

## SHORT COMMUNICATION

# Para-aortic Lymph Node Status in Patients with Resected Distal Cholangiocarcinoma

Héloïse Seux<sup>1</sup>, Jonathan Garnier<sup>1</sup>, Jacques Ewald<sup>1</sup>, Ugo Marchese<sup>1</sup>, Flora Poizat<sup>2</sup>, Jean-Robert Delpero<sup>1</sup>, Olivier Turrini<sup>3</sup>

<sup>1</sup>Department of Surgical Oncology, Institut Paoli-Calmettes, Marseille, France

<sup>2</sup>Department of Pathology, Institut Paoli-Calmettes, Marseille, France

<sup>3</sup>Aix-Marseille University, Institut Paoli-Calmettes, Department of Surgical Oncology CNRS, Inserm, CRCM, Marseille, France

### ABSTRACT

**Background** The status of the para-aortic lymph node in pancreaticoduodenectomy patients has been thoroughly reported concerning pancreatic ductal adenocarcinoma, but not for other malignancies. The present study evaluated para-aortic lymph node status and its impact on eligible pancreaticoduodenectomy patients with distal cholangiocarcinoma. **Methods** From 2011 to 2019, all patients in our center who underwent pancreaticoduodenectomy were prospectively analyzed. In patients with suspected distal cholangiocarcinoma or pancreatic ductal adenocarcinoma, a frozen para-aortic lymph node section was routinely created. Sections reported as negative were immunohistochemically analyzed for micro-metastases. This study included all distal cholangiocarcinoma tumor specimens (not pancreatic ductal adenocarcinoma), as confirmed by an experienced pathologist. **Results** Forty-two patients underwent pancreaticoduodenectomy for distal cholangiocarcinoma. The median number of para-aortic lymph node analyzed was 2 (range 1-7) out of a median number of 15 lymph nodes. The R1 resection rate was 19%. All Para-aortic lymph node section analyses were negative, as were the definitive pathology results; overall median survival was 59 months. **Conclusion** Para-aortic lymph nodes are a rare site of lymphatic spread in patients with distal cholangiocarcinoma. Although our small sample size precludes definitive conclusions, it highlights the debate about lymphatic drainage in distal cholangiocarcinoma.

### INTRODUCTION

Classification of cholangiocarcinoma depends on the anatomical location, and it is divided into intrahepatic, perihilar, or distal subtypes. Distal Cholangiocarcinoma (DC) originates anywhere from the cystic duct to the ampulla of Vater and mainly requires a Pancreaticoduodenectomy (PD) when deemed resectable. Even though the prognosis is poor [1], patients with DC tend to have better survival outcomes than those with Pancreatic Ductal Adenocarcinoma (PDAC). In patients with PDAC, Para-Aortic Lymph Node (PALN) involvement was identified as a prognostic factor [2] when detected intra-operatively

by frozen section analysis. Despite the lack of consensus on a valid PD, our strategy is not to resect when positive intraoperative PALNs are found [3]. As the indisputable distinction between PDAC and other periampullary tumors is sometimes difficult to confirm preoperatively, we have routinely assessed the PALN status in patients eligible for PD with malignant pancreatic head tumours. Although they arise from the same anatomical location, PDAC and DC may vary in their lymphatic spread [4]. The present study aimed to evaluate PALN status and its impact on patients with DC eligible for a PD.

### METHODS

#### Patient Selection

From January 2011 to December 2019, 63 patients with DC underwent curative PD at Paoli-Calmettes Institute (Marseille, France). Of them, forty-two patients had available information about their pathological PALN status. Twenty-one patients did not have a PALN resection because the supposed aetiology was not PDAC or DC; however, they were ultimately diagnosed with DC. The study was approved by the Institutional Review Board. The study participants provided written informed consent as their data are listed in our declared prospective institutional database and labelled

Received May 18<sup>th</sup>, 2020 - Accepted July 06<sup>th</sup>, 2020

**Keywords** Distal cholangiocarcinoma, Para-aortic lymph node, Para-aortic sampling

**Abbreviations** PALN para-aortic lymph node; PD pancreaticoduodenectomy; PDAC pancreatic ductal adenocarcinoma; DC distal cholangiocarcinoma; BMI Body Mass Index; FS Frozen-Section; PE Paraffin-Embedded; POPF Postoperative Pancreatic Fistula;

**Correspondence** Jonathan Garnier  
Department of Surgical Oncology,  
Institut Paoli-Calmettes, Marseille, France

**Tel** +33491223660

**Fax** +3349223550

**E-mail** garnierj@ipc-unicancer.fr

by the National Institute for Data Protection (CNIL N°Sy50955016U; NCT02871336). The study protocol adhered to the tenets of the Declaration of Helsinki. All patients were initially staged following NCCN guidelines, and all cases were discussed and validated for surgery during a multidisciplinary board meeting.

### Operative Technique

After careful abdominal exploration to eliminate the possibility of metastatic disease, PALN sampling (station 16b1 of the Japanese staging and classification for pancreatic and periampullary cancer) [5] was performed after an extended Kocher manoeuvre by harvesting the lymphocellular aortocaval tissue located below the left renal vein to the origin of the inferior mesenteric artery. We routinely achieved frozen sections (except in six patients due to technical issues). Half of the collected PALNs were stained with haematoxylin and eosin and examined for the presence of metastases. The remaining sections were for paraffin embedding examinations. PALNs that were negative were further analysed immunohistochemically for micrometastases detection. All tumours were analysed according to a standardized pathological protocol, and an experienced pathologist confirmed that they were DCs (not PDACs) [6, 7].

### Studied Variables

Numerous clinical variables were evaluated: age, sex, BMI, biliary stenting, number of PALNs examined, positive PALNs (after frozen section or at definitive histological report), numbers of examined and positive lymph nodes, margin status (i.e., R0 or R1 resection), tumor size or stage, postoperative morbidity according to the Clavien-Dindo classification, and survival.

### Statistical Analysis

Analyses were performed using GraphPad Prism 8 (La Jolla, CA, USA). Categorical factors were compared using Fisher’s exact test or chi-squared test, and continuous variables were analysed using the Student’s t-test. Overall survival was calculated according to the Kaplan-Meier method. All statistical significance levels were set at  $P < 0.05$ .

### RESULTS

Patient characteristics, histopathological analysis of the operative specimens, postoperative courses, and survival are summarized in **Table 1**. The median number of PALN analysed was 2 (range 1-7) out of a median of 15 lymph nodes. All PALN frozen section analyses were negative, as were the definitive pathology results. Most patients had an advanced stage (stage I: 11.9%; stage II: 38.1%; stage III: 50%) and R1 resection rate was 19%. Postoperative Pancreatic Fistula (POPF) occurs in 43% leading to a 24% of Clavien  $\geq 3$  complications, and 7% of postoperative deaths. The median overall survival time was 59 months. The 5-year overall survival rate was 48.6%.

**Table 1.** Patient characteristics, pathologic finding, and outcomes.

Patients, n	42
Sex Male, n (%)	20 (48)
Age, mean (SD)	71 ( $\pm$ 8.13)
BMI, mean (SD)	23.9 ( $\pm$ 3.38)
Biliary stenting, n (%)	38 (90.5)
<b>Pathology</b>	
Median number of resected PALN (range)	2 (1-7)
FS, n (%)	36 (85.7)
Positive FS	0
PE, n (%)	42 (100)
Positive PE	0
Median number of LN (range)	15 (0-33)
Positive LN, n (%)	27 (64.3)
Tumour Stage, n (%)	
I	5 (11.9)
II	16 (38.1)
III	21 (50)
R1 Resection Status, n (%)	8 (19)
Mean Tumour Size, mm (SD)	25 ( $\pm$ 12.7)
<b>Outcomes, n (%)</b>	
Overall morbidity	24 (57.1)
Grade III-V morbidity	10 (23.8)
POPF	17 (43.6)
In Hospital Mortality	3 (7)
<b>Survival</b>	
Median (month)	59
5-years overall (%)	48.6

SD Standard Deviation; BMI Body Mass Index; PALN Para-aortic Lymph Node; FS Frozen-Section; PE Paraffin-Embedded; LN Lymph Node; POPF Postoperative Pancreatic Fistula

### DISCUSSION

During an eight-year study, we analyzed forty-two PDs for DC, and PALNs were not found to be a site of lymphatic spread in patients with DC. In several reports, tumor-infiltrative PALNs were found in about 10% of patients with PDAC and were associated with poor survival [2]. To our knowledge, PALN status in patients who underwent PD for malignant tumors other than PDAC has yet been reported. We want to emphasize that an experienced pathologist performed all histo-pathological analyses; this ensures accurate diagnosis of DC and also the relevance of the PALN analysis even if the median number of PALN analyzed was low. Although our small sample size precludes definitive conclusions, it highlights the debate about lymphatic drainage in DC.

Yoshida et al. [8] reported a high rate (55%) of tumor infiltrated PALNs in patients with DC that has never before been observed. None of these PALNs were involved in our study (despite a majority of tumor stages II and III according to the 7<sup>th</sup> edition of the AJCC staging), only 13% and 7.5% in the more recent studies [9, 10]. Overall, lymph node status (N+) in patients with DC was consistently reported as similar to patients with PDAC, and this was confirmed here with a 64% tumor-infiltrated lymph node status. However, the lymphatic network of the pancreatic head is complex, and mechanisms regulating lymphatic invasion are poorly understood. Furthermore, DC seems

to have a similar capacity for lymphatic spread as PDAC, but does not seem to reach the PALNs despite the claims of previous literature [11]. As PDAC and DC are different diseases with a unique extension [12] including within the DC subtype [13, 14, 15] it makes sense that a different lymphatic network should result in a different PALN invasion capacity.

## CONCLUSION

Our findings suggest that PALN sampling and frozen section examination is futile for analyzing DC. However, as the specific preoperative distinction between DC and PDAC is difficult, PALN dissections during PD must be routinely accomplished in uncertain cases. The question remains about adjuvant treatment in patients with positive PALN on Paraffin-Embedded (PE) analysis, as they have to be assumed to be metastatic. In such situations, unusual adjuvant therapy could be considered rather than the standard regimen of capecitabine treatment.

---

## Conflicts of Interest

All named authors hereby declare that they have no conflicts of interest to disclose.

---

## REFERENCES

1. Ethun CG, Lopez-Aguilar AG, Pawlik TM, Poultsides G, Idrees K, Fields RC, et al. Distal Cholangiocarcinoma and Pancreas Adenocarcinoma: Are They Really the Same Disease? A 13-Institution Study from the US Extrahepatic Biliary Malignancy Consortium and the Central Pancreas Consortium. *J Am Coll Surg* 2017; 224:406-413. [PMID: 28017812]
2. Schwarz L, Lupinacci RM, Svrcek M, Lesurtel M, Bubenheim M, Vuarnesson H, et al. Para-aortic lymph node sampling in pancreatic head adenocarcinoma. *Br J Surg* 2014; 101:530-538. [PMID: 24633831]
3. Marchese U, Ewald J, Gilibert M, Delpero J-R, Turrini O. Outcomes of pancreatic adenocarcinoma that was not resected because of isolated para-aortic lymph node involvement. *J Visc Surg* 2019; 156:97-101. [PMID: 30026012]
4. Pomianowska E, Westgaard A, Mathisen Ø, Clausen OPF, Gladhaug IP. Prognostic Relevance of Number and Ratio of Metastatic Lymph Nodes in Resected Pancreatic, Ampullary, and Distal Bile Duct Carcinomas. *Ann Surg Oncol* 2013; 20:233-241. [PMID: 22893118]
5. Tol JAMG, Gouma DJ, Bassi C, Dervenis C, Montorsi M, Adham M, et al. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). *Surgery* 2014; 156:591-600. [PMID: 25061003]
6. Verbeke CS, Gladhaug IP. Resection margin involvement and tumour origin in pancreatic head cancer. *Br J Surg* 2012; 99:1036-1049. [PMID: 22517199]
7. Delpero JR, Bachellier P, Regenet N, Le Treut YP, Paye F, Carrere N, et al. Pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: a French multicentre prospective evaluation of resection margins in 150 evaluable specimens. *HPB* 2014; 16:20-33. [PMID: 23464850]
8. Yoshida T, Aramaki M, Bandoh T, Kawano K, Sasaki A, Matsumoto T, et al. Para-aortic lymph node metastasis in carcinoma of the distal bile duct. *Hepatogastroenterology* 1998; 45:2388-2391. [PMID: 9951929]
9. Nappo G, Borzomati D, Perrone G, Valeri S, Amato M, Petitti T, et al. Incidence and prognostic impact of para-aortic lymph nodes metastases during pancreaticoduodenectomy for peri-ampullary cancer. *HPB* 2015; 17:1001-1008. [PMID: 26335256]
10. Hempel S, Oehme F, Müsle B, Aust DE, Distler M, Saeger H-D, et al. Prognostic impact of para-aortic lymph node metastases in non-pancreatic periampullary cancer. *World J Surg Oncol* 2020; 18:16. [PMID: 31964383]
11. Yoshida T, Matsumoto T, Sasaki A, Morii Y, Shibata K, Ishio T, et al. Lymphatic spread differs according to tumor location in extrahepatic bile duct cancer. *Hepatogastroenterology* 2003; 50:17-20. [PMID: 12629981]
12. Menon KV, Gomez D, Smith AM, Anthony A, Verbeke CS. Impact of margin status on survival following pancreatoduodenectomy for cancer: the Leeds Pathology Protocol (LEEPP). *HPB* 2009; 11:18-24. [PMID: 19590619]
13. Kamposioras K, Anthony A, Fernández Moro C, Cairns A, Smith AM, Liaskos C, et al. Impact of intrapancreatic or extrapancreatic bile duct involvement on survival following pancreatoduodenectomy for common bile duct cancer. *Br J Surg* 2014; 101:89-99. [PMID: 24375301]
14. Miyazaki M, Ohtsuka M, Miyakawa S, Nagino M, Yamamoto M, Kokudo N, et al. Classification of biliary tract cancers established by the Japanese Society of Hepato-Biliary-Pancreatic Surgery: 3(rd) English edition. *J Hepato-Biliary-Pancreat Sci* 2015; 22:181-196. [PMID: 25691463]
15. Primrose JN, Fox RP, Palmer DH, Malik HZ, Prasad R, Mirza D, et al. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. *Lancet Oncol* 2019; 20:663-673. [PMID: 30922733]