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ORIGINAL ARTICLE

Outcomes of pancreatic adenocarcinoma that was not resected because of isolated para-aortic lymph node involvement

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Borderline Tumour

Summary
Purpose: Survival appears to be poor in cases of pancreatic ductal adenocarcinoma (PDAC) with para-aortic lymph node involvement (PALN+). However, resection is still performed in these cases because the prognostic impact of PALN+ remains controversial.
Methods: PALN+ was intraoperatively found in 14 patients (4.8%) with resectable PDAC who consequently did not undergo pancreatectomy.
Results: The median overall survival time after laparotomy was 21 months. The 1- and 3-year overall survival rates were 58.3% and 25%, respectively.
Conclusions: We support the advisability of reconsidering pancreatectomy in patients with intraoperatively detected PALN+ because the reported survival of such patients who undergo pancreatectomy is poorer than the survival observed for patients in our series.

Abbreviations

PDAC	pancreatic ductal adenocarcinoma
PALN	para-aortic lymph node
PALN+	para-aortic lymph node involvement

Introduction

For patients with pancreatic ductal adenocarcinoma (PDAC) who are eligible for surgery (upfront surgery for an initially resectable tumour or surgery after medical treatment for a borderline tumour), poor survival has been reported if there is para-aortic lymph node involvement (PALN+) [1—3]. Intraoperative frozen section examinations have confirmed PALN+ in 14% of patients with resectable PDAC [3], and such patients have exhibited worse survival than patients with PALN+ confirmed by definitive histological examination. Patients with intraoperatively detected PALN+ have appeared to exhibit the same survival as patients for whom visceral (i.e., liver and/or peritoneal) metastatic disease was confirmed and pancreatectomy was consequently not

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achieved [4—6]. Based on these findings, in 2011, we started routine sampling of para-aortic lymph nodes as the first stage of pancreatectomy for resectable PDAC. If PALN+ was identified intraoperatively, we opted not to perform the planned pancreatectomy.

The aim of this study was to determine survival outcomes for patients who did not undergo pancreatectomy due to PALN+ but instead received exclusive medical treatment.

Materials and methods

From January 2011 to May 2017, 291 patients underwent laparotomy for PDAC at Institut Paoli-Calmettes, Marseille, France. Data were retrospectively collected in a prospective database.

All patients selected for this study were either initially eligible for pancreatic resection or eligible after induction chemotherapy in cases involving initially borderline tumours, based on NCCN guidelines [7] (no patients received preoperative chemoradiation). Diagnosis and initial staging included clinical examination; CT (with arterial and venous phases and high-resolution examinations of thin sections around pancreatic tissue and surrounding vascular structures); endoscopic, ultrasound-guided biopsies with 22-gauge Wilson-Cook needles in cases involving a tumour that required immediate medical treatment; and, under non-cholestatic circumstances, an evaluation of carbohydrate antigen 19-9 (CA19-9) serum level. Resectability was assessed by experienced pancreatic surgeons during a multidisciplinary meeting.

Surgery and postoperative treatment

Patients without evidence of metastatic intraabdominal spread at laparotomy underwent a large Kocher manoeuvre: PALN of the 16b1 station (according to the Japan Pancreas Society) were removed and were subjected to intraoperative frozen section analysis. In cases with PALN+, pancreatectomy was not achieved even if the tumour was determined to be resectable. With respect to biliary/digestive tract management, our approach was to perform surgical bypass only in patients who required multiple (≥ 2) preoperative endoscopic procedures to ensure biliary track vacuity or in patients with symptoms of biliary stent dysfunction and/or gastric outlet obstruction at the time of laparotomy. For the remaining patients, our approach was to not perform routine surgical bypass and to opt for an ''on demand'' endoscopic policy. After definitive confirmation of PALN+, patients received further treatment based on oncologist recommendations (i.e., FOLFIRINOX or a gemcitabine-based regimen depending on a patient's age and/or performance status).

Collected data

Age, sex, tumour type (i.e., resectable or borderline), surgery duration (minutes, mn), the necessity of biliary/digestive bypass procedures, postoperative morbidity (according to the Clavien-Dindo classification [8], with Clavien-Dindo grade 3 and Clavien-Dindo grade 4 morbidities defined as severe complications), 30-day mortality rate, type of postoperative chemotherapy regimen and number of courses administered were recorded. The number of resected PALN and number of PALN+ analysed were noted.

Table 1 Characteristics, postoperative courses, histological findings, and adjuvant treatment of patients with PALN+ detected by frozen section examination.

Patients	($n = 14$)
Sex ratio, M/F	1.3
Age (years)	68 ± 10.4
Mean BMI (kg/m^2)	25.4 ± 2.18
Borderline tumour/neoadjuvant chemotherapy	5 (35.7)/5 (35.7)
Mean number of chemotherapy cycles prior to laparotomy	5 ± 4.5
Biliary stenting	11 (78.6)
Preoperative CA19-9 Serum Level (IU/mL)	158.3 ± 160.6
Mortality	0
Overall morbidity	4 (28.6)
Clavien-Dindo grade 3—4 morbidity	2 (14.3)
Mean resected PALN	3 ± 2.1
Mean lymph node ratio	0.66 ± 0.33
Postoperative chemotherapy	14 (100)

Categorical variables are described in terms of frequencies (n/N) and percentages (%). The distributions of continuous variables are described in terms of means $\pm$ standard.

Follow-up was ensured by physicians and included clinical examinations, routine chest and abdominal CT scans, and determinations of CA19-9 serum levels. Survival time since laparotomy and cause of death (if applicable) were recorded; the censor date was September 1st, 2017.

Statistical analysis

Categorical variables are described in terms of frequencies and percentages. The distributions of continuous variables are described in terms of means $\pm$ standard error. Kaplan-Meier estimates of overall and progression-free survival were calculated from the date of surgery and compared using the log-rank test. The threshold for statistical significance was set at $P < 0.05$. Data analyses were performed using GraphPad Prism software, version 5.0d (GraphPad Software, Inc., La Jolla, CA).

Results

We identified 14 patients (4.8%) with a resectable tumour who were intraoperatively contraindicated for pancreatectomy because of PALN+. No patients were lost to follow-up, and the mean follow-up duration was 35 ± 22 months.

Patient characteristics and treatment induction

The mean age of the patients was 68 years (Table 1). Five patients (35%) had a borderline tumour and received neoadjuvant chemotherapy (FOLFIRINOX, $n = 4$; gemcitabine, $n = 1$). Preoperative biliary stenting was needed for 11 patients (78.6%). The mean CA19-9 serum level at the time of laparotomy was 158 ± 132 IU/mL.

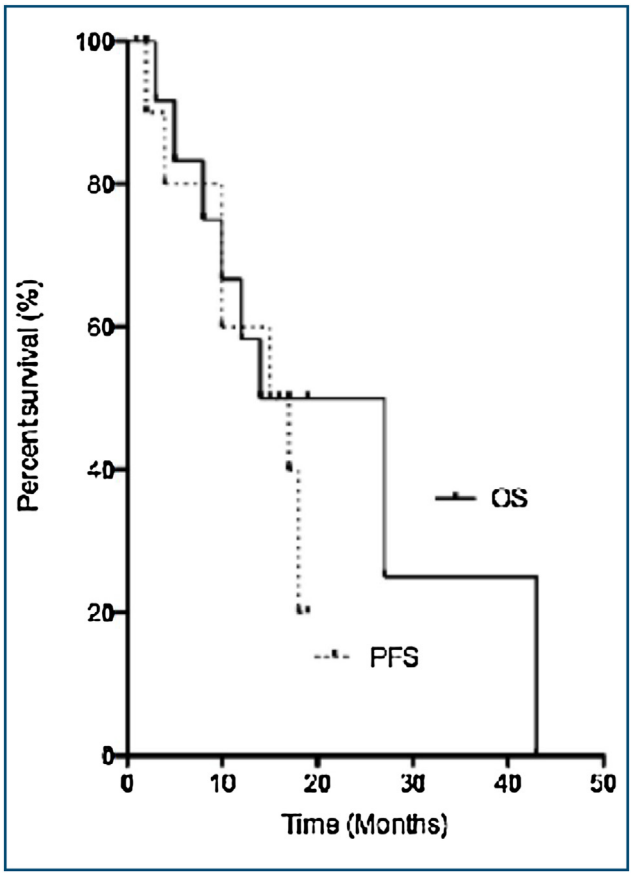

Figure 1. Overall survival (OS) and progression-free survival (PFS) rates.

Surgery, postoperative courses, pathological findings, and postoperative treatment

The mean surgery duration was 65 ± 19 mn. No patients required biliary or digestive bypass (Table 1). The overall morbidity rate was 28%, and severe complications occurred in 2 patients (14%): one patient had a postoperative angiocholitis with necessity of an endoscopic clearance of the biliary tract and one patient needed re intervention for postoperative symptomatic hematoma. No patient died postoperatively. The mean number of resected PALN was $3 \pm 2{,}1$, and the mean lymph node ratio on the was $0.66 \pm 0{,}33$. Definitive histopathology confirmed the frozen section results in 100% of cases.

All patients received at least one course of postoperative chemotherapy (gemcitabine, $n = 8$; FOLFIRINOX $n = 6$). Seven patients (50%) received two different lines of chemotherapy, and 3 patients (21%) received chemoradiation. Seven patients (50%) required endoscopic procedures for biliary obstruction and 4 (28,6%) of them also required a duodenal stent.

Survival

During follow-up, 7 patients (50%) died from disease progression due to metastatic spread, 4 patients (28.6%) remained alive without disease progression, 2 patients (14.3%) remained alive with metastatic disease, and one patient (7.1%) died from a lung infection during chemotherapy (Fig. 1). The median overall survival time after laparotomy was 21 months, and there were no significant survival differences between patients with initially resectable tumours and patients with borderline tumours ($P = 0.9$). The 1- and 3-year overall survival rates for all patients were 58.3% and 25%, respectively. The median progression-free survival time was 16 months.

Discussion

Our series showed that not proceeding to pancreatectomy in cases involving the intraoperative detection of PALN+ led to interesting overall survival outcomes.

PALN+ has been recognized as a poor prognostic factor since 2006 [2], and it has been suggested that patients with PALN+ should be regarded as metastatic patients. However, initial reports still referred to PALN+ detected postoperatively during definitive pathological analysis. In 2014, it was confirmed that patients with intraoperatively detected PALN+ had markedly reduced median survival of approximately 9 months [9,10] worse than that of patients with PALN+ detected during definitive pathological analysis. We can hypothesize that intraoperative detection could be facilitated by wider lymph node involvement, which would indicate more advanced disease and correspondingly worse prognoses. Despite these findings, the prognostic significance of PALN+ continues to be debated [11,12]. However, we were convinced that intraoperative detection of PALN+ is a relevant prognostic factor and chose not to perform planned pancreatectomy for patients with intraoperatively detected PALN+.

It should have been better to avoid useless surgical exploration using preoperative exploration but the preoperative accuracy of PALN+ diagnosis is still insufficient, especially in the absence of PALN enlargement, and surgical exploration is mandatory because of possible false negative [13,14].

Our exclusive medical treatment led to a median overall survival time of 21 months, which was longer than the survival time for patients with intraoperatively detected PALN+ who underwent pancreatectomy in several reported series [15,16] (Table 2). Moreover, it has been recently reported, in a Korean series, similar postoperative overall survival rates for patients who underwent potentially curative pancreatectomy with R0 resection [17].

Several arguments could explain these results. First, our series included only fit patients with resectable disease based on careful abdominal examination. Second, our patients did not experience postoperative immune depression or severe postoperative morbidity due to a major surgery, which might have delayed or precluded necessary adjuvant therapy [18,19]. Third, recent progress due to FOLFIRINOX chemotherapy [20,21]. Thus, on the one hand, we could support the perspective that our strategy was appropriate because it allowed patients to receive more relevant treatment (i.e., chemotherapy in a metastatic situation). On the other hand, we did not observe long-term survival in our series, and the question of whether to take advantage of the opportunity to perform a pancreatectomy could therefore be debated. Indeed, several reported series have described patients who exhibited long-term survival despite PALN+ [22,23], and these data suggest that certain patients with intraoperative PALN+ might benefit from pancreatectomy. Those series unfortunately didn't have a chemotherapy group control to access the fact that surgery provide better results than chemotherapy alone. Additional knowledge regarding the genomic characteristics of PDAC

Table 2 Reported series indicating the impact of PALN+ on overall survival among patients with PDAC.

	n, (%)	Intraoperative detection	Pancreatectomy achieved	Median survival time, (months)
Yoshida et al. [1]	9 (26)	No	Yes	8
Doi et al. [2]	19 (14)	No	Yes	5,1
Shimada et al. [3]	27 (20)	No	Yes	13
Schwarz et al. [4]	12 (11)	Yes	Yes	9,7
Sho et al. [16]	102 (12)	No	Yes	16,9
Present Series	14 (5)	Yes	No	21

may facilitate the selection of good candidates for a curative resection strategy, even maybe among patients with intraoperatively detected PALN+ [24]. However, given that we could not identify patients who might be good candidates for resection, an aggressive approach of performing pancreatectomy to treat metastatic disease should not be routinely proposed; instead, a chemotherapy-first strategy should be suggested.

All obstructive symptoms have been managed endoscopically but half of the patients needed a postoperative endoscopic procedure. This can lead to discuss the systematic biliary and duodenal surgical bypass during the explorative procedure but this may induce an extended delay to postoperative chemotherapy and should be evaluated.

Our series included extremely few patients, and we could not reach indisputable conclusions. However, we are convinced that PALN staging must be included in the decision-making tree for patients diagnosed with resectable PDAC. We then started to include systematic PALN sampling in the preoperative laparoscopic exploration [25] for patients diagnosed with resectable PDAC. Indeed, patients with PALN+ detected by frozen section analysis should be spared from pancreatectomy and receive only chemotherapy. Patients with PALN+ found on definitive pathologic examination should be included in a trial to evaluate the interest of a secondary resection after chemotherapy if the primary tumor remains resectable without evidence of metastatic disease on imaging. This trial could also include the evaluation of an extended lymphadenectomy which can show an interest in this particular indication, with already known distant lymph node metastatic spread.

Conclusions

Our study suggested that examination of frozen sections of PALN samples should help avoid deleterious pancreatectomy. We support the idea that intraoperative PALN sampling must be systematically integrated into the management strategy for PDAC. Furthermore, laparoscopy should be useful for identifying patients who are ineligible for pancreatectomy or patients who should be included in a trial of neoadjuvant chemotherapy.

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Disclosure of interest

The authors declare that they have no competing interest.

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