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SPECIAL FEATURE: REVIEW ARTICLE

Everything you need to know about ultrasound for diagnosis of gallbladder diseases

Transabdominal ultrasound evaluation of vascularity of gallbladder lesions: particularly those with wall thickening

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Abstract

Gallbladder wall thickening is relatively common in clinical settings, and for appropriate diagnosis, the size, shape, internal structure, surface contour, and vascularity of the gallbladder wall must be evaluated. Morphological evaluation is the most important; however, some gallbladder lesions resemble gallbladder cancer in imaging studies, making differential diagnosis challenging. Vascular evaluation is indispensable for a precise diagnosis in these cases. In this review, we present the current status of vascular evaluation using US and diagnosis using vascular imaging for gallbladder lesions, including those presenting with wall thickening. To date, several ultrasound imaging techniques have been developed to assess vascularity, including Doppler imaging with high sensitivity, use of contrast agents, and microvascular imaging using a novel filter for Doppler imaging. Although conventional color Doppler imaging is rarely used for the diagnosis of gallbladder lesions, the efficacy of contrast-enhanced ultrasound in assessing the vascularity, enhancement pattern, or timing of enhancement/washout has been reported. Presence of multiple irregular microvessels has been speculated to indicate malignancy. However, few reports on microvessels have been published, and further studies are required for the precise diagnosis of gallbladder lesions with microvascular evaluation.

Keywords Gallbladder wall thickening · Contrast-enhanced ultrasound · Superb microvascular imaging · Detective flow imaging

Abbreviations

US	Ultrasound
GBC	Gallbladder cancer
ADM	Adenomyomatosis
XGC	Xanthogranulomatous cholecystitis
CDI	Color Doppler imaging
PDI	Power Doppler imaging
ADF	Advanced dynamic flow
CEUS	Contrast-enhanced ultrasound
CT	Computed tomography
MRI	Magnetic resonance imaging
MFI	Micro flow imaging
SMI	Superb microvascular imaging
DFI	Detective flow imaging
MVI	Microvascular imaging
GWBF	Gallbladder wall blood flow

Introduction

Gallbladder wall thickening is relatively commonly encountered in clinical settings and during medical examinations. Most gallbladder lesions presenting with wall thickening are detected using ultrasound (US). However, it is challenging to appropriately diagnose them as the wall structure is frequently modified by cholecystitis or adenomyomatosis (ADM). Hence, some gallbladder cancers (GBCs) are revealed in resected specimens after cholecystectomy, which are referred to as incidental cancer [1, 2]. Cholecystitis is occasionally misdiagnosed as invasive GBC, leading to unnecessary extended surgical resection, such as hepatectomy [3–5]. Therefore, various aspects of gallbladder wall thickening should be evaluated, including size, shape, internal structure, surface contour, and vascularity prior to making a definitive diagnosis [6].

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In this review, we present the current status of vascular evaluation using US and diagnosis using vascular imaging for gallbladder lesions, including those presenting with wall thickening.

Significance of vascular evaluation for the diagnosis of gallbladder lesions presenting wall thickening

Various gallbladder lesions with wall thickening have been reported [7, 8] (Table 1). The fundamental approach to diagnosing these lesions is morphological evaluation, and vascular evaluation is not always necessary. For instance, edematous gallbladder wall thickening caused by diseases of other organs, such as hepatitis, heart failure, or renal failure, shows uniform gallbladder wall thickening; however, the structure of the gallbladder wall layer is retained, which is distinctly different from advanced GBC presenting wall thickening. Gallbladder wall thickening with a retained layer is easily detected on US; therefore, mild cholecystitis or edematous wall thickening of the gallbladder can be diagnosed using US alone, and vascular evaluation is not mandatory.

Table 1 Gallbladder lesions that present with wall thickening

Benign lesions	Adenomyomatosis
	Cholecystitis
	Xanthogranulomatous cholecystitis
	Mucosal hyperplasia
	Cholesterolosis
	Edematous wall thickening of the gallbladder
	IgG4-related cholecystitis
Malignant lesions	Gallbladder cancer
	Metastatic gallbladder tumor
	Carcinosarcoma of gallbladder
	Malignant lymphoma of gallbladder

However, some gallbladder lesions present with imaging findings similar to those of GBC, and their differential diagnosis using imaging studies is occasionally challenging. Some inflammatory diseases, such as severe acute cholecystitis, show irregular wall thickening with an obscured structure of the wall layer, which is similar to the findings in invasive GBC. In particular, xanthogranulomatous cholecystitis (XGC), which presents as localized wall thickening on imaging studies, is frequently misdiagnosed as a malignant gallbladder neoplasm [5]. Adenomyomatosis (ADM) is characterized by wall thickening with a dilated Rokitansky-Ashoff sinus [9], and a small cystic structure or comet-like echo is a representative finding of ADM on US [10, 11]. However, these findings have also been observed in nodular invasive GBC with cancerization. Additionally, GBC and ADM may be present concomitantly, and the diagnosis of GBC with ADM in imaging studies is difficult [12] (Fig. 1).

Vascular evaluation provides informative findings in these situations, and hence, should be considered during the differential diagnosis of benign and malignant gallbladder diseases.

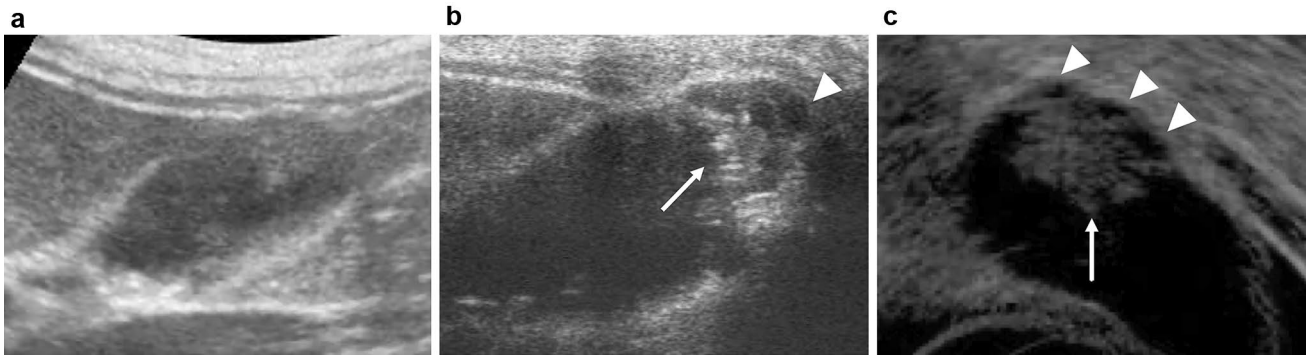

Fig. 1 Findings of gallbladder cancer concomitant with adenomyomatosis. **a** Ultrasound. A protruded lesion was detected on the fundal part of the gallbladder. **b** Ultrasound. A small cystic structure was observed in the gallbladder lesion, suggesting fundal adenomyomatosis (arrowhead). The mucosal part of the gallbladder lesion was slightly thickened. **c** Endoscopic ultrasound. A small cystic structure was present in the bottom of the lesion, compatible with adenomyomatosis. However, an elevated lesion protruding into the gallbladder lumen was also seen on the mucosal part of the adenomyomatosis, which is not typical of adenomyomatosis. This case was ultimately diagnosed as gallbladder cancer concomitant with adenomyomatosis

Imaging techniques to assess vascularity using ultrasound

Current imaging techniques for visualizing blood flow are summarized in Table 2. The blood flow is generally visualized using US with Doppler effect. Color Doppler imaging (CDI), which has been conventionally used for US vascular imaging, is a vascular imaging technique based on the time between the transmission of ultrasound waves radiated at a certain frequency and the reception of ultrasound reflected by blood cells. CDI allows visualization of the velocity, direction, and signal intensity of blood flow [13]. In addition, power Doppler imaging (PDI) detects blood flow with higher sensitivity than CDI by visualizing the signal intensity of ultrasound alone [14]. However, the transmitted ultrasound waves are also reflected from tissues other than blood cells, which is a cause of artifacts in CDI or PDI. Thus, a filter is used to eliminate these noises (clutter). Clutter is typically low-frequency signals, and CDI utilizes a filter to eliminate signals below a certain frequency. Consequently, low-frequency signals from low-velocity blood flow are ignored, and microvessels with a low flow velocity cannot be visualized using conventional CDI [13].

Several techniques have been developed to improve blood flow detection sensitivity. Advanced dynamic flow (ADF) developed by Canon Medical Systems (Tochigi, Japan) and eFLOW developed by Fujifilm (Tokyo, Japan) improved the local resolution and frame rate of CDI [15, 16] (Fig. 2a). These imaging techniques enable the separate display of fine vessels. B-flow, developed by GE Healthcare (Chicago, IL, USA), detects blood flow by amplifying signals from blood cells [17] (Fig. 2b).

In addition, contrast-enhanced US (CEUS) has been used to evaluate vascularity [18, 19]. Contrast agents for US are composed of microbubbles (2–3 μm); a second-generation hypersonic ultrasound contrast agent (Sonazoid; Dai-ichi Sankyo, Tokyo, Japan) containing perflubutane is now widely used. These microbubbles resonate and collapse upon ultrasound irradiation, generating hyperechoic signals. CEUS visualizes blood flow by detecting hyperechoic signals. The contrast agent for US does not diffuse into extravascular organs, which is a distinctive characteristic from that of computed tomography (CT) and magnetic resonance imaging (MRI). Therefore, CEUS allows the precise evaluation of minute vessels. For instance, microflow imaging (MFI) developed by Canon Medical Systems detects the flow of microvessels without involvement of clutter by observation under a low mechanical index [20] (Fig. 2c). MFI generates microvascular images by tracing and overlapping the hyperechoic signals in each frame. In addition, precise imaging of microvessels is possible using ADF, eFLOW, and B-flow with a contrast agent that provides a distinct contrast between blood flow and extravascular organs (Fig. 2d).

Recently, a novel filter was developed to distinguish tissue motion artifacts from low-velocity blood flow. This filter enables visualization of microvessels. This imaging technique for visualizing microvessels is attracting much attention and is utilized in superb microvascular imaging (SMI), detective flow imaging (DFI), and microvascular imaging (MVI), developed by Canon Medical Systems, Fujifilm, and GE Healthcare, respectively [21–24] (Fig. 2e, f). SMI has been reported to be useful in various assessments, such as evaluation of liver fibrosis or intrahepatic vascular architecture in chronic hepatitis and differentiation of benign and malignant thyroid, breast, and prostate masses [25–27]. DFI is also utilized in endoscopic ultrasound (EUS) processors, and its efficacy in the diagnosis of pancreatobiliary disease using EUS has also been reported [28–30].

Table 2 Current imaging techniques for assessing vascularity using ultrasound

Conventional Doppler imaging	Color Doppler imaging (CDI)
	Power Doppler imaging (PDI)
Doppler imaging with high sensitivity	Advanced dynamic flow (ADF)
	eFLOW
	B-flow
Doppler imaging using a novel filter for the visualization of microvessels	Superb microvascular imaging (SMI)
	Detective flow imaging (DFI)
	Microvascular imaging (MVI)
Use of contrast agent	Contrast-enhanced ultrasonography
	Micro flow imaging (MFI)

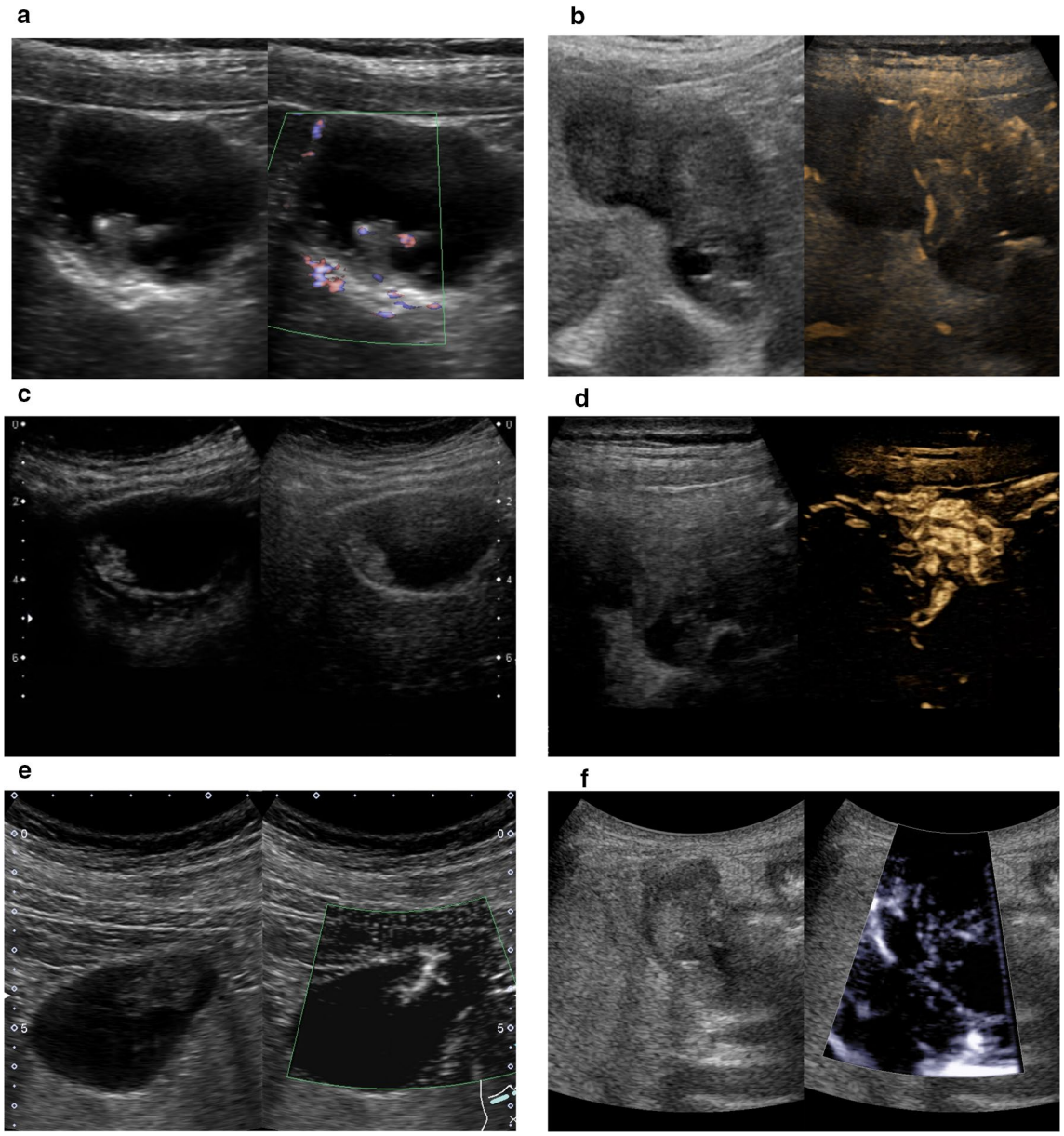

Fig. 2 Imaging techniques for assessing vascularity using ultrasound. **a** Advanced dynamic flow (ADF). **b** B-flow. **c** Micro flow imaging (MFI). **d** B-flow imaging under contrast-enhanced ultrasound. **e** Superb microvascular imaging (SMI). **f** Microvascular imaging (MVI)

Evaluation of the vascularity of gallbladder wall thickening

The evaluation of blood flow using CDI or PDI has been mainly applied to differentiate between neoplastic and non-neoplastic gallbladder lesions or to assess the activity of cholecystitis [31, 32]. As for the differential diagnosis between benign and malignant gallbladder lesions, gallbladder wall blood flow (GWBF) has been evaluated [6, 33–38]. Li et al. reported that high-velocity arterial blood flow was detected in the cases with GBC while 40% of the cases with benign gallbladder lesions showed a low-velocity blood flow signal [34]. Hirooka et al. reported that GBC showed higher velocity and lower resistive index of GWBF as compared to benign lesions. They also demonstrated through an additional prospective study with 10 and 21 patients with GBC and benign polyp, respectively, that the differentiation between GBC and benign polyps was possible by means of estimation of GWBF velocity when 20 cm/s for velocity and 0.65 for resistive index were set as the cut-off values [35]. Hayakawa et al. also proved the presence of rapid GWBF in 12 patients with GBC as compared to that of 80 patients with no or benign gallbladder lesions, and suggested a GWBF velocity of 30 cm/s as a cut-off

value [36]. In addition, Kawashima et al. showed that GWBF velocity was significantly higher in the patients with pancreatobiliary maljunction than those without, and concluded that the measurement of GWBF velocity could be a clue for the diagnosis of pancreatobiliary maljunction [37].

However, the gallbladder lesion should be hypervascular for the evaluation of GWBF using CDI or PDI, which may be a limitation of GWBF evaluation using CDI or PDI [32, 38]. Paulson et al. reported that arterial flow could not be detected in over 60% of the patients regardless of the presence or absence of cholecystitis [38]. Gallbladder lesions with wall thickening, such as inflammatory gallbladder disease and GBC, generally show hypovascularity owing to abundant fibrosis, and GWBF estimation using CDI or PDI for these lesions is not easy.

As for evaluation using microvascular imaging techniques, some studies have been reported (Table 3, Fig. 3). Kin et al. performed SMI in 20 gallbladder lesions, including seven cases presenting with wall thickening, and reported that the quality of microvascular imaging was significantly higher on SMI using a contrast agent as compared to that without, which was due to the vascularity of the gallbladder or the depth between the gallbladder and body surface [39]. They also suggested that the presence of tortuous microvessels or abrupt changes in vessel caliber may indicate malignancy. Osakabe et al. detected multiple tortuous microvessels flowing from the base to the interior of the lesion during GBC examination using DFI [40]. Microvascular evaluation using DFI was also performed using EUS. Yamashita et al. reported that DFI is more sensitive than e-FLOW for the detection of microvessels, and that irregular vessels may be a significant predictor of malignant gallbladder lesions [28]. Miwa et al. examined four patients with gallbladder lesions using EUS and reported that DFI was effective for the precise evaluation of microvessels. They also demonstrated that a single vessel at the base of the lesion might be a sign of non-neoplastic lesions [29]. Considering the results of these studies, morphological evaluation of microvessels may provide important insights for the diagnosis of gallbladder lesions.

Table 3 Microvascular imaging for the diagnosis of gallbladder lesions

Authors	Modality of ultrasonography	Microvascular imaging technique	Use of contrast agent	Imaging findings
Kin et al. [39]	TUS	SMI	Yes	Presence of tortuous microvessels or abrupt changes in vessel caliber may indicate malignancy
Osakabe et al. [40]	TUS	DFI	No	Multiple tortuous microvessels flowing from the base to the interior of the lesion were observed in gallbladder cancer
Yamashita et al. [28]	EUS	DFI	No	Irregular vessels may be a significant predictor of malignant gallbladder lesions
Miwa et al. [29]	EUS	DFI	No	A single vessel at the base of the lesion might be a sign of non-neoplastic lesions

TUS transabdominal ultrasound, *EUS* endoscopic ultrasound, *SMI* superb microvascular imaging, *DFI* detective flow imaging

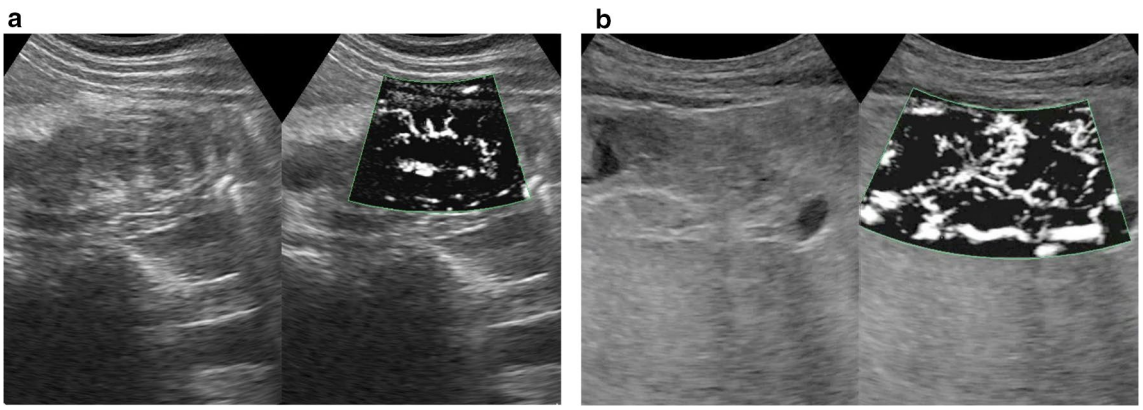

Fig. 3 Microvascular findings of a gallbladder lesion on superb microvascular imaging under contrast-enhanced ultrasound. **a** Adenomyomatosis. Linear microvessels without caliber change are noted. **b** Gallbladder cancer. Microvessels are tortuous and present with caliber change

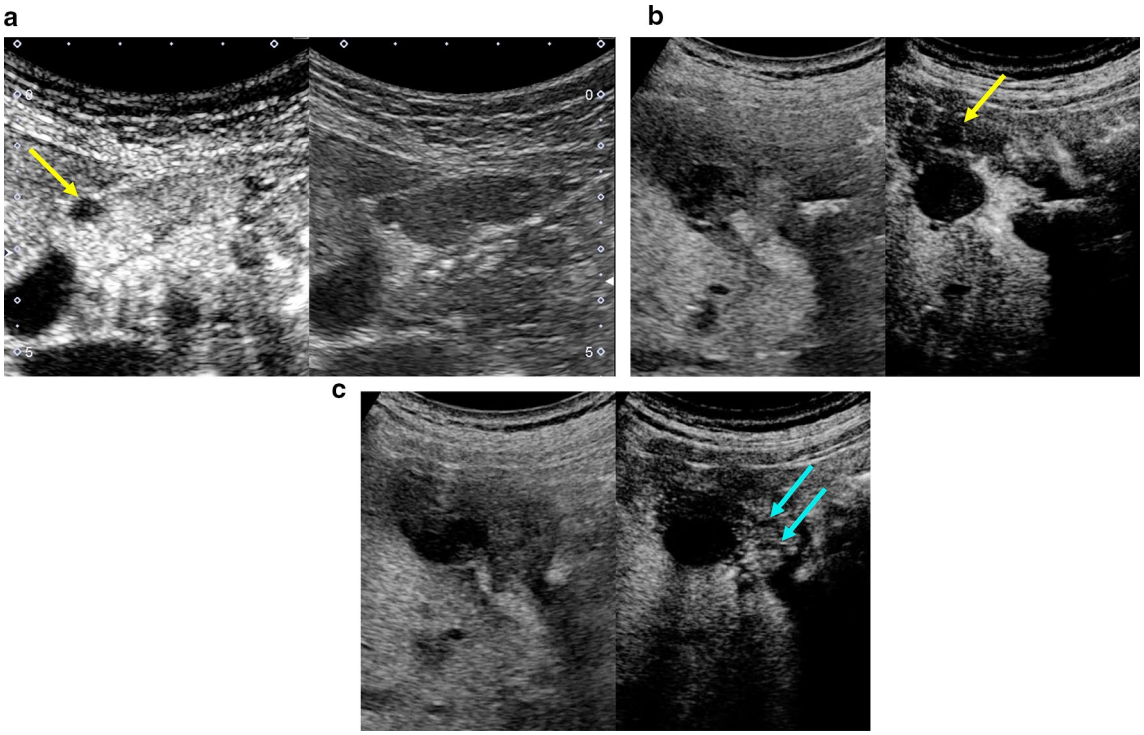

Fig. 4 Findings of gallbladder lesions on contrast-enhanced ultrasound. **a** Adenomyomatosis. Gallbladder lesions were uniformly enhanced 32 s after injection of contrast agent. A small cystic structure was also found in the lesion (arrow). **b** Gallbladder cancer. A gallbladder lesion was heterogeneously enhanced, and a perfusion defect was observed 22 s after injection of contrast agent (arrow). **c** Gallbladder cancer (same case as in **b**). Contrast agent was partially washed out 53 s after injection of contrast agent (arrow)

Some reports on the evaluation of gallbladder lesions using CEUS are presented (Fig. 4). Tsuji et al. classified 25 cases of GBCs into six patterns according to their enhancement pattern on CEUS and speculated that branched patterns might be a sign of malignancy [41]. Zhang et al. examined 105 cases of gallbladder lesions using CEUS and demonstrated a 95.2% diagnostic accuracy rate [42]. They considered heterogeneous enhancement with rapid washout as a typical finding in GBC. A prospective observational study conducted by Kumar et al. to evaluate the enhancement patterns of 26 cases with gallbladder lesions presenting wall thickening on CEUS concluded that gallbladder cancer showed early washout of contrast compared to benign wall thickening [43]. Kong et al. observed 49 cases of gallbladder lesions on US with and without enhancement and reported that malignant gallbladder lesions showed more vascularity and required longer to achieve iso-enhancement in comparison with the liver parenchyma than benign lesions [44]. In addition, the diagnostic accuracy of US can be improved in combination with CEUS, which is prominent in cases of gallbladder wall thickening. These studies suggest that analysis of the vascularity, enhancement pattern, or timing of enhancement/washout on CEUS is quite effective for the diagnosis of gallbladder lesions presenting with wall thickening (Table 4).

Table 4 Imaging findings of malignant/benign gallbladder lesions on contrast-enhanced ultrasound

	Malignant GB lesion	Benign GB lesion
Enhancement pattern	Heterogeneous Branched pattern	Homogeneous Small cystic structure in adenomyomatosis
Time to washout	Early	Late
Time to iso-enhancement	Late	Early

Limitations and future perspective of microvascular imaging

Visualization of microvessels is considered a promising technique, but some problems still exist. Visualization of microvessels on US is still under development, and further improvements are required especially for the improvement of local resolution and the reduction of artifacts. Benign or malignant diagnosis based on microvascular findings largely depends on subjective judgement, and the morphological findings of microvessels only serve as a reference at present. There have been few US studies

regarding microvessels, and validation of the reported findings has not been fully discussed. However, further studies on the morphology of microvessels will reveal microvascular findings specific to benign and malignant gallbladder lesions.

Conclusion

Although morphological evaluation is fundamental for the diagnosis of gallbladder lesions presenting wall thickening, difficult cases are sometimes encountered. Hemodynamic evaluation is important in such cases. Recent advances in US imaging have made microvascular imaging possible, and detailed hemodynamic evaluations including the enhancement pattern on CEUS and morphological findings of microvessels are expected to aid in differentiating between benign and malignant gallbladder lesions.

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Declarations

Conflict of interest AK has received honoraria from Olympus. The other authors declare no conflicts of interest.

Ethical statements All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

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