Title: Optimal lymph node dissection in pancreatic tail cancer

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Short title: LND in pancreatic tail cancer

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Abstract

Purpose: The optimal range for lymph node dissection in pancreatic tail cancer remains unclear. This study aimed to determine the proper range for lymph node dissection in pancreatic tail cancer by investigating the location and frequency of lymph node metastases.

Methods: The clinical data of patients with resectable left-sided pancreatic cancers who underwent distal pancreatectomy between February 2006 and March 2021 were retrospectively analyzed. Eligible patients were divided into two groups according to the tumor location: patients with pancreatic tail cancer (Pt group) and those with pancreatic body or body and tail cancer (non-Pt group).

Results: Of the 96 patients analyzed, sixty-one (64%) were assigned to the Pt group, and the remaining thirty-five (36%) to the non-Pt group. Metastases to stations 7, 8, 9, 10, 11, 14 and 18 were found in 0 (0%), 0 (0%), 0 (0%), 4 (7%), 18 (30%), 2 (4%), and 10 (17%) patients in the Pt group, and in 1 (3%), 4 (12%), 2 (6%), 1 (3%), 18 (51%), 3 (9%), and 6 (17%) patients in the non-Pt group, respectively.

Conclusion: Lymph node dissection at stations 7, 8, and 9 might not be necessary in patients with resectable pancreatic cancer confined to the pancreatic tail.

Keywords: distal pancreatectomy, pancreatic ductal carcinoma, tumor metastasis,

Introduction

Pancreatic ductal carcinoma (PDAC) is one of the most lethal malignant tumors and is the fourth leading cause of cancer-related deaths in Japan[1], the United States[2], and Europe[3]. Surgical resection is the only curative treatment option for PDAC, and distal pancreatectomy (DP) concomitant with regional lymph node dissection is generally recommended for left-sided PDAC [4-7]. Lymph node metastasis has been reported to be a strong prognostic factor for patients with PDAC[8-11]; therefore, optimal regional lymph node dissection is mandatory to achieve curative resection.

However, the definition of left-sided PDAC and the recommended extent of regional lymph node dissection differ among the classifications of the Japan Pancreas Society (JPS)[12], American Joint Committee of Cancer (AJCC)[13], and International Study Group of Pancreatic Surgery (ISGPS)[14] (Figs. 1 and 2). The AJCC and ISGPS classifications define pancreatic tail cancer as a tumor in which its center is located on the left side of the aortic left border, whereas the JPS classification defines it as a tumor that is located completely on the left side of the aorta (Fig. 1). The extent of regional lymph nodes in left-sided PDAC also differs depending on the classification (Fig. 2). Among the three classifications, the extent is similar in the JPS and AJCC classifications; however, it is completely different in the ISGPS classification, wherein, the extent of regional lymph nodes for left-sided PDAC is separated according to pancreatic body and tail cancers.

The optimal range of lymph node dissection remains unclear in left-sided PDAC; however, a few recent reports described that the dissection of lymph nodes around the common hepatic artery (CHA) and the celiac artery (CA) might not be necessary because lymph node metastasis around them is rare in pancreatic tail cancers [15-17]. In this study, we evaluated the optimal range of lymph node dissection for resectable pancreatic tail cancer by investigating the location and frequency of lymph node metastases.

Patients and Methods

Study design

The clinical data of eligible patients were collected through a retrospective review of the medical records. This study was approved by the ethics review board of the Hiroshima University Hospital (No. E-2204), and informed consent was waived. All procedures performed were in accordance with the ethical standards

of the 1964 Declaration of Helsinki and its later amendments.

Patient selection

Patients with resectable PDAC who underwent DP between December 2005 and March 2021 were eligible. Patients who underwent completion pancreatectomy after pancreaticoduodenectomy were not included. Patients who had previous histories of surgery for gastric cancer or transverse colon cancer were also excluded. The definition of resectable PDAC was based on the JPS classification[12]/ NCCN guidelines[18]. The patient data were retrieved from the hospital database.

Treatment strategy

Patients with resectable PDAC had usually underwent upfront surgery. However, the prolonged survival period after neoadjuvant chemotherapy (NAC) with gemcitabine plus S1 for resectable PDAC was demonstrated in a randomized phase II/III clinical trial (Prep02/JSAP05 study) in Japan in 2019 [19]. Since the results of this trial was reported, patients received NAC before the surgery.

Our standard procedure for DP in PDAC is radical antegrade modular pancreatosplenectomy (RAMPS) [20] with regional lymph node dissection. We performed the procedure by laparotomy until March 2020 and by laparoscopic surgery from April 2020. Regional lymph nodes were defined as follows: station 7 (along the left gastric artery), station 8 (along the CHA), station 9 (along the CA), station 10 (at the splenic hilum), station 11 (along the splenic artery), station 14 (along the superior mesenteric artery) and station 18 (along the inferior side of the pancreas), according to the JPS classification (Figure 2).

Diagnosis of lymph node metastasis

The pathological examination was performed using surgically resected specimens. Retrieved regional lymph nodes were fixed in formalin, embedded with paraffin, sliced into 3 μm sections, and stained with hematoxylin and eosin. Two experienced pathologists, who specialized in gastrointestinal malignancies, diagnosed the presence or absence of lymph node metastasis. Further, all the pathological findings were double-checked by the chief pathologist.

Outcome measures

Eligible patients were assigned to two groups according to the tumor location based on the JPS classification: Pt group (pancreatic tail cancer) and non-Pt group (pancreatic body cancer, and body and tail cancer). The tumor location was determined based on the preoperative CT, and it was confirmed intraoperatively. A comparison between the two groups was performed involving the following factors: age, sex, carbohydrate antigen 19-9 (CA19-9) level, NAC, surgery-related factors, pathological findings, and postoperative lymph node recurrences. The number of patients who had lymph node metastases was investigated and compared between the Pt and non-Pt groups. The patient was regarded as having lymph node metastasis, if the metastasized lymph node was detected in the resected specimen, regardless of the number of it. The number of retrieved lymph nodes and metastasized lymph nodes at each station were also investigated and compared between the two groups.

Statistical analyses

A normality test failed to verify the normality of the data; therefore, median values and nonparametric statistical testing procedures were utilized. Clinicopathologic factors were compared using the chi-square test, Fisher's exact test, and Mann-Whitney U test. *P*-values < 0.05 were considered statistically significant. All statistical analyses were performed using JMP statistical software (version 13.0; SAS Institute, Cary, NC, USA).

Results

Clinical characteristics

A total of 96 patients with resectable PDAC who underwent DP were enrolled in this study. Regional lymph node dissections including stations 7, 8, 9, 10, 11, 14, 15, and 18 were completed in all enrolled patients. The extent of lymph node dissection was constant during the study period. The clinicopathological characteristics of the eligible patients are summarized in Table 1. Of these, 61 (64%) patients were assigned to the Pt group and the remaining 35 (36%) to the non-Pt group. All patients had neither scoliosis nor tortuosity of aorta, and they could be clearly classified into the two groups. 9 (15%) in the Pt group and 3 (9%) in the non-Pt group had received NAC with gemcitabine plus S1. There were no

statistically significant differences regarding age, sex, CA19-9 level, neoadjuvant chemotherapy, operation time, blood loss, transfusion, and incidence of postoperative pancreatic fistula (POPF) between the two groups. Among the pathological findings, the median diameter of the tumor was significantly larger in the Pt group (25 mm) compared to that in the non-Pt group (18 mm); $P = 0.028$. There were no significant differences in histologic type, ratio of regional lymph node metastasis, and R0 resection between the two groups. The median follow-up period was 76 months ranging from 3 to146 months. Lymph node recurrence during follow-up was also investigated, and it was found at station 8 only in one patient in the non-Pt group.

The number of patients with lymph node metastasis

The number of patients with regional lymph node metastasis in the Pt and non-Pt groups were as follows: Station 7: 0 (0%) vs. 1 (3%), Station 8: 0 (0%) vs. 4 (12%), Station 9: 0 (0%) vs. 2 (6%); Station 10: 4 (7%) vs. 1 (3%), Station 11: 18 (30%) vs. 18 (51%), Station 14: 2 (4%) vs. 3 (9%), and Station 18: 10 (17%) vs. 6 (17%), respectively (Table 2). In both groups, the most common metastatic node was station 11, followed by station 18. Metastases were found in all regional lymph nodes in the non-Pt group, whereas none of the patients in the Pt group exhibited metastases to stations 7, 8, and 9.

The number of metastasized lymph nodes in retrieved lymph nodes

The number of metastasized lymph nodes at each station in the Pt and non-Pt groups were as follows: Station 7: 0 (0%) vs. 1 (2%), Station 8: 0 (0%) vs. 6 (8%), Station 9: 0 (0%) vs. 2 (4%); Station 10: 7 (5%) vs. 2 (3%), Station 11: 51 (14%) vs. 36 (17%), Station 14: 2 (1%) vs. 5 (6%), and Station 18: 16 (7%) vs. 13 (10%), respectively (Table 3). In the Pt group, 92, 157, and 98 lymph nodes were retrieved at stations 7, 8, and 9, respectively, and no metastasis was found there.

Discussion

Surgical resection is the only curative treatment known to provide long-term survival in patients with PDAC. PDAC usually has high malignant potential and can easily metastasize to regional lymph nodes [8-11,21,22]. Therefore, optimal lymph node dissection is mandatory to achieve curative resection.

Regarding the extent of lymph node dissection, a few recent reports have demonstrated that metastasis to stations 8 and 9 is rare in pancreatic tail cancer [15-17]. Zhou et al. [15] reported the location and frequency of lymph node metastasis in 55 patients with left-sided PDAC, which were located > 25 mm from the splenic artery root, and only one patient exhibited metastasis to Station 9. Imamura et al. [16] reported that only one of 47 patients with pancreatic tail cancers in the AJCC classification experienced metastasis to Stations 8 and 9. Hirashita et al. [17] demonstrated that 18 patients with pancreatic tail cancer according to the JPS classification did not have metastasis to stations 8 and 9.

The current study demonstrated results similar to these previous reports and included the largest patient cohort. PDAC in the non-Pt group could metastasize to any region of the regional lymph nodes as defined in the JPS classification. On the other hand, patients in the Pt group exhibited no metastases at stations 7, 8, and 9, despite having larger tumors than those in the non-Pt group. No previous reports referred to station 7, and this study is the first report that demonstrated the absence of metastasis at station 7 in the Pt group. The dissection of stations 7, 8, and 9 might not be necessary for JPS-classified pancreatic tail cancer. The rarity of metastases to Stations 7, 8, and 9 in pancreatic tail cancer might depend on the drainage pathway of lymphatic flow. The main lymphatic pathway is heading to the splenic hilum in the pancreatic tail, whereas it drains to the superior or inferior edge of the pancreatic head in the pancreatic body [21,23].

On the other hand, in this study, lymph node metastasis to station 14 was identified in two patients in the Pt group, and dissection of lymph nodes along the superior mesenteric artery was considered necessary, although the node was not included in the regional lymph nodes in the ISGPS classification.

This study has several limitations. First, this study was based on data from a single-center database, and the unexpected bias cannot be completely excluded. Second, this study included 12 patients (13%) who received NAC, and the lymph node metastases in those patients might be affected by the therapy. Some reports described that the rates of lymph node metastasis were decreased by NAC in patients with PDAC[24-26]. However, the efficacy of NAC in left-sided PDAC remains unclear. Therefore, we think that the extent of lymph node dissection shouldn't be changed depending on the presence or absence of NAC at this time. Third, the benefit of non-dissection at stations 7, 8, and 9 remains unclear. However, it has been reported that lymph node dissection of the cranial edge is difficult in obese patients or in laparoscopic cases [27-30].

Non-dissection around the left gastric artery, common hepatic artery, and celiac artery might lead to less intraoperative blood loss and shorter operation time. Further investigation is necessary to elucidate the validity and efficacy of non-dissection of these nodes.

In conclusion, lymph node dissection at stations 7, 8, and 9 might not be necessary in patients with resectable PDAC confined to the pancreatic tail.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Figure Legends

Figure 1. Definition of left-sided pancreatic cancer

A) Definition according to the Japan Pancreas Society (JPS). The border between pancreatic body cancer and tail cancer is the left edge of the aorta (dotted line). When a tumor exists on both sides of the border, it is defined as pancreatic body and tail cancer. T, tumor; SMV, superior mesenteric vein; Ao, Aorta.

B) Definition according to the American Joint Committee on Cancer (AJCC)/International Study Group of Pancreatic Surgery (ISGPS). The border between pancreatic body cancer and tail cancer is the left edge of the aorta (dotted line).

Figure 2. Recommended extent of lymphadenectomy in distal pancreatectomy

The numeral in the circle indicates the station number of the lymph nodes. Station 7: lymph node along the left gastric artery; station 8: lymph node along the common hepatic artery; station 9: lymph node around the celiac axis; station10: lymph node at the splenic hilum; station 11: lymph node along splenic artery; station 14: lymph node along superior mesenteric artery; station 18: lymph node along the inferior margin of the pancreas.

JPS, Japan Pancreas Society; AJCC, American Joint Committee on Cancer; ISGPS, International Study Group of Pancreatic Surgery; LGA, left gastric artery; CHA, common hepatic artery; PHA, proper hepatic artery; CA, celiac axis; SPA, splenic artery; SMA, superior mesenteric artery; SMV, superior mesenteric vein

Table 1 Clinicopathological characteristics

	Pt (***n*** **= 61)**	**non-Pt** (***n*** **= 35)**	***p*-value**
Age, years (median, range)	72 (44-87)	71 (42-84)	0.964
Sex (male/female)	38 /23	25 /10	0.361
Preoperative factors			
CA19-9, U/mL (median, range)	43 (2-20734)	33 (2-1287)	0.237
Neoadjuvant therapy, *n*	9 (15%)	3 (9%)	0.366
Surgery related factors			
Operation time, min (median, range)	201 (112-424)	190 (133-405)	0.566
Blood loss, mL (median range)	352 (5-2815)	335 (20-2140)	0.866
Blood transfusion, *n*	4 (7%)	2 (6%)	0.881
POPF Grade B or C, *n*	20 (33%)	9 (26%)	0.486
Pathological findings			
Tumor diameter (mm), (median range)	25 (10-63)	18 (6-56)	0.028
Histologic type (well/mod/poor), *n*	19/36/6	17/14/4	0.182
Regional lymph node metastasis, *n*	28 (46%)	22 (63%)	0.108
R0 resection, *n*	51 (84%)	29 (83%)	0.925
Lymph node recurrence, *n*	0 (0%)	1 (3%)	0.154

Pt, pancreatic tail cancer; non-Pt, pancreatic body cancer and pancreatic body and tail cancer; CA19-9, carbohydrate antigen 19-9; POPF, postoperative pancreatic fistula

Table 2 The number of patients with regional lymph node metastasis

	Pt (***n*** **= 61)**	**non-Pt** (***n*** **= 35)**
Station 7: LNs along left gastric artery*	0/53 (0%)	1/32 (3%)
Station 8: LNs along common hepatic artery*	0/59 (0%)	4/34 (12%)
Station 9: LNs around celiac axis*	0/57 (0%)	2/33 (6%)
Station 10: LNs at the splenic hilum*	4/60 (7%)	1/33 (3%)
Station 11: LNs along splenic artery*	18/61 (30%)	18/35 (51%)
Station 14: LNs along superior mesenteric artery*	2/56 (4%)	3/33 (9%)
Station 18: LNs along inferior margin of the pancreas*	10/60 (17%)	6/35 (17%)

* Number of patients with lymph node metastasis/number of patients in whom the lymph nodes were detected in the resected specimen

LNs, lymph nodes; Pt, pancreatic tail cancer; non-Pt, pancreatic body cancer and pancreatic body and tail cancer

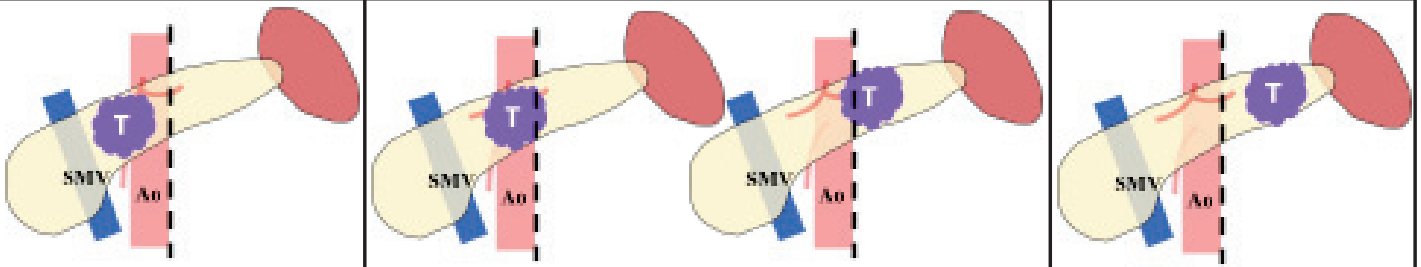
Table 3 The number of metastasized lymph nodes.

Station 7: LNs along left gastric artery*	0/92 (0%)	1/60 (2%)
Station 8: LNs along common hepatic artery*	0/157 (0%)	6/78 (8%)
Station 9: LNs around celiac axis*	0/98 (0%)	2/56 (4%)
Station 10: LNs at the splenic hilum*	7/140 (5%)	2/58 (3%)
Station 11: LNs along splenic artery*	51/365 (14%)	36/212 (17%)
Station 14: LNs along superior mesenteric artery*	2/140 (1%)	5/82 (6%)
Station 18: LNs along inferior margin of the pancreas*	16/239 (7%)	13/129 (10%)

*Total number of metastasized lymph nodes/total number of harvested lymph nodes.

LNs, lymph nodes; Pt, pancreatic tail cancer; non-Pt, pancreatic body cancer and pancreatic body and tail cancer

Fig. 1 (A)

	Pancreatic body cancer	Pancreatic body and tail cancer	Pancreatic tail cancer
JPS			

(B)

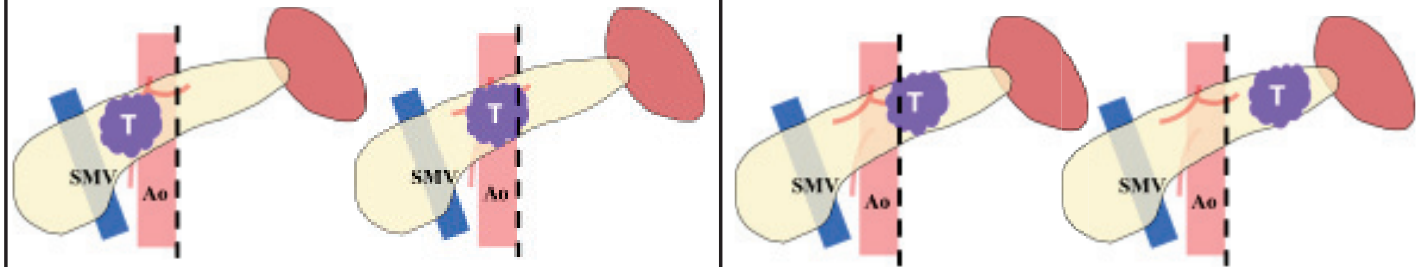
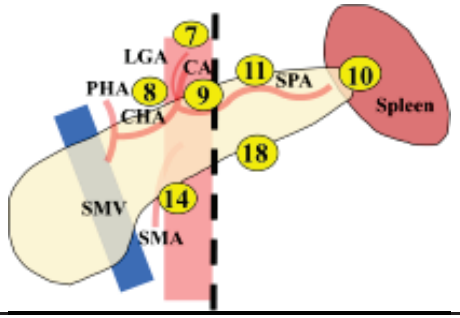
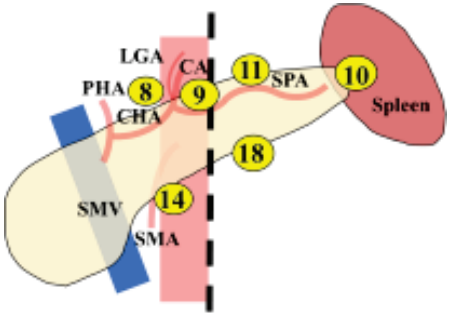
	Pancreatic body cancer	Pancreatic tail cancer
AJCC/ ISGPS		

Fig. 2

	Pancreatic body cancer	Pancreatic tail cancer
JPS		
AJCC		
ISGPS