**Name of journal:** ***World Journal of Gastroenterology***

**Manuscript NO: 37455**

**Manuscript Type: ORIGINAL ARTICLE**

***Clinical Practice Study***

**value of contrast enhanced ultrasound in the differential diagnosis of gallbladder lesion**

Zhang HP *et al.* CEUS for gallbladder lesions

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**Author contributions:** Zhang HP and Du LF design the research; Bai M, Gu JY and He YQ performed the research; Qiao XH analyzed the data; Zhang HP wrote the paper.

**Supported by** the National Natural Science Foundation of China, No. 81301232.

**Institutional review board statement:** This study was reviewed and approved by the Ethics Committee of Shanghai General Hospital (No. 2013-094).

**Informed consent statement:** All study participants provided written informed consent prior to study enrollment.

**Conflict-of-interest statement:** None of the authors have any conflict of interest disclosures to make.

**Data sharing statement:** No additional data are available.

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**Manuscript source:** Unsolicited manuscript

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**Telephone:** +86-21-63240090

**Received:** December 8, 2017

**Peer-review started:** December 8, 2017

**First decision:** December 21, 2017

**Revised:** January 3, 2018

**Accepted:** January 16, 2018

**Article in press:**

**Published online:**

**Abstract**

***AIM***

To describe contrast enhanced ultrasound (CEUS) features and evaluate differential diagnosis value of CEUS and conventional ultrasound for patients with benign and malignant gallbladder lesions.

***METHODS***

This study included 105 gallbladder lesions. Before surgical resection and pathological examination, conventional ultrasound and CEUS examined for the lesions. Then all the lesions diagnosed as (1) benign, (2) probably benign, (3) probably malignant or (4) malignant using both conventional ultrasound and CEUS. The CEUS features of these gallbladder lesions were analyzed and diagnostic efficiency between conventional ultrasound and CEUS was compared.

***RESULTS***

There were total 17 cases of gallbladder cancer and 88 cases of benign lesion. Some gallbladder lesions had typical characteristics on CEUS (*e.g.*, Gallbladder adenomyomatosis had typical characteristics of small non-enhanced areas on CEUS). The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of CEUS were 94.1%, 95.5%, 80.0%, 98.8% and 95.2%, respectively. These were significantly higher than conventional ultrasound (82.4%, 89.8%, 60.9%, 96.3% and 88.6%, respectively). CEUS had an accuracy of 100% for gallbladder sludge and CEUS help the differential diagnosis among gallbladder polypus, gallbladder adenoma and gallbladder cancer.

***CONCLUSION***

CEUS may provide useful information and improve the diagnosis efficiency for the diagnosis of gallbladder lesions than conventional ultrasound.

**Key words:** Contrast enhanced ultrasound; Conventional ultrasound; Gallbladder carcinoma; Gallbladder adenomyomatosis

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**Core tip:** With the advent of ultrasound contrast agents, contrast enhanced ultrasound (CEUS) is playing a more and more important role clinically. However, the value of CEUS in gallbladder lesions was not widely accepted yet. In this study, we evaluated differential diagnosis value of CEUS and conventional ultrasound for patients with benign and malignant gallbladder lesions. Our results showed that CEUS may provide useful information and improve the diagnosis efficiency for the diagnosis of gallbladder lesions than conventional ultrasound.

Zhang HP, Bai M, Gu JY, He YQ, Qiao XH, Du LF. value of contrast enhanced ultrasound in the differential diagnosis of gallbladder lesion. *World J Gastroenterol* 2018; In press

**INTRODUCTION**

Conventional ultrasound is the primary and the most important imaging modality of gallbladder diseases. The excellent image contrast between anechoic bile and gallbladder wall or gallbladder diseases and the increasingly improved ultrasound spatial resolution ensure conventional ultrasound of high detection rate of gallbladder diseases[1]. With the advantages of real-time imaging, safety with no radiation, great cost-effectiveness and great spatial resolution, conventional ultrasound makes itself more suitable than computed tomography (CT) and magnetic resonance imaging (MRI) for the detection of gallbladder diseases[2].

Despite of the above-mentioned advantages of conventional ultrasound, the sensitivity and the accuracy are not satisfied, especially when stones or some other gallbladder lesions fill the gallbladder lumen[3,4]. With no information of micro-vascularity, it is very hard to differentiate some benign diseases, such as benign gallbladder wall thicken or motionless sludge from malignant ones using conventional ultrasound. The application of microbubbles could help the differential diagnosis by providing useful perfusion information in the lesions[5].

Contrast enhanced ultrasound (CEUS) has been widely used in liver disease, with an excellent diagnostic efficiency comparable with contrast enhanced computed tomography[6-8]. The value of CEUS in other organs, such as kidney, breast, *et al.*, has also been well established and identified[9,10]. Although the value in gallbladder has not been recognized and accepted by European Federation of Societies for Ultrasound in Medicine and Biology[11], there were some studies which showed the usefulness of CEUS in the differential diagnosis between benign and malignant gallbladder lesions[5,12].

In this study, we described contrast enhanced ultrasound (CEUS) features and evaluated differential diagnosis value of CEUS and conventional ultrasound for patients with benign and malignant gallbladder lesions.

**MATERIALS AND METHODS**

***Study design***

The Ethics Committee of our hospital approved this study. Before the sonographic examination, we obtained all patients’ Written Informed Consent. The features of gallbladder lesions in CEUS were analyzed and described retrospectively. The study and comparison of the diagnostic efficiency between CEUS and conventional ultrasound was designed prospectively.

***Patients***

Between December 2012 and October 2016, 136 gallbladder lesions in 133 patients were imaged using both conventional ultrasound and CEUS in our hospital. Of these, 31 lesions were excluded in this study because the patients did not undergo cholecystectomy and were without pathological diagnosis. Therefore, 105 gallbladder lesions in 103 patients (47 male and 56 female, mean age ± standard deviation, 42.5 ± 10.6 years) were included in this study.

***Conventional ultrasound and CEUS***

All the conventional ultrasound and CEUS examinations were performed by an ultrasound physician with 13 years’ experience in conventional ultrasound and 5 years’ experience in CEUS. An Acuson S2000 diagnostic ultrasound system or an Acuson Sequoia 512 diagnostic ultrasound system (Siemens Medical Solutions, Mountain View, United States) which equipped with a transabdominal curvilinear transducer running on CadenceTM Contrast pulse sequence (CPS) software were used for all the ultrasound examinations. All the patients fasted at least for 8 h before the examinations.

Conventional ultrasound examinations went first to detect the gallbladder lesions. A lesion’s size, location, shape, stalk, boundary, echogenicity and wall destruction was analyzed and recorded. Then Doppler vascularity was observed using color Doppler ultrasound. A diagnosis of benign, probably benign, probably malignant or malignant was made according to conventional ultrasound features by two radiologists with at least 10 years’ experience in both conventional ultrasound and CEUS. If they had different diagnosis, a third radiologist (with 25 years’ experience in conventional ultrasound and 12 years’ experience in CEUS) discussed together with them and got a final diagnosis.

For CEUS examinations, the same ultrasound machines were used. SonoVue (Bracco, Italy), the only microbubbles permitted for clinical use in China, was used in this study and was prepared following the appropriate guidelines before examinations. Every patient was instructed to take gentle and steady breaths to minimize the influence by respiratory movement. When the target lesion was shown clearly using conventional ultrasound, the CPS mode (MI: 0.21) was activated. A dose of 1.6 mL of SonoVue was administrated through the antecubital vein as a bolus immediately followed by 5 mL 0.9% saline solution. A stopwatch was started at the same time. The image was observed and recorded for 2 min and then the whole gallbladder and the liver were scanned to find out other lesions and liver infiltration. After that, CEUS features of the lesion were analyzed and a diagnosis of benign, probably benign, probably malignant or malignant was made according to CEUS features by the above-mentioned radiologists.

After the resection of gallbladder lesions and the final pathological diagnosis was made, CEUS images were reviewed and the features of each kind of gallbladder lesions in CEUS were analyzed and summarized.

***Statistical analysis***

SPSS version 13.0 software (IBM Corporation, Chicago, IL, United States) was used for statistical analysis. *P* < 0.05 was considered statistically significant difference. The diagnostic efficiency of conventional ultrasound and CEUS was assessed in terms of sensitivity, specificity, positive predictive value, negative predictive value and accuracy and was compared using Chi-square test and the Fisher’s exact test.

**RESULTS**

***Pathological results***

There were 17 malignant and 88 benign gallbladder lesions in total in this study according to the histopathological diagnosis after cholecystectomy, including 17 cases of gallbladder cancer, 11 case of gallbladder sludge, 28 cases of gallbladder adenomyomatosis, 36 cases of gallbladder polypus and 13 cases of gallbladder adenoma.

***Sonographic features on CEUS***

All the cases of gallbladder sludge were shown as completely non-enhanced on CEUS and the diagnostic accuracy was 100% (Figure 1).

Gallbladder adenomyomatosis was mostly shown as heterogeneously enhanced with some small non-enhanced areas (represented as Rokitansky-Aschoff sinuses) on both arterial phase and venous phase (Figure 2). Some of them were together with echogenic foci and tail sign.

Gallbladder polypus and gallbladder adenoma were mostly shown as homogeneously hyper-enhanced on arterial phase and iso-enhanced on venous phase. The gallbladder wall was intact and the surrounding tissue was normal with no invasion (Figure 3).

The appearances of gallbladder cancer on CEUS were various. It could be a mass in gallbladder which was heterogeneously hyper-enhanced on arterial phase and washed out quickly (shown in Figure 4). Or the irregular thickness of gallbladder which was also heterogeneously hyper-enhanced on arterial phase and washed out quickly could be a sign of malignancy. In some cases, the intact of gallbladder wall was destructive. Or the surrounding liver tissue was invaded.

Besides providing micro-vascular information, CEUS makes the contour of a lesion much clearer and the evaluation of a lesion’s shape, size and boundary much more accurate.

***Diagnostic efficiency of conventional ultrasound***

The diagnostic results of conventional ultrasound were showed in Table 1. There were 3 malignant lesions misdiagnosed as probably benign and 5 diagnosed as probably malignant. There were 8 benign lesions (2 case of sludge, 3 cases of adenomyomatosis, 2 cases of polypus and 1 cases of gallbladder adenoma) misdiagnosed as probably malignant and one benign lesion misdiagnosed as definitely malignant (one case of adenoma). Eighteen benign lesions (3 cases of sludge, 5 cases of adenomyomatosis, 5 cases of polypus and 5 cases of gallbladder adenoma) were diagnosed as probably benign.

The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of conventional ultrasound were shown in Table 2.

***Diagnostic efficiency of CEUS***

The diagnostic results of CEUS were showed in Table 3. Two malignant lesions which were misdiagnosed as probably benign by conventional ultrasound were correctly diagnosed as probably malignant by CEUS; and one malignant lesion which was diagnosed as probably malignant by conventional ultrasound was conformed as malignant by CEUS. For benign lesions, all the cases of sludge were confirmed as benign. All cases of adenomyomatosis but 3 (1 diagnosed as probably malignant and 2 as probably benign) and all cases of polypus but 3 (1 diagnosed as probably malignant and 2 as probably benign) were confirmed as benign. Two cases of adenoma were misdiagnosed as probably malignant and another two cases of adenoma were diagnosed as probably benign; the rest 9 cases of adenoma were confirmed as benign.

The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of CEUS were shown in Table 2. The diagnostic efficiencies of CEUS were all significantly higher than those of conventional ultrasound, though the differences were not statistically significant.

**DISCUSSION**

In this study, we compared the value of CEUS in the differential diagnosis of benign and malignant gallbladder lesions with conventional ultrasound. Our results showed that the diagnostic efficiencies of CEUS were much higher than those of conventional ultrasound, though the differences were not statistically significant. With all the advantages and information of conventional ultrasound, CEUS provides more information about the important micro-vascularity in lesions. Also, with the application of microbubbles, the contour, the boundary and the shape of a lesion, the intactness of gallbladder wall and the invasion of the surrounding tissue could be revealed more clearly. So the diagnostic efficiencies were highly improved, though the differences between the diagnostic efficiencies were not statistically significant.

Although the clinical significance of gallbladder sludge has not been confirmed yet, the accurate diagnosis is still of importance to avoid unnecessary examination and treatment[13]. Gallbladder sludge is usually shown on ultrasound as movable, echogenic matter which could be easily diagnosed. However, sometimes gallbladder sludge could be shown as an intraluminal mass and imitates tumors such as gallbladder cancer or adenoma[14]. Then the differential diagnosis is very difficult using conventional ultrasound. CEUS is very useful at this time. As sludge has no blood supply inside it, it shows a complete non-enhancement on both arterial phase and venous phase. The diagnostic accuracy was 100% in our study and the result was similar with some previous studies[11,15].

Gallbladder adenomyomatosis is a non-infectious and non-tumorous disease of gallbladder which is usually found accidentally, with no malignant potential and needs no specific treatment[16]. It has some typical characteristics on CEUS too. With the small non-enhanced areas on arterial phase and venous phase (represented as Rokitansky-Aschoff sinuses), together with echogenic foci and tail sign or not, the correct diagnosis would be easily made[17,18]. The study of Tang *et al*[17] showed that small anechoic spaces or intramural echogenic foci were 100% detected using CEUS, which made the diagnostic accuracy much higher than conventional ultrasound. In this study, besides one case with no small anechoic spaces was misdiagnosed as probably malignant, the rest cases were all diagnosed correctly as gallbladder adenomyomatosis.

The differential diagnosis among gallbladder polypus, gallbladder adenoma and gallbladder cancer was not easy on CEUS. However, some studies showed that some CEUS features were useful and significant for differentiating malignancy from benignity. The study of Xu JM showed that focal gallbladder wall thickening, inner layer discontinuity and outer layer discontinuity were associated with gallbladder malignancy[19]. Branched or linear intralesional vessels, tortuous-type tumor vessel, enhanced heterogeneously in the artery phase and washed-out quickly in the late phase were usually considered as signs for malignancy[20-22]. On the contrary, gallbladder polypus or gallbladder adenoma was usually enhanced homogenously and the microbubbles inside the lesions washed out together with normal gallbladder wall. Recently, the study of the differential diagnosis of localized gallbladder lesions using contrast-enhanced harmonic endoscopic ultrasonography also confirmed the value of CEUS for the evaluation and differentiation of localized gallbladder lesions[23]. Although CEUS provides the micro-vascular information, conventional ultrasound is still very important and is the foundation of CEUS. The size, shape and boundary of a lesion, the intactness of gallbladder wall and the invasion of surrounding tissue are very important for the differential diagnosis. Besides providing micro-vascular information, CEUS makes the contour of a lesion much clearer and the evaluation of a lesion’s shape, size and boundary much more accurate. That is an important reason for the improvement of CEUS diagnostic efficiency, compared with conventional ultrasound.

Our study has some limitations. First, the sample was not large enough, especially for the malignant lesions. The pathological types of the lesions were not enough, either. For example, all the gallbladder adenomyomatosis in our study were localized type and no segmental and diffuse types were included. And there were only a few early-stage cancers in this study and this made it hard to compare the difference between benign lesions and early-stage cancers on CEUS. Second, the CEUS features weren’t analyzed using quantitative analysis software, but by naked eyes. No quantitative parameters were acquired and analyzed. Furthermore, the interobserver agreement in CEUS and conventional ultrasound was not compared in this study.

In conclusion, gallbladder sludge and gallbladder adenomyomatosis had special features on CEUS and the diagnostic accuracy was really high. CEUS helped the differential diagnosis among gallbladder polypus, gallbladder adenoma and gallbladder cancer. The diagnostic efficiency of CEUS was highly improved compared with conventional ultrasound.

**ARTICLE HIGHLIGHTS**

***Research background***

With the advent of ultrasound contrast agents, contrast enhanced ultrasound (CEUS) is playing a more and more important role clinically. CEUS is a safe, convenient and repeatable imaging method with no risk of serious allergy and radiation. CEUS has an excellent diagnostic efficiency for hepatic focal lesions, which is comparable with contrast-enhanced computed tomography (CT). However, the value of CEUS in gallbladder lesions was not widely accepted yet.

***Research motivation***

European Federation of Societies for Ultrasound in Medicine and Biology guidelines 2011 did not recognize the value of CEUS for the differential diagnosis of gallbladder lesions. However, there were still some studies published which showed the usefulness of CEUS in the differential diagnosis between benign and malignant gallbladder diseases. So, the value of CEUS for gallbladder is still unclear.

***Research objectives***

We aim to describe CEUS features and evaluate differential diagnosis value of CEUS and conventional ultrasound for patients with benign and malignant gallbladder lesions.

***Research methods***

This study included 105 gallbladder lesions which were examined using the conventional ultrasound and CEUS before surgical resection and pathological examination in our hospital between December 2012 and October 2016. Each lesions was diagnosed as (1) benign, (2) probably benign, (3) probably malignant or (4) malignant using both conventional ultrasound and CEUS by two radiologists with at least 10 years’ experience in both conventional ultrasound and CEUS. CEUS features of these gallbladder lesions were analyzed. Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of conventional ultrasound and CEUS was calculated and compared.

***Research results***

Gallbladder sludge was completely non-enhanced on CEUS. Gallbladder adenomyomatosis had typical characteristics of small non-enhanced areas on CEUS, together with echogenic foci and tail sign sometimes. Gallbladder cancer on CEUS was usually heterogeneously hyper-enhanced on arterial phase and washed out quickly. Besides providing micro-vascular information, CEUS makes the contour of a lesion much clearer and the evaluation of a lesion’s shape, size and boundary much more accurate.

The sensitivity, specificity, positive predictive value, negative predictive value and accuracy of CEUS were 94.1%, 95.5%, 80.0%, 98.8% and 95.2%, respectively, these were significantly higher than conventional ultrasound (82.4%, 89.8%, 60.9%, 96.3% and 88.6%, respectively).

***Research conclusions***

CEUS helped the differential diagnosis between among different kinds of gallbladder lesions. The diagnostic efficiency of CEUS was highly improved compared with conventional ultrasound.

According to our results, for a gallbladder lesion, when a definite diagnosis could not be made using conventional ultrasound, CEUS examination could be used as a further diagnostic method.

***Research perspectives***

In this study, we proved the value of CEUS for gallbladder lesions. Prospective study with large numbers of patients and different kinds of gallbladder lesions will be needed to confirm the results. The application of endoscopic CEUS may provide more useful information for differentiating between benign and malignant gallbladder lesions.

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**P-Reviewer:** Parakkal D, Shentova R **S-Editor:** Gong ZM

**L-Editor: E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** China

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**Table 1 The diagnostic results of conventional ultrasound *n* (%)**

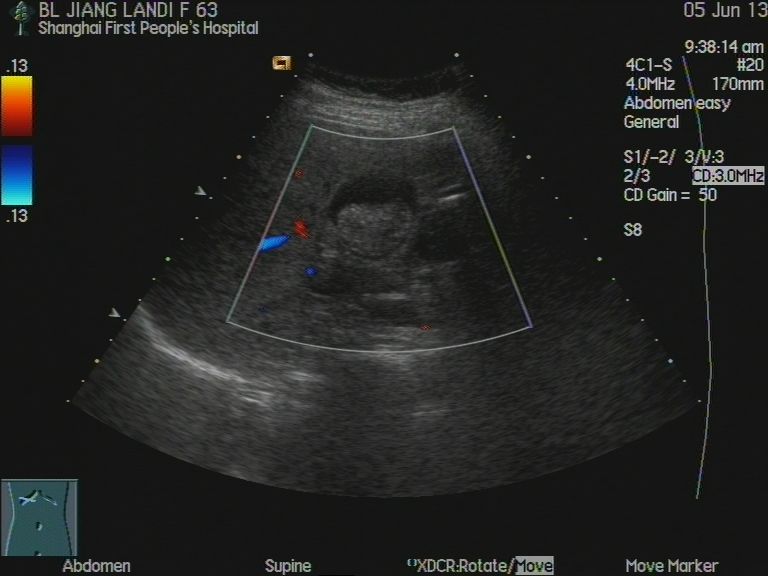
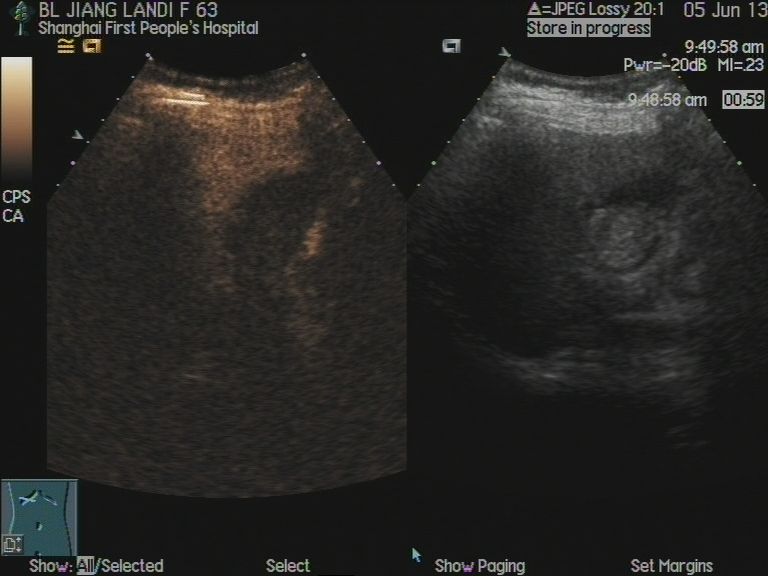
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **definitely benign** | **probably benign** | | **probably malignant** | **definitely malignant)** |
| Benign (*n* = 88) | 61 (69.3) | | 18 (20.5) | 8 (9.1) | 1 (1.1) |
| Malignant (*n* = 17) | 0 (0) | | 3 (17.6) | 5 (29.4) | 9 (52.9) |

**Table 2 Diagnostic efficiency of conventional ultrasound and contrast enhanced ultrasound between benign and malignant gallbladder lesions**

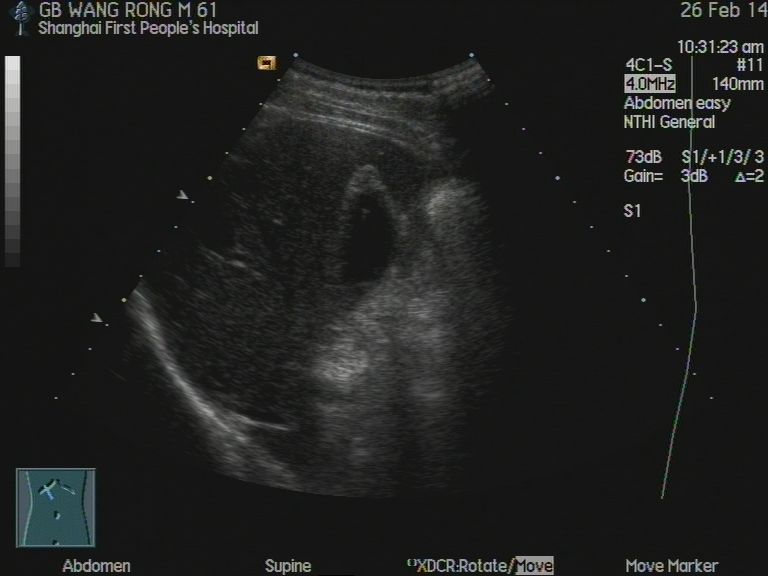
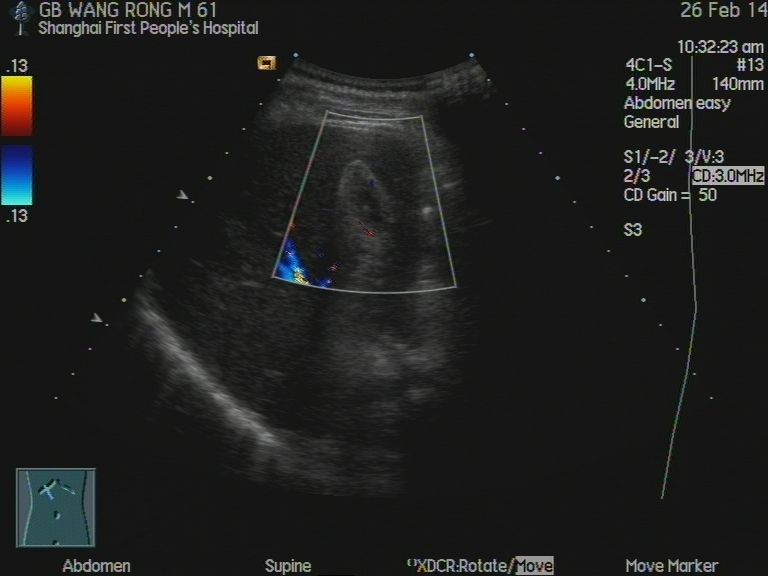
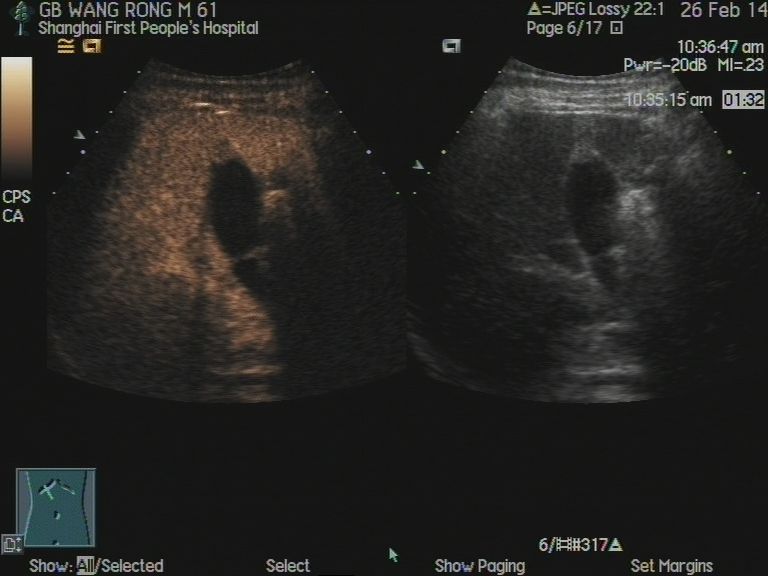
|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Features of lesions** | **Sensitivity (%)** | **Specificity (%)** | **Positive predictive value (%)** | **Negative predictive value (%)** | **Accuracy (%)** |
| Conventional ultrasound | 82.4 | 89.8 | 60.9 | 96.3 | 88.6 |
| Contrast enhanced ultrasound | 94.1 | 95.5 | 80.0 | 98.8 | 95.2 |
| *P* value | 0.301 | 0.124 | 0.152 | 0.297 | 0.064 |

**Table 3 The diagnostic results of contrast enhanced ultrasound *n* (%)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **definitely benign** | **probably benign** | **probably malignant** | **definitely malignant** |
| Benign (*n* = 88) | 78 (88.6) | 6 (6.8) | 4 (4.5) | 0 (0) |
| Malignant (*n* = 17) | 0 (0) | 1 (5.9) | 6 (35.3) | 10 (58.8) |

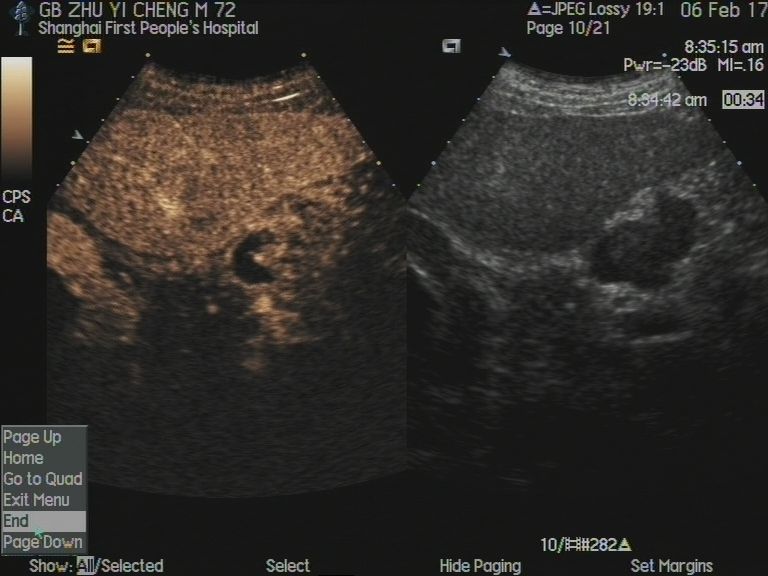
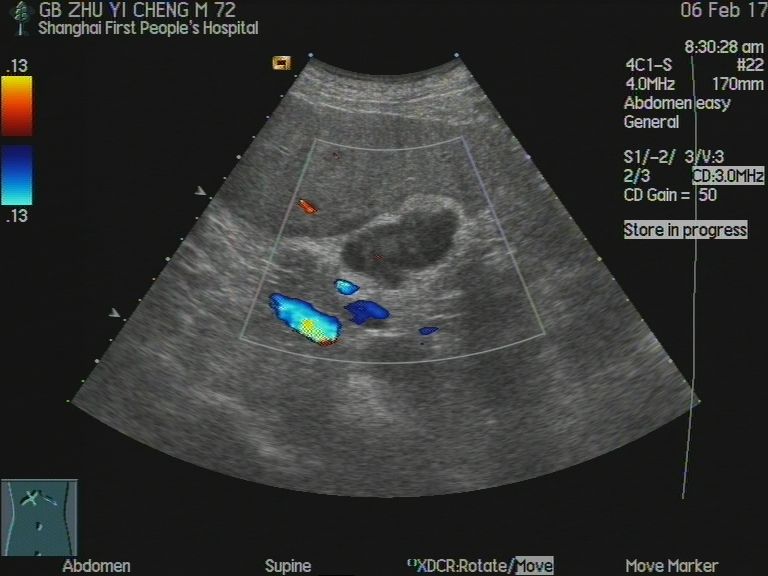
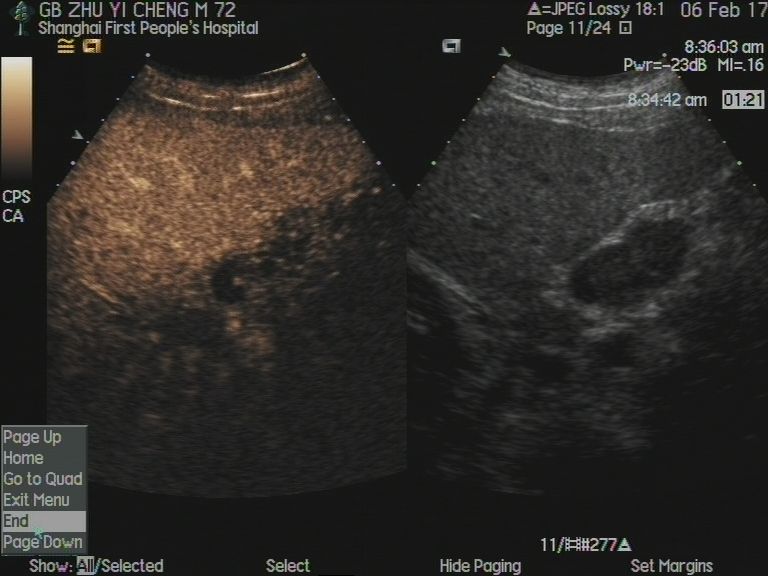
**Figure 1 Gallbladder sludge in a 54-year-old female patient.** A: B-mode sonography showed a hypoechoic, well-defined mass in the gallbladder with an intact gallbladder wall; B: Color Doppler ultrasound showed no color Doppler signal in the lesion. According to A and B, a diagnosis of probably benign was made; C: CEUS showed completely non-enhanced on arterial phase; D: CEUS showed completely non-enhanced on venous phase. According to C and D, a diagnosis of benign as gallbladder sludge was made.

**Figure 2 Gallbladder adenomyomatosis in a 62-year-old male patient.** A: B-mode sonography showed a heterogeneously hypoechoic lesion on the gallbladder wall with an intact gallbladder wall; B: Color Doppler ultrasound showed no color Doppler signal in the lesion. According to A and B, a diagnosis of probably benign was made. C: CEUS showed heterogeneously enhanced with some small non-enhanced areas on arterial phase; D: CEUS showed heterogeneously enhanced with some small non-enhanced areas on venous phase. According to C and D, a diagnosis of benign as gallbladder adenomyomatosis was made.

**Figure 3 Gallbladder polypus in a 38-year-old male patient.** A: B-mode sonography showed a homogeneously ioechoic lesion in the gallbladder with an intact gallbladder wall; B: Color Doppler ultrasound showed no color Doppler signal in the lesion. According to A and B, a diagnosis of probably benign was made. C: CEUS showed a homogeneous and a little hyper-enhanced lesion in the gallbladder on arterial phase; D: CEUS showed the enhancement of the lesion is similar to the surrounding gallbladder wall on venous phase. According to C and D, a diagnosis of benign lesion was made.

**Figure 4 Gallbladder cancer in a 46-year-old male patient.** A: B-mode sonography showed a heterogeneously hypoechoic mass in the gallbladder and the posterior wall of the gallbladder was not very clear; B: Color Doppler ultrasound showed no color Doppler signal in the lesion. According to A and B, a diagnosis of probably malignant was made. C: CEUS showed a heterogeneously hyper-enhanced mass with tortuous-type tumor vessel on arterial phase and the boundary of the mass was not clear; D: CEUS showed the enhancement of the lesion is much lower than that of the surrounding gallbladder wall on venous phase. According to C and D, a diagnosis of malignant mass was made.