Original Article

Unusual, Metastatic, or Neuroendocrine Tumor of the Pancreas: A Diagnosis with Endoscopic Ultrasound–guided Fine-needle Aspiration and Immunohistochemistry

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ABSTRACT

Background/Aim: To determine the yield of endoscopic ultrasound–guided fine-needle aspiration (EUS–FNA) in combination with immunostains in diagnosing unusual solid pancreatic masses (USPM) in comparison with pancreatic adenocarcinoma (ACP). **Patients and Methods:** All EUS–FNA of solid pancreatic masses performed with a 22-gauge needle were included. Data on clinical presentations, mass characteristics, presence of pancreatitis, yield of tissue, and final diagnosis were compared between the two groups. On site cytopathology was provided and additional passes were requested to perform immunostains. **Results**: Two hundred and twenty-nine cases with either adenocarcinoma or USPM were included. The median age of the cohort was 65 years. ACP (210/229, 92%) accounted for the majority of the cases. The USPM included neuroendocrine (NET) masses (n=13), metastatic renal carcinoma (n=3), metastatic melanoma (n=1), lymphoma (n=1), and malignant fibrous histiocytoma (n=1). Subjects with ACP were significantly more likely to present with loss of weight (P=0.02) or obstructive jaundice (P<0.001). Subjects with ACP were more likely to have suspicious/atypical FNA biopsy results as compared with USPM (10% *vs* 0%). The sensitivity of EUS–FNA with immunostains was 93% in ACP as compared with 100% in USPM. Diagnostic accuracy was higher in USPM as compared with ACP (100% *vs* 93%). **Conclusions:** EUS–FNA using a 22-gauge needle with immunostains has excellent diagnostic yield in patients with USPMs, which is comparable if not superior to the yield in pancreatic adenocarcinoma.

Key Words: Cytology, endoscopic ultrasound, fine needle aspiration, immunostains, metastasis, neuroendocrine tumors, pancreas

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Since its introduction in 1992, endoscopic ultrasound–guided fine-needle aspiration (EUS–FNA) has evolved to become a leading method to confirm the diagnosis of pancreatic cancer.[1] The largest prospective series reports that EUS–FNA has a sensitivity of 95% and specificity of 92% in the evaluation of solid pancreatic masses.[2] Nonetheless, pancreatic malignancy can be missed even by the most experienced endosonographers, particularly in the setting of acute or chronic pancreatitis.[3] Approximately 90% of pancreatic tumors are ductal tumors, 5% are neuroendocrine tumors (NETs), and the remainder comprise rare lesions, including lymphomas, metastases, and dysontogenic cysts.[4] In an influential study, Voss *et al* identified that EUS–FNA was 81.4% accurate for adenocarcinomas but only 46.7% accurate for NETs and 75% for other lesions.[5] We aimed to compare the yield of EUS–FNA for adenocarciomas versus other tumors in a center utilizing an onsite cytology team.

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PATIENTS AND METHODS

We analyzed 229 consecutive solid pancreatic masses evaluated by EUS–FNA during a 3-year period (July 2000 to July 2003). We maintain an Institutional Review Board (IRB)-approved prospective database at the University of Alabama at Birmingham Endoscopic Ultrasound Program (UAB) strictly for research purposes. The IRB of UAB approved this research protocol for EUS–FNA of solid pancreatic masses. All patients

referred with a pancreatic solid mass and provided written informed consent to undergo the procedure were included in this study as stated above. Patients were placed in the left lateral decubitus position and were sedated with intravenous meperidine, midazolam, and/or droperidol according to the judgment of the endoscopist as previously described. Once a solid focal pancreatic lesion was identified, EUS–FNA was performed with a curvilinear echoendoscope (Olympus UC-30P, or UCT 140, Melville, NY, USA) as previously described. Color Doppler sonography was performed to exclude intervening vascular structures and to choose a vessel-free needle track. All EUS–FNAs were performed utilizing a 22-gauge needle (Echotip, Wilson-Cook, Winston Salem, NC, USA, or the Olympus EZ shot 22-gauge needle, Melville, NY, USA) inserted through the working channel of the echoendoscope as previously described.[2] No suction was applied during biopsy unless the initial attempt yielded no cellular material (<5% of the cases). The aspirates were then placed onto glass slides and were prepared as previously described.[2] The smears were reviewed immediately by a cytopathologist on site to ensure specimen adequacy. At least 5 passes were obtained from each target lesion unless cytology evaluation performed on site confirmed the presence of malignant cells. We utilized the final cytology reports in our analysis. The cytologic diagnoses were classified into either malignant or benign (including chronic pancreatitis). The cytologic diagnoses were then categorized into following groups: positive for malignancy, suspicious for malignancy, atypical cells–indeterminate for malignancy, benign/reactive process, or nondiagnostic. Final diagnosis of pancreatic cancer was defined by the following criteria: (1) histologic evidence of pancreatic cancer, and (2) initial malignant cytology with a clinical and/or imaging follow-up that was consistent with the diagnosis of pancreatic cancer, such as death from disease or clinical progression. Lesions were considered benign if there was a lack of tumor progression for at least 6 months in conjunction with continued patient wellbeing. Reference standard for classification of disease included surgical resection, death from pancreatic cancer, and repeat radiologic and/or clinical follow-up.

Statistical analysis

Although 300 procedures were performed during this period; for the present study, we included only those cases diagnosed to be adenocarcinoma or other type of pancreatic cancers (n=229) for comparative purposes. Thus, we excluded the cases with benign (definite) mass (n=64) or truly "indeterminate" lesions whose origin remains enigmatic despite long-term follow-up (n=7). The procedures were categorized into 2 groups: adenocarcinoma versus other types of cancers. We examined the 2 groups for differences related to clinical presentation, prior investigations, and the physical characteristics of the mass. Continuous variables were reported as mean with standard deviation, median, and range. Medians were compared among the 2 groups using Mann–Whitney–Wilcoxon test. Categorical variables were compared using Fisher's exact two-tailed test. We also reported odds ratios (OR) with corresponding exact 95% CI for the categorical variables. Sensitivity (TP/TP+FN), specificity (TN/TN+FP), diagnostic accuracy (TP+TN/total number of subjects) and positive predictive value (TP/TP+FP) of the EUS–FNA procedure were compared among the 2 categories. Statistical significance (P) was set at 0.05. Data was analyzed using SAS statistical software (Cary, NC, USA).

RESULTS

The vast majority of the patients were confirmed to have adenocarcinoma (210/229, 92%) The "other" category included neuroendocrine masses (n=13) [Figure 1a–d], metastatic renal masses (n=3) [Figure 2a–c], metastatic melanoma (n=1), lymphoma (n=1), and malignant fibrous histiocytoma (n=1). Median age of the subjects was 65 years [Table 1]. We observed significant differences with regard to median age between the 2 groups (P=0.04), those with adenocarcinoma were older. No significant differences were observed between the 2 groups for sex and race. Overall, the male to female ratio was 1.0:0.7. Most (182/229, 80%) subjects were white.

Table 1: General characteristics of the subjects, by type of cancer

Characteristics	Adenocarcinoma (*N*=210) (%)	Other cancer (*N*=19) (%)	*P*	Total (*N*=229) (%)
Age (years)				
Range (min, max)	36, 88	33, 80		33, 88
Mean (SD)	64.9 (10.7)	57.8 (14.1)		64.3 (11.2)
Median	65.0	61.0	0.04[a]	65.0
Sex				
Women	85 (40)	8 (42)	1.00[b]	93 (41)
Men	125 (60)	11 (58)		136 (59)
Race[c]				
African-Americans	44 (21)	2 (10)	0.38[b]	46 (20)
White	165 (79)	17 (90)		182 (80)

[a]Mann–Whitney–Wilcoxon test. [b]Fisher's two-tailed exact test. [c]The category "Native Americans" (n=1, adenocarcinoma) excluded, SD: Standard deviation

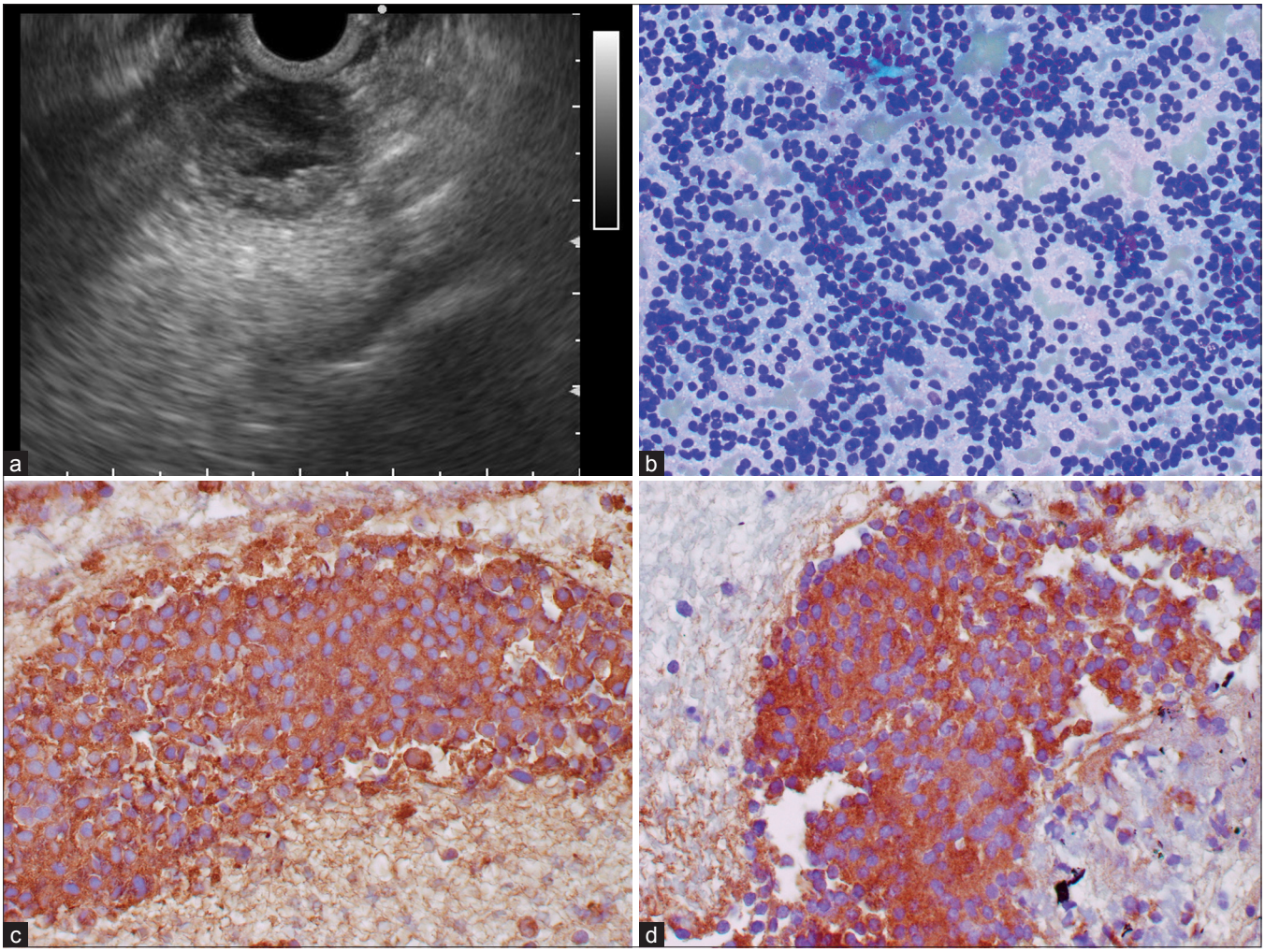

Figure 1: (a) EUS shows a well-circumscribed 1.9 cm pancreatic mass with a small cystic space consistent with a neuroendocrine tumor (Olympus UC 30 P imaging at 7.5 MHz); (b) EUS–FNA cytology shows discohesive to loosely cohesive plasmacytoid cells with abundant cytoplasm and eccentrically placed nuclei. The nuclei are round and have smooth nuclear membranes. Occasional cells show binucleation consistent with a neuroendocrine tumor that is confirmed by immunostains. (Diff quick stain ×40); (c and d) immunostains with chromogranin and synaptophysin confirms the neuroendocrine nature of the tumor in (a)

Most (191/229, 83%) subjects had prior computed tomography (CT) scan as one of the investigations, whereas 44% (100/229) had prior tissue diagnosis attempt [Table 2]. Most of these prior attempts consisted of either ERCP brushings (most common 80%) or image-guided biopsy (20%). Subjects with adenocarcinoma were significantly ($P=0.01$) more likely to have tissue-diagnosis attempt as compared with those with other neoplasms. We did not find any significant differences between the 2 groups with regard to size (long axis) or number of FNA passes. While there was a trend toward adenocarcinoma patients having more head lesions and concomitant chronic pancreatitis. These findings did not achieve statistical significance.

Subjects with adenocarcinoma were significantly more likely to present with loss of weight ($P=0.02$) or obstructive jaundice ($P<0.001$) as compared with those with other types of cancers [Table 3]. We did not find significant differences among the 2 groups with regard to pain in the abdomen and early satiety.

Diagnosis (benign/malignant) was confirmed by surgery in 30% (69/229) of the subjects, the remainder by clinical and radiologic follow-up. The overall median follow-up was 192 days. Sensitivity of EUS–FNA was 93% in the subjects with adenocarcinoma as compared with 100% in other cancers. Subjects with adenocarcinoma were more likely to have suspicious/atypical FNA biopsy results as compared with other types (10% *vs* 0%). Diagnostic accuracy was higher in "other" cancers as compared with "adenocarcinomas" (100% *vs* 93%) and Positive predictive value being 100% in both.

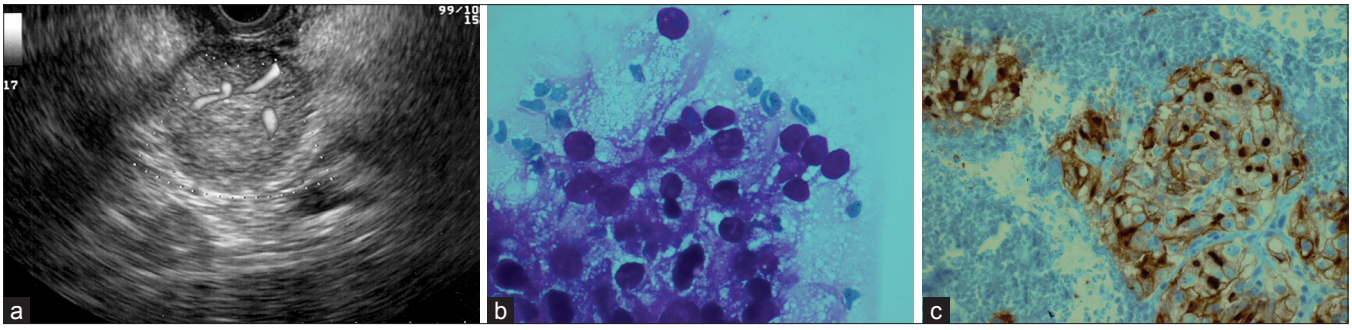

Figure 2: (a) Endoscopic ultrasound shows a well circumscribed mass in the neck of the pancreas with increased vascularity consistent with renal cell carcinoma. Endoscopic ultrasound–guided fine-needle aspiration (EUS–FNA confirmed the presence of renal cell carcinoma. (Olympus UC 30 P imaging at 7.5 MHz); (b) EUS–FNA shows a group of atypical cells with abundant, finely vesicular cytoplasm and relatively uniform but hyperchromatic nuclei consistent with renal cell carcinoma. (Diff Quick ×400); (c) atypical cells are immunoreactive for CD10, vimentin, and broad spectrum cytokeratin, supporting the diagnosis of metastatic renal cell carcinoma (Pancreas, cell block, ×200, immunohistochemical stain for Renal cell carcinoma)

DISCUSSION

This represents the first major study whose primary focus was to compare the diagnostic accuracy of EUS–FNA for adenocarcinoma versus other pancreatic tumors. This prospective study revealed that EUS–FNA is as robust a technique to evaluate unusual tumors of the pancreas as it is for adenocarcinoma. For unusual solid pancreatic masses (USPM) optimal management probably requires the close cooperation of an onsite cytologist and the use of special stains. Limitations in the evaluation of adenocarcinoma lie in the difficulty in evaluating patients with concomitant pancreatitis, although promising technology may improve this over time. A major strength of our project was that patients were prospectively enrolled throughout the 3 years of the study. The most important limitation of this analysis was the paucity of USPM, which statistically limited comparison with the adenocarcinoma group for clinical features such as EUS findings of chronic pancreatitis in which important trends were observed as well as the resulting very wide confidence intervals for some of the odds ratios were calculated.

Our principal finding was that the yield of EUS–FNA in unusual tumors was equivalent if not better than the results for adenocarcinoma. These findings counter the report by Voss *et al* in which the performance of EUS–FNA was inferior in nonadenocarcinoma, particularly NETs. An important potential explanation was that in the current series an onsite cytopathologist was present for all biopsies in contrast to the previous report. It has been demonstrated that centers that have the benefit of an onsite pathologist are less likely to have inadequate specimens and more likely to gain definitive answers through the procedure.[6] In the study by Voss *et al*, 47% of neuroendocrine specimens were rejected by the cytopathologist as bloody and unusable after the procedure was completed.[5]

NETs represented the largest group (13/19) of USPM in the current study and meticulous and timely use of special stain was a critical diagnostic step. At our institution the presence of monomorphic cells and other features suggestive of NET, prompts the cytopathologist to request additional passes for special stains. Particularly in cases in which the cytomorphologic features are confusing, special stains including chromogranin, synaptophysin, neuron-specific enolase (NSE), neuron cell adhesion molecule, and others improve diagnostic accuracy.[7] A previous study at our institution demonstrated that EUS–FNA is favored over CT–FNA in the evaluation of NETs because the former provides more tissue for additional stains.[8]

Several groups have reviewed their experience with neuroendocrine and other USPM and their reports suggest that the accuracy of EUS–FNA are within the range reported in the literature for adenocarcinoma. In the largest study of EUS–FNA in pancreatic NETs, Chatzipantelis *et al* report that 40 out of 48 patients were correctly diagnosed on the basis of the biopsy material and the remaining 8 were felt to be suspicious for NET.[9] An attending cytopathologist was present onsite for all cases and 83% of samples were positive for the synatophysin, NSE, and chromogranin stains. Ardengh *et al* reviewed a preoperative experience of EUS–FNA with 30 patients. In this cohort in which the majority had hormone-producing tumors, EUS–FNA was 82.6% sensitive and 85.7% specific.[10] After NETs, metastases to the pancreas represented the most significant group of USPM. DeWitt *et al* reported that in a series of 24 patients with metastases to the pancreas, the performance of EUS for detection of these lesions was comparable to that for 80 patients with adenocarcinoma. Additionally, there was no difference in the number of FNA passes required to confirm pancreatic metastases compared with adenocarcinoma.[11]

In addition to special stains optimizing the diagnosis of NETs, we observed that there were limitations of EUS–FNA

Table 2: Characteristics of mass and other clinical features, by type of cancer

Characteristics	Adenocarcinoma (*n*=210)	Other Ca* (*n*=19)	*P*	OR (95% CI)	Total
	N (%)	*N* (%)			*N* (%)
Prior CT done					
No	37 (18)	1 (5)		1.0	38 (17)
Yes*	173 (82)	18 (95)	0.21[a]	3.8 (0.6-164.7)	191 (83)
Prior tissue diagnosis attempt					
Yes	97 (46)	3 (16)	0.01[a]	4.6 (1.2-25.1)**	100 (44)
No*	113 (54)	16 (84)		1.0	119 (56)
EUS finding of CP					
Yes	22 (10)	1 (5)	0.70[a]	2.1 (0.3-91.7)	23 (10)
No*	188 (90)	18 (95)		1.0	206 (90)
Mass location					
Head	132 (63)	9 (47)	0.22[a]	1.9 (0.7-5.5)	141 (62)
Other*	78 (37)	10 (53)		1.0	88 (38)
Long axis (mm)					
>30	117 (56)	10 (53)	0.81[a]	1.1 (0.4-3.2)	127 (56)
≤30*	93 (44)	9 (47)		1.0	102 (44)
Range (min, max)	11, 95	7, 62		-	7, 95
Median	32.5	37.0	0.59[b]	-	33.0
Number of passes[c]					
≥5	54 (26)	5 (26)	1.00	1.0 (0.3-3.7)	59 (26)
1–4*	152 (74)	14 (74)		1.0	166 (74)
Range (Min, Max)	1, 11	1, 5		-	1, 11
Median	2	2	0.56	-	2
FNA reading[d]					
Malignant	174 (83)	19 (100)	0.22	-	193 (84)
Suspicious/atypical*	21 (10)	-		1.0	21 (9)
Benign	11 (5)	-		-	11 (5)
Failed	4 (2)	-		-	4 (2)

EUS: Endoscopic ultrasound, FNA: Fine-needle aspiration.*Reference category. **Statistically significant. [a]Fisher's two-tailed exact test. [b]Mann–Whitney–Wilcoxon test. [c]'Failed' procedures (*n*=4), all from the "Adenocarcinoma" category, excluded for calculating *P* value. [d]Adenocarcinomas with "benign" FNA reading (*n*=11) and "failed" procedures excluded for calculating *P* value. CP: Chronic pancreatitis, CT: Cmputerized tomography, CI: Confidence intervals

Table 3: Clinical presentation of patients, by type of cancer

Clinical feature	Adenocarcinoma (*N*=210)	Other Ca* (*N*=19)	*P*[a]	OR (95% CI)	Total (*N*=229)
	N (%)	*N* (%)			*N* (%)
Pain in abdomen					
Yes	136 (75)	12 (63)	1.00	1.1 (0.3–3.1)	148 (65)
No*	74 (35)	7 (37)		1.0	81 (35)
Loss of weight					
Yes	173 (82)	11 (58)	0.02	3.4 (1.1–10.0)	184 (80)
No*	37 (18)	8 (42)		1.0	45 (20)
Obstructive jaundice					
Yes	111 (53)	1 (5)	<0.001	20.2 (3.0–848.0)	112 (49)
No*	99 (47)	18 (95)		1.0	117 (51)
Early satiety					
Yes	19 (9)	1 (5)		1.8 (0.3–78.5)	20 (9)
No*	191 (91)	18 (95)		1.0	209 (91)
Presentation w/acute pancreatitis					
Yes	9 (4)	3 (16)	0.07	0.2 (0.1–1.5)	12 (5)
No*	201 (96)	16 (84)		1.0	217 (95)

*Reference category. **Statistically significant. [a] Fisher's two-tailed exact test. CI: Confidence intervals

in the confirmation of adenocarcinoma. Although 100% of NETs (n=19) were confirmed to be malignant, 21 patients with adenocarcinoma had atypical or suspicious cytology, 11 were false negatives, and attempts failed in 4 patients. The most important reason for atypical cytology and false negatives in those with adenocarcinoma was coinciding chronic pancreatitis. There was a greater prevalence of chronic pancreatitis in those with adenocarcinoma compared with those with NETs, although this lacked statistical significance due to the small number of patients with USPM (only one of whom had chronic pancreatitis). In a large series of patients with pancreatic masses from our center, Varadarajulu *et al* reported a significant decrement in the sensitivity of EUS–FNA in those with chronic pancreatitis, 73.9%, compared to those without, 91.3%.[12] Fritscher-Ravens *et al* similarly reported an even lower yield for EUS–FNA of pancreatic masses in patients with chronic pancreatitis, 54%, compared with 89.3% in those with normal pancreatic parenchyma. In the absence of "special stains" in these difficult scenarios surgical exploration may need to be considered.[13] Consistently, we demonstrated that those with adenocarcinoma of the pancreas were more likely to be referred for EUS following a failed prior biopsy attempt; and a significant portion of these patients had chronic pancreatitis, making the diagnosis even more challenging.

Particularly, given the limitations of EUS–FNA in this arena, it is important for the endosonographer to be alert to the clinical presentation. Our findings demonstrate that patients with adenocarcinoma were significantly more likely to present with clinical symptoms of inanition and jaundice. These findings likely reflect the aggressive nature of adenocarcinoma relative to NETs. Even among those with stage I or II adenocarcinoma who undergo resection, the five year survival ranges from 11.5% to 22.5%.[14] In contrast the overall 5 year survival for NETs is 45% and it is 59.3% for those who undergo resection.[15,16] Even patients with large tumors (>4 cm) and nodal metastasis are surgical candidates and more than half have greater than a 5-year survival.[16] The greater prevalence of jaundice in patients with adenocarcinoma not only reflects the more aggressive nature of adenocarcinoma but potentially its ductal nature and proximity to the bile duct when arising from the head of the gland. Our results suggest that adenocarcinomas tend to arise from the head of the pancreas to a greater extent than USPM.

The development of further advanced imaging techniques, improved endoscopic technology, and molecular markers may eventually impact the accuracy and the clinical utility of EUS–FNA for both adenocarcinoma and unusual tumors. Giovannini, Saftoiu, and others have demonstrated that EUS combined with elastography, in which the "hardness" of the pancreatic tissue as assessed by bulk modulus may enhance differentiation of pancreatic masses.[17,18] Additionally, harmonic EUS enhanced by intravenous contrast also promises to improve the performances of endosonography to characterize pancreatic lesions.[19]

One important technical finding is that we achieved 100% accuracy with the use of a 22-gauge FNA needle. EUS trucut biopsy (TCB) with a large needle provides tissue for histology as well as cytology; theoretically this could be useful in NETs where additional stains can be useful for confirmation.[20,21] However, further work suggests that TCB performs poorly in transduodenal pancreatic biopsies.[22-24] Tip deflection necessary to access pancreatic lesions from the duodenum prevents passage of the bulky trucut device through the scope as well as deployment of the needle into the target. However, future version of trucut technology may overcome these limitations. Recently, Sakamoto *et al* demonstrated that a 25-gauge FNA needle is more technically successful in tissue acquisition than the 22-gauge needle due to the latter's decreased performance for uncinate lesions, although the overall cytologic success was no different between the 25- and 22-gauge needles.[25] While the use of the 22-gauge needle did not diminish our results in this study we have recently been increasingly using the 25-gauge needle for pancreatic FNA, particularly of the uncinate process.

One criticism suggests that EUS-guided FNA cannot predict biological behavior of the tumor and hence histology is needed for better defining tumor grade according to the new World health organization classification. Using EUS-guided FNA specimen, one study[9] suggests that neuroendocrine tumor tumor biologic behavior can be predicted by KI-67 (proliferative activity) and the presence of nuclear pleomorphism/multinucleation and the presence of nucleoli.

Additionally, more sophisticated use of EUS-acquired tissue may further improve performance. A recent multicenter study demonstrated that the use of KRAS mutation analysis using restriction fragment length polymorphisms could be used to improve the sensitivity of EUS–FNA to differentiate adenocarcinoma from pseudotumoral chronic pancreatitis from 83% to 88%.[26] Fasanella *et al* recently demonstrated that in pancreatic endocrine tumors the loss of microsatellite markers correlated with increased mortality.[27]

CONCLUSION

In summary this represents the first study comparing the performance of EUS–FNA in the evaluation of adenocarcinoma versus unusual pancreatic tumors. There was a trend toward better performance in the latter. We postulate that this is likely related to the presence of an experienced onsite cytopathologist and the expeditious use of special staining protocols. The performance of EUS–FNA

of adenocarcinoma may have been limited by the frequent concomitant presence of chronic pancreatitis. In the absence of "special stains" for adenocarcinoma in these difficult scenarios it is critical of the endosonographer to be vigilant for clinical features which differentiate adenocarcinoma from USPM. We demonstrated that patients undergoing EUS–FNA for the evaluation of NET present less often with weight loss and jaundice than their counterparts. As new EUS technologies as well as more sophisticated methods of tissue analysis are introduced this issue will need to be intermittently readdressed.

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