Original Article

Utility of Contrast-Enhanced Ultrasound in Differentiation between Benign Mural Lesions and Adenocarcinoma of Gallbladder

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Abstract

Background: Mural lesions of gallbladder on ultrasound (US) are often difficult to characterize as benign or malignant. **Purpose:** The aim of the study was to evaluate the role of contrast-enhanced US (CEUS) in characterization of gallbladder (GB) wall lesions and making distinction between benign wall thickening and GB adenocarcinoma, utilizing both quantitative and qualitative parameters. **Methods:** A total of 26 patients with GB wall lesions detected on sonography underwent CEUS. Lesions were evaluated on the basis of morphological imaging features, enhancement pattern, dynamic real-time contrast uptake, and intralesional vascularity. **Results:** Overall, 19 patients had final diagnosis of GB adenocarcinoma, whereas seven patients had benign etiology. CEUS has enabled the differentiation of nonenhancing tumefactive sludge from enhancing mural lesions, thus improving the accuracy of morphological assessment of lesions. The intactness of outer wall was better assessed on CEUS. The dynamic postcontrast assessment showed that carcinoma showed early washout of contrast compared to benign thickening ($P = 0.002$). Nonlayered mural enhancement or thick enhancing inner layer with nonenhancing thin outer layer was associated with adenocarcinoma. The classification of intralesional vascularity on CEUS was not helpful in distinguishing benign lesions and adenocarcinoma. **Conclusion:** CEUS can increase the diagnostic confidence in differentiation between benign mural lesions and adenocarcinoma of GB.

Keywords: Carcinoma gallbladder, contrast-enhanced ultrasound, ultrasound

Introduction

Gallbladder (GB) adenocarcinoma is the most prevalent malignancy of the biliary tree. Despite the advent of various diagnostic modalities, most of these tumors tend to spread liver bed and locoregional lymph nodes at the time of diagnosis, accounting for its poor prognosis. Appropriate and prompt surgical planning with lymph node dissection, extrahepatic bile duct resection, hepatic bed resection, and segmental hepatectomy is associated with survival. Various studies have established the value of early diagnosis in determining the prognosis.[1,2]

Ultrasound (US) is usually the first imaging modality employed in the evaluation of GB lesions. The diagnostic accuracy of sonography is traditionally considered inferior to computed tomography (CT) scan, especially for the mural lesions of GB. The diagnosis of any mural thickening of GB on US can cause dilemma as a sizable proportion of malignant GB wall thickening can present with preserved mural stratification and diffuse thickening.[3] However, the advent of microbubble contrast agent combined with low mechanical index (MI) contrast-specific imaging techniques has fortified the ability of the US in the characterization of soft-tissue lesions. Contrast-enhanced US (CEUS) is the only modality that enables real-time dynamic assessment of contrast uptake by GB lesions. Moreover, CEUS offers other advantages such as the absence of radiation and risk of nephrotoxicity, lower cost, and

Received: 24-06-2019 **Revised:** 09-08-2019 **Accepted:** 22-10-2019 **Available Online:** 16-12-2019

Access this article online

Quick Response Code:

Website: www.jmuonline.org

DOI: 10.4103/JMU.JMU_62_19

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How to cite this article: Kumar I, Yadav YK, Kumar S, Puneet, Shukla RC, Verma A. Utility of contrast-enhanced ultrasound in differentiation between benign mural lesions and adenocarcinoma of gallbladder. J Med Ultrasound 2020;28:143-50.

a shorter scan time.[4-7] In this study, we prospectively evaluated the role of CEUS in the diagnosis of GB adenocarcinoma and differentiating them from benign pathologies of GB wall. The primary objectives of this study were as follows:

a. To evaluate the efficacy of qualitative parameters in differential diagnosis of benign GB mural lesions and adenocarcinoma and
b. To evaluate the accuracy of quantitative parameters in the differential diagnosis of benign GB wall lesions and adenocarcinoma.

Materials and Methods

Subjects

This was a prospective observational study carried out over a duration of 2 years (August 2016–August 2018) at a University-Based Tertiary Care Hospital after approval from the Institutional Review Board (approval no. ECR/526/Inst/UP/2014 obtained on Jan. 31st, 2014). Informed consent was obtained from all the patients who were included in this study. Patients in this study were recruited from among those who were referred for the evaluation of focal or diffuse GB thickening on an initial sonography. One hundred and thirty patients were diagnosed on sonography with GB mural lesions during this time. Of these 130 patients, 33 patients were re-referred for CEUS from the department of general surgery by one of the coauthors (P). Seven patients were excluded from this study because of (a) nonwillingness to participate in the study, (b) presence of severe cardiopulmonary disease, and (c) pregnant woman. Twenty-six patients (male = 7 and female = 19) were finally included in this study and underwent contrast-enhanced sonography of GB.

Scan technique

A preliminary focused US of hepatobiliary system was performed after a minimum of 6 h fasting, using a convex electronic array transducer (1–6 MHz) on SonoScape S30 (SonoScape medical corp., Shenzhen, China). After the initial scan, 2.4 mL of a second-generation microbubble US contrast agent, SonoVue (Bracco, Geneva, Switzerland) was administered through the antecubital vein in a bolus injection (within 1–2 s), followed by a flush of 9 mL of 0.9% normal saline using a 20-G cannula. In contrast, the powder form was first mixed with the provided solvent (normal saline) forming microbubbles of approximately 2.5 microns. The contrast agent was used within an hour of opening the seal. To generate pure microbubble images and effective tissue cancellation, continuous low MI (MI <0.2) contrast-specific imaging mode was employed. The target lesion was placed in the center of the screen, and the transducer was kept as stable as possible. The focus was positioned just below the bottom of the lesion and maintained the same position during the examination. Time was monitored using an on-screen real-time stopwatch from the time of contrast media administration. CEUS cine loop was acquired for 120 s from the injection, without any change in the machine settings. Subsequently, the adjacent liver tissue, hepatic vascular and biliary structures, and all other abdominal organs were evaluated.

Image interpretation

A baseline US was performed, and the lesions were categorized into suspicious mass, diffuse or asymmetrical mural thickening, or intraluminal polypoid lesion. Sludge was excluded by the standard protocol of examination in various patient postures. The size, intactness of outer GB wall, and suspicion of infiltration into adjacent liver segments were recorded. CEUS was performed by a junior consultant radiologist (observer 1) with 7 years of experience (IK) in abdominal sonography.

The term "polypoidal lesion" was used for protruding or elevated lesion in the GB lumen without obvious extraluminal component. The lesions with significant extraluminal intrahepatic and/or extrahepatic component were classified as "mass." Focal or diffuse wall thickness >3 mm was considered as mural thickening. After contrast injections, the lesions were analyzed for perceivable enhancement in signal, and the lesions completely lacking any enhancement throughout analyzed time were labeled as sludge. The degree of abundance of vascular structures within the suspected mass was recorded. The intactness of the outer wall and infiltration of adjacent liver segments was analyzed. The continuous assessment of the contrast enhancement was done visually using retrospective frame-by-frame review of cine loop. Time taken for the first perceivable appearance of microbubble was designated as arrival time. Peak time was defined as time needed to achieve the highest echogenicity. The time of washout was defined as the time of the transition of the GB lesion from isoechoic to hypoechoic compared to adjacent normal hepatic parenchyma.[8-10] The liver was taken as a reference in the present study, as done in the previous studies, as it was difficult to define "normal" appearing GB for comparison in cases of GB adenocarcinoma.[10]

For diffuse and asymmetric mural thickenings of GB, in addition to the evaluation of intactness of outer wall of GB and dynamic evaluation of contrast arrival, peak, and washout time, these lesions were analyzed for pattern of contrast enhancement by observer 1 as well as by another senior consultant radiologist (AV) (observer 2) with 17 years of experience. Observer 2 was assessed the images recorded by observer 1 and was blinded to other findings of noncontrast ultrasonography. First, the reviewers were assessed the extent and inner surface of the mural thickening, that is, diffuse, asymmetrical, or both; smooth or irregular. Enhancement was classified as one of the five patterns [Figure 1a-e]:

- Type 1-a – heterogeneously enhancing gallbladder wall thickening without obvious layered pattern
- Type 2 – strongly enhancing thick inner layer and weakly enhancing or nonenhancing thin outer layer
- Type 3 – borderline enhancement and thickness of the inner layer with small cystic spaces and nonenhancing outer layer

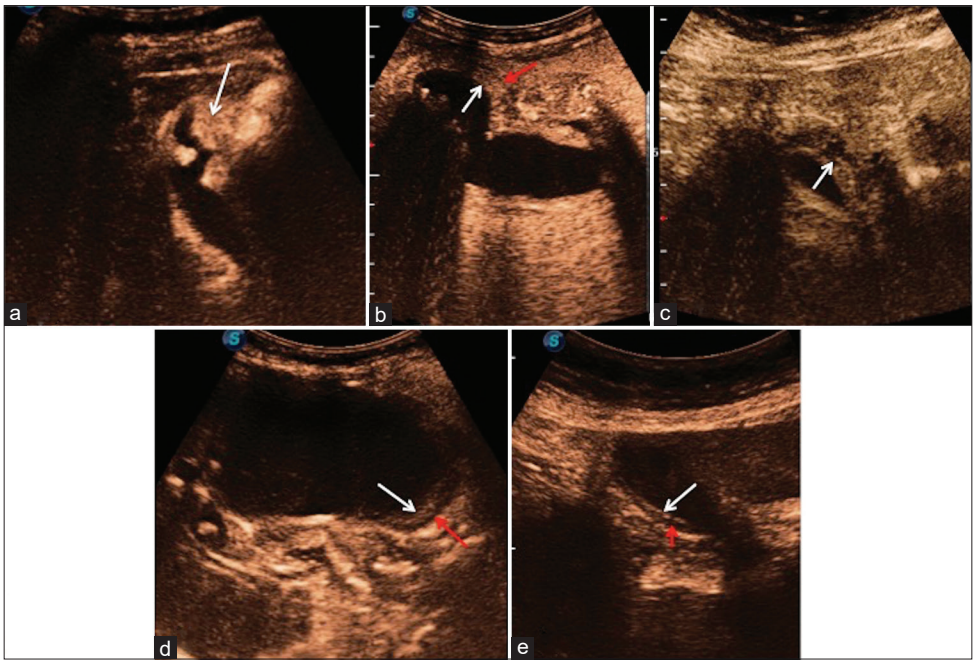

Figure 1: Analysis of enhancement pattern following contrast administration. Type 1 enhancement (a) with heterogeneously enhancing thickening (white arrow) with indistinguishable layering; Type 2 enhancement (b) with strongly enhancing thick inner layer (white arrow) and nonenhancing thin outer layer (red arrow); Type 3 enhancement (c) with borderline enhancement and thickness of the inner layer with small nonenhancing cystic appearing intramural spaces (white arrow); Type 4 enhancement (d) showing weakly enhancing thin inner layer and nonenhancing thin outer layer; and Type 5 enhancement (e) showing weakly enhancing thin inner layer and nonenhancing thick outer layer

- Type 4 – weakly enhancing thin inner layer and nonenhancing thin outer layer
- Type 5 – weakly enhancing thin inner layer and nonenhancing thick outer layer.

Type 1 and 2 enhancement patterns were considered as malignant. Type 4 and 5 were considered as benign thickening. Type 3 pattern consisted of cystic spaces in GB wall and was considered as a sign of adenomyosis or xanthogranulomatous cholecystitis.

Reference standard

The final diagnosis was made either on the basis of histopathological evaluation of the cholecystectomy specimen or in cases of unresectable disease, on the basis of contrast-enhanced CT scan, performed using multidetector 64-slice CT scanner (General Electric Medical Systems, Milwaukee, WI, USA), as per the current optimized protocol. In the patients who were not subjected to surgical resection, the final diagnosis was confirmed by image-guided (CT or US) biopsy and subsequent histopathological evaluation.

Statistical analysis

SPSS version 16.0 software (IBM Corporation, Chicago, IL, United States) was used for statistical analysis. For the assessment of enhancement pattern, a kappa test was applied to evaluate interobserver agreement. Receiver operating characteristic (ROC) curve was drawn for the arrival, peak, and washout time, and area under the curve and cutoff values were obtained. Comparison of mean values of the arrival, peak, and washout time between benign lesions and adenocarcinoma was done using Mann–Whitney U-test.

Results

A total of 26 (male = 7 and female = 19) patients had a mean age of 52.46 ± 11.14 years. CT scan was done in 24 patients, of which 18 were reported as adenocarcinoma, and six were reported as benign lesions. Two patients, who did not undergo CT scan, were diagnosed as benign thickening and benign polyp, respectively, on CEUS and were taken up for surgery, where the resection of GB was performed. Of the 24 patients undergoing CECT, 11 had mass-like lesions of GB and were correctly reported as malignant. Remaining 13 cases presented as mural thickenings of GB, of which, all except one case were correctly identified as malignant or benign on CT. One case of diffuse mural thickening was reported more in favor of benign thickening on CT, which turned out to be malignant on the final histopathological evaluation after surgical resection. A total of 18 patients underwent surgical resection of the GB, and the final diagnosis was obtained by histopathological examination. On histopathological evaluation of surgical specimen, 11 patients were reported as adenocarcinoma, whereas seven cases were reported as benign pathology (chronic cholecystitis-5, GB polyp-1, and xanthogranulomatous cholecystitis-1). The remaining eight patients had unresectable GB malignancies and CT scan, and subsequent image-guided biopsy was performed in those patients, and diagnosis of carcinoma was confirmed on histopathological examination. Overall,

19 patients had final diagnosis of GB adenocarcinoma, which was characterized on histopathological examination as well-differentiated ($n = 4$), moderately differentiated ($n = 10$), and poorly differentiated ($n = 5$). Of the 19 cases of adenocarcinoma, nine measured ≥3 cm in longest diameter, seven measured between 1 and 3 cm, and three lesions presenting as asymmetrical mural thickenings measured <1 cm. Most of the GB adenocarcinomas were located in the body ($n = 7$), followed by diffuse mural involvement ($n = 5$), neck ($n = 4$), and in three cases, masses were seen in GB fossa replacing the normal GB. Eight patients in this study presented with T stage (T1/T2), whereas advanced T stage (T3/T4) was present in nine patients. N0 stage was present in 11 patients who were operated with radical cholecystectomy. Seven patients had N1/N2 nodal disease, whereas one had N3 nodal spread. Distant metastasis was not seen in any patients.

Evaluation of qualitative parameters

Morphological imaging findings

The results of morphological imaging assessment on Gray-scale US and CEUS are summarized in Table 1. On precontrast evaluation, 13 patients were initially reported as mass-forming GB lesion, and two were reported as intraluminal polypoidal lesion. Of the 11 mass-forming lesions, two were reported as asymmetrical thickening of GB wall, and it appeared as mass because of coexisting impacted sludge [Figure 2a and b]. Similarly, one of the intraluminal polypoidal lesions was also categorized as wall thickening of GB after clear demarcation of coexisting sludge [Figure 2c and d]. CEUS revealed nonintact outer wall and liver infiltration in one case, which was missed on precontrast sonography [Figure 2e and f]. It was noted that

Table 1: Assessment of morphological types of gallbladder wall lesions evaluated on ultrasonography and contrast-enhanced ultrasound

Morphology	Noncontrast US			CEUS		
	Total	Malignant	Benign	Total	Malignant	Benign
Mass forming	13	13	0	11	11	0
Wall thickening	11	5	6	14	8	6
Polypoidal	2	1	1	1	0	1
Total	26	19	7	26	19	7

Mass forming - The lesions with significant extraluminal , intrahepatic/extrahepatic component. Polypoid lesion - Protruding or elevated lesion in the GB lumen without obvious extraluminal component. Wall thickening–Asymmetrical or diffuse wall thickness >3 mm. US: Ultrasound, CEUS: Contrast-enhanced US, GB: Gallbladder

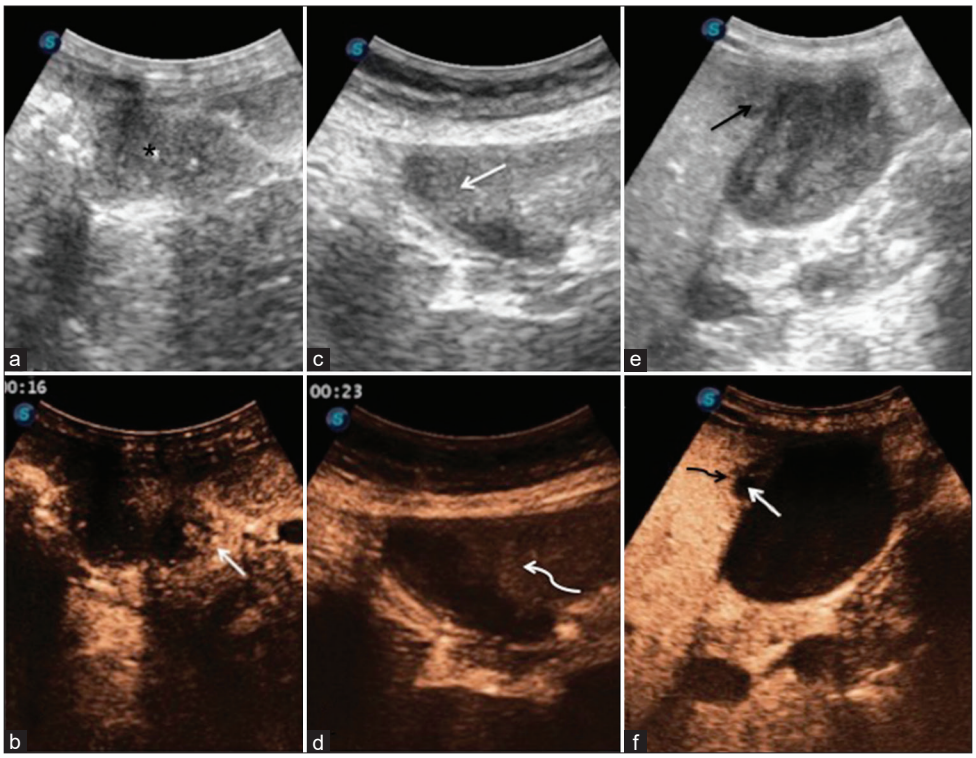

Figure 2: Contrast-enhanced ultrasound (a and b) reveals asymmetrical thickening of gallbladder wall (white arrow) after effective distinction from nonenhancing sludge, which was categorized as mass lesion (*) on ultrasonography. Ultrasound image (c) of the another patient, in which impacted gallbladder sludge was categorized as intraluminal polypoidal lesion (white arrow) on ultrasonography. Contrast-enhanced ultrasound (d) identified the sludge, and the lesion was categorized as diffuse gallbladder mural thickening. Also noted is nonintact outer wall (white curved arrow) favoring gallbladder adenocarcinoma. Ultrasound image of another case (e) shows the presence of gallbladder neck mass, with lumen of the body and fundus completely filled with sludge. An area of asymmetrical thickening in fundus (black arrow) is indistinctly delineated. Contrast-enhanced ultrasound (f) enabled improved visualization of liver bed infiltration (white arrow) and nonintact outer wall (black curved arrow) by malignant gallbladder thickening at the fundus (adenocarcinoma)

portal venous phase optimized the assessment of liver bed assessment because of washout of contrast from GB lesions and peak enhancement of adjacent liver parenchyma.

Enhancement pattern

The diagnostic performance of enhancement pattern analysis and the final diagnoses of the 14 cases of gallbladder wall thickening are summarized in Table 2. Using the five pattern analyses, the interobserver agreement between the two readers showed substantial agreement with a kappa value of 0.816. Two discrepant observations were made between the two radiologists. One of the cases of carcinoma, which presented with asymmetrical mural thickening, was rated as Type 1 pattern by observer 1, whereas observer 2 was rated it as Type 3 pattern. A case of chronic cholecystitis was rated as Type 3 pattern by observer 1 and as Type 4 pattern by observer 2.

The sensitivity for detecting GB adenocarcinoma was 87.5% and 75%, respectively, for the two observers, and the positive predictive value was 100% for each of them, as no false-positive diagnosis of GB cancer was made for either of the observers.

There were three false-negative observations made, one by observer 1 and two by observer 2. Of these, one case was interpreted as Type 4 pattern by both observers and one patient was reported as Type 3 pattern by observer 2, and Type 1 pattern by observer 1. The negative predictive value for adenocarcinoma was 85.7% and 75% for observers 1 and 2, respectively. Of the benign lesions, one case of xanthogranulomatous cholecystitis was identified as Type 3 pattern by both the observers. Of the five cases of chronic cholecystitis, one patient was rated as Type 5 pattern by both the observers. Of the remaining four, observer 2 was rated all the cases as Type 4 pattern, whereas observer 1 was rated three cases as Type 4 pattern and one as Type 3 pattern.

Of the rest 11 cases of the mass-forming carcinoma, all the lesions showed heterogeneous enhancement with no identifiable layered pattern.

Intralesional vascular structure

The abundance of vascularity of the lesions was assessed on CEUS adenocarcinoma demonstrated abundant vascularity in five cases, scarce vascularity in nine cases, and absence of vascularity in five cases. Of the benign lesions, one case of xanthogranulomatous cholecystitis showed abundant vascularity, whereas others showed scarce (n = 2) or absent (n = 4) vascularity. However, the differentiation between linear and branching pattern was difficult to be made.

Evaluation of quantitative parameters

Three parameters, that is, arrival time, peak time, and washout time, were analyzed by ROC curves [Figure 3] in the prediction of GB adenocarcinoma. Of these three, washout time of contrast had the highest area under the curve with cutoff value of 53 s showing high sensitivity and specificity in the

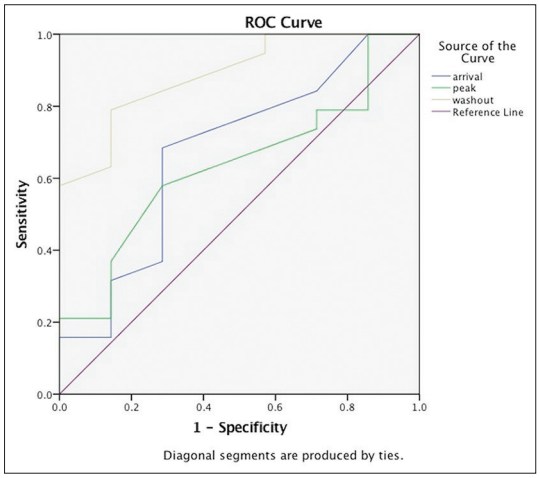

Figure 3: Receiver operating characteristic curve of the arrival time, peak time, and washout time after contrast injection in the prediction of gallbladder adenocarcinoma

Table 2: Qualitative assessment of enhancement pattern on contrast-enhanced ultrasound

Enhancement pattern	GB carcinoma	Xanthogranulomatous cholecystitis	Chronic cholecystitis	Total
Observer 1				
Type 1	5	0	0	5
Type 2	2	0	0	2
Type 3	0	1	1	2
Type 4	1	0	3	4
Type 5	0	0	1	1
Observer 2				
Type 1	4	0	0	4
Type 2	2	0	0	2
Type 3	1	1	0	2
Type 4	1	0	4	5
Type 5	0	0	1	1
Total	8	1	5	14

Type 1 pattern was heterogeneously enhancing one-layer GB wall or indistinguishable layering of the GB wall; Type 2, strongly enhancing thick inner layer and weakly enhancing or nonenhancing outer layer; Type 3, borderline enhancement or thickness of the inner layer with small cystic spaces and nonenhancing outer layer; Type 4, weakly enhancing thin inner layer and nonenhancing thin outer layer; and Type 5, weakly enhancing thin inner layer and nonenhancing thick outer layer. GB: Gallbladder

Table 3: Comparison of mean values of quantitative parameters (contrast arrival, peak time, and washout time) and summary of receiver operating characteristic curve analysis between benign mural lesions of gallbladder and adenocarcinoma

	Mean±SD (ms)		*P* (Mann-Whitney)	Area under ROC curve	Cut off value (ms)	Sensitivity	Specificity
	Benign (*n*=7)	Malignant (*n*=19)					
Arrival time	16.29±7.2	12.58±3.8	0.188	0.637	14.5	68.4	71.4
Peak time	30±17.9	21.8±5.8	0.306	0.673	23.00	57.9	71.4
Washout time	78.4±30.9	46.58±8.4	0.002	0.887	53.00	78.9	85.7

ROC: Receiver operating characteristic, SD: Standard deviation

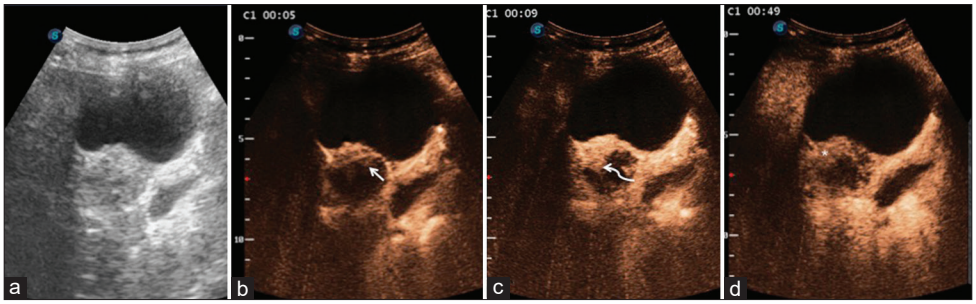

Figure 4: Dynamic real-time assessment of a patient with gallbladder neck adenocarcinoma (a) after contrast administration. The lesion shows early arrival of contrast (straight arrow) at 5 s (b), peak enhancement (curved arrow) at 9 s (c) and washout of contrast when gallbladder lesion becomes isoechoic/hypoechoic (asterisk) compared to the liver at 49 s (d)

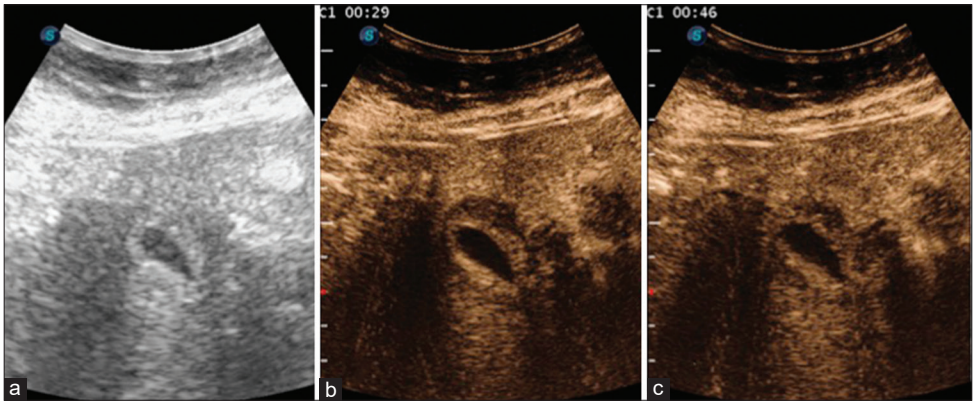

Figure 5: Dynamic postcontrast evaluation of benign thickening of gallbladder (a) showed delayed peak and washout of contrast. The peak contrast enhancement time is 29 s (b), and contrast is retained at 49 s (c)

diagnosis of cancers [Table 3]. GB cancers showed earlier arrival, peak, and washout of contrast compared to benign GB wall lesions [Figures 4 and 5]. On comparison of the mean value of these three parameters between benign mural lesions and adenocarcinoma, washout time showed significantly lower value (P = 0.002) for adenocarcinoma (mean 46.58 s) than benign lesions (78.4 s). Other two parameters yielded nonsignificant difference of means.

Discussion

Early diagnosis is a key factor for successful surgery and improved survival in GB adenocarcinoma. US has been traditionally utilized in the assessment of GB in differentiation between malignant and benign mural thickening utilizing morphological features such as thickness, symmetry, surface, adjacent liver bed, and vascularity on Doppler study. The introduction of microbubble contrast agents has expanded the clinical utility of sonography in the characterization of soft-tissue lesions, and various researchers have convincingly reported on the utility of CEUS in differentiating carcinoma from benign mural lesions of GB.[4-7] A meta-analysis was done by Wang *et al*., of 16 studies using CEUS on 1673 patients, which revealed a sensitivity of 84% for lesions <1 cm and a sensitivity of 97% for larger lesions.[11] Rifai *et al*. suggest that the application of contrast in sonographic examinations can lead to change in diagnosis of up to 38% cases.[12] In the present study, CEUS proved to be a reliable technique in the characterization of lesions suspicious of GB adenocarcinoma. Various benefits of sonography after contrast administration were highlighted in our study.

Identification of gallbladder sludge and determination of morphological pattern

CEUS could easily distinguish between tumor and sludge by lack of contrast uptake in the later. Moreover, in cases of coexisting immobile sludge with GB mural lesion, CEUS clearly demarcated the margins of mural thickening by providing effective separation from nonenhancing sludge. This benefit of contrast administration has been unanimously highlighted in various previous studies[13,14] and could significantly impact the diagnostic opinion of the sonologist. The outer margin of the lesions was also better appreciated on CEUS because GB wall enhanced on arterial phase in most of the cases when the liver still remained largely unenhanced.

Enhancement pattern of gallbladder wall

Our study showed that the enhancement patterns of GB wall thickening could be categorized without significant inter-observer variation. The patterns associated with GB adenocarcinoma are Type 1 (nonlayered diffuse enhancement) and 2 (inner thick enhancing layer and outer thin nonenhancing layer). Our study could reproduce the results of Kim *et al*., who tried to evaluate the layered pattern of GB wall on CECT abdomen and conclude that a nonlayered thickening of GB wall (Type 1), thickened enhancing inner layer ≥2.6 mm (Type 2), stronger enhancement of inner layer than liver parenchyma, and irregular contour were associated with adenocarcinoma.[15] However, they included only flat GB thickening in their study, and CECT was done in portal phase, which might not be optimal for GB evaluation as blood supply of GB is from cystic artery. A study by Yun *et al*. done using biphasic CT of all morphological type of GB conclude that nonenhancing inner layer was associated with benign thickening, whereas thick enhancing inner layer was associated with adenocarcinoma.[16] Our study showed that CEUS can be efficiently used to evaluate the layered pattern of GB and can aid in the differentiation of benign and malignant GB wall thickening with higher accuracy and lower false-positive rates compared to CT, as it allows a continuous real-time evaluation of contrast uptake. CEUS could also increase the visualization of intramural cystic lesions (Rokitansky–Aschoff sinuses) and can better characterize xanthogranulomatous cholecystitis or adenomyomatosis (Type 3 pattern).[17]

Dynamic signal time evaluation

Various researchers have tried to analyze signal time pattern of contrast enhancement on CEUS showing variable results. The results of previous such studies are summarized in Table 4.[10,18-23] In our study, there was statistically significant shorter washout time in adenocarcinoma, which concurred with previous studies that have shown that adenocarcinoma shows earlier washout of contrast compared to benign lesions of GB. Moreover, early arrival time in adenocarcinoma has also been demonstrated in many previous studies. Our study also demonstrated shorter arrival time in GB adenocarcinoma although the difference was statistically insignificant which might be due to small sample size. Arrival time <14 s could predict the presence of adenocarcinoma with approximately 68% sensitivity and 71% specificity.

Intralesional vascular structure

Various studies have stressed the importance of visualization of intralesional vessels in diagnosing adenocarcinoma of GB. However, studies with Color Doppler sonography could not conclusively distinguish between carcinoma, adenomyomatosis, cholecystitis, and even normal healthy individuals.[24] CEUS increases the sensitivity of sonography to visualize the tumor vessels and linear, branching, and tortuous vessels are the features on CEUS, reported to be associated with malignancy.[12,13,16,23] In the present study, we found it difficult to characterize the type of vascularity. Moreover, the majority of adenocarcinoma in our study had scarce or absent vascularity. Our observations concur with that of Inoue *et al*. who conclude that the abundance of vascularity and the pattern might just reflect the size of lesion and is of limited utility in diagnosing carcinoma.[25]

Table 4: Summarizing the results of various studies evaluating the real-time signal changes (quantitative analysis) in the prediction of gallbladder adenocarcinoma

Study	Number of patients	Results
Sun *et al*.	34	Significantly shorter arrival and time to peak in adenoma; significantly shorter washout time in canceration (cutoff 28 s)
Xie *et al*.	80	Hyper-or iso-enhancement in the early phase and then fading out to hypoenhancement within 35-60 s suggestive of carcinoma
Liu *et al*.	192	Shorter washout time for the malignant GB diseases (36.5 s) was quicker than that for the benign GB diseases
Zheng *et al*.	116	Time-to-peak is significantly shorter in the benign lesion and time-to-hypoenhancement shorter in malignant lesion (nonsignificant)
Zhang *et al*.	105	Carcinoma heterogeneously hyperenhanced on arterial phase and showed quick wash out of contrast
Hattori *et al*.	60	Early arrival of contrast and persistence of high signal till 120 s suggestive of carcinoma
Hyun *et al*.	10	Enhancement and washout time similar regardless of the nature of the lesions with most of the lesions showing early enhancement within 15 s and washout around 1 min
Present study	26	Arrival time shorter than 14 s and washout time <53 s indicative of carcinoma

GB: Gallbladder

We realize that our study had many limitations. The small sample size is one of the major limitations of this study. Other major limitation of this study is the heterogeneous study group, both in terms of the variable morphological patterns of the GB mural lesions as well as different stages of adenocarcinoma in different patients. Moreover, the dynamic real-time evaluation of contrast uptake and washout was done subjectively, which can potentially introduce bias. Further, we did not attempt to compare the diagnostic performance of CEUS and CECT to differentiate between malignant and benign mural lesions. The strength of this study was its prospective nature.

Conclusion

This study showed that the evaluation of pattern analysis of GB enhancement following contrast administration is a sensitive qualitative parameter for identification of GB adenocarcinoma, whereas analysis of washout time of contrast is the most sensitive quantitative parameter in identifying GB adenocarcinoma. This study emphasizes the increased ability of CEUS in characterization of GB wall lesions by differentiation from sludge, intactness of the outer wall and its relationship with liver bed, real-time evaluation of arrival and washout of contrast, and evaluation of the layered pattern of contrast enhancement. The assessment of these aspects of GB can impart increased diagnostic confidence in determining whether the lesion is benign or malignant.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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