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Endoscopic Ultrasound Imaging for Differential Diagnosis of Pancreatic Neoplasms: A 7-Year Study in a Chinese Population

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Background: Currently, non-invasive methods for screening pancreatic cancer are lacking. There is little information regarding whether endoscopic ultrasound (EUS) imaging has a discriminatory ability for detecting benign and malignant pancreatic neoplasms. In this study, we retrospectively analyzed the demographic, clinicopathologic, and EUS features and follow-up information.

Material/Methods: A total of 58 patients with pancreatic neoplasms who underwent endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) over a 7-year period (2009–2016) at our Department of Digestive Diseases were enrolled in our study.

Results: Of the 58 patients, 38 (65.5%) were diagnosed with malignant pancreatic neoplasms and 20 (34.5%) were benign ones. Of all the EUS findings, size of neoplasm (P=0.037) and regularity of margin (P=0.011) were significantly different between malignant and benign pancreatic neoplasms. However, age, sex, location, echo pattern, and dilation of main pancreatic duct did not show any significant difference (P>0.05). Size combined with regularity to detect malignant pancreatic neoplasms showed the following diagnostic values: sensitivity, 73.68%; specificity, 90%; positive predictive value, 76.60%; negative predictive value 81.82%; and area under the receiver operating characteristic curve, 0.887 (95% CI: 0.777–0.955, P<0.0001).

Conclusions: Our results showed the high value of EUS for differentiating malignant pancreatic neoplasms from benign ones. Due to this and its non-invasive nature, EUS should be the first-line method for detection of neoplastic pancreatic lesions.

MeSH Keywords: Diagnosis • Endoscopy, Gastrointestinal • Pancreatic Neoplasms

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Background

Pancreatic cancer (PC) is a highly aggressive tumor with a dismal prognosis [1]. Most patients with PC remain asymptomatic until the disease reaches an advanced stage [2]. Pancreatic ductal adenocarcinoma (PDAC) accounts for approximately 85% of all PCs and is projected to become the second leading cancer-associated death [3]. Pancreatic cystic neoplasms (PCNs) are a broad group of tumors that have varying malignant potential. Pseudocysts and serous cystic neoplasms (SCNs) are known to behave like benign tumors, whereas the mucinous cystic neoplasms (MCNs) and the intraductal papillary mucinous neoplasms (IPMNs) are well known for their malignant potential [4]. The therapeutic strategy of choice remains an individual decision, taking into account the risk of malignant transformation, as well as patient age, life circumstances, comorbidities, and personal preferences [5]. Thus, it is critical to accurately differentiate malignant neoplasms from benign ones to achieve successful early management.

The suspicion of PC is often first raised by abdominal imaging, such as computerized tomography (CT) and magnetic resonance imaging (MRI), but smaller lesions and locoregional lymph node metastases are often not detectable by these means [6]. Currently, endoscopic ultrasound (EUS) affords superb visualization of the pancreas and remains one of the most accurate means to identify pancreatic lesions; it is considered a first-line modality for diagnosing and staging of PC [7]. Moreover, endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) offers a high diagnostic accuracy of more than 85–90% for PC [2]. However, the overall diagnostic yield of EUS-FNA may be affected by a variety of factors such as the location of the lesion [8] and technical aspects [9]. In addition, it is relatively costly, uncomfortable for patients, and is not appropriate in low-risk areas; therefore, non-invasive diagnostic modalities are required in this population. Currently, few studies have assessed the potential role of EUS in the differentiation between malignant and benign pancreatic neoplasms in a Chinese population. Furthermore, the utility of EUS in discriminating between malignant and benign pancreatic neoplasms are uncertain.

The aim of this study was to retrospectively investigate the EUS characteristics and the discriminative ability of EUS for the identification of malignant and benign pancreatic neoplasms using receiver operator characteristics (ROC) curves.

Material and Methods

Patients

This was a retrospective study based on a population in northern China. A total of 58 patients with pancreatic neoplasms detected by EUS-FNA were enrolled in the study. All subjects were histologically certificated at Tianjin Medical University General Hospital from 2009 to 2016. The final diagnoses of the patients were determined according to the comprehensive findings of EUS-FNA and clinical follow-up. Information on sex and age and relevant clinical data were obtained from the database of the Digestive Endoscopy Center of Tianjin Medical University General Hospital. This study was approved by the Human Ethics Review Committee of Tianjin Medical University General Hospital (Tianjin, China).

EUS-FNA examination

Informed consents for EUS-FNA were granted by all patients prior to the procedure. The patients were placed in left lateral decubitus position during the EUS procedure and received conscious sedation with intravenous propofol. EUS procedures were performed by 2 experienced faculty endoscopists with more than 10 years of experience who used radial scanning echoendoscopes (GF-UCT260; Olympus, Tokyo, Japan). All EUS procedures were performed after CT and/or MRI. EUS-FNA was performed using a 19- or 22-gauge biopsy needle (ECHO-HD-19-C or ECHO-HD-22-C EchoTip ProCore; Cook Endoscopy, Limerick, Ireland). The needle was advanced into the lesion under EUS guidance. All biopsy specimens were sent to the Department of Pathology for histological examination and were assessed by 2 experienced cytopathologists.

EUS features

To determine the EUS features of pancreatic neoplasms that differentiate malignant neoplasms from benign ones, we established the following 6 factors: size, location, clarity of the neoplasms edge, regularity of margin, internal echo pattern, and dilation of the main pancreatic duct (MPD). The differences in the EUS features between the malignant and benign pancreatic neoplasms were investigated. The size of the pancreatic neoplasms was defined as the maximum size of the cut surface, clarity of the neoplasms edge was defined as a clear demarcation between the neoplasm and the surrounding normal tissue, and regularity of margin was defined as a round or oval shape of the neoplasm.

Statistical analysis

All statistical analyses were performed using SPSS (version 20.0; Chicago, IL, USA) for Windows. The chi-square test and univariate logistic regression analysis were used in the initial analyses, and multivariate logistic regression was used in the final analysis to assess the differences. Multivariate analysis was performed using stepwise selected logistic regression analysis. Receiver operating characteristic (ROC) curves and the area under the curve (AUC) were used to evaluate

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Table 1. Clinical characteristics.

Age in years, mean ±SD (range)	58.3±12.3	(21–87)
Sex, n (%)		
Male	35	(60.3)
Female	23	(39.7)
Symptoms, n (%)		
Abdominal pain	37	(63.8)
Jaundice	6	(10.3)
Asymptomatic	15	(25.9)
Size of neoplasms in mm, mean ±SD (range)	38.3±11.2	(16.0–65.0)
Number of passes, mean ±SD (range)	2.2±0.9	(1–5)
Size of needle, n (%)		
19G	33	(56.9)
22G	25	(43.1)
Lesion location, n (%)		
Head	28	(48.3)
Neck	2	(3.5)
Body	22	(37.9)
Tail	6	(10.3)

the diagnostic performance of EUS. The AUC and 95% confidence interval (CI) were estimated and compared to the different means or their combination. The level of statistical significance was set at two-tailed P<0.05.

Results

The baseline clinical characteristics of the study population are summarized in Table 1. The mean age of all patients was 58.3±12.3 years (range, 21–87 years), with the majority being male (n=35, 60.3%). Abdominal pain was the most common symptom, which was found in 37 patients (63.8%). Most patients (n=43, 74.1%) had CT, whereas 7 patients (12.1%) had MRI before EUS; 8 patients (13.8%) underwent both CT and MRI before EUS. Most neoplasms were located in the head of the pancreas (n=28, 48.3%). Mean neoplasm size was 38.3±11.2 mm (range, 16.0–65.0 mm). The total puncture procedures per patient varied from 1 to 5 passes, with a median of 2.2±0.9 passes.

Table 2. Baseline characteristics of final diagnosis.

Malignant, n (%)	38 (65.5)
Solid neoplasms	
Pancreatic ductal adenocarcinoma	10
Miscellaneous	5
Unclassified tumor	15
Cystic neoplasms	
Mucinous cystic neoplasms(MCNs)	7
Intraductal papillary mucinous neoplasm (IPMN)	1
Benign, n (%)	20 (34.5)
Solid neoplasms	
Focal pancreatitis	8
Autoimmune pancreatitis	7
Cystic neoplasms	
Pancreatic pseudocyst	2
Serous cystic neoplasms (SCNs)	3

Miscellaneous including Acinar cell cancer, Neuroendocrine tumour, Solid pseudopapillary neoplasm, Sarcomatoid carcinoma, Lymphadenoma.

The malignant or benign status of the EUS-FNA diagnoses and final diagnoses of the 58 neoplasms are shown in Table 2. Among them, 38 neoplasms (65.5%) were diagnosed as malignant, including 10 PDAC, 1 acinar cell cancer, 1 neuroendocrine tumor, 1 solid pseudopapillary neoplasm, 1 sarcomatoid carcinoma, 1 lymphadenoma, 15 unclassified tumors, 7 MCNs, and 1 IPMN. Twenty (34.5%) neoplasms were diagnosed as benign, including 8 focal pancreatitis, 7 autoimmune pancreatitis, 2 pancreatic pseudocysts, and 3 SCNs. Out of 58 patients, 41(70.69%) patients died of pancreatic neoplasms and 17 (29.31%) patients were alive after a minimum median follow-up of 2 years.

A malignant solid neoplasm was the most common (n=30; median age 56.1 years; 21–75), followed by benign solid neoplasms (n=15; median age 58.0 years; 27–83) and cystic lesions (n=13; median age 56.5 years; 31–87). Among the malignant neoplasms, PDAC was by far more common than other ones (n=10). The most common benign neoplasm was focal pancreatitis (n=10) (Table 2).

The representative EUS features of the patients with malignant or benign pancreatic neoplasms are shown in Figure 1 and the differences in clinical characteristics are shown in Table 3. Mean size of malignant neoplasms was 41.7±10.5 mm, and

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the mean size of benign ones was 31.9±9.9 mm. There were 31(81.6%) malignant neoplasms with unclear neoplasms edges and 29 (76.3%) malignant ones had irregular margins. The size of the neoplasm (P=0.003), clarity of neoplasm edge (P<0.001), and regularity of margin (P<0.001) were significantly different between malignant and benign pancreatic neoplasms in univariate analysis. However, age, sex, location of the neoplasm, regularity of the neoplasm edge, internal echo pattern, and dilation of MPD did not show any significant difference between malignant and benign pancreatic neoplasms. Next, we performed multivariate analysis for these factors using stepwise selected logistic regression analysis. We found that size of neoplasm (odds ratio=2.385) and regularity of margin (odds ratio=12.620) were statistically significant predictors for malignant pancreatic neoplasm (Table 4).

ROC curves were plotted for EUS to discriminate between benign and malignant lesions. For patients with malignant pancreatic neoplasms, the AUCs were 0.974 (0.893–0.998) for EUS-FNA, 0.759 (95% CI: 0.629–0.862) for size of neoplasm, 0.797(95% CI: 0.671–0.892) for regularity of margin, and 0.887 (95% CI: 0.777–0.955) for the combination method using size and regularity (Figure 2). The AUC with the combination of size and regularity was nearly equal to that of EUS-FNA (P=0.06). Overall, the efficiency of EUS imaging for discriminating malignant pancreatic neoplasms was promising, with corresponding validity parameters of 73.68% sensitivity, 90.0% specificity, 76.60% positive predictive value (PPV), and 81.82% negative predictive value (NPV). The results of ROC analysis and the corresponding diagnostic indices are summarized in Table 5.

Discussion

The increasing prevalence of PC and the challenging nature of pancreatic surgery have increased the demand for accurate diagnosis of PC. The diagnostic modalities for PC have recently improved and include EUS, CT, MRI, and positron emission tomography (PET). Mouen et al. [10] enrolled 154 patients who underwent EUS and subsequent surgical resection of the pancreatic cyst to evaluate the performance characteristics of EUS compared to CT/MRI. They observed that EUS with or without FNA was superior to CT alone in accurately classifying a cyst as neoplastic (76% *vs.* 48%, P<0.0001), and EUS with or without FNA was more likely to be correct than MRI alone (76% *vs.* 34%, P<0.0001) for prediction of neoplasia.

Currently, EUS provides high-quality images and offers a means to establish tissue analysis through FNA [11]. EUS-FNA can be used to obtain detailed imaging information as well as tissue and cystic fluid for analysis. Dalal et al. [12] reported a case of a symptomatic solitary true cyst of the pancreatic head in an adult that was identified via computed-enhanced computed tomography (CECT), laparoscopic ultrasonography (USG), and FNA. USG further helps estimate the internal flow characteristics of the blood within the pancreas [13]. Jeong et al. [14] showed 100% specificity for EUS-FNA in diagnosing pancreatic neoplasm, and the sensitivity and accuracy of EUS-FNA were 81.8% and 83.4%, respectively. Korenblit et al. [15]recently found the sensitivity and diagnostic accuracy of EUS-FNA were 87.6% and 89%, respectively. However, The overall diagnostic yield of EUS-FNA may be affected by the following variables: location of the lesion [8], skills of the endosonographers and cytopathologists [14], type and diameter of needle [16], use of suction and expression by air flushing [17], number of passes performed, and rapid on-site cytopathological evaluation (ROSE) [18]. In addition, FNA requires an experienced endoscopist and is a relatively dangerous procedure. Jonkman et al. [19] reported the case of a previously healthy 59-year-old woman who suffered severe acute pancreatitis after EUS-FNA of a pancreatic cyst and required admission to the intensive care unit (ICU); the development of infected pancreatic necrosis and bowel ischemia led to multiple organ failures. A systematic review and meta-analysis [20] indicated that overall morbidity as a result of adverse events of EUS-FNA was 2.66% (95% confidence interval [CI]: 1.84–3.62%), and the associated mortality was 0.19% (95% CI: 0.09–0.32%). Most common post-procedure adverse events included pancreatitis 0.92% (95% CI: 0.63–1.28%), hemorrhage 0.69% (95% CI: 0.42–1.02%), pain 0.49% (95% CI: 0.27–0.79%), infection 0.44% (95% CI: 0.27–0.66%), desaturation 0.23% (95% CI: 0.12–0.38%), and perforation 0.21% (95% CI: 0.11–0.36%). There was no peritoneal seeding in our study. The incidence of adverse events associated with prophylactic periprocedural antibiotic use was 2.77% (95% CI: 1.87–3.85%). In fact, the guidelines of the Japan Gastroenterological Endoscopy Society once proposed that EUS-guided FNA should not be permitted for the diagnosis of PCNs due to a serious risk of seeding following aspirated cystic fluid collection [16].

Alternatives for EUS-FNA depend on the morphology of the pancreatic lesion, symptoms, and patient comorbidity, and consist of watchful waiting using repeat EUS. In the present study, we investigated the best available sensitivity and specificity of EUS imaging for the prediction of malignant pancreatic neoplasm in connection with cancer diagnosing using ROC analysis.

As a result, size of neoplasm (odds ratio=2.385) and regularity of margin (odds ratio=12.620) were statistically significant predictors for malignant pancreatic neoplasm. These findings highlight the clinical usefulness of this method in identifying malignant and benign pancreatic neoplasms within a general population.

The conclusion of our study is partly in agreement with the study of Akira et al. [21], who revealed that an irregular tumor

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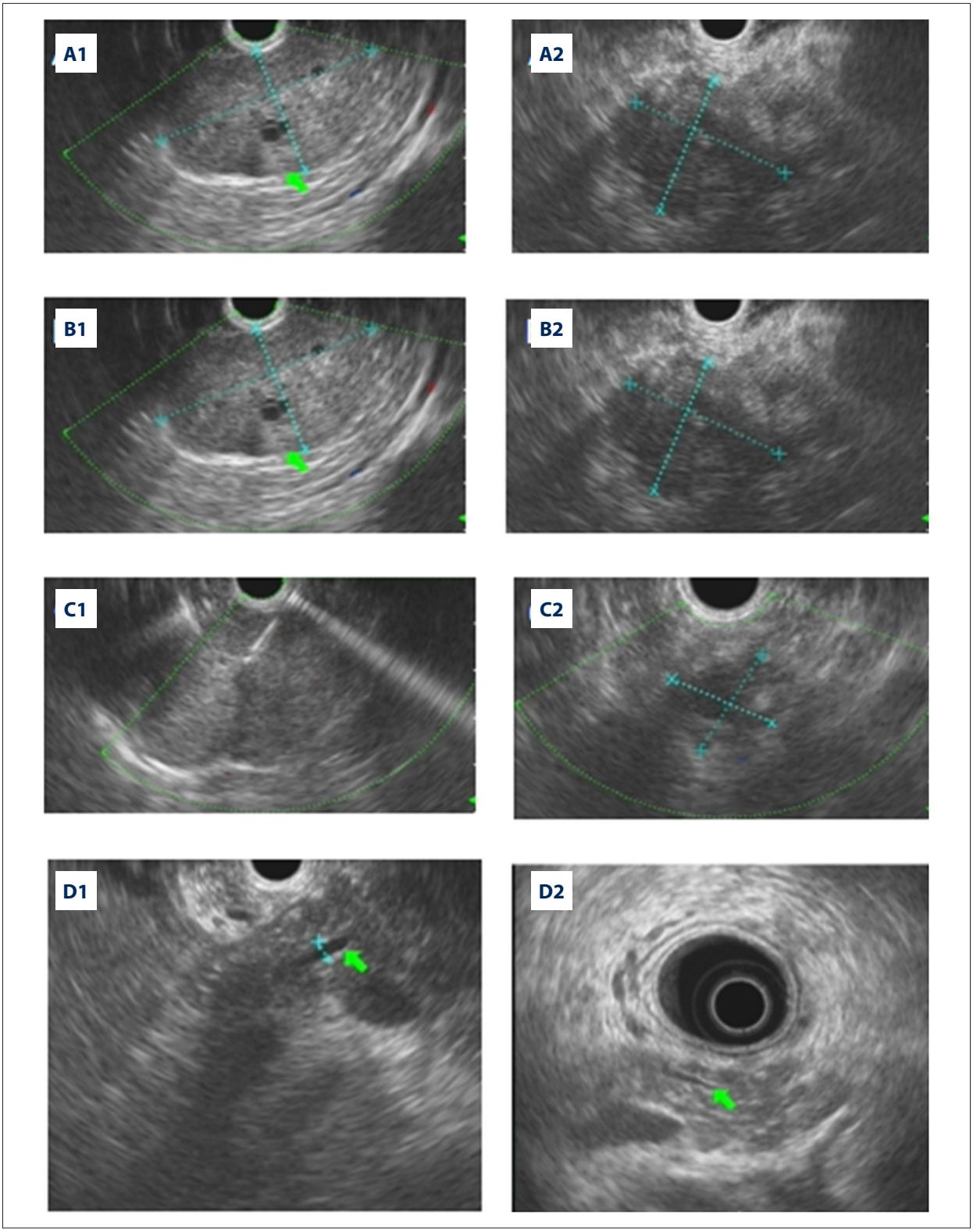

Figure 1. The EUS features of pancreatic neoplasm. The representative EUS imaging for pancreatic neoplasms including clarity of edge (**A1**), unclarity of edge (**A2**), regularity of the margin (**B1**), irregularity of the margin (**B2**), homogeneous internal echo pattern (**C1**), inhomogeneous internal echo pattern (**C2**), presence of dilation of MPD (**D1**), and absence of dilation of MPD (**D2**) are shown.

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Table 3. Comparison of clinical characteristics, EUS features of the patients with malignant or benign pancreatic neoplasms according to the final diagnosis.

	Malignant (N=38)	Benign (N=20)	*P* value
Age, years (mean ±SD)	59.8±11.4	55.6±13.6	0.221
Sex, n (Female/Male)	13/25	10/10	0.245
Size of neoplasms, mm (mean±SD)	41.7±10.5	31.9±9.9	0.003*
Localization of neoplasms			
Head	20	8	0.473
Neck	1	1	
Body	13	9	
Tail	4	2	
Clear neoplasms edge	7	14	<0.001*
Unclear neoplasms edge	31	6	
Regular margin	4	14	<0.001*
Irregular margin	34	6	
Homogeneous echo pattern	7	5	0.558
Inhomogeneous echo pattern	31	15	
Presence of dilation of MPD	6	4	0.687
Absence of dilation of MPD	32	16	

* Significantly different (chi-square test, p<0.05).

Table 4. EUS imaging discriminating malignant pancreatic neoplasm as shown by multivariate analysis.

	Odds ratio (95% CI)	*P* value
Size of neoplasm	2.385 (1.054–5.396)	0.037*
Clarity of edge	1.989 (0.320–12.365)	0.461
Regularity of margin	12.620 (1.777–89.621)	0.011*

edge, main pancreatic duct dilation, and tumor location in the pancreatic head were significantly indicative of PDAC, and predicted that the probability for PDAC was 80%, 92.6%, and 74.1%, respectively.

To the best of our best knowledge, previous studies have focused mostly on the relationship between tumor size and risk of metastasis and death in a large PDAC cohort [22], whereas our study is the first to assess the relationship between tumor size and the differentiation of pancreatic neoplasms. The AUC was 0.759 (95% CI: 0.629–0.862) with a sensitivity of 78.95% and specificity of 65.0% for the predication of malignant pancreatic neoplasms. However, further study with a larger population is required to confirm and identify the best cutoff value.

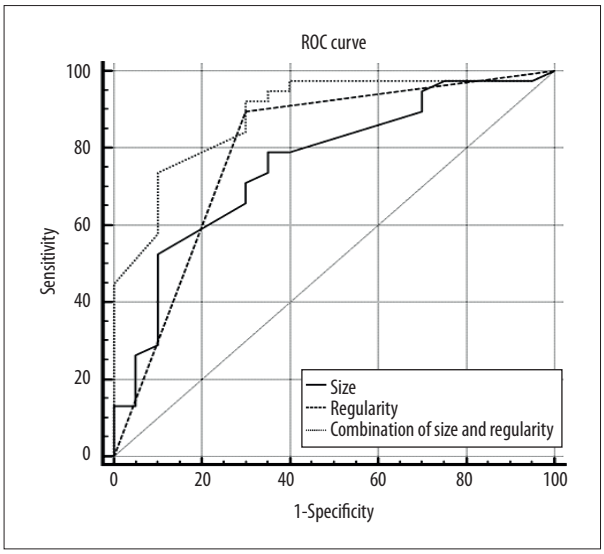

Figure 2. Receiver operating characteristics curve of size of neoplasm, regularity of the margin, and combination of size and regularity, for the diagnosis of malignant pancreatic neoplasms.

Several biochemical markers can be helpful in the diagnosis of pancreatic disease. Dilek et al. [23] found the cyst fluid carcinoembryonic antigen (CEA) 365 ng/mL had a sensitivity of

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Table 5. Summary of the receiver operating characteristic (ROC) curve analysis for malignant pancreatic neoplasm detection by EUS imaging.

	EUS-FNA	Size	Regularity	Size and regularity
ROC area(95%CI)	0.974 (0.893–0.998)	0.759 (0.629–0.862)	0.797 (0.671–0.892)	0.887 (0.777–0.955)
Optimal sensitivity	94.74%	78.95%	89.47%	73.68%
Optimal specificity	100.0%	65.0%	70.,0%	90.0%
PPV	100.0%	81.08%	85.0%	76.6%
NPV	90.91%	61.9%	77.78%	81.82%
+LR	/	2.26	2.98	7.37
–LR	0.053	0.32	0.15	0.29
P value	<0.0001	0.0001	<0.0001	<0.0001

PPV – positive predictive value; NPV – negative predictive value; LR – likelihood of ratio.

100% for the detection of malignant cystic lesions. A study by Chiba et al. [24] indicated that CEA 5.8 ng/ml had a sensitivity of 58.8%, specificity of 77.7%, and accuracy of 65.4%, while carbohydrate antigen (CA) 19-9 37.0 U/ml had a sensitivity of 94.4%, specificity of 55.6%, and accuracy of 81.4% in detecting PDAC. They also determined the S100P protein cutoff value for PDAC diagnosis to be 99.8 ng/ml. The S100P protein levels combined with EUS-FNA cytology to discriminate between PDAC and benign pancreatic lesions showed a sensitivity of 94.4%, specificity of 88.9%, and accuracy of 92.6%. A recent study has shown that a serum protein biomarker panel consisting of CA125, CA19-9, and laminin γC (LAMC2) can significantly improve performance in discriminating PDAC from other benign disease compared with CA19-9 alone [25].

Novel technologies such as contrast harmonic EUS (CH-EUS) and EUS elastography are in progress and might assist in differentiating benign from malignant pancreatic disease. CH-EUS was reportedly excellent in the differential diagnosis of pancreatic solid tumors [26]. In addition, Fusaroli et al. [27] found that malignant vegetations inside pancreatic cysts were clearly shown by CH-EUS as solid components with features of hyperenhancement, thus directing EUS-FNA to potential neoplastic areas and avoiding puncture of debris and mucus plugs. However, a study by Mayerle et al. [28] included 91 patients with focal pancreatic lesions and found that semiquantitative EUS elastography is not superior to the standard investigation by B-mode EUS and EUS-FNA for distinguishing between benign and malignant pancreatic lesions. Further investigation, however, is required.

Our study has certain limitations. First, it was a retrospective analysis of a computerized database and some data were missing. However, the database was accurately managed in a prospective manner with the purpose of collecting data for clinical research. Second, surgical control was not available for comparison in all patients. Thus, we used substitute diagnostic criterion standards, including EUS-FNA and long-term follow-up. Third, our findings were applied only to differentiate between malignant and benign pancreatic neoplasms because it is difficult to differentiate between all types of pancreatic neoplasms. A larger, prospective, multi-institutional study may alleviate these shortcomings to further explore the characteristics of EUS imaging in the clinical management of patients with pancreatic neoplasms.

Conclusions

Our results showed the high value of EUS for differentiating malignant pancreatic neoplasms from benign ones, suggesting that EUS should be the first-line method for detection of neoplastic pancreatic lesions and faster diagnosis, and better disease management can thus be acquired.

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