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Para-aortic lymph nodes and ductal adenocarcinoma of the pancreas: Distant neighbors?

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ABSTRACT

Background: Para-aortic lymph nodes in the ductal adenocarcinoma of the pancreatic head are regarded as distant metastases. Chemotherapy is considered the only treatment option if para-aortic lymph nodes metastases are detected preoperatively or intraoperatively. The role of standardized para-aortic lymph node lymphadenectomy during pancreaticoduodenectomy remains controversial. The aim of this study was to evaluate complication profiles and survival.

Methods: All cases of ductal adenocarcinoma of the pancreatic head were evaluated from a prospectively maintained database ($n = 289$). Para-aortic lymph node lymphadenectomy was routinely performed in all patients with suspected ductal adenocarcinoma of the pancreatic head. Subgroup analysis was performed between patients with histologically positive (+) and negative (-) para-aortic lymph nodes. Patients receiving pancreaticoduodenectomy without para-aortic lymph node lymphadenectomy for other causes served as a control group.

Results: A total of 192 patients received para-aortic lymph node lymphadenectomy, of which 41 were positive for para-aortic lymph node metastases. In 97 patients with ductal adenocarcinoma of the pancreatic head, no para-aortic lymph node lymphadenectomy was performed owing to postoperative pancreatic ductal adenocarcinoma diagnosis. Clinicopathologic data were homogenously distributed. Hospital stay and postoperative morbidity demonstrated no significant difference between the 3 subgroups. The median overall survival of 19.63 months (95% confidence interval: 14.57–24.79 months) in para-aortic lymph node− patients was not statistically different when compared with the median overall survival of 18.22 months (95% confidence interval: 12.68–23.75 months) in para-aortic lymph node + patients (log-rank test $P = .223$). Preoperative computed tomography was a poor predictor for para-aortic lymph node status (sensitivity = 10.3%, specificity = 97.8%).

Conclusion: This study represents the largest cohort receiving routine para-aortic lymph node lymphadenectomy. Extended lymphadenectomy can be performed safely and, although disease-free survival of para-aortic lymph node+ patients was significantly shorter, overall survival and postrelapse survival were on par with that of para-aortic lymph node− patients. Preoperative computed tomography indicating para-aortic lymph node metastasis should not preclude curative resection.

Introduction

Pancreatic ductal adenocarcinoma of the pancreas head (hPDAC) has a very poor prognosis with an overall 5-y survival of <5% and is estimated to become the second leading cause of cancer-related death by the year 2030.[1] For localized disease, primary surgery is combined with an adjuvant treatment regimen. Although different adjuvant chemotherapeutic agents have been used since gemcitabine in 1997, only a minor improvement was achieved in long-term overall survival (OS).[2–7] Poor survival of pancreatic cancer patients is mainly attributable to advanced stage at diagnosis and high rates of cancer recurrence even after initially successful curative therapy.[8]

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CT of the abdomen remains the gold standard in preoperative diagnostics and staging for periampullary carcinomas. Sensitivity in detection of tumor and dilatation of the main pancreatic duct is comparable with MRI.[9] Nevertheless, preoperative detection of para-aortic lymph node (PALN) involvement using CT remains controversial.[10]

We have already demonstrated the oncologic benefit of mesopancreatic excision during structured pancreaticoduodenectomy (PD).[11] Histopathologic examination of these patients demonstrated infiltration of the mesopancreatic fat in ~80% of the patients, indicating that even primarily resectable patients are routinely diagnosed in an advanced stage of disease.[11]

The survival impact of positive PALN (PALN+) is not yet fully elucidated. In the majority of literature, PALNs were only resected in patients with suspicious infiltration, or the analysis for survival of patients with PALN+ was performed within a conservative treated patient cohort that was treated conservatively.[10,12] PALN lymphadenectomy (LAD) is a standard step during pancreaticoduodenectomy (PD) for hPDAC in our institution (Heinrich-Heine-University and University Hospital, Duesseldorf, Germany), independent of preoperative radiographic findings. In patients receiving PD for unspecific lesions (eg intraductal papillary mucinous neoplasms), PALN LAD was not routinely performed. These patients served as a control group for complication profile analysis.

As the majority of patients with resectable hPDAC present with locally advanced disease,[11] the utilization of PALN status for treatment stratification may lead to unnecessary treatment restrictions. The aim of this study was to examine survival outcome of patients with PALN+. Furthermore, correlation analysis was performed between CT-predicted PALN involvement and histopathologic analysis. To our knowledge, a similar analysis within a consecutively treated cohort of patients is not available in the literature.

Materials and Methods

Patients who underwent PD with curative intent for hPDAC, irrespective of tumor stage and microscopic resection margin, at the University Hospital of Duesseldorf, Germany, between 2004 and 2018 were included for primary evaluation ($n = 289$). Exclusion criteria were: (1) pancreatic tumors other than hPDAC, (2) borderline-resectable hPDAC, (3) synchronous hepatic metastasis or peritoneal carcinomatosis, (4) R2 resection status, and (5) neoadjuvant therapy. Although meticulous PALN LAD is a routine step in PD for hPDAC in our institution, in patients receiving PD for unspecific lesions (eg intraductal papillary mucinous neoplasms), PALN LAD was not routinely performed. In some of these patients, however, hPDAC was detected in the resected specimen, and these patients were included in our cohort. All patients with hPDAC were categorized in 3 groups: (1) patients with positive PALN (PALN+), (2) patients with negative PALN (PALN−) and (3) patients in which a PALN LAD during PD was not performed (PALNcontrol). The PALNcontrol patients served as a control group for postoperative morbidity analysis. Information on tumor size/site, lymph node involvement, metastatic spread (TNM) staging, grading, perineural invasion as well as lymphatic and venous invasion were retrospectively obtained from the original pathology reports. The dissected peripancreatic (pp [lymph node {LN} 5, 6, 13/17]), extraperipancreatic (extrapp [LN 8, 9, 12, 14, 15]) as well as the PALN stations (LN 16a2 + b1) were histopathologically analyzed.[13] The extrapp LNs included all dissected LNs in the hepatoduodenal ligament, periportal LNs, and LNs around the celiac trunk, superior mesenteric artery, and common hepatic artery. The staging system was updated to the eighth edition of the Union for international cancer control (UICC) TNM classification for the total cohort.[14] An experienced pancreatic radiologist blinded for histopathologic and survival outcome reviewed available preoperative CT scans of patients with PALN LAD (PALN+ and PALN−).

Clinicopathologic data—including age, sex, OS, disease-free survival (DFS), and time and site of metastases—were reviewed. Postrelapse survival (PRS) of patients with metachronous disease was calculated from date of relapse until death or last follow-up. The study was carried out in accordance with good clinical practice guidelines as well as with the Declaration of Helsinki. Institutional review board approval of the Medical Faculty, Heinrich-Heine University Duesseldorf, was received (2019-437).

Surgical and pathologic procedure

After a Kocher manoeuver, extended para-aortic lymphadenectomy (group 16a2 + b1, Japanese classification) was performed as a standard of care for patients with hPDAC. The dissection plane incorporates at least all lymphatic tissue between the right crus of the diaphragm, cranially, and the branching of the inferior mesenteric artery from the aorta caudally, with the aorta and the vena cava as lateral borders of dissection.[11] This area is usually covered by the pancreatic head (Fig 1). During para-aortic lymphadenectomy a bipolar sealing scissor is primarily used. Small para-aortic and interaortic vessels that have been missed during dissection are sealed selectively with 5-0 or 6-0 Prolene sutures (Ethicon, Somerville, NJ). The specimens were harvested for histopathologic analysis and were directly preserved in formaldehyde. No fresh frozen sections were performed for intraoperative decision making.

Postoperative evaluation and follow-up

All patients were evaluated postoperatively in a multidisciplinary tumor board regarding adjuvant therapy and additional treatment. Median follow-up was 15 months (range: 1 month−124 months). If the follow-up examinations were performed in our institution, irrespective of the adjuvant treatment constellation, examinations were performed every 3 months for the first 2 y, then twice annually, including clinical examinations, serologic tumor marker evaluation, and CT of the thorax and abdomen. Patients with suspicious masses at follow-up were again discussed in the multidisciplinary tumor board for further treatment. If follow-up was performed externally, survival status of patients was gathered from the legal registration offices twice annually. If available, results from external follow-up were gathered.

Statistical Analysis

The Wilcoxon test was used to analyze the differences in clinicopathologic data. The Mann-Whitney *U* test was used to examine numeric data and clinicopathologic variables. For categorical data, the χ^2 test was applied. OS was determined as the period from the date of surgery until the date of death for any cause or last follow-up (censored). DFS was defined as the period from the date of surgery until the date of clinically diagnosed metastasis or local recurrence. PRS was defined as the period from relapse diagnoses until death or last follow-up. Kaplan-Meier curves were generated and analyzed using the log-rank (Mantel Cox) test and hazard ratios with 95% confidence intervals (CIs) were estimated. To perform a multivariate survival analysis, all variables were included in a Cox regression analysis. Sensitivity and specificity, as well as predictive values for preoperative CT scans to evaluate PALN status were calculated. Analyses were performed using SPSS statistics for Windows v 26.0 (IBM, Armonk, NY). $P < .05$ was considered statistically significant.

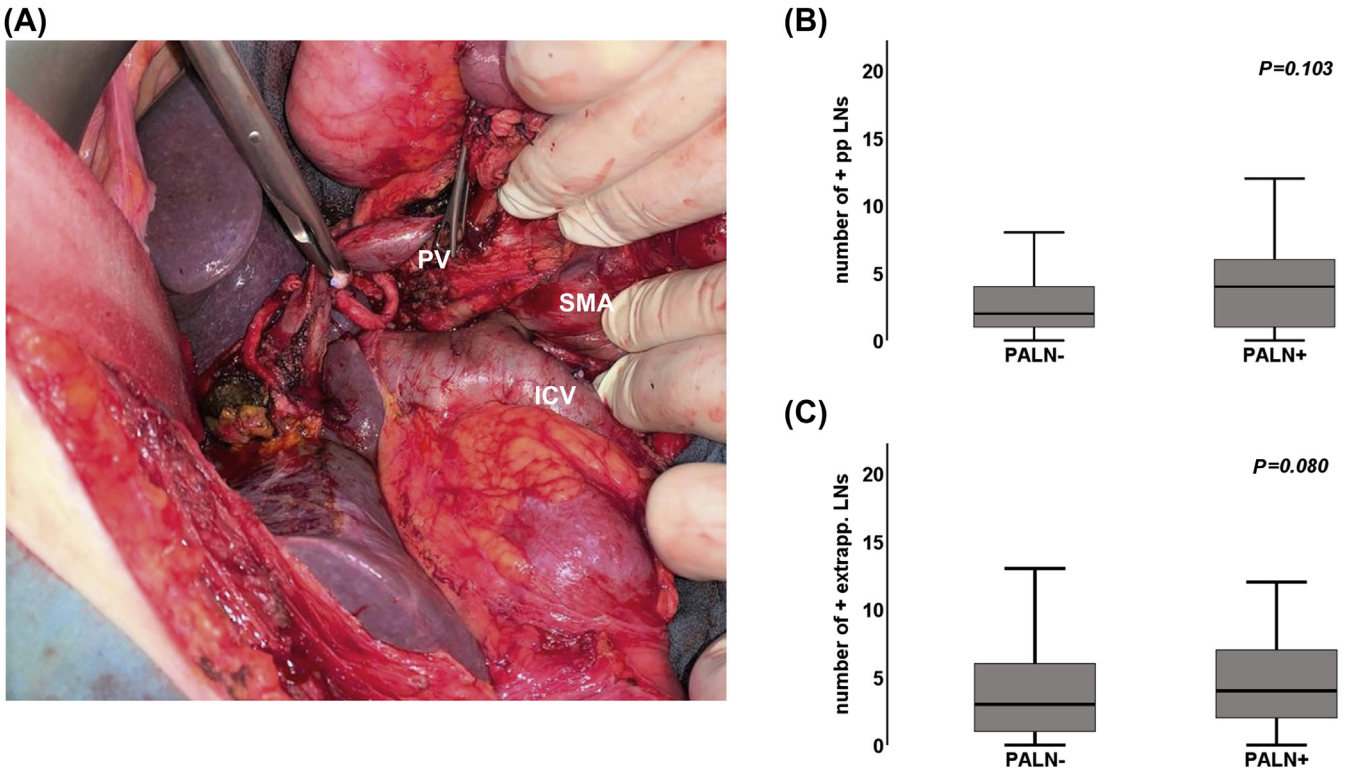


Fig 1. (A) Intraoperative situs from patient's right side after PALN LAD during Kocher manoeuver. (B) Box plot of the number of pp and (C) extrapp LNs stratified by patients PALN status. The Mann-Whitney *U* test was used to test for significance. *extrapp*, extra peripancreatic; *ICV*, inferior caval vein; *LNs*, lymph nodes; *pp*, positive peripancreatic; *PALN*, para-aortic lymph node; *PV*, portal vein; *SMA*, superior mesenteric artery.

Results

Demographic data

Clinicopathologic characteristics of the study cohort are summarized in Table I. Between 2004 and 2018, a total of 289 patients treated in our tertiary referral center met the inclusion criteria (139 female, 150 male). Of these, 192 (66.4%) patients received PALN LAD during PD, and 97 (33.6%) patients received PD without PALN LAD; however, hPDAC was detected in the histopathologic specimen. A total of 41 (21.4%) patients were diagnosed with metastatic PALN (PALN+, median number of positive PALN: 1.0; range: 1–14), the remaining 151 (78,6%) patients were histopathologically free from PALN metastases (PALN−). A median of 5 (range: 1–25) para-aortic LNs were dissected during surgery in the entire cohort (PALN+ and PALN−). All clinicopathologic variables were homogeneously distributed among the 3 studied groups (Table I). The median age at the time of surgery for all 289 patients was 69 years (range: 41–95 years).

Correlation analysis on nodal status between PALN+ and PALN−

All patients with nodal positive disease (pN+) harbored peripancreatic LN metastases. A median of 15 (range: 6–42) peripancreatic LNs were dissected during surgery in all 192 patients. Of note, in 1 patient with nodal negative disease (pN0), PALN metastases were histopathologically evident (Table I). We observed no significant correlation between the number of positive peripancreatic lymph nodes and PALN status ($P = .103$ [Fig 1, B]). The amount of positive extrapp LNs was again not statistically different in patients with positive and negative PALN status ($P = .080$ [Fig 1, C]). Hence, patients who were PALN+ did not harbor significantly more pp or extrapp LN metastases compared with patients who were PALN−.

In correlation analysis between the PALN status and the studied LN stations, only patients with positive LN #14 (superior mesenteric artery) had a significantly increased risk of positive PALN status (Fisher exact test: $P = .020$).

Preoperative CT evaluation

In 120 PALN LAD patients, preoperative CT scans were available for re-evaluation. Of these 120 patients, 29 were diagnosed with PALN metastases in the dissected specimen. In only 4.2% (5/120), retropancreatic LN involvement was predicted radiographically. However, only 3 of these 5 patients were indeed PALN+ in the histopathologic evaluation (sensitivity = 10.3%, specificity = 97.8%, PPV = 60%, NPV = 77.4% [Supplemental Table S1]).

Postoperative complication profile

The distribution of postoperative complications is summarized in Table II. Patients with PALN LAD had a similar rate of postoperative lymphatic fistula when compared with patients without PALN LAD. The rate of other typical postoperative complications specific to pancreatic surgery was not different among the subgroups. We observed that PALN LAD did not increase the LOS, compared with PD without PALN LAD (Table II). In the total cohort of 289 patients, 15 patients succumbed during the first 30 postoperative days (Clavien-Dindo V: 5.2%), which is on par with published mortality rates.[15]

Table I
Demographic data of patient collective from 2004 to 2018 ($N = 289$)

	PALN negative n = 151		PALN positive n = 41		No PALN LAD n = 97		P value
Age (y)							.179
Median (range)	68 (41–90)		67 (51–81)		70 (45–95)		
Sex							.231
Male	83	55.0	16	39.0	51	52.6	
Female	68	45.0	25	61.0	46	47.1	
T stage							.442
T1	11	7.3	1	2.4	9	9.3	
T2	84	55.6	21	51.2	58	59.3	
T3	53	35.1	18	43.9	28	28.9	
T4	3	2.0	1	2.4	2	2.1	
N stage							.479 (PALN− versus No PALN LAD)
N0	26	17.2	1	2.4	22	22.7	
N1	72	47.7	10	24.4	48	49.5	
N2	53	35.1	30	73.2	27	27.8	
Grading							.259
G1/G2	84	55.7	30	73.2	55	56.7	
G3	66	43.7	11	26.8	41	42.3	
n/a	1	0.7	0	0	1	1.0	
Pn							.292
Pn0	25	16.6	10	24.4	22	22.7	
Pn1	114	75.5	26	63.4	63	64.9	
n/a	12	7.9	5	12.2	12	12.4	
L							.190
L0	77	51.0	16	39.0	49	50.5	
L1	62	41.1	22	53.7	36	37.1	
n/a	12	7.9	3	7.3	12	12.4	
V							.117
V0	107	70.9	25	61.0	70	72.2	
V1	32	21.2	12	29.3	15	15.5	
n/a	12	7.9	4	9.8	12	12.4	
R-status							.138
R0CRM-	83	55.0	19	46.3	46	47.4	
R1/R0CRM+	68	45.0	22	53.7	51	52.6	
Adjuvant CTx							.331
Gemcitabine	88	58.3	29	70.7	57	58.8	
MD regime	39	25.8	7	17.1	17	17.5	
n/a	24	15.9	5	12.2	23	23.7	

Staging is revised to the 8th edition of the UICC TNM classification of malignant tumors. Statistical significance was calculated by Kruskal-Wallis test for numeric data and $\alpha 2$ test for ordinal data. All *P* values were not significant.
CTx, chemotherapy; *L*, lymphatic invasion; *LAD*, lymphadenectomy; *MD*, multidrug; *n/a*, data not available; *PALN*, para-aortic lymph nodes; *Pn*, perineural invasion; *UICC TNM*, union for international cancer control (T: tumor size/site, N: lymph node involvement, M: metastatic spread); *V*, venous invasion.

Overall survival analysis of patients with PALN LAD

Only patients with PALN LAD were included. Of these 192 patients, the11 patients who suffered in-hospital 30-day-mortality were not included. Of the remaining 181 patients, 179 (98.9%) patients died during the follow-up period. The mean follow-up period was 28.5 months (95% CI: 22.8–34.2 months). Overall survival was evaluated using official records from the registration office. A total of 163 patients received an adjuvant treatment, 117 patients received gemcitabine, and 46 patients received a combination therapy of gemcitabine and paclitaxel or capecitabine. None of the patients included received folinic acid, fluorouracil, irinotecan, oxaliplatin or neoadjuvant treatments.

At univariate survival analysis, higher tumor grading, positive resection margins (R1) and single-agent chemotherapy were significantly associated with poor OS. Of interest, nodal and PALN

Table II
Complication profile analysis and length of stay

Morbidity						
	No complication	Bleeding	Pancreatic fistula	GI bleeding	Chyle fistula	*P* value
PALN LAD $n = 192$	147 (76.6%)	10 (5.2%)	29 (15.3%)	1 (0.5%)	4 (2.1%)	.170
No PALN LAD n = 97	81 (83.5%)	4 (4.1%)	10 (10.3%)	1 (1.0%)	1 (1.0%)	
		LOS in days Median (range)		Clavien-Dindo V		
PALN LAD $n = 192$		23 (9.0–262.0)		11 (5.7%)		.601
No PALN LAD $n = 97$		20.5 (10.0–154.0)		4 (4.1%)		

Statistical significance was calculated by Kruskal-Wallis test for numeric data and α^2 test for ordinal data. All *P* values were not significant.
GI, gastrointestinal; *LAD*, lymphadenectomy; *LN*, lymph nodes; *LOS*, length of stay; *PALN*, para-aortic lymph nodes.

Table III
Univariate and multivariate analysis for overall survival ($N = 181$)

	Univariate analysis	Multivariate analysis		
	P value	*P* value	HR	CI (95%)
Age (≥/<median)	.785	.329	—	—
Sex (male/female)	.795	.891	—	—
T-stage (T1;T2/T3;T4)	.871	.498	—	—
N stage (N0/N1; N2)	.305	.334	—	—
PALN (PALN+/PALN−)	.223	.167	—	—
Grading (G1;G2/G3)	.009	.001	2.051	1.358 − 3.098
Pn (Pn1/Pn0)	.530	.134	—	—
L (L1/L0)	.581	.421	—	—
V (V1/V0)	.120	.295	—	—
R status (R0CRM−/R0CRM+; R1)	.024	.310	—	—
CTx (MD regime versus Gemca mono)	.049	.397	—	—

Analyses were performed by log-rank test and forward logistic Cox regression.
CI, confidence interval; *CTx*, chemotherapy; *Gemca*, gemcitabine; *HR*, hazard ratio; *L*, lymphatic invasion; *MD*, multidrug regime; *PALN*, para-aortic lymph nodes; *Pn*, perineural invasion; *V*, venous invasion.

status were not prognostic factors in our cohort (PALN+ versus PALN−) [Table III]). Thus, the median OS of 19.63 months (95% CI: 14.57−24.79 months) in patients who were PALN− was not statistically different when compared with the median OS of 18.22 months (95% CI: 12.68−23.75 months) in patients who were PALN+ (log-rank test $P = .223$ [Fig 2, A]). At multivariate analysis, only tumor grading remained a significant prognostic factor ($P = .001$ [Table III]).

To elucidate the spatial LN involvement and its potential influence on OS, patients with PALN LAD were divided into 4 subgroups depending on the location of metastatic LN stations: (1) patients with isolated pp LN metastases (LN 5, 6, 13/17; $n = 120$; median OS: 19.63 months [95% CI: 16.93−22.34 months]); (2) patients with LN metastases in the pp and extrapp stations *except* PALN (LN 5, 6, 8, 9, 12, 13/17, 14, 15; $n = 21$; median OS: 7.1 months [95% CI: 1.22−12.99 months]); (3) patients with LN metastases in the pp *and* PALN stations (LN 5, 6, 13/17, 16; $n = 11$; median OS: 16.63 months [95% CI: 9.66−23.59 months]); and (4) patients with positive LN metastases in all locations (LN 5, 6, 8, 9, 12, 13/17, 14, 15 16; $n = 29$; median OS: 18.22 months [95% CI: 9.77−26.67 months]). We observed no statistical difference in OS among the 4 subgroups ($P = .196$ [Fig 2, B]).

Overall survival analysis of all patients

Of the 97 patients without PALN LAD, 4 patients succumbed during the 30-day mortality and were removed from survival analysis (Table II). Patients who received PALN LAD ($n = 181$) and patients without PALN LAD ($n = 93$) were included in this analysis. The median OS in the complete cohort was 19.2 months (95% CI: 16.5−21.9 months).

The median OS of the patients with PALN LAD ($n = 181$) was 19.2 months (95% CI: 15.9−22.6 months), the median OS of patients without PALN LAD ($n = 93$) was 18.9 months (95% CI: 14.4−23.3 months), indicating no statistical difference between these 2 groups ($P = .963$ [Supplemental Fig S1]).

Pathologic assessment, metachronous disease and DSF

In 93 patients with PALN LAD, a detailed follow-up was available to analyze DFS (79 PALN−, 14 PALN+). Of these, 68.8% (64 of 93) were diagnosed with relapse during the available follow-up. Anatomic distribution of metachronous disease is summarized in Table IV. A total of 28.6% (4 of 14) and 21.4% (3 of 14) of PALN+ patients were diagnosed with metachronous pulmonary and hepatic metastases, respectively. In the PALN− group, 11.4% (9 of 79) and 31.6% (25 of 79) of patients developed metachronous pulmonary and hepatic relapse, respectively (PALN+ versus PALN−: $P = .050$).

At univariate and multivariate analysis, only PALN+ status correlated with worse DFS (Table V). Thus, the median DFS of 12.00 months (95% CI: 5.97−18.03 months) in patients who were PALN− was significantly longer when compared with the median DFS of 8.60 months (95% CI: 2.21−14.99 months) in patients who were PALN+. Kaplan-Meier curves and a log-rank test revealed a significantly worse DFS for patients who were PALN+ ($P = .002$ [Fig 2, C]).

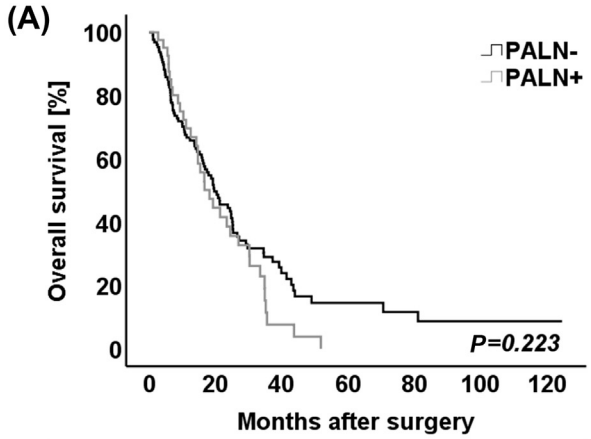
To assess survival after cancer recurrence in patients with PALN LAD, an analysis of PRS was performed. All 64 patients with metachronous relapse entered analysis (PALN+ $n = 11$; PALN− $n = 53$). The median PRS of 15.14 months (95% CI: 8.89−21.39 months) in patients who were PALN− was not statistically different when compared with the median PRS of 12.73 months (95% CI: 6.51−18.94 months) in patients who were PALN+ ($P = .923$ [Fig 2, D]).

Discussion

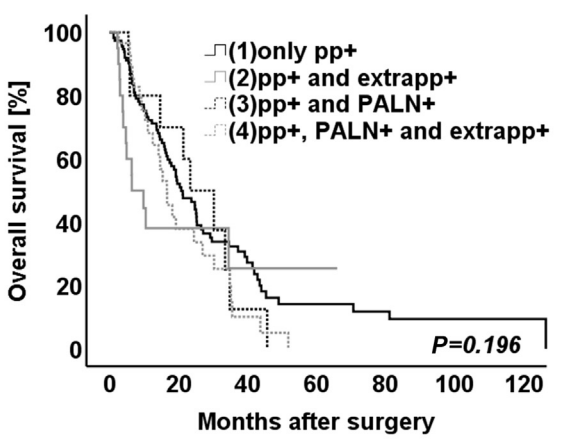
The present study elucidates the impact of PALN status in the largest published cohort of patients receiving structured PD—including aortocaval lymphadenectomy for hPDAC. PALN status was of no prognostic significance both in univariate and multivariate analysis of OS in our cohort. Likewise, patients receiving PALN LAD had no different OS compared with patients not receiving PALN LAD. However, although PALN status had no significant influence on OS, PALN+ patients suffered a significantly worse DSF, indicating the oncologic impact of PALN involvement.

Although still considered a major determinant of appropriate treatment stratification and prognosis, the UICC TNM staging system for pancreatic ductal adenocarcinoma (PDAC) has been a matter of debate due to the weak survival prediction. To improve staging, the recently published eighth TNM edition (2016) introduced a size-based T staging system and a refined N stage for PDAC.[14,16] Still, LN staging in PDAC remained inferior to pT stage for survival prediction.[16] Furthermore, the impact of distant LN metastases (M1) on survival remains elusive, complicating the decision of an upfront surgical approach versus a chemotherapeutic regime in these cases.

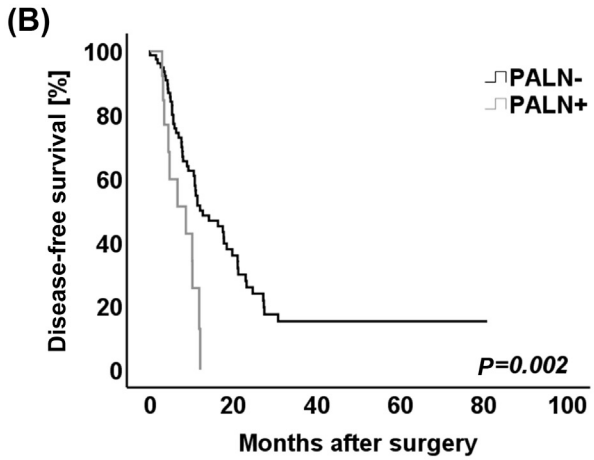
In a recent systematic review of 13 studies, PALN metastasis was correlated to poor prognosis in patients with PDAC.[17] Furthermore, the largest retrospective multicenter study from Japan, including 882 patients who had received PD with standardized PALN LAD, revealed similar survival outcomes.[18] Of note, positive resection



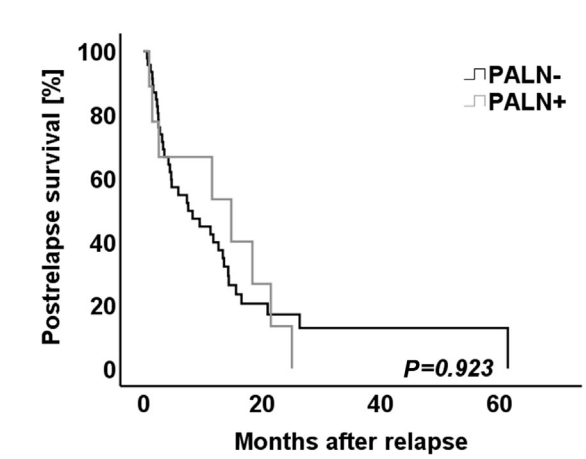
	0	20	40	60	80	100	120
PALN -	141	49	16	8	5	2	2
PALN +	40	16	3	0	0	0	0



	0	20	40	60	80	100	120
(1)	120	52	21	7	5	2	2
(2)	21	3	1	1	n/a	n/a	n/a
(3)	11	7	1	0	0	0	0
(4)	29	9	2	0	0	0	0



	0	20	40	60	80	100
PALN -	79	18	4	2	1	n/a
PALN +	14	0	0	0	0	0



	0	20	40	60
PALN-	53	6	2	1
PALN+	11	2	0	0

Fig 2. Kaplan-Meier curves for (A) overall survival of all patients stratified by PALN status and (B) overall survival of all patients stratified by metastasized lymph node stations. Only pp+ denotes patients with isolated peripancreatic lymph node metastases; pp+ and extrapp+ denotes patients with peripancreatic and extra peripancreatic lymph node metastases except PALN; pp+ and PALN+ denotes patients with peripancreatic and PALN involvement; and pp+, extrapp+, and PALN+ denote patients with metastasized peripancreatic, extra peripancreatic, and PALN. (C) Disease- free survival of all patients stratified by PALN status. (D) Postrelapse survival of all patients stratified by PALN status. The log-rank test was used to test for significance. *pp*, positive peripancreatic; *PALN*, para-aortic lymph node.

status (R+) and N-staging were heterogeneously distributed between patients who were PALN+ and PALN−, which limits the assessment of survival outcomes.[18] In contrast, Shrikhande et al[19] reported divergent results. In their study, a similar survival of patients who were PALN+ and PALN− PDAC after resection was demonstrated, albeit in a much smaller cohort.[19] Hackert et al[12] compared the survival after resection in M1 PDAC patients, including a subgroup with patients who were PALN+. They report long-term survival rates of 10% in resected patients who were PALN+.[19] These conflicting results are reflected in a recent consensus statement by the International Study Group on Pancreatic Cancer on structured extended LAD during PD for PDAC.[20]

Para-aortic LNs (PALN, LN16 a2 + b1) are still considered "distant" lymphatic metastases in PDAC, supposedly indicating a late stage in the lymphatic spread.[20] However, we detected no difference in distant LN involvement between patients who were PALN+ and PALN− in our cohort, indicating no extended lymphatic spread in patients who were PALN+, as proposed by others.[17,18] One explanation may be spread of cells through the mesopancreatic plane into the PALN, due to the close anatomic relation of the pancreatic head and the aorta and inferior vena cava, which was already postulated by Peparini.[21] Complete mesopancreatic excision was recently demonstrated to improve survival and reduce local recurrence, probably attributable to the high rate of

Table IV
Distribution of metachronous disease according to PALN status ($N = 93$)

	PALN− n = 79	%	PALN+ n = 14	%	P value
					.050
No metastases	28	35.0	4	26.7	
Hepatic	24	30.0	3	20.0	
Pulmonary	9	11.3	4	26.7	
Local	15	18.8	1	6.7	
Peritoneal	2	2.5	2	14.3	
Osseous	1	1.2	—	—	

Statistical significance was calculated by Mann-Whitney U test.
PALN, para-aortic lymph nodes.

mesopancreatic fat infiltration.[11] On the other hand, we did not detect a correlation between LN status and survival in our cohort. The removal of PALN might thus only mitigate the risk of local recurrence in patients with mesopancreatic fat infiltration and secure a tumor-free dorsal resection margin.[11] Taking the results of this study and previous studies[11] together, most patients with resectable hPDAC nevertheless suffer from a locally advanced disease (mesopancreatic infiltration rate of ~80%, positive nodal status ~80%, PALN+ status ~20%). This highlights the need for ongoing neoadjuvant trials.[22,23] These results also argue that, using the current preoperative standard, patients might not yet be stratified adequately. It may thus seem sensible to offer neoadjuvant treatment regimens not only to borderline-resectable or synchronously metastasized patients, but also to locally advanced patients with an oncologic high-risk mesopancreatic fat infiltration. Preoperative imaging cut-off points have to be reclassified and the quality of imaging has to be improved to detect those patients with up-to-date subradiographic LN involvement or local fat infiltration who are at high risk of shorter DFS, as well as incomplete resection (circumferential resection margin +).[24,25]

Furthermore, we and others[10] observed a poor correlation between preoperative CT scans and histopathologic analysis of PALN status, making the preoperative decision based on radiographic analysis even more challenging. The importance of LAD is additionally emphasized by the fact that skip-lymphatic metastases and a low yield in LAD are known prognostic factors for poor survival outcome in PDAC.[26] Our results thus demonstrate that subradiographic, histopathologic positive PALN nevertheless portend a worse DSF in patients suffering from patients with hPDAC.

One limitation of our analysis is the lack of randomization and the retrospective design. However, our study is the first to compare outcomes of patients who were PALN+ and PALN− after PD and structured PALN LAD for hPDAC, thus limiting selection bias. Another limitation of this study is the absence of a control group of patients in which PALN metastases were intraoperatively evident, but not resected.

Of note, the pattern of metachronous metastasis was statistically different in patients who were PALN+ and PALN− in our cohort, even if the number of patients included was limited. Although the majority of patients who were PALN− suffered from metachronous hepatic disease, patients who were PALN+ were more prone to pulmonary metastases. Chemotherapeutic treatment or surgical resection for isolated metachronous pulmonary metastatic disease has been demonstrated to significantly improve survival in metastatic PDAC.[27–29] Potentially, pulmonary metastasis was caused by lymphatic spread via the thoracic duct, and metachronous hepatic spread is most likely caused by intravasation via the portal vein. Of note, only patients with complete follow-up were included in the analysis of DFS, resulting in a smaller subset. However, as there was no obvious selection bias, our results presumably reflect the statistical relevance of the outcomes discussed earlier.

We were unable to detect a detrimental effect of PALN LAD on the postoperative morbidity. Patients receiving PD without PALN LAD during the study were included as internal control. There was no significant difference regarding LOS, complication rate, and mortality, which reflects the safety of PALN LAD during PD for hPDAC.[15]

Metastatic involvement of PALN is still considered distant metastasis (M1) by the American Joint Commission of Cancer and the UICC,[14,30] and resection is therefore not generally recommended.[20] Considering the results of this study and others,[10,12,31,32]

Table V
Univariate and multivariate analysis of patient collective for DFS ($N = 93$)

	Univariate analysis	Multivariate analysis		
	P value	P value	HR	CI (95%)
Age (≥/<median)	.109	.133	—	—
Sex (male/female)	.208	.168	—	—
T-stage (T1;T2/T3; T4)	.114	.871	—	—
N stage (N0/N1; N2)	.172	.168	—	—
PALN (PALN+/PALN−)	.002	.034	2.517	1.072–5.909
Grading (G1; G2/G3)	.265	.550	—	—
Pn (Pn1/Pn0)	.957	.841	—	—
L (L1/L0)	.198	.885	—	—
V (V1/V0)	.307	.948	—	—
R status (R0CRM−/R0CRM+; R1)	.907	.679	—	—
CTx (MD regime versus Gemca mono)	.868	.613	—	—

Analysis was performed by log-rank test.
CI, confidence interval; *CTx*, chemotherapy; DFS, disease-free survival; *HR*, hazard ratio; *L*, lymphatic invasion; MD, multidrug; *PALN*, para-aortic lymph nodes; *Pn*, perineural invasion; *V*, venous invasion.

this paradigm should be at least questioned. Reflecting the similar overall survival, it seems unjustified to regard PALN metastases as distant metastases or as an indicator for palliative treatment in PDAC patients.[18,33]

Complete surgical resection including local LN clearance and primary negative resection margins (R0) remain the goal of surgical therapy and the only opportunity for cure.[34–37] Routine removal of PALN may also improve dorsal margin clearance.

In conclusion, most patients with primarily resectable hPDAC still harbor advanced stages of disease. An adjustment of the international guidelines for the treatment of patients with PALN+ hPDAC has to be evaluated, as PALN status is unlikely to be correctly diagnosed preoperatively. However, PALN status was no prognostic factor in univariate and multivariate OS analysis. Extended LAD did not prolong OS when compared with patients without PALN LAD. Until sufficient and robust preoperative survival stratification of PDAC patients is feasible, PALN involvement should not preclude curative resection.

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Conflict of interest/Disclosure

The authors declare that they have no competing interests.

Supplementary materials

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