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● *Original Contribution*

**DIFFERENTIAL DIAGNOSIS OF GALLBLADDER WALL THICKENING:
 THE USEFULNESS OF CONTRAST-ENHANCED ULTRASOUND**

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Abstract—The purpose of this study was to evaluate the usefulness of contrast-enhanced ultrasound (CEUS) in the differential diagnosis of gallbladder wall (GBW) thickening and determine the predictors of malignant GBW thickening. One hundred fifty-nine patients with GBW thickening, including 76 men and 83 women, from eight institutions were enrolled. CEUS was performed after injection of a sulfur hexafluoride microbubble-based ultrasound contrast agent. Multiple logistic regression analysis was used to reveal independent predictors associated with malignant GBW thickening. The final diagnoses were 48 gallbladder carcinomas and 111 benign gallbladder diseases. Maximal thicknesses of the GBW in malignant and benign GBW thickening were 17.3 ± 5.2 (6–30) mm and 8.6 ± 5.1 (4–26) mm respectively ($p < 0.001$). CEUS revealed significant differences in intralésional vessels, enhancement homogeneity, time to hypo-enhancement, inner layer discontinuity, outer layer discontinuity and adjacent liver involvement (all p -values < 0.05) between malignant and benign GBW thickening. Patient age > 46.5 y, focal GBW thickening, inner layer discontinuity and outer layer discontinuity were found to be associated with malignancy by multiple logistic regression analysis (all p -values < 0.05). Receiver operating characteristic curve analysis revealed Az values for patient age, focal GBW thickening, inner wall discontinuity and outer wall discontinuity of 0.709 (95% confidence interval [CI]: 0.627–0.790), 0.714 (95% CI: 0.630–0.798), 0.860 (95% CI: 0.791–0.928) and 0.858 (95% CI: 0.783–0.933), respectively. CEUS is useful in the differential diagnosis between malignant and benign GBW thickening. Focal GBW thickening, inner wall discontinuity and outer wall discontinuity observed on CEUS are diagnostic clues for malignant GBW thickening. (E-mail: xuhuixiong@hotmail.com) © 2014 World Federation for Ultrasound in Medicine & Biology.

Key Words: Gallbladder, Wall thickening, Contrast-enhanced ultrasound, Differential diagnosis, Chronic cholecystitis, Gallbladder carcinoma.

INTRODUCTION

Gallbladder wall (GBW) thickening is a frequently detected finding on ultrasound (US) in the daily clinical practice of abdominal imaging examination (Joo et al. 2013; Kim et al. 2012; Yoshimitsu et al. 2001). Differentiation between commonly observed causes of

GBW thickening such as chronic cholecystitis, acute cholecystitis, adenomyomatosis and GB carcinoma is difficult with conventional US (Joo et al. 2013; Kim et al. 2012; Wibbenmeyer et al. 1995; Yoshimitsu et al. 2001). The survival rates for patients with GB cancer remain dismal; thus, diagnosis at an early stage has important implications in selecting the appropriate surgical method and improving the long-term prognosis (Kapoor et al. 2011; Wibbenmeyer et al. 1995). In the early stage, 30% to 40% of GB carcinomas present as wall thickening. Unfortunately, GB carcinoma is sometimes diagnosed at an advanced stage, after tumors

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Table 1. Patient characteristics and conventional US features of the 159 patients with GBW thickening

| | Malignant (n = 48) | Benign (n = 111) | p-value |
|--|--------------------|---------------------|---------|
| Patient characteristics | | | |
| Age (y) | 63.0 ± 9.6 (28–78) | 52.4 ± 14.6 (24–78) | <0.001* |
| Gender (male/female) | 22/26 | 54/57 | 0.746 |
| GBW thickness (mm) | 17.3 ± 5.2 (6–30) | 8.6 ± 5.1 (4–26) | <0.001* |
| 4–10 mm | 5 | 77 | <0.001* |
| 11–20 mm | 30 | 32 | |
| >20 mm | 13 | 2 | |
| GBW thickening morphology | | | |
| Diffuse thickening | 8 | 66 | <0.001* |
| Focal thickening | 40 | 45 | |
| GBW thickening location | | | |
| Total | 9 | 65 | <0.001* |
| Bottom | 12 | 18 | |
| Body | 16 | 23 | |
| Neck | 11 | 5 | |
| GBW echogenicity | | | |
| Hyper-echogenic | 4 | 46 | <0.001* |
| Iso-echogenic | 26 | 40 | |
| Hypo-echogenic | 18 | 15 | |
| Mixed | 0 | 10 | |
| Intramural cystic spaces (yes/no) | 0/48 | 12/99 | 0.018* |
| Intramural echogenic foci (yes/no) | 0/48 | 10/101 | 0.032 |
| Intralesional color Doppler signals | | | |
| None | 2 | 39 | <0.001* |
| Scarce | 28 | 57 | |
| Abundant | 18 | 15 | |
| Involvement of adjacent liver (present/absent) | 28/20 | 23/88 | <0.001* |
| Coexisting gallstones (present/absent) | 13/35 | 37/74 | 0.439 |

GBW = gallbladder wall.

* Statistically significant difference.

have invaded adjacent organs. Approximately 15%–30% of patients manifest no pre-operative or intra-operative evidence of malignancy and are not diagnosed until the typical histologic appearance is identified on post-operative microscopic evaluation (Contini et al. 1999).

Although transabdominal US and computed tomography (CT) are widely used, these imaging modalities may not yield a precise pre-operative assessment of the nature of GBW thickening (Chun et al. 1997; Yoshimitsu et al. 2001). Therefore, new US techniques such as 3-D US, high-frequency US, endoscopic US and contrast-enhanced US (CEUS), have been employed with the aim of improving diagnosis (Liu et al. 2012; Xie et al. 2010; Xu et al. 2003; Zheng et al. 2013). Among them, increasing attention has been paid to CEUS, which can reveal the macro- and microcirculation of GB lesions, thus providing additional diagnostic information in comparison with conventional US, and may in turn facilitate the diagnosis of GB diseases (Adamietz et al. 2007; Inoue et al. 2007; Liu et al. 2012; Meacock et al. 2010; Piscaglia et al. 2012; Sparchez and Radu 2012; Tsuji et al. 2012; Xie et al. 2010; Zheng et al. 2013). However, until now, no reports have been published to evaluate the usefulness of CEUS in the differentiation diagnosis between malignant and benign GBW thickening. The aim of this

study was to evaluate the diagnostic performance of CEUS in diagnosing GBW thickening prospectively.

METHODS

Patients

This study received approvals from the institutional ethics committees of the eight university hospitals. All patients gave written informed consent after the procedure had been carefully explained to them. The clinical investigation was conducted according to the principles expressed in the Declaration of Helsinki. Between January 2007 and December 2013, we prospectively examined, with CEUS, patients referred to eight university hospitals with GBW thickening identified on conventional US and scheduled for surgery by the clinicians. The inclusion criteria were as follows: (i) GBW thickness ≥ 4 mm at conventional US; (ii) willingness to participate in the study and undergo CEUS examination; (iii) confirmation of diagnoses by pathologic examination after surgical excision or typical clinical and imaging results. Exclusion criteria included recent coronary syndrome or unstable angina, pregnancy or lactation, age < 18 y or > 80 y and inability to retrieve imaging data. Finally, a total of 201 patients met the inclusion criteria. Among the 201 there were 22 patients with recent unstable

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