Value of contrast-enhanced ultrasound combined with percutaneous ultrasound-guided fine-needle aspiration in the diagnosis of solid pancreatic lesions

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Abstract

Background: Contrast-enhanced ultrasound (CEUS) can detect lesions hidden in inflammatory regions and find necrosis or areas of severe fibrosis within the lesion. This retrospective study aimed to compare the diagnostic accuracy of solid pancreatic lesions using percutaneous ultrasound (US)-guided fine-needle aspiration (FNA) with or without CEUS assessment.

Methods: Clinical, imaging, and pathologic data of 181 patients from January 2014 to December 2018 in Pecking Union Medical College Hospital, with solid pancreatic masses who underwent percutaneous US-FNA and ThinPrep cytologic test were retrospectively evaluated. Patients were divided into CEUS and US groups according to whether CEUS was performed before the biopsy. According to FNA cytology diagnoses, we combined non-diagnostic, neoplastic, and negative cases into a negative category. The positive category included malignant, suspicious, and atypical cases. The final diagnosis was confirmed by pathology or clinical and radiological follow-up for at least 12 months. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of US-FNA were evaluated between the two groups.

Results: This study enrolled 107 male and 74 female patients (average age: 60 years). There were 58 cases in the US group and 123 cases in the CEUS group. No statistically significant differences in age, gender, or lesion size were found between the two groups. The diagnostic accuracy of the CEUS group was 95.1% (117/123), which was higher than the 86.2% (50/58) observed in the US group ($P = 0.036$). The sensitivity, specificity, PPV, and NPV of the CEUS group were increased by 7.5%, 16.7%, 3.4%, and 18.8%, respectively, compared with the US group. However, the differences of the two groups were not statistically significant.

Conclusions: Compared with the conventional US, the use of CEUS could improve the biopsy accuracy and avoid the need for a repeat biopsy, especially for some complicated FNA cases.

Keywords: Biopsy; Contrast-enhanced ultrasound; Cytology; Fine-needle aspiration; Pancreatic lesion; Pancreatic neoplasms; Percutaneous ultrasound

Introduction

Pancreatic carcinomas are aggressive tumors with high mortality rates. The overall 5-year survival rate for patients with pancreatic cancer is only 7%.[1] Most solid pancreatic lesions are malignant; however, other lesions such as focal pancreatitis can complicate the diagnosis. The differential diagnosis of solid pancreatic masses is a common challenge, and the treatment decision is mainly based on the establishment or exclusion of malignancies. Accurate diagnosis of the pancreatic masses is essential to improve the prognosis.[2]

A pancreatic biopsy is often required for the proper diagnosis of pancreatic lesions; even for cases with evidence of definitive malignancy, a biopsy may be necessary to determine the neoplasm's histopathological features for further treatment. Methods of percutaneous ultrasound

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(US)-guided biopsy include fine-needle aspiration (FNA) and core needle biopsy (CNB). Percutaneous US-guided FNA (US-FNA) of solid pancreatic lesions has sensitivity and accuracy comparable to percutaneous US-guided CNB, but it is associated with fewer complications.[3] Rapid on-site cytological evaluation enhances the accuracy and efficiency of FNA[4]; however, many diagnostic centers lack this ability because of resource shortages. The smear cytology (SC) has the problem of cell crowding. A new cytological method named ThinPrep (Hologic Inc., Marlborough, MA, USA) cytologic test (TCT) could overcome the deficiency of SC and result in an accurate diagnosis.[5] In the absence of an on-site cytopathologist, TCT offers good diagnostic efficacy in patients with pancreatic mass lesions.[6] In our study, only the TCT process was included to avoid the impact of methodological differences.

US has a crucial role in evaluating pancreatic diseases, such as US-guided percutaneous invasive diagnostic of pancreatic masses, especially in European and Asiatic countries.[7] It has the benefits of convenience, real-time visualization, safety, lack of radiation exposure, and low cost. However, it is difficult to find more detailed information on the lesion from gray-scale and color Doppler US. Examples of the need to obtain such detailed information can be the questions of whether there is necrosis or severe fibrosis within the lesion and whether the lesion is hidden in inflammatory regions. These factors may cause the possibility of inaccurate biopsy, false-negative results, and non-diagnostic results. Contrast-enhanced ultrasound (CEUS) is a reliable modality for the differential diagnosis of pancreatic lesions.[8] Compared with the conventional US, CEUS can more accurately characterize the microvascular perfusion within the lesions, improve the observation of tumors, and identify the best percutaneous biopsy route.[9]

This study aimed to evaluate the efficacy of percutaneous US-FNA in diagnosing solid pancreatic lesions and determine whether CEUS before biopsy affects the diagnostic result.

Methods

Ethical approval

This study was approved by the Institutional Review Board of Peking Union Medical College Hospital (No. SK-811). All patients signed informed consent forms to undergo initial CEUS and percutaneous US-FNA.

Patient population

This retrospective study obtained the results and the clinical records for consecutive patients who underwent percutaneous US-FNA for suspected solid pancreatic lesions from January 2014 to December 2018 in Pecking Union Medical College Hospital ($n = 202$). We reviewed the computerized patient record system to obtain patient demographics, characteristics of the lesion, and clinical data. The patients who were lost to follow-up or for whom integral clinical information was unavailable were excluded from this study. Only those patients who had complete clinical data were included.

Contrast agent and ultrasonic procedures

CEUS was performed within 1 week before the biopsy, and the sonography contrast agent used was SonoVue (Bracco, Spa, Milan, Italy). A 2.4-mL suspension was administered by intravenous injection in 2 to 3 s for the first time; 1.2 mL was used for the second time if a detailed observation was necessary. CEUS was performed using the iU22 unit (Philips Healthcare Systems, Bothell, WA, USA). The size, location, shape, margin, composition of lesions, vascularity of neoplasms, and peri-pancreatic major blood vessels were evaluated by the conventional US. Lesion size was defined as the greatest measured diameter. Contrast-enhanced imaging was then initiated after administration, and the target lesions were continuously observed for over 2 min. The dynamic images were recorded on the ultrasonic machine's hard disk. The CEUS analysis was performed based on the review of stored footage. The CEUS-performing doctor and the biopsy-performing doctor assessed the CEUS together on the review of stored clips.

We mainly observed the perfusion and enhancement patterns. The perfusion of the tumor area was different from normal pancreatic tissue. For example, the typical enhancement pattern of ductal adenocarcinoma was hypo-enhancement in the arterial phase and rapid decrease in the venous phase. The enhancement and the reduction of the inflammatory region were synchronous with normal pancreatic tissue. There was no enhancement in the lesion's necrosis area with sharp boundaries in all phases. Very little enhancement in the fibrous tissue of the lesion was found in the arterial phases. The imaging of the severe fibrotic area displayed no enhancement either with an ill-defined margin. The best percutaneous biopsy path and the sampling site were established by reviewing all the above information to avoid necrotic areas, severe fibrosis, and blood vessels.

Biopsy indications and contraindications

The indication for US-guided percutaneous biopsy of pancreatic lesions was as follows: (1) suspicion of non-resectable pancreatic neoplasm, (2) inconclusive or controversial imaging findings, and (3) suspicion of an unusual neoplasm with prognostic or therapeutic implications such as metastasis or lymphoma. The exclusion criterion for biopsy included was as follows: (1) the lesion could not be displayed by the percutaneous US, (2) no safe percutaneous puncture route, (3) coagulation disorders (platelet count $<50 \times 10^9$/L or prothrombin time >13 s), (4) increasing serum amylase level, and (5) the patient was unable to control their breathing. Anticoagulants were discontinued 1 week before the biopsy.

Biopsy technique

Patients underwent US-FNA using an Esaote MyLab70 US unit (Esaote Biomedica, Genova, Italy) and 20-gauge × 200 mm FNA needles (Hakko Co., Ltd, Chikuma-shi, Nagano, Japan). After careful planning, the skin was sterilized, and 5 mL of local anesthetic (lidocaine 2%) was injected at the chosen entry point. After the probe was fixed, a puncture needle was inserted into the lesion under US guidance. A 10-mL syringe was connected to the puncture needle, and 15 to

30 to-and-fro movements in the lesion were done with negative pressure created by the syringe until a sufficient amount of material was obtained. To avoid injury and reduce bleeding, the patients were requested to hold their breath when the needle was inserted into or pulled out from the lesion. On every pass, the samples were deposited into preservative solutions for TCT examination. The entire biopsy procedure was continuously monitored using the conventional US. After the biopsy, routine ultrasonography was performed for active bleeding or other complications. Patients were requested to rest in bed, monitored in an observation room for 1 h, and put on an absolute diet for 2 h after the procedure. The solution was sent to the pathology department for cytological examination.

Cytology analysis

According to the guidelines for pancreaticobiliary cytology from the Papanicolaou Society of Cytopathology, FNA cytology diagnoses are classified into six categories: (1) non-diagnostic, (2) negative (for malignancy), (3) atypical, (4) neoplastic (benign or others), (5) suspicious (for malignancy), and (6) positive/malignant.[10] We combined non-diagnostic, neoplastic, and negative cases into a negative category for analysis. The positive category included malignant, suspicious, and atypical cases.

Final diagnosis

The final diagnosis was confirmed by pathology or clinical and radiological follow-up for at least 12 months. Biopsy sampling and surgery were essential methods to obtain tumor tissue and make a pathological diagnosis. The final diagnosis was malignant if typical malignant features were found upon pathological analysis. All patients without characteristic malignant pathology were followed up with clinical and radiological evaluations. Disease progression during follow-up, apparent distant metastases on imaging examination, or the patient's death indicated malignancy. An imaging result of unchanged shape and size suggested benignancy. As in Itonaga's research,[11] mucinous cystic neoplasms (MCN), neuroendocrine tumors (NET; G1 or G2), and solid pseudo-papillary neoplasms (SPNs) were defined as benign in this study.

Statistical analysis

All analyses were performed using SPSS 21.0 statistical analysis software (IBM, Corp., Armonk, NY, USA) and GraphPad Prism version 6.07 (GraphPad Software Inc., San Diego, CA, USA). Continuous variables are presented as median (Interquartile range, IQR). They were analyzed by the Mann–Whitney U-test. The diagnostic rate, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were evaluated and compared between the US and CEUS groups. Categorical variables were presented as frequencies and analyzed with Pearson χ^2 and Fisher exact tests. $P < 0.050$ was considered statistically significant.

Results

Baseline characteristics of the patients

Forty-one patients were lost to follow-up and were excluded. This retrospective study finally evaluated data from 181 patients who had complete clinical information. Fifty-eight patients underwent biopsy after conventional US examination and constituted the US group. The other 123 patients underwent CEUS before biopsy and formed the CEUS group.

The baseline patient characteristics are shown in Table 1. There were 107 males and 74 females. Age of participants ranged from 16 to 82 years, with a median age of 60 years. A total of 123 patients were enrolled in the CEUS group and 58 patients in the US group. Data on the patients' ages, genders, and lesion sizes were gathered, and there were no statistically significant differences between the two groups. Thirteen patients from the CEUS group underwent a second biopsy on account of unclear diagnostic results in the previous biopsy conducted with endoscopic US (EUS) or at other hospitals. All the patients of the US group underwent their first biopsy at our hospital.

Final diagnosis of the two groups

The final diagnoses were made by pathological and clinical follow-up and are listed in Table 1. The samples for pathological diagnosis were obtained by biopsy or surgery. According to the pathological results, malignancy was confirmed in 123 cases (76.4%). However, 38 cases (23.6%) were only confirmed by clinical and radiographic progression or death. Four patients with a final benign diagnosis were confirmed by surgical

Table 1: Baseline characteristics of patients in the two groups.

Items	Total ($n = 181$)	CEUS group ($n = 123$)	US group ($n = 58$)	*P* values
Male/female	107/74	68/55	39/19	0.127
Age (years)	58.3 ± 12.4 (16–82)	58.3 ± 11.9 (16–81)	58.2 ± 13.6 (27–82)	0.986
Lesion location				
Head/body and tail of pancreas	80/101	59/64	21/37	0.137
Longest diameter (cm)	5.0 ± 1.9 (1.6–15.4)	5.0 ± 1.6 (2.1–10.0)	5.0 ± 2.3 (1.6–15.4)	0.790
Final diagnosis (pathology/clinical)	127/54	91/32	36/22	0.102
Malignant lesions	123/38	90/21	33/17	0.037
Benign lesions	4/16	1/11	3/5	0.304

Data are presented as mean ± standard deviation (range). CEUS: Contrast-enhanced ultrasound; US: Ultrasound.

Table 2: Final diagnosis of the CEUS and US groups, *n* (%).

Diagnosis	Total (*n* = 181)	CEUS group (*n* = 123)	US group (*n* = 58)
Malignant lesions	161	111	50
Ductal adenocarcinoma	118 (73.3)	87 (78.4)	32 (64.0)
Metastatic carcinoma	7 (4.3)	6 (5.4)	1 (2.0)
Cystadenocarcinoma	2 (1.2)	2 (1.8)	0 (0)
Adenosquamous carcinoma	1 (0.6)	1 (0.9)	0 (0)
Acinar cell carcinoma	1 (0.6)	1 (0.9)	0 (0)
Neuroendocrine carcinoma	1 (0.6)	1 (0.9)	0 (0)
Undifferentiated carcinoma	1 (0.6)	0 (0)	1 (2.0)
Lymphoma	2 (1.2)	2 (1.8)	0 (0)
Other malignant lesions	28 (17.3)	11 (9.9)	16 (32.0)
Benign lesions	20	12	8
NET	8 (40.0)	5 (41.7)	3 (37.5)
SPN	3 (15.0)	2 (16.7)	1 (12.5)
Chronic pancreatitis	3 (15.0)	2 (16.7)	1 (12.5)
Autoimmune pancreatitis	3 (15.0)	2 (16.7)	1 (12.5)
MCN	1 (5.0)	0 (0)	1 (12.5)
Other benign lesions	2 (10.0)	1 (8.2)	1 (12.5)

CEUS: Contrast-enhanced ultrasound; MCN: Mucinous cystic neoplasms; NET: Neuroendocrine tumors; SPN: Solid pseudo-papillary neoplasm; US: Ultrasound.

Cytopathologic diagnosis of the two groups

Table 3 shows the final diagnosis of different cytological diagnoses in the CEUS and US groups. All suspicious diagnoses were clinically confirmed to be malignant. Of the subject with atypical diagnoses, 8/9 and 4/6 cases were confirmed as malignant in the CEUS and US groups. One case in CEUS group was clinically identified to be a benign lesion at follow-up. Of the two benign cases in the US group, one patient was finally identified as NET,the other one was determined to be a SPN. Of the subjects with neoplastic diagnoses, 3/10 and 3/6 of cases were eventually confirmed as malignant in the CEUS and US groups, respectively. In the subjects with negative diagnoses, two out of six cases were identified as metastatic carcinoma in the CEUS group, while one out of six metastatic cases and two other malignant cases were identified in the US group. For the repeated biopsy cases in the CEUS group, 10/13 of patients were diagnosed as malignant or SPN, and 3/13 of patients remained with atypical diagnoses.

Comparison of diagnostic accuracy between the two groups

The diagnostic accuracy rate of the CEUS group was 95.1% (117/123), which was statistically >86.2% (50/58)

Table 3: Final cytological diagnoses in CEUS and US groups, *n* (%).

Cytological diagnosis	CEUS group		US group	
	Benign lesions (*n* = 12)	Malignant lesions (*n* = 111)	Benign lesions (*n* = 8)	Malignant lesions (*n* = 50)
Negative	4 (33.3)	2 (1.8)	3 (37.5)	3 (6.0)
Atypical	1 (8.3)	8 (7.2)	2 (25.0)	4 (8.0)
Neoplastic	7 (58.4)	3 (2.7)	3 (37.5)	3 (6.0)
Suspicious	0	14 (12.6)	0	10 (20.0)
Malignant	0	84 (75.7)	0	30 (60.0)

Data are presented as *n* (%). CEUS: Contrast-enhanced ultrasound; US: Ultrasound.

Table 4: Comparison of diagnostic yields between the CEUS and US groups.

Items	CUES group	US group	*P* values
Accuracy	95.1 (89.5–98.0)	86.2 (74.8–93.1)	0.036
Sensitivity	95.5 (89.3–98.3)	88.0 (75.0–95.0)	0.081
Specificity	91.7 (59.8–99.6)	75.0 (35.6–95.5)	0.701
PPV	99.1 (94.2–100.0)	95.7 (84.0–99.2)	0.447
NPV	68.8 (41.5–87.9)	50.0 (22.3–77.8)	0.315

Data are presented as percentage (95% confidence interval). CEUS: Contrast-enhanced ultrasound; CI: Confidence interval; NPV: Negative predictive value; PPV: Positive predictive value; US: Ultrasound.

pathology. The other 16 patients with benign diagnoses had clinical courses compatible with a benign disease without progressive imaging, and all 20 patients with benign diagnoses survived during follow-up. The results of pathological classification are summarized in Table 2. The proportions of different diagnoses in malignant and benign lesions are listed separately. There was no significant difference in the final diagnosis of malignant or benign tumors between the two groups ($P = 0.419$).

in the US group ($P = 0.036$). This information is shown in Table 4. CEUS could reveal the necrosis in large masses and improve the diagnostic accuracy [Figure 1]. CEUS may also help identify the biopsy paths, avoid puncturing inflammatory areas around malignant masses and improve biopsy success rates [Figure 2]. The sensitivity, specificity, PPV, and NPV of the CEUS group were increased by 7.5%, 16.7%, 3.4%, and 18.8%, respectively, compared with the US group. However, the differences between the two groups were not statistically significant.

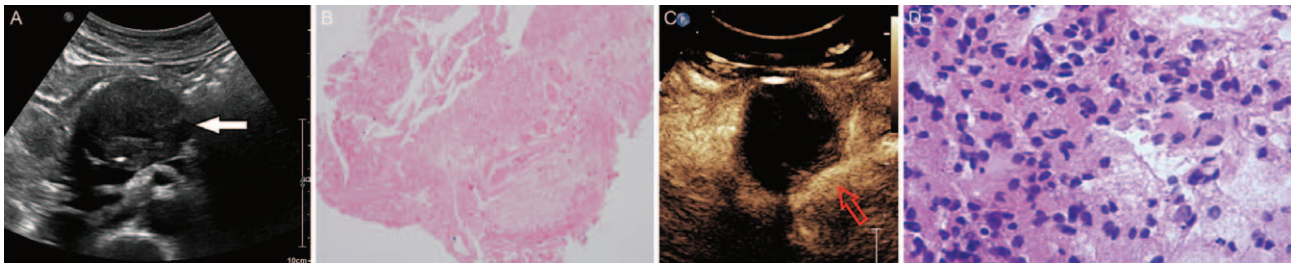

Figure 1: Solid pseudo-papillary neoplasm in a 28-year-old woman. (A) Gray-scale ultrasound imaging shows a hypoechoic lesion (arrows) in the body and tail of the pancreas. (B) Sample collected by US-CNB without CEUS. The pathology shows degeneration (hematoxylin and eosin stain ×100). (C) CEUS shows a small part of a hypo-enhanced area in the lesion's edge at 24 s (arrow). (D) US-FNA of the hypovascularity site shows pathology of SPN (hematoxylin and eosin stain ×200). CEUS: Contrast-enhanced ultrasound; CNB: Core needle biopsy; FNA: Fine-needle aspiration; US-FNA: Ultrasound-guided FNA.

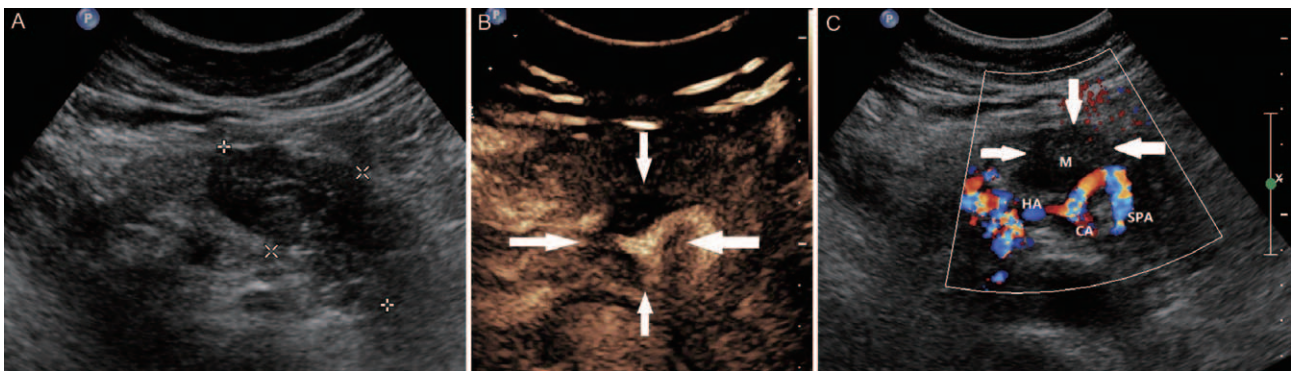

Figure 2: Pancreatic adenocarcinoma in a 60-year-old woman. (A) Gray-scale ultrasound imaging shows a hypoechoic lesion in the tail of the pancreas. (B) CEUS shows a hypo-enhanced area on the left part of the lesion at 85 s (arrows). (C) According to CEUS, a definite diseased area in color (arrows) was determined by Doppler US imaging. Biopsy of the area revealed pancreatic adenocarcinoma. CA: Coeliac artery; CEUS: Contrast-enhanced ultrasound; HA: Hepatic artery; M: Mass; SA: Splenic artery.

Complication rate

No severe procedure-related complication or death happened in any of the patients. There was only one case of acute pancreatitis after biopsy in each group. The two patients presented with severe abdominal pain on the same night as the procedure and were sent to the emergency department. Their biochemical blood indexes indicated increased amylase levels. They were admitted to the hospital and discharged after 2 weeks of conservative treatment. The complication rate was 1.7% and 0.8% in the US and CEUS groups, respectively, which indicated no statistically significant difference ($P > 0.05$).

Discussion

This study compared the diagnostic performance of US-FNA for pancreatic lesions with or without CEUS. The diagnostic accuracy statistically increased in the CEUS group. The results also demonstrate that CEUS helped improve diagnostic accuracy, sensitivity, specificity, PPV, and NPV, but the differences were not statistically significant. The lack of significance may be due to the facts that the patients' number was small and differences in difficulties were associated with biopsy between the two groups. Thirteen CEUS patients were not diagnosed by the previous biopsy, and these could be defined as complicated cases. Ten received confirmed pathological diagnoses during the second biopsy using CEUS.

The variability in the accuracy and sensitivity of biopsies in the previous study may be due to differences in cytological diagnostic interpretations and the final diagnostic classification of SPN, NET, MCN, etc. Hou *et al*[12] reported that considering atypical and suspicious reports as diagnostic of malignancy could increase diagnostic sensitivity and accuracy. According to the 2010 World Health Organization terminology classification, most NET and SPN are considered neoplasms rather than carcinomas, and the management approaches for these lesions are increasingly conservative.[10] Our research classified SPN, NET, and MCN as benign, which caused an increase of false-positive value.

The failure of pancreatic lesion biopsy was mainly due to the small number of sample tissues, and the fact that most of the sample tissues were necrotic. The European Federation of Societies for Ultrasound in Medicine and Biology recommends CEUS to improve the accuracy of percutaneous US-guided pancreatic procedures,[13] especially in biopsies of larger lesions.[14] CEUS is valuable to accurately guide pancreatic biopsy. Our research demonstrated that CEUS before the biopsy was an essential tool to identify the biopsy paths. Conventional US sometimes failed to detect pancreatic lesions in cases with pancreatitis. CEUS can successfully visualize the microvascular architecture of the lesions and may play a pivotal role in the differential diagnosis of malignant lesions and pancreatitis.[15] CEUS helps physicians target invisible lesions and viable areas that are difficult to visualize.[16]

Three cases with negative diagnoses were finally identified as having metastatic renal carcinoma (two in the CEUS group and one in the US group). The optimal treatment for metastatic tumors of the pancreas (MTPs) had not been established. In Endo et al's research,[17] pancreatectomy has been shown to confer a benefit in patients with metastatic renal cell carcinoma, and chemotherapy may be necessary to improve patients' prognosis with metastatic colorectal cancer. Therefore, a pathological diagnosis by biopsy is required for the treatment of MTP. During sampling of the metastatic pancreatic lesion, a large amount of blood was quickly taken up by the syringe. The final blood sample contained few tumor cells, which led to a false-negative diagnosis. Fortunately, CEUS of the metastatic lesion showed a rapid hyper-enhancement in the arterial phase and revealed a slight reduction in the venous phase, which led to hyper-enhancement in the late venous phase. The typical progression was significantly different from that seen in pancreatic ductal adenocarcinoma. Although there were not enough tumor cells for diagnosis, a diagnosis of metastasis was made according to the patient's clinical history and imaging features.

CEUS-FNA is more expensive than US-FNA, and it has a longer operating time. However, considering the higher accuracy rate and lower repeat biopsy rate, we believe CEUS-FNA for solid pancreatic lesions will be more cost-effective. EUS guidance has been increasingly used worldwide for sampling pancreatic lesions, especially for small lesions in the pancreatic tail. The high accuracy rate of US-guided percutaneous biopsy is comparable to that of EUS-guided biopsy.[18] We suggest that advanced pancreatic lesions could first be evaluated for percutaneous US-guided biopsy; if the lesions are located in areas invisible to the percutaneous US, then EUS should be considered.

This study has some limitations. First, this was a non-randomized, single-center, retrospective study, and the number of patients in the two groups was significantly different. Second, the sample size did not enable us to form a significant conclusion. More extensive multicenter prospective studies are required to confirm our results. Third, the number of passes was not evaluated, and the impact on the results cannot be excluded. Fourth, as this was a retrospective study, we could not identify the number of cases in which CEUS added important information influencing the puncture points and biopsy paths. Finally, most of the final diagnoses were made according to the clinical course rather than from the point-of-view of surgery. Despite this limitation, the assessment of pancreatic tumor vascularity by CEUS could help identify the best sampling site and improve FNA results.

To conclude, CEUS can visualize both the parenchymal perfusion and the microvasculature of the pancreatic lesions. Assessment by CEUS can help detect lesions hidden in inflammatory regions, necrosis, or severe fibrosis within the lesions, which provides valuable information to correctly identify the puncture points and biopsy paths. Compared with the conventional US, the use of CEUS may improve accuracy and avoid repeat biopsies. CEUS should be used to evaluate solid pancreatic masses, especially in some problematic FNA cases.

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Conflicts of interest

None.

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