- and Pt-PDAC should be dissected routinely during DP to detect the status of LN metastasis, but not improve OS with lymphadenectomy, whereas sampling of other LN stations may be performed as needed. Although it has been reported that adjuvant chemotherapy significantly improves OS,[2] a previous study from the Netherlands indicated that adjuvant chemotherapy after neoadjuvant folinic acid, 5-fluorouracil, irinotecan plus oxaliplatin combination therapy and pancreatic resection improved survival only in patients with N1 disease in a multicenter retrospective setting.[31] Therefore, it is important to detect LN metastases and assess the need for adjuvant chemotherapy. In addition, patients with new regional LN metastases, as defined in this study, may be treated with adjuvant chemotherapy for a long time, to be examined in a prospective study.

Various advantages of neoadjuvant therapy for R/BR-PDAC have recently been described, such as early treatment of occult metastases, reduction of intraoperative tumor seeding risk, and better tolerance than adjuvant therapy.[32] Currently, Japanese guidelines recommend surgery after neoadjuvant chemotherapy for R/BR PDAC as a general rule.[33] Moreover, the survival advantage of conversion surgery in patients with UR-PDAC with favorable responses to chemotherapy has been described in recent studies.[34] The present study also demonstrated better survival in patients who received preoperative chemotherapy for both Pb- and Pt-PDAC, and that the status of LN metastasis was significantly associated with OS even after preoperative therapy. Importantly, the incidence and extent of LN metastasis decreased in patients who received preoperative therapy for both Pb- and Pt-PDAC. Thus, preoperative therapy may prevent excessive LN dissection, and this newly defined regional LN will become more important in the future.

This study had several limitations that should be considered. First, since this was a single-center study and the number of cases was limited, future studies including multiple institutions and cases are needed. Second, the present study did not compare laparoscopic surgery with open surgery because the study cohort included only three cases of laparoscopic surgery. Currently, we are actively performing laparoscopic surgery, mainly for R-PDAC, and this point should be clarified in future studies. Third, the incidence of LN metastasis at the inferior margin of the pancreas (No. 18) was low; however, this location should have been definitely dissected and metastases could have been present due to proximity to the pancreatic parenchyma. As a rule, LNs are located along arteries; therefore, it is necessary to reexamine the number of LN present at the inferior margin of the pancreas. Fourth, there was no basis for the definition of the new regional lymph node, as LN with metastasis in >3.0% of patients. Although the present study achieved certain results, this definition should be discussed by many experts in the future. The JPS published the summary of the Pancreatic Cancer Registry including 23,302 patients in 2003.[35] It indicated that the incidence of metastasis of the regional LN station recommended for dissection in the current JPS rule was almost always more than 3% in the patients with pancreatic head.[18,35] On the other hand, that of the station beyond the regional LN was less than 3%, except for paraaortic LN. Dissection of paraaortic LN was routine in this era, and the current JPS rule treats a metastasis of this LN as distant metastasis.[18] A metastasis rate of 3% seems reasonable to define the regional LN based on these data, although there were no data of Pb- and Pt-PDAC.

In conclusion, based on the detailed mapping of LN metastasis, a new regional LN was defined for Pb- and Pt-PDAC. LN of both CA and SMA systems should be dissected routinely for Pb-PDAC during DP. On the other hand, LN around the CHA, LGA, CA, and SMA may be avoided for Pt-PDAC, although it needs to be verified in future multicenter studies.

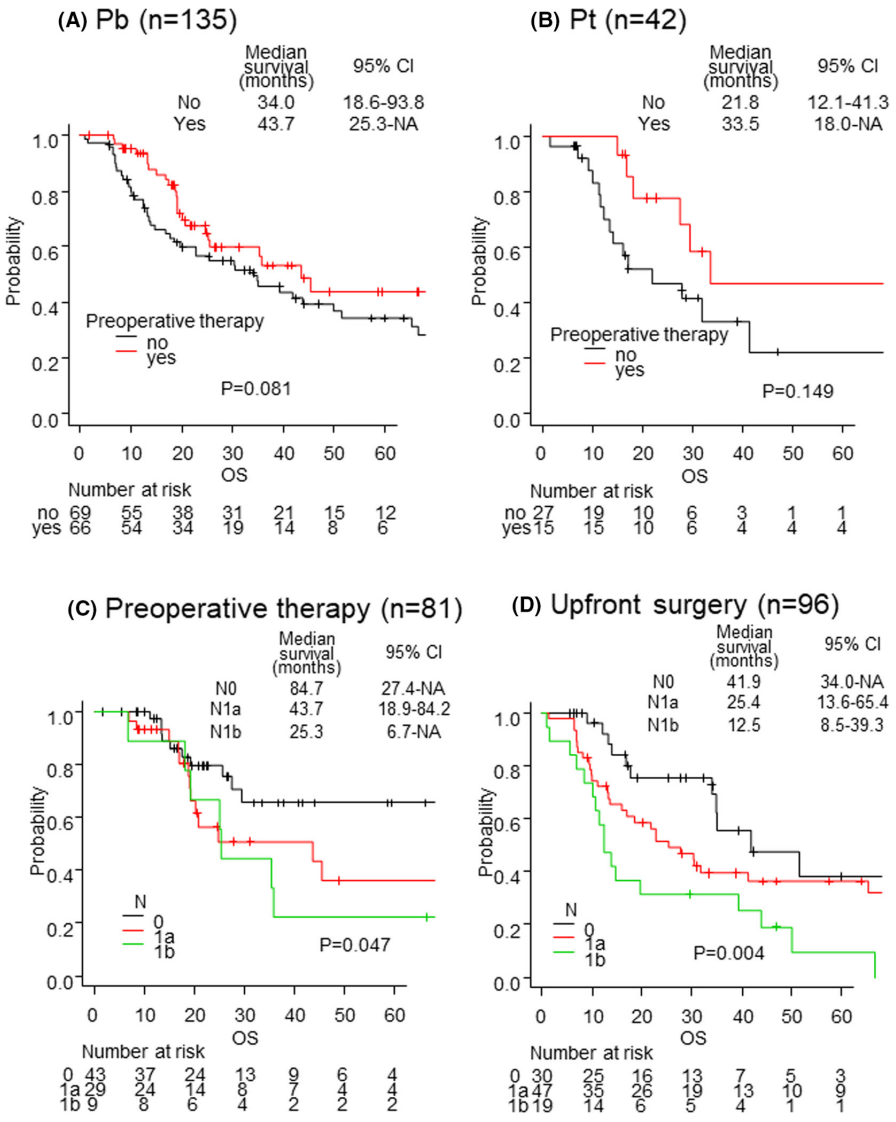

FIGURE 4 Overall survival stratified according to the presence of preoperative chemotherapy in pb- (A) and Pt- (B) PDAC, and those stratified with LN metastasis in patients who received preoperative chemotherapy (C) and upfront surgery (D). Metastasis in 1–3 LN is defined as N1a, and 4 or more is defined as N1b

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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