ORIGINAL ARTICLE
Turk J Surg 2025;41(1):5-18



# Clinical significance of para-aortic lymph node metastasis for prognosis in patients with pancreaticobiliary cancer who underwent radical surgical resections

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## ABSTRACT

**Objective:** To elucidate surgical strategies for patients undergoing radical resection, in cases where solitary distant lymph node metastasis is identified intraoperatively, we investigated the prognostic significance of para-aortic lymph node (PALN) metastases and other regional lymph node (RLN) metastases in pancreatic carcinomas (PC) and biliary duct cancers (BDC).

**Material and Methods:** This study retrospectively analyzed data from 181 PC patients and 116 BDC patients who underwent radical resections at two institutions between 1994 and 2021.

**Results:** Among PC patients, metastases were observed in RLN and PALN in 54% and 9% of cases, respectively. Similarly, RLN and PALN metastases were present among BDC patients in 39% and 9% of cases, respectively. Survival analysis revealed that patients with BDC and PALN metastases exhibited significantly reduced disease-free (DFS) and overall survival (OS) compared to those without PALN involvement. Multivariate analysis identified PALN metastasis as an independent predictor of OS in BDC patients ($p<0.05$), while RLN metastasis was independently associated with DFS ($p<0.05$). Additional clinicopathological factors associated with PALN and RLN metastases were also identified. Preoperative serum levels of Duke Pancreas II monoclonal antibody were significantly elevated in patients with PALN metastases. Histological findings of lymphatic or perineural infiltration and hepatic or pancreatic invasion were independently associated with RLN metastases.

**Conclusion:** Based on these findings, radical resection may be considered for PC patients with isolated PALN metastases only in the absence of additional adverse prognostic factors. Prospective clinical trials are warranted to further refine the criteria for surgical intervention when solitary PALN metastases are detected intraoperatively.

**Keywords:** Biliary duct carcinoma, pancreatic carcinoma, para-aortic lymph node, node metastasis, histology, prognosis

## INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer death worldwide, and its lethality is high as only 20% of tumors are deemed radically resectable at the time of diagnosis. About 5% of patients are alive five years after diagnosis, according to the recent review of the meta-analysis by Paiella et al. (1). The para-aortic lymph node (PALN) metastasis was associated with increased poor prognosis when compared with negative PALN regardless of regional nodal status However, definite avoidance of resection of intraoperative metastatic PALN would need further investigation. Thus, the clinical significance of limited PALN metastasis regarding the radicality of distal bile duct cancer and pancreatic cancer remains unclear.

In pancreatic and bile duct cancers, radical surgical resections, such as pancreaticoduodenectomy, distal pancreatectomy, and hepatectomy, are the only curative options, even when RLN metastasis is diagnosed (2-5). However, in cases where node metastasis around the para-aortic area is observed, radical resection should be avoided because of distant metastasis (6). If occult PALN metastasis, which is not detected on preoperative imaging, is diagnosed through intraoperative histological findings using a solitary sampling node, it becomes challenging to

**Cite this article as:** Nanashima A, Arai J, Hiyoshi M, Imamura N, Hamada T, Tsuchimochi Y, et al. Clinical significance of para-aortic lymph node metastasis for prognosis in patients with pancreaticobiliary cancer who underwent radical surgical resections. *Turk J Surg.* 2025;41(1):5-18

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**Received:** 07.12.2024
**Accepted:** 22.01.2025
**Publication Date:** 27.02.2025

**DOI:** 10.47717/turkjsurg.2025.6587

Available at www.turkjsurg.com

determine whether to continue the scheduled operation. It is critical to decide whether to recognize PALN metastasis as a systemic or localized disease. The decision-making process regarding the radical resection of pancreaticobiliary cancer with PALN metastasis, is crucial for hepatobiliary-pancreas surgeons. Therefore, an intraoperative histological diagnosis using frozen specimen tissue was performed. However, the clinical significance of this modality in influencing postoperative survival remains unclear. We hypothesize that radical surgery is worthwhile when occult solitary PALN metastasis is first diagnosed using intraoperative PALN node sampling.

To clarify our hypothesis and to determine the institutional strategy for radical surgical resection in cases where a solitary cancer-positive lymph node is observed, we retrospectively examined the postoperative survival of patients with pancreatic and bile duct cancer with or without PALN metastasis who underwent radical resections at two institutes, performed consecutively by the principal author as chief staff, between 1994 and 2021. Additionally, clinicopathological factors associated with PALN were analyzed. The findings of this paper will refer to the mentioned institutional strategy and suggest that they have implications for general practice.

## MATERIAL and METHODS

### Patients

Either all patients included or only those treated by the authors, were consecutively examined. This study retrospectively collected data on 144 consecutive patients with pancreatic carcinoma (PC) (n=82) and bile duct carcinoma (BDC) (n=62) at the Division of Surgical Oncology, Department of Translational Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences (NUGSBS), who were treated by the first author between April 1994 and March 2015. Other data were obtained from 153 consecutive patients with PBC (PC, n=99 and BDC, n=54), who were treated by the first author, at the Division of Hepatobiliary Pancreatic Surgery, Department of Surgery, University of Miyazaki Faculty of Medicine (UoM) between April 2015 and December 2021. The first author has mainly managed and organized all patients during the study period. The in-hospital data of all patients were retrospectively and consecutively collected from the patient charts at the two institutions. The study design was approved by the Ethics Review Board of NUGSBS and UoM (approval numbers: #24031804, March 19, 2024, and #O-1503, January 24, 2024), and patients' consent was confirmed via an opt-out procedure. This was done through a public announcement at an outpatient clinic and on our institutional website, according to our ethical policy, for a month. No financial support was received for this study, and the authors declare no conflicts of interest. This study adhered to the Declaration of Helsinki's statement on the ethical principles for medical research involving human participants, including research on identifiable human materials and data.

Data were retrieved from both the anesthetic and patient electronic charts and the NUGSBS and UoM databases for the duration of initial hospitalization following radical operations.

Serum levels of carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19-9 were measured as tumor markers for PC and BDC before and after the primary treatment every three months. Enhanced computed tomography of the liver was performed every six months after hepatectomy to monitor tumor recurrence. The minimum follow-up period after hepatic resection in patients with BDC who survived was 26 months (range, 12–128 months). The patient outcomes and recurrence or survival information were confirmed during examinations at the outpatient clinic, through periodic reports from other facilities, and via entries in electronic medical records at both institutes. With this information, patient outcomes were determined based on the data collected by the co-author investigators.

If the radiologist of PALN had pointed out the lymph node metastasis, we would not have selected radical operation according to our policy. Preoperative cancer-related contraindications of radical resection are 1) the existence of extra-regional lymph nodes, including PALN swelling over 10 mm with enhancement, diagnosed as distant node metastases by computed tomography, 2) distant organ metastases, 3) cancer invasion to main hepatic arteries and superior mesenteric artery trunk, and 4) the existence of peritoneal dissemination. The preoperative boundary criteria for radical operation is 1) a unilateral abutment (<180 degrees) of soft tissue density from primary cancer to the arterial trunk and 2) extra-regional lymph node (RLN) swelling less than 10 mm. During the operation, the paraaortic regional dissection of surrounding tissues of PALN at the dorsal part of the pancreatic head was performed when the occult solitary PALN metastasis was observed, to detect any other occult PALN metastases. If multiple suspicious nodes of PALN metastasis were macroscopically found, we would not have continued the scheduled radical operations in such cases.

### Comparative Measurement of Tumor Markers and Histological Findings Before Surgery

Patient clinicopathological data were retrieved from the archives of our institute. Peripheral blood samples were collected from each patient early in the morning before surgery when the patient was stable. In our hospital, the normal levels of CEA, CA19-9, and Duke Pancreas II monoclonal antibody (DUPAN-II) (7) in patients were <5 ng/mL, <37 U/mL, and <150 U/mL, respectively, and elevated levels were defined as those exceeding these thresholds. Tumor-related factors were compared with the histopathological findings of the resected specimen. For the clinicopathological assessment of PC and BDC, we used the 7$^{th}$ edition of General Rules for the Study of Pancreatic Cancer by the Japan Pancreas Society (8) and the 7$^{th}$ edition of General Rules for

Clinical and Pathological Studies on Cancer of the Biliary Tract by the Japanese Society of Hepato-Biliary-Pancreatic Surgery (9).

### Statistical Analysis

For the first survival analyses, univariate and multivariate analyses were performed using the Cox proportional hazards regression model. Disease-free intervals and overall survival were calculated using the Kaplan-Meier method, and differences between groups were tested for significance using the log-rank test (Figures 1, 2). A log-rank regression analysis test was performed to determine independent risk factors, and a 95% confidence interval was indicated for each (Tables 1, 2). A two-tailed p-value of <0.05 was considered significant.

For the comparisons of clinicopathological parameters, and RLV and PALN metastasis, differences in categorical data between the groups and prevalence were assessed using the chi-square test, Fisher's exact test, or Dunnett's multiple comparisontest

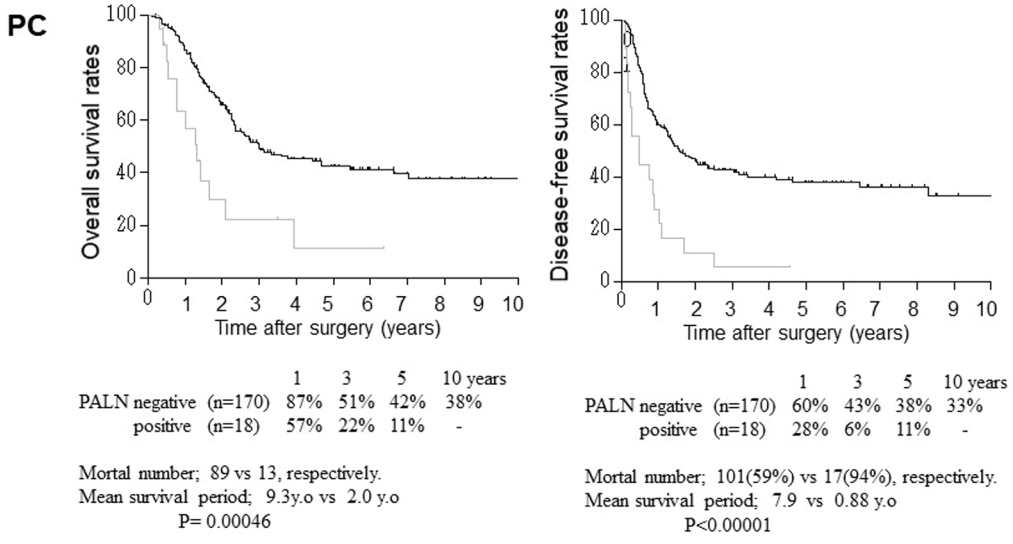


**Figure 1.** Overall (OS) and disease-free survival (DFS) in patients with pancreatic cancer (PC) with or without para-aortic lymph node (PALN) metastasis. The Kaplan-Meier survival curves and log-rank test. Survival rates in each year, number of cancer deaths, and mean survival periods (months) were compared between patients with PALN metastasis and those without PALN metastasis.

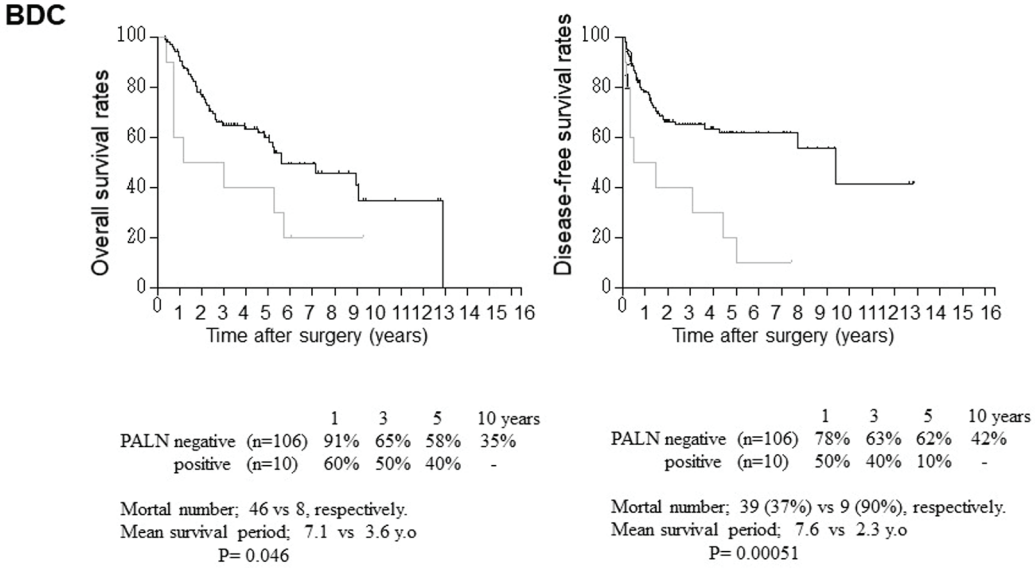


**Figure 2.** Overall (OS) and disease-free survival (DFS) in patients with bile duct cancer (BDC) with or without para-aortic lymph node (PALN) metastasis. The Kaplan-Meier survival curves and log-rank test. Survival rates in each year, number of cancer deaths, and mean survival periods (months) were compared between patients with and without PALN metastasis.

**Table 1.** Cox's proportional hazard analysis for patient prognosis in PC undergoing surgical resection (n=181)
**a) Overall survival**

| | Univariate analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | **Probability (p-value)** | **Risk ratio** | **95% CI Lower-upper** | **Probability (p-value)** | **Risk ratio** | **95% CI Lower-upper** |
| Age, >70 years (n=112) | 0.983 | 0.995 | 0.651-1.521 | | | |
| Sex, female (n=81) | 0.428 | 1.172 | 0.792-1.735 | | | |
| CEA, >5 ng/mL (n=32) | 0.706 | 1.099 | 0.672-1.797 | | | |
| CA199, >37 U/mL (n=147) | 0.004 | 1.800 | 1.212-2.674 | 0.419 | 1.211 | 0.761-1.926 |
| DUPAN-II, >150 U/mL (n=21) | 0.143 | 1.504 | 0.871-2.597 | | | |
| NAC, yes (n=9) | 0.021 | 0.459 | 0.237-0.887 | 0.003 | 0.269 | 0.114-0.641 |
| PD, yes[1] (n=117) | 0.015 | 1.711 | 1.111-2.637 | 0.076 | 1.760 | 0.942-3.288 |
| Morphology, invasive[2] (n=105) | 0.004 | 1.489 | 1.138-1.949 | 0.075 | 0.693 | 0.462-1.038 |
| Tumor size, >2 cm (n=165) | 0.101 | 1.485 | 0.925-2.383 | | | |
| Differentiation, | | | | | | |
| Moderately or poorly[3] (n=102) | 0.000 | 2.837 | 1.768-4.555 | 0.004 | 2.442 | 1.326-4.499 |
| Histologic infiltration, yes | | | | | | |
| Lymphatic (n=101) | 0.000 | 3.289 | 2.094-5.166 | 0.028 | 1.967 | 1.077-3.594 |
| Venous (n=131) | 0.000 | 4.582 | 2.365-8.876 | 0.824 | 0.824 | 0.320-2.122 |
| Perineural (n=129) | 0.000 | 4.036 | 2.339-6.964 | 0.005 | 2.841 | 1.376-5.865 |
| Tumor involvement, yes | | | | | | |
| Retroperitoneal (n=101) | 0.000 | 2.145 | 1.400-3.287 | 0.662 | 0.878 | 0.489-1.574 |
| Choledochal (n=60) | 0.004 | 1.653 | 1.178-2.321 | 0.259 | 0.736 | 0.432-1.253 |
| Duodenal (n=54) | 0.000 | 1.781 | 1.363-2.326 | 0.105 | 1.395 | 0.932-2.088 |
| Portal vein (n=43) | 0.005 | 1.879 | 1.208-2.922 | 0.199 | 1.461 | 0.820-2.604 |
| Node metastasis, yes | | | | | | |
| **Regional (RLN) (n=98)** | 0.000 | 3.325 | 2.162-5.113 | 0.167 | 1.481 | 0.849-2.582 |
| **Para-aortic (PALN) (n=17)** | 0.004 | 2.447 | 1.332-4.493 | 0.234 | 1.597 | 0.739-3.449 |
| Cancer positive at surgical margin, | | | | | | |
| Proximal bile duct (n= 5) | 0.022 | 3.874 | 1.212-12.385 | 0.069 | 3.268 | 0.912-11.704 |
| Exposed area (n=14) | 0.000 | 4.966 | 2.572-9.591 | 0.041 | 2.483 | 1.036-5.948 |
| Histological curability, R1 (n=8) | 0.011 | 2.208 | 1.197-4.072 | 0.632 | 1.195 | 0.576-2.480 |
| Adjuvant chemotherapy,[4] yes (n=74) | 0.686 | 1.085 | 0.731-1.609 | | | |
| Chemotherapy for cancer recurrence, yes (n=60) | 0.770 | 1.063 | 0.706-1.599 | | | |

(Tables 3, 4). Differences in continuous data between groups were evaluated using the Student's t-test or the Mann-Whitney U test Tables 3, 4. Furthermore, parameters with a significance of p-value <0.05 by the univariate analysis were used in the multivariate analysis for associating RLN and PALN metastasis. Statistical analyses were performed using the SPSS software version 23 (Statistical Package for the Social Sciences, Inc., Chicago, IL, USA).

## RESULTS

### Perioperative Parameters

The basic patient data of 181 PC patients are summarized as follows: A mean age of 68.1±9.4 years at the time of surgery. The mean CEA, CA19-9, and DUPAN-II levels were 10.8±60.5 ng/mL (median 2.6), 509±1.732 U/mL (median 62), and 591±1.605 U/mL (median 92), respectively. The mean tumor size was 3.2±1.7 cm. The mean blood loss was 0.560±1.018 mL (median 1.120 mL). All patients underwent complete macroscopic radical resection without remnant cancer. The final histological curability was classified as R0 in 171 (95%) patients, R1 in 8 (4%), and R2 in 2 (1%). RLN and PALN metastases were observed in 98 (54%) and 17 patients (9%), respectively. Cancer recurred in 117 patients (65%) after surgery. The recurrence was observed in the liver in 61 patients, lymph nodes in 19, lungs in 24, local in 13, peritoneum in 16, bone in 4, and remnant pancreas in 6. All patients except those who experienced recurrence in the

**Table 1b)** Cancer-free survival

| | Univariate analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | Probability (p-value) | Risk ratio | 95% CI Lower-upper | Probability (p-value) | Risk ratio | 95% CI Lower-upper |
| Age, >70 years | 0.936 | 1.016 | 0.690-1.496 | | | |
| Sex, female | 0.279 | 1.222 | 0.850-1.757 | | | |
| CEA, >5 ng/mL | 0.440 | 1.188 | 0.767-1.842 | | | |
| CA199, >37 U/mL | 0.001 | 1.911 | 1.324-2.759 | 0.258 | 1.279 | 0.835-1.960 |
| DUPAN-II, >150 U/mL | 0.119 | 1.501 | 0.901-2.501 | | | |
| NAC, yes | 0.051 | 0.232 | 0.061-1.020 | | | |
| PD, yes | 0.461 | 1.155 | 0.788-1.693 | 0.801 | 1.078 | 0.600-1.937 |
| Blood loss, >1500 mL | 0.098 | 1.788 | 0.897-2.033 | | | |
| Morphology, invasive | 0.000 | 1.609 | 1.243-2.082 | 0.389 | 0.839 | 0.562-1.251 |
| Tumor size, >2 cm | 0.540 | 1.139 | 0.752-1.752 | | | |
| Differentiation, | | | | | | |
| Moderately or poorly | 0.000 | 2.860 | 1.858-4.403 | 0.005 | 2.195 | 1.271-3.789 |
| Infiltration, yes | | | | | | |
| Lymph duct | 0.000 | 3.726 | 2.417-5.746 | 0.062 | 1.727 | 0.973-3.065 |
| Venous | 0.000 | 4.358 | 2.425-7.835 | 0.870 | 1.068 | 0.486-2.349 |
| Perineural | 0.000 | 3.654 | 2.286-5.841 | 0.013 | 2.206 | 1.180-4.121 |
| Tumor involvement, yes | | | | | | |
| Retroperitoneal | 0.000 | 2.853 | 1.885-4.320 | 0.970 | 1.011 | 0.578-1.768 |
| Choledochal | 0.033 | 1.404 | 1.029-1.917 | 0.131 | 0.674 | 0.404-1.125 |
| Duodenal | 0.000 | 2.018 | 1.520-2.679 | 0.051 | 1.522 | 0.997-2.322 |
| Portal vein | 0.007 | 1.762 | 1.168-2.658 | 0.570 | 1.173 | 0.676-2.036 |
| Node metastasis, yes | | | | | | |
| **Regional (RLN)** | 0.000 | 3.705 | 2.460-5.580 | 0.110 | 1.536 | 0.908-2.600 |
| **Para-aortic (PALN)** | 0.004 | 2.779 | 1.632-4.731 | 0.198 | 1.578 | 0.788-3.158 |
| Cancer positive at surgical margin, | | | | | | |
| Proximal bile duct | 0.041 | 3.337 | 1.052-10.588 | 0.217 | 2.209 | 0.627-7.785 |
| Exposed area | 0.000 | 4.838 | 2.684-8.721 | 0.101 | 2.049 | 0.870-4.823 |
| Curability, R1 | 0.010 | 2.146 | 1.199-3.842 | 0.749 | 1.133 | 0.527-2.440 |
| Adjuvant chemotherapy, yes | 0.360 | 0.840 | 0.579-1.219 | 0.099 | 0.670 | 0.416-1.078 |
| Chemotherapy for cancer recurrence, yes | 0.001 | 1.862 | 1.283-2.702 | 0.077 | 1.539 | 0.954-2.485 |

CI: Confidence interval, CEA: Carcinoembryonic antigen, CA19-9: Cancer antigen-19-9, DUPAN-II: Duke pancreatic mono-clonal antigen type 2, NAC: Neoadjuvant chemotherapy by gemcitabine+S-1, PD: Pancreaticoduodenectomy, R1: Histologically cancer positive at the cutting edge of specimens
[1]: Otherwise, distal pancreatectomy in 60, and total pancreatectomy in 4.
[2]: Otherwise, nodular type in 46, cystic type in 28, and dilated main duct type in 2 patients.
[3]: Otherwise, papillary in 3, well in 37, mucinous in 2, acinar in 4, adenosquamous in 2, anaplastic in 2, unknown in 29 patients
[4]: Six months after surgery as S-1 alone

remnant pancreas underwent chemotherapy. Three of the six patients with recurrence in the remnant pancreas underwent total pancreatectomy. Of the 181 patients, 50 survived without cancer recurrence (28%), 22 with cancer recurrence (12%), 94 died of cancer (52%), and 15 died of other diseases without cancer recurrence (8%); thus, 87 patients (48%) were censored.

The basic patient data of the BDC cohort (116 patients) were described as follows: A mean age of 68.5±11.4 years at the time of surgery. Distal BDCs were observed in 68 patients (59%), and proximal BDCs were observed in 48 patients. The mean CEA and CA19-9 levels were 5.1±18.9 ng/mL (median 2.4) and 2.815±25,639 U/mL (median 37), respectively. The mean tumor size was 1.9±1.7 cm (median 1.6 cm). Pancreaticoduodenectomy was performed in 78 patients (68%), hepatectomy in 45 patients (39%), and hepato pancreaticoduodenectomy in 7 patients. All patients underwent complete macroscopic radical resection

**Table 2.** Cox's proportional hazard analysis for patient prognosis in BDC undergoing surgical resection (n=116)
**a) Overall survival**

| | Univariate analysis | | | Multivariable analysis | | |
|---|---|---|---|---|---|---|
| | **Probability (p-value)** | **Risk ratio** | **95% CI Lower-upper** | **Probability (p-value)** | **Risk ratio** | **95% CI Lower-upper** |
| Age, >70 years (n=75) | 0.052 | 0.564 | 0.316-1.006 | | | |
| Sex, female (n=31) | 0.984 | 1.003 | 0.739-1.362 | | | |
| Jaundice, yes (n=85) | 0.115 | 1.740 | 0.874-3.466 | | | |
| CEA, >5 ng/mL (n=10) | 0.040 | 2.128 | 1.034-4.379 | 0.660 | 1.280 | 0.427-3.839 |
| CA19-9, >37 U/mL (n=109) | 0.005 | 2.222 | 1.272-3.883 | 0.003 | 3.325 | 1.103-10.019 |
| Cholangitis of bile duct, yes (n=29) | 0.026 | 2.042 | 1.087-3.835 | 0.495 | 1.398 | 0.535-3.652 |
| PBMJ, yes (n=4) | 0.002 | 5.256 | 1.834-15.068 | 0.672 | 0.776 | 0.239-2.517 |
| Blood loss, >1500 mL (n=26) | 0.008 | 2.163 | 1.220-3.836 | 0.051 | 2.817 | 0.996-7.968 |
| Morphology, invasive[1] (n=97) | 0.150 | 1.974 | 0.781-4.989 | | | |
| Tumor size, >2 cm (n=31) | 0.229 | 1.438 | 0.795-2.603 | | | |
| Differentiation,[2] | | | | | | |
| Moderately or poorly (n=52) | 0.056 | 1.712 | 0.986-2.975 | | | |
| Infiltration, yes | | | | | | |
| Lymph duct (n=73) | 0.008 | 2.390 | 1.252-4.561 | 0.025 | 4.042 | 1.191-13.718 |
| Venous (n=77) | 0.001 | 3.640 | 1.711-7.744 | 0.025 | 5.290 | 1.240-22.71 |
| Perineural (n=78) | 0.000 | 5.376 | 2.290-12.619 | 0.004 | 7.529 | 1.930-29.374 |
| Depth, beyond subserosa[3] | 0.000 | 2.283 | 1.452-3.590 | 0.654 | 1.195 | 0.548-2.604 |
| Organ invasion, yes | | | | | | |
| Liver (n=21) | 0.710 | 1.096 | 0.676-1.776 | | | |
| Gallbladder (n=6) | 0.257 | 1.276 | 0.837-1.946 | | | |
| Pancreas (n=47) | 0.026 | 1.696 | 1.066-2.699 | 0.169 | 2.012 | 0.743 -5.449 |
| Duodenum (n=18) | 0.416 | 1.350 | 0.655-2.780 | | | |
| Vascular invasion, yes | | | | | | |
| Portal vein (n=9) | 0.002 | 2.215 | 1.340-3.660 | 0.864 | 1.188 | 0.166-8.506 |
| hepatic artery (n=2) | 0.046 | 2.532 | 1.017-6.301 | 0.922 | 1.152 | 0.068-19.435 |
| Node metastasis, yes | | | | | | |
| **Regional (RLN) (n=45)** | 0.003 | 2.254 | 1.310-3.877 | 0.255 | 1.625 | 0.705-3.745 |
| **Para-aortic (PALN) (n=10)** | 0.049 | 2.215 | 1.010-4.614 | 0.049 | 6.896 | 1.008-61.629 |
| Cancer positive at surgical margin | | | | | | |
| Proximal bile duct (n=23) | 0.080 | 1.643 | 0.943-2.862 | | | |
| Exposed area (n=10) | 0.000 | 7.039 | 3.205-15.458 | 0.006 | 18.114 | 2.339-140.733 |
| Distal bile duct (n=18) | 0.348 | 1.611 | 0.595-4.361 | | | |
| Histological curability, R1 (n=18) | 0.005 | 2.156 | 1.259-3.691 | 0.140 | 2.851 | 0.708-11.473 |
| Adjuvant chemotherapy, yes[4] (n=33) | 0.078 | 1.632 | 0.947-2.811 | | | |
| Chemotherapy for cancer recurrence, yes (n=48) | 0.000 | 3.158 | 1.821-5.477 | 0.000 | 5.438 | 2.400-12.320 |

without remnant cancer. RLN and PALN metastases were observed in 45 (39%) and 10 patients (9%), respectively. The final histological curability by surgery was classified as R0 in 98 patients (85%), R1 in 18 (15%), and R2 in none. Postoperative complications of Clavien-Dindo classification greater than II were observed in 65 patients (56%). Adjuvant chemotherapy, administered over six months, after surgery, as S-1 alone or as a gemcitabine-cisplatin combination, was administered in 33 patients (28%). Cancer recurrence was observed in 48 patients (41%) after surgery; in the liver in 23 patients, lymph node in 8, lung in 5, local in 12, peritoneum in 12, and bone in 1 patient. Out of the 116 patients, 50 survived without cancer recurrence

| **Table 2b)** Cancer-free survival | | | | | | |
|---|---|---|---|---|---|---|
| | **Univariate analysis** | | | **Multivariable analysis** | | |
| | **Probability (p-value)** | **Risk ratio** | **95% CI Lower-upper** | **Probability (p-value)** | **Risk ratio** | **95% CI Lower-upper** |
| Age, >70 years | 0.048 | 0.544 | 0.298-0.994 | 0.010 | 3.662 | 1.370-3.661 |
| Sex, female | 0.563 | 0.905 | 0.645-1.270 | | | |
| Jaundice, yes | 0.126 | 1.765 | 0.853-3.652 | | | |
| CEA, >5 ng/mL | 0.105 | 1.854 | 0.979-3.909 | | | |
| CA199, >37 U/mL | 0.145 | 1.561 | 0.858-2.838 | | | |
| Cholangitis of the proximal bile duct, yes | 0.008 | 2.368 | 1.248-4.491 | 0.481 | 1.427 | 0.531-3.836 |
| PBMJ, yes | | | | | | |
| Blood loss, >1500 mL | 0.059 | | | | | |
| Morphology, invasive | 0.056 | | | | | |
| Tumor size, >2 cm | 0.100 | | | | | |
| Differentiation, | 0.118 | | | | | |
| Moderately or poorly | | | | | | |
| Histologic infiltration, yes | 0.019 | 1.996 | 1.118-3.565 | 0.110 | 2.027 | 1.143-9.831 |
| lymphatic | | | | | | |
| venous | 0.009 | 2.485 | 1.255-4.922 | 0.028 | 3.352 | 1.560-8.792 |
| perineural | 0.071 | 2.760 | 1.323-5.759 | | | |
| Depth, beyond subserosa | 0.001 | 4.165 | 1.845-9.403 | 0.350 | 1.704 | 0.557-5.216 |
| Organ invasion, yes | 0.000 | 2.646 | 1.618-4.326 | 0.879 | 0.939 | 0.418-2.109 |
| Liver | | | | | | |
| Gallbladder | 0.863 | 0.952 | 0.545-1.665 | | | |
| Pancreas | 0.169 | 1.368 | 0.875-2.138 | | | |
| Duodenum | 0.007 | 2.022 | 1.214-3.368 | 0.097 | 2.585 | 0.842-7.934 |
| Vascular invasion, yes | 0.210 | 1.597 | 0.769-3.317 | | | |
| Portal vein | | | | | | |
| Hepatic artery | 0.001 | 2.916 | 1.536-5.535 | 0.836 | 1.218 | 1.258-6.765 |
| Node metastasis, yes | 0.002 | 4.998 | 1.813-13.781 | 0.321 | 3.971 | 0.140-2.383 |
| **Regional (PLN)** | | | | | | |
| **Para-aortic (PALN)** | 0.000 | 3.166 | 1.769-5.667 | 0.013 | 2.917 | 1.258-6.765 |
| Cancer positive at surgical margin | 0.001 | 3.373 | 1.626-6.999 | 0.447 | 0.577 | 0.140-2.383 |
| Proximal bile duct | | | | | | |
| Exposed area | 0.221 | 1.477 | 0.791-2.757 | | | |
| Distal bile duct | 0.000 | 4.789 | 2.181-10.516 | 0.242 | 2.551 | 0.530-12.260 |
| Histological curability, R1 | 0.596 | 1.300 | 0.493-3.425 | | | |
| Adjuvant chemotherapy, yes | 0.048 | 1.921 | 1.003-3.024 | 0.049 | 2.763 | 1.005-7.597 |
| Chemotherapy for cancer recurrence, yes | 0.249 | 1.632 | 0.786-2.530 | | | |
| | 0.000 | 5.735 | 3.147-10.450 | 0.000 | 12.944 | 4.640-36.104 |

CI: Confidence interval, CEA: Carcinoembryonic antigen, CA19-9: Cancer antigen-19-9, DUPAN-II: Duke pancreatic mono-clonal antigen type 2, NAC: Neoadjuvant chemotherapy by gemcitabine+S-1, PD: Pancreaticoduodenectomy, R1: Histologically cancer positive at the cutting edge of specimens,
[1)]: Otherwise, papillary, nodular, or flat type without invasiveness in 19 patients
[2)]: Otherwise, papillary in 14, well in 49, unknown in 1 patient
[3)]: Mucosal in 17 patients, subserosal in 60, serosal in 23, and extraserosal in 16
[4)]: S-1 alone (n=30) or gemcitabine-cisplatin combination (n=3) for 6 months

**Table 3.** Relationship between clinicopathological factors and regional or para-aortic lymph node metastasis in PC

**a) Univariate analysis**

| | RLN metastasis | | Probability | PALN metastasis | | Probability |
|---|---|---|---|---|---|---|
| | Negative (n=83) | Positive (n=98) | (p-value) | Negative (n=164) | Positive (n=17) | (p-value) |
| Age (years) | 69.3±8.8 | 67.0±9.9 | 0.190 | 68.5±9.4 | 64.0±9.2 | 0.103 |
| Gender, Male/female | 47/36 | 44/54 | 0.846 | 91/73 | 9/8 | 1.0 |
| CEA (ng/mL) | 14.6±86.5 | 7.7±24.1 | 0.884 | 6.8±20.5 | 50.6±189.8 | 0.886 |
| CA199 (U/mL) | 449±2280 | 557±1130 | <0.001 | 406±982 | 1473±4710 | 0.115 |
| DUPAN-II (U/mL) | 543±2018 | 630±1188 | 0.004 | 569±1685 | 778±620 | 0.0012 |
| Neoadjuvant chemotherapy, no/yes | 78/5 | 93/4 | 0.810 | 92/72 | 13/4 | 0.056 |
| Operation, DP/ PD/ TP | 36/44/3 | 24/73/1 | 0.009 | 56/106/2 | 4/13/0 | 0.588 |
| Morphology, Nodular/mixed/invasive/cystic/MPD | 14/1/40/26/2 | 27/1/68/2/0 | <0.001 | 36/1/97/28/2 | 5/1/10/0/0 | 0.106 |
| Histological differentiation, Papillary/ well/moderately/poorly/other | 1/19/52/5/6 | 1/23/58/12/4 | 0.379 | 2/39/90/23/10 | 1/5/9/2/0 | 0.887 |
| Tumor size (cm) | 3.16±2.20 | 3.26±1.23 | 0.024 | 3.17±1.78 | 3.74±1.21 | 0.067 |
| Tumor infiltration, no/yes | | | | | | |
| Lymphatic duct | 55/28 | 19/79 | <0.001 | 73/91 | 1/16 | 0.125 |
| Venous | 37/46 | 8/90 | <0.001 | 45/119 | 1/16 | 0.126 |
| Perineural | 36/47 | 10/88 | <0.001 | 43/121 | 2/15 | 0.0047 |
| Extra-pancreatic involvement, no/yes | | | | | | |
| Retro-pancreatic | 55/28 | 21/77 | <0.001 | 75/89 | 0/17 | <0.001 |
| Choledochal | 69/14 | 51/47 | <0.001 | 113/51 | 6/11 | 0.038 |
| Duodenal | 73/10 | 54/44 | <0.001 | 116/48 | 10/7 | 0.436 |
| Portal vein | 70/13 | 67/31 | 0.022 | 126/38 | 10/7 | 0.332 |
| **PALN metastasis, no/yes** | 81/2 | 83/15 | 0.0037 | - | - | - |
| Histological curability R, 0/ 1 | 82/1 | 91/7 | 0.062 | 156/8 | 17/0 | <.001 |
| Adjuvant chemotherapy, no/yes | 48/35 | 59/39 | 0.864 | 92/72 | 15/2 | 0.021 |
| Cancer recurrence, no/yes | 49/34 | 15/83 | <0.001 | 63/101 | 1/16 | 0.016 |
| Recurrence-free survival (days) | 1385±472 | 472±553 | <0.001 | 948±1129 | 333±416 | <0.002 |
| Overall survival (days) | 1599±1275 | 815±802 | <0.001 | 1235±1139 | 595±582 | 0.0028 |

**b) Multivariate logistic regression analysis**

| | PLN | | | | PALN | | | |
|---|---|---|---|---|---|---|---|---|
| | Probability p-value | Odds ratio | 95% CI lower | 95% CI upper | Probability p-value | Odds ratio | 95% CI lower | 95% CI upper |
| Op., PD | 0.363 | 0.260 | 0.014 | 4.719 | | | | |
| CA199, >37 U/mL | 0.957 | 1.028 | 0.377 | 2.801 | | | | |
| Dupan-II, >150 u/mL | 0.598 | 1.000 | 1.000 | 1.000 | 0.023 | 4.921 | 1.243 | 19.475 |
| Morphology, invasive | 0.261 | 1.614 | 0.701 | 3.719 | | | | |
| Size, >20 mm | 0.406 | 1.637 | 0.511 | 5.244 | | | | |
| Lymphatic invasion | 0.089 | 2.483 | 0.872 | 7.070 | | | | |
| Venous invasion | 0.884 | 0.887 | 0.176 | 4.458 | | | | |
| Perineural invasion | 0.104 | 3.222 | 0.786 | 13.217 | 0.141 | 0.2807 | 0.025 | 1.689 |
| Extra-pancreatic involvement Retro-pancreatic | 0.080 | 2.681 | 0.888 | 8.091 | 0.997 | 5.760 | 0.001 | 16.355 |
| Choledochal | 0.383 | 1.654 | 0.535 | 5.114 | 0.226 | 2.380 | 0.585 | 9.673 |
| Duodenal | 0.189 | 2.376 | 0.654 | 8.627 | | | | |
| **PALN metastasis, yes** | 0.502 | 1.889 | 0.295 | 12.106 | | | | |

DP: Distal pancreatectomy, TP: Total pancreatectomy, CI: Confidence interval, CEA: Carcinoembryonic antigen, CA19-9: Cancer antigen-19-9, DUPAN-II: Duke pancreatic mono-clonal antigen type 2, NAC: Neoadjuvant chemotherapy by gemcitabine+S-1, PD: Pancreaticoduodenectomy

**Table 4.** Relationship between clinicopathological factors and regional or para-aortic lymph node metastasis in BDC

**a) Univariate analysis**

| | **RLN metastasis** | | **Probability** | **PALN metastasis** | | **Probability** |
|---|---|---|---|---|---|---|
| | **Negative (n=71)** | **Positive (n=45)** | **(p-value)** | **Negative (n=106)** | **Positive (n=10)** | **(p-value)** |
| Age (years) | 69.8±10.6 | 66.4±12.3 | 0.092 | 69.5±10.2 | 58.2±17.3 | 0.027 |
| Gender, male/female | 55/16 | 30/15 | 0.286 | 79/27 | 6/4 | 0.454 |
| Total bilirubin (mg/dL) | 1.49±2.40 | 1.45±1.39 | 0.120 | 1.51±2.14 | 1.10±0.40 | 0.593 |
| Alkaline phosphatase (U/mL) | 475±438 | 634±540 | 0.037 | 521±477 | 702±562 | 0.196 |
| CEA (ng/mL) | 6.0±24.3 | 3.8±3.6 | 0.089 | 5.3±19.8 | 3.0±2.2 | 0.928 |
| CA199 (U/mL) | 4394±33262 | 502±995 | 0.0019 | 3075±26940 | 324±729 | 0.310 |
| Jaundice, no/yes | 20/51 | 10/35 | 0.677 | 28/78 | 3/7 | 0.713 |
| PBMJ, no/yes | 69/2 | 43/2 | 1.0 | 103/3 | 9/1 | 0.809 |
| Operation, PD/HPD/Hepatectomy<br>Morphology, Papillary/nodular/invasive/IPNB | 44/4/23<br>15/31/24/1 | 26/7/12<br>3/6/36/0 | 0.238<br>0.300 | 66/7/33<br>17/7/81/1 | 4/4/2<br>0/0/10/0/0 | 0.0092<br>0.362 |
| Cholangitis of the proximal bile duct, no/yes | 52/19 | 31/14 | 0.484 | 81/25 | 6/4 | 0.078 |
| Histological differentiation, papillary/well/moderately/poorly/other | 12/31/19/9 | 2/19/19/5 | 0.134 | 13/43/36/14 | 1/5/3/1/0 | 0.535 |
| Tumor size (cm) | 1.56±1.55 | 2.34±1.69 | 0.036 | 1.72±1.57 | 3.54±1.62 | 0.0006 |
| Depth of invasion, m,fm/ss/se/si | 16/35/12/8 | 1/23/13/8 | 0.056 | 15/49/21/13 | 0/5/2/3 | 0.252 |
| Tumor infiltration, no/yes<br>Lymphatic duct<br>Venous<br>Perineural | <br>37/34<br>31/40<br>30/41 | <br>5/40<br>6/39<br>6/39 | <br><0.001<br>0.001<br>0.002 | <br>41/65<br>37/69<br>35/71 | <br>0/10<br>0/10<br>1/9 | <br>0.033<br>0.052<br>0.238 |
| Extra-pancreatic involvement, no/yes<br>Liver<br>Gallbladder<br>Pancreas<br>Duodenum<br>Portal vein<br>Hepatic artery | <br>63/8<br>68/3<br>52/19<br>63/8<br>68/3<br>70/1 | <br>38/7<br>43/2<br>19/26<br>3510<br>39/6<br>44/1 | <br>0.017<br>0.055<br>0.0005<br>0.196<br>0.163<br>0.333 | <br>87/19<br>104/2<br>67/39<br>88/18<br>100/6<br>104/2 | <br>6/4<br>6/4<br>3/7<br>10/0<br>7/3<br>10/0 | <br>0.201<br><0.001<br>0.029<br>0.358<br>0.011<br>0.907 |
| Number of node metastasis | 0.82±4.09 | 1.94±1.56 | <0.001 | 1.17±3.59 | 1.96±2.22 | 0.226 |
| **PALN metastasis, no/yes** | 69/2 | 37/8 | 0.0139 | - | - | - |
| Cancer positive at cutting edge, no/yes<br>Bile duct<br>Exposed area | <br>58/13<br>68/3 | <br>35/10<br>38/7 | <br>0.578<br>0.079 | <br>87/19<br>100/6 | <br>6/4<br>6/4 | <br>0.202<br>0.002 |
| Histological curability, R, 0/1 | 57/14 | 30/15 | 0.212 | 82/24 | 4/6 | 0.029 |
| Cancer recurrence, no/yes | 49/34 | 15/83 | <0.001 | 67/39 | 1/9 | 0.00034 |
| Recurrence-free survival (days) | 14195±1105 | 787±942 | <0.001 | 1203±1096 | 836±941 | 0.171 |
| Overall survival (days) | 1605±1083 | 1059±943 | 0.0014 | 1411±1058 | 1206±1132 | 0.400 |

| b) Multivariate logistic regression analysis | | | | | | | |
|---|---|---|---|---|---|---|---|
| | RLN metastasis | | | PALN metastasis | | | |
| | Probability p-value | 95% CI lower | 95% CI upper | Probability p-value | Odds ratio | 95% CI lower | 95% CI upper |
| Age, >70 | | | | 0.161 | 0.182 | 0.017 | 1.969 |
| ALP, >400 U/mL | 0.694 | 0.221 | 2.731 | | | | |
| CA199, >37 U/mL | 0.177 | 0.680 | 8.084 | | | | |
| Size, >20 mm<br>Operation, PD | 0.876 | 0.292 | 4.241 | 0.156<br>0.286 | 4.380<br>4.345 | 0.569<br>0.292 | 33.702<br>64.649 |
| Lymphatic invasion | 0.016 | 1.376 | 22.468 | 0.997 | 2.512 | 0.001 | 100.678 |
| Venous invasion | 0.361 | 0.104 | 2.282 | | | | |
| Perineural invasion | 0.032 | 1.152 | 22.523 | | | | |
| Organ involvement<br>Liver<br>Gallbladder<br>Pancreas<br>Portal vein | 0.026<br>0.002 | 2.123<br>3.455 | 24.448<br>42.159 | <br>0.290<br>0.143<br>0.204 | <br>3.325<br>7.843<br>2.788 | <br>0.359<br>0.497<br>0.573 | <br>30.797<br>123.835<br>13.560 |

PBMJ: Pancreaticobiliary maljunction, HPD: Hepato-pancreaticoduodenectomy, DP: Distal pancreatectomy, TP: Total pancreatectomy, CI: Confidence interval, CEA: Carcinoembryonic antigen, CA19-9: Cancer antigen-19-9, DUPAN-II: Duke pancreatic mono-clonal antigen type 2, NAC: Neoadjuvant chemotherapy by gemcitabine+S-1, PD: Pancreaticoduodenectomy

(43%), 13 survived with cancer recurrence (11%), 43 died of cancer (37%), and 10 died of other diseases without cancer recurrence (9%); therefore, 73 patients (63%) were censored.

### Relationship Between Clinicopathological Parameters and Disease-free and Overall Survival After Surgery

Figure 1 illustrates that the disease-free survival (DFS) and overall survival (OS) of patients with paraaortic lymph node (PALN) metastasis was significantly lower than for those without PALN involvement; however, three patients survived for more than three years. Figure 2 demonstrates that the DFS and OS of patients with BDC and PALN metastasis were significantly lower than those without PALN, however, five patients survived for greater than 3 years. To clarify the influence of other clinicopathological factors on survival in patients with BDC compared with those with PC, we performed comprehensive survival analyses. With respect to OS in patients with PC (Table 1a), univariate analysis showed that 17 parameters, including RLN and PALN metastases, were significantly associated with OS. Furthermore, multivariate analysis showed that NAC, poorer histological differentiation, and histological evidence of lymphatic and perineural infiltration of cancer were independently related factors for OS, whereas RLN and PALN were not ($p<0.05$). With respect to DFS in patients with PC (Table 1b), univariate analysis showed that 17 parameters, including RLN and PALN metastases, were significantly associated with DFS. Furthermore, multivariate analysis revealed that poorer histological differentiation and histological evidence of perineural infiltration were independently related factors, whereas RLN and PALN were not ($p<0.05$).

With respect to OS in patients with BDC (Table 2a), univariate analysis showed that 17 parameters, including RLN and PALN metastases, were significantly associated with OS. Furthermore, multivariate analysis revealed that the serum CA19-9 levels, histological evidence of lymphatic, venous, and perineural infiltration of cancer, PALN, positive margin at the exposed surgical margin, and chemotherapy for recurrence were independent factors of OS ($p<0.05$). With respect to DFS of patients with BDC (Table 2b), univariate analysis showed that 14 parameters, including RLN and PALN metastases, were significantly associated with DFS. Furthermore, multivariate analysis revealed that histological lymphatic infiltration of cancer, RLN, histologically non-curative resection, and chemotherapy for cancer recurrence were independent associated factors, whereas PALN was not ($p<0.05$).

### Relationship Between PALN Metastasis and Other Clinicopathological Factors

Table 3 lists the correlations between RLN and PALN metastases and other clinicopathological factors in patients with PC. Univariate analysis revealed that 16 parameters were significantly associated with the presence of RLN metastasis, and nine parameters were significantly associated with the presence of PALN metastasis ($p<0.05$), (Table 3a). Multivariate regression analysis showed that no factors were associated with RLN. A higher serum DUPAN-II level before surgery was significantly associated with the presence of PALN metastasis ($p<0.05$) (Table 3b). Table 4 details the correlations between RLN and PALN metastases and other clinicopathological factors in patients with BDC. Univariate analysis showed that 13 parameters were

significantly associated with RLN metastasis, and 10 parameters were significantly associated with PALN metastasis ($p<0.05$) (Table 4a). Multivariate regression analysis (Table 4b) revealed that histological lymphatic or perineural infiltration and hepatic or pancreatic involvement were significantly, independently associated with RLN metastasis ($p<0.05$); no other factors were associated with the presence of PALN metastasis.

## DISCUSSION

Specific PBC markers such as CEA or CA19-9 levels are commonly used in Japan to diagnose or evaluate malignant tumor aggressiveness (10-13). The existence of paraaortic lymph node swelling or a positivity on a positron emission computed tomography before surgery is a worrisome indication of distant node metastasis, which is considered a non-curative factor for surgery on digestive organs, including surgery for PBC (14,15). However, in the era of systemic solid chemotherapy or immunotherapy, some investigators have shown better survival with scheduled surgery, even with positive PALN cancer (12,16-19). Furthermore, the concept of oligometastasis in organs distant from the PBC has been proposed, but the significance of radical surgery remains controversial (11). Thus far, it has been reported that PALN metastasis is associated with the worst patient survival, and the preoperative or intraoperative diagnosis of PALN metastasis resulted in unresectability (6,20,21). Recently, with respect to bile duct cancer, the 5-year survival rate varies from 5% to 15%, depending on cancer locations such as intrahepatic, perihilar or distal bile duct (22). Recently, Terasaki et al. (23) showed that the frequency of metastasis in PALNs was 4.7%, with 5-year OS rates and efficacy index both at 0%, which were worse than those of RLN metastasis. For distal cholangiocarcinoma, the rates of PALN metastasis were 4.0%, 25.0%, and 0.99. These results are better compared to those for proximal cholangiocarcinoma (23,24). In contrast, Hempel et al. (25) and other investigators reported that PALN metastasis, a predictive factor, can be confirmed during postoperative pathological diagnosis (10,24). The survival of patients with PALN metastasis who underwent radical surgery was poorer than that of those without PALN metastasis; however, the survival of patients with PALN metastasis who underwent surgery was better than that of patients who did not undergo surgery (26,27). This issue regarding the significance of radical surgery in cases of PALN metastasis remains unclear, and this might be influenced by neoadjuvant or adjuvant chemotherapy with novel, effective anti-cancer drugs (19,21). Due to the oligometastatic condition, the significance of metastasectomy has been elucidated in patients with PC undergoing adjuvant chemotherapy (28). The number of intraoperative PALN metastases is a notable issue (12,20,29) that we recently experienced. In case a solitary PALN is unexpectedly found during intraoperative sampling, we were challenged to choose whether an appropriate strategy was borderline resectable, or unresectable. Fortunately, additional oncological difficulties are not observed in PBC surgery. Thus, the present study attempted to clarify our hypothesis and establish an institutional strategy for cases of solitary PALN metastasis in PBC that were conducted before the era of aggressive chemotherapy. The study was conducted at two institutes where, for 27 years, the principal author performed the same quality radical operations with PALN dissection or sampling. Until 2015, when we initially found the PALN metastasis by intra-operative frozen section pathology, we considered the possibility of localized PALN metastasis in the case of solitary or tiny node metastasis. The concept or strategy of conversion chemotherapy for PALN metastasis could not be considered because of the lack of solid evidence worldwide. In recent years, we may attempt conversion chemotherapy when the preoperative or intraoperative PALN metastases are detected, because we can choose some effective chemotherapy regimens at this stage (19,21,25).

First, patient survival with PALN metastasis from PBC was examined. The results demonstrated that patients with PBC and PALN metastasis had poorer survival than those without PALN metastasis. However, the 5-year OS of patients with PALN metastasis remained stable in both PC and BDC groups, and a two-year median survival period was observed. In this study, cases of unexpected solitary PALN metastasis with curative surgery based on preoperative imaging diagnosis were included, whereas cases of multiple PALN metastases were not. Certainly, DFS was poor, however, this can be improved in the future using adjuvant chemotherapy or chemotherapy in recurrent cases (26-28). Furthermore, in the second step, the statistical weights of PALN for patient survival and other regional node metastases (PLN) were examined along with various clinicopathological factors using multivariable analyses. In a recent nationwide Japanese study, gemcitabine, and S-1 combination therapy as neoadjuvant chemotherapy were found to be significantly beneficial for the survival of patients with PC. CA19-9 level, a valuable marker of PC aggressiveness, showed high significance in the univariate analysis in this study; however, this may have been influenced by obstructive jaundice or NAC. Thus, this was not observed in multivariate analysis. During this long period, anti-cancer drugs have gradually been developed. Until the early 2010s, the medical evidence of adjuvant chemotherapy was not well established. At this stage, the adjuvant chemotherapy with S-1 for a duration of 6-12 months has been available in my country. However, the effective regimen and the administration period are not established at this stage. As a result, the rate of adjuvant chemotherapy use was not frequent in the present study. Adjuvant chemotherapy has been available since 2016. Recently, the significance of adjuvant chemotherapy in perihilar BDC patients with occult PALN positivity who underwent radical

hepatic resection was reported (30). Thus, the development of neoadjuvant or adjuvant chemotherapy may change the treatment strategy of PBC with solitary or occult PALN metastasis. Histological features of cancer, such as lower differentiation and vascular infiltration, were consistent markers associated with poor DFS and OS in this series, as well as in a previous study (12,16,20,24,31,32). Recently, preoperative endoscopic ultrasonography-guided fine needle aspiration or biopsy (EUS-FNA or FNB) has been shown to perform better than pancreatic duct aspiration in most patients with PC (33). However, most samples could not be used to evaluate all PC patients' survival predictions. In contrast, in BDC CA19-9 was a significant marker for poor survival and histological vascular infiltration in this study and in a previous study (34). No NAC was administered in this study. CA19-9 remains the most reliable surrogate marker at this stage. If multiple nodes or related findings of advanced local extension of the primary cancer are found, it is generally reasonable to decide on an exploratory laparotomy (10-12,16,24). Usually, the diagnostic accuracy of regional or distant node metastasis using preoperative multimodal image diagnosis with conventional ultrasonography, computed tomography, magnetic resonance, and positron emission tomography, is approximately 4-21% in the field of pancreaticobiliary cancers (PBC) (11-12,35,36).

In both PC and BDC, the impact of PALN and PLN metastasis on survival differed. In PC, these tended to be associated with poor survival; however, multivariate analysis did not identify the association. Additionally, other histological markers might exhibit malignant behavior. In BDC, both PALN and PLN were significantly associated with poor survival. In addition to PC, other histological factors may contribute to aggressiveness. As described above, a previous study demonstrated that the histological factors related to tumor vascular infiltration showed a higher significance in terms of poor survival (12,16,20,24,31,32). Furthermore, as a surgical factor, cancer-positive margins, such as exposed margins or R1 resection, were significantly associated with poor prognosis in this study as well as in previous reports (11,16,24,35,36). In this series, R12 patients (n=10, 5%) were included, and we have routinely performed the intraoperative pathological diagnosis of cancer infiltration at the resected edge. Even now, the final pathological diagnosis has often changed, particularly in BDC, due to the accompanying cholangitis or degree of dysplasia. A lower degree of pathological diagnostic ability was observed in two patients with R2 during the operation. Although both PALN and PLN were prognostic factors, solitary PALN metastasis was not a definitive prognostic factor, determining the decision for radical surgery in our study. Even in PC, the lymphatic flow into the PALN depends on the location of the primary tumor, whether it is in the pancreatic head or tail. PALN metastasis from the pancreatic tail would be considered a distant metastasis via the systemic lymphatic flow, although the pathological evidence is not easily clarified.

Next, the clinicopathological factors associated with PLN and PALN were examined. On univariate analysis of PC, many clinicopathological factors were significantly more associated with PLN than with PALN. None of the factors was related to PLN metastasis, whereas only DUPAN-II was significantly associated with PALN metastasis. DUPAN-II is associated with tumor aggressiveness in PC. In BDC (in this study), histological infiltration of cancer and organ involvement was significantly associated with PLN metastasis, whereas no association with PALN metastasis was observed in a previous report (24). Some PALN metastases may be skip metastases, but they do not follow the course of lymph vessels, unlike other PLN metastases in BDC. In gallbladder cancer, such a direct metastatic route has been identified in a previous report (37). Based on our hypothesis, if such a case exists without other prognostic factors, it is possible to perform radical surgery when a solitary PALN metastasis is observed. To elucidate the clinical significance of regional node metastasis, including PALN, the efficacy index calculated based on the survival rate or period would be required (38).

We aimed to assess how radical surgery affects outcomes in this study, and based on our findings, we can determine a strategy as follows: 1) If solitary PAL was observed during preoperative or intraoperative examination in PC, and NAC was mostly successful, with DUPAN-II levels > than 150 U/mL, and there was no retropancreatic involvement, then radical surgery is considered. In addition, histological differentiation and vascular infiltration were investigated using preoperative biopsy specimens and discussed with the pathologists. If DUPAN-II levels increase to >150 U/mL and retro-pancreatic infiltration is positive, PALN node dissection is attempted. If an increased level of the promising alternative tumor marker for malignant behavior, DUPAN-II, is observed and is accompanied by suspicious PALN metastasis or pre- and intraoperative PALN swelling, NAC or conversion chemotherapy should be considered. This is especially relevant given the current availability of effective anticancer drugs. This indicates better survival, and suggests that R1 resection is prospectively permissible. 2) When a solitary PAL is observed during preoperative or intraoperative examination, in BDC, PAL metastasis alone is considered a significantly poor prognostic factor, and radical surgery must be limited to younger patients (<70 years). If CA19-9 is very high, i.e., >100 U/mL, R0 or non-exposed surgery cannot be achieved. Even if histological findings associated with poor prognostic factors were not observed in the preoperative specimens, radical surgery should be performed in the prospective setting.

**Study Limitations**

The limitations of the present study are as follows: 1) retrospective two-institutional consecutive cohort for a long period but not

prospective; all these patients included or only those treated by the principal author, which might introduce the selective bias; although the minimal follow-up period was the same at both two institutes, the maximum follow-up was longer at the former institute; 2) the number of patients with PALN metastasis was not high in the recent 6 years due to institutional bias; 3) In this study, we did not operate PBC patients with PALN metastasis by the preoperative radiological imaging diagnosis such as a larger size, enhancement of contrast media by computed tomography, increased number, or positron emission tomography, which was excluded from the evaluation. If we have a database of this group, we must compare patient survival compared to those with occult PALN metastasis who underwent an operation. This comparison may show the clinical significance of the operation in PALN-positive patients who were intraoperatively diagnosed; 4) DUPAN-II levels were not routinely examined, and this must be examined prospectively; 5) surgical indications at the two institutions were due to operator decision bias. These limitations must be verified via interim survival analysis using the proposed operative indication conducted over the next 5 years, as outlined in the prospective institutional criteria for PBC. However, these unexpected and contradictory results must be confirmed in a more significant number of participants at a single institute.

## CONCLUSION

We conducted a retrospective and consecutive analysis of the outcomes of 297 patients with PBC, consisting of 181 patients with PC and 116 patients with BDC who underwent curative surgical resections focusing on solitary PALN metastasis. We analyzed the relationship between PLN and PALN metastasis, conventional clinicopathological parameters, and patient long-term survival. Although histological findings of cancer infiltration, differentiation, and organ involvement were significantly associated with poor prognosis, independent prognostic factors before surgery were limited. They varied between PC and BDC in the multivariable analysis. A prospective trial based on the present results is necessary to clarify the institutional operative indication when a solitary PALN metastasis is diagnosed by sampling during surgery, until a definite proposal or recommendation is provided by nationwide guidelines. Novel adjuvant chemotherapy regimens or treatments for recurrence are expected to control PALN metastasis or other oligometastases in distant regions of PBC.

### Ethics

**Ethics Committee Approval:** This study protocol was approved by the two institutions and the study design was approved by the Ethics Review Board of NUGSBS and UoM (approval numbers: #24031804, March 19, 2024, and #O-1503, January 24, 2024).

**Informed Consent:** Informed consent was obtained.

### Acknowledgments

The entire text was edited by the English editing company for science and medicine, Elsevier (reference number ASLESTD1045174) on February 20th, 2024.

### Footnotes

### Author Contributions

Surgical and Medical Practices - A.N., J.A., M.H., N.I., T.H., Y.T., W.T.; Concept -A.N.; Design - A.N.; Data Collection or Processing - J.A., M.H., N.I., T.H., Y.T., I.S., W.T., T.O.; Analysis or Interpretation – H.K., Y.S.; Literature Search - A.N.; Writing - A.N.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

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