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ORIGINAL RESEARCH

The Role of CT in Assessment of Extraregional Lymph Node Involvement in Pancreatic and Periampullary Cancer: A Diagnostic Accuracy Study

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Purpose: To investigate the diagnostic accuracy of CT in assessing extraregional lymph node metastases in pancreatic head and periampullary cancer.

Materials and Methods: This prospective observational cohort study was performed at two tertiary hepatopancreatobiliary (HPB) referral centers between March 2013 and December 2014. Patients undergoing pancreatoduodenectomy or bypass surgery with or without palliative radiofrequency ablation were included. Extraregional lymph node involvement was defined as positive lymph nodes in the aortocaval window. Two expert HPB radiologists assessed aortocaval lymph nodes at preoperative CT according to a standardized protocol. All tissue from the aortocaval window was collected intraoperatively. Positive histopathologic finding was the reference standard. Analysis of predictive values and diagnostic accuracy was performed.

Results: A total of 198 consecutive patients (mean age, 66 years; range, 39–86 years; 105 men) with pancreatic head or periampullary carcinoma were included. In 70% of patients, a pancreatoduodenectomy was performed, 4% underwent total pancreatectomy, 4% underwent radiofrequency ablation, and 22% underwent bypass surgery. Forty-four patients (22%) had histologically positive aortocaval lymph nodes. Negative predictive value of CT in assessing aortocaval lymph nodes was 80% for both observers, and positive predictive value was 31%–33%. Overall diagnostic accuracy was 69%–70%.

Conclusion: CT has a low diagnostic accuracy in assessing extraregional lymph node metastases in patients suspected of having pancreatic or periampullary cancer.

Pancreatoduodenectomy is the only curative treatment in patients with periampullary or pancreatic malignancy (1). Preoperative staging is essential to exclude distant metastases and evaluate potential resectability. Next to local resectability, the staging of extraregional lymph node involvement is important, especially in the current era of neoadjuvant treatment. CT is the diagnostic modality most widely used in the staging of pancreatic and periampullary cancer (2). However, the diagnostic accuracy of CT for adequate assessment of extraregional lymph nodes is unclear.

In a previous meta-analysis, diagnostic accuracy varied widely among studies and the included studies were of intermediate quality (3). Nevertheless, the suspicion of extraregional lymph node metastases can have major therapeutic consequences. In most Western countries, extensive extraregional lymph node involvement (ie, involvement of lymph nodes beyond the standard lymphadenectomy) is formally considered a contraindication for resection with curative intent (4–7). In clinical practice, however, limited extraregional involvement (eg, the aortocaval window) or inconclusive findings at CT are not a contraindication per se and often lead to resections. As neoadjuvant therapy evolves into standard treatment, adequate preoperative lymph node staging is essential in optimizing personalized treatment strategies. Data from a recent retrospective analysis suggest that the positive predictive value (PPV) of enlarged lymph nodes for local-regional nodal involvement decreases after neoadjuvant therapy, with a PPV of 42.9% after neoadjuvant therapy and 77.3% in patients without neoadjuvant therapy (8).

The aim of this study was to evaluate the diagnostic accuracy of CT in assessment of aortocaval lymph nodes in patients undergoing explorative laparotomy with or without resection for pancreatic or periampullary carcinoma.

Abbreviations

NPV = negative predictive value, PPV = positive predictive value

Summary

Assessment of aortocaval extraregional lymph node metastases in pancreatic and periampullary cancer with CT resulted in a low positive predictive value and poor diagnostic accuracy.

Key Points

- CT has frequent false-positive results (ranging from 17% to 18% for two different observers) in assessing extraregional lymph node metastases in patients suspected of having pancreatic or periampullary cancer.
- The negative predictive value of CT was 80% for both readers, whereas the positive predictive value ranged from 31% to 33%.
- Signs of aortocaval lymph node metastases at CT should not be a contraindication for surgical exploration.

Keywords

- CT, Abdomen/GI, Pancreas, Oncology

Materials and Methods

Study Design

We performed a prospective observational cohort study in the University Medical Center Utrecht (center 1) and the University Medical Center Groningen (center 2). The study was approved by the local institutional review board. We adhered to the STARD guidelines for reporting on diagnostic accuracy studies (9,10). We prospectively included consecutive patients from the University Medical Center Utrecht undergoing pancreatoduodenectomy or laparotomy and radiofrequency ablation for suspected periampullary or pancreatic malignancy between March 1, 2013, and December 2014. From the University Medical Center Groningen, data from patients who underwent pancreatoduodenectomy or laparotomy for suspected periampullary or pancreatic malignancy were added to the prospective cohort from the University Medical Center Utrecht post hoc from a prospective database. Patients from center 2 were included from January 2010 to December 2014. Patients with positive nodes from the previous 5 years (2004–2009) were added to our series. Patients were excluded when aortocaval nodes were either not harvested during resection, or these lymph nodes were not correctly supplied to the pathologist (ie, marked separately from the pancreatic resection specimen).

CT Imaging

General routine pretreatment evaluation of all patients was performed. This always included an abdominal and thoracic CT and endoscopic US only when there was no visible mass at CT. Preoperative multisection detector CT was performed using a specific pancreas protocol. For center 1, various spiral CT scanners were used: 16-section AX 8000 IDT, 64-section Brilliance 64, and a 128-section iCT (Philips Medical Systems, Best, the Netherlands). For intravenous contrast material, iopromide (Ultravist 300 mg I/mL; Bayer, Berlin, Germany) was used. The injection protocol varied according to weight (< 70

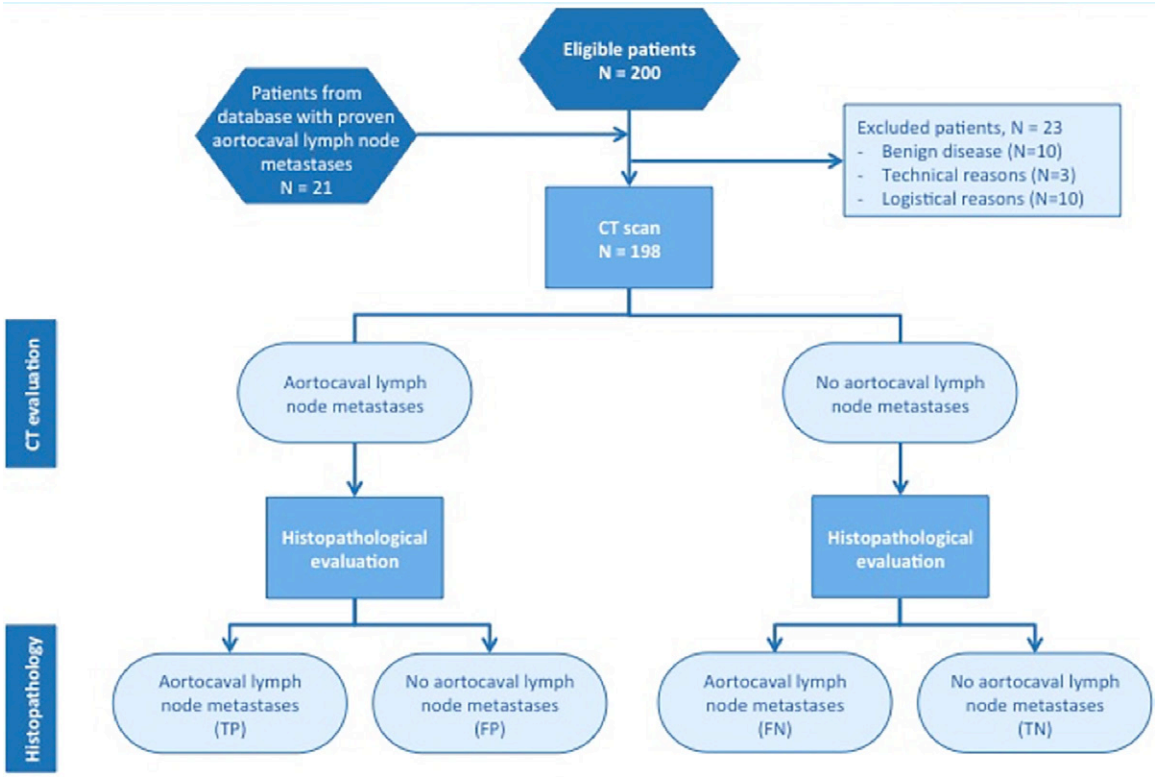


Figure 1: Flowchart patient inclusion. FN = false negative, FP = false positive, TN = true negative, TP = true positive.

Table 1: Patient Baseline Characteristics

Parameter	No. of Patients
Age (y)	66 (39–86)
Men	105 (53)
Surgical procedure	
Whipple	18 (9.1)
PPPD	121 (61.1)
Total pancreatectomy	7 (3.5)
RFA	7 (3.5)
Bypass	45 (22.7)
Pathologic finding	
Adenocarcinoma	88 (44.4)
Ampullary carcinoma	31 (15.6)
Cholangiocarcinoma	11 (5.5)
IPMN	10 (5.1)
Other (pre-)malignancy*	13 (6.6)
No histopathologic specimen obtained	45 (22.7)
Tumor diameter (cm)	3.0 (1–8)
T stage	
T1	5 (2.5)
T2	37 (18.6)
T3	83 (41.9)
T4	14 (7.0)
Unknown	59 (29.8)
Nodal stage	
N0	46 (23.2)
N1	90 (45.4)
Unknown	62 (31.3)
Surgical margins	
Radical (R0)	84 (42.4)
Irradical (R1)	51 (25.7)
Not applicable†	63 (31.8)

Note.—Continuous variables shown as mean (range) and categorical variables are shown as value (percentage). A total of 198 patients were included in the final analysis. IPMN = intraductal papillary mucinous neoplasm, PPPD = pylorus preserving pancreatoduodenectomy, RFA = radiofrequency ablation.
* Not applicable for patients with IPMN, other diagnosis includes duodenal carcinoma, neuroendocrine tumor.
† Other is neuroendocrine tumor, serous cystadenoma, not specified, periampullary tumor, or gastric carcinoma.

kg, 90 mL at 3 mL/sec; 70–90 kg, 120 mL at 4 mL/sec; and > 90 kg, 150 mL at 5 mL/sec). In all patients, 50 mL of saline chaser was injected at the same injection rate as the contrast material injection. A region of interest was placed in the aorta lumen above the diaphragm, with threshold set at 100 HU. Twenty seconds after the 100-HU threshold was reached, late arterial phase images were acquired from above the diaphragm to the iliac crests. Images were reconstructed with 5-mm thickness, at a reconstruction index of 4 mm. In addition, contiguous 1-mm sections were reconstructed for multiplanar reformat. After a 55-second delay, portal venous phase images were acquired from above the diaphragm to below the symphysis. Images were reconstructed with 5-mm thickness, at a reconstruction index of 4 mm, and contiguous 1-mm sections were reconstructed for multiplanar reformat.

For center 2, the following CT scanners were used: Siemens Sensation 16, Siemens Sensation 64, Siemens Definition DS–2 × 64 section. Prior to February 2012, 120 mL of iodixanol (Visipaque 320; GE Healthcare) at 4 mL/sec was used for intravenous contrast material, and after February 2012, 110 mL of iomeprol (Iomeron 350; Guerbet, Villepinte, France) at 4 mL/sec was used. In all patients, 40 mL of saline was injected at 4 mL/sec. A region of interest was placed in the aorta lumen above the diaphragm, with threshold set at 100 HU. For the arterial phase, there was an interscan delay of 7 seconds. Thickness of 0.75 and 0.5 mm was used (soft kernel, termed B30f). For the portal venous phase, we used a 40-second interscan delay after the arterial phase until February 2012. After February 2012, a 75-second fixed delay after injection was used. For thickness at the portal venous phase, sections of 5 mm (B30f) were used for all scanners. In this period, two reconstructions were made: thick-section reconstruction (5 mm with increment of 5 mm) for all scanners and thin section for Siemens Sensation 16 (3 mm with increment of 1.5 mm) and Siemens Sensation 64 and definition DS (2 mm with increment of 1.5 mm).

CT Image Assessment

The preoperative CT images were systematically and independently reviewed by two pancreatic radiologists (M.S.v.L. with 32 years of experience and J.P.P. with 2 years of experience) using a standardized case record form, reporting on tumor characteristics such as size, localization, invasion of adherent organs or vessels, distant metastases, and lymph node involvement. Images were viewed interactively, using scroll-mode and multiplanar reformat.

Radiologists were blinded for histopathologic outcomes. In this study, extraregional lymph node involvement was defined as lymphadenopathy in the aortocaval window (ie, the area between the aorta and inferior vena cava, confined cranially by the left renal vein and caudally by origin of the inferior mesenteric artery). Of these lymph nodes (localization 16b1 according to the Japan Pancreas Society Classification of Nodes in Pancreatic Cancer), the short-axis diameter was recorded, as was the radiologic suspicion on lymph node metastases (11). This suspicion was based on the following lymph node characteristics: presence of central necrosis, round shape, size of greater than 1 cm (short-axis diameter), irregular margins, and proximity to primary tumor (12). Multiplanar reconstructions were used for viewing and for selecting the shortest axis of lymph nodes for measurements. In the case of multiple nodes, the largest measurement was recorded.

Procedures and Histopathologic Evaluation

Pancreatoduodenectomy, radiofrequency ablation, and bypass procedures were performed by experienced hepatopancreatobiliary surgeons. The decision to proceed to surgery was irrespective of the radiologic suspicion of lymph node metastases (ie, any features implying positive aortocaval nodes at CT never precluded laparotomy). For procedures

at center 1, all tissue from the aortocaval window was removed to assess aortocaval lymph node status, and no frozen section analysis was performed according to the standard treatment in this center. For procedures at center 2, all tissue from the aortocaval window was removed and sent for frozen section analysis. In the case of observed metastases, resection was aborted.

At both centers, lymph nodes were sent for definitive histopathologic evaluation. Pathology reports cohered to the guidelines of the Dutch Pancreatic Cancer Group. According to these guidelines, the number of resected lymph nodes, the number of positive lymph nodes, and in the case of positive lymph nodes, the presence of extranodal growth was recorded. The pathologist evaluated whether there were metastases present within the collected lymph nodes from the aortocaval window, but no description of the size of the metastases was provided. Lymph nodes with micrometastases or isolated tumor cells were also considered metastatic.

Statistical Analysis

Using the rule that one predictor should be examined in 10 events and assuming a prevalence of aortocaval lymph node metastases of 15%, at least 66 patients should be included (11,13,14). All statistical analyses were performed using SPSS version 21 (SPSS). A two-sided $P < .05$ was considered statistically significant.

Diagnostic accuracy, PPV, negative predictive value (NPV), sensitivity, and specificity were evaluated with a 95% CI. Specificity and sensitivity were calculated using histopathologic results as the reference standard using a 2 × 2 contingency table. An interrater reliability analysis using the κ statistic was performed to determine consistency among raters. Associations between individual tumor characteristics at CT and the presence of aortocaval lymph node metastases were assessed by univariable logistic regression. Characteristics potentially associated with aortocaval lymph node metastases were entered in backward stepwise multiple logistic regression models to assess the most optimal model for the prediction of aortocaval lymph node metastases. All analyses were performed on combined data.

Results

Patient Characteristics

Between March 1, 2013, and December 2014, 100 consecutive patients in center 1 underwent pancreatoduodenectomy or laparotomy and radiofrequency ablation. A total of 100 consecutive patients from center 2 were included post

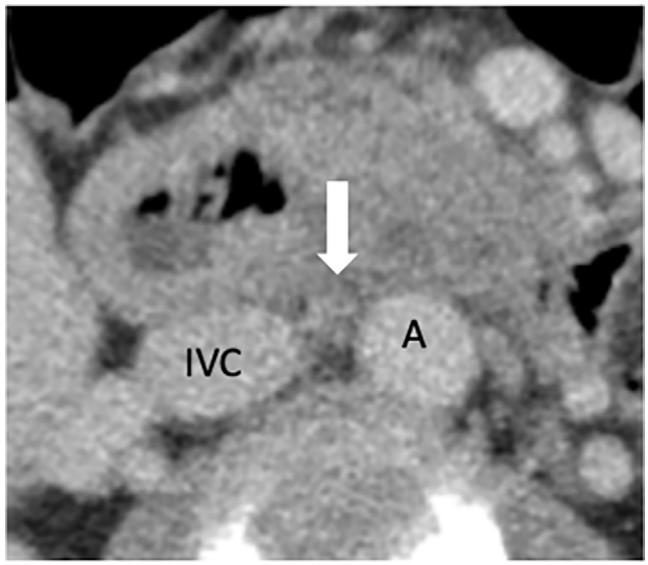
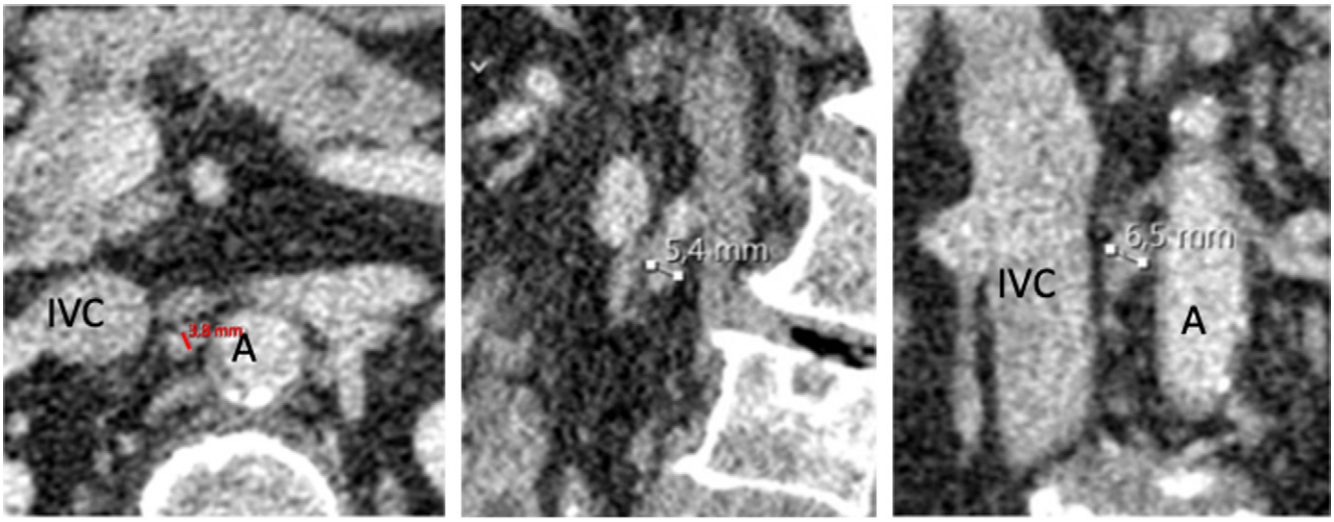


Figure 2: Patient is a 52-year-old woman. Transverse section of 7-mm node (arrow) between aorta (A) and inferior vena cava (IVC), scored as positive based on ill-defined border (true positive).



a. b. c.

Figure 3: Patient is a 68-year-old woman. Marked differences of minimal node size in the different orthogonal planes: **(a)** transverse 3.8 mm, **(b)** sagittal 5.4 mm, and **(c)** coronal 6.5 mm. Consequently, 4 mm (3.8 rounded to a whole number) was recorded as node size. Node was scored as negative but was a false negative. A = aorta, IVC = inferior vena cava.

hoc. In addition, 21 patients with proven aortocaval lymph node metastases from a prospective database from center 2 were included. From these 221 patients, 23 patients were excluded for the following reasons: technically impossible to resect aortocaval lymph nodes (n = 3), benign disease (n = 10), and logistical reasons (n = 10). In the patients who were excluded because of logistic reasons, this was because aortocaval lymph nodes were either not harvested during resection or these lymph nodes were not correctly supplied to the pathologist (ie, marked separately from the pancreatic resection specimen). A total of 198 patients were included in the analysis. Figure 1 shows a flowchart of patients who were included and excluded for this study. Baseline characteristics are summarized in Table 1.

Table 2: Contingency Tables for Lymph Node Suspicion of Metastasis

	Observer 1		Observer 2	
Metastasis Suspicion	Metastatic	Not Metastatic	Metastatic	Not Metastatic
General suspicion				
Suspected	13 (29.5)	26 (16.9)	12 (27.3)	30 (19.5)
Not suspected	31 (70.5)	128 (83.1)	32 (72.7)	124 (80.5)
Suspicion based on size of less than 1 cm				
Suspected	8 (18.2)	15 (9.7)	7 (15.9)	23 (14.9)
Not suspected	36 (81.8)	139 (90.3)	37 (84.1)	131 (85.1)
Suspicion based on round shape				
Suspected	10 (22.7)	20 (13.0)	10 (22.7)	21 (13.6)
Not suspected	34 (77.3)	134 (87.0)	34 (77.3)	133 (86.4)
Suspicion based on central necrosis				
Suspected	4 (9.1)	5 (3.2)	4 (9.1)	5 (3.2)
Not suspected	40 (90.9)	149 (96.8)	40 (90.9)	149 (96.8)
Suspicion based on irregular margins				
Suspected	6 (13.6)	7 (4.5)	5 (11.4)	3 (1.9)
Not suspected	38 (86.4)	147 (94.5)	39 (88.7)	151 (98.1)

Note.—Data are numbers of patients with percentages in parentheses. There were a total of 44 metastatic and 154 nonmetastatic lymph nodes.

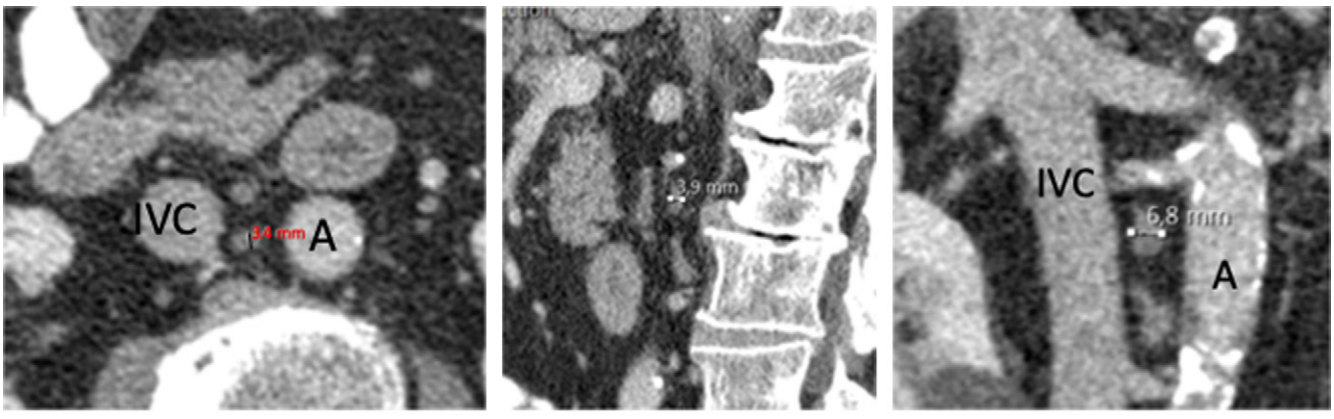
Histopathologic Findings

A median of two aortocaval lymph nodes (interquartile range, one to four) were collected from each patient. Forty-five patients had histopathologic-proven aortocaval lymph node metastases; one of these patients only had isolated tumor cells. Seventeen patients had more than one aortocaval lymph node metastasis with a median number of positive lymph nodes of one (range, one to six). The prevalence of aortocaval lymph node metastases was 22.7%.

CT Evaluation

Preoperative CT assessment identified 39 patients with suspected aortocaval lymph node metastases for observer 1 and 42 patients for observer 2. Suspicion was based on size in 23 and 30 patients, presence of central necrosis in nine and nine patients, round shape in 30 and 31 patients, and irregular margins in 13 and eight patients for observer 1 and 2, respectively. For both observers, 23 patients had two or more characteristics of metastases present. The median size of all lymph nodes in the aortocaval window was 5 mm ± 3.1 (standard deviation) (range, 0–21 mm) and 6 mm ± 2.9 (range, 2–21 mm) for observer 1 and 2, respectively. For histologic-proven metastases, median size at CT remained at 5 mm ± 3.9 (range, 0–21 mm) and 6 mm ± 3.7 (range, 3–21 mm). For negative histopathologic results, median size at CT was also 5 mm ± 2.8 (range, 0–12 mm) and 6 mm ± 2.5 (range, 2–12 mm).

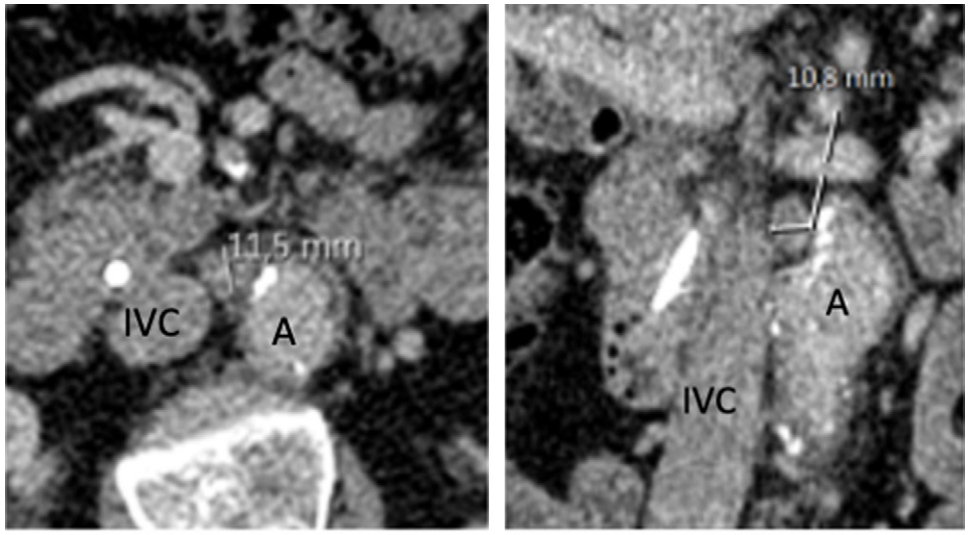
Of 45 patients with histopathologic-proven aortocaval lymph node metastases, both



a. b. c.

Figure 4: Patient is a 79-year-old man. **(a)** Transverse, **(b)** coronal, and **(c)** sagittal images of aortocaval node, with minimal diameters of 3.4 mm, 3.9 mm, and 6.8 mm, respectively. Consequently, 3 mm (3.4 mm rounded to a whole number) was recorded for node size. Node was scored as negative (true negative).

observers correctly identified 13 patients (true positive). An example of a true-positive aortocaval lymph node is shown in Figure 2. Thirty-two patients for both observers had aortocaval lymph node metastases despite negative findings at CT (false negative, Fig 3). In patients without lymph node metastases, CT assessment was correct in 83% (128 of 154) and 81% (124 of 154) of patients and false positives were recorded in 17% (26 of 154) and 19% (29 of 154) of patients, respectively, for observer 1 and 2 (Table 2; Figs 4, 5). In 33 patients, observers agreed on suspicion of aortocaval lymph node metastases; 12 of these patients were identified correctly (ie, confirmed by histopathologic results). Interrater reliability (κ) was 0.767 for general suspicion of aortocaval lymph nodes.



a. b.

Figure 5: Patient is a 64-year-old man. **(a)** Transverse and **(b)** coronal images of node between aorta (A) and inferior vena cava (IVC), with minimal diameter of 11.5 and 10.8 mm, respectively. Because the coronal image yielded the lowest diameter, 11 mm (10.8 rounded to a whole number) was recorded as node size. The node was scored as positive based on size and round shape but was false positive.

Diagnostic Accuracy

The NPV and PPV of CT for the assessment of aortocaval lymph nodes was 80% (95% CI: 76%, 83%) and 33% (95% CI: 21%, 47%) for observer 1 and 80% (95% CI: 76%, 83%) and 31% (95% CI: 20%, 44%) for observer 2. The sensitivity and specificity were 29% (95% CI: 16%, 44%) and 83% (95% CI: 76%, 89%) for observer 1 and 27% (95% CI: 15%, 43%) and 81% (95% CI: 74%, 87%) for observer 2. Diagnostic accuracy was 71% and 69% for observer 1 and 2, respectively.

Individual lymph node characteristics, such as short-axis diameter and central necrosis, were not of prognostic value for predicting lymph node metastases (Fig 6). Multiple logistic regression with a stepwise backward variable selection procedure showed that the best model was obtained with irregular margins of aortocaval lymph nodes on CT. (Table 3).

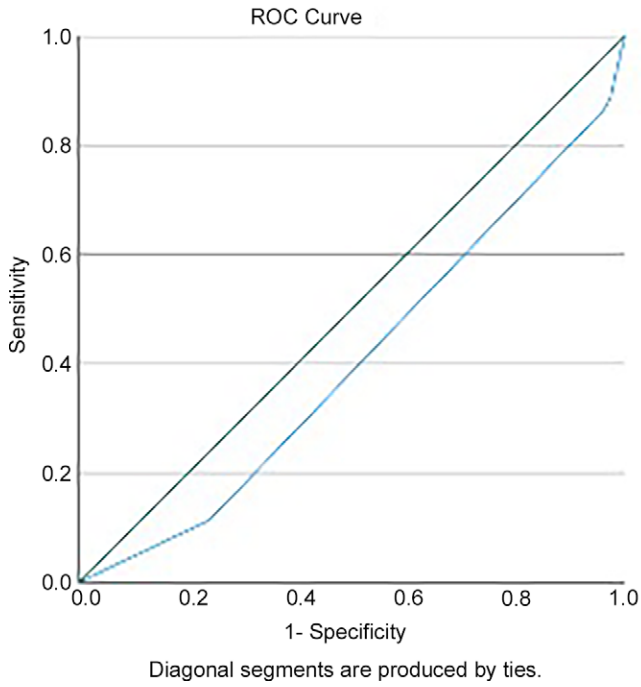


Figure 6: Receiver operating characteristic curve for the model best predicting aortocaval lymph node metastases. Model included tumor growth in surrounding tissue and irregular margins of aortocaval lymph node.

Discussion

In this prospective cohort study, we found a diagnostic accuracy of CT in the assessment of aortocaval lymph nodes in a range of 69%–71%. Although interrater reliability was high (indicating that radiologists agreed on the radiologic suspicion of aortocaval lymph node involvement), suspicion based on CT was not an indicator for true lymph node metastases. Diagnostic accuracy was mostly influenced by a high number of false-positive results (ie, low PPV), despite the fact that there was also a high number of false-negative cases.

In a previous meta-analysis, similar results were found. However, despite a pooled PPV of 25%, outcomes of individual studies in this meta-analysis varied from 0% to 100% (3). Although CT is the most commonly used imaging modality for staging of pancreatic or periampullary cancer, other modalities such as endoscopic US and PET/CT can also be used. Contrary to common belief, accuracy of these modalities does not surpass the accuracy of CT in assessing the presence of lymph node metastases. Moreover, these modalities come with their own limitations. Endoscopic US can depict local-regional lymph node metastases, but the region of interest for aortocaval lymph nodes often lies beyond the field of visibility. For PET/CT, there is a size limitation because only lymph node metastases beyond a certain diameter can be visualized (15–19). A recent study on predicting

Table 3: Univariable Analysis and Multivariable Analysis with Stepwise Backward Variable Selection for the Prediction of Aortocaval Lymph Node Metastases

	Univariable Analysis			Multivariable Analysis		
Predictor	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Tumor growth in surrounding tissues	2.1	0.8, 5.4	.11	2.2	0.86–5.7	.101
Local-regional lymph node metastases	2.0	1.0, 4.0	.04			
General suspicion	2.1	0.9, 4.5	.07			
Size > 1 cm	2.1	0.8, 5.2	.13			
Round shape	1.9	0.8, 4.6	.12			
Central necrosis	2.9	0.8, 11.6	.12			
Irregular margins	3.3	1.1, 10.4	.04	4.0	1.2, 13.4	.02

Note.—CI = confidence interval, OR = odds ratio.

local-regional lymph node metastasis in pancreatobiliary cancer with MRI showed an overall accuracy of 85%, thus exceeding accuracy of CT (20).

Despite adhering to the STARD guidelines for studies on diagnostic accuracy, this study had some limitations. First, for practical reasons, we confined the assessment of extraregional lymph nodes to aortocaval lymph nodes, and all collected tissue from the aortocaval window were collected. These lymph nodes were easily identified both with CT and preoperatively. However, collected lymph nodes were not marked individually, thus no guarantee could be given that nodes assessed with CT were the same as nodes assessed by the pathologist. In other extraregional lymph nodes (eg, station nine along the celiac trunk), resection of the exact same lymph nodes as assessed with CT can be even more challenging. We believe that the diagnostic accuracy of CT in the assessment of extraregional lymph nodes would not differ for various lymph node stations.

Second, although our study indicated a low sensitivity and PPV, the confidence intervals were wide. Given the current results, one can assume that increasing the study population would narrow the confidence intervals but would not change the results. Furthermore, even if CT performed at its best and generated outcomes at the top end of the confidence intervals, sensitivity and PPV would be only 49% and 46%, respectively. In our opinion, with these results, CT still had an inadequate accuracy to assess extraregional lymph nodes.

Notably, because of the era of inclusion and the national guidelines at that moment, none of the patients in our study received neoadjuvant treatment. Although there are numerous studies on the effects of neoadjuvant chemoradiotherapy on imaging regarding resectability, studies assessing the effect on potential lymph node metastases are scarce (21–24), and the clinical relevance remains to be determined. If tumor downstaging is evident, one can assume that lymph node metastases have also responded. In contrast, obvious growth of lymph nodes at follow-up CT will prompt further analysis and will most likely be mirrored by tumor growth. Because it is most likely that after neoadjuvant treatment the accuracy of CT will be comparable or worse than in patients who did not receive neoadjuvant treatment, suspicion for extraregional lymph node metastases on CT scan should not prevent a patient from undergoing an explorative laparotomy with the intent of resection (8). Suspicion on CT scan should be supported by histologic proof to have clinical impact.

In conclusion, CT had a diagnostic accuracy in the assessment of aortocaval lymph nodes of around 70%, with a low sensitivity (30%) and a specificity of around 80%. In daily practice, decisions are made on PPV and NPV, and the low PPV in this study implicated that no sound decision can be made based on CT findings regarding the presence or absence of aortocaval lymph node metastases in patients suspected of having pancreatic or periampullary cancer.

Author contributions: Guarantors of integrity of entire study, D.S.J.T., J.I.E., I.Q.M.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, D.S.J.T., J.I.E., I.Q.M.; clinical studies, D.S.J.T., M.S.v.L., J.P.P., L.A.B., N.H.M., V.E.d.M., J.I.E., I.Q.M.; statistical analysis, D.S.J.T., B.K.P., J.I.E.; and manuscript editing, all authors.

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