Abdominal Radiology

Published online: 18 August 2018

Abdom Radiol (2019) 44:559–567
https://doi.org/10.1007/s00261-018-1746-2

Double contrast-enhanced ultrasound improves the detection and localization of occult lesions in the pancreatic tail: a initial experience report

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Abstract

Purpose : The aim of this study is to review our initial experience of Double contrast-enhanced ultrasonography (DCEUS) in the preoperative detection of pancreatic tail occult tumors.
Methods : Thirty-five patients were recruited to undergo DCEUS of the pancreas suspected by occult lesions of pancreatic with MRI or clinical evidence. The radiologists assessed the images (conventional US, DCEUS, and MRI) for enhancement phases, tumor presence, location, enhancement characteristics, and tumor conspicuity. The differences in the onset times of the phases between DCEUS and MRI were noted. Tumor conspicuity was graded on a four-point scale for conspicuity comparison among three imaging modalities.
Results : Pancreatic tail tumors were missed on conventional transabdominal US in 11 of 35 patients. DCEUS revealed 12 lesions of 35 patients. Pancreatic tail tumors were identified on MRI in 10 of 35 patients. The sensitivity and specificity of DCEUS for depicting occult lesions of ≤ 2.2 cm were 92% and 95%, respectively. In contrast, the sensitivity and specificity of conventional US were 67% and 66%, respectively. The sensitivity and specificity of MRI were 91% and 88%, respectively. The conspicuity ratings of the three phases did not significantly differ between the DCEUS and MRI groups ($P > 0.05$). The DCEUS phases started much earlier than the corresponding MRI phases.
Conclusion : DCEUS is a promising technique in the detection of occult pancreatic tail tumors and is possibly superior to dynamic enhanced MRI in the case of some peripheral lesions.

Key words: Contrast-enhanced ultrasound—Contrast-enhanced MRI—Double contrast-enhanced ultrasound—Pancreatic tail tumor

Solid tumors of the pancreatic tail are relatively uncommon, but are surgically important because they can be highly malignant, e.g., islet cell tumors and adenocarcinoma [1, 2]. The management of these tumors has progressed notably over the past decade, paralleling advances in technology and surgical technique. Improvements in ultrasonography (US) have enabled the diagnosis of these tumors with a good degree of certainty [2]. The management of a patient with a solid tumor of the tail of the pancreas includes an attempt to obtain a preoperative diagnosis. For this purpose, US is considered a first-line examination. US is valuable in the identification of tumor type and is essential for preoperative staging, which in turn guides further management [3].

The entire pancreas can be visualized on US by taking the following measures: minimum preprocedural fasting period of 6 h, examination during suspended inspiration or expiration, application of compression with the transducer to displace bowel gas after filling the stomach with water, and examination of the patient in different positions such as erect, supine, and left and right decubitus [4]. However, the diagnostic accuracy and confidence of US for pancreatic tail tumors remains considerably low in patients with air distension of the

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gastrointestinal tract and occasionally in obese patients. In such cases, a direct second-line examination is needed, especially for small or occult lesions of the pancreatic tail. Thus, the diagnosis of occult lesions in the pancreatic tail continues to pose a challenge to surgeons and sonographers.

In this study, we attempted to use double contrast-enhanced ultrasonography (DCEUS) to localize pancreatic tail tumors. DCEUS is performed with both luminal and intravascular contrast agents and is a valuable method for the evaluation of gastrointestinal tumors [5, 6]. In the present study, we found that DCEUS is also valuable for the detection and localization of occult lesions of the pancreatic tail. The aim of this study is to review our experience of DCEUS technology in the preoperative detection of occult tumors of the pancreatic tail.

Materials and methods

We recruited 35 patients who underwent DCEUS of the pancreas suspected by occult lesions of pancreatic with MRI or clinical evidence between January 2010 and April 2017. From these 35 patients, we selected 13 consecutive patients with sporadic tumors of the pancreatic tail and 12 of 13 had undergone surgery since 2010 at West China Hospital and retrospectively reviewed their medical records. The mean age of these 13 patients (six women) was 42 years. Each patient had a small tumor of the pancreatic tail and had been referred to us for conventional ultrasonography (US), DCEUS, and magnetic resonance imaging (MRI). The results of the imaging tests were compared with the surgical, histopathological, and clinical (follow-up) findings. All treatments were approved by the ethics committee of West China Hospital. Written informed consent was obtained from all patients at enrollment.

DCEUS protocol

Conventional US of the pancreas is performed after the patient has fasted for a minimum of 6 h in order to improve gland visualization, limit bowel gas, and ensure an empty stomach. The fasting period prior to DCEUS was 6 h.

An iU22 ultrasound system (Philips, Bothell, WA, USA) equipped with a 2–5 MHz convex array probe (C5-1) was used. A single sonographer (XZ) who has 15 years of experience in abdominal US and 8 years of experience in contrast-enhanced ultrasonography (CEUS) performed all DCEUS examinations.

We used a powdered luminal contrast agent (Tianxia, HuZhou, China) composed of a common yam rhizome derivative (50 g per package). It has a strong effect of reducing the surface tension of the gas bubble, and can effectively remove the ultrasonic artifact and interference caused by the gas bubble. The luminal contrast agent was reconstituted by adding boiling water (1000 mL per package) and gently stirred to form a homogeneous suspension. The reconstituted suspension was used to provide an echo window and eliminate gas adhering to the intestinal wall. The suspension was allowed to cool to 35–40 °C and then orally administered to the patients over 2–3 min. We also used a second-generation intravenous contrast agent (SonoVue; Bracco SpA, Milan, Italy).

Conventional transabdominal US was performed to thoroughly scan the entire abdomen, with particular focus on the pancreatic tail. The gastrointestinal lumen appeared to be a homogeneous echoic acoustic window. The pancreatic tail and structures were evaluated through the window of the stomach, which was filled with the luminal contrast agent. Approximately 500–1000 mL luminal contrast was used, depending on the distention of the stomach and the patients' tolerance. DCEUS was performed with patients in a slight left lateral decubitus or semi-supine position in order to promote flow of the luminal contrast agent toward the transducer, which was in the transverse-anterior position, and to maintain the luminal contrast agent in the position of the pancreatic tail.

When a tumor was found, its location and shape were recorded. The largest section of the tumor was found, and its largest diameter recorded. DCEUS was performed under the preset "contrast general," and dual images in the fundamental and contrast-enhanced modes were set side-by-side in a split screen display. In our study, the mechanical index (MI) was 0.06–0.08, the dynamic range was 50 dB, and the depth was 10 cm. The focus was placed at a depth of 7–9 cm, and the length of the focus was 1 cm. Tissue gain was 80%, and contrast gain was 85%. Through a 20-gauge needle, 0.025 mL/kg body weight of SonoVue was injected into the antecubital vein as a bolus within 3 s, followed by a 5 mL flush of 0.9% sodium chloride solution. The transducer was fixed in position in the largest section of the lesion. Contrast scans were obtained during quiet respiration. The patients were asked to breathe gently for 120 s. The target lesions and the surrounding structures were observed continuously at the largest longitudinal section of the tumor. The entire dynamic DCEUS process was stored on a hard disk.

MRI protocol

All patients underwent MRI using a 1.5 T MR system (Siemens Sonata, Erlangen, Germany) and a torso phased-array coil. A 22-gauge intravenous catheter was placed in an arm vein and connected to an MR-compatible power injector. For each patient, unenhanced acquisitions were obtained prior to enhanced sequences. The unenhanced MR sequences during MR cholan-

giopancreatography were as follows: axial fast spin-echo (FSE) T2-weighted images (repetition time [TR], 1000 ms; echo time [TE], 83 ms; slice thickness, 8 mm), two-dimensional gradient echo (2D-GE) T1-weighted images (TR, 100 ms; TE, 4.8 ms; slice thickness, 8 mm), and 2D oblique coronal single-shot FSE (SSFSE) images (TR, 4500 ms; TE, 760 ms; slab thickness, 60 mm; angle change between adjacent slabs, 6–8°; acquisition, 9–12 times). Three-dimensional (3D) T1-weighted thin-section dynamic enhanced MRI with volumetric interpolated breath-hold examination (3D-VIBE) sequence was started at 15 s, 40 s, and 65 s after initialization of contrast material injection in order to obtain tri-phasic enhanced images corresponding to the early arterial, late arterial, and portal venous phases, respectively. The imaging parameters of the 3D sequence were as follows: TR, 4.2 ms; TE, 1.8 ms; flip angle, 12°; field of view, 300–360 mm; matrix, 256 × 256; and in-plane spatial resolution, 2.0 mm or less. The entire slab thickness ranged from 80 to 100 mm, and the partition thickness was 2 mm (in Kz spatial resolution of 2.0 mm). Acquisition of 3D thin-section images for each phase was finished during a single breath-hold at the end of expiration (time range 14–16 s; mean time, 15.1 s). The total table time for the completion of dynamic tri-phasic acquisition averaged approximately 80 s. The hepatic hilum was defined as the center of the scanning coverage in every patient. All patients received 10 mL gadolinium contrast material (dose range 0.12–0.18 mmol/kg) at a flow rate of 2–3 mL/s, followed by a 20 mL flush of normal saline. After 3D dynamic scanning, axial enhanced scanning with 2D-GE T1-weighted imaging (TR, 124 ms; TE, 2.5 ms; slice thickness, 8 mm) was immediately performed to acquire images of the equilibrium phase.

Image analyses

All preoperative imaging reports were reviewed to determine the difference of each imaging technique (conventional US, DCEUS, and MRI).

Image post-processing and analysis were performed at the workstation of the MR system (Leonardo, Siemens, Germany). Images of three sequences were analyzed: (a) the original and (b) reconstructed tri-phasic 3D thin-section dynamic enhanced images, and (c) the enhanced 2D T1-weighted images in the equilibrium phase. Observation was especially focused on tumor location, morphological type, and enhancement pattern.

The radiologist interpreting the examinations was not blinded prospectively to any of the other imaging results. MRI and US scans were then retrospectively reviewed by two of three radiologists (WZ,YZ) in consensus. These radiologists were aware of the surgical reports, so that tumor presence and location were correlated with imaging findings in each case. The radiologists assessed the scans for phases of enhancement acquired, tumor presence and location, relative tumor conspicuity in each phase, tumor appearance (solid vs. cystic), and enhancement characteristics.

The images were reviewed to determine the number of phases of enhancement performed. The DCEUS pancreatic enhancement phases were classified as follows: arterial (10–30 s), venous (30–120 s), and late venous (> 120) phases [7]. The MRI phases were classified as arterial (arterial opacification without superior mesenteric vein opacification), late arterial (superior mesenteric vein opacification), and portal venous (portal and hepatic vein opacification). The early arterial, late arterial, and portal venous phases of MRI were differentiated on the basis of the degree of enhancement of the superior mesenteric vein. The differences in the onset times of the imaging phases between DCEUS and MRI were noted.

Each phase was reviewed to determine if the tumor could be conclusively visualized, and the phase in which the tumor was most conspicuous was noted. Tumor enhancement in each phase was assessed and subjectively classified as hypo-, hyper-, or isoenhanced compared with the surrounding pancreas. Tumors were noted to have either homogeneous or heterogeneous internal attenuation.

For qualitative analysis, one reader with 15 years of experience in abdominal imaging (WZ) evaluated tumor conspicuity on DCEUS in all patients with proven pancreatic tail tumors. Tumor conspicuity was graded on a four-point scale, as follows: 0, absent (i.e., the tumor mass was not seen); 1, poor (i.e., faint perceptibility, hard to detect the tumor); 2, good (i.e., unequivocal perceptibility, well-recognizable tumor); and 3, excellent (i.e., excellent tumor perceptibility, obvious tumor).

Statistical analyses

The sensitivity of MRI and DCEUS for the detection of pancreatic tail tumors was calculated as the proportion of true-positive results divided by the total number of patients with a tumor; the specificity was calculated as the ratio of the true-negative results to the total number of patients without any tumor. The positive predictive value was calculated as the number of true-positive results divided by the sum of true-positive and false-positive results. The negative predictive value was the ratio of true-negative results to the sum of true-negative and false-negative results. In the statistical analyses, the χ^2 test was used to calculate proportions, and a P value of less than 0.05 was considered significant.

Results

No complications were observed after the administration of hyoscyamine butylbromide (luminal contrast agent) and microbubble contrast agent. Occult pancreatic tail

tumors were confirmed by histopathology in 13 patients, most of whom did not have obvious clinical symptoms, except for three patients with neuroendocrine tumors (2 cases of islet cell tumors and 1 case of neuroendocrine tumors). The general characteristics and results of DCEUS and MRI analyses of the 13 patients with pancreatic tail tumors are shown in Table 1.

The islet cell tumor in case 3 was missed on MRI, but surgically confirmed to be a 0.8-cm-wide tumor in the peripheral margin of the pancreas tail. The MRI quality was poor in this patient because of blurring related to irregular excursions during breathing (Fig. 1F). In the case of the other tumor that was not detected on MRI (case 6), clinical and laboratory test results showed hyperinsulinism persisting since more than 3 years, but the patient refused surgery. DCEUS in this patient revealed a slightly strong echo signal indicative of an indeterminate nodule at the pancreatic tail. DCEUS showed normal enhancement of the nodule compared with the surrounding pancreatic tissue (Fig. 2). The tumors were histopathologically identified as follows: two solid pseudopapillary tumors (cases 1 and 5, Fig. 3), one insulinomas (case 3), one cystadenoma (case 2), one adenocarcinoma (case 4), one pseudocyst (case 7), 2 microcystic cystadenomas (case 10 and 13), 2 neuroendocrine tumors (case 11 and 12), and two mucinous cysts (cases 8 and 9). The average tumor diameter was 1.6 ± 0.4 cm.

Pancreatic tail tumors were missed on conventional transabdominal US in 11 of 13 patients. DCEUS clearly revealed 12 lesions with the patients in a semi-recumbent position. Apart from the neuroendocrine tumors (islet cell tumor in case 3 and 6, neuroendocrine tumors in case 11 and 12), which appeared to have a rich blood supply (Fig. 1), 11 tumors seemed to lack blood supply on contrast images and one lesion (case 6) seemed to be similar with pancreatic tissue. Pancreatic tail tumors were identified on MRI in 10 of 13 patients and were missed in three patients.

The sensitivity and specificity of DCEUS for depicting occult lesions of 2.2 cm or less in diameter were 92% and 95%, respectively. In contrast, the sensitivity and specificity of conventional US were 67% and 66%, respectively. The positive predictive and negative predictive values of DCEUS were 92% and 95%, respectively, whereas the corresponding values for conventional US were 15% and 95%, respectively.

The sensitivity and specificity of MRI for depicting occult lesions of 2.2 cm or less in diameter were 91% and 88%, respectively. The positive predictive and negative predictive values of MRI were 77% and 95%, respectively.

Qualitative analysis

On DCEUS, the conspicuity of the lesions decreased slightly in the venous and late venous phases, owing to the smaller difference in signal intensity between the markedly enhancing pancreatic lesion and the enhancing pancreatic parenchyma (Fig. 1, 2). Cases 3 and 6 showed no islet cell tumor on MRI, and their tumor conspicuity was therefore set as 0.

Tumor conspicuity in the DCEUS and MRI groups is shown in Table 2. The enhancement features of DCEUS and MRI were similar in all three phases and in all patients (except cases 3 and 6, in which the tumors were missed in MRI), Table 2. The qualitative ratings of the three phases did not significantly differ between the DCEUS and MRI groups ($P > 0.05$).

Table 1. General patient characteristics

Case	Sex	Age (years)	Histopathological diagnosis	Tumor size (cm)	Detected on		
					US	DCEUS	MRI
1	Female	36	Solid pseudopapillary tumor	1.8	–	+	+
2	Male	40	Cystadenoma	0.8	–	+	+
3	Female	37	Insulinoma	1.2	–	+	–
4	Male	50	Adenocarcinoma	1.6	–	+	+
5	Female	37	Solid pseudopapillary tumor	1.1	–	+	+
6	Male	48	Insulinoma (highly indicated by lab tests)	1.9	–	±	–
7	Male	39	Pseudocyst	1.8	+	+	+
8	Female	27	Mucinous cyst	1.7	–	+	+
9	Female	30	Mucinous cyst	1.9	–	+	+
10	Male	45	Microcystic cystadenomas	2.2	–	+	+
11	Female	50	Neuroendocrine tumor	1	–	+	+
12	Male	56	Neuroendocrine tumor	2	+	+	+
13	Male	47	Microcystic cystadenomas	1.3	–	+	–
Mean		42		1.6 ± 0.4[a]			

–, Not detected; +, detected; ±, uncertain; US, ultrasonography; DCEUS, double contrast-enhanced US; MRI, magnetic resonance imaging
[a]Mean ± SD

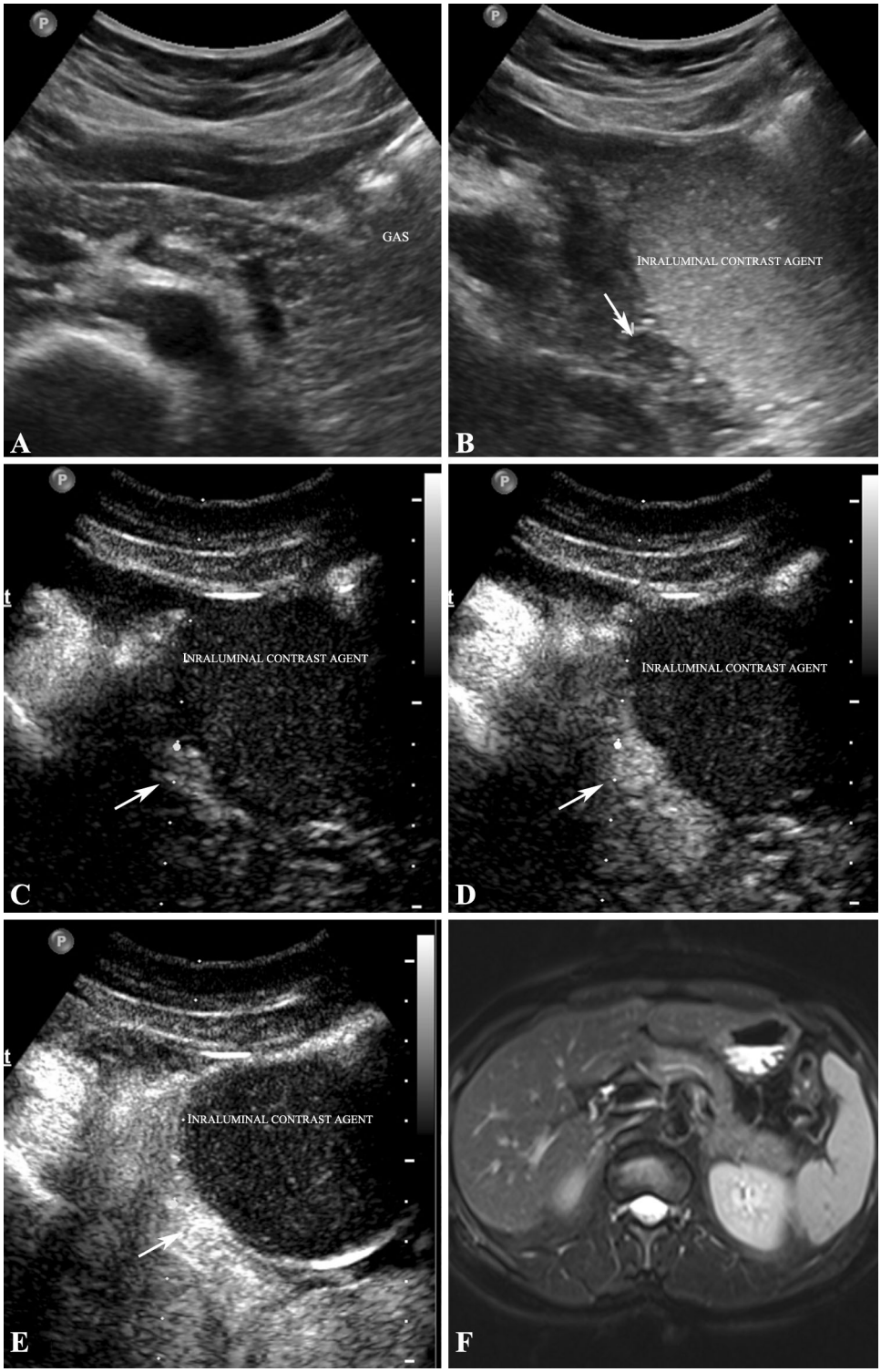

Fig. 1. Case 3. A 37-year-old woman with pancreatic tail islet tumor (arrows). **A** The pancreatic tail was not seen in traditional US because of gas refraction. **B** Two-dimensional conventional US with intraluminal contrast agent demonstrated that a lowly echogenic mass with a diameter of 0.8 cm was located in the pancreatic tail. **C** DCEUS showed high intense enhancement within the tumor at the phase of artery, **D** DCEUS imaging at the spleen vein phase showed that the mass was apparently enhanced in comparison with adjacent pancreatic parenchyma; **E** DCEUS imaging at venous phase was slightly enhanced in comparison with pancreatic parenchyma. **F** T2-weighted MRI at the transverse plane showed that no mass was found.

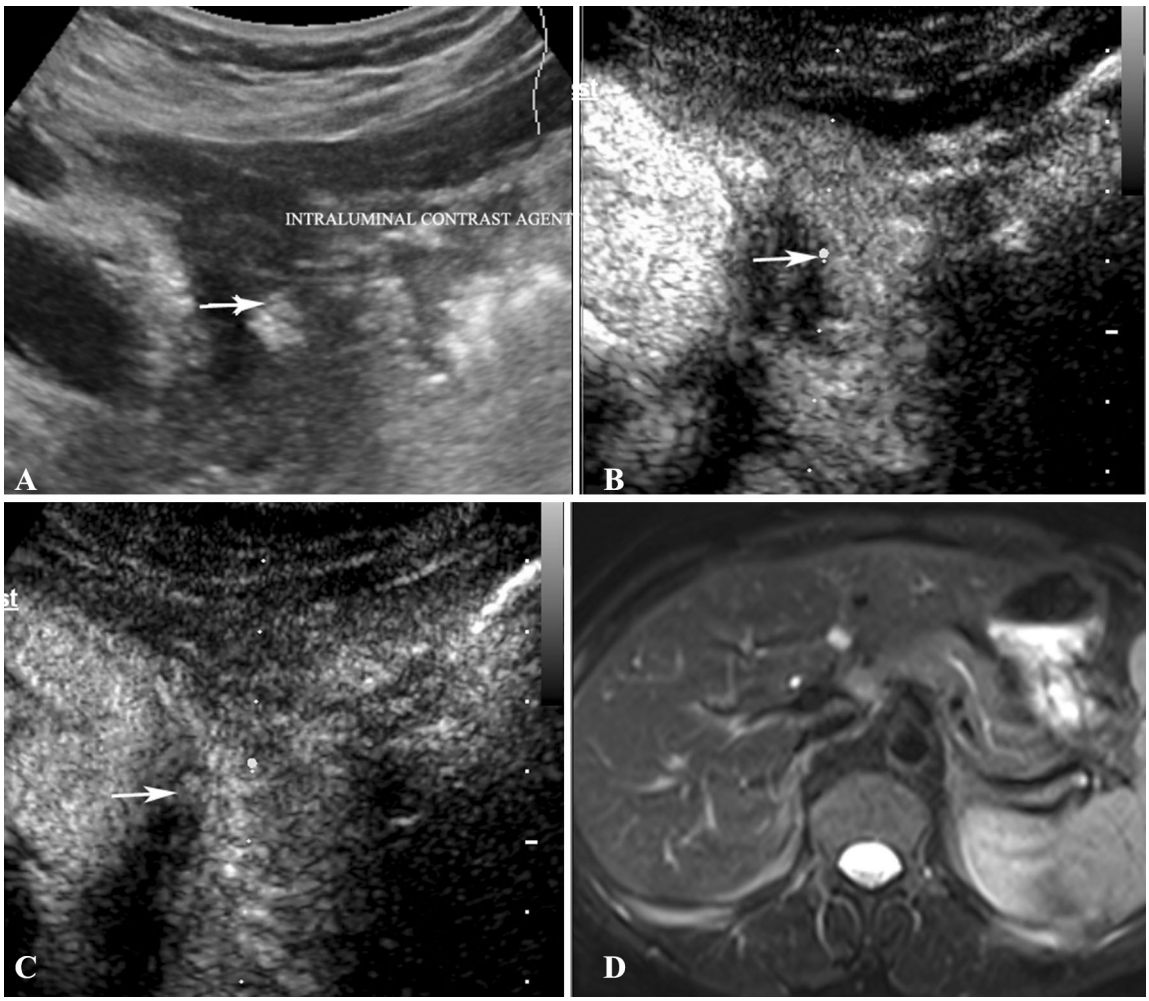

Fig. 2. Case 6. A 48-year-old man with clinical and laboratory test results showed hyperinsulinism. **A** DCEUS revealed a slightly strong echo signal indicative of a indeterminate nodule (arrows) at the pancreatic tail. DCEUS showed normal enhancement of the nodule compared with the surrounding pancreatic tissue. **B** T2-weighted MRI at the transverse plane showed that no mass was found.

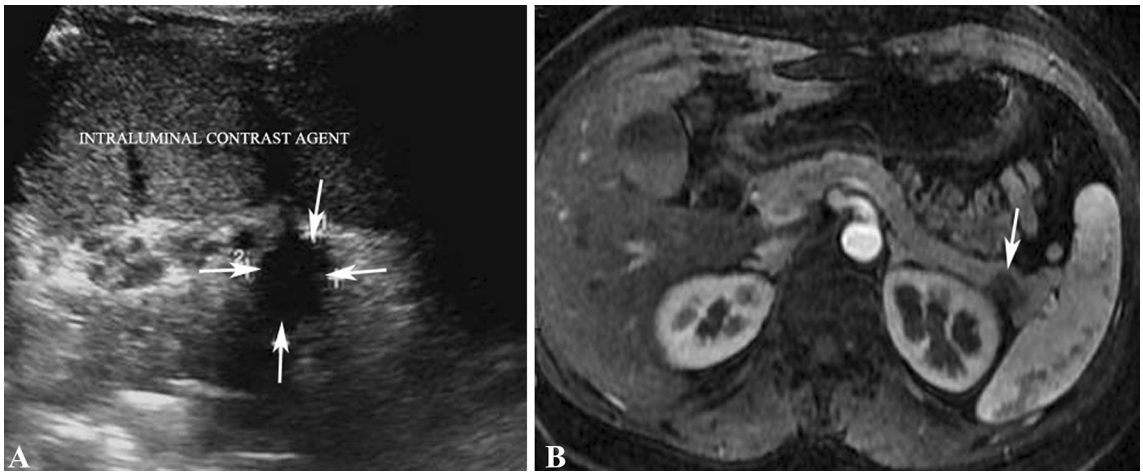

Fig. 3. Case 1. A 36-year-old woman with solid pseudopapillary tumor (arrows). **A** DCEUS demonstrated that a hypo-enhancement mass with a diameter of 2.1 cm was located in the pancreatic tail. **B** contrast-enhanced T2-weighted MRI showed that the mass was hypo-enhanced heterogeneously.

Table 2. Tumor enhancement and conspicuity on DCEUS and MRI

Tumor conspicuity							Tumor enhancement					
DCEUS				MRI			DCEUS			MRI		
Cases	Arterial phase	Venous phase	Late venous phase	Early arterial	Late arterial	Portal vein	Arterial phase	Venous phase	Late venous phase	Early arterial	Late arterial	Portal vein
1.	3	3	2	3	3	3	hypo-	hypo-	hypo-	hypo-	hypo-	hypo-
2.	3	3	3	3	2	2	hypo-	hypo-	hypo-	hypo-	hypo-	hypo-
3.	3	1	0	0	0	0	hyper-	iso-	iso-	/	/	/
4.	2	2	1	2	2	1	iso-	iso-	iso-	iso-	iso-	iso-
5.	3	3	3	3	3	3	hypo-	hypo-	hypo-	hypo-	hypo-	hypo-
6.	0	0	0	0	0	0	iso-	iso-	iso-	/	/	/
7.	2	3	2	3	3	3	hypo-	hypo-	hypo-	hypo-	hypo-	hypo-
8.	2	3	3	3	3	3	hypo-	hypo-	hypo-	hypo-	hypo-	hypo-
9.	3	3	2	3	3	3	hypo-	hypo-	hypo-	hypo-	hypo-	hypo-
10	2	3	3	3	3	3	hypo-	hypo-	hypo-	hypo-	hypo-	hypo-
11	3	3	2	2	3	3	hyper-	iso-	iso-	hyper-	hyper-	iso-
12	3	3	3	2	3	3	hyper-	iso-	iso-	hyper-	hyper-	iso-
13	2	3	3	2	3	3	iso-	hypo-	hypo-	iso-	hypo-	hypo-
Mean	2.3	2.5	2.1	2.3	2.4	2.3	/	/	/	/	/	/

DCEUS, double contrast-enhanced ultrasonography; MRI, magnetic resonance imaging; hypo-, hypointense; hyper-, hyperintense; iso-, isointense

Differences in phase onset times between DCEUS and MRI

Significant differences were noted in the timing of appearance of contrast medium between DCEUS and MRI. The DCEUS phases started much earlier than the corresponding MRI phases (Table 3).

Discussion

Occult pancreatic tail tumors, though uncommon, are clinically important because some of these tumors are highly malignant, for example, malignant islet cell tumors and adenocarcinoma [1, 2]. Preoperative determination of the location and number of pancreatic tail tumors can be very difficult in cases of extremely small tumors. The detection of occult pancreatic tail tumors is a formidable clinical challenge for any medical imaging modality [1, 3, 8, 9]. Such lesions are usually missed on both MRI and US, even with contrast enhancement, because they appear isointense with the pancreatic parenchyma. Moreover, these tumors generally do not alter the pancreatic contour and are difficult to distinguish from the gastric wall.

A large number of diagnostic procedures are available for the workup of patients with pancreatic tumors. No single "correct" approach exists; each modality has its strengths and weaknesses. Nonetheless, local expertise and interest and the availability of high-end technology will determine a "preferred" strategy for the workup of most patients [2, 8, 10–14]. Dynamic contrast-enhanced MRI is a common non-invasive preoperative radiologic technique used in the evaluation of pancreatic tail tumors

Table 3. Differences between DCEUS and MRI in the onset of contrast phases after administration of contrast agents

Cases	DCEUS, phase onset (s)			MRI, phase onset (s)		
	Arterial phase	Venous phase	Late venous phase	Early arterial	Late arterial	Portal vein
1.	10	32	130	15	40	65
2.	11	35	120	15	40	65
3.	10	32	121	15	40	65
4.	11	30	125	15	40	65
5.	12	35	127	15	40	65
6.	10	30	128	15	40	65
7.	14	35	129	15	40	65
8.	13	37	120	15	40	65
9.	15	37	120	15	40	65
10	11	30	120	15	40	65
11	15	38	120	15	40	65
12	17	39	120	15	40	65
13	10	30	120	15	40	65
Mean[a]	12.2 ± 2.4	33.8 ± 3.3	123.1 ± 4.1	15	40	65

[a]Mean ± SD

[10, 11, 15]. However, spatial misregistration related to different depths of breath-holds, leading to the non-detection of small peripancreatic occult nodes remains a limitation for MRI. This limitation may have contributed to the failure of MRI to detect the tumors in cases 3 and 6. Other reasons for missing islet cell tumors on MRI are obesity associated with irregular breathing that causes poor image quality, lack of patient cooperation; very small lesion, extensive fibrosis within the lesion, and ectopic lesion, such as lesions in the duodenal wall [16].

Recently, CEUS has been successfully applied in the imaging of pancreatic and other abdominal organ-specific diseases, because it allows real-time imaging during a single bolus administration of contrast material, which optimizes organ enhancement and lesion conspicuity [17–19]. Nonetheless, the use of CEUS in the evaluation of occult pancreatic tail tumors is limited by the presence of gas in the stomach and the pancreatic and stomach depths during breath-holds. Several authors [5, 6] have reported that the combination of luminal contrast and intravenous contrast improves the detection of gastrointestinal tumors because the luminal contrast can minimize the influence of gas. In this study, we evaluated the advantages of DCEUS over plain US and CEUS in the investigation of occult pancreatic tumors; these advantages include higher contrast resolution and higher sensitivity for contrast enhancement. The dominant factors for this diagnostic improvement were caused by both luminal contrast agents and intravenous contrast agent, which luminal contrast can reduce gas artifact significantly, and CEUS improved conspicuity of pancreatic tumor. From the practical point, gray scale and CEUS contributed equally to the detection of pancreatic tail tumor as CEUS can give more perfusion information for confident diagnosis and localization.

We found that the sensitivity of DCEUS for depicting occult pancreatic tail tumors is slightly higher than that of MRI (92% vs. 91%). DCEUS is likely to improve the detection rate of such occult tumors because this technique offers optimal depiction of pancreatic structures, without the influence of stomach gas and with improved tumor enhancement. We classified the DCEUS contrast phases as arterial, venous, and late venous phases according to the latest guideline of the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) because the pancreatic tail and portal vein (or inferior vena cava) are not simultaneously visualized on US images. CEUS is superior to Doppler US techniques for the visualization of intrapancreatic vessels [7]. Enhancement begins immediately after aortic enhancement, with an arterial phase (10–30 s), a venous phase (30 to approximately 120 s). With a pancreatic mass, the CEUS examination also aims to characterize and confirm peripancreatic vascular associations. The late venous phase begins about 120 s after the contrast injection and lasts for about 4 min [7].

We also found that the onset of US contrast phases was significantly earlier than that of the corresponding MRI phases. The later onset of MRI phases may be one of the reasons for the missed diagnoses in 2 cases. Islet cell tumors, which show early rapid enhancement, may not be visualized on MRI if the most significant early arterial phase contrast images are missed because of acquisition time delay. On the basis of our discussion with MRI specialists, we recommend that a specific image-acquisition setup is required for the MRI detection of small lesions of the pancreatic tail. Therefore, for the limitations of conventional standard MRI VIBE technology, perhaps in the future, we could employ methods to detect contrast arrival in aorta like care bolus technique or time-resolved sequences with three consecutive arterial phase in one breath-hold to better capture the real enhancement of the liver and pancreas. Meanwhile, there are several other limitations in our study such as, only a limited number of tumors of the pancreatic tail have been described. Although these tumors are relatively rare, it still might be difficult to extrapolate the results of this study to the entire population of these neoplasms. Meanwhile, most importantly, only tumors visible on US can be considered, which is not always the case for tumors of the pancreatic tail, even though they are examined with a dedicated approach. On the other hand, it also means that this DCEUS technology is highly skilled operator-dependent.

The superior DCEUS results in our study are based on the improved depiction of the pancreatic tail by the luminal contrast agent, which enables clearer imaging, better tumor conspicuity, and superior imaging of early microbubble enhancement. Our experience shows that CEUS with a luminal contrast agent and the patient in a semi-supine position is the best protocol for depicting small pancreatic tail tumors. In this protocol, the luminal contrast agent is expected to cover the entire pancreas, leading to higher lesion conspicuity.

Both luminal and intravenous contrast agents are used in DCEUS: the former clearly depicts small lesions of the pancreas tail, and the latter helps confirm the properties of lesions. Considering these advantages, we have concluded that DCEUS is a promising technique in the detection of occult pancreatic tail tumors and is possibly superior to dynamic enhanced MRI in the case of some peripheral lesions.

Compliance with ethical standards

Conflict of interest We declare no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Bipat S, Phoa SS, van Zeldan OM (2005) Ultrasonography, computed tomography, and magnetic resonance imaging for diagnosis and determining respectability of pancreatic adenocarcinoma: a meta-analysis. J Comput Assist Tomogr 29:438–445
2. Morgan KA, Adams DB (2010) Solid tumors of the body and tail of the pancreas. Surg Clin N Am 90:287–307
3. D'Onofrio M, Gallotti A, Pozzi Mucelli R (2010) Imaging techniques in pancreatic tumors. Expert Rev Med Devices 7(2):257–273
4. Rumack C, Wilson SR, Charboneau JW (1991) *Diagnostic ultrasound*. Maryland Heights: Mosby Inc, pp 145–177
5. Shiyan L, Pintong H, Zongmin W, et al (2009) The relationship between enhanced intensity and microvessel density of gastric carcinoma using double contrast- enhanced ultrasonography. Ultrasound Med Biol 35:1086–1091
6. Zhuang H, Yang ZG, Wang ZQ, et al (2012 Apr) Features of time-intensity curve parameters of colorectal adenocarcinomas evaluated by double-contrast enhanced ultrasonography: initial observation. Eur J Radiol 81(4):677–682
7. Sidhu PS, Cantisani V, Dietrich CF, et al (2018) The EFSUMB guidelines and recommendations for the clinical practice of contrast-enhanced ultrasound (CEUS) in non-hepatic applications: update 2017 (Long Version). Ultraschall Med. 39(2):e2–e44
8. Kalra MK, Maher MM, Mueller PR, Saini S (2003) State-of-the-art imaging of pancreatic neoplasms. Br J Radiol 76:857–865
9. Sahani DV, Shah ZK, Catalano OA, Boland GW, Brugge WR (2008) Radiology of pancreatic adenocarcinoma, current status of imaging. J Gastroenterol Hepatol 23:23–33
10. Kartalis N, Lindholm TL, Aspelin P, Permert J, Albiin N (2009) Diffusion-weighted magnetic resonance imaging of pancreas tumours. Eur Radiol 19(8):1981–1990
11. Cantisani V, Mortele KJ, Levy A, et al (2003) MR imaging features of solid-pseudopapillary tumor of the pancreas in adult and pediatric patients. AJR 181:395–401
12. Fletcher JG, Wiersema MJ, Farrell MA, et al (2003) Pancreatic malignancy, value of arterial, pancreatic, and hepatic phase imaging with multi-detector row CT. Radiology 229:81–90
13. Kitano M, Kudo M, Maekawa K, et al (2004) Dynamic imaging of pancreatic diseases by contrast enhanced coded phase inversion harmonic ultrasonography. Gut 53:854–859
14. Itoh T, Hirooka Y, Itoh A, et al (2005) Usefulness of contrast-enhanced transabdominal ultrasonography in the diagnosis of intraductal papillary mucinous tumors of the pancreas. Am J Gastroenterol 100:144–152
15. Owen NJ, Sohaib SA, Peppercorn PD, et al (2001) MRI of pancreatic neuroendocrine tumors. Br J Radiol 74:968–973
16. Thoeni RF, Mueller-lisse UG, Do NK, Shyn PB (2000) Dectection of small, fuctional islet cell tumors in the pancreas: selection of MR imaging sequences for optimal sensitivity. Radiology 214:483–490
17. D'Onofrio M, Zamboni G, Faccioli N, Capelli P, Pozzi Mucelli R (2007) Ultrasonography of the pancreas. 4. Contrast-enhanced imaging. Abdom Imaging 32:171–181
18. Zhou Xiang, Liu Ji-Bin, Luo Yan, et al (2010) Characterization of focal liver lesions by means of assessment of hepatic transit time with contrast-enhanced US. Radiology 256:648–655
19. Zhou Xiang, Luo Yan, Peng Yu-Lan, et al (2011) Contrast-enhanced ultrasound feature of hepatic perfusion disorder related to focal liver lesions: a correlation study with contrast-enhanced CT. Radiology 260:274–281