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Endoscopic ultrasonography in suspected pancreatic malignancy and indecisive CT

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ABSTRACT

Background: In the assessment of patients with a clinical suspicion of malignant pancreatic disease, computed tomography (CT) findings are sometimes negative or inconclusive.

Aims: To determine whether endoscopic ultrasonography (EUS) with or without fine needle aspiration (EUS/FNA) was conclusive in patients with a clinical suspicion of pancreatic malignancy, in whom CT scan was negative or inconclusive.

Methods: Retrospective case series in a tertiary referral centre. From February 2006 to December 2007, EUS/FNA was performed in all patients suspected of having malignant pancreatic disease with negative or inconclusive CT findings. Main outcome measurement was the diagnostic yield of EUS in these patients.

Results: 34 patients had a negative (n=11) or inconclusive (n=23) CT scan. EUS/FNA established a correct diagnosis in 30/34 cases (88%). Malignancy was diagnosed in 19/34 patients and nonmalignant disease in 8/34 cases. In 3/34 patients no lesions were found and no malignant disease developed during follow-up (mean=728 days). EUS/FNA was inconclusive in 4/34 patients.

Conclusion: In patients with a clinical suspicion of pancreatic malignancy with negative or inconclusive CT findings, EUS/FNA was able to establish a diagnosis in 88% of cases. EUS should therefore be considered a diagnostic modality in this complex group of patients.

KEYWORDS

Endoscopic ultrasonography, computed tomography, pancreatic disease, malignancy

INTRODUCTION

Pancreatic malignancy is notorious for its long asymptomatic onset and poor prognosis. In 2006 the incidence of malignant pancreatic disease in the Netherlands was 8.3/100,000.[1] Curative treatment options are limited in most cases because of unfavourable tumour characteristics at the time of diagnosis. Therefore long-term survival after surgery is still limited with an overall five-year survival of less then 10%. Early detection of pancreatic cancer is of utmost importance for optimal treatment.

Computed tomography (CT) and endoscopic ultrasound (EUS) have both shown to be sensitive diagnostic modalities in patients suspected of having malignant pancreatic disease. CT is a widely available diagnostic modality and has obtained the first place in the work-up of these patients. Multiple studies have investigated the value of EUS and CT for the detection and assessment of pancreatic masses. A pooled analysis comparing the diagnostic accuracy of helical CT and EUS showed that EUS is a sensitive imaging modality for detecting pancreatic lesions.[2] For the detection of pancreatic malignancy, and the assessment of resectability and vascular invasion, EUS is equivalent[3,4] or even superior to helical CT scan.[5,6] Compared with helical CT, EUS has a remarkably higher detection rate for small tumours (<20 mm).[2,3,7]

As a result of current developments in CT imaging techniques, multidetector computed tomography (MDCT) is slowly taking over the position of helical CT. In MDCT both spatial and temporal resolution are improved. Dual-phase, contrast-enhanced MDCT imaging optimises pancreatic vascular enhancement, therefore improving tumour detection and staging.[8] Reconstruction of curved multiplanar reformatted MDCT images allows a better evaluation of the main pancreatic duct, which may lead to a higher detection rate of small tumours.[9] Despite these advances in CT imaging, EUS showed to be superior for

tumour detection (sensitivity 98 *vs* 86%) and staging in patients with known or suspected loco regional pancreatic cancer.[10] In addition EUS yields the practical advantage that tissue diagnosis can be obtained during the same procedure by performing fine needle aspiration (FNA).

In clinical practice there are a substantial number of patients with a high suspicion of a pancreatic lesion, based on characteristic clinical criteria or findings at endoscopic retrograde cholangiopancreatography (ERCP) or abdominal ultrasonography (US), in whom no lesions can be identified on CT imaging.

Although CT and EUS have both independently demonstrated their diagnostic value, the role of EUS in cases where CT fails to establish a diagnosis is still undefined. Therefore our aim was to determine whether EUS with or without FNA (EUS/FNA) was able to establish a correct diagnosis in patients with a clinical suspicion of pancreatic malignancy, in whom CT scan was negative or inconclusive.

METHODS

Patients were retrospectively identified through a database of all patients who underwent EUS/FNA at the endoscopy facility of the Department of Gastroenterology and Hepatology at University Medical Centre Groningen (UMCG), the Netherlands, which is a tertiary referral centre. From February 2006 until December 2007, 34 consecutive patients were identified who were suspected of having malignant pancreatic disease and referred for an EUS/FNA because of negative or inconclusive CT findings. Clinical suspicion of malignant pancreatic disease was defined by the referring clinician and included abdominal pain and/or painless jaundice and/or weight loss and/or double-duct sign established at previous ERCP or abdominal US. CT findings were classified as 'negative' if CT images appeared completely normal, and 'inconclusive' if a mass was seen on CT. This mass could be solid, cystic or both cystic and solid. Patients with a documented history of acute pancreatitis within 12 months were excluded. All patients initially underwent an abdominal CT scan followed by EUS/FNA. CT scans were performed using a Siemens Sensation 64-slice multidetector CT scan (Erlangen, Germany) using a standardised pancreas protocol with rapid administration of contrast and 2-mm slices. CT images were evaluated by a specialised experienced radiologist (EWvdJ). CT scans from patients referred from other hospitals were re-evaluated by the same specialised experienced radiologist (EWvdJ).

EUS was performed on an outpatient basis using conscious sedation (midazolam and pethidine) by two experienced endosonographers (HvD and RKW). The endoscopists were not blinded for the findings at CT scan. For EUS imaging a Pentax linear array EG-3870UTK echo-endoscope was used in combination with a Hitachi EUB-8500 processor. FNA was performed with a Medi-globe 22-gauge SonoTip® II FNA needle system, using standard techniques.[11] A cytological analyst judged the amount and quality of the aspirate on-site. If the quality or quantity was insufficient a second or third FNA pass was performed.

An EUS procedure was defined as 'conclusive' if 1) EUS identified suspected malignant lesions with cytological FNA confirmation of malignancy or 2) EUS identified suspected malignant lesions without cytological FNA confirmation but confirmation of malignancy in resected surgical specimens was established or 3) in the case of nonmalignant disease, when the diagnosis of chronic pancreatitis, autoimmune pancreatitis or pancreatic pseudocysts was established during EUS and no malignancy developed in the follow-up period. An EUS procedure was defined as 'inconclusive' when no diagnosis could be established during EUS with or without FNA. EUS findings of a lesion were described as 'suspected for malignant lesion' when the lesion was hypo-echogenic, sharply delinated and located within the parenchyma of the pancreas.

RESULTS

Thirty-four patients were included. Eleven patients had a negative CT scan (group I) and 23 patients had inconclusive CT findings (group II).

Patient characteristics are shown in *table 1*. The study cohort consisted of 21 men and 13 women. Mean age of patients included in group I was 66.4 years (range 37 to 75) and 56.2

Table 1. *Characteristics of patients suspected of having malignant pancreatic disease with completely normal (group I: negative CT) or inconclusive CT findings (group II: inconclusive CT)*

	Group I: negative CT (n=11)	Group II: inconclusive CT (n=23)
Age (years)	66.4 (37-75)	56.2 (17-83)
Gender		
• Male	6	15
• Female	5	8
Time between CT and EUS (days)	25.7 (range 7-61)	49.8 (range 4-184)
EUS		
• Number of patients with identified lesions	8	19
• Mean lesion diameter (mm)	20.9 (median 21.8 / range 14-32.5)	22.3 (median 20.75 / range 5-39.5)
• FNA performed	7	13
- Mean number of punctures	2.3 (range 1-5)	1.9 (range 1-4)

CT = computed tomography; EUS = endoscopic ultrasonography; FNA = fine needle aspiration.

years (range 17 to 83 years) in group II. The mean interval between initial CT scan and EUS was 43 days (range 4 to 184 days). In 27 patients a lesion was identified with EUS. Lesions seen with EUS had a mean diameter of 20.9 mm in group I (median 21.8 mm/range 14 to 32.5 mm) and 22.3 mm in group II (median 20.75 mm/range 5 to 39.5 mm). In 20 patients EUS was accompanied by FNA.

Table 2. *Distribution of malignant, nonmalignant and no disease found, in case of conclusive and inconclusive EUS/FNA findings in group I (negative CT) and group II (inconclusive CT) patients (total n=34)*

		CT	
		Group I: negative	**Group II: inconclusive**
EUS/FNA	**Conclusive**		
	Malignant	8	11
	Nonmalignant	-	8
	No disease	2	1
		10	20 30/34
	Inconclusive		
	Malignant	1	-
	Nonmalignant	-	2
	No disease	-	1
		1	3 4/34

An EUS procedure was defined as 'conclusive' if 1) EUS identified suspected malignant lesions with FNA confirmation of malignancy or 2) EUS identified suspected malignant lesions without FNA confirmation but confirmation of malignancy in resected surgical specimens was established or 3) in the case of nonmalignant disease, when the diagnosis of chronic pancreatitis, autoimmune pancreatitis or pancreatic pseudocysts was established during EUS and no malignancy developed in the follow-up period. An EUS procedure was defined as 'inconclusive' when no diagnosis could be established during EUS with or without FNA. CT = computed tomography; EUS/FNA = endoscopic ultrasound-guided fine needle aspiration.

Figure 1A. *Abdominal multidetector computed tomography scan (2-mm slices) of a patient with a clinical suspicion of pancreatic malignancy using a Siemens Sensation 64-slice multidetector CT scan (Erlangen, Germany). No lesion can be identified in the pancreatic head*

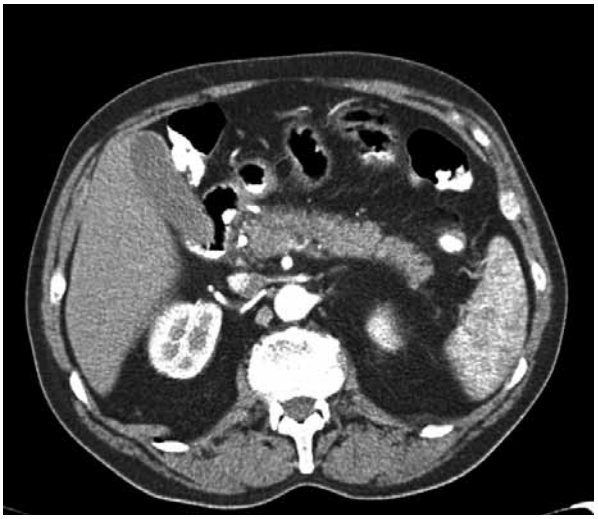


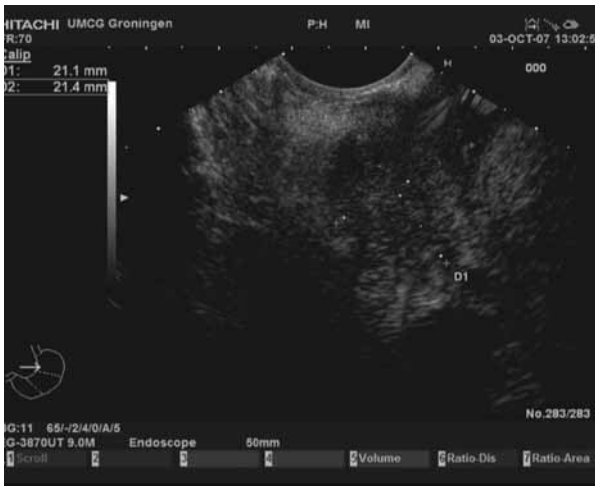
Table 2 shows whether EUS/FNA was conclusive or inconclusive in these patients and the distribution of malignant, nonmalignant disease and no lesions seen on EUS. Overall EUS/FNA was able to establish a diagnosis in 30/34 cases (88.2%). In eight out of 11 patients with normal CT findings, lesions with a diameter of up to 32.5 mm could be identified (*figure 1A* and *1B*). Final diagnostic results of the EUS/FNA procedures are summarised in *table 3*.

In 19/34 (55.9%) patients a malignancy was diagnosed. Pancreatic adenocarcinoma was proven in 12 patients of

Table 3. *Diagnosis established with EUS/FNA in patients with negative or inconclusive CT findings and clinical suspicion of pancreatic malignancy*

Diagnosis	**N**
Malignant disease	19
• Pancreatic adenocarcinoma	12
• Neuroendocrine tumour	2
• Cholangiocarcinoma	1
• Metastatic lung carcinoma	1
• Metastatic melanoma	1
• Intraductal papillary mucinous neoplasma	1
• Mucinous cystic tumour	1
Nonmalignant disease	8
• Chronic pancreatitis	5
• Pseudocysts	2
• Autoimmune pancreatitis	1
No lesion	3
• No diagnosis	4
• No disease in follow-up	1
• Pancreatic adenocarcinoma (at surgery)	1
• Chronic pancreatitis (at surgery)	2
Total N	**34**

Figure 1B. *Endosonography of the pancreatic head of the same patient using a Pentax linear array EG-3870UTK echo-endoscope and Hitachi EUB-8500 processor. An apparent hypoechogenic irregular-shaped lesion can be identified with a maximum diameter of 21.4 mm. Fine needle aspiration revealed adenocarcinoma*



whom seven underwent surgical resection. In two cases the tumour was irresectable. Of those who underwent pylorus-saving pancreaticoduodenectomy, one patient was still alive at the end of follow-up (974 days). Palliation was the only therapeutic option for the single patient diagnosed with cholangiocarcinoma, as was the case for five patients with pancreatic adenocarcinoma who were not eligible for surgery. One out of two neuroendocrine tumours was due to Von Lippel-Hindau disease and this was managed without surgery. The second neuroendocrine tumour turned out to be irresectable at surgery. Successful resection was possible in case of intraductal papillary mucinous neoplasma. EUS/FNA revealed one cystic mucinous tumour which was managed expectantly. In two patients metastases were found from either lung carcinoma or melanoma. Palliative therapy was instituted in both cases.

EUS/FNA revealed nonmalignant disease in 8/34 cases (23.5%). In one of these patients EUS was suspect for malignancy, but FNA revealed an autoimmune pancreatitis. In 3/34 patients no lesions were found (8.8%). Mean follow-up in these patients was 728 days (range 683 to 767 days) and revealed no pancreatic disease.

In 4/34 patients (11.8%) EUS/ FNA was not able to establish a definite diagnosis. Out of these four patients, one had a pancreatic adenocarcinoma at surgery and two patients had chronic pancreatitis confirmed by surgery. In case of the last patient in whom no definite diagnosis could be made, the lesion seen on CT and EUS was most likely a pseudocyst. Therefore surgery was not indicated and watchful waiting could be justified. Follow-up of 1054 days did not reveal benign nor malignant disease.

DISCUSSION

EUS/FNA established a correct diagnosis in 30 out of 34 patients (88%) suspected of having malignant pancreatic disease with completely normal or inconclusive CT findings. In 19 out of 34 patients EUS/FNA confirmed the clinical suspicion of pancreatic malignancy. Pancreatic malignant disease could be excluded using EUS/FNA in 11 out of 34 patients. These findings show the strength of EUS/FNA in this complicated group of patients.

Pancreatic cancer is known for its insidious course. Pancreatic cancer proves to be one of the most difficult diagnoses to establish just on clinical grounds. Hence, there are abundant data that show the effectiveness of both EUS/FNA and CT in the detection and staging of pancreatic malignancy. However, in everyday clinical practice, CT may fail to establish a diagnosis. Relatively little is known about the value of EUS/FNA in these cases with a negative or inconclusive CT scan. One study showed that both EUS and EUS/FNA had an accuracy of 92% in patients suspected of having malignant pancreatic disease although no definite mass was seen on MDCT.[12] In our study, EUS has proven to be a highly valuable diagnostic modality in these cases of unconvincing CT findings and sustained clinical suspicion. These results are supported by an earlier publication presenting ten patients with obstructive jaundice and inconclusive US and CT, in whom EUS established a correct diagnosis.[13] Performing FNA enables a cytological diagnosis and therefore increases the diagnostic capability of EUS. EUS/FNA is known for its high sensitivity, specificity and diagnostic accuracy in the assessment of pancreatic masses in patients suspected of having malignant pancreatic disease.[14,15] With a complication rate <1%, EUS/FNA may be considered a safe procedure.[7,16]

Based on symptoms we suspected 34 patients of having malignant disease, which was confirmed by EUS/FNA in 19 cases and by surgery in one patient. In addition EUS has proven to be extremely helpful for excluding pancreatic disease. In this study none of the patients (3/34) in whom no lesion was found by EUS developed pancreatic malignancy during follow-up. These findings are consistent with two studies showing a negative predictive value of 100% in case of clinical suspicion of pancreatic cancer, indeterminate CT scan and normal pancreatic EUS.[17,18] Yet, standardised helical CT imaging techniques were not standard of care in all patients included in these studies.

One of the limitations of our study is the variability in time between CT and EUS procedures. The mean number of days between CT and EUS was 26 for group I and 50 days for group II. This might be explained by different reasons. First of all it reflects the diagnostic difficulty and delay in this complex group of patients. Second it reflects the relative unfamiliarity of clinicians with the capacities of EUS/FNA and thirdly, it reflects the relatively low availability of EUS in the Netherlands. In one case it took 184 days before EUS was performed. This patient turned out to have chronic pancreatitis at the final diagnosis.

Based on our findings CT scan should immediately be considered by an EUS/FNA when there is a clinical suspicion of malignant pancreatic disease.

In conclusion, we show that in patients with a clinical suspicion of pancreatic malignancy with negative or inconclusive CT findings, EUS with or without FNA was able to establish a diagnosis in the majority of cases. Complementary to CT, the use of EUS/FNA should therefore be considered as an accurate diagnostic modality in the work-up of this complex group of patients.

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