Clinical Impact of Unexpected Para-Aortic Lymph Node Metastasis in Surgery for Resectable Pancreatic Cancer

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Abstract

Radiologically identified para-aortic lymph node (PALN) metastasis is contraindicated for pancreatic cancer (PC) surgery. There is no clinical consensus for unexpected intraoperative PALN. To analyse the prognostic role of unexpected PALN in resectable PC, we retrospectively reviewed data of 1,953 PC patients in a single tertiary centre. Patients with intraoperative PALN without radiological PALN (group A1, negative pathology, n = 59; group A2, positive pathology, n = 13) showed median overall survival (OS) of 24.6 (95% confidence interval [CI]: 15.2–33.2) and 13.0 (95%CI: 4.9–19.7) months, respectively. Patients with radiological PALN metastasis without other metastases (group B, n = 91) showed median OS of 8.6 months (95%CI: 7.4–11.6). Compared with group B, groups A1 and A2 had hazard ratios (HRs) of 0.37 (95%CI, 0.2–0.6) and 1.04 (95%CI: 0.7–1.4), respectively. Compared with group A2, group A1 had HR of 0.33 (95%CI: 0.2–0.7). Analysing regional lymph nodes (LNs), the positive LN ratio affected survival (HR: 2.67, 95%CI: 1.6–4.5), while the absolute number of positive LNs (HR: 1.79, 95%CI: 0.7–4.6) did not. Thus, unexpected malignant PALN has a negative prognostic impact comparable to radiological PALN metastasis. Prompt pathologic evaluation for unexpected PALN and maximal harvest of regional LNs during PC surgery are suggested.

Introduction

Pancreatic ductal adenocarcinoma is the second most common gastrointestinal cancer in the United States and is responsible for 43,000 deaths annually[1]. It is one of the most aggressive tumours, with a 1-year mortality rate of 20–25%[2–4]. Approximately 80% of patients with pancreatic cancer (PC) are diagnosed with metastatic lesions. Surgical resection is the only curative treatment for patients with no distant metastasis.

Previous studies on PC have shown that regional lymph node (LN) metastasis results in poor prognosis[5–7]. The American Joint Committee on Cancer (AJCC) 8th edition defines N stage according to the number of regional LN metastases[8]. In addition to regional LNs, the definition of metastatic LNs depends on the location of the primary tumour, either in the head or tail[8].

In both pancreatic head and pancreatic tail cancers, para-aortic LN (PALN) metastasis is defined as distant metastasis[8]. PALN metastasis may imply systemic illness with aggressive tumour behaviour, resulting in a grave prognosis. Previous studies showed that radiologically observed PALN metastasis correlates directly with poor prognosis[9–11]. Therefore, patients with radiologically observed PALN metastasis preoperatively are recommended to undergo chemotherapy or radiotherapy rather than surgical resection.

Nevertheless, when surgeons discover unexpected PALN enlargement during surgery, which was not recognised in preoperative imaging studies, there is no definite consensus on whether there should be any change in the treatment strategy. In this study, we evaluated the prognostic value of unexpected PALN metastasis in patients with clinically resectable PC with no other distant metastases.

Results

Baseline characteristics

A total of 1,953 patients were diagnosed with pancreatic ductal adenocarcinoma from January 2004 to December 2019 (Fig. 1). Patients were categorised according to their clinical stages. In the clinical staging based on the imaging studies, a total of 440 patients were diagnosed with resectable PC, 455 were diagnosed with locally advanced PC, and 1,059 were diagnosed with metastatic PC.

Among 440 resectable PC patients, a total of 358 patients underwent curative resection for pancreatic cancer. Among them, unexpected intraoperative PALN enlargement was found in 72 patients, who were categorised as group A. Based on the final pathologic report, patients with benign PALN were categorised into group A1 (n = 59), and those with malignant PALN were categorised into group A2 (n = 13).

Among 1,059 patients with metastatic PC, ninety-one patients had no distant metastasis other than PALN metastasis and were categorised as group B.

No significant difference was observed in the baseline demographic information among the three patient groups (Table 1).

Table 1
Patient's baseline characteristics

Variable	Group A1 (n = 59)	Group A2 (n = 13)	Group B (n = 91)	Total patients (n = 163)
Age (years)	63 (53–72)	60 (57–66)	67 (60–76)	65 (58–74)
Sex				
Male	29 (49.1)	5 (38.5)	45 (49.5)	79 (48.5)
Female	30 (50.8)	8 (61.5)	46 (50.6)	84 (51.5)
BMI	22.1 (20.5–23.9)	21.30 (19.7–23.5)	22.58 (20.7–25.0)	22.33 (20.5–24.8)
Initial tumour markers				
CA 19 – 9	101.8 (38.2–430)	191.9 (41–1653.75)	240 (74–731.3)	180.9 (49–607.5)
CEA	2.9 (1.4–5.15)	4.9 (3.6–5.4)	2.55 (1.9– 5)	2.8 (1.65–5.1)
Tumour location				
Head	49 (83.1)	13 (100)	62 (68.1)	124 (76.1)
Body	7 (11.9)	0	15 (16.5)	22 (13.5)
Tail	2 (3.3)	0	11 (12.1)	13 (8.0)
Multiple	1 (1.7)	0	3 (3.3)	4 (2.4)
Tumour size (cm)				
	2.7 (2–3.3)	2.7 (2.1–3.3)	3.2 (2.5–4.2)	3.00 (2.4–3.9)
Concomitant	5 (8.5)	1 (7.7)	39 (42.9)	45 (27.6)
Regional lymph node				
Data are presented as median (interquartile range) or number of patients (%), unless otherwise stated.				

Survival of patients with unexpected PALN

Figure 2 and Table 2 shows the overall survival of the three patient groups. The median survival of patients in group B was 8.6 months, and that of patients in group A1 was 24.6months, (hazard ratio [HR]: 0.37, 95% confidence interval [CI]: 0.2–0.7, P < 0.001) compared to group B). On contrary, the median survival of patients in group A2 was 13.0 months (HR: 1.04, 95% CI: 0.7–1.4, P = 0.905, compared to group B).

Table 2
Univariate and multivariate analyses

Variable (n)	Median Survival(month)	95% CI	Univariate			Multivariate		
			HR	95% CI	P-value	HR	95% CI	P-value
Overall patients	14.6	11.1–17.1						
Sex								
Male (67)	16.9	11.5–20.4	–					
Female (67)	13.0	8.8–15.5	0.92	0.6–1.3	0.680			
Age								
Age ≤ 65 (65)	19.6	14.9–27.4	–			–		
Age > 65 (69)	8.7	6.6–13.0	1.98	1.4–2.9	0.000	1.73	1.1–2.7	0.012
BMI								
BMI ≤ 22.33 (61)	14.8	10.3–17.1	–					
BMI > 22.33 (54)	21.5	11.1–29.3	0.70	0.5–1.1	0.089			
Group (ref B)								
Group B	8.6	7.4–11.6	–					
Group A2	13.0	4.9–19.7	1.04	0.7–1.4	0.905	1.49	0.7–3.1	0.289
Group A1	24.6	15.2–33.2	0.37	0.2–0.6	0.000	0.58	0.3–0.9	0.041
Group (ref A2) *						–		
Group A2	13.0	4.9–19.7	–			–		
Group A1	24.6	15.2–33.2	0.33	0.2–0.7	0.003	–		
Regional lymph node								

*Not applied in the multivariate analysis

Variable (n)	Median Survival(month)	95% CI	Univariate			Multivariate		
			HR	95% CI	P-value	HR	95% CI	P-value
No metastasis	14.9	11.2–20.4						
Metastasis	11.6	7.9–16.5	1.69	1.1–2.5	0.010	1.32	0.8–2.3	0.315
CA19–9								
CA19–9 ≤ 180 (60)	21.5	14.5–28.8	–			–		
CA19–9 > 180 (56)	11.6	9.2–15.5	1.70	1.1–2.6	0.011	1.49	0.97–2.3	0.067
CEA								
CEA ≤ 2.8 (39)	15.5	11.2–21.5	–					
CEA > 2.8 (51)	13.0	8.0–18.3	1.16	0.7–1.8	0.543			
Tumour size								
Tumour size ≤ 3.0 (59)	14.8	11.2–24.6						
Tumour size > 3.0 (75)	13.0	8.5–18.0	1.43	1.0–2.1	0.069			
*Not applied in the multivariate analysis								

Other prognostic factors affecting overall survival

Table 2 shows other factors affecting the overall survival. Sex, body mass index (BMI) at diagnosis, initial carcinoembryonic antigen (CEA), and tumour size failed to show a significant difference in patient survival. No significant survival difference was observed between patients in group B and those in group A2 (HR: 1.04, 95% CI: 0.7–1.4, P = 0.905). Patients in group A1 had significantly better prognosis than those in group B (HR: 0.37, 95% CI: 0.2–0.6, P < 0.000).

Multivariate analysis showed no prognostic significance according to the initial CA19-9 level or regional LN status. Multivariate analysis still showed significantly better survival in group A1 than in group B (HR: 0.58, 95% CI: 0.3–0.9, P = 0.041).

Surgical information including postoperative complications

Surgical information of groups A1 and A2 is summarised in Table 3. No significant differences were found in the operation type, the most common being pancreaticoduodenectomy. The total numbers of

LNs resected were 24 in group A1 and 25 in group A2. The numbers of para-aortic LNs resected were 17 in group A1 and 22 in group A2. The positive LN ratio (LNR) is defined as the ratio of the number of positive LNs to the total number of LNs harvested during surgery. The median LNR in group A1 was 5.6 and that in group A2 was 26 months (P = 0.0002).

Table 3
Surgical information of groups A1 and A2

Patient Group (n, %)	A1 (59, 100%)	A2 (13, 100%)	P-value
OP type			0.477
Pancreaticoduodenectomy*	47 (80%)	11 (85%)	
Distal pancreatectomy	5 (8.5%)	0 (0%)	
Total pancreatectomy	5 (8.5%)	1 (7.5%)	
Others†	2 (3.4%)	1 (7.5%)	
Resection margin			0.272
Negative	41 (69%)	6 (46%)	
Positive	14 (24%)	5 (38%)	
Overall number of dissected LN (median, IQR)	24 (16–33)	25 (15–32)	0.915
No of dissected PALN	5 (2–9)	3 (1–5)	0.117
No of dissected regional LN	17 (11–25)	22 (12–31)	0.476
Pathologic T staging			0.505
Tx	0 (0%)	2 (15%)	
T1–T2	47 (80%)	10 (77%)	
T3–T4	12 (20%)	1 (8%)	
Pathologic N staging			0.191
Nx	2 (3%)	2 (15%)	
N0	27 (46%)	0 (0%)	
N1	33 (56%)	3 (23%)	

Data are presented number of patients (%), unless otherwise stated.

*Pancreaticoduodenectomy includes PPPD, PRPD, and Whipple operation.

†Others included palliative cholecystectomy and O&C.

‡ includes PALN

§Because groups A1 and A2 had no metastasis other than distant LN metastasis, M stage depends only on the presence or absence of distant LN metastasis

||Others include chylous ascites, bacteraemia, acute kidney injury, postoperative ileus, and cholangitis.

Patient Group (n, %)	A1 (59, 100%)	A2 (13, 100%)	P-value
N2	7 (12%)	8 (62%)	
Ratio of positive LN (%)‡			
	8.1 (0–30.7)	26.67 (0–51.9)	0.0002
Pathologic M staging §			
M0	58 (98%)	0 (0%)	
M1	1 (2%)	11 (100%)	
Moderate to severe surgical complication			
All complication	32 (54%)	4 (31%)	0.163
Surgical site infection	4 (7%)	1 (8%)	0.826
Postoperative haemorrhage	4 (7%)	0 (0%)	0.831
Pancreas fistula	9 (15%)	0 (0%)	0.344
Liver abscess	1 (2%)	0 (0%)	0.647
Others‖	14 (24%)	3 (23%)	
Data are presented number of patients (%), unless otherwise stated.			
*Pancreaticoduodenectomy includes PPPD, PRPD, and Whipple operation.			
†Others included palliative cholecystectomy and O&C.			
‡ includes PALN			
§Because groups A1 and A2 had no metastasis other than distant LN metastasis, M stage depends only on the presence or absence of distant LN metastasis			
‖Others include chylous ascites, bacteraemia, acute kidney injury, postoperative ileus, and cholangitis.			

The number of surgical complications did not differ between the two patient groups. (Table 3) The most common surgical complications in the two patient groups were pancreatic fistula, followed by surgical site infection and postoperative haemorrhage.

Effects of overall lymph node status

Patient survival was analysed based on the number of metastatic LNs (LNS) (Fig. 3A). Patients were grouped as follows: those with fewer than four metastatic LNs and those with more than three metastatic LNs. The median survival of patients with less than four metastatic LNs was 22.5 months and that of patients with more than three metastatic LNs was 4.4 months (HR: 1.79, 95% CI: 0.7–4.6, P = 0.233).

Patient survival was also analysed based on the LNR (Fig. 3B). The median LNR was 4.2%. We categorised the patients into two groups: patients with LNR ≤ 4.2% and patients with LNR > 4.2%. The median survival of patients with lower LNR was 38.6 months and that of patients with higher LNR was 15.2 months (HR: 2.67, 95% CI: 1.6–4.5, P < 0.001).

Other medical information

Non-surgical therapies performed in patients are summarised in Table 4. The most common first-line palliative chemotherapy regimen was FOLFIRINOX. Gemcitabine monotherapy was the most common adjuvant therapy regimen.

Table 4
Treatment information other than surgery

Patient Group (n, %)	A1 (59)	A2 (13)	B (91)	P-value
First-line palliative chemotherapy*				0.036
FOLFIRINOX	2 (3.4%)	3 (23.1%)	18 (19.8%)	
Gemcitabine with nab-paclitaxel	0 (0%)	0 (0%)	5 (5.5%)	
Gemcitabine monotherapy	1 (1.7%)	1 (7.7%)	6 (6.6%)	
Other gemcitabine-based chemotherapy	3 (5.1%)	1 (7.7%)	12 (13.2%)	
Adjuvant chemotherapy				0.164
FOLFIRINOX	1 (1.7%)	0 (0%)	3 (3.3%)	
Other 5-FU-based regimen	1 (1.7%)	0 (0%)	0 (0%)	
Gemcitabine monotherapy	28 (47.5%)	3 (23.1%)	6 (6.6%)	
Other gemcitabine-based chemotherapy	5 (8.5%)	1 (7.7%)	3 (3.3%)	
Radiation therapy				0.038
Yes	37 (62.7%)	9 (69.2%)	73 (80.2%)	
No	22 (37.3%)	4 (30.8%)	18 (19.8%)	
Data are presented as number of patients (%).				
*Palliative chemotherapy after tumour recurrence is excluded.				

The ratio of patients receiving radiotherapy varied among the three patient groups. Seventy-three out of 91 patients in group B (80%) received radiotherapy, 9 out of 13 patients in group A2 (69.2%), while 37 out of 59 patients in group A1 (62.7%) received radiotherapy.

Discussion

This study was a retrospective analysis of the prognostic role of unexpected PALN metastasis in PC. In our study, unexpected intraoperative PALN metastasis resulted in shorter patient survival. Additionally, this study showed that the number of metastatic LNs was not a determinant of prognosis. On the contrary, patients with high LNR showed worse prognosis than those with low LNR.

In PC, the prognostic role of distant metastasis has been well established in various studies[14–16]. Nevertheless, the prognostic value of PALN metastasis has not been firmly established.[9–11, 17, 18] When unexpected PALN enlargement is found during curative resection of PC, there is no consensus on whether additional treatment strategies will be implemented. A systematic review and meta-analysis by Paiella suggested that PALN metastasis correlates with poor prognosis in patients with pancreatic adenocarcinoma.[9] On the contrary, a multicentre study by Masayuki Sho suggested that some patients with PC having metastatic PALN may survive longer than expected after undergoing pancreatectomy.[10, 17] Moreover, the prognosis of patients with 'PALN metastasis only' without other metastases remains unclear.

In this study, the patients were primarily categorised into two groups: group A, patients with radiologically resectable PC who had unexpected intraoperative PALN enlargement; and group B, patients with clinical metastatic PC having only PALN metastasis, with no evidence of other distant metastases. Patients in group A were further grouped into group A1, comprising patients with pathologically benign PALN, and group A2, comprising patients with pathologically proven PALN metastasis.

The median survival of patients in group B (median: 8.6 months, 95% CI: 15.2–33.2 months) was similar to historical data of that of metastatic PCs[15,16, 19, 20]. Group A1 also showed similar overall survival of historical data of resectable PC[19,20]. Therefore, median survival of patients in group A1 were significantly longer than that of patients in group B (HR: 0.37, 95% CI: 0.2–0.6, $P < 0.001$). The survival of patients in group A2 were not different from those of patients in group B (HR: 1.04, 95% CI: 0.7–1.4, $P = 0.905$).

Patients in group A1 had significantly longer median survival compared to that of group A2 (HR: 0.33, 95% CI: 0.2–0.7, $P = 0.003$). This result suggests negative prognostic impact of PALN, and surgeons are recommended to perform frozen biopsy for unexpected intraoperative PALN enlargements. This result is consistent with that of a systemic review by Paiella[9].

In addition to PALN metastasis, the number of other LN metastases is an important confounding factor in this study. Various studies have reported that lymph node ratio, rather than absolute number of metastatic LN is inversely associated to survival[21–23]. No significant survival differences were found according to the number of metastatic LNs. Nevertheless, patients with lower LNR had better prognosis than those with higher LNR. This result suggests that it is important for surgeons to harvest a sufficient number of LNs during surgery.

This study has a few limitations. The number of patients was relatively small. Nevertheless, the statistical analysis resulted in significant survival differences, and further studies with larger numbers of patients

are warranted to yield more significant differences. Not all patients in the study had information on frozen biopsy, and we analysed the PALN metastasis status based on the final pathologic report. Nevertheless, Alexandre Doussot reported that frozen sections of PALN yielded accurate PALN assessment[13, 24–26].

In conclusion, unexpected malignant PALN could have a negative prognostic impact on the survival of patients with radiologically resectable PC comparing to those with clinically metastatic PALN. Patients with higher LNR had shorter survival than those with lower LNR. This study suggested that frozen sections need to be performed when unexpected PALN enlargement is found during surgery. Moreover, as LNR functions as an independent prognostic factor, surgeons are advised to harvest as many LNs as possible during curative surgery.

Materials And Methods

Patients

Medical and pathologic records of patients diagnosed with pancreatic adenocarcinoma in a single tertiary centre (Seoul National University Bundang Hospital) from 2004 to 2019 were retrospectively reviewed. Patients who were previously diagnosed with PC and treated with chemotherapy, radiotherapy, or surgery from other hospitals were excluded from the study. Patients with malignant tumours other than PC were also excluded.

Results of all imaging tests were reviewed and the patients categorised in accordance with the AJCC 8th edition[8]. Patients diagnosed with locally advanced PC and borderline resectable PC were excluded. Patients with metastatic PC were divided into those with PALN metastasis alone and those with other distant metastases.

Surgical records and pathology reports of patients with radiologically resectable PC, with clinical stage TxN0M0, were reviewed. Among patients who underwent surgical resection, those who had unexpected intraoperative PALN enlargement during surgery were categorised as group B. All patients in group B had para-aortic LN dissection, and the final pathologic diagnosis was made. Patients with negative para-aortic LNs were categorised as group A1, while those with positive para-aortic LNs were categorised as group A2 (Fig. 1). Patients with no other distant metastasis, but only PALN metastasis, were classified as patient group B.

Study design

This study was conducted as a single-centre, retrospective cohort study. The primary endpoint was the overall survival of patients.

Statistical analysis

Statistical analyses were performed using Stata version 15.0. Categorical data on the three patient groups were analysed using a 2 × 3 chi-square test or 2 × 3 Fisher's exact test. Numerical data with a normal distribution were analysed using analysis of variance, and those that failed to follow a normal distribution were analysed using the Kruskal-Wallis test. Survival data were analysed using the Cox proportional hazard model. Categorical variables are expressed as percentages, and continuous variables are expressed as IQR. A p-value < 0.05 was considered to indicate statistical significance.

This study was approved by the institutional review board of Seoul National University Bundang Hospital (Protocol No. B-2104-681-105), and informed consent was waived. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Declarations

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Author contributions

Study concept and design by Lee HK, Yoon YS, Lee JC; Statistical analysis plan by Lee HK, Hwang JH, Lee JC; Data recruitment by Park JW, Jung KR; Data management by Lee HK, Jung JH, Kin JH, Lee JC; Pathologic data manipulation by Na HY, Ahn SM; Statistical analysis by Lee HK, Hwang JH, Lee JC; Visualization by Lee HK, Lee JC; Interpretation of result by Lee HK, Yoon YS, Lee JS, Han HS, Lee JC; Draft writing by Lee HK, Lee JS, Na HY, Lee JC; Draft revising by Lee HK, Han HS, Lee JS, Ahn SM, Park JW, Jung KR, Jung JH, Kim JH, Hwang JH, Lee JC

Competing interest

The authors declare no potential conflicts of interest, including patents, familial relationships, and affiliations with any organisation with direct or indirect financial interest in the subject matter discussed in the manuscript.

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Figures

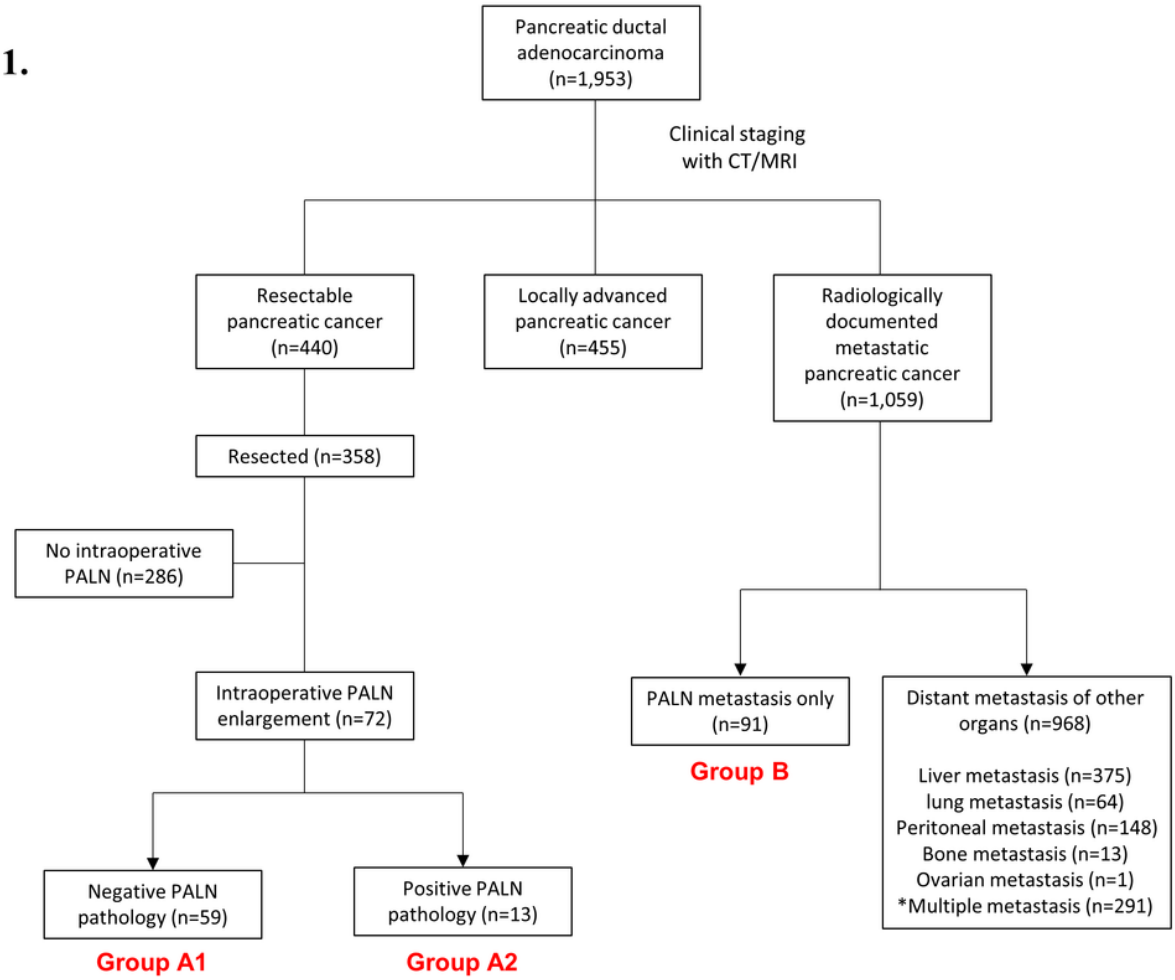

Figure 1

Flowchart of the patient selection process *This group included patients with PALN metastasis and other metastases.

Figure 2.

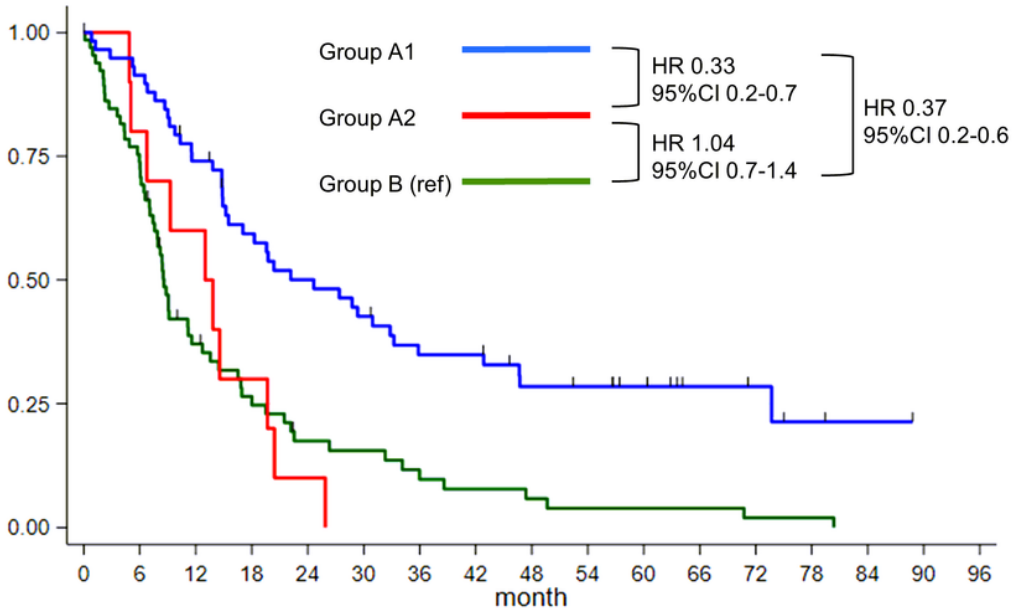

Figure 2

Kaplan-Meier survival analysis of the three patient groups Group A1, unexpected PALN with negative pathology; Group A2, unexpected PALN with positive pathology; Group B, metastatic PALN in imaging study.

Figure 3A.

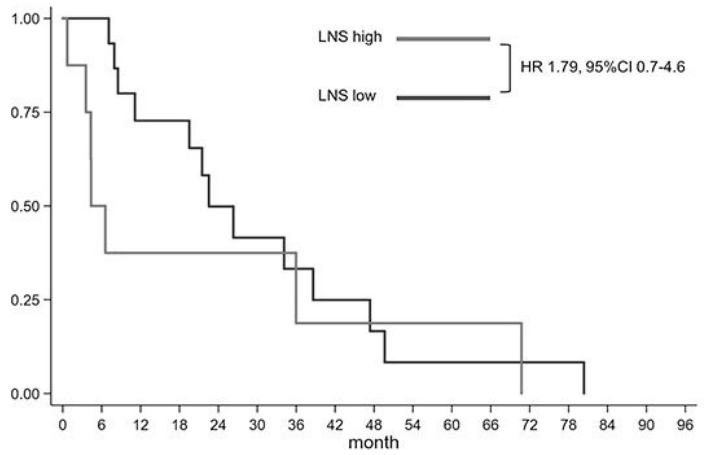

Figure 3B.

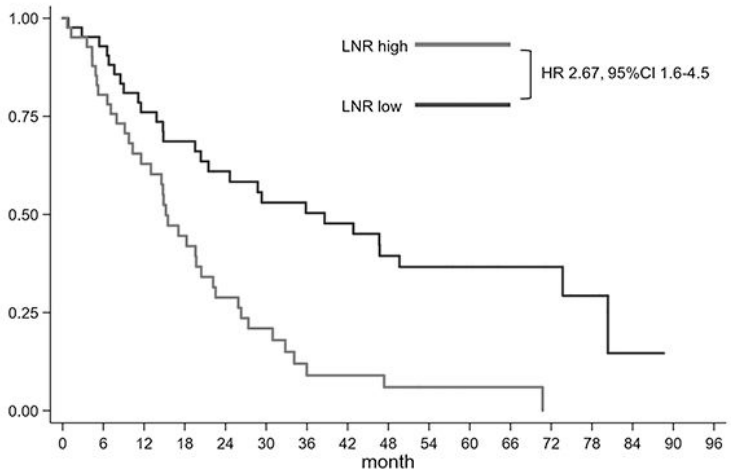

Figure 3

Kaplan-Meier survival analysis according to the status of lymph node metastasis. (A) survival analysis for patients with ≤3 lymph node metastasis and patients with ≥4 lymph node metastasis. LNS low: median survival 22.5 months; LNS high: median survival 4.4 months; HR: 1.79, 95% CI: 0.7–4.6, P = 0.233. (B) Survival analysis of patients with LNR of <4.42 and patients with LNR of ≥4.42. LNR low

(≤4.42): median survival 38.6 months; LNR high (>4.42): median survival 15.2 months; HR: 2.67, 95% CI: 1.6–4.5, $P < 0.001$