Incidentally Detected Liver Metastases during Pancreas Contrast-enhanced Ultrasound

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Abstract

Purpose: The purpose of current study was to investigate the value of the late-phase enhancement features of pancreas contrast-enhanced ultrasound (CEUS) in the detection of liver metastases in patients with pancreatic ductal adenocarcinomas (PDAC).

Methods: From October 2020 to March 2021, 86 patients were prospectively enrolled. The gold standard of liver metastatic and PDAC lesions were based on histopathologically diagnoses and multiple imaging modalities results. B-mode ultrasound (BMUS) was performed to detect suspected liver metastases before CEUS. During the late phase of pancreas CEUS, the entire liver was scanned again to detect hypoenhanced liver metastases. Liver metastases were confirmed by biopsy and histopathological results. The number and size of liver metastases detected by BMUS and during CEUS late phase were recorded and compared.

Results: Suspected liver metastases were detected in 14 patients by BMUS (n = 23). During the late phase of CEUS, hypoenhanced liver metastases were detected in 23 patients (n = 87). When compared with BMUS, whole-liver scan during the late phase of CEUS detected more isoechoic, small, or superficially located lesions. Compared with BMUS, the specificity, sensitivity, positive predictive value, and negative predictive value of CEUS in diagnosing of liver metastases in PDAC patients were significantly improved (96.72% vs. 100%, 48% vs. 92%, 85.71% vs. 100%, and 83.10% vs. 96.83%, respectively) ($P < 0.05$).

Conclusion: The late phase whole liver scan during CEUS of pancreas helps to detect more liver metastases, which is important for further clinical decision-making.

Keywords

Liver metastasis, pancreatic ductal adenocarcinoma (PDAC), contrast-enhanced ultrasound (CEUS), detection, diagnosis.

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Background

Pancreatic ductal adenocarcinoma (PDAC) is the most common malignant tumor of the pancreas, and it has poor prognosis and high mortality rate [1]. Surgical resection remains the most effective curative treatment for PDAC, but more than 80% of patients are not amenable for surgery because of extensive local vascular involvement or the presence of distant metastasis [2]. Patients who underwent surgical radical resection has better survival outcomes and quality of life than patients who were not suitable for resection [3]. Liver is the most common organ for pancreatic metastasis [4, 5]. According to current National Comprehensive Cancer Network (NCCN) guidelines, surgery operation is not suitable for patients with pancreatic cancer and multiple liver metastases [6]. Instead, the most accepted therapeutic regimen for pancreatic cancer with hepatic metastases is chemotherapy [7]. Therefore, preoperative noninvasive detection of potential liver metastasis is of vital importance to avoid unnecessary surgery. However, preoperative sensitivity and accurate detection of liver metastasis remain a clinical challenge. Previously, up to 50% of liver metastases, especially small ones, could not be detected before operation [8]. Approximately 70% of small lesions (<1 cm) were undetected due to location close to the diaphragm and under the liver capsule [9]. Besides, approximately 7.5% of liver metastases showed isoechoic on conventional B-mode ultrasound (BMUS) [10].

Preoperative imaging evaluation is used to detect potential metastatic lesions. Currently, computed tomography (CT) and magnetic resonance image (MRI) are

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most widely used imaging approaches, with sensitivity of 90% [11]. Nevertheless, because of the nephrotoxicity and claustrophobia, clinical applications of CT and MRI are limited in some patients [11, 12]. Contrast-enhanced ultrasound (CEUS) is a real-time and noninvasive imaging method with no risk of exposure to radiation or nephrotoxicity. With injection of ultrasound contrast agent, CEUS has significantly improved the detection rate of focal liver lesions (FLLs) [13]. It was reported that CEUS could correctly characterize FLLs, with 92% sensitivity and 98% specificity [14]. In patients who was incidentally diagnosed with FLLs, the pooled estimates of sensitivity and specificity of CEUS for malignancy were 95.1% and 93.8%, respectively [15]. According to current World Federation for Ultrasound in Medicine and Biology (WFUMB) guidelines, distinctive punched washout during the portal venous and late phases are characteristic features of liver metastatic lesions [16].

The purpose of the current study was to evaluate the value of late-phase whole-liver scan during pancreatic CEUS in detection of liver metastases.

Patients and Methods

This research was approved by the ethical committee of our institute (no. B2021-144). Written informed consent was provided by each patient before CEUS examination.

Patients

From October 2020 to March 2021, patients who underwent preoperative pancreatic CEUS were included. The inclusion criteria were patients with clinically suspected pancreatic malignant lesions, those who planned to undergo surgical resection of pancreatic malignant lesion or biopsy of suspected liver metastatic lesion, those who underwent pancreatic CEUS 1 week before surgery, those who underwent at least two imaging modalities other than CEUS, those whose liver metastasis of PDAC was proven by biopsy and histopathology, or those whose imaging proved no liver metastasis.

Patients with no other imaging scan results except for ultrasound and those who could not tolerate CEUS procedure were excluded.

Ultrasound equipment

The ultrasound equipment was a Siemens ACUSON Sequoia equipment (Siemens Medical Solutions, Chicago, IL, USA) with a 5 C-1 transducer (1–6 MHz). The contrast agent was SonoVue (Bracco Imaging SpA, Milan, Italy), and the injection dose was 1.0–1.5 mL for each patient.

All BMUS and CEUS examinations were performed by an experienced radiologist who was blinded to other imaging diagnoses. The images of CEUS were interpreted according to current WFUMB liver CEUS guidelines [16].

B-mode ultrasound of liver and pancreas

First, BMUS scan of the pancreas was performed. Then, the whole liver was scanned to detect possible metastasis on BMUS. Any hypoechoic or hyperechoic solid lesion was considered a potential liver metastasis. The location, size, echogenicity, and margin of suspected lesions were recorded.

Contrast-enhanced ultrasound examination

After the injection of contrast agent, the enhancement patterns and degree of pancreatic lesion were observed and recorded for 2 minutes. During the late phase of CEUS (2–5 minutes after the initiation of contrast agent injection), the whole liver was scanned carefully under CEUS mode. Liver metastasis was defined as a marked washout lesion on CEUS during late phase. The number and location of those lesions were recorded and compared.

If the diagnosis of a suspicious metastasis was inconclusive, another 1–1.5 mL contrast agent would be injected to confirm enhancement features during the arterial phase.

Ultrasound-guided biopsy and histopathological analysis were performed for the final diagnosis of liver metastasis. In multi-lesion cases, the largest lesion of suspected metastases was chosen for histological confirmation. For patients without liver metastatic lesion, the standard diagnosis was based on at least two imaging modalities except for CEUS.

Statistical analysis

SPSS version 20.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. Descriptive analyses were performed using mean ± standard deviation for quantitative variables. The comparison of diagnostic accuracy between BMUS and CEUS was analyzed with paired chi-square test. A P value <0.05 was considered statistically significant.

Results

Clinical features

From October 2020 to March 2021, a total of 86 patients diagnosed with pancreatic malignant tumors were included. Among them, 25 patients were diagnosed with liver metastases.

B-mode ultrasound

Suspected liver metastases were detected in 14 patients (n = 23) during BMUS scan. Single and multiple lesions were detected in 8 and 6 patients, respectively. All lesions were heterogeneously hypoechoic (21/23) (**Figure 1**) or
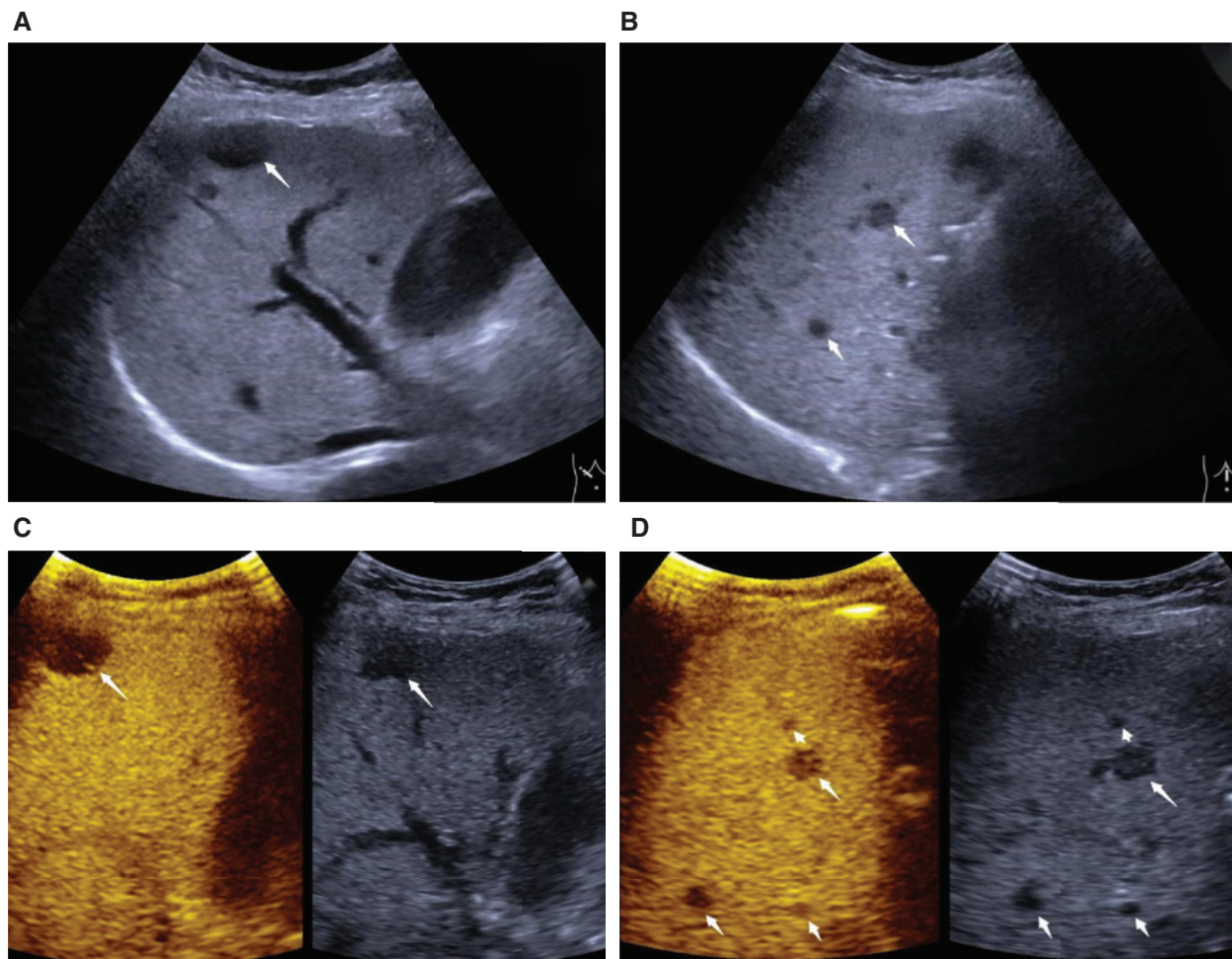
Figure 1 A 63-year-old woman was diagnosed with pancreatic ductal adenocarcinoma with multiple hepatic metastases (arrow). All liver metastases were heterogeneously hypoechoic on B-mode ultrasound (A, B) and hypoenhanced on contrast-enhanced ultrasound during the late phase (C, D).

hyperechoic (2/23) solid masses with ill-defined margins (**Figure 2**). The mean size was 19.6 ± 9.4 mm (range, 10.1–44.0 cm) (**Table 1**).

Contrast-enhanced ultrasound features

After injection of ultrasound contrast agent, liver metastases were detected in 23 patients (n = 87). During the late phase of CEUS scanning of the whole liver, all lesions showed hypoenhancement. Single and multiple lesions were detected in 3 and 20 patients, respectively. The mean size of the 87 lesions was 1.64 ± 0.94 cm (range, 0.45–4.94 cm) (**Table 1**).

Comparison between BMUS and CEUS

Sixty-seven additional liver metastasis lesions were detected on CEUS in 22 patients (**Figure 3**). However, all those lesions showed isoechoic or slightly hypoechoic on BMUS. Among the 67 lesions that were not visible on BMUS,

71.64% (48/67) were smaller than 2 cm and 31.34% (21/67) were less than 1 cm. When compared with BMUS, CEUS detected more isoechoic, small, or superficial located lesions (**Table 1**).

Among BMUS-detected lesions, one hypoechoic lesion was proved to be liver hemangioma and 2 hypoechoic lesions were proved to be focal fatty infiltration by multiple image modalities. The hemangioma lesion was a hypoechoic mass with clear margin on BMUS. After the injection of contrast agent, this lesion showed peripheral nodular hyperenhancement with centripetal progression during arterial phase and continuous hyperenhancement during portal venous and late phase. While the focal fatty infiltration lesion was hyperechoic on BMUS and iso-enhancement during all phases of CEUS.

Diagnostic efficiency

Among 25 patients with histologically confirmed hepatic metastatic lesions of pancreatic cancers, BMUS correctly diagnosed hepatic metastatic lesions of 13 patients, whereas CEUS correctly diagnosed of 23 patients and the diagnostic
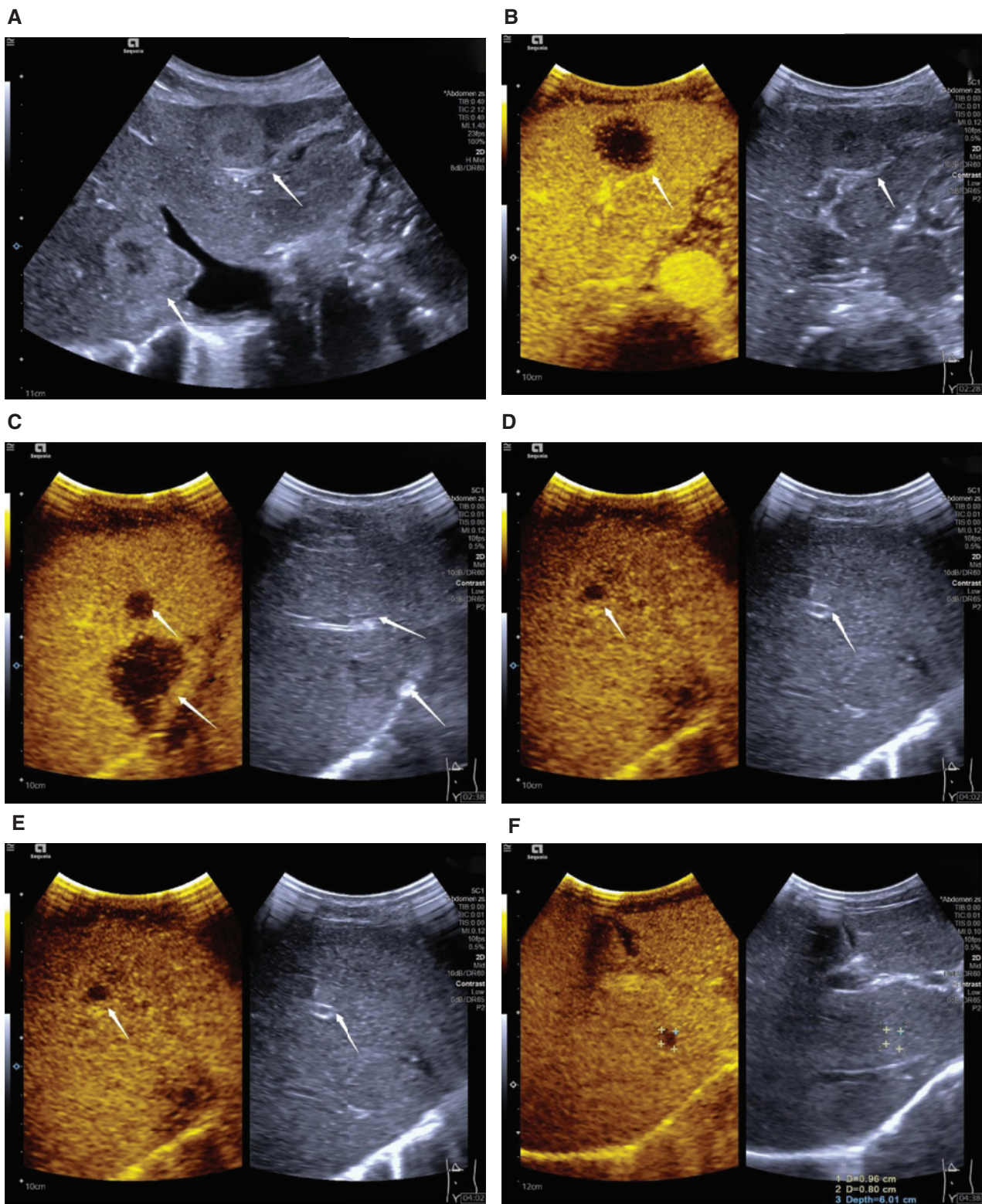
Figure 2 A 67-year-old woman was diagnosed with pancreatic ductal adenocarcinoma and multiple liver metastases (arrow). On B-mode ultrasound, two hypoechoic lesions with hyperechoic rim were detected in the right lobe of the liver (A). During late-phase of pancreatic contrast-enhanced ultrasound, more hypoenhanced and occult lesions were detected (B–F).

accuracy of CEUS was significantly higher than that of BMUS. Taking pathological and multiple imaging modalities results as gold standard, the sensitivity, specificity, positive predictive value, and negative predictive value of BMUS and CEUS for correctly diagnosing hepatic metastases were 48% and 92%, 96.72% and 100%, 85.71% and 100%, and 83.10% and 96.83%, respectively.

Discussion

Accurate detection of potential liver metastases in PDAC patients is important for preoperative staging and further therapeutic decision-making plans of PDCA patients. BMUS is the first-line imaging methods for detection FLLs. However, although the sensitivity and accuracy of BMUS in detecting

Table 1 Comparison of BMUS and CEUS in Detecting Liver Metastases of PDAC

	BMUS	CEUS
Number	20	87
Single	8	3
Multiple	6	20
Size (mm)		
Mean size	19.6 ± 9.4	16.4 ± 9.4
Range	10.1–44.0	4.5–49.4
<1 cm	0	22
<2 cm	15	66
Echogenicity of liver lesion		
Hypoechoic	18	18
Isoechoic	0	67
Hyperechoic	2	2
Location		
<2 cm to the ventral liver capsule	9	36
>2 cm to the ventral liver capsule	11	51

BMUS, B-mode ultrasound; CEUS, contrast-enhanced ultrasound; PDAC: pancreatic ductal adenocarcinoma.

potential liver metastasis remain unsatisfactory [17, 18], application of CEUS may provide added diagnostic evidence and improve the diagnostic confidence of FLLs [19, 20].

Currently, it is still challenging for BMUS to detect small or isoechoic FLLs [17, 18]. CEUS could improve the diagnose rate of small (<1 cm) and occult lesions. Whole-liver scan during the portal venous and late phases of pancreatic CEUS enables better detection of liver metastases in patients with primary non-hepatic malignant tumors [21]. The washout appearance during the venous and late phases of CEUS may play a confirmatory role when evaluating suspected lesions on BMUS. In our study, 67 additional lesions detected on CEUS were not visible on BMUS. A high proportion of these lesions were small. The smallest lesion detected on CEUS was only 0.45 cm in diameter. Therefore, CEUS might be helpful to make better treatment plans for these patients.

CEUS features may help to differentiate suspected liver metastasis on BMUS. In our study, a hypoechoic hemangioma was detected on BMUS. After injection of contrast agent, this lesion showed typical enhancement pattern on CEUS. In our study, one focal liver infiltration (FFI) lesion was hypoechoic on BMUS. However, on CEUS, the lesion showed no wash-out during the late phase of CEUS. FFI is one of the most common benign liver entities, and it could be misdiagnosed as malignancy on BMUS [22, 23]. FFI shows no difference in vascularity from peripheral parenchyma and contains normal undisturbed vessels [24]. Typically,
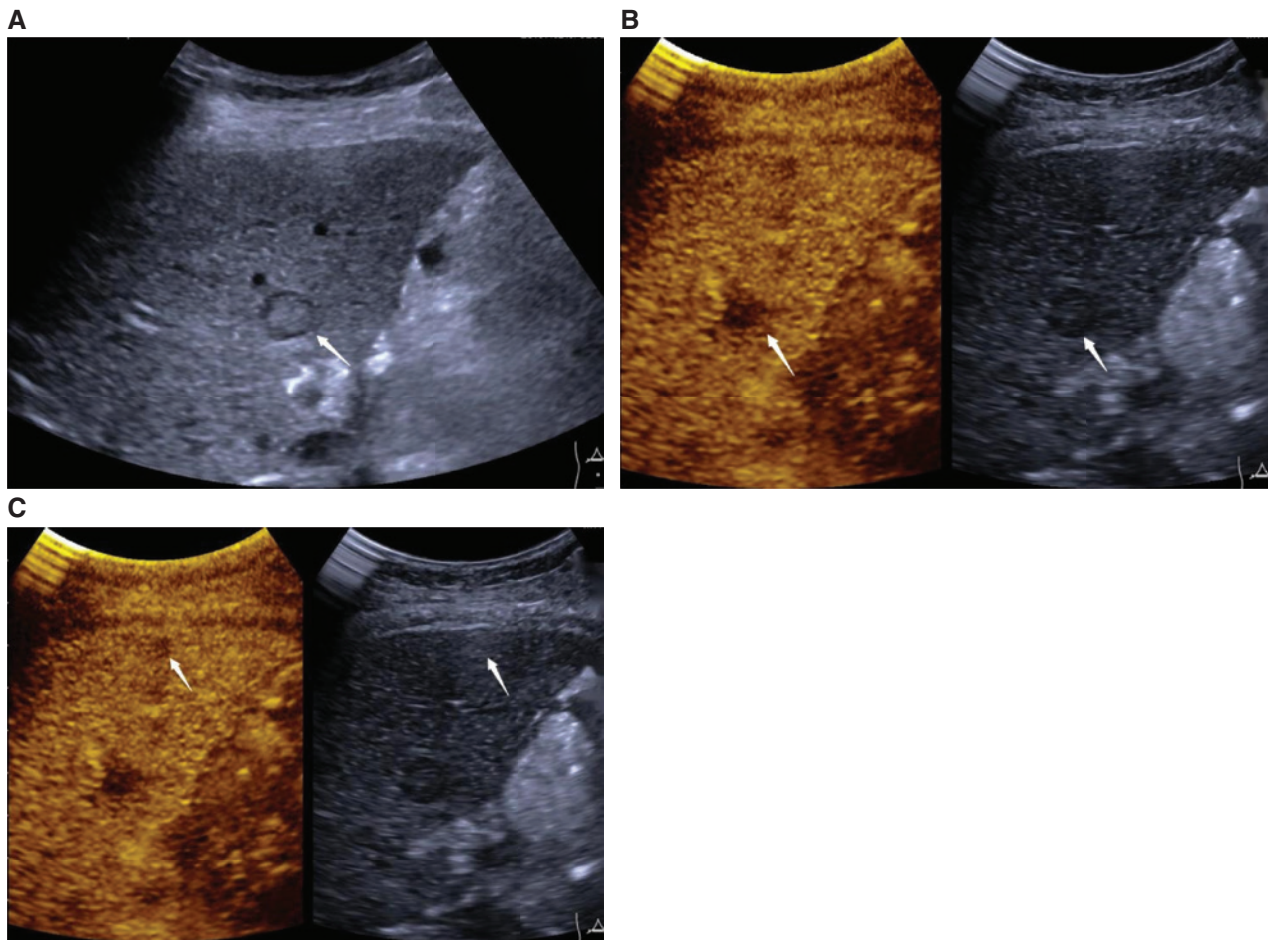
Figure 3 An 80-year-old woman was diagnosed with pancreatic ductal adenocarcinoma with multiple hepatic metastases (arrow). A hepatic metastatic lesion was heterogeneously hypoechoic and ill-defined on B-mode ultrasound (BMUS) (A) with marked washout during the late phase of contrast-enhanced ultrasound (CEUS) (B). During the late phase of CEUS, another smaller, hypoenhanced lesion was detected, which was not visible on BMUS (C).

homogenous iso-enhancement in all phases of CEUS has been regarded as a distinctive feature of FFI [16].

Over the last decade, although CEUS has significantly improves the detection rate of FLLs, it is still to be difficult to detect lesions located close to liver capsule [25, 26]. Compared with conventional low-frequency convex transducer, a high-frequency transducer (7–9 MHz) provides high resolution and better near-field investigations [27, 28]. CEUS performed with high-frequency transducers is an exciting technique for detection of small and superficial lesions. In 2006, Schacherer et al. compared the capability of low- and high-frequency transducers in the detection of liver metastases. They concluded that high-frequency transducer sonography revealed new, potentially malignant hepatic lesions in almost every patient [29]. In 2017, Wang et al. reported that CEUS performed with high-frequency transducer significantly improved the detection rate of FLLs, with overall sensitivity, specificity. and diagnostic accuracy of 88.9%, 92.6%, and 96.2%, respectively [25]. In our study, compared with conventional CEUS, 3 lesions located close to liver capsule showed more imaging details with high-frequency mode (**Figure 4**).

Limitation

The limitation of this study is the limited number of patients. Future studies with larger samples size should be performed
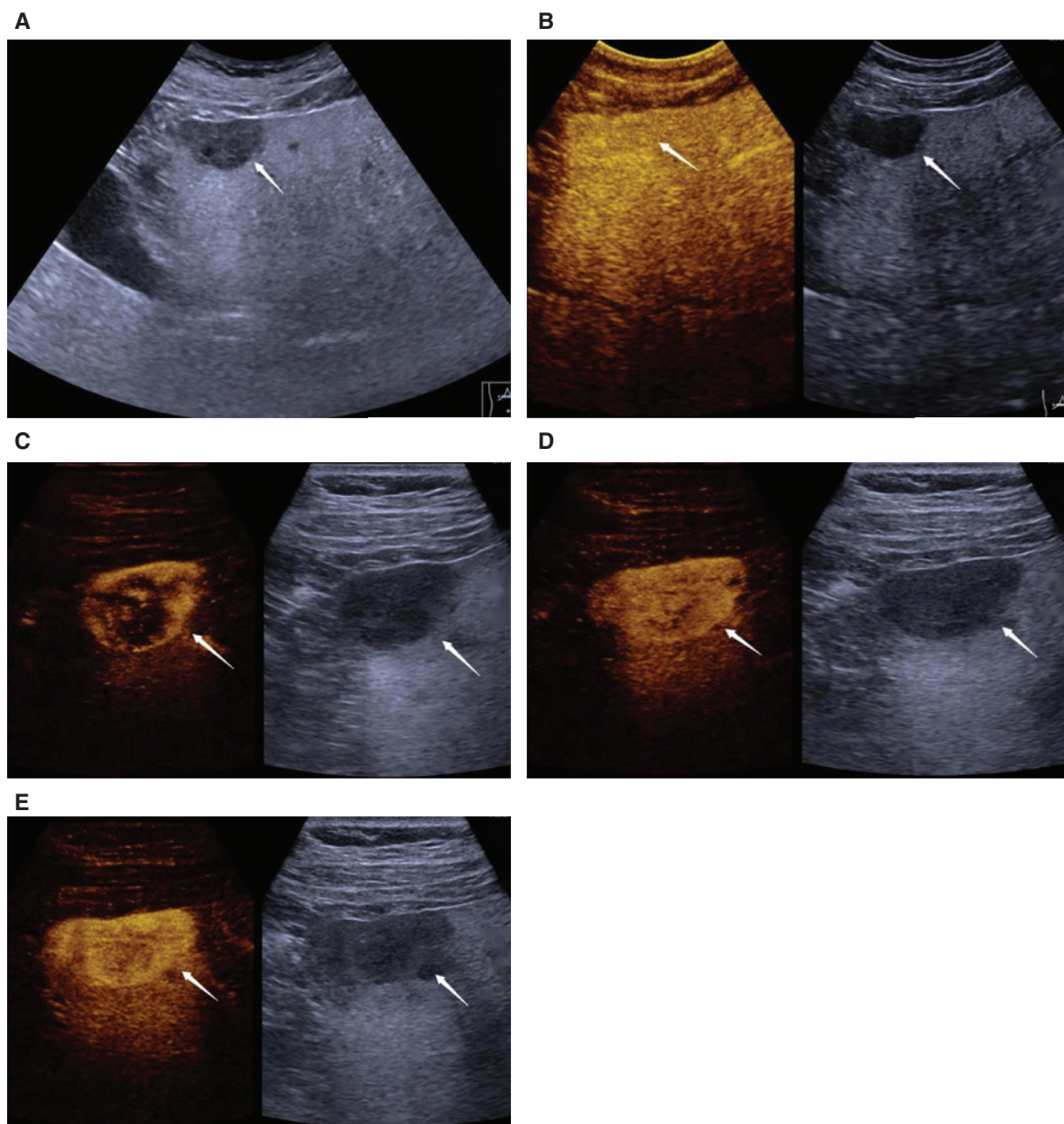

Figure 4 A 48-year-old man was diagnosed with pancreatic ductal adenocarcinoma. A hypoechoic mass was detected in the left lobe of the liver on B-mode ultrasound (A). The lesion showed iso-enhancement with peripheral liver parenchyma during the late phase of contrast-enhanced ultrasound (B). After contrast agent injection, the lesion showed peripheral nodular hyperenhancement with centripetal progression during the arterial phase (C–E).

to further verify the value of CEUS in preoperative detection of liver metastases in PDAC.

Conclusion

The whole-liver scan during the late phase of CEUS is helpful for detecting potential liver metastasis in patients with PDAC.

Acknowledgements

Conflicts of interest

There were no conflicts of interest with respect to the authorship or publication of this article.

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