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Diagnostic performance of endoscopic ultrasound for detection of pancreatic malignancy following an indeterminate multidetector CT scan: a systemic review and meta-analysis

Somashekar G. Krishna[1,2] · Bhavana B. Rao[3] · Emmanuel Ugbarugba[4] · Zarine K. Shah[5] · Alecia Blaszczak[6] · Alice Hinton[7] · Darwin L. Conwell[2] · Phil A. Hart[2]

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Abstract

Background Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis in part due to delayed diagnosis. Even with advances in cross-sectional imaging, small pancreatic malignancies can be missed. We sought to determine the performance of endoscopic ultrasound (EUS) in those without an obvious mass on multi-detector CT scan (MDCT), but with clinical suspicion for pancreatic malignancy.

Methods Multiple databases were systematically searched to identify studies that assessed the diagnostic performance of EUS after negative or inconclusive pancreatic protocol MDCT for detection of pancreatic malignancy when clinically suspected. A total of four studies met the inclusion criteria. The point estimates in each study were compared to the summary pooled estimates of sensitivity and specificity with the aid of forest plots. Funnel plots and Egger's test were employed to evaluate possible publication bias.

Results EUS-guided fine needle aspiration was performed in all studies. EUS was performed in 206 subjects with a clinical suspicion of a pancreatic mass but with an indeterminate MDCT. A pancreatic mass (mean size 21 ± 1.2 mm) was identified in 70% ($n = 144$) of the subjects, and 42.2% ($n = 87$) were diagnosed with PDAC. The pooled estimates of EUS for diagnosing pancreatic malignancy in the setting of an indeterminate MDCT were a sensitivity of 85% (95% CI 69–94%), specificity of 58% (95% CI 40–74%), positive predictive value of 77% (69–84%), negative predictive value of 66% (95% CI 53–77%), and an accuracy of 75% (95% CI 67–82). The summary area under the ROC curve was 0.80 (95% CI 0.52–0.89). The funnel plots and Egger's test did not show a significant publication bias.

Conclusions The yield of EUS is comparatively higher for the diagnosis of a pancreatic malignancy in patients with suspected cancer, but a non-diagnostic MDCT. Importantly, the majority of the lesions missed on CT represent PDAC, in which early diagnosis is essential.

Keywords Endoscopic ultrasound · Fine needle aspiration · Pancreas · Pancreatic cancer · Multidetector CT Scan

Pancreatic ductal adenocarcinoma (PDAC) has a poor 5-year survival of approximately 7% and is now the second leading cause of cancer-related deaths in the United States

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✉ Somashekar G. Krishna
sgkrishna@gmail.com

1 Section of Advanced Endoscopy, Division of Gastroenterology, Hepatology and Nutrition, The Ohio State University Wexner Medical Center, 395 West 12th Avenue, Columbus, OH 43210, USA

2 Section of Pancreatic Disorders, Division of Gastroenterology, Hepatology and Nutrition, The Ohio State University Wexner Medical Center, Columbus, OH, USA

3 Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, OH, USA

4 Department of Internal Medicine, The Ohio State University Wexner Medical Center, Columbus, OH, USA

5 Department of Radiology, The Ohio State University Wexner Medical Center, Columbus, OH, USA

6 The Ohio State University College of Medicine, Columbus, OH, USA

7 Division of Biostatistics, College of Public Health, The Ohio State University, Columbus, OH, USA

[1]. The poor survival rate is due to a combination of factors including late diagnosis, aggressive tumor biology, and ineffective oncologic treatment options. Early detection by imaging studies continues to be challenging. There have been important advancements in cross-sectional imaging over the last decade, including the widespread use of multidetector computed tomography (MDCT) which offers improved spatial and temporal resolution by thinner sectioning of images, faster image acquisition, and optimized pancreatic vascular enhancement; thus leading to improved sensitivity for detection of smaller pancreatic tumors [2]. Despite the improvements in cross-sectional imaging, tumors smaller than 1 cm may still not be visualized. For example, it has been observed that patients often do not have a radiographically apparent mass within 6 months of PDAC diagnosis [3]. However, other imaging abnormalities, namely pancreatic duct dilation with an abrupt cutoff, or vague, focal enlargement may precede the appearance of a discrete mass. It is necessary to diagnose PDAC as early as possible during this window of radiographic progression to optimize the chance for long-term survival.

In patients with radiographic features suggestive of pancreatic malignancy, but no discrete mass on MDCT imaging, the use of endoscopic ultrasound (EUS) may assist with obtaining an earlier diagnosis. In multiple retrospective studies, EUS has been shown to be more sensitive for tumor detection than CT imaging, including MDCT [4–7]. In a prospective pancreatic screening study, it was demonstrated that MDCT maintains a slim advantage over magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) for detection of solid lesions [8]. Consequently, some clinicians perform EUS in these patients to avoid missing an opportunity for early diagnosis. However, the use of EUS in this context has only been analyzed in a few reports, but the study settings, designs, and results are heterogeneous.

Therefore, we systematically examined the literature to more accurately characterize the effectiveness of EUS for lesion identification in those with suspected pancreatic malignancies, but no visualized mass on MDCT imaging.

Materials and methods

This study was conducted using a protocol created a priori in accordance with guidelines for systematic reviews and meta-analyses [9].

Search strategy

Multiple databases (including Medline, Embase, Cochrane library, SCOPUS, Google scholar, and CINAHL Plus) were searched for studies published between 1980 and December 2015. The systematic literature search was performed with the assistance of a medical librarian using the following search terms: pancreatic cancer, pancreatic adenocarcinoma, pancreatic neoplasm, multidetector computed tomography, tomography X-ray computed, endoscopic ultrasound, endoscopic ultrasonography, and endoscopic ultrasound-guided fine needle aspiration (S.K. & E.U) (online Appendix 1). Two investigators (S.K. & B.R.) independently screened the titles and abstracts of all the articles according to the study criteria; discrepancies were resolved by discussion. Additionally, we screened the reference list of all the selected articles for any potentially related manuscripts that were not identified during the initial search. Our search was restricted to studies involving human subjects published in the English language. Abstracts and case reports were not included due to the inability to assess for methodological bias.

Study selection

The study flow is illustrated in Fig. 1. The study objective was to evaluate the diagnostic yield of EUS for detecting a pancreatic malignancy in those where it was suspected either by clinical or laboratory evaluation, but not visualized by a pancreatic protocol MDCT. We selected studies meeting the following criteria (Table 1): (i) Patients with suspected pancreatic malignancy, who did not have a mass on MDCT. Scenarios in which pancreatic cancer would be suspected in the absence of a mass include the presence of focal enlargement or fullness of the pancreatic head, or the presence of pancreatic and/or biliary duct dilation. (ii) MDCT imaging was performed using a 'high-quality' pancreatic protocol. For the purposes of this study, high-quality was defined as MDCT performed with 'pancreatic protocol' and with a slice thickness of $\leq$2.5 mm. (iii) Patients who underwent a subsequent linear array EUS with an intent for fine needle aspiration (FNA). Radial EUS is not suitable for EUS-guided fine needle aspiration. Compared to radial echoendoscopes, linear array scopes permit FNA and detect more pancreatic lesions [1]. (iv) The outcome included detection of pancreatic neoplasm, either based on FNA results, surgical pathology, or clinical follow-up (for patients deemed non-operative).

From the selected studies, three investigators (S.K., E.U., & A.B.) independently reviewed and extracted data regarding study characteristics, patient characteristics, interventions (i.e., details of CT imaging and EUS procedures), and assessment of study bias, and entered these data into a standardized data form. Radiologist (Z.S.) specialized in pancreatic imaging reviewed the studies for appropriate CT technique and imaging data. We assessed the quality of each study using the Newcastle–Ottawa Scale for non-randomized studies in meta-analyses [10]. Any disagreement

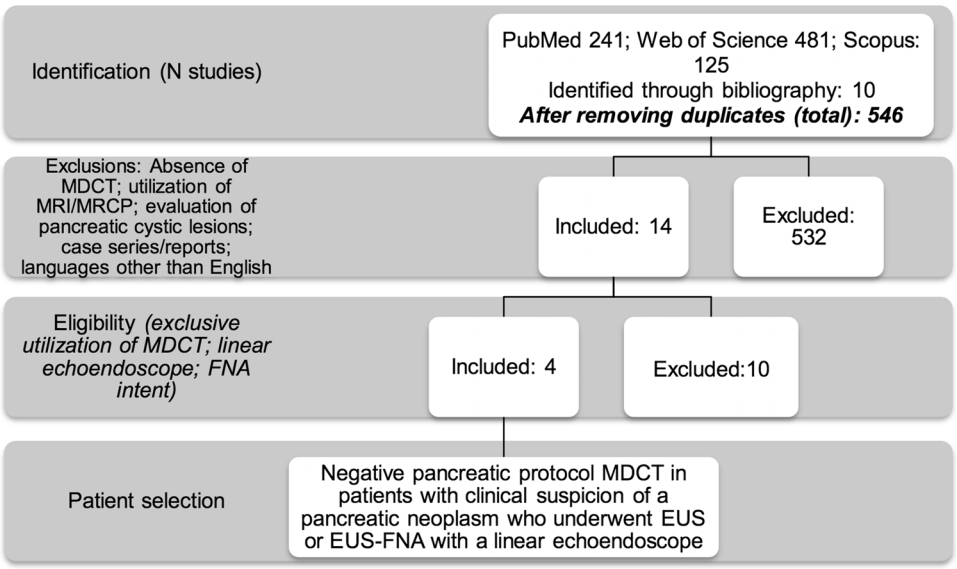

Fig. 1 Study flow diagram. *EUS* endoscopic ultrasound, *MDCT* multidetector computed tomography, *FNA* fine needle aspiration, *MRI/MRCP* magnetic resonance imaging/magnetic resonance cholangiopancreatography

Table 1 Study inclusion and exclusion criteria for meta-analysis

Inclusion criteria	Exclusion criteria
EUS in subjects with suspected pancreatic malignancy[a] with negative pancreatic protocol MDCT	Case series or reports of including only subjects with a positive EUS or EUS-FNA and negative pancreatic protocol MDCT scan
Written in English	Use of any other CT scan modality other than pancreatic protocol MDCT
Full text available	Use of MRI/MRCP with CT Scan for evaluation of pancreatic lesions
Utilization of a linear echoendoscope with intent for FNA	Diagnostic evaluation of only cystic pancreatic lesions
Utilization of high-quality pancreatic protocol MDCT	
Patient follow-up of 6 months (minimum) after EUS	

EUS endoscopic ultrasound, *MDCT* multidetector computed tomography, *FNA* fine needle aspiration, *MRI/MRCP* magnetic resonance imaging/magnetic resonance cholangiopancreatography

[a]Pancreatic malignancy encompasses pancreatic ductal adenocarcinoma, pancreatic neuroendocrine tumor, distal bile duct extrahepatic cholangiocarcinoma (within the region of the head of the pancreas), and primary pancreatic lymphoma

was discussed and reconciled with an additional investigator (P.H.). Studies with duplicate or overlapping data were excluded from the meta-analysis.

Statistical analysis

A meta-analysis was performed to determine pooled estimates of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) of EUS to diagnose pancreatic malignancy in patients with a clinical suspicion but indeterminate or negative pancreatic protocol MDCT. For the purpose of the analysis, pancreatic malignancy encompasses PDAC, pancreatic neuroendocrine tumor, distal bile duct extrahepatic cholangiocarcinoma, and primary pancreatic lymphoma. The pooled estimates were calculated using a random effect model. The point estimates in each study were compared to the summary pooled estimates with the aid of forest plots. Funnel plots and Egger's test were employed to evaluate for publication bias. Inter-study heterogeneity was assessed with Cochran's Q test and the I^2 statistic. Stata version 13.1 (College Station, TX), Comprehensive Meta-analysis 2.0, and Meta DiSc versions 1.4 were used to perform the statistical analyses.

Results

Qualitative analysis

After deduplication, 546 articles were identified. Fourteen studies were selected for review after applying the inclusion criteria (Table 1). Subsequently confines involving exclusive utilization of pancreatic protocol MDCT, a linear echoendoscope, FNA intent, and minimum follow-up duration of 6 months limited the results to only four studies. Further these studies included patients that had both a negative MDCT followed by EUS findings (Table 2). The studies were of medium to high quality with scores of 6–7 on the Newcastle–Ottawa quality assessment scale (online Appendix 2). Two studies were from the United States

Table 2 Characteristics of studies included in the meta-analysis

	Agarwal et al. [7]	Deerenberg et al. [5]	Meijer et al. [6]	Wang et al. [3]	Total/mean
Country	USA	Netherlands	Netherlands	USA	
University/hospital	UT MD Anderson	Maasstad Hospital	University Medical Center	UT MD Anderson	
Year	2001 (2000–2001)	2011	2010	2013 (2002–2010)	
Database	EUS referral	EUS referral	Radiology	EUS referral	
Inclusion criteria	Jaundice, acute pancreatitis (>2 episodes)	Jaundice, cholestasis, weight loss, abdominal/back pain	Weight loss, abdominal pain, jaundice, double-duct sign on ERCP/US	Clinical suspicion of pancreatobiliary malignancy, EUS performed within 3 months of abdominal CT scan	
Exclusion criteria	Suspected PNETs, ampullary tumors, pancreatic cysts	Patients with a mass identified on cross-sectional imaging (i.e., CT or MRI)	Acute pancreatitis within 12 months	Patients with a mass identified on cross-sectional imaging (i.e., CT or MRI)	
Design	Retrospective	Retrospective	Retrospective	Retrospective	
Center	Single	Single	Single	Single	
Endosonographers (*N*)	1	3	2	5	11
Reviewing radiologists (*N*)	Specialty radiologist	2	1	Specialty radiologist	
MDCT	Spiral CT, 1.25 mm	Yes	Yes	Yes	
Pancreatic protocol	Yes	Yes	Yes	Yes	
Contrast phase	Altered[a]	Optimal	Optimal	Optimal	
Repeat review of MDCT	No	No	No	No	
Minimum f/u (months)	12	6	22	12	13 (mean)
EUS in patients without mass on CT	25	31	34	116	206
Linear echoendoscope	Yes	Yes	Yes	Yes	
EUS normal/inconclusive	7	16	7	32	62
EUS mass	18	15	27	84	144
Size (mean ± SD, mm)	≤20	13–45 (median 20)	21.6 (range 5–39.5)	22.4 ± 0.88	21 ± 1.2 (mean)
Pancreatic malignancy identified by EUS	18	13	19	64	114
PDAC identified by EUS	18	13	12	44	87
PDAC/malignant neoplasm not identified by EUS	0	6	1	12	19
Diagnostic EUS-FNA	16	3[b]	19	44	102
Non-diagnostic EUS-FNA	2	NA	1	20	23

Table 2 (continued)

	Agarwal et al. [7]	Deerenberg et al. [5]	Meijer et al. [6]	Wang et al. [3]	Total/mean
Other malignant lesions		NET 1 Ampullary adenocarcinoma 1	NET 2 Cholangiocarcinoma 1 IPMN1 MCN1 Metastatic: 2 *Lung cancer 1* *Melanoma 1*	NET 8 Ampullary adenocarcinoma 2 Cholangiocarcinoma 6 IPMN 4 MCN 1 B cell lymphoma 1 Metastatic: 4 *Renal cell carcinoma 1* *Bladder cancer 1* *Melanoma 1* *Ovarian cancer1*	
Factors associated with pancreatic lesions when CT is negative	History of pancreatitis, Total bilirubin > 2 mg/dL	Total bilirubin > 2 mg/dL, presence of biliary endoprosthesis	Abdominal pain, weight loss, double duct sign on ERCP/MRCP	Bile duct stricture, dilation of main pancreatic duct, increased size of the pancreatic head, history of pancreatitis, Total bilirubin > 2 mg/dL, peripancreatic lymphadenopathy	
New Castle–Ottawa quality assessment	6/9	7/9	7/9	7/9	

CT computed tomography, *EUS* endoscopic ultrasound, *PNET* pancreatic neuroendocrine tumor, *ERCP* endoscopic retrograde cholangiopancreatography, *MDCT* multidetector computed tomography, *f/u* follow-up; *SD* standard deviation, *PDAC* pancreatic ductal adenocarcinoma, *FNA* fine needle aspiration, *IPMN* intraductal papillary mucinous neoplasm, *MCN* mucinous cystic neoplasm, *MRCP* magnetic retrograde cholangiopancreatography

[a]Arterial and venous phase scans were performed at 25 s and 10–15 s after injection of contrast, respectively. The most optimal late arterial phase scan is obtained at 35–40 s after start of injection

[b]FNA not performed in 10 patients where EUS visualized mass. They underwent exploratory surgery: 7 pylorus-preserving pancreaticoduodenectomies, 2 palliative (vascular invasion), 1 chemotherapy

(from the same institute during non-overlapping study periods) and the others were from the Netherlands.

Study characteristics for meta-analysis

The final four studies selected for the meta-analysis were all single-center retrospective cohort studies at tertiary care hospitals (Table 2). The mean follow-up period was 13 ± 7 months. A total of 206 subjects met study criteria where an EUS was performed in subjects with a clinical suspicion of a pancreatic mass but with an indeterminate MDCT. A pancreatic mass was identified in 70% (*n*: 144) of the subjects. Specifically, 55.3% (*n*: 114) of the subjects were diagnosed with a pancreatobiliary malignant neoplasm which included 87 (42.2% of 206) PDACs. A FNA was performed in 87% (*n*: 125) of 144 subjects with a pancreatic mass. Among these FNAs, 102/144 (82%) were diagnostic where as 23 (18%) were non-diagnostic. The mean size of the pancreatic lesion diagnosed by EUS was 21 ± 1.2 mm. One of the studies did not specify mean size of the lesion but documented that all lesions were ≤20 mm [7]. In all, 19/206 (9% of 206) subjects with pancreatobiliary neoplasms were neither detected by MDCT nor EUS, among which 11 (5% of 206) were diagnosed with PDAC.

EUS was normal or inconclusive with non-visualization of an obvious pancreatic mass in 30% (*n* = 62) of subjects. Among these 62 subjects, 11 (18%) had PDAC, 10 (16%) had non-PDAC pancreatic neoplasia, and a malignant pathology was not identified in 41 (66%) subjects.

Evaluation of pooled diagnostic performance of EUS for detecting a pancreatic neoplasm

The pooled estimates of EUS (Fig. 2, online Appendix 3) in detecting a pancreatic neoplasm demonstrated a sensitivity of 85% (95% confidence interval [CI] 69–94%), specificity of 58% (95% CI 40–74%), PPV of 77% (95% CI 69–84%), NPV of 66% (95% CI 53–77%), and accuracy of 75% (95% CI 67–82%). Pooled estimates calculated by fixed and random effect models were comparable. Summary ROC curves demonstrated an area under the curve of 0.80 (95% CI 0.52–0.89; Fig. 3). A sensitivity analysis was performed to evaluate influence of each individual study on the pooled estimates (online Appendix 4). While the estimates for pooled sensitivity did not vary considerably from the pooled results, there were variations in the pooled specificity, but within the limits of 95% CI.

Publication bias and heterogeneity

Overall, the funnel plots for sensitivity and specificity did not reveal any significant publication bias (Fig. 4). This visual asymmetry observed for plots depicting sensitivity

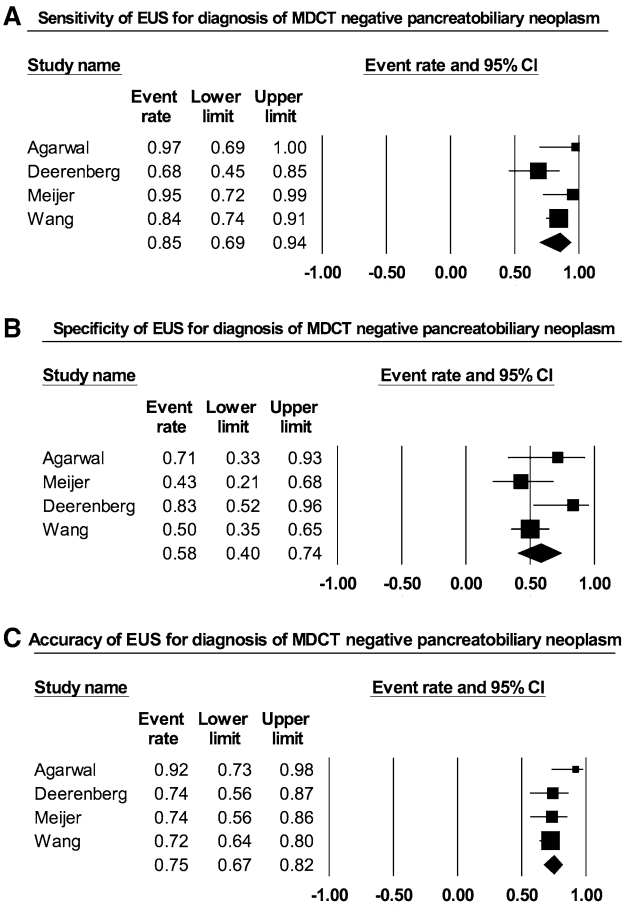

Fig. 2 Forrest plots of pooled diagnostic performance of endoscopic ultrasound for detecting a pancreatic malignancy following a negative or indeterminate MDCT: **A** Sensitivity, **B** specificity, and **C** accuracy. *MDCT* multidetector computed tomography. The only biliary neoplasm included was distal bile duct cholangiocarcinoma within the region of the head of the pancreas

was not significant as demonstrated by Egger's regression test. The publication bias indicators for sensitivity (1.48, 95% CI −4.98, 7.94; $p = 0.43$) and specificity (2.14, 95% CI −4.11, 8.40; $p = 0.28$) were not significant. The Cochran's *Q* test demonstrated "low" heterogeneity for pooled specificity ($I^2 = 49.02\%$), but moderate heterogeneity for pooled sensitivity ($I^2 = 54.11\%$).

Discussion

In this systematic review and meta-analysis, we demonstrate three relevant findings. First, EUS increases the diagnostic yield in patients with clinically suspected pancreatic malignancy, but without radiographically discrete mass on pancreatic protocol MDCT imaging. Next, three-fourths of all pancreatic malignancies not detected by MDCT are PDACs highlighting the implication of missed lesions. And

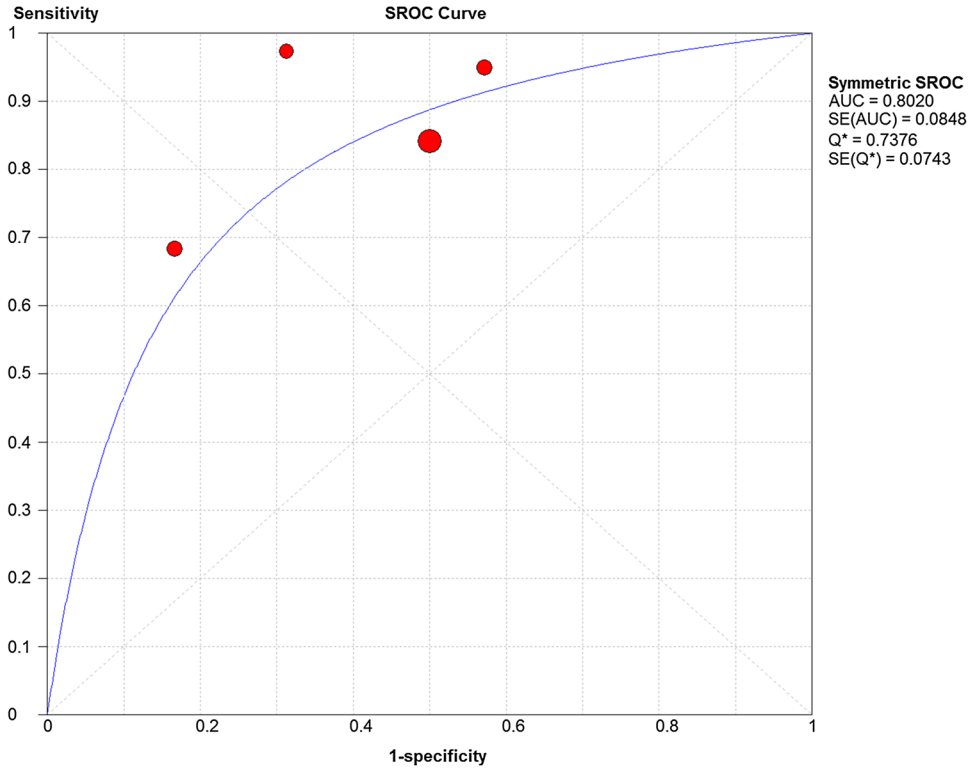

Fig. 3 Summary receiver operating characteristic curve (SROC) of endoscopic ultrasound for detecting a malignant neoplasm in the pancreas. *AUC* area under the curve

third, a comprehensive evaluation with pancreatic protocol MDCT and subsequent EUS can fail to detect a small subset of patients with PDACs. Collectively, applying stringent selection criteria, this meta-analysis suggests that EUS examination is clinically valuable for patients presenting with clinical or laboratory evidence of a pancreatic malignancy that otherwise remains undetected after a dedicated high-quality CT scan.

Prior studies comparing diagnostic sensitivities of EUS (94–99%) and MDCT (86–89%) for detection of pancreatic neoplasm have demonstrated the superiority of EUS [11, 12]. Specifically, compared to sensitivity of MDCT (70%), it has been demonstrated the EUS has higher sensitivity (96%) for lesions smaller than 2 cm in size [11]. Thus, we assessed the sensitivity of EUS for detecting pancreatic neoplasms for which pancreatic protocol MDCT findings were either indeterminate or negative. In our meta-analysis, two of the studies were from a tertiary cancer care center with specialized services catering to a large volume of patients with pancreatic neoplasms, whereas the other two centers were more representative of community practices. Amongst other studies conducting similar investigations, a major limiting factor is that a dedicated pancreas protocol CT was not consistently used [13–15].

There is limited research to guide the clinician in the evaluation of patients with abnormal clinical and/or radiographic findings potentially suspicious for pancreatic malignancy, but without a definite mass on pancreatic protocol MDCT imaging. The latest guidelines for management of PDAC from the National Comprehensive Cancer Network (NCCN) recommends EUS as the preferred diagnostic test in this clinical setting (category 2A) [16]. However, in our experience, the diagnostic approach varies depending on the provider's clinical experience, subspecialty expertise, and institutional resources. Although some may proceed directly to EUS evaluation, others may elect to obtain serial imaging. When the underlying etiology is benign, the initial diagnostic strategy is less relevant; however, for patients with PDAC, a diagnostic delay of 3–6 months can be detrimental. In fact, for those who develop PDAC, the ideal time window for diagnosis is when the mass is too small to be radiographically visible [17].

The application of EUS with or without FNA in the diagnostic evaluation of suspected pancreatic neoplasm is evolving. Historically, there was an inclination to avoid FNA of an apparently resectable pancreatic mass as it would not affect clinical decision making, and would expose patients to the risk of adverse events, including seeding of the needle track. This has been a deterrent to some clinicians for utilizing EUS in this scenario. However, as shown in this study EUS can often diagnose a pancreatic neoplasm (especially PDAC) in the absence of a radiographically apparent mass. One of the four studies in the meta-analysis investigated the application of FNA when a definitive mass was "not visualized on EUS"[4]. FNA of transition points in biliary/pancreatic ducts or areas of

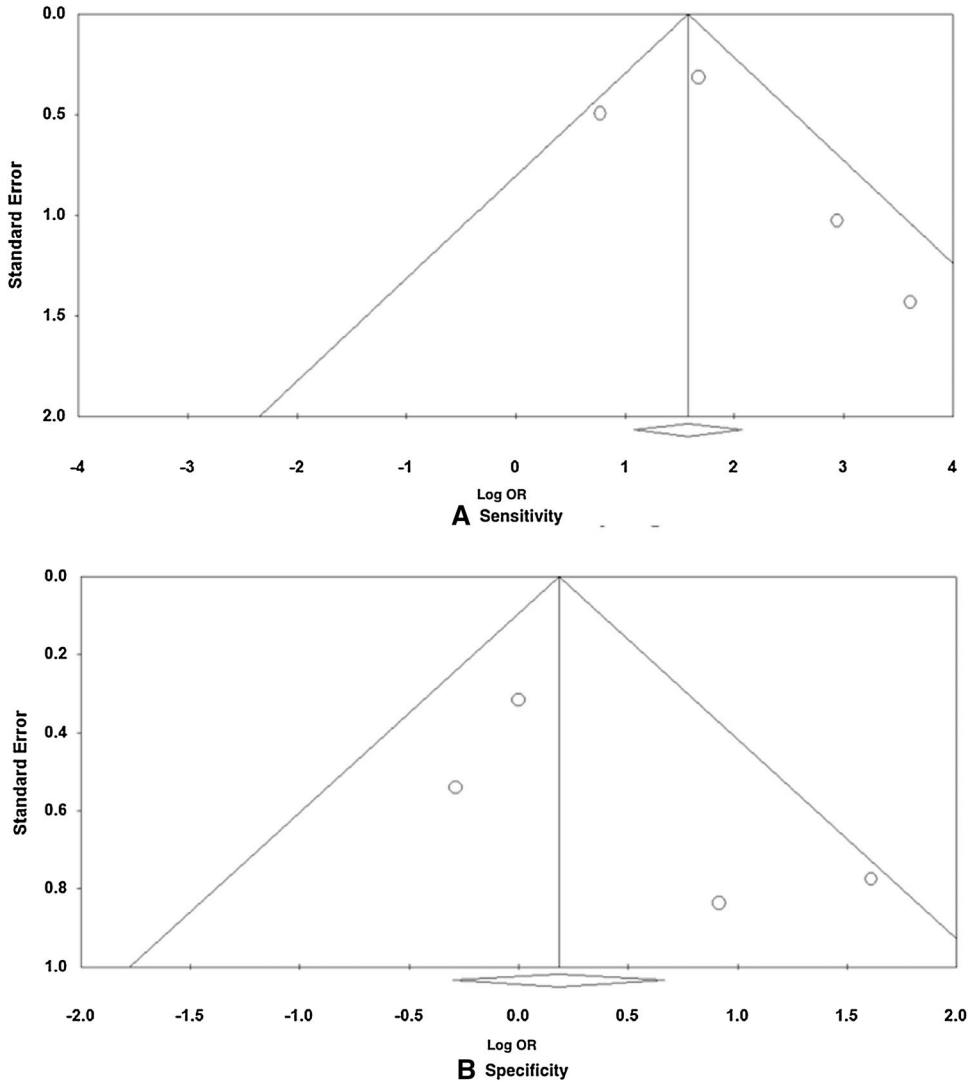

Fig. 4 Funnel plots do not reveal publication bias for either **A** sensitivity or **B** specificity among the studies included in this meta-analysis

fullness or altered echogenicity in the pancreas resulted in a positive diagnosis in 37.5% of cases (12/32). Furthermore, EUS may identify radiographically occult lesions in the left lobe of the liver (including lesions < 5 mm) and peritoneum [18–21]. The potential risk of needle track seeding was not supported by a recent analysis of the SEER database demonstrating no impairment in survival for those undergoing EUS-FNA [22]. Lastly, the adverse event rate following EUS-FNA of solid pancreatic masses is exceedingly low including a < 2% risk of pancreatitis and similar risk of infection with a standard upper endoscopy [23].

There were minor variations in the imaging protocols studied (e.g., thickness of slices varied from 1.25 to 3 mm), but all studies utilized a multidetector CT scanner, which reflects the most commonly utilized cross-sectional modality to evaluate for a suspected pancreatic neoplasm. The appropriate pancreatic protocol CT scans which included acquisition at the late arterial phase (35–40 s after injection of contrast) and the portal venous phase were performed in all but one study [4–7]. The early arterial phase beginning with the liver was at 25 s after contrast injection in the study by Agarwal et al.; however, the timing of the pancreatic phase is not specified. If scanning was initiated at the top of the liver at 25 s after injection of contrast, it would require 35–40 s to scan the pancreas. Furthermore, published literature utilizing pancreatic protocol MDCTs from the same institute (University of Texas MD Anderson Cancer Center) and similar study period (years 1999 to 2004) reveals that the that the pancreatic phase was initiated between 35 and 45 s [11, 24–26].

While a majority (76%; 87 of 114) of the lesions diagnosed by EUS in this meta-analysis were PDACs, 21 neoplasms including 11 PDACs were neither diagnosed by MDCT nor initial EUS-FNA. When the index EUS is negative, there are different approaches including additional imaging with MRI/MRCP, or repeating an EUS immediately or after a short period of time has lapsed. Wang et al. demonstrated a repeat EUS-FNA in this situation increased

the specificity (from 95% to 98%), but did not affect the sensitivity [4]. Considering prospective PDAC screening studies that have demonstrated that EUS is more sensitive for early diagnosis of a solid pancreatic neoplasm compared to MDCT or MRI/MRCP, we favor repeating an EUS in 2–3 months; however, this approach requires further study [27].

The most important limitation is that our meta-analysis includes a small number of studies. Due to our stringent inclusion criteria, there were only a few studies reflecting current clinical practice of performing MDCT in patients with a clinical suspicion of pancreatic neoplasm where there was an intent for FNA during EUS [16]. Only one of the four studies were relative large in size ($n > 100$); however, sensitivity analysis excluding this study did not alter our findings (online Appendix 3). Despite the potential preference to publish studies in which EUS demonstrated a statistically significant advantage over MDCT, our tests did not reveal such publication bias. None of the included studies performed a dedicated review of the MDCT images for a second reading, which may have underestimated the diagnostic performance of CT. Finally, the prevalence of patients with pancreatic neoplasm undergoing testing may be overestimated due to referral bias. Thus, the positive and negative predictive values may not accurately reflect the performance of EUS in a community-based practice (i.e., an artificially increased PPV and decreased NPV).

In summary, we demonstrate the comparatively higher sensitivity of EUS for detecting a pancreatic neoplasm in those with a suspected malignancy, but no radiographically discernable mass on MDCT. The majority of the missed lesions are PDAC; however, other malignant and benign diseases may be diagnosed. Although a larger, prospective, multicenter study is necessary to evidence these findings including yield of FNA in this setting, the evidence in support of EUS may possibly prevent the implementation of such a study in the absence of a significant leap in CT technology. Thus, considering the low risk of adverse events, we propose that EUS with an intent to FNA should be performed in patients with suspicion for pancreatic malignancy, but a negative or indeterminate MDCT.

Compliance with ethical standards

Disclosures Drs. Somashekar G. Krishna, Bhavana B. Rao, Emmanuel Ugbarugba, Zarine K. Shah, Alecia Blaszczak, Alice Hinton, Darwin L. Conwell, and Phil A. Hart have no conflicts of interest or financial ties to disclose.

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