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Endoscopic ultrasound-guided tissue acquisition of pancreatic masses

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ABSTRACT

Endoscopic ultrasound (EUS) has assumed an increasing role in the management of pancreaticobiliary disease over the past 2 decades but its impact is particularly evident in the management of pancreatic masses. EUS helps improve patients' outcomes by enhancing tumor detection and staging while providing safe and reliable tissue diagnosis. This review provides an evidence-based approach to the use of EUS for the diagnosis of pancreatic cancer, its staging, and for the determination of resectability compared to other imaging modalities. We will focus on techniques specific to obtaining tissue from solid pancreatic masses and will review best practices in EUS-guided tissue acquisition.

1. Introduction

Advancements in radiologic and endoscopic ultrasound (EUS) imaging have improved our ability to detect and stage pancreatic masses allowing for more selective surgical intervention for patients with "resectable disease." Owing to the low sensitivity of cross-sectional imaging to detect small tumors in the pancreas, endoscopic diagnosis by using EUS has become a mainstay for the assessment of pancreatic masses. EUS also provides a reliable method for tissue sampling hence securing a histopathologic diagnosis [1-3]. This review will focus on the role of EUS in the evaluation of pancreatic masses compared to other imaging modalities, and highlights the best practices to improve tissue yield from EUS-guided tissue acquisition (EUS-TA).

2. Pancreatic cancer

2.1. Background and epidemiology

Pancreatic cancer is the fourth leading cause of cancer-related mortality in the United States. Over 45,000 patients are diagnosed each year in the United States, and the majority of these patients succumb to their disease [4]. Eighty percentage of patients are diagnosed with advanced, unresectable disease. According to the latest statistics, only 7% of patients survive 5 years after diagnosis [4]. While the 5-year survival rate improves to 25% in patients presenting with stage 1 or localized disease, only 9% of patients are identified at this early stage. The majority of patients (53%) presents with distant, metastatic disease, and have a 5-year survival of 2%. Identification of risk factors and establishing earlier detection methods are therefore of paramount importance [5].

2.2. Cross-sectional imaging

2.2.1. Computed tomography

Computed tomography (CT) is the most widely used imaging modality for the assessment of suspected pancreatic ductal adenocarcinoma (PDAC). CT imaging has significantly improved with the introduction of multiple-detector CT (MDCT), which allows high-resolution and multiplanar image reconstruction. CT is reported to have a sensitivity of 89%-97% for PDAC, though it is less effective in diagnosing small ($<$ 2 cm) lesions with a sensitivity of 65%-75% [6]. In this respect, EUS is superior in tumor detection. Comparative studies between EUS and MDCT for pancreatic tumors have demonstrated the superiority of EUS for tumor detection compared to multirow CT. Agarwal et al [7] reported an EUS sensitivity of 100% for the diagnosis of cancer compared to 86% for MDCT. Similarly, DeWitt et al [8] reported that the sensitivity of EUS (98%) was statistically superior to MDCT (86%) in a cohort of 80 patients with pancreatic cancer.

2.2.2. Magnetic resonance imaging

Contrast-enhanced magnetic resonance imaging (MRI) has a sensitivity and accuracy at least similar to that of MDCT for diagnosis and staging of pancreatic cancer, but it is costlier and less readily available than MDCT. MRI, however, may more reliably detect smaller, non–contour-deforming tumors compared with CT [9]. MRI also more accurately detects and characterizes smaller hepatic metastases [10]. A recent study concluded that MRI was

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superior to CT for tumor detection but performed similarly for the evaluation of resectability [11]. In a study that compared the diagnostic performance (detection, local staging) of multiphasic 64-detector CT with gadobenate dimeglumine-enhanced 3.0-T MRI in patients suspected of having pancreatic cancer, both CT and MRI were found to be equally suited for detecting and staging pancreatic cancer [12]. Therefore, the choice of imaging modality for detection and staging of pancreatic cancer depends on test availability and local expertise.

2.2.3. Positron emission tomography and integrated PET/CT

Q5 The role of functional imaging especially positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with CT (FDG-PET/CT) is still uncertain in the staging of pancreas cancer. The NCCN guidelines list the possible performance of PET/CT for the detection of regional lymph nodes and extrapancreatic metastases, although it has not been incorporated in routine practice [13]. The sensitivity and specificity of FDG-PET/CT in the diagnosis and evaluation of pancreas cancer ranges from 71%-100% and 64%-95%, respectively, significantly higher than those of CT alone [14,15]. The sensitivity of PET/contrast-enhanced CT in detecting local recurrence, abdominal lymph node metastasis, and peritoneal dissemination are 83%, 88%, and 83%, respectively [16]. A meta-analysis of 51 studies involving 3857 patients compared the diagnostic performance of ^{18}FDG PET alone, ^{18}FDG PET/CT, and EUS for diagnosing pancreatic cancer [17]. The study concluded that the pooled sensitivity for combined PET/CT (90.1%) was significantly higher than PET (88%) and EUS (81%). However, the pooled specificity estimate for EUS (93.2%) was significantly higher than PET (83%) and PET/CT (80%).

F2 2.3. Staging of pancreatic adenocarcinoma

Staging of pancreatic cancer is performed according to the American Joint Committee for Cancer (AJCC) Staging TNM classification, which describes the tumor extension (T), lymph node (N), and distant metastases (M) of tumors, respectively [18]. The accuracy of EUS for T staging of pancreatic tumors ranges from 62%-94% [19-21]; while its accuracy for N staging ranges from 41%-86% [5].

Para-aortic lymph nodes (PALNs) are considered nonregional lymph nodes for both pancreatic head and body or tail cancers, thus meticulous survey of this region is critical during staging of all pancreatic tumors [22]. Kurita et al [23] conducted a prospective, nonrandomized single-center trial, of 208 patients with pancreatobiliary cancers without apparent distant metastases except for PALNs. PET/CT and EUS-guided fine-needle aspiration (EUS-FNA) were performed sequentially as a single combined procedure to evaluate PALN metastasis. EUS-FNA had higher sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for the diagnosis of PALNs metastasis than PET/CT. The differences for the sensitivity and accuracy were significant ($P < 0.001$). An EUS survey of mediastinal stations for metastatic adenopathy is also warranted since these are also considered nonregional lymph nodes.

For detection of nonnodal metastatic cancer, CT and MRI are superior to EUS due to both anatomical considerations of the upper gastrointestinal tract and the limited range of EUS imaging. However, EUS still has an important role in the evaluation of F1 hepatic metastasis in the left or caudate lobe (Figure 1) and malignant ascites, some of which can be missed on cross-sectional imaging and both of which can be accessible by EUS-FNA. Identification of liver metastases or malignant ascites by EUS-FNA may preclude surgical resection and is associated with poor survival following diagnosis [24].

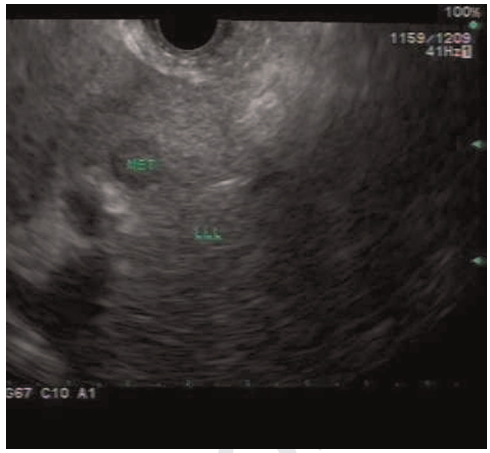

Fig. 1. A linear EUS image of a small liver lesion not visualized on CT scan in a patient undergoing staging and FNA of a pancreatic body mass. Cytology from the lesion confirmed metastatic pancreatic adenocarcinoma. (Color version of figure is available online.)

2.4. Assessment of vascular invasion

The overall accuracy of EUS for vascular invasion ranges from 68%-93% [19,25-27]. The overall accuracy of CT is reportedly equivalent [19,26] or inferior [25] to EUS. The overall accuracy of MRI is reportedly equivalent [19] or superior [26] to EUS.

The overall sensitivity and specificity of EUS for malignant vascular invasion range from 42%-91% and 89%-100%, respectively [19,25-27]. The sensitivity of EUS for tumor invasion of the PV or porto-splenic confluence is 60%-100% [28,29] with most studies demonstrating sensitivities over 80%. The sensitivity of EUS for PV invasion (Figure 2) is consistently superior to that of CT [28,30,31]. For the superior mesenteric vein, superior mesenteric artery (Video 1), and celiac artery, the sensitivity of EUS is 17%-83% [27], 17% [32], and about 50% [28], respectively. The sensitivity of CT for staging of the superior mesenteric artery [31,32] and celiac artery [28] appears to be better than EUS. Until further conclusive data becomes available, assessment of tumor resectability should be done by both EUS and CT (or MRI) rather than by EUS alone.

2.5. Resectability of pancreatic tumors

In a pooled analysis of 9 studies involving 377 patients, the sensitivity and specificity of EUS for resectability of pancreatic cancer was 69% and 82%, respectively [8,19,25-27,33-36]. The

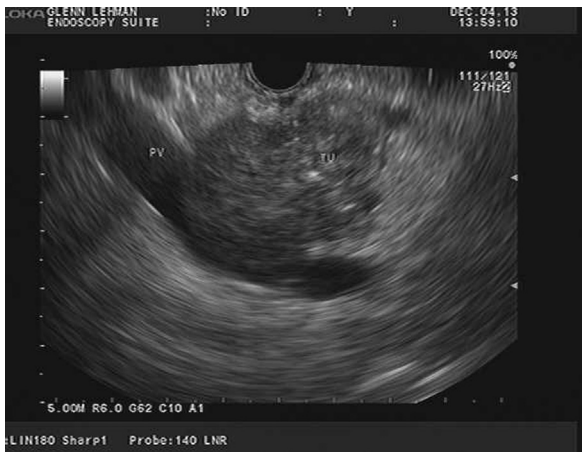

Fig. 2. A linear EUS image of a pancreatic head mass invading the portovenous confluence. This patient underwent neoadjuvant therapy to downstage the tumor followed by pancreaticoduodenectomy with venous reconstruction.

accuracy of EUS for tumor resectability was 77%. Using a decision analysis, Soriano et al [19] found that accuracy for tumor resectability was maximized and costs were minimized when CT or EUS was performed initially followed by the other tests in those with potentially resectable neoplasms. Ahmad et al [33] proposed that although EUS and MRI individually are not sensitive for tumor resectability, their combined use may increase positive predictive value of resectability compared to either test alone. When surgery is performed only when MDCT and EUS agree on tumor resectability, DeWitt et al [8] reported a nonsignificant trend toward improved accuracy of resectability compared to either study alone. However, a study by Bao et al [37] found that MDCT was a better predictor of resectability than EUS. In the recent years, higher resolution assessment for vascular invasion and distant metastasis by multiphasic CT has assumed a larger role than EUS in determining surgical candidacy of patients with pancreatic cancer.

2.6. EUS-guided tissue acquisition of pancreatic cancer

EUS-FNA remains the first-line modality for tissue sampling in patients with pancreatic masses [38,39]. Based on the results of 2 meta-analyses [40,41], the pooled sensitivity and specificity of EUS-FNA for diagnosis of pancreatic adenocarcinoma ranged between 85%-89% and 96%-98%, respectively. The presence of chronic pancreatitis may impair the visualization of tumors endosonographically or hinder the cytologic interpretation of the sampled pancreatic tissue, thus reducing sensitivity. In a series of 207 consecutive patients with focal pancreatic lesions, Fritscher-Ravens et al [42] found that the sensitivity of EUS-FNA for the diagnosis of malignancy in patients with normal parenchyma to be superior (89%) to those with parenchymal evidence of chronic pancreatitis (54%).

Today, EUS-TA by FNA (EUS-FNA) and fine-needle biopsy plays a pivotal role in the diagnosis of pancreatic masses. Obtaining an adequate sample and reaching an accurate diagnosis are fundamental endpoints of EUS-TA [39]. This is of particular importance since many patients with malignancy are often subjected to neoadjuvant systemic therapy prior to surgery nowadays, where a tissue diagnosis is essential to move this process forward. Significant efforts have been made in recent years to identify the ideal EUS-TA technique, one that is efficient, effective, and associated with high diagnostic yield, specimen adequacy, accuracy, and low adverse event rate [43]. These efforts have focused on studying several variables associated with EUS-TA outcomes and can be categorized as: (1) those related to sampling methods and techniques (use of suction and stylet, fanning and capillary technique, number of passes, methods of sample expression); (2) availability of rapid on-site evaluation (ROSE), (3) endosonographer and cytopathologist qualifications (experience, training, and competency); and (4) type of specimen and needle used. We will expand on each one of these variables in the subsequent sections of this review.

2.6.1. Sampling methods and techniques

2.6.1.1. Use of suction vs capillary suction technique. Use of air vacuum (suction) remains widely practiced during FNA of a variety of solid and cystic lesions. Suction is generally recommended for pancreatic solid lesions, particularly PDACs which can carry a variable degree of stromal fibrosis and desmoplasia. In highly vascular lesions such as lymph nodes and neuroendocrine tumors, a nonsuction technique is recommended allowing for a better quality and less bloody sample. Avoiding suction in vascular lesions can improve the quality of ROSE with less blood that could interfere with tumor visualization; however, in passes dedicated solely for cell block, suction may be reintroduced to improve tissue acquisition.

The wet suction technique (WEST) relies on preflushing the needle with saline to replace the column of air with fluid followed by applying negative pressure on the proximal end of the needle. In a prospective, single-blind, randomized, controlled trial using a 22-gauge needle for EUS-FNA of solid lesions, WEST resulted in significantly better cellularity and specimen adequacy in cell blocks of EUS-guided FNA aspirate of solid lesions than the conventional FNA technique [44]. A new modified WEST (hybrid suction technique) relies on preloading the needle with saline, but having continuous negative pressure with a prevacuum syringe to avoid manual intermittent suction. Data about this technique is limited to a single-center pilot study by Berzosa et al [45]. Another recent randomized controlled trial showed that high negative pressure suction (generated by using a 60-mL syringe) was associated with superior diagnostic yield compared to standard negative pressure using a 10-mL syringe in patients with pancreatic masses undergoing EUS-FNA [46]. In our practice, we continue to use suction during aspiration of solid pancreatic masses when collecting for cell block but would limit its use when the on-site review from the initial pass indicates large amounts of blood and paucity of tumor cells.

Capillary suction technique utilizes capillary aspiration created by slow and staggered withdrawal of the stylet. This has been suggested in limited studies to enhance quality of the specimen obtained for diagnostic purposes [47,48]. Based on 1 study, this technique was associated with better cellular quality and diagnostic yield in pancreatic and liver masses [49].

2.6.1.2. Use of stylet. The presence of a stylet should prevent the introduction of gastrointestinal wall tissue to the needle as it traverses this to access the target lesion. However, current data suggest that the use of a stylet does not confer any advantage during EUS-FNA [50]. Furthermore, the use of stylet is considered to be labor intensive and time consuming (particularly with 25 G needles), which could prolong procedure time and theoretically increase the risk of inadvertent needle injuries in the endoscopy suite.

2.6.1.3. Needle size. Current EUS-FNA needles are available in 25-gauge, 22-gauge, and 19-gauge needles. Needle size is probably the most widely studied factor as a predictor of cytologic adequacy and diagnostic yield of malignancy. The 22-gauge needle were considered the default needle for a long time but a recent reduction in its utilization has been described in favor of 25-gauge needles, particularly when sampling pancreatic head and uncinate process lesions. To date, 3 meta-analysis compared the diagnostic accuracy of EUS-FNA for pancreatic masses by using 22- and 25-gauge needles demonstrated superior sensitivity of 25-gauge needles for diagnosing pancreatic malignancy [51-53]. In addition, randomized controlled trials suggest that there is no incremental diagnostic yield of 19 G vs 22 or 25 G with overall similar safety profile [54,55]. Table 1 summarizes the studies comparing the diagnostic yield of malignancy between 22 G and 25 G needles during EUS-FNA of pancreatic masses [56-61].

2.6.1.4. Fanning technique. The fanning technique for EUS-FNA involves sampling multiple areas within a lesion by changing the angle of the tip of the scope or (when smaller gauge needles are used) by using the elevator. Bang et al [62] compared this technique to the standard technique for EUS-FNA of solid pancreatic mass lesions, and found fanning to be superior by establishing a diagnosis in fewer passes, and resulted in higher first pass diagnostic rate (86% vs 58%; $P = 0.02$). While further data

Table 1

Summary of studies comparing diagnostic yield of malignancy between 22-gauge and 25-gauge needles during EUS-FNA of pancreatic masses.

Author	Study design	No. of patients 22G/25G	Sensitivity (95% CI) 22G	Sensitivity (95% CI) 25G
Siddiqui et al [56]	RCT	64/67	0.88 (0.77-0.94)	0.96 (0.87-0.99)
Yusuf et al [57]	Retrospective	540/302	0.84 (0.80-0.88)	0.92 (0.87-0.99)
Siddiqui et al [58]	Retrospective	26/17	0.85 (0.62-0.97)	0.91 (0.59-1.00)
Camellini et al [59]	RCT	43/41	0.86 (0.70-0.95)	0.89 (0.75-0.97)
Uehara e al [60]	Retrospective	54/66	0.88 (0.74-0.96)	1.00 (0.91-1.00)
Fabbri e al [61]	Prospective	50/50	0.85 (0.71-0.94)	0.94 (0.82-0.99)

Abbreviations: G, gauge; RCT, randomized controlled trial.
(Adapted with permission from Wani et al [39]).

is awaited, we routinely perform fanning during sampling of solid pancreatic lesions.

2.6.2. Rapid on-site evaluation

The availability of a cytopathologist on site (for ROSE) has been shown to improve the diagnostic yield of EUS-FNA for malignancy. Prior studies demonstrated a 10%-15% increase in diagnostic yield in the presence of ROSE and 20% rate of nondiagnostic aspirates in its absence [70,71]. The beneficial role of ROSE for EUS-FNA of solid pancreatic masses was confirmed by a meta-analysis of 34 studies (3644 patients) [70]. However, recent data from 2 multicenter trials showed no significant difference in the diagnostic yield of malignancy, proportion of inadequate specimens, and accuracy in patients with pancreatic mass undergoing EUS-FNA with or without ROSE [71,72]. In these studies, ROSE was associated with fewer number of passes. It has been suggested that ROSE may have a role only during the learning phase of EUS-FNA in recently established EUS services. In our practice, we find ROSE to be of significance in limiting the number of passes and hence improve procedural efficiency and reduce patient risk. It also allows a real-time decision to be made on whether additional tissue assays are needed (such as microbiology studies, flow cytometry, and molecular assays). In the absence of ROSE, it is recommended performing 4-5 passes in solid pancreatic lesions and 2-3 passes in lymph nodes, liver, and adrenal lesions.

The interobserver variability among cytopathologists with regard to EUS-FNA and fine-needle biopsy specimens is an issue that has significant implications for patient management. In a pilot study, Mounzer et al [73] evaluated the interobserver variability among 4 cytopathologists in assessing EUS-FNA cytology specimens of solid pancreatic lesions using a novel standardized scoring system. The study demonstrated that the interobserver agreement for the final diagnosis was moderate ($\kappa = 0.45$) with minimal improvement when combining suspicious and malignant diagnoses ($\kappa = 0.54$). Similar to recent advances in EUS performance secondary to improved training and better competence and quality metrics assessment [74], cytopathologists need to address these critical issues in cytology performance in future studies.

2.6.3. Type of specimen

EUS-FNA remains the standard procedure for sampling of pancreatic masses. However, EUS-FNA has certain limitations. First, primary pancreatic lymphomas (PPLs) and well-differentiated ductal adenocarcinomas are often difficult to diagnose by use of cytology alone. Second, chronic pancreatitis, if present, can obscure the detection of pancreatic tumors and hinder a cytological diagnosis of malignancy. Third, the low negative predictive value of EUS-FNA does not permit exclusion of malignancy in negative specimens. To address these limitations, core biopsy devices have been developed to obtain histologic tissue samples using a standard linear array echoendoscope. Two such devices introduced over the last decade include the Quick-Core and ProCore biopsy needles (Cook Medical, Bloomington, IN). In a multicenter cohort study of 109 patients with intestinal and extraintestinal lesions (including 47 pancreatic tumors), the ProCore needle provided adequate histology and a correct diagnosis in 96% and 89% of cases, respectively [75]. However, in a recent meta-analysis including 9 studies of 576 patients, there was no difference in diagnostic adequacy (75% vs 89%), diagnostic accuracy (86% vs 86%), or rate of histologic core specimen acquisition (78% vs 77%) between the ProCore and standard FNA needles, respectively. The mean number of passes required for diagnosis, however, was significantly lower when using the ProCore needle (standardized mean difference - 1.2, $P < 0.001$) [76]. Table 2 summarizes the various published studies comparing the ProCore needle to standard FNA needles. Nevertheless, core biopsy needles will continue serving niche applications such as aiding the diagnosis of autoimmune pancreatitis (Figure 3) [77] and pancreatic lymphoma [78], where its superiority has been demonstrated in previous studies. In addition, core biopsy needles could be used as a rescue technique when on-site FNA results are inconclusive or if this service is not available (Video 2; Figure 4) [75].

2.6.4. Ancillary studies

In an attempt to increase the sensitivity of EUS-FNA to detect malignancy in pancreatic masses, investigators have evaluated the presence of certain genetic mutations. A meta-analysis of

Table 2

Summary of studies that assessed the Procore needle for EUS-FNB compared to FNA when comparative data is available.

Author	Study design	No. of patients	Needle gauge FNB	SA FNB (%)	DY FNB (%)	DY FNA (%)	*P* value
Bang et al [63]	RCT	28	22	89	80	67	0.66
Larghi et al [64]	Prospective cohort	61	22	89	89	n/a	n/a
Iwashita et al [65]	Retrospective	38	25	n/a	86/96	n/a	n/a
Vanbiervliet et al [66]	RCT	80	22	n/a	84	88	NS
Strand et al [67]	Prospective cohort	32	22	n/a	28	93	<0.001
Choi et al [68]	Retrospective	80	22	n/a	90	62	<0.005
Singh et al [69]	Retrospective	40	22	n/a	100	93	NS

Abbreviations: DY, diagnostic yield; FNB, Fine needle biopsy; RCT, randomized controlled trial; SA, specimen adequacy.
(Adapted with permission from Wani et al [39]).

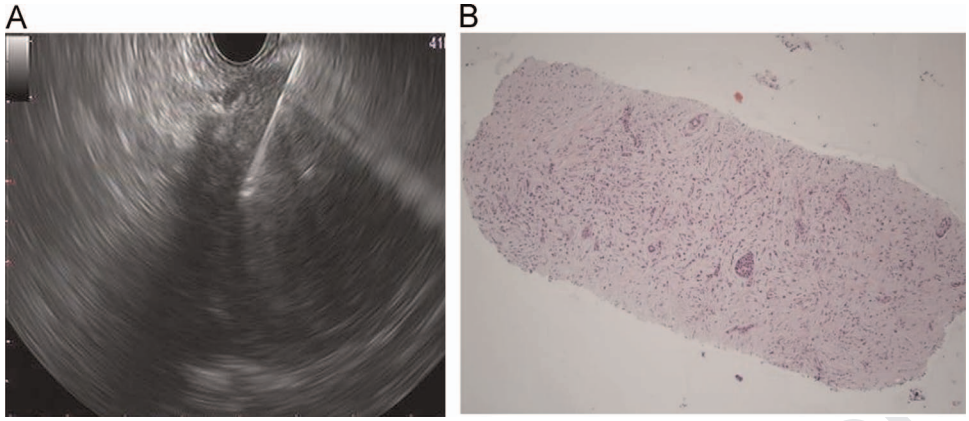

Fig. 3. (A) A 78-year-old man presenting with painless jaundice was found to have diffuse enlargement of the pancreas on CT and confirmed on EUS. Fine needle biopsy was performed from the neck area using a core biopsy device. (B) A photomicrograph of a core biopsy obtained in the patient in 3A demonstrating dense lymphoplasmacytic infiltration in the stroma. This was confirmed with plasma cells staining positive for IgG4 stains (not shown) (H&E stain ×40). H&E, hematoxylin and eosin stain. (Color version of figure is available online.)

8 prospective studies involving 931 patients who had KRAS mutation analysis on EUS-FNA specimens reported a pooled sensitivity and specificity of 77% and 93%, respectively [79]. When combined with EUS-FNA alone, the addition of k-ras mutation testing increased sensitivity from 81%-89% but reduced specificity from 97%-92%.

Fluorescence in situ hybridization (FISH) processing of EUS-guided FNA specimens are other assays that were found to increase the sensitivity and accuracy of routine cytology examination [80]. Furthermore, Kubiliun et al [81] showed that in patients with suspected pancreatic cancer, FISH analysis can detect additional cases missed by cytology without compromising specificity. Authors recommended EUS-FNA with rescue FISH for the diagnosis of pancreatic carcinoma in patients with inconclusive on-site cytopathology results. Finally, combining routine cytology with FISH and KRAS analyses improves diagnostic yield of EUS-FNA of solid pancreatic masses, according to Reicher et al [82]. Such assays can be included to further investigate atypical cytology from pancreatic EUS-FNA.

It should be noted though that KRAS mutations can be present in the setting of chronic pancreatitis and could lead to false positive results in $>10\%$ of cases, however, the specificity of FISH in this setting remains high exceeding 95% [82]. To overcome such limitations, differential miRNA expression in tissue specimens has been explored as an adjunct to cytopathology for the diagnosis and prognostication of individuals with pancreatic cancer [83,84]. A study measuring miR-10b expression in EUS-FNA tissue samples revealed an association between decreased miR-10b expression in pancreas cancer cells with improved survival, response to neoadjuvant radiochemotherapy, and delayed time to metastasis [83]. Brand et al [85] developed and validated a 5-miRNA panel derived from EUS samples that were prospectively collected at multiple centers. This 5-miRNA panel can accurately predict which preoperative pancreatic EUS-FNA specimens contain PDAC. This test might aid in the diagnosis of pancreatic cancer by reducing the number of FNAs without a definitive adenocarcinoma diagnosis, thereby reducing the number of repeat EUS-FNA procedures, which could reduce procedure complications and the need for multiple needles, and provide faster times to complete EUS-FNA. As the list of known microRNAs involved in pancreatic cancer pathogenesis continues to expand, we expect the utilization of such assay to grow over the next decade and become commercially available.

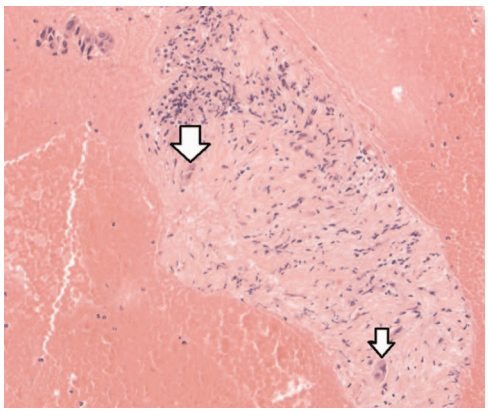

Fig. 4. (H&E ×200) A patient with pancreatic head mass and previously inconclusive EUS-FNA. Fine needle biopsy confirmed pancreatic adenocarcinoma. Rare malignant cells can be seen in a fibrous stroma (arrows). (Color version of figure is available online.)

2.7. Safety of EUS and EUS-FNA

EUS is a safe procedure with a reported overall adverse event rate of 1.1%-3% [86].

Two major possible adverse events of EUS-FNA of solid pancreatic masses include acute pancreatitis and the risk of needle tract seeding. The reported risk of acute pancreatitis after EUS-FNA of solid pancreatic masses is 0.26%-0.85% [87-89]. This risk can be decreased by minimizing the number of needle passes, minimizing the amount of normal appearing pancreatic parenchyma traversed with each pass, and avoiding needle insertion through the pancreatic duct unless it is absolutely necessary. Needle tract seeding is a consideration with biopsy of pancreatic masses, but most of the published data are limited to case reports [90]. The reported incidence of needle tract seeding after EUS-FNA is believed to be lower than percutaneous CT or transabdominal ultrasound-guided sampling (2.2% vs 16.3%) [91]. The majority of the reported cases of EUS-FNA needle tract seeding are for body and tail cancers, which were sampled through the gastric wall [90]. Needle tract seeding is of less significance in resectable pancreatic head tumors sampled transduodenally, because the site of needle puncture is included within the resection margins of a pancreatoduodenectomy.

3. Pancreatic neuroendocrine tumors

The use of EUS-FNA permits tissue confirmation of a suspected pancreatic neuroendocrine tumors (PNET) [92,93]. Data from a large retrospective case series of 80 patients, suggested that EUS should be included in the diagnostic workup of all patients with suspected PNETs, even when the CT study was negative for a primary lesion in the pancreas.

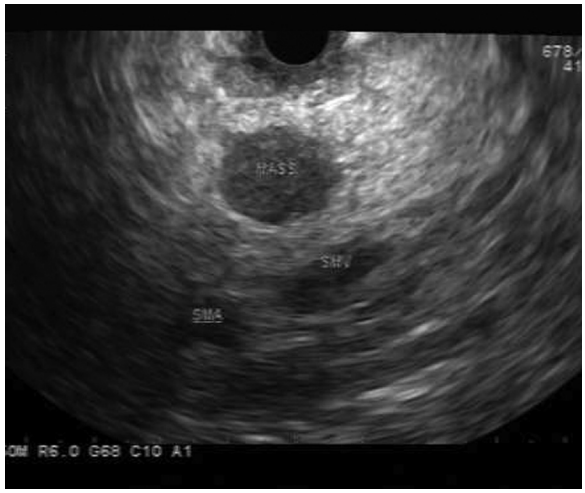

Fig. 5. A small mass in the pancreatic head in a patient with MEN1 noted on EUS screening examination. This lesion was not seen on CT scan but was confirmed to be PNET on FNA. MEN1, multiple neuroendocrine neoplasia type 1.

EUS and EUS-FNA are highly sensitive and accurate for the diagnosis of PNETs [94-96]. Characteristic EUS findings are helpful for the diagnosis and grading of PNETs (Figure 5) [94,95]. However, location of the tumor in the pancreatic head and presence of rich stromal fibrosis can negatively impact sampling adequacy [96]. Purely cystic and mixed solid-cystic PNETs have distinct clinical and EUS characteristics, and are associated with less aggressive biological behavior compared with solid PNETs. EUS-FNA is accurate for determining malignant potential on preoperative evaluation. Despite complete resection, recurrence is observed up to 5 years following surgery [97]. Cytology is usually diagnostic in PNETs (Figure. 6), which typically stains positively for chromogranin and synaptophysin (Figure 7). Recently, molecular assays allowed genetic mutations to be reliably assessed on FNA specimens from PNETs. A recent study of 29 patients with PNETs followed for an average of 33 months showed that the presence of allelic microsatellite loss was associated with increased PNET recurrence, progression, and mortality [98].

4. Primary pancreatic lymphoma

EUS-FNA with flow cytometry is very accurate for PPL. In a case series of 16 patients with PPL, Khashab et al [99] reported a sensitivity and specificity of EUS-FNA with cytology and flow cytometry of 84.6% and 100%, respectively. This is in contrast to EUS-FNA with cytology alone, which had sensitivity and specificity less than 30%. This diagnosis should be suspected based on clinical appearance, lack of definite malignancy, and abundance of abnormal lymphocytes on rapid cytological review.

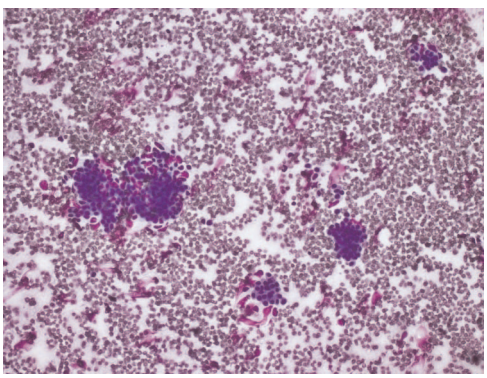

Fig. 6. FNA from a PNET demonstrating classic cytopathologic findings including predominantly small loosely cohesive groups of cells that are small to medium in size with a uniform round to oval, and often peripherally located nuclei. (H&E stain ×100). H&E, hematoxylin and eosin stain. (Color version of figure is available online.)

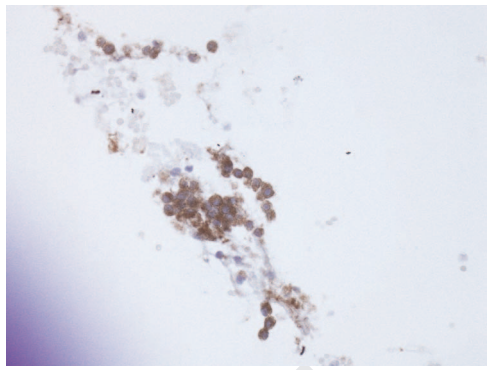

Fig. 7. Immunostains from a PNET aspirate staining positive for chromogranin (golden brown color) (H&E ×200). H&E, hematoxylin and eosin stain. (Color version of figure is available online.)

5. Pancreatic metastases

EUS-FNA permits an accurate cytologic diagnosis of metastatic lesions to the pancreas. In the largest series to date of 72 masses in 49 patients, El Hajj et al [100] reported metastatic lesions from kidney (renal cell carcinoma in 21), lung ($n = 8$), skin ($n = 6$), colon ($n = 4$), breast ($n = 3$), small bowel ($n = 2$), stomach ($n = 2$), liver ($n = 1$), ovary ($n = 1$), and bladder ($n = 1$). Metastasis to the pancreas may occur many years (especially for renal cell carcinoma; Figure 8) after diagnosis of the primary tumor. Obtaining a detailed medical history for previous malignancy may raise suspicion for this diagnosis. In patients with a remote history of malignancy, obtaining additional cytological material for cell block and the use of immunocytochemistry may be helpful to confirm the diagnosis of pancreatic metastases and confirm recurrent malignancy.

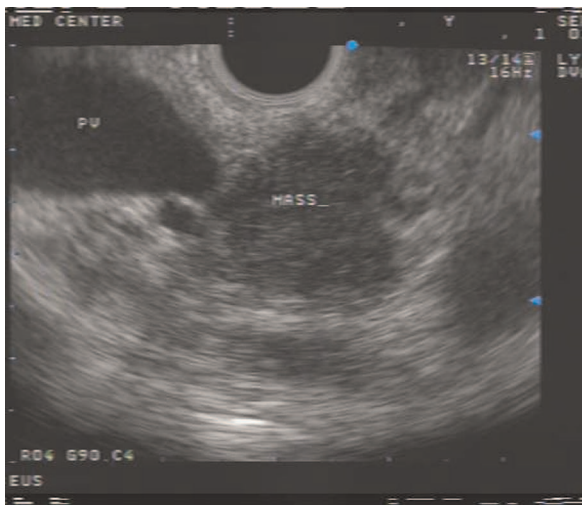

Fig. 8. A patient with known history of renal cell carcinoma treated 15 years earlier presented with painless jaundice. A pancreatic head lesion was found on EUS, confirmed on FNA to be renal cell carcinoma.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.tgie.2018.01.002.

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