

REVIEW ARTICLE

# Prognostic value of lymph node metastases detected during surgical exploration for pancreatic or periampullary cancer: a systematic review and meta-analysis

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## Abstract

**Background:** Hepatic-artery and para-aortic lymph node metastases (LNM) may be detected during surgical exploration for pancreatic (PDAC) or periampullary cancer. Some surgeons will continue the resection while others abort the exploration.

**Methods:** A systematic search was performed in PubMed, EMBASE and Cochrane Library for studies investigating survival in patients with intra-operatively detected hepatic-artery or para-aortic LNM. Survival was stratified for node positive (N1) disease.

**Results:** After screening 3088 studies, 13 studies with 2045 patients undergoing pancreatoduodenectomy were included. No study reported survival data after detection of LNM and aborted surgical exploration. In 110 patients with hepatic-artery LNM, median survival ranged between 7 and 17 months. Estimated pooled mean survival in 84 patients with hepatic-artery LNM was 15 [95%CI 12–18] months (13 months in PDAC), compared to 19 [16–22] months in 270 patients with N1-disease without hepatic-artery LNM ( $p = 0.020$ ). In 192 patients with para-aortic LNM, median survival ranged between 5 and 32 months. Estimated pooled mean survival in 169 patients with para-aortic LNM was 13 [8–17] months (11 months in PDAC), compared to 17 (6–27) months in 506 patients with N1-disease without para-aortic LNM ( $p < 0.001$ ). Data on the impact of (neo)adjuvant therapy on survival were lacking.

**Conclusion:** Survival after pancreatoduodenectomy in patients with intra-operatively detected hepatic-artery and especially para-aortic LNM is inferior to patients undergoing pancreatoduodenectomy with other N1 disease. It remains unclear what the consequence of this should be since data on (neo-) adjuvant therapy and survival after aborted exploration are lacking.

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## Introduction

Pancreatic and periampullary cancer remain a deadly disease. Five-year survival rates are as low as 5%.<sup>1,2</sup> In pancreatic cancer, forty percent of patients present with locally advanced disease, with an overall survival following palliative chemotherapy of 10 months.<sup>3,4</sup> In those patients with metastatic disease survival (7 months) is even shorter.<sup>5</sup> Surgery is feasible in 20% of patients, and following adjuvant chemotherapy may achieve a

5-year survival rate of 20%.<sup>6</sup> Following resection of periampullary cancer, 5-year survival may reach 20–50%.<sup>7</sup> As such, currently the best survival rates are achieved with resection, and adjuvant chemotherapy. As operative techniques and peri-operative outcomes continue to improve, optimizing the eligibility criteria for resection is of great interest.<sup>6,8</sup> Furthermore, due to limited survival times, identifying those patients who do not benefit from a resection is equally important.

Lymph node metastases (LNM) are regarded as a strong negative prognostic factor in patients with pancreatic and periampullary cancer, and most studies have focused on the hepatic-artery (station 8a) and para-aortic (station 16b1) lymph nodes. In most centers, patients with preoperatively detected extra-regional LNM do not undergo resection.<sup>9,10</sup> A standard lymphadenectomy, which includes the hepatic-artery but not para-aortic lymph nodes, was recently defined by the International Study Group of Pancreatic Surgery (ISGPS).<sup>11</sup> As pre-operative imaging is often not reliable to exclude LNM, intra-operative detection of extra-regional LNM regularly confronts surgeons with the decision to abort the exploration or continue with resection.<sup>12</sup> The primary aim of this study was to perform a systematic review and meta-analysis to determine survival after pancreatoduodenectomy or aborted exploration in patients with intra-operatively detected hepatic-artery and para-aortic LNM in pancreatic and periampullary cancer. The secondary aim of this study was to compare survival between patients with hepatic-artery or para-aortic LNM versus other N1 disease.

## Methods

### Study selection

A systematic review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.<sup>13</sup> Two systematic literature searches were performed in PubMed, EMBASE and The Cochrane Library up to October 15th, 2015. A clinical librarian checked the searches. The first search identified articles investigating the prognostic impact of LNM in patients undergoing pancreatoduodenectomy for cancer. The second search identified articles investigating the prognostic impact of LNM in patients in whom surgical exploration was aborted after detection of LNM. Two independent reviewers (LB and PN for the first search, LB and NCM for the second search) screened title and abstract for eligibility. Discrepancies were solved through discussion and consensus, and in case of any doubt resolved with the senior author. Next, the eligibility of full text articles was assessed similarly. References of finally included articles were checked manually for studies that had not been identified in the primary search.

### Study eligibility and outcomes

Studies investigating the prognostic value of LNM on overall survival in patients with pancreatic cancer were considered eligible. From studies of patients undergoing resection, only patients undergoing pancreatoduodenectomy were included. Reviews, case reports and editorials were excluded. Study and baseline characteristics, LNM location and survival outcomes were obtained.

LNM-specific data were analyzed if in total, there were at least 75 node positive patients per lymph node station involved. This was an arbitrary cut-off, chosen to obtain sufficient data for a robust analysis. Attention was paid to the characteristics of the

control group; whether they consisted of node negative (N0) patients or patients with node positive (N1) disease, but negative to the specific lymph node station being analyzed.

### Assessment of methodological quality

Methodological quality was assessed using the Oxford Centre for Evidence-Based Medicine Levels of Evidence.<sup>14</sup> Risk of bias in each of the included studies was assessed using the Newcastle–Ottawa Quality Assessment Scale for cohort studies.<sup>15</sup> The criteria for ‘comparability’ in the Newcastle–Ottawa Quality Assessment Scale to assess varieties within the arranged cohort was used for a complete analysis.

### Statistical analysis

To perform a meta-analysis, using the random effects model, pooled mean survival was estimated using a validated and widely used formula.<sup>16</sup> This formula estimates the mean, variance and standard deviation of a sample using the reported sample size, median and range. If not reported, median survival and ranges were deducted from Kaplan–Meier curves. In these cases, if patients were alive at last follow-up, the maximum range was set at the time of censoring. Heterogeneity between studies was assessed using the I-squared statistic considering the following margins: low (0–40%), moderate (30–60%), substantial (60–90%) and considerable (75–100%) heterogeneity. Meta-analysis was performed using Review Manager (The Nordic Cochrane Centre, The Cochrane Collaboration) version 5.3.<sup>17</sup> Differences with  $P < 0.05$  were considered statistically significant. Sensitivity analysis was performed for patients with pancreatic ductal adenocarcinoma (PDAC) only.

## Results

### Study selection

A total of 3088 articles were screened (first search 1255 articles, second search 2097 articles). The PRISMA flowchart for study selection regarding the first search (i.e. patients receiving resection) is shown in Fig. 1. The second search, despite extensive screening, revealed not a single study fulfilling the eligibility criteria. Finally in 13 full text articles were included a total of 2045 patients receiving pancreatoduodenectomy.

Table 1 summarizes the characteristics of included studies.<sup>18–29</sup> One study was excluded due to overlap in its patient population with another study assessing additionally extra-regional LNM.<sup>29,30</sup> No studies were excluded due to inadequate methodological quality (Supplementary Table).

### Hepatic-artery LNM (station 8a)

Survival data related to hepatic-artery LNM in patients receiving pancreatoduodenectomy are given in Table 2. In total there were 539 patients; 110 (20%) patients with and 429 (80%) patients without hepatic-artery LNM. Median survival of patients with

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