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Pancreatic ductal adenocarcinoma and paraaortic lymph nodes metastases: The accuracy of intraoperative frozen section

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ABSTRACT

Background: Pancreatoduodenectomy for pancreatic ductal adenocarcinoma (PDAC) with paraaortic lymph nodes metastases (PALN +) is associated with poor survival. Still, there are no current guidelines advocating systematic detection of PALN+.
Methods: All consecutive patients who underwent surgical exploration/resection with concurrent paraaortic (group 16) lymphadenectomy for PDAC between 2009 and 2016 were considered for inclusion. Resection was systematically aborted in case of intraoperative PALN + detection. Diagnostic performance of preoperative imaging upon blind review and intraoperative PALN dissection with frozen section (FS) for PALN detection were evaluated. Additionally, the prognostic significance of PALN + on overall survival (OS) was analyzed.
Results: Over the study period, among 129 patients undergoing surgery for PDAC, 113 had intraoperative PALN dissection with FS analysis. Median number of resected PALN was 3 (range, 1–15). Overall, PALN+ was found in 19 patients (16.8%). Upon blind review, preoperative imaging performed poorly for PALN + detection with a low agreement between imaging and final pathology (Kappa-Cohen index<0.2). In contrast, PALN FS showed high detection performances and strong agreement with final pathology (Kappa-Cohen index = 0.783, 95%CI 0.779–0.867, p < 0.001). Regarding survival outcomes, there was no difference between patients with PALN+ and patients not resected in the setting of liver metastases or locally unresectable disease found at exploration (p = 0.708).
Conclusions: Before PD for PDAC, intraoperative PALN dissection and FS analysis yields accurate PALN assessment and allows appropriate patient selection. This should be routinely performed and aborting resection should be strongly considered in case of PALN+.

Introduction

Pancreatoduodenectomy (PD) with perioperative chemotherapy stands as the only curative option for pancreatic ductal adenocarcinoma (PDAC) but actual 5-year overall survival (OS) rates remains below 20% [1,2]. Although both morbidity and mortality after PD have decreased overtime, patient selection remains critical to avoid futile resection in patients who might not benefit from surgery [3,4].

Retroduodenal and paraaortic lymph nodes (PALN) are known as being the primary lymphatic drainage pathway of the periampullary region [5]. Consequently, PALN metastases (PALN+) can be found at the time of resection in up to 30% [6]. PALN metastases are known as an adverse prognostic factor associated with a worse survival as compared to N1 disease [6]. In the setting of PDAC, PALN + disease is considered as stage IV disease in the Japanese Pancreas Society Classification (group 16) associated with a decreased OS similar to that of patients with unresected metastatic disease as already extensively reported in the literature [7–14].

Preoperative cross-sectional CT imaging has been reported as not reliable for assessing extraregional nodal involvement in periampullary cancers [15]. Consequently, routine paraaortic lymphadenectomy (group 16) with intraoperative frozen section (FS) during PD for PDAC has been advocated by some centers, with the

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recommendation to abort resection in case of metastatic involvement [14]. Yet, systematic preoperative PALN assessment and routine intraoperative PALN dissection with FS is not clearly recommended in current guidelines [16–18].

The current study first aimed to evaluate the diagnostic performance of preoperative imaging and intraoperative PALN dissection with FS for PALN involvement. Additionally, survival of patients who underwent systematic PALN dissection and FS was analyzed.

Methods

Study population

All consecutive patients who underwent surgical exploration/resection for a suspected PDAC between January 2009 and August 2016 were considered for inclusion. Patients with a final diagnosis of periampullary malignancy other than PDAC, benign periampullary tumor or chronic pancreatitis of the head of the pancreas were excluded. Additionally, patients who underwent pancreatic resection without concurrent PALN dissection and FS analysis were not included in analysis. All variables were retrospectively collected upon medical chart review.

Preoperative management

Preoperative evaluation included thoracoabdominal computed tomography (CT), to assess locoregional and distant disease extent. Endoscopic ultrasonography (EUS) was performed in order to refine diagnosis or assess local resectability when needed. Tumor fine needle aspiration was performed only in case of unclear diagnosis. Preoperative diffusion weighted liver MRI became routine in 2013 for ruling out liver metastases. Patients deemed borderline resectable or locally advanced were generally assigned to neoadjuvant chemotherapy first before reevaluation for resection. Preoperative biliary drainage was restricted to patients with acute cholangitis, renal failure, severe denutrition and was generally performed endoscopically. One week of preoperative immunonutrition was prescribed to all patients.

Operative management

Using either a laparoscopic or an open approach the peritoneal cavity was explored and tumor stage was assessed to rule out metastatic or unresectable disease. After a wide Kocher maneuver, the para-aortic region was inspected and palpated before performing lymphadenectomy of the group 16 (Fig. 1). FS analysis was systematically performed before starting resection. In case of positive PALN, resection was aborted and palliative by-pass surgery was performed at the discretion of the attending surgeon. Conversely, in case of negative PALN and in the absence of metastatic/unresectable disease, PD without pylorus preservation and with standard lymphadenectomy was performed. Reconstruction after PD was performed according to the Child technique. A wide omentoplasty covering vascular stumps and abdominal drainage were routinely performed.

Pathology examination

All harvested nodes were examined by frozen section analysis. Briefly, nodes were bisected along the longest axis after clearing away surrounding fat. The two halves were then frozen in a Shandon Cryomatrix (Thermo Electron Corporation, Cergy Pontoise, France); a section of each half was then stained with haematoxylin and eosin, and examined for the presence of metastases.

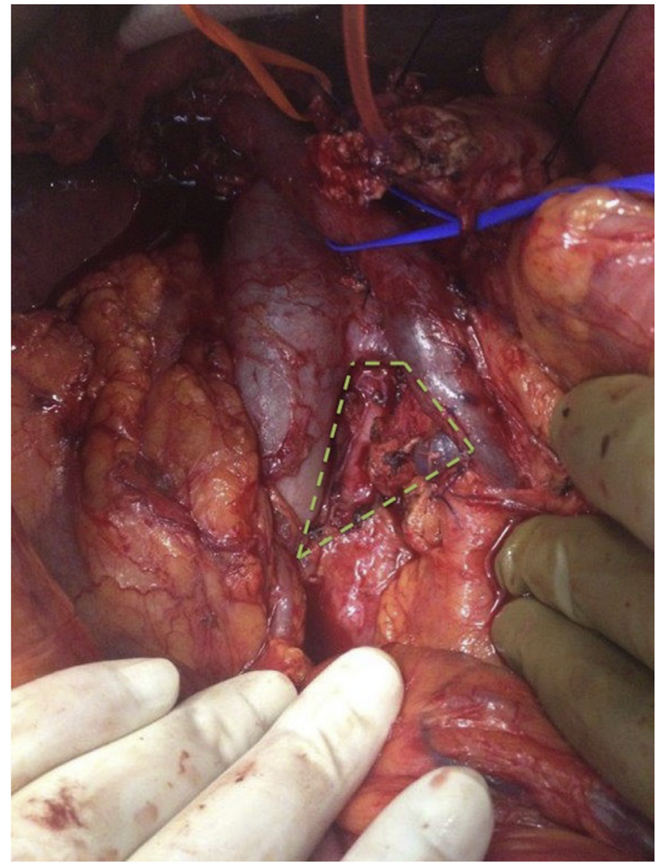


Fig. 1. Intraoperative view of the group 16 lymphadenectomy dissecting out all the lymphocellular tissue found below the left renal vein and between the left side of the inferior vena cava and the mesenteric root (green lines).

Micrometastases were not routinely searched at frozen section.

The remaining tissue was fixed in formalin overnight. After paraffin embedding, a 4-μm thick section of each half was stained with haematoxylin and eosin solution. Lymph nodes deemed as negative were subsequently examined for micrometastases.

Postoperative management

Ninety-day morbidity was graded according to the Dindo Clavien classification [19]. Adjuvant chemotherapy administration and postoperative follow-up were based on national guidelines [18].

Blinded radiological review

All images from patients who underwent PALN dissection were reviewed. Preoperative imaging included computed tomography (CT) and magnetic resonance imaging (MRI) performed within six weeks prior to surgery. These imaging studies were reviewed by one radiologist or one surgeon (A.D., A.B.) blinded to all clinical and pathological data. Reviewers excluded suboptimal imaging studies, such as CT or MRI without intravenous contrast. PALN were deemed suspicious when measured larger than 10 mm in the short axis and/or with an enlarged ovoid shape and/or with a heterogeneous internal architecture. Based on all available imaging and using these criteria, reviewers recorded their suspected diagnosis for each patient.

Statistical analysis

Categorical variables were summarized using percentages and continuous variables were summarized using the median (range). Characteristics of patients were compared using the chi-square test for categorical variables and the Mann–Whitney *U* test for continuous variables to determine statistically significant differences between groups. The diagnostic accuracy of each diagnostic modality was assessed using sensitivity and specificity calculation. Agreement between final pathology and other detection modalities was evaluated and graded using a Kappa–Cohen test [20,21]. Survival distributions were estimated using the Kaplan–Meier method. OS was calculated from the date of surgery to the date of death or last follow-up. All P-values were based on two-tailed statistical analysis and a P-value <0.05 was considered to indicate statistical significance. All analyses were performed with SPSS software, version 22.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Study population

Among the 193 patients who underwent surgical exploration for a periampullary tumor during the study period, 113 met study criteria (Fig. 2). Reasons for not proceeding with PALN dissection and FS analysis (n = 16) were based on preoperatively suspected diagnosis (n = 3, ampulloma or IPMN) or owing to findings of unresectable/metastatic disease at exploration (n = 4) and not clearly identified in medical records (n = 9). There was no trend towards more systematic PALN dissection with FS analysis overtime (p = 0.192).

Among the 113 patients included (Table 1), 4 patients (3.5%) underwent laparoscopic PALN dissection. Overall, 86 patients (76.1%) underwent pancreatic resection consisting of PD in 81 patients (94.2%) and total duodenopancreatectomy in five patients (5.8%). One patient underwent resection after response under neoadjuvant chemotherapy. Among the 27 other patients, resection was precluded and double by-pass surgery was performed in 15 patients (55.5%), gastrojejunostomy alone in eight patients (29.6%), choledocoduodenostomy alone in two patients (7.4%) and surgical exploration alone was performed in two patients (7.4%). Reasons for precluding resection were as follow: PALN + upon FS (n = 13), intraoperative finding of local unresectability (n = 6), intraoperative finding of occult liver metastases (n = 5), and distant nodal metastases (celiac, n = 2 and mesenteric, n = 1) found at exploration.

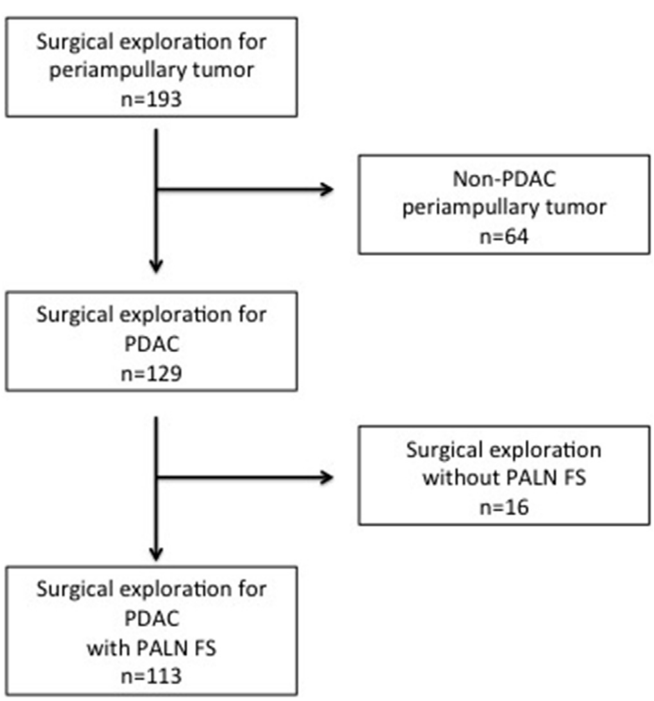


Fig. 2. Study flowchart.

Final pathology

Median number of resected PALN was 3 (range, 1–15). Overall, 19 patients (16.8%) had PALN + at final pathology. In case of PALN+, median number of positive nodes and median ratio were one (range, 1–6) and 0.66 (range, 0.13–1), respectively. Among patients deemed PALN + on final pathology (n = 19), 15 patients underwent palliative surgery due to PALN + on FS analysis (n = 13) or local unresectability while deemed PALN- on FS analysis (n = 2). The remaining four patients underwent curative-intent pancreatectomy while deemed PALN- on FS analysis.

Among resected patients (n = 86), 6 (7%), 7 (8.1%), 65 (75.6%) and 8 (9.3%) patients had pT1, pT2, pT3 and pT4 disease, respectively. Complete R0 resection rate was 81.3% (n = 70) and positive N1 disease was found in 60 patients (69.8%). Of note, four (4.6%) patients among those resected were PALN+. Regarding final pathology, PALN+ was not associated with pT status (p = 0.622), pN status (p = 0.310) and R status (p = 0.249) (Table 2).

Detection modalities and performances

Preoperative detection

Details regarding preoperative work-up are listed in Table 1. CT was the sole preoperative imaging in 25 patients (22.1%), 53 patients (46.9%) had two preoperative imaging modalities (CT + MRI, n = 23; CT + EUS, n = 29; MRI + EUS, n = 1) and 35 (31%) underwent preoperative CT, MRI and EUS. No patient was excluded because of the absence of optimal imaging for blind review. Upon blind review, involvement of PALN was suspected on CT (n = 17), on MRI (n = 6) Regarding EUS, PALN+ was suspected in 1 patient. In case of PALN-, imaging showed acceptable detection performances with high negative predictive value and specificity (Table 3). Conversely, in case of PALN+, detection performances were low. Agreement between imaging and final pathology was slight (Kappa-Cohen index<0.2) for all modalities (Table 3). Combining all available imaging for each patient did not increase agreement between imaging and final pathology (Kappa-Cohen index = 0.089, 95%CI 0.001–0.177, p = 0.259).

Intraoperative detection

Suspicion of PALN + upon intraoperative inspection and palpation was raised in two patients (1.8%). Agreement between intraoperative palpation and final pathology was slight (Kappa-Cohen index = 0.164, 95%CI 0.061–0.267, p = 0.002). Combining preoperative imaging with intraoperative palpation did not increase PALN assessment performances (Kappa-Cohen index = 0.101, 95%CI -0.004-0.206, p = 0.281). As listed in Table 3, FS showed high detection performances and strong agreement with final pathology (Kappa-Cohen index = 0.783, 95%CI 0.779–0.867, p < 0.001).

Outcomes and survival analysis

Overall mortality rate was 5.3% (n = 6). Overall morbidity and

Table 1
Patient characteristics.
Values are presented as mean (standard deviation), unless otherwise specified.

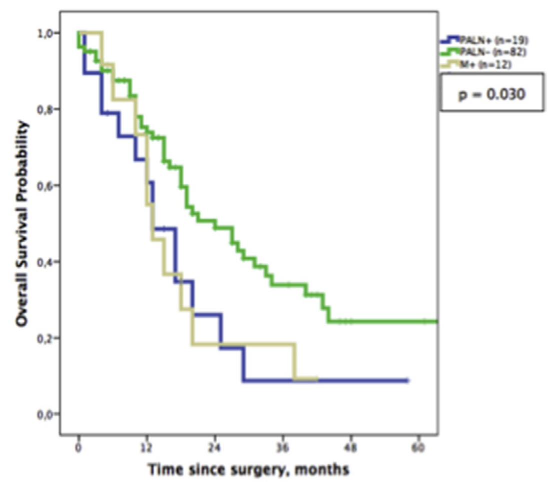
		Full cohort (n = 113)	PALN + (n = 19)	PALN − (n = 94)	*P*
Age, years		65.8 (10.3)	64.8 (10.8)	66 (10.3)	0.305
Gender	Male	60 (53.1%)	11 (57.9%)	49 (52.1%)	0.802
ASA score	1	15 (13.3%)	3 (15.8%)	12 (12.8%)	0.476
	2	67 (59.8%)	9 (47.4%)	58 (62.4%)	
	3	31 (27.7%)	7 (36.8%)	24 (25.8%)	
Preoperative imaging	TDM	112 (99.1%)	19 (100%)	93 (98.9%)	>0.999
	MRI	59 (52.2%)	14 (73.7%)	45 (47.9%)	0.047
	EUS	65 (57.5%)	13 (68.4%)	52 (55.3%)	0.322
CA 19–9>37, U/ml		36 (31.8%)	9 (47.3%)	27 (28.7%)	0.175
Preoperatively suspected PALN		20 (17.7%)	5 (26.3%)	15 (16%)	0.324
Intraoperatively suspected PALN		2 (1.8%)	2 (10.5%)	–	0.027
Positive PALN on FS		13 (11.5%)	13 (68.4%)	–	<0.001

Table 2
Final pathology in resected patients (n = 86).

		PALN + (n = 4)	PALN − (n = 82)	*P*
pT stage	1	–	6 (7.3%)	0.622
	2	–	7 (8.5%)	
	3	4 (100%)	61 (74.4%)	
	4	–	8 (9.8%)	
pN stage	0	–	22 (26.8%)	0.310
	1	4 (100%)	56 (68.2%)	
R status	0	2 (50%)	68 (83%)	0.249
	1	2 (50%)	14 (17%)	

severe morbidity rates were 46% (n = 52) and 16.8% (n = 19), respectively. No intraoperative or postoperative complication was specifically related to PALN. Adjuvant therapy was administered to 94 patients (83.2%). Median OS was 19 months (95%CI 16.5–21.5). The 1-, 3- and 5-year OS rates were 74, 29 and 12% respectively.

Median OS varied significantly according to resection completion and PALN status (p = 0.03, Fig. 3). Median OS was significantly higher in patients who underwent resection with PALN- (24 months, 95%CI 16.4–31.6) while median OS was similar between patients with PALN+ (median OS = 13 months, 95%CI 8.4–17.6) and patients not resected in the setting of liver metastases or locally unresectable disease found at exploration (median OS = 13 months, 95%CI 8.2–17.8, p = 0.708). The 1-, 3- and 5-year OS rates are displayed in Table 4. Among the four patients deemed PALN- on FS analysis while PALN + on final pathology and who underwent pancreatectomy, one died of multiorgan failure on POD 27 and three died of disease recurrence after 13, 17 and 24 months respectively.



Resected PALND- (n=82)	55	27	14	5	4
PALND+ (n=19)	11	3	1	1	-
M+ (n=12)	12	8	2	-	-

Fig. 3. Kaplan Meier estimates of overall survival for patients surgically explored for pancreatic ductal adenocarcinoma only.

Discussion

Paraaortic lymph node involvement in PDAC was found in 16.8% of the present cohort and was poorly detected on preoperative imaging. In this context, intraoperative PALN dissection and systematic FS analysis was found as an accurate and safe tool for PALN + detection that may help avoiding futile pancreatoduodenectomies.

When routinely performed in the setting of PDAC, PALN + disease is frequent, ranging from 14% to 29% [11,22]. Considering that preoperative detection of PALN + disease through imaging has been reported as inaccurate in previous series, there is a strong rationale routine PALN dissection and intraoperative assessment [23–25]. The current study confirmed low accuracy and poor agreement between preoperative imaging and final pathology. Further, combining preoperative imaging with intraoperative assessment based on inspection and palpation alone did not improve diagnostic accuracy, as previously reported [11]. Of note, while associated with PDAC resectability, CA19-9 serum levels appeared lower in patients with PALN- disease as compared to PALN + disease without reaching statistical significance [26]. Yet, elevated preoperative CA19-9 serum level was identified as a risk

Table 3
Diagnostic performances of imaging and frozen section for paraaortic lymph nodes assessment.

	Positive predictive value	Sensitivity	Negative predictive value	Specificity	Agreement
CT (n = 112)	23.5%	21%	84.2%	86%	0.074
MRI (n = 59)	50%	21.4%	79.2%	93.3%	0.184
EUS (n = 65)	33.3%	7.7%	80.3%	94.2%	0.062
FS (n = 113)	100%	68.4%	94%	100%	0.783

Table 4
Estimated overall survival rates.

	PALN-PDAC Resected (n = 86)	PALN + PDAC Not resected (n = 13)	Metastatic/LU PDAC Not resected (n = 14)
1-year OS	76%	67%	74%
3-year OS	26%	9%	8%
5-year OS	15%	–	–

LU, locally unresectable; PALN, paraaortic lymph nodes; PDAC, pancreatic ductal adenocarcinoma.

factor for PALN+ in larger series and should prompt intraoperative PALN FS analysis [27].

Intraoperative PALN FS showed high accuracy and strong agreement with final pathology. Nevertheless, six patients were falsely deemed negative upon FS analysis. Micrometastases were found in two of these patients on final pathology although macrometastases were missed at FS in four patients. According to the FS protocol, all harvested nodes were examined but full nodal tissue analysis was not performed. Indeed, FS was performed on one slice of each half node. This technique might have missed small metastases albeit only slightly larger than micrometastases defined as sized within 0.2 and 2 mm. As reported by Schwarz and colleagues, micrometastases detection remains challenging upon FS analysis [11]. In their series, 15 out of 90 patients had PALN micrometastases detected on immunohistochemical staining although initially deemed negative on FS and final pathology. Intraoperative micrometastases detection techniques would be needed for appropriate PALN disease detection.

In the current cohort, no difference was found in term of survival between patients not resected because of PALN + disease and those not resected for locally unresectable disease or metastatic disease to the liver. This observation confirmed results from two recent systematic reviews showing that OS in case of PALN involvement is inferior to patients with other N1 disease [6,14]. Similar conclusions were drawn in the setting of micrometastases [28–30]. However, aborting resection in case of PALN + remains debated as some authors advocate the potential curative effect of resection. In the current study, four patients with PALN + underwent resection and died from disease within 24 months after surgery. As reported in the current study series among others, survival in patients with PALN + disease did not differ from those observed in unresected metastatic population receiving palliative chemotherapy [6,11,31]. Based on these data, systematic PALN dissection and FS should be routinely considered for refining patient selection before PD. First, PALN dissection is safe and does not extend operative time as PALN are easily harvested during the Kocher maneuver that is a key step of PD. Second, PALN dissection is laparoscopically feasible and may thus avoid laparotomy. Third, PALN + disease was associated with dismal outcomes and whether those patients benefit from resection remains unlikely.

Considering this, the role of modern chemotherapy regimen in case of PALN + remains to be explored. One option in case of PALN + may involve upfront resection and adjuvant FOLFIRINOX. Indeed, adjuvant FOLFIRINOX is significantly assoiated to prolonged survival [32]. However, the benefit of such a therapeutic sequence in the setting of PALN + disease remains unclear. Instead, PALN + might benefit from neoadjuvant FOLFIRINOX as already observed in case of locally advanced disease [33]. In the current cohort, one patient with locally resectable PDAC underwent first surgical exploration aborted for PALN + before receiving Folfirinox induction. Because disease remained stable, R0 resection was subsequently performed. This patient recurred within 36 months and eventually died of disease 58 months after PALN + diagnosis. Further prospective studies in the setting of PALN + disease would be warranted.

Before PD for PDAC, intraoperative PALN dissection and FS analysis yields accurate PALN assessment and allows appropriate patient selection. This should be routinely performed and aborting resection should be strongly considered in case of PALN+.

Meeting presentation

This study was presented in part at the 13th World Congress of the International HepatoPancreatoBiliary Association, held in Geneva, Switzerland, September 2018.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2019.05.465.

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