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%.[1,2] In pancreatic cancer, forty percent of patients present with locally advanced disease, with an overall survival following palliative chemotherapy of 10 months.[3,4] In those patients with metastatic disease survival (7 months) is even shorter.[5] Surgery is feasible in 20% of patients, and following adjuvant chemotherapy may achieve a 5-year survival rate of 20%.[6] Following resection of periampullary cancer, 5-year survival may reach 20–50%.[7] 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.[6,8] 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.[9,10] 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).[11] As preoperative imaging is often not reliable to exclude LNM, intraoperative detection of extra-regional LNM regularly confronts surgeons with the decision to abort the exploration or continue with resection.[12] 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.[13] 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.[14] Risk of bias in each of the included studies was assessed using the Newcastle–Ottawa Quality Assessment Scale for cohort studies.[15] 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.[16] 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.[17] 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.[18–29] One study was excluded due to overlap in its patient population with another study assessing additionally extra-regional LNM.[29,30] 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

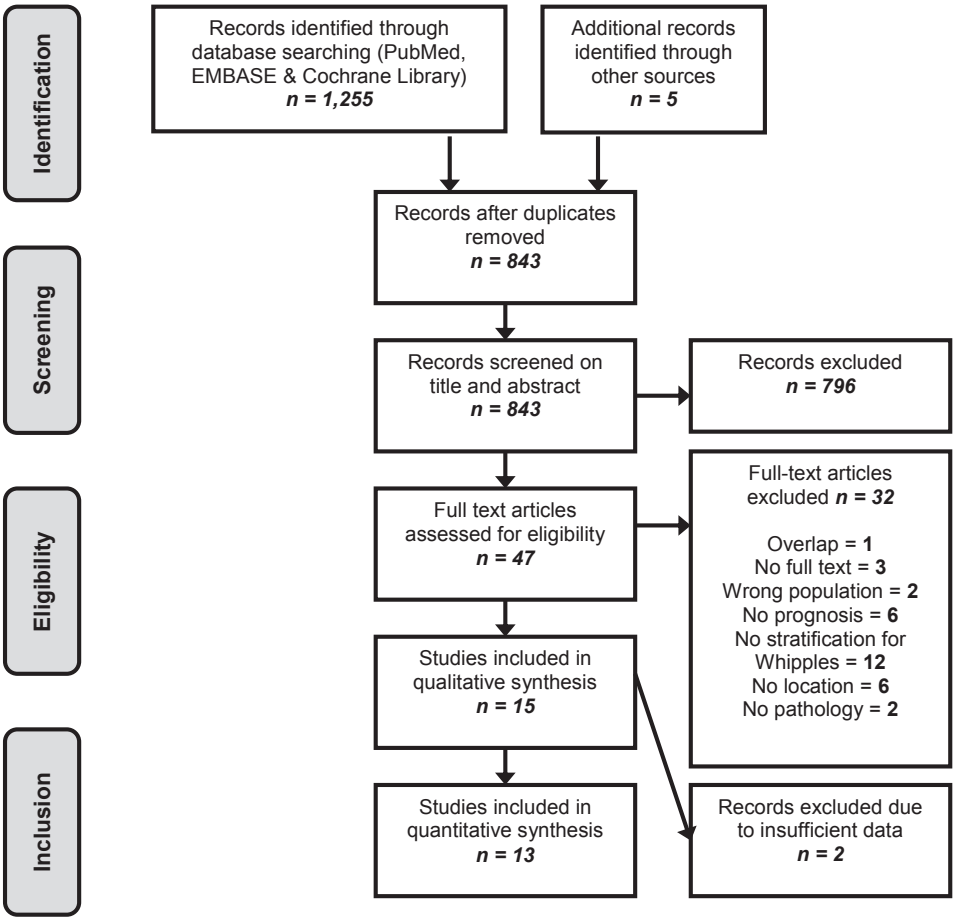

Figure 1 PRISMA flow diagram

hepatic-artery LNM ranged between 7 and 17 months and 3-year survival was 0% in one study among 17 patients. In patients with N1-disease but without hepatic-artery LNM, median survival ranged from 16 to 21 months and 3-year survival was 23% among 60 patients in one study.[25]

Estimated pooled mean survival was 15 [95%CI 12–18] months in 84 patients with hepatic-artery LNM compared to 19 [16–22] months in 270 patients with N1-disease without hepatic-artery LNM. Estimated pooled mean difference could be generated from 3 studies and was 3 [95%CI 0–5, p = 0.020] months. There was low statistical heterogeneity among these 3 pooled studies (I^2 = 0%, p = 0.5).

Para-aortic LNM (station 16b1)

Survival data related to para-aortic LNM in patients receiving pancreatoduodenectomy are presented in Table 3. In total there were 794 patients; 192 (24%) patients with and 602 (76%) patients without para-aortic LNM. Median survival of patients with para-aortic LNM ranged between 5 and 32 months and 3-year survival ranged between 0 and 3%, although the latter was deducted from 53 patients in two studies only. In patients with N1-disease but without para-aortic LNM median survival ranged between 13 and 34 months and 3-year survival was only reported in one study: 12% in 84 patients.[25]

Estimated pooled mean survival was 13 [95%CI 8–17] months in 169 patients with para-aortic LNM compared to 17 [6–27] months in 506 patients with N1-disease without para-aortic LNM. Estimated pooled mean difference could be generated from 5 studies and was 5 [95%CI 2–7, P < 0.001] months. There was moderate statistical heterogeneity among these 5 pooled studies (I^2 = 53%, p = 0.080).

Sensitivity analysis

Sensitivity analysis was performed after excluding all non-PDAC cancers (Table 1). Three studies included patients with both pancreatic and periampullary cancer.[18,19,31] One study did not report separate survival times and was excluded from the sensitivity analysis.[18]

For PDAC, estimated pooled mean survival was 13 [95%CI 5–21] months in 33 patients with hepatic-artery LNM compared to 15 [12–19] months in 119 patients with N1-disease without hepatic-artery LNM. Estimated pooled mean difference was 3 [95%CI 2–7, p = 0.250] months. For PDAC, estimated pooled mean survival was 11 [95%CI 5–16] months

Table 1 Study characteristics

	Reference and year	Study design	No. PD	Cancer location	JPS lymph node station(s)	Lymph node resection
1	Andersen *et al.* (1994)[18]	Prospective cohort	117	PDAC + periampullary cancer	16	Unknown
2	Connor *et al.* (2004)[19]	Prospective cohort	121	PDAC + periampullary cancer	8a and 16b1	Routine
3	Cordera *et al.* (2007)[20]	Retrospective cohort	175	Pancreatic head cancer	8 and peripancreatic	On indication, reason unknown
4	Doi *et al.* (2007)[21]	Retrospective cohort	133	PDAC	6, 8, 9, 11, 12, 13, 14, 15, 16a2, 16b1, 17, 18	Routine
5	LaFemina *et al.* (2013)[22]	Retrospective cohort	147	PDAC	8a and peripancreatic	On indication, per surgeon preference
6	Massucco *et al.* (2009)[23]	Prospective cohort	77	PDAC	6, 8, 9, 12, 13, 14, 16 and 17	On indication, reason unknown
7	Nappo *et al.* (2015)[31]	Prospective cohort study	135	PDAC + periampullary cancer	16	Routine
8	Paiella *et al.* (2015)[29]	Retrospective cohort	67	PDAC	8, 12, 13, 14, 16 and 17	On indication, per surgeon preference
9	Philips *et al.* (2014)[24]	Prospective cohort	420	PDAC	8a and peripancreatic	unclear
10	Sakai *et al.* (2005)[25]	Retrospective cohort	178	PDAC	8	Routine
11	Schwarz *et al.* (2014)[26]	Prospective cohort	111	Pancreatic head cancer	16	Routine
12	Shrikhande *et al.* (2007)[27]	Retrospective cohort	29	PDAC	16	On indication, reason unknown
13	Yamada *et al.* (2009)[28]	Retrospective cohort	335	Pancreatic head cancer	16	Routine

PD, pancreatoduodenectomy; JPS, Japanese Pancreas Society; PDAC, pancreatic ductal adenocarcinoma.

Table 2 Survival related to hepatic-artery lymph node status

Study	(neo)Adjuvant therapy (n/N)	Hepatic-artery LNM	Percentage of patients (N)	Survival rate				Median survival (months)	P-value[c]
				1 y	2 y	3 y	5 y		
Cordera *et al.* (2007)[20]	Adjuvant chemotherapy and/or radiation	Yes	26% (10)				0%	15	0.05
		No	74% (28)				17%	16	
LaFemina *et al.* (2013)[22]	10/147 neo-adjuvant.	Yes	21% (23)					13	0.10
		No	79% (86)					17	
Paiella *et al.* 2015[29]	NR	Yes	13% (9)				0%	NR	N/A
		No	87% (58)				18.3%	NR	
Philips *et al.* (2014)[24]	17/41 adjuvant	Yes	20% (38)					17	0.659
	56/156 adjuvant	No	80% (156)					21	
Sakai *et al.* (2005)[25]	NR	Yes	22% (17)	29%	6%	0%		NR	N/A
		No[a]	78% (60)	57%	32%	23%		NR	
Connor *et al.* (2004)[19]	3/13 adjuvant	Yes	32% (13)	0%				7	0.037
	9/39 adjuvant	No[b]	68% (41)					15	

NR, not reported; N/A, not applicable.
[a] The assessed metastatic lymph node station was compared to N0 patients.
[b] The assessed metastatic lymph node station was compared to N1/8a- and N0 patients together, instead of N1/8a-only.
[c] P-value for difference in median survival.

Table 3 Survival related to para-aortic lymph node status

Study	(neo)adjuvant therapy (n/N)	Para-aortic LNM	Percentage of patients (N)	Survival rate				Median survival (months)	P-value[b]
				1 y	2 y	3 y	5 y		
Doi *et al.* (2007)[21]	75 adjuvant 5FU, 66 radiation	Yes	14% (19)	16%		0%		5	< 0.05
		No	86% (114)					13	
Nappo *et al.* (2015)[31]	14/135 neoadjuvant	Yes	17% (15)					32	> 0.05
		No	83% (75)					34	
Paiella *et al.* (2015)[29]	54/67 adjuvant	Yes	?% (14)				0%	17	NR
		No					20.3%	30	
Sakai *et al.* (2005)[25]	NR	Yes	29% (34)	30%	7%	3%		8	0.1175
		No	71% (84)	42%	19%	12%		9	
Schwarz *et al.* (2014)[26]	69/111 adjuvant 5FU/gemcitabine	Yes	34% (32)					15	0.110
		No	66% (62)					21	
Shrikhande *et al.* (2007)[27]	23/29 (neo)adjuvant 5FU, gemcitabine or radiation	Yes	?% (9)					27	N/A
		No							
Yamada *et al.* (2009)[28]	14/45 adjuvant 5FU/gemcitabine and 26/45 radiation	Yes	19% (45)					8	0.0029
	NR	No	81% (188)					11	
Andersen *et al.* (1994)[18]	NR	Yes	24% (14)					6	0.004
		No	76% (45)					16	
Connor *et al.* (2004)[19]	5/8 adjuvant chemo (NOS)	Yes	23% (10)			0%		15	NR
	5/29 adjuvant chemo (NOS)	No[a]	77% (34)				0%	17	

NR, not reported; 5FU, 5-fluorouracil; N/A, not applicable.
[a] The assessed metastatic lymph node station was compared to N1/16b- and N0 patients together, instead of N1/16b- only.
[b] P-value for difference in median survival.

in 65 patients with para-aortic LNM compared to 20 [8–31] months in 246 patients with N1-disease without para-aortic LNM. Estimated pooled mean difference was 8 [95%CI 0–16, p = 0.040] months.

Discussion

In the first systematic review on this subject, reduced survival was found following intraoperative detection of hepatic-artery or para-aortic LNM in patients undergoing pancreatoduodenectomy for cancer. Survival was reduced further in patients with para-aortic LNM, compared to patients with hepatic-artery LNM. Data on survival in patients in whom the surgical exploration was aborted after intraoperative detection of LNM are lacking.

No studies were specifically designed to investigate if positive hepatic-artery, or para-aortic LNM should automatically preclude a resection in all patients. None of the included studies reported survival after aborted explorations due to detection of intraoperative LNM. Patients with metastasized pancreatic cancer have an overall survival of about 7 months when treated with gemcitabine and up to 11 months when treated with FOLFIRINOX, which is reserved for fitter patients.[5] Survival of patients with locally advanced pancreatic cancer is around 10 months.[3,4,32] The pooled data demonstrate that patients with (pancreatic) cancer and hepatic-artery LNM had an estimated pooled mean survival of 15 months. Estimated pooled mean survival following pancreatoduodenectomy with para-aortic LNM was 13 months. The interpretation of the aggregated data is challenging due to several factors. Most of the included studies performed lymph node sampling in a subset of patients only, although these indications were mostly not given. It could be based on a surgeon's preference, i.e. an intraoperative finding of macroscopically suspicious lymph nodes or patients with other risk factors for poor survival such as extensive disease. As such, lymph node sampling may have been selectively performed in patients with a poorer prognosis, leading to worse survival rates. Conversely, resection in case of LNM may have been performed in younger patients with fewer comorbidities, as it is felt these patients might still benefit from a resection. The influence of comorbid conditions on outcomes following surgery is well known.[33,34] Furthermore, few data were available on (neo) adjuvant treatment, for instance with FOLFIRINOX, in the included studies. All studies described only the total number of patients receiving adjuvant or neoadjuvant treatment. They did

not describe the number of patients with, or without LNM specifically receiving these treatments. It was therefore not possible to analyze the impact of neoadjuvant or adjuvant therapy on outcomes in patients with, or without LNM. It could be hypothesized that neoadjuvant treatment may reduce the amount of LNM but data are currently lacking. Finally, there was no detailed information concerning the histopathological examination of lymph nodes (H&E, PCR, sentinel node). A recent analysis among 67 patients undergoing pancreatoduodenectomy with extended lymphadenectomy for pancreatic head cancer, demonstrated by matched case–control analysis demonstrated that the disease-free survival of patients with resected para-aortic LNM (19 months) was in between patients with resected negative para-aortic nodes (27 months), and patients with locally advanced disease (14 months).[29] This review confirms the need for large, prospective studies in which in all patients lymph nodes are sampled and baseline characteristics are well documented in order to create a clinical risk model for survival after intra-operatively detected LNM.

Sensitivity analysis was performed for PDAC separately, as outcomes may differ from periampullary (distal CBD, papilla, duodenum) cancers, and clear differences exist in survival between the various periampullary cancers and PDAC.[35,36] Therefore, some of the largest studies in this review describing only 'cancer of the pancreatic head' which may involve distal cholangiocarcinoma were excluded from sensitivity analysis. Survival in patients with PDAC and LNM was shorter compared to patients with other periampullary cancers and LNM: survival in patients with PDAC and hepatic-artery or para-aortic LNM was 13 and 11 months, respectively, compared to 15 and 13 months for all patients. Estimated pooled mean difference in survival was not significant for PDAC patients with, or without hepatic-artery LNM undergoing resection. However, interpretation of the data remains difficult due to the issues raised above, and low patient numbers.

According to the TNM classification, para-aortic lymph nodes are extra-regional nodes for both pancreatic and periampullary cancer. According to the TNM, the hepatic-artery lymph node is either regional (pancreatic and bile duct cancer) or extra regional (ampullary cancer).[37] Recently, the ISGPS introduced a consensus definition of a standard lymphadenectomy in patients with pancreatic cancer which included the hepatic-artery lymph node, but not the para-aortic lymph nodes.[11] The ISGPS consensus was partly based on 4 randomized controlled trials (RCT's) investigating the value of an extended lymphadenectomy, which included various lymph node stations.[38–41]

Prior studies have demonstrated that both preoperative CT-imaging and visual inspection cannot reliably determine LNM.[12,26] The accurate determination of (loco) regional LNM by endoscopic ultrasonography (EUS) even seems similar.[42–44] Extra-regional lymph nodes may not be visible on EUS. This suggests that in case of clinical consequences such as aborting a surgical exploration, standard intraoperative sampling of hepatic-artery and para-aortic lymph nodes should be performed. Previous studies have demonstrated that the para-aortic lymph node station is important in pancreatic lymphatic drainage.[45,46] Indeed, occurrence of para-aortic LNM has been associated with LNM in more proximal nodes such as stations 13, 14 and other peripancreatic lymph nodes.[26,29,47]

The method to estimate mean survival times using reported medians, ranges and sample sizes has been widely used and validated.[16] Although survival times may be skewed due to some patients surviving longer, the estimation is distribution-free. Furthermore, long-term survival following resection of pancreatic cancer is extremely rare, which restricts the skewness of survival data.[48] Attempts have been made to improve the estimations, but they remain to be validated.[49] Therefore the methods were used as described. Survival ranges needed to estimate mean survival times were deducted from Kaplan–Meier curves in 6 out of 7 studies of patients with para-aortic LNM. In these cases <10% of patients were alive at the end of follow-up. This has been taken into account when interpreting the pooled data. There was moderate statistical heterogeneity in the pooled studies regarding para-aortic LNM. However, the I-squared static has lower power when studies have small sample sizes. While the methodological quality of the included studies is adequate, studies were mostly small and retrospective. Large, prospective studies are needed to establish clinical risk models to determine if, and if so which patients might benefit of a resection. These studies should report outcomes of PDAC and peri-ampullary cancer separately. With the introduction of the ISGPS consensus on a standard lymphadenectomy, larger and prospective studies can now be performed and compared.

Conclusion

Hepatic-artery and especially para-aortic LNM detected during exploration for pancreatic or periampullary cancer is associated with reduced survival. Resection in patients with hepatic-artery LNM seems reasonable as survival times are better compared to patients with irresectable disease and this node is part of the ISGPS standard lymphadenectomy. In patients with para-aortic LNM proceeding with resection is less obvious, but due to a lack of adequate control groups and data on (neo)adjuvant therapy it remains unclear whether intra-operative detection of para-aortic LNM should automatically preclude resection in all patients.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.hpb.2016.05.001.