

## Adenocarcinoma of the pancreas: Does prognosis depend on mode of lymph node invasion?



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### Abstract

**Background:** Lymph node (LN) invasion in pancreatic ductal adenocarcinoma (PDAC) is the most important prognostic factor after surgical resection. The mechanisms of LN invasion include lymphatic spreading and/or direct extension from the main tumor. However, few studies have assessed the impact of these different patterns of invasion on prognosis.

**Patients and methods:** Pathologic reports of pancreatic resections for PDAC from 1997 to 2007 were retrospectively analyzed. The mode of LN invasion was defined as follows: standard lymphatic metastases (S), contiguous from the main tumor (C) and standard with extracapsular invasion (EI). Clinical outcomes were compared according to the mode of invasion and the number of invaded LN.

**Results:** 306 patients were reviewed. Median age at resection was 61 years (range, 34–81). Eighty seven patients were N– (28.9%) and 214 were N+ (71.1%). Of the N+ patients, 195 (91.1%) were S+, 35 (16.3%) were C+, and 24 (12.3% of the S+ patients) were EI+. Median survival in N+ patients was lower than in N– patients (29 vs. 57 months,  $p < 0.001$ ). In patients without standard involvement, C+ patients ( $n = 19$ ) had worse survival than C– patients ( $n = 47$ ) (34 vs. 57 months,  $p = 0.037$ ). In S+ patients, C status was correlated with prognosis when the number of LN S+ was  $< 2$  ( $p = 0.07$ ). EI status had no influence on prognosis. On multivariate analysis, only perineural invasion ( $p = 0.02$ ) and LN ratio ( $p = 0.042$ ) were independent prognostic factors.

**Conclusion:** Direct invasion of LN by the tumor is predictive of reduced survival, but has little impact compared to standard LN involvement and perineural invasion.

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**Keywords:** Pancreatic cancer; Lymph node; Prognosis

### Introduction

Surgical resection is the only curative treatment of pancreatic ductal adenocarcinoma (PDAC). Adjuvant gemcitabine-based chemotherapy has been shown to

decrease recurrence rates and to improve overall survival.<sup>1,2</sup> However, adequate indication for adjuvant chemotherapy can be hard to define, particularly when adverse prognostic factors are absent.

Lymph node (LN) involvement in PDAC is one of the strongest adverse prognostic factors, with five-year survival rate falling from 40% to less than 10% in cases of metastatic LN.<sup>3,4</sup> LN involvement is usually a binary criterion, defined as positive or negative. However, both mode of LN spreading and number of invaded LN could have an impact on survival.<sup>3,5</sup>

Classically, LN invasion is the consequence of migration of tumor cells in the lymphatic system. Studies on the value

*Abbreviations:* PDAC, pancreatic ductal adenocarcinoma; LN, lymph nodes; LNR, lymph node ratio; IPMN, intraductal papillary mucinous neoplasm; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy.

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of extended lymphadenectomy corroborate this mechanism since distant LN metastases without involvement of the peripancreatic LN have been exceptionally observed.<sup>6</sup> Migration of these tumor cells is first sinusal and then cortical, and can lead to invasion of the capsule in advanced disease, which is of poor prognosis in some gastrointestinal cancers (colorectal, gastric and oesophageal).<sup>7,8</sup> Another mechanism is direct LN invasion by contiguity from the main tumor to the LN, from outside to inside, first cortical and then sinusal. The possibility of direct extension to the LN seems more likely in PDAC than in other cancers owing to the great number of LN around the gland, but the subsequent impact on prognosis is still debated.<sup>5,9</sup>

The aim of this study was to describe the different modes of LN involvement in PDAC, to assess the prognosis of each mode of invasion and to determine a cut-off from which the number of positive lymph node could have a negative impact on survival.

### Patients and methods

Pathologic specimens of all pancreatic resections for PDAC performed from 1997 to 2007 were extracted from our prospective database. Patients with PDAC or intraductal papillary mucinous neoplasm (IPMN) with invasive carcinoma who had undergone resection as initial treatment were included in the study. We excluded patients with extrahepatic cholangiocarcinoma, ampullary cancers and duodenal adenocarcinoma, and patients with preoperative

borderline resectable tumors (portal vein involvement and T4 tumors defined as involvement of the superior mesenteric artery, the hepatic artery or the celiac axis) treated by neo-adjuvant chemotherapy or chemoradiotherapy.

### Surgical technique

Whipple resection was the standard procedure for cephalic PDAC. LN dissection included LN around the head of the pancreas, along the common hepatic artery, in the hepatic pedicle and on the right aspect of the superior mesenteric artery and celiac axis. Involvement of the portal or superior mesenteric vein was treated by PD with en-bloc resection of the vein, and was associated with retroperitoneal dissection and sharp division of the soft tissues at the right aspect of the superior mesenteric artery to obtain disease-free margins.<sup>10,11</sup> For tumors located on the left of the splenoportal confluence, the standard procedure was distal pancreatectomy with splenectomy and LN dissection along the left aspect of the celiac axis and the superior mesenteric artery. Total pancreatectomy was performed only in patients with multifocal invasive adenocarcinoma or diffuse IPMN complicated by invasive carcinoma, as indicated by routine frozen sectioning of the pancreatic margin.

### Samples analysis

LN involvement was classified as follows (Fig. 1): 1) standard (S+), when invasion was predominant in the

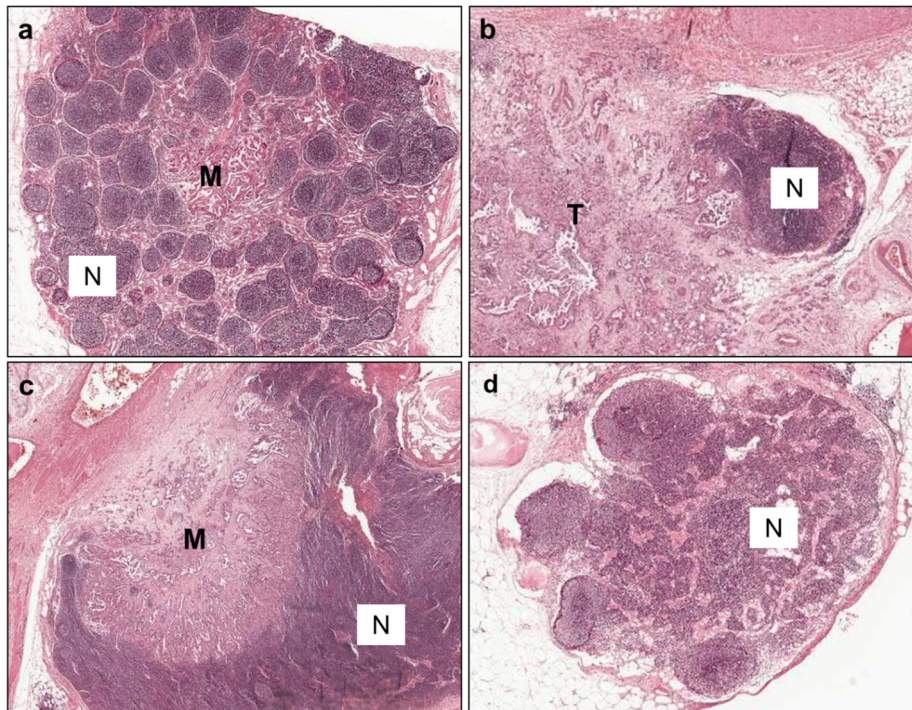


Figure 1. Mechanism of lymph node invasion. a) Standard lymph node metastasis (M) located within the sinusal area, without invasion of the cortex; b) lymph node invasion from outside to inside in contiguity to the main tumor (T); c) standard lymph node metastasis (M) with extracapsular invasion from inside to outside, with absence of continuous extension from the main tumor; d) normal lymph node with no metastasis. N: node.

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