Clinical implications of lymphadenectomy for invasive ductal carcinoma of the body or tail of the pancreas

Takuya Minagawa1 | Teiichi Sugiura1 | Yukiyasu Okamura1 | Takaaki Ito1
Yusuke Yamamoto1 | Ryo Ashida1 | Katsuhisa Ohgi1 | Keiko Sasaki2 | Katsuhiko Uesaka1

Original Article

Objective: The appropriate extent of lymphadenectomy for pancreatic cancer of the body/tail has not been standardized worldwide. The present study evaluated the optimal extent of harvesting lymph nodes.

Methods: Patients who underwent distal pancreatectomy for invasive ductal carcinoma of the pancreas between 2007 and 2018 were retrospectively reviewed. Patients were subclassified into three groups depending on the tumor location: pancreatic body (Pb), proximal pancreatic tail (Ptp), and distal pancreatic tail (Ptd). The pancreatic tail was further divided into even sections of Ptp and Ptd. Patterns of lymph node metastasis and the impact of lymph node metastasis on the prognosis were examined.

Results: A total of 120 patients were evaluated. Fifty-eight patients had a tumor in the Pb, 38 in the Ptp, and 24 in the Ptd. No patients with a Ptd tumor had metastasis beyond the peripancreatic and splenic hilar lymph nodes (LN-PSH). All patients with metastasis to the lymph nodes along the common hepatic artery (LN-CHA) or along the left lateral superior mesenteric artery (LN-SMA) also had metastasis to the LN-PSH. Recurrence after surgery occurred significantly earlier in this population. In a multivariate analysis, metastasis to the LN-CHA or LN-SMA (hazard ratio [HR] 3.3; \( P = .04 \)) was an independent risk factor for overall survival. Furthermore, high levels of preoperative serum CA19-9 (HR 10.9; \( P = .013 \)) were a predictive factor for metastasis to the LN-CHA or LN-SMA.

Conclusions: Metastasis to the LN-CHA or LN-SMA was rare but a significant prognostic factor in patients with pancreatic body/tail cancer.

Keywords: dissection, lymph node station, lymphatic metastasis, pancreatic cancer, tumor location

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited. © 2022 The Authors. Annals of Gastroenterological Surgery published by John Wiley & Sons Australia, Ltd on behalf of The Japanese Society of Gastroenterological Surgery.
1  |  INTRODUCTION

Lymph node status is well known to be a significant prognostic marker in patients with pancreatic cancer.\(^1\)–\(^5\) Pancreatectomy with lymphadenectomy has been the standard procedure for treating pancreatic cancer.\(^6\)–\(^7\) However, the optimal extent of lymphadenectomy has been controversial. Based on previous randomized controlled trials, extended lymphadenectomy with pancreatoduodenectomy has not been recommended for pancreatic head cancer.\(^8\)–\(^14\) Particularly for patients with adenocarcinoma in the body or tail of the pancreas, few studies have focused on the influence of lymph node involvement on the prognosis.

The recommended extent of lymph node dissection during distal pancreatectomy (DP) for pancreatic cancer differs somewhat between the seventh edition of the rules of the Japan Pancreas Society (JPS)\(^15\) and the consensus statement by the International Study Group on Pancreatic Surgery (ISGPS).\(^7\) The JPS recommends harvesting lymph nodes along the common hepatic artery and the celiac axis for both pancreatic body and tail cancers. In contrast, the ISGPS recommends that the lymph nodes around the celiac axis be resected, particularly when the tumor is close to the celiac axis in the body of the pancreas, and the lymph nodes along the common hepatic artery not to be dissected for pancreatic body or tail cancers, as resection of these lymph nodes has been considered to constitute extended lymphadenectomy.\(^7\)

Clarifying the incidence of metastasis in a specific regional lymph node station and the impact of lymph node metastasis on the prognosis has proven useful for understanding the patterns of tumor spread and examining the extent of lymph node dissection. However, to our knowledge, few studies have investigated the rates of lymph node metastasis, especially for distal pancreatic cancer.\(^16\)–\(^17\)

The present study evaluated the patterns of lymph node metastasis in patients with pancreatic cancer in the body or tail and proved the validity of the current extent of lymphadenectomy during DP.

2  |  METHODS

2.1  |  Patients

From January 2007 to December 2018, 305 consecutive patients underwent DP, including 17 who underwent DP with celiac axis resection (DP-CAR), in Shizuoka Cancer Center, Japan. Among them, 135 patients who were histologically proven to have invasive ductal carcinoma of the pancreatic body or tail were included in this study. Of these, patients who underwent R2 resection (n = 1), those who underwent DP as total remnant pancreatectomy (n = 9), and those with double cancers (n = 5) were excluded from this study. Ultimately, 120 patients were included as subjects in this study. The clinical data of these patients were obtained from a prospectively collected database.

This study was approved by the Institutional Review Board of the Shizuoka Cancer Center (approval number: J2020-164-2020-1-3).

2.2  |  Treatment strategy

Until 2012, upfront surgery was routinely performed for patients with tumors that were considered resectable. Starting in 2013, however, the surgical strategy was determined based on the resectability criteria according to the National Comprehensive Cancer Network (NCCN)\(^18\) and the JPS guidelines.\(^15\) Patients with resectable tumors received upfront surgery; those with borderline resectable (BR) tumors received neoadjuvant therapy (NAT) using chemotherapy, with or without radiotherapy (FOLFIRINOX; S-1 + radiation; or GEM + nab-paclitaxel [PTX]) prior to surgery; and those with locally advanced unresectable (UR-LA) tumors received chemotherapy, with or without radiotherapy (FOLFIRINOX; GEM + radiation; or GEM + nab-paclitaxel [PTX]). Three patients with UR-LA underwent DP or DP-CAR as conversion surgery. Four patients with resectable lesions received NAT followed by surgery for a clinical trial (gemcitabine [GEM] + S-1; or S-1 + radiation).

2.3  |  Surgical procedures

All surgical procedures were performed with an open approach. No laparoscopic surgery was conducted during the study period. Peritoneal lavage cytology and sampling of the para-aortic lymph nodes were performed after laparotomy. If unresectable factors were found, the planned procedure was abandoned. The surgical procedures performed for DP and DP-CAR were described previously.\(^9\) Indications for DP-CAR in our institution included (a) the celiac axis was involved, whereas the aorta, superior mesenteric artery, and gastro-duodenal artery remained free from the tumor; or (b) preserving the splenic artery root was technically or oncologically difficult.\(^9\) To achieve complete lymph node dissection around the splenic artery and the splenic hilum, the spleen was routinely resected in both procedures. The extent of lymph node dissection was either equal to or greater than that recommended by the ISGPS.\(^7\) In detail, the lymph nodes along the common hepatic artery (LN-CHA), around the celiac artery (LN-CA), along the left lateral superior mesenteric artery (LN-SMA; only in tumors in the body of the pancreas), at the splenic hilum (LN-SH), along the splenic artery (LN-SA), and the retroperitoneal lymph nodes (LN-RP) were routinely dissected. A schematic image of these lymph nodes is shown in Figure 1A. The intraoperative histological evaluation of the stump of the pancreas was always performed by pathologists to ensure that the surgical margin remained negative for cancer cells.

2.4  |  Histological evaluation and numbering of lymph nodes

A histological assessment was carried out by at least two specialized pathologists. Surgeons named the lymph nodes to be dissected. Lymph nodes that had adhered to the tumor (mainly LN-SH, LN-SA,
and LN-RP) were not retrieved from the specimen, as the evaluation of the dissected margin would become difficult. These lymph nodes collectively included the peripancreatic and splenic hilar lymph nodes (LN-PSH). The tumors were staged according to the eighth edition of the TNM staging manual.

2.5 Subclassification of the tumor location

A schematic illustration of the subclassification of the tumor location is also described in Figure 1B. Tumors located at the tail of the pancreas were classified into two groups: proximal pancreatic tail (Ptp) and distal pancreatic tail (Ptd). The boundary between Ptp and Ptd was defined as the line that equally divided the left border of the abdominal aorta and the end of the pancreatic tail. If the tumor was located in more than two areas, classification was performed according to the location of the center of the tumor. Preoperative computed tomography (CT) images were used for this analysis.

2.6 Postoperative treatment and follow-up

Our standard treatment for pancreatic cancer was surgery alone until 2006 and surgical resection and subsequent postoperative adjuvant chemotherapy from 2007. Adjuvant chemotherapy was conducted using gemcitabine or S-1 for 6 mo if possible. Within the first 2 y after resection, follow-up examinations, including physical examinations, laboratory tests, assessment of tumor markers, and CT, were performed at 3-mo intervals. If the patients had no signs of recurrence for 2 y after resection, follow-up examinations were performed at 6-mo intervals. The median follow-up period of the censored patients was 22 mo.

2.7 Statistical analyses

Categorical variables were compared using the chi-square test or Fisher’s exact test, as appropriate. Continuous variables were compared using the Mann–Whitney U-test. The survival was analyzed using Kaplan–Meier curves and the log-rank test. The optimum cutoff values of each continuous parameter for the overall survival (OS) and predicting metastasis to the LN-CHA or LN-SMA were determined using the minimum P values calculated using the log-rank test. Especially, as to tumor marker, cutoff values were shown to be 15.0 ng/mL for CEA (P = .0029) and 400 U/mL for CA19-9 (P = .00047) (Figure S1A, B). Hazard ratios were estimated by univariate and multivariate survival analyses using the Cox regression model. Variables with P < .05 using the univariate log-rank test were further explored in the multivariate setting. Differences were considered statistically significant at P < .05. All analyses were performed using the SPSS software program, v. 25.0 (IBM, Armonk, NY, USA).

3 RESULTS

Patients’ demographics and operative characteristics are summarized in Table 1. Fifty-eight patients had tumors in the Pb, 38 in the Ptp, and 24 in the Ptd. Patients with tumors in the Ptd were younger than those with tumors in the Pb (P < .05). All patients with tumors in the Ptd had resectable lesions and underwent DP. DP-CAR was performed in 17 patients with tumors in the Pb or Ptp. There were no other significant differences among these three groups.

No significant difference was shown in the OS and the disease-free survival (DFS) for patients in the Pb, Ptp, and Ptd groups (Figure S2). Pathologic characteristics are also shown in Table 1. Nodal involvement was observed in 64 (53%) patients. The median number of examined regional lymph nodes was 16. R1 resection was
## TABLE 1  Patient characteristics stratified by tumor location

| Variables                      | Pb (N = 58) | Ptp (N = 38) | P value<sup>a</sup> | Ptd (N = 24) | P value<sup>b</sup> | P value<sup>c</sup> |
|--------------------------------|-------------|--------------|----------------------|--------------|----------------------|----------------------|
| **Clinical variables**         |             |              |                      |              |                      |                      |
| Sex                            |             |              |                      |              |                      |                      |
| Male                           | 28 (48)     | 23 (39)      | .297                 | 15 (63)      | .332                 | 1.000                |
| Female                         | 30 (52)     | 15 (61)      | .198                 | 9 (37)       | .044*                | .483                 |
| Age                            | 72 [66–77]  | 70 [62–77]   | .370                 | 68 [61–75]   | .091                 | .096                 |
| CEA (ng/mL)                    | 2.6 [1.8–3.9] | 3.0 [1.8–4.7] | .359                 | 5.7 [2.6–17.1]| .483                 | .483                 |
| CA19-9 (U/mL)                  | 35 [10–121] | 35 [11–176]  | .359                 | 77 [10–288]  | .359                 | .915                 |
| **Resectable status**          |             |              |                      |              |                      |                      |
| Resectable                     | 45 (78)     | 35 (92)      | .092                 | 24 (100)     | .008*                | .277                 |
| BR/UR                          | 13 (22)     | 3 (8)        |                      | 0 (0)        |                      |                      |
| Neoadjuvant therapy            |             |              |                      |              |                      |                      |
| No                             | 45 (78)     | 34 (89)      | .176                 | 23 (96)      | .056                 | .640                 |
| Yes                            | 13 (22)     | 4 (11)       |                      | 1 (4)        |                      |                      |
| **Surgical variables**         |             |              |                      |              |                      |                      |
| Procedure                      |             |              |                      |              |                      |                      |
| DP                             | 44 (76)     | 35 (92)      | .056                 | 24 (100)     | .008*                | .277                 |
| DP-CAR                         | 14 (24)     | 3 (8)        |                      | 0 (0)        |                      |                      |
| Portal vein reconstruction     |             |              |                      |              |                      |                      |
| No                             | 53 (91)     | 36 (95)      | .700                 | 24 (100)     | .031*                | .518                 |
| Yes                            | 5 (9)       | 2 (5)        |                      | 0 (0)        |                      |                      |
| Combined resected organ        |             |              |                      |              |                      |                      |
| Yes                            | 4 (7)       | 4 (11)       | .708                 | 6 (25)       | .057                 | .166                 |
| Left adrenal gland             | 3           | 3            |                      | 5            |                      |                      |
| Stomach                        | 1           | 0            |                      | 2            |                      |                      |
| Colon                          | 0           | 1            |                      | 3            |                      |                      |
| Others                         | 2           | 0            |                      | 1            |                      |                      |
| No                             | 54 (93)     | 34 (90)      | 18 (75)              |              |                      |                      |
| Operation time (min)           | 261 [217–317]| 216 [182–259]| .010*               | 224 [182–290]| .639                 | .673                 |
| Blood loss (g)                 | 443 [264–674]| 247 [145–509]| .003*               | 414 [241–625]| .076                 | .061                 |
| **Pathologic variables**       |             |              |                      |              |                      |                      |
| Tumor size (mm)                | 30 [22–47]  | 32 [26–45]   | .898                 | 35 [25–53]   | .278                 | .344                 |
| Tumor differentiation          |             |              |                      |              |                      |                      |
| Well                           | 22 (38)     | 11 (29)      | .422                 | 8 (33)       | .901                 | .781                 |
| Mod                            | 34 (59)     | 27 (71)      |                      | 16 (67)      |                      |                      |
| Por                            | 2 (3)       | 0 (0)        |                      | 0 (0)        |                      |                      |
| pT stage (UICC 8th)            |             |              |                      |              |                      |                      |
| T1                             | 10 (17)     | 6 (16)       | 1.000                | 0 (0)        | .107                 | .135                 |
| T2                             | 29 (50)     | 19 (50)      |                      | 15 (63)      |                      |                      |
| T3                             | 17 (29)     | 12 (32)      |                      | 9 (37)       |                      |                      |
| T4                             | 2 (3)       | 1 (3)        |                      | 0 (0)        |                      |                      |
| pN stage (UICC 8th)            |             |              |                      |              |                      |                      |
| N0                             | 27 (47)     | 19 (50)      | .295                 | 10 (42)      | .491                 | .809                 |
| N1                             | 24 (41)     | 18 (47)      |                      | 13 (54)      |                      |                      |
| N2                             | 7 (12)      | 1 (3)        |                      | 1 (4)        |                      |                      |
performed in eight patients (at the pancreatic cut margin in four and at the dissected margin in four). Recurrence was observed in 66 (55%) patients during the follow-up period. No recurrence was detected at the original area of the regional lymph nodes, although 12 patients experienced local recurrence.

### 3.1 Lymph node mapping according to the tumor location

Figure 2 shows lymph node mapping in patients stratified depending on the tumor location. The most frequent metastatic lymph node was the LN-PSH, which was attached to the pancreas. Metastasis to the LN-PSH was observed in all patients with lymph node metastasis, regardless of tumor location. Metastasis to the LN-CHA or LN-SMA was observed in only four and two cases, respectively. Regarding the LN-CA, there was only one case with a tumor in the Pb with nodal involvement. Of note, no patients with tumors in the Ptd had nodal involvement at the LN-CHA, LN-CA, or LN-SMA. All patients with metastasis to the LN-CHA or LN-SMA had also metastasis to the LN-PSH.

### 3.2 Characteristics and prognosis of patients with metastasis to the LN-CHA or LN-SMA

Early recurrence at distant organs within 1 y after surgery was observed in all cases with metastasis to the LN-CHA or LN-SMA.
Compared to patients with metastasis to the LN-PSH alone, the prognosis of those with metastasis to the LN-CHA or LN-SMA tended to be worse (Figure 3A, B).

### 3.3 | Prognostic factors for OS and DFS

Multivariate analyses revealed that lymph node metastasis to the LN-CHA or LN-SMA, serosal invasion, portal venous system invasion, and a lack of adjuvant chemotherapy were risk factors for OS (Table 3). Similarly, a high level of serum CA19-9, large tumor, lymph node metastasis, portal venous system invasion, and no adjuvant chemotherapy were shown to be risk factors for DFS by multivariate analyses (Table S1).

### 3.4 | Predictive factors for metastasis to the LN-CHA or LN-SMA

Univariate analysis showed that high levels of preoperative serum CA19-9 were a predictive factor for lymph node metastasis to the LN-CHA or LN-SMA (Table 4).

### 4 | DISCUSSION

LN-CHA and LN-SMA are considered appropriate for dissection, regardless of tumor location, according to the classification of pancreatic carcinoma in Japan. However, few studies have described the metastasis rate of those stations and the effect of dissection of those lymph nodes, especially for pancreatic tail cancer. This study describes the patterns of lymph node metastasis for patients with pancreatic body/tail cancer who underwent DP. Specifically, it revealed that LN-CHA and LN-SMA metastasis was rare but still a significant prognostic factor in patients with pancreatic body/tail cancer. According to the mapping of the metastatic lymph nodes, metastasis to the LN-CHA was observed in only 3.3% of patients with tumors in the pancreatic body or proximal tail, and metastasis to the LN-SMA was only found in 3.4% of cases in the body of the pancreas. Furthermore, no patients with tumors in the distal tail of the pancreas had metastasis to the LN-CHA or LN-SMA. A single cancer center in Japan reported that metastasis to the LN-CHA was observed in only two cases (4%) among 50 patients who underwent standard DP for pancreatic cancer. Similar to our study, no patients in that study with tumors located in the tail of the pancreas had metastasis to the...
MINAGAWA et al.

LN-CHA, although one had metastasis to the LN-SMA. These results support our own findings.

With regard to the lymphatic flow and neural invasion, the lymph nodes along the common hepatic artery to the celiac axis and at the root of the superior mesenteric artery are considered important. The present study also clarified the characteristics and prognosis of patients with metastasis to the LN-CHA or LN-SMA. All of them developed early recurrence at distant organs within a year after surgery. Although their prognoses were poor, they were not significantly worse than those of patients with metastasis only to the LN-PSH, probably because of the extremely small number of subjects included in our study. A multivariate analysis revealed that metastasis to the LN-CHA or LN-SMA was a prognostic factor for pancreatic body/tail cancer. Furthermore, a high level of preoperative serum CA19-9 was a predictive factor for metastasis to the LN-CHA or LN-SMA.

Along with these findings, the extent of lymphadenectomy might be reconsidered for patients with pancreatic body/tail cancer. Lymphadenectomy of LN-CHA and LN-SMA should be performed, especially for tumors in the pancreatic body or the proximal tail, as such tumors have a relatively high risk of metastasis to those lymph nodes. In contrast, retrieval of those lymph node stations might be omitted for select patients with tumors in the distal tail of the pancreas, who have a lower metastasis rate of those lymph nodes. Indeed, in cases where the LN-CHA or LN-SMA were not fully dissected, recurrence was not detected in those remnant lymph nodes during the follow-up period in this study.

While surgical resection of malignant tumors with lymphadenectomy has been an integral part of the treatment for various types of cancer, advances in chemotherapy and radiation therapy have changed the concept of the role of surgery. For early-stage stomach cancer without lymph node metastasis as a preoperative diagnosis, a low extent of lymphadenectomy has been recommended.23 For breast cancer without clinically lymph node metastasis, as confirmed by a sentinel node biopsy, axillary lymph node dissection has been omitted.24 These treatments have been supported by an accurate diagnosis for tumor staging. Regarding pancreatic cancer, in general, the concept of the sentinel lymph node hypothesis has not been adopted, and a preoperative diagnosis for staging is sometimes difficult to make, compared to cases of stomach or breast cancer. Further advances in imaging studies along with the accumulation of evidence will help resolve this issue.

The pancreatic resection line during DP is determined by considering the margin from the tumor. For tumors in the Pb or Ptp, the pancreas is often resected above the portal vein. In contrast, for tumors located only in the Ptd, the pancreas resection line can be set at the left border of the SMA. These two procedures differ in their complexity, especially with laparoscopic pancreatic resection; the procedure for tumors in the Pb or Ptp is more difficult than that for tumors in the Ptd, according to the difficulty scoring system of laparoscopic DP, which is advocated by the Japanese Society of Hepato-Biliary-Pancreatic Surgery.25 The
FIGURE 3  Survival analyses according to the status of lymph node metastasis. Kaplan–Meier curves for the overall survival rates (A) and disease-free survival rates (B) of patients with no lymph node metastasis (LN met [−]), metastasis to the LN-PSH, and metastasis to the LN-CHA or LN-SMA. (A) $P < .001$ (LN met [−] vs. LN-PSH met and LN-CHA or LN-SMA met), $P = .145$ (LN-PSH met vs. LN-CHA or LN-SMA met); (B) $P < .001$ (LN met [−] vs. LN-PSH met and LN-CHA or LN-SMA met), $P = .032$ (LN-PSH met vs. LN-CHA or LN-SMA met). LN, lymph node; LN-CHA, lymph nodes along the common hepatic artery; LN-PSH, peripancreatic and splenic hilar lymph nodes; LN-SMA, lymph nodes along the left lateral superior mesenteric artery; met, metastasis. *$P < .05$, **$P < .01$.

TABLE 3  Univariate and multivariate analyses for the overall survival

| Variables            | N   | Median OS | Univariate P value | Multivariate HR (95% CI) | P value |
|----------------------|-----|-----------|--------------------|--------------------------|---------|
| Tumor location       |     |           |                    |                          |         |
| Pb                   | 58  | 49        | .255               |                          |         |
| Ptp                  | 38  | 27        |                    |                          |         |
| Ptd                  | 24  | 57        |                    |                          |         |
| Resectable status    |     |           |                    |                          |         |
| BR/UR                | 16  | 45        | .929               |                          |         |
| R                    | 104 | 49        |                    |                          |         |
| CEA (ng/mL)          |     |           |                    |                          |         |
| ≥15                  | 8   | 13        | .003*              | 1.95 (0.71–5.32)         | .193    |
| <15                  | 112 | 49        |                    | 1 (ref)                  |         |
| CA19-9 (U/mL)        |     |           |                    |                          |         |
| ≥400                 | 17  | 25        | .001*              | 1.14 (0.31–4.20)         | .846    |
| <400                 | 103 | 54        |                    | 1 (ref)                  |         |
| Neoadjuvant therapy  |     |           |                    |                          |         |
| No                   | 102 | 47        | .076               |                          |         |
| Yes                  | 18  | NA        |                    |                          |         |
| Procedure            |     |           |                    |                          |         |
| DP-CAR               | 17  | 26        | .003*              | 1.35 (0.59–3.08)         | .480    |
| DP                   | 103 | NA        |                    | 1 (ref)                  |         |
| Portal vein reconstruction | |       |                    |                          |         |
| Yes                  | 7   | 45        | .693               |                          |         |
| No                   | 113 | 54        |                    |                          |         |
| Tumor size (mm)      |     |           |                    |                          |         |
| >50                  | 26  | 23        | .001*              | 1.22 (0.54–2.74)         | .638    |
The present study was associated with some limitations. First, this study had a retrospective design and was performed at a single center. Furthermore, several potential biases may have influenced the results of this study. Second, the number of lymph nodes that

| Variables                              | N   | Median OS | Univariate P value | Multivariate HR (95% CI) | P value |
|----------------------------------------|-----|-----------|--------------------|--------------------------|---------|
| ≤50                                    | 94  | 54        | .464               | 1 (ref)                  |         |
| Tumor differentiation                  |     |           |                    |                          |         |
| Mod/Por                                | 79  | 47        | .464               | 2.05 (0.95–4.42)         | .067    |
| Well                                   | 41  | NA        |                    | 1 (ref)                  |         |
| Lymph node metastasis                  |     |           |                    |                          |         |
| Yes                                    | 64  | 34        | <.001*             | 2.05 (0.95–4.42)         | .067    |
| No                                     | 56  | NA        |                    | 1 (ref)                  |         |
| Metastasis to LN-CHA or LN-SMA         |     |           |                    |                          |         |
| Yes                                    | 5   | 21        | .017*              | 3.30 (1.06–10.31)        | .040*   |
| No                                     | 115 | 49        |                    | 1 (ref)                  |         |
| Microscopic venous invasion            |     |           |                    |                          |         |
| Yes                                    | 56  | 42        | .037*              | 1.17 (0.54–2.55)         | .693    |
| No                                     | 64  | NA        |                    | 1 (ref)                  |         |
| Intrapancreatic nerve invasion         |     |           |                    |                          |         |
| Yes                                    | 107 | 47        | .056               | 1 (ref)                  |         |
| No                                     | 13  | NA        |                    | 1 (ref)                  |         |
| Serosal invasion                       |     |           |                    |                          |         |
| Yes                                    | 37  | 30        | .005*              | 2.36 (1.24–4.48)         | .009*   |
| No                                     | 83  | NA        |                    | 1 (ref)                  |         |
| Retroperitoneal invasion               |     |           |                    |                          |         |
| Yes                                    | 107 | 47        | .206               | 1 (ref)                  |         |
| No                                     | 13  | NA        |                    | 1 (ref)                  |         |
| Nerve plexus invasion                  |     |           |                    |                          |         |
| Yes                                    | 17  | 25        | <.001*             | 1.33 (0.50–3.50)         | .568    |
| No                                     | 103 | NA        |                    | 1 (ref)                  |         |
| Portal venous system invasion          |     |           |                    |                          |         |
| Yes                                    | 59  | 27        | <.001*             | 3.05 (1.46–6.37)         | .003*   |
| No                                     | 61  | NA        |                    | 1 (ref)                  |         |
| Arterial invasion                      |     |           |                    |                          |         |
| Yes                                    | 33  | 27        | .029*              | 1.12 (0.53–2.36)         | .776    |
| No                                     | 87  | NA        |                    | 1 (ref)                  |         |
| Residual tumor                         |     |           |                    |                          |         |
| Yes (R1)                               | 8   | 26        | .003*              | 1.86 (0.78–4.41)         | .163    |
| No (R0)                                | 112 | 57        |                    | 1 (ref)                  |         |
| Adjuvant chemotherapy                  |     |           |                    |                          |         |
| Yes                                    | 95  | 57        | .001*              | 3.65 (1.84–7.25)         | <.001*  |
| No                                     | 25  | 24        |                    | 1 (ref)                  |         |

Note: Categorical data are expressed as n (%).

Abbreviations: BR, borderline resectable; CA, carbohydrate antigen; CEA, carcinoembryonic antigen; CI, confidence interval; DP, distal pancreatectomy; DP-CAR, distal pancreatectomy with celiac axis resection; HR, hazard ratio; LN-CHA, lymph nodes along the common hepatic artery; LN-SMA, lymph nodes along the left lateral superior mesenteric artery; Mod, moderately; NA, not applicable; OS, overall survival; Pb, pancreatic body; Por, poorly; Ptd, pancreatic distal tail; Ptp, pancreatic proximal tail; R, resectable; ref, reference; UR, unresectable.

*P < .05.

Present findings suggest that if it is acceptable to omit lymphadenectomy of the LN-CHA and LN-SMA for tumors in the Ptd, laparoscopic DP for those tumors may be an easier and safer procedure to perform.
TABLE 4 Univariate analysis for metastasis to LN-CHA or LN-SMA

| Variables                      | N  | Met | Univariate                           |
|-------------------------------|----|-----|--------------------------------------|
|                               |    |     | OR (95% CI)                           | P value  |
| **Tumor location**            |    |     |                                       |          |
| Pb                            | 58 | 3   | 1 (ref)                              |          |
| Ptp                           | 38 | 2   | 1.02 (0.16–6.40)                     | 1.000    |
| Ptd                           | 24 | 0   | 0.95 (0.89–1.01)                     | .552     |
| **Resectable status**         |    |     |                                       |          |
| BR/UR                         | 16 | 0   | 0.95 (0.91–1.00)                     | 1.000    |
| R                             | 104| 5   | 1 (ref)                              |          |
| **CEA (ng/mL)**               |    |     |                                       |          |
| ≥15                           | 8  | 0   | 0.96 (0.92–1.00)                     | 1.000    |
| <15                           | 112| 5   | 1 (ref)                              |          |
| **CA19-9 (U/mL)**             |    |     |                                       |          |
| ≥400                          | 17 | 3   | 10.82 (1.66–70.53)                   | .020*    |
| <400                          | 103| 2   | 1 (ref)                              |          |
| **Neoadjuvant chemotherapy**  |    |     |                                       |          |
| Yes                           | 18 | 0   | 0.95 (0.91–1.00)                     | 1.000    |
| No                            | 102| 5   | 1 (ref)                              |          |
| **Procedure**                 |    |     |                                       |          |
| DP-CAR                        | 17 | 2   | 4.44 (0.69–28.83)                    | .146     |
| DP                            | 103| 3   | 1 (ref)                              |          |
| **Portal vein reconstruction**|    |     |                                       |          |
| Yes                           | 7  | 0   | 0.96 (0.92–1.00)                     | 1.000    |
| No                            | 113| 5   | 1 (ref)                              |          |
| **Tumor size (mm)**           |    |     |                                       |          |
| >50                           | 26 | 3   | 6.00 (0.95–38.03)                    | .067     |
| ≤50                           | 94 | 2   | 1 (ref)                              |          |
| **Tumor differentiation**     |    |     |                                       |          |
| Mod/Por                       | 79 | 3   | 0.77 (0.12–4.80)                     | 1.000    |
| Well                          | 41 | 2   | 1 (ref)                              |          |
| **Microscopic venous invasion**|    |     |                                       |          |
| Yes                           | 56 | 1   | 0.27 (0.03–2.52)                     | .370     |
| No                            | 64 | 4   | 1 (ref)                              |          |
| **Intrapancreatic nerve invasion**|    |     |                                       |          |
| Yes                           | 107| 5   | 1.05 (1.00–1.09)                     | 1.000    |
| No                            | 13 | 0   | 1 (ref)                              |          |
| **Serosal invasion**          |    |     |                                       |          |
| Yes                           | 37 | 0   | 0.94 (0.89–1.00)                     | .322     |
| No                            | 83 | 5   | 1 (ref)                              |          |
| **Retroperitoneal invasion**  |    |     |                                       |          |
| Yes                           | 107| 5   | 1.05 (1.00–1.09)                     | 1.000    |
| No                            | 13 | 0   | 1 (ref)                              |          |
| **Nerve plexus invasion**     |    |     |                                       |          |
| Yes                           | 17 | 1   | 1.55 (0.16–14.74)                    | .541     |
| No                            | 103| 4   | 1 (ref)                              |          |
| Portal vein system invasion   |    |     |                                       |          |
were evaluated was relatively small. Although we try to dissect lymph nodes according to the recommendation of the ISGPS as much as possible, in some cases the regional lymph nodes were not able to be fully dissected based on tumor- or patient-related factors, which might have impaired the quality of surgery and the long-term prognosis. In particular, the number of LN-CA dissection procedures performed was extremely small. Several factors may have contributed to this issue: the LN-CA was not always dissected up to the "root of the celiac artery," and since the LN-CA is usually resected en bloc with the LN-SA or LN-CHA, the LN-CA may often be mixed into the LN-SA or LN-CHA when separated from the resected specimen. Thus, it is possible that the lymph nodes were not included in the tissues dissected and submitted as the LN-CA. In addition, the numbers of metastatic LN-CHA and LN-SMA were extremely small, possibly due to our selection of patients for surgery. This might also be associated with our institutional policy, where the LN-SMA is usually dissected only in cases with Pb tumors. Thus, given these potential biases, we recognize that we cannot draw any absolute conclusions from these data. To confirm the current results, a further multicenter study including data from high-volume centers should be conducted. Nevertheless, we believe that the results of the study will help refine classical procedures because of the retrospective nature of the study, and the anonymous clinical data were used for the analysis.

**DISCLOSURES**
Funding: None.

Conflict of Interest: The authors declare no conflicts of interest for this article.

Ethical Approval: This study was approved by the Institutional Review Board of the Shizuoka Cancer Center (approval number: J2020-164-2020-1-3) and it conforms to the provisions of the Declaration of Helsinki. Informed consent was substituted by the informed opt-out procedure because of the retrospective nature of the study, and the anonymous clinical data were used for the analysis.

**ORCID**
Teiichi Sugiura  [https://orcid.org/0000-0001-7163-4084](https://orcid.org/0000-0001-7163-4084)

**REFERENCES**

1. Strobel O, Hinz U, Gluth A, Hank T, Hackert T, Bergmann F, et al. Pancreatic adenocarcinoma: number of positive nodes allows to distinguish several N categories. Ann Surg. 2015;261(5):961–9.

2. Murakami Y, Uemura K, Sudo T, Hayashidani Y, Hashimoto Y, Nakashima A, et al. Number of metastatic lymph nodes, but not lymph node ratio, is an independent prognostic factor after resection of pancreatic carcinoma. J Am Coll Surg. 2010;211(2):196–204.

3. Malleo G, Maggino L, Capelli P, Gulino F, Segattini S, Scarpa A, et al. Reappraisal of nodal staging and study of lymph node station involvement in pancreaticoduodenectomy with the standard International Study Group of Pancreatic Surgery definition of lymphadenectomy for cancer. J Am Coll Surg. 2015;221(2):367–79.

4. Basturk O, Saka B, Balci S, Postlewait LM, Knight J, Goodman M, et al. Substaging of lymph node status in resected pancreatic ductal adenocarcinoma has strong prognostic correlations: proposal for a revised N classification for TNM Staging. Ann Surg Oncol. 2015;22(Suppl 3):S1187–95.

5. Tarantino I, Warschkow R, Hackert T, Schmied BM, Büchler MW, Strobel O, et al. Staging of pancreatic cancer based on the number of positive lymph nodes. Br J Surg. 2017;104(5):608–18.

6. Egawa S, Toma H, Ohigashi H, Okusaka T, Nakao A, Hatori T, et al. Japan pancreatic cancer registry; 30th year anniversary: Japan Pancreas Society, Pancreas. 2012;41(7):985–92.

7. Tol JA, Gouma DJ, Bassi C, Dervenis C, Montorsi M, Adham M, et al. Substaging of lymph node status in resected pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). Surgery. 2014;156(3):591–600.

8. Pedrazzoli S, DiCarlo V, Dionigi R, Mosca F, Pedzeroli P, Pasquali C, et al. Standard versus extended lymphadenectomy associated with pancreaticoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: a multicenter, prospective, randomized study. Ann Surg. 1998;228(4):508–17.

---

**TABLE 4** (Continued)

| Variables                      | N   | Met     | Univariate OR (95% CI) | P value |
|-------------------------------|-----|---------|-----------------------|---------|
| Arterial invasion             |     |         |                       |         |
| Yes                           | 33  | 1       | 0.65 (0.07–6.02)      | 1.000   |
| No                            | 87  | 4       | 1 (ref)               |         |
| Residual tumor                |     |         |                       |         |
| Yes (R1)                      | 8   | 1       | 3.86 (0.38–39.28)     | .296    |
| No (R0)                       | 112 | 4       | 1 (ref)               |         |

Note: Categorical data are expressed as n (%).

Abbreviations: CA, carbohydrate antigen; CEA, carcinoembryonic antigen; CI, confidence interval; DP, distal pancreatectomy; DP-CAR, distal pancreatectomy with celiac axis resection; Met, metastasis; Mod, moderately; NA, not applicable; OR, odds ratio; OS, overall survival; Pb, pancreatic body; Por, poorly; Ptd, pancreatic distal tail; Ptp, pancreatic proximal tail; R, resectable; ref, reference.

*p < .05.
9. Yeo CJ, Cameron JL, Sohn TA, Coleman J, Sauter PK, Hruban RH, et al. Pancreaticoduodenectomy with or without extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma: comparison of morbidity and mortality and short-term outcome. Ann Surg. 1999;229(5):613. discussion 622–614.

10. Yeo CJ, Cameron JL, Lillemoe KD, Sohn Taylor A, Campbell KA, Sauter PK, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. Ann Surg. 2002;236(3):355–68, discussion 366–358.

11. Riall TS, Cameron JL, Lillemoe KD, Campbell K, Sauter P, Coleman J, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma–part 3: update on 5-year survival. J Gastrointest Surg. 2005;9(9):1191–204. discussion 1204–1196.

12. Farnell MB, Pearson RK, Sarr MG, DiMagno EP, Burgart LJ, et al. A prospective randomized trial comparing standard pancreaticoduodenectomy with pancreaticoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surgery. 2005;138(4):618–30. discussion 628–630.

13. Nimura Y, Nagino M, Takao S, Takada T, Miyazaki K, Kawarada Y, et al. Standard versus extended lymphadenectomy in radical pancreaticoduodenectomy for ductal adenocarcinoma of the head of the pancreas: long-term results of a Japanese multicenter randomized controlled trial. J Hepato-Biliary Pancreat Sci. 2012;19(3):230–41.

14. Jang JY, Kang MJ, Heo JS, Choi SH, Choi DW, Park SJ, et al. 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. 2014;259(4):656–64.

15. Japan Pancreas Society. Classification of Pancreatic Carcinoma, 4th English edn. Tokyo: Kanehara and Co., Ltd; 2017.

16. Nakao A, Harada A, Nonami T, Kaneko T, Nomoto S, Koyama H, et al. Lymph node metastasis in carcinoma of the body and tail of the pancreas. Br J Surg. 1997;84(8):1090–2.

17. Fujita T, Nakagohri T, Gotohda N, Takahashi S, Konishi M, Kojima M, et al. Evaluation of the prognostic factors and significance of lymph node status in invasive ductal carcinoma of the body or tail of the pancreas. Pancreas. 2010;39(1):e48–54.

18. Tempero MA, Malafa MP, Al-Hawary M, Asbun H, Bain A, Behrman SW, et al. Pancreatic adenocarcinoma, version 2.2017. NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2017;15(8):1028–61.

19. Sugiuira T, Okamura Y, Ito T, Yamamoto Y, Uesaka K. Surgical indications of distal pancreatectomy with celiac axis resection for pancreatic body/tail cancer. World J Surg. 2017;41(1):258–66.

20. Brierley JD, Gospodarowicz MK, Wittekind C. TNM Classification of Malignant Tumours. Chichester: Wiley and Sons Ltd; 2017.

21. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA. 2013;310(14):1473–81.

22. Uesaka K, Boku N, Fukutomi A, Okamura Y, Konishi M, Matsumoto I, et al. Adjuvant chemotherapy of 5-1 versus gemcitabine for resected pancreatic cancer: a phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet. 2016;388(10041):248–57.

23. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer. 2017;20(1):1–19.

24. Lyman GH, Somerfield MR, Bosserman LD, Perkins CL, Weaver DL, Giuliano AE. Sentinel lymph node biopsy for patients with early-stage breast cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2017;35(5):561–4.

25. Ohtsuka T, Ban D, Nakamura Y, Nagakawa Y, Tanabe M, Gotoh Y, et al. Difficulty scoring system in laparoscopic distal pancreatectomy. J Hepato-Biliary Pancreat Sci. 2018;25(11):489–97.

SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

How to cite this article: Minagawa T, Sugiuira T, Okamura Y, Ito T, Yamamoto Y, Ashida R, et al. Clinical implications of lymphadenectomy for invasive ductal carcinoma of the body or tail of the pancreas. Ann Gastroenterol Surg. 2022;6:531–542. doi:10.1002/ags3.12551