



● *Review*

INCIDENTAL FINDINGS OF GALLBLADDER AND BILE DUCTS—MANAGEMENT STRATEGIES: GENERAL ASPECTS, GALLBLADDER POLYPS AND GALLBLADDER WALL THICKENING—A WORLD FEDERATION OF ULTRASOUND IN MEDICINE AND BIOLOGY (WFUMB) POSITION PAPER

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Abstract—The World Federation of Ultrasound in Medicine and Biology (WFUMB) is addressing the issue of incidental findings with a series of position papers to give advice on characterization and management. The biliary system (gallbladder and biliary tree) is the third most frequent site for incidental findings. This first part of the position paper on incidental findings of the biliary system is related to general aspects, gallbladder polyps and other incidental findings of the gallbladder wall. Available evidence on prevalence, diagnostic work-up, malignancy risk, follow-up and treatment is summarized with a special focus on ultrasound techniques. Multi-parametric ultrasound features of gallbladder polyps and other incidentally detected gallbladder wall pathologies are described, and their inclusion in assessment of malignancy risk and decision-making on further management is suggested. (E-mail: c.f.dietrich@googlemail.com) © 2022 World Federation for Ultrasound in Medicine & Biology. All rights reserved.

Key Words: Incidental, Gallbladder, Polyp, Wall, Cancer, Ultrasound, Management.

INTRODUCTION

Definition and aim

Incidental findings (IFs) on imaging studies are asymptomatic and unexpected pathology unrelated to the presenting illness. The World Federation of Ultrasound in Medicine and Biology (WFUMB) is addressing the issue of IFs with a series of publications, “Incidental Imaging Findings—The Role of Medical Ultrasound,” with each position paper uniformly structured to help readers interpret the key messages (Dietrich et al. 2020a, 2020b).

The WFUMB position paper on IFs of the biliary system (gallbladder and bile ducts) addresses both the referrer and US practitioners performing ultrasound (US) at the point of care and in radiology and US departments, and will:

1. Describe prevalence of IFs of the biliary system
2. Define terms and US imaging features associated with IFs of the biliary system
3. Identify red flag (worrisome or high-risk) US imaging features associated with IFs of the biliary system
4. List a set of recommendations on the role of US imaging in the evaluation and management of IFs of the biliary system.

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Summary Statements

- Incidental findings of the gallbladder (GB) and biliary tree are common.
- Transcutaneous abdominal ultrasound (US) is the primary examination method for the detection and characterization of biliary pathology.
- Gallbladder polyps (GBPs) have a prevalence of 5%–12% and are predominantly benign pseudopolyps, while other incidentally detected GB wall abnormalities are less common.
- Incidental GBPs and GB wall abnormalities may be further characterized by employing advanced US techniques such as high-frequency abdominal and endoscopic US without and with contrast enhancement.
- Malignancy risk assessment and management should not be based on GBP size or wall thickness alone but should include individual clinical risk factors and additional multiparametric US features.
- Ultrasound-guided and/or endoscopic US-guided fine-needle aspiration may be used for characterization of focal or general GB wall thickening in selected cases after careful consideration of benefits and risks.
- Surgical management (cholecystectomy) is recommended in cases of GB incidental findings where malignancy cannot be reliably excluded by imaging modalities.

This position paper consists of two parts, with this first part related to general aspects, GBPs, and other IFs of the GB wall and the second to anomalies of the GB and biliary tree and to silent gallstones. Reading this first part should enable the reader to:

- Define IFs of the biliary system and appreciate their clinical significance
- Know the prevalence and potential malignancy risk of incidentally detected focal and diffuse GB wall lesions
- Understand the need for and potential limitations for risk stratification of IFs of the GB wall by US techniques and complementary imaging, and
- Apply predictors of potential malignancy of IFs of the GB wall to guide their clinical management.

Prevalence of biliary incidental findings

Incidental findings of the biliary system are common. A prospective study from a Greek hospital found IFs by using US, other imaging modalities and endoscopy related to the cause of admission in a total of 28.8% of consecutive patients admitted to the

Department of Medicine. Most IFs were detected on abdominal US, with the biliary system being the third most frequent anatomical location (asymptomatic gallstones, 11.7%) (Soulmati et al. 2010). Another study from Germany reported on 5720 screening US examinations in patients without abdominal symptoms. IFs of the biliary system were detected in 6.2% of patients, almost all of them being “silent gallstones.” In only 0.1% of cases were dilated bile ducts observed (Kremer et al. 1984). In a large cohort of asymptomatic subjects, whole-body computed tomography (CT) detected IF of the GB in 12.7% of cases (cholelithiasis in 6.1%) (Millor et al. 2019). Other frequently detected IFs of the biliary system are GBPs, focal or diffuse thickening/mass lesions of the GB wall, GB wall calcification, echoic/dense GB contents (“sludge,” “floating reflexes”), pericholecystic fluid, GB distension and bile duct dilatation (Sebastian et al. 2013; Bird et al. 2020).

A focused follow-up interview, with a review of previous findings, and a thorough clinical re-examination may reveal symptoms or findings associated with a presumed incidental imaging finding. Therefore, the following questions should be addressed after the discovery of a biliary IF:

1. Are there really no symptoms that potentially could be related to the biliary IF?
2. Has imaging of the biliary system been performed before and what findings were obtained?
3. Is there an increase in liver enzymes or inflammation parameters?

This clinical re-evaluation allows for re-appraisal and assessment of the clinical relevance of biliary IFs. All IFs should be documented carefully in the examination report using standardized terminology, representative images and video loops (Jenssen et al. 2019; Gupta et al. 2022; Wüstner et al. 2022). Clinical evaluation in the context of medical history, clinical and laboratory findings and a proposal for medical management is mandatory. Only a minority of biliary IFs deserve diagnostic work-up or follow-up (Sebastian et al. 2013; Bird et al. 2020). The frequency and clinical significance of some biliary IFs differ between pediatric and adult populations and with geographical and ethnic backgrounds.

Is the biliary IF (pre-)malignant?

Gallbladder cancer (GBC) represents 80%–95% of biliary tract cancers and is a deadly disease with an incidence rate of 3/100,000 worldwide, exhibiting substantial geographical and ethnic variations (Middle Africa 0.35/100,000, Western Europe 1.7/100,000, North America 1.8/100,000, South America 2.8/100,000, Eastern Asia 3.0/100,000). In some regions and ethnic

groups, especially in indigenous populations, GBC is an epidemic disease. An extremely high incidence has been reported from Bolivia, Pakistan, South Korea and Northern India. The northern Indian Ganges belt is considered to account for 10% of the global GBC burden. The most important risk factors are gallbladder calculi (particularly those ≥ 30 mm and *in situ* for > 20 y), a body mass index > 30 kg/m², GBPs (especially those ≥ 10 mm, solitary, broad based and associated with calculi) and chronic typhoid, paratyphoid and *Helicobacter pylori* infection of the GB mucosa. Rare, but strong risk factors are primary sclerosing cholangitis (PSC), congenital biliary dilatation and an anomalous pancreaticobiliary junction (Hundal and Shaffer 2014; Rawla *et al.* 2019; Miranda-Filho *et al.* 2020).

Because late diagnosis is common, the prognosis of GBC is dismal compared with those of other gastrointestinal cancers. According to Surveillance, Epidemiology, and End Results (SEER) Program data from 2010 to 2015, the 5-y survival rate in the United States was 28.8%, with a significant survival advantage for stages I (pT1 pN0 pM0: 82.7%) and II (pT2 pN0 pM0: 73.4%) compared with locally advanced, node-positive and metastatic GBC (stage IIIa: 31.9%; stage IIIb: 24.1%; stage IVb: 10%) (Zhu *et al.* 2020, 2022). Globally, a 5-y survival rate of only 5% is reported (Hundal and Shaffer 2014; Rawla *et al.* 2019). Therefore, detection and precise characterization of pre-malignant conditions of the GB and biliary tree, as well as the early detection of GBC and bile duct cancer, should be a challenging health care policy priority.

Currently, incidental detection of GBC and other biliary neoplasms with imaging modalities occurs rarely. At least 50% of all GBCs are found by pathological review of cholecystectomy specimens after surgery performed for presumed benign GB disease. The incidence of unexpected GBC in cholecystectomy cases operated for symptomatic gallstone disease and other pathology considered to be benign is 0.6%–0.7% and is associated with advanced age and comorbidities. Only a minority of GBCs detected unexpectedly in cholecystectomy specimens are early (Tis and T1) cancers, and up to 23% of GBC cases turn out to be unresectable (Choi *et al.* 2015; Pyo *et al.* 2020). These findings highlight the shortcomings of current imaging techniques and practice in detection of early-stage, asymptomatic GBC. Careful pre-operative imaging with identification of clinical findings that may indicate the presence of GBC can potentially influence patient management by expanding the pre-operative diagnostic work-up and modifying the surgical approach. The most important pre-operative US findings predicting GBC detected incidentally by surgery are large, often solitary GB calculi (≥ 30 mm), large (≥ 10 mm) and especially solitary GBPs (essentially

focal), GB wall thickening (without perivesical fluid) and an indistinct GB–liver interface (Zhu *et al.* 2015; Goussous *et al.* 2018; Kellil *et al.* 2021; Rana *et al.* 2022). The final diagnosis of GBC will always rest on histopathological findings.

Role of ultrasound and other imaging modalities

Ultrasound is by far the most common and useful primary imaging modality used to detect and characterize pathology of the GB and the biliary tree. US diagnosis of cholecystolithiasis, acute cholecystitis, bile duct dilatation and obstructive jaundice is highly reliable (Jenssen *et al.* 2019; Murphy *et al.* 2020) and recommended in guidelines (Gutt *et al.* 2018). A multimodality imaging approach is often required for the differentiation of biliary IFs, often including advanced transabdominal and endoscopic US (EUS) techniques, CT, magnetic resonance imaging (MRI), including magnetic resonance cholangiopancreatography (MRCP), and occasionally positron emission tomography (PET). Transabdominal US using high-frequency probes (7–9 MHz, high-resolution US) can help to detect and characterize pathological GB wall thickening and determine the T stage of GBC by visualizing the detailed wall layer pattern and wall pathology (Jang *et al.* 2009; Joo *et al.* 2013, 2014; Bang *et al.* 2014; Kim *et al.* 2015; Lee *et al.* 2017; Choi *et al.* 2018; Dong *et al.* 2020a, 2020b). EUS has the advantage of having the highest resolution (5–13 MHz) for examination of the ampullary region, the extrahepatic bile duct and the GB, and is the most sensitive technique for the detection of CBD calculi and assessment of the etiology of distal bile duct obstruction (Garrow *et al.* 2007; Fusaroli *et al.* 2012; Jenssen 2013; Navaneethan *et al.* 2015; De Castro *et al.* 2016; Meeralam *et al.* 2017; Tanaka *et al.* 2021).

Color Doppler Imaging (CDI), new highly sensitive Doppler techniques visualizing microvascular flow and contrast-enhanced US (CEUS) can be performed using standard convex probes and high-frequency linear probes to assess the vascularity of indeterminate wall thickening and focal lesions of the GB and bile ducts, to differentiate pseudo-tumorous biliary sludge from GB neoplasms and to diagnose vascular complications and infiltration caused by biliary pathology (Wang *et al.* 2016; Cheng *et al.* 2018; Ratanaprasatporn *et al.* 2018; Sidhu *et al.* 2018; Kalra *et al.* 2019; Kin *et al.* 2020; Liang and Jing 2020; Yu *et al.* 2020; Behzadmehr and Salarzaei 2021). CT is the non-invasive diagnostic test of choice for diagnosis, staging and resectability assessment of biliary cancer. Dual-energy CT and MRI improve diagnosis of cholelithiasis and of wall thickening of the GB and bile ducts (Ratanaprasatporn *et al.* 2018; Kalra *et al.* 2019). Both MRCP and EUS are the gold standard techniques for evaluation of the bile ducts, with MRCP allowing high-

quality delineation of the complete biliary tree (Romagnuolo et al. 2003; Shanmugam et al. 2005; Welle et al. 2020).

Role of sampling techniques

Because of the relatively high procedural risk, small lesion size and limited diagnostic yield, percutaneous image-guided sampling of focal lesions or wall thickening of the GB and the biliary tree is rarely performed and not recommended in current European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines (Sidhu et al. 2015). Large series of US-guided fine-needle aspiration of GB wall lesions are reported from northern India, where the incidence of both GBC and xanthogranulomatous cholecystitis is very high. An acceptable high diagnostic yield of approximately 85%–90% and no major complications have been reported in two retrospective cohort series including nearly 1400 patients. Whether incidentally detected GB wall pathologies were also included was not reported (Rana et al. 2016; Kumar et al. 2017).

Whereas EUS-FNA of indeterminate or suspicious biliary strictures and mass lesions is recommended by recent EFSUMB and European Society of Gastrointestinal Endoscopy (ESGE) guidelines (Jenssen et al. 2016; Dumonceau et al. 2017), EUS-FNA of GB wall lesions has been reported in only small case series (Jacobson et al. 2003; Meara et al. 2006; Hijioka et al. 2010, 2012; Wu et al. 2011; Kim et al. 2012; Ogura et al. 2014; Singla et al. 2019), with only one study including asymptomatic cases (Ogura et al. 2014). In conclusion, percutaneous US- and CT-guided as well as EUS-guided fine-needle sampling for assessment of incidentally detected focal and general gallbladder wall thickening is feasible and may be decided on an individual basis considering the potential risk of bile leakage into the peritoneal cavity after a gallbladder biopsy. In countries with easy access to laparoscopic cholecystectomy, FNA of GB wall pathologies does not have clinical relevance.

Role of surgery

Laparoscopic cholecystectomy is a very safe surgical technique with low mortality (0.08–0.14%) and morbidity. Bile duct injury (0.08%–0.5%), bile leak (0.42%–1.1%) and surgical site infections (1.9% with prophylactic antibiotics) are rare. More common but less serious complications are retained common bile duct calculi (0.8%–5.7%), postcholecystectomy syndrome (10%–15%) and postcholecystectomy diarrhea (5%–12%) (Pucher et al. 2018; Ahmad and Faulx 2020; Yang et al. 2021).

Therefore, in the case of GB IFs, which are associated with an increased cancer risk or where malignancy cannot be reliably excluded by non-invasive or

minimally invasive diagnostic techniques, surgical management is recommended. Indications may vary depending on geographical region or ethnicity. The frequency of GBC in patients operated for thickened GB wall without obvious malignant features is relatively low, and most patients can be treated by laparoscopic cholecystectomy (Srikanth et al. 2004).

INCIDENTAL FINDINGS OF THE GALLBLADDER WALL

Gallbladder polyps

Definition, risk assessment and epidemiology. The term gallbladder polyp refers to any elevated immobile lesion on the surface of the GB mucosa without shadowing on US. An early pathological description by Christensen and Ishak (1970) differentiated between true (neoplastic) polyps and pseudopolyps (non-neoplastic). Pseudopolyps (cholesterol polyps, fibromyoglandular polyps, polypoid pyloric gland metaplasia, inflammatory polyps, focal adenomyomatosis) in general have no malignant potential (Bhatt et al. 2016; Christensen and Ishak 1970; Taskin et al. 2020a). Rarely, non-neoplastic GBPs with high-grade dysplasia have been described in the pathological literature (Taskin et al. 2020a, 2020b). True, neoplastic GBPs include intracholecystic papillary-tubular neoplasms (IPTNs, previously referred to as adenomas), rare benign and malignant neoplasms and adenocarcinomas (Christensen and Ishak 1970; Adsay et al. 2012; Saei Hamedani and Garcia-Buitrago 2020; Roa et al. 2021). IPTNs are primarily benign; however, they might have malignant potential as seen in the adenoma–carcinoma sequence in colorectal cancer (Kozuka et al. 1982; Aldridge and Bismuth 1990; Adsay et al. 2012). Five subtypes have been described, which differ in terms of their histopathology and risk of malignancy. Importantly, IPTNs represent precursor lesions of only a minority of GBCs (5%–23%), and the duration of malignant transformation remains unknown (Kozuka et al. 1982; Aldridge and Bismuth 1990; Adsay et al. 2012; Albores-Saavedra et al. 2012; Hundal and Shaffer 2014; Wiles et al. 2014; Saei Hamedani and Garcia-Buitrago 2020; Roa et al. 2021).

Gall bladder polyps are commonly detected as IFs on abdominal US or on histopathological examination after cholecystectomy. In rare cases, GBPs can present with symptoms and require surgery if they cause cholecystitis, acute pancreatitis or obstructive jaundice by detachment from the mucosal surface (Taskin et al. 2020a, 2020b).

The prevalence of GBPs is 5%–12.1% in the global population (Heyder et al. 1990; Jorgensen and Jensen 1990; Collett et al. 1998; Okamoto et al. 1999; Myers et al. 2002; Lin et al. 2008; Park et al. 2008; Kratzer et al.

2011; Lee *et al.* 2014b; Heitz *et al.* 2019; Szpakowski and Tucker 2020). According to systematic reviews, the vast majority (65%–97%) of these GBPs are pseudopolyps (Bhatt *et al.* 2016; Elmasry *et al.* 2016; Martin *et al.* 2018). The prevalence of IPTNs (“adenomas”) among individuals with incidentally detected GBPs is below 5% (Kratzer *et al.* 1999; Okamoto *et al.* 1999; Taskin *et al.* 2020a). Among GBPs found in cholecystectomy specimens, 8.4% are malignant (Bhatt *et al.* 2016). Risk factors for malignancy of GBPs have been identified and include age >50 y (Bhatt *et al.* 2016; Lee *et al.* 2016; Chou *et al.* 2017; Sun *et al.* 2019) and Indian ethnicity (Aldouri *et al.* 2009; Gautam *et al.* 2021). Up to 60% of GBPs found in patients with PSC or gastrointestinal polypoid syndromes are neoplastic (Buckles *et al.* 2002; Zielinski *et al.* 2009; van Erp *et al.* 2020).

Imaging and diagnostic work-up

Transabdominal ultrasound. GBPs are often detected incidentally on transabdominal US (Elmasry *et al.* 2016; Foley *et al.* 2022; Jorgensen and Jensen 1990). According to a recent systematic review, the pooled sensitivity of transabdominal US for detection of GBPs is 84%, with a high specificity of 96% (Wennmacker *et al.* 2018). GBPs detected on transabdominal US can be classified, using B-mode, CDI and CEUS criteria, into pedunculated or sessile lesions and described with respect to location, number, size, shape, stalk width and relation to GB wall layering, surface, echogenicity, internal echo pattern (including presence of cysts, hyperechoic foci and calcifications), vascularity and artifacts (Liu *et al.* 2018, Okaniwa 2021; Wennmacker *et al.* 2021a, 2021b; Wu *et al.* 2018) (Fig. 1).

Differentiation between pseudopolyps and true polyps and reliable identification of features suggestive of malignancy are prerequisites for a risk-adjusted medical management after detection of GBPs. However, polypoid lesions of the GB often seem to be inadequately described in US reports (Abdullah *et al.* 2019), and only a few studies have compared US features and pathological criteria of GBPs (Sugiyama *et al.* 2000; Zielinski *et al.* 2009; Zhang *et al.* 2010, 2021; Guo *et al.* 2015; Kim *et al.* 2016; Chou *et al.* 2017; Liu *et al.* 2018; Sun *et al.* 2019; Wennmacker *et al.* 2019, 2021a, 2021b; Fujiwara *et al.* 2021; Bao *et al.* 2021).

Although B-Mode US alone is unable to reliably distinguish pseudopolyps from true polyps (Wennmacker *et al.* 2018; Martin *et al.* 2018; Ostapenko *et al.* 2020), it represents the basis of risk assessment:

1 Size. GBP diameter is a significant risk factor for neoplastic character and malignancy of GBPs, and size measurement of GBPs has been reported to be reliable

(Lee *et al.* 2020). The vast majority of all GBPs are <6 mm, and the probability of their being malignant is close to zero (Zielinski *et al.* 2009; Corwin *et al.* 2011; Kratzer *et al.* 2011; Pedersen *et al.* 2012; Babu *et al.* 2015; Bhatt *et al.* 2016; Elmasry *et al.* 2016; Heitz *et al.* 2019; Fujiwara *et al.* 2021; Metman *et al.* 2020; Szpakowski and Tucker 2020; Bao *et al.* 2021; Walsh *et al.* 2022). One systematic review reported malignancy in no GBP measuring <5 mm and in only 1.2% of GBPs ≤10 mm (Babu *et al.* 2015). On the other hand, according to meta-analytic data, GBPs >10 mm are malignant in 7.6% (Elmasry *et al.* 2016) to 8.5% of cases (Babu *et al.* 2015), respectively. Statistically, the optimum size cutoff for surgical treatment is 10 mm (Bhatt *et al.* 2016; Wennmacker *et al.* 2019). Limitations of a rigid decision threshold based on GBP size are as follows:

- As many as 15.3% of malignant GBPs measure <10 mm (Bhatt *et al.* 2016).
- Several other risk factors (*e.g.*, single, sessile morphology, age >50 y)
- significantly increase the malignancy risk of GBPs <10 mm (Bhatt *et al.* 2016).
- A cutoff of 10 mm proved not to be safe in some Asian cohorts (Aldouri *et al.* 2009; Park *et al.* 2009; Chou *et al.* 2017).
- US measurement tends to overestimate GBP size in comparison to histopathologic measurement (Guo *et al.* 2015; Wennmacker *et al.* 2021b).
- The negative (NPV) and positive (PPV) predictive values of a 10-mm cutoff size are relatively low at 65.1% and 72.9%, respectively, indicating inadequate management including surgery without (pre)malignant findings in surgical pathology in nearly one-third of cases (Wennmacker *et al.* 2019).

These data agree well with those of a recent pathologic study ($n = 643$), in which 90% of GBPs ≥10 mm and 15% of polyps <10 mm were classified as neoplastic. The NPV of GBP size 6–9 mm for neoplasia was only 86% (Taskin *et al.* 2020a).

2 Growth status. Significant growth of GBPs <10 mm has been suggested to predict the malignant potential of GBPs (Koga *et al.* 1988; Moriguchi *et al.* 1996; Park *et al.* 2008; Cairns *et al.* 2012), but a systematic review did not find enough evidence to establish a correlation between growth of GBP and development of malignancy (Wiles *et al.* 2014). In studies included in this systematic review, an increase in GBP size was observed in only 1%–23% of cases, but case numbers were small and follow-up was relatively short (Wiles *et al.* 2014). Subsequent studies reported fluctuations in GBP size and number at follow-up and a lack of correlation between polyp growth and

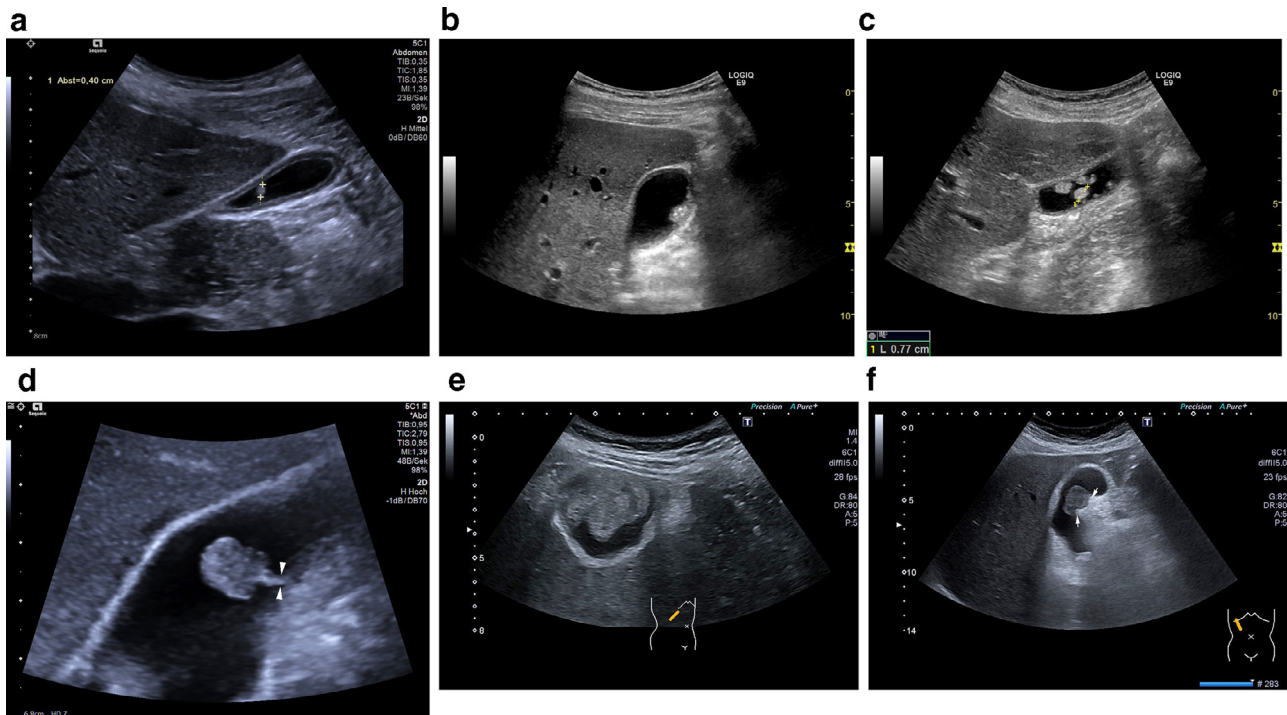


Fig. 1. Examples of incidentally detected gallbladder polyps (GBPs). (a) Small (4 mm) echogenic round GBP with a smooth surface, typical example of a cholesterol polyp. Neither diagnostic work-up nor follow-up is necessary. (b) Eight-millimeter echogenic oval GBP with smooth surface and hyperechoic spots, predictive of a cholesterol polyp. Follow-up is recommended. (c) Multiple echogenic round and oval GBPs with a maximum diameter of 7.7 mm. Follow-up is recommended. (d) Echogenic, inhomogeneous polyp with lobulated surface, thin stalk and a diameter of 12 mm. Diagnostic work-up was performed and cholecystectomy recommended. (e) Large (37 mm), echogenic GBP with lobulated outline and smooth outer GB wall. Diagnostic work-up was performed and cholecystectomy performed. (f) Large (22 mm), broad-based hypo-echoic GBP with smooth surface, but disrupted GB wall (*arrowheads*). Open cholecystectomy was performed and pT3 GBC was diagnosed. Figures provided by the authors: C.F.D. (a), T.L. (b, c), C.J. (d–f).

malignancy risk (Heitz et al. 2019; Rafaelsen et al. 2020; Szpakowski and Tucker 2020; Bao et al. 2021; Walsh et al. 2022). The largest study so far included a cohort of 6359 patients with GBPs and follow-up up to 20 y and found GBP growth to be common (66.2% in GBPs <6 mm and 52.9% in GBPs of 6–9 mm) and slow, and growth beyond the 10-mm threshold not associated with subsequent diagnosis of GBC. Of relevance to follow-up strategies is the observation that two of three GBCs were diagnosed within the first year of initial GBP diagnosis (Szpakowski and Tucker 2020). Long-term observation of GBP size beyond 24 mo therefore seems not to be useful for detection of malignant GBPs.

3 Number of GBPs. Single GBPs are more likely to be (pre-)malignant than multiple GBPs (Bhatt et al. 2016; Wennmacker et al. 2019; Zhang et al. 2021).

4 Shape. Sessile GBPs are significantly more frequently associated with malignancy than pedunculated GBPs with an odds ratio of 7.32 (Bhatt et al. 2016),

probably because most GBCs arise from flat dysplastic epithelium (Kwon et al. 2009; Guo et al. 2015; Kim et al. 2015, 2016; Lee et al. 2016; Xu et al. 2017; Choi et al. 2018; Liu et al. 2018; Miwa et al. 2019; Sun et al. 2019; Fujiwara et al. 2021; Zhang et al. 2021). Accordingly, a low long axis/short axis diameter (height/width) ratio (<0.9 or <1.05) was described as a predictive feature of IPTNs (“adenomas”) (Liu et al. 2018; Zhu et al. 2021a).

5 Echogenicity and echo pattern. Typically, non-neoplastic GBPs are described to be hyperechoic with a smooth surface (Sugiyama et al. 2000; Kim et al. 2015, 2016). Hyperechoic foci have been described to be characteristic features of cholesterol polyps (Fig. 1b) and small cysts and hyperechoic foci of focal adenomyomatosis (Sugiyama et al. 2000; Kim et al. 2016; Liu et al. 2018; Wennmacker et al. 2021a, 2021b; Zhu et al. 2021a). In the pathological literature, typical morphological criteria of the different types of neoplastic and non-neoplastic GBPs have been described (Adsay et al. 2012;

Taskin *et al.* 2020a, 2020b), which potentially may be evaluated using high-resolution US techniques.

6 Artifacts. Although a wide spectrum of artifacts during US examination of the GB may interfere with correct diagnosis (side-lobe artifacts, slice-thickness artifacts, the “searchlight phenomenon,” which is localized anterior to ring-down artifacts arising from adjacent duodenal gas) (Naganuma *et al.* 2016), a few artifacts can contribute to differential diagnosis. Sometimes, directly behind a pseudopolyp (cholesterol polyp or focal adenomyomatosis), the hyperechoic V-shaped “comet-tail” artifact can be seen, caused by reverberations of cholesterol crystals (Shapiro and Winsberg 1990; Sugiyama *et al.* 2000). The comet-tail artifact is observed in several benign GB pathologies, but not in GB malignancy (Oh *et al.* 2019). The more intense equivalent of the comet-tail artifact on CDI is the twinkling artifact (Yu *et al.* 2012; Hammad *et al.* 2016).

Multiparametric ultrasound. To improve the differentiation of GBPs, several US-based imaging modalities, including conventional B-Mode US, high-frequency US, CDI and CEUS, have been suggested. Multiparametric and algorithmic approaches that combine several US features to predict the malignancy potential of GBPs are used (Liu *et al.* 2018; Wu *et al.* 2018; Wennmacker *et al.* 2019, 2021a, Chen *et al.* 2020) (Figs. 2–4). Recently, scoring systems including weighted B-mode and CDI features (maximum or short diameter, height/width ratio, base diameter, echogenicity, hyperechoic spots and presence of vascularity) were reported to improve the differential diagnosis of GBPs (Liu *et al.* 2018; Zhang *et al.* 2021; Zhu *et al.* 2021a).

If technically possible, high-resolution US should be applied to detect lobulated surface contour, presence of central vessels and hypo-echoic foci within the polyp as typical findings of neoplastic GBPs (Jang *et al.* 2009; Kim *et al.* 2015; Choi *et al.* 2018; Chen *et al.* 2020). However, according to pathological literature reports, benign (injury-related) fibromyoglandular polyps, which are associated with gallstones and chronic cholecystitis, are also characterized by a broad base or short thick stalk, lobulation and a fibromuscular stroma with vessels (Taskin *et al.* 2020a, 2020b).

Promising preliminary data on the use of automated digital image analysis and neuronal networks to improve the specificity and PPV of US diagnosis of (pre-)malignant GBPs have been published recently (Chen *et al.* 2020; Jeong *et al.* 2020; Yuan *et al.* 2020; Kim *et al.* 2021).

The use of CEUS is well established in the clinical practice of hepatic and abdominal US (Dietrich *et al.* 2018, 2020a; Sidhu *et al.* 2018); however, its role in

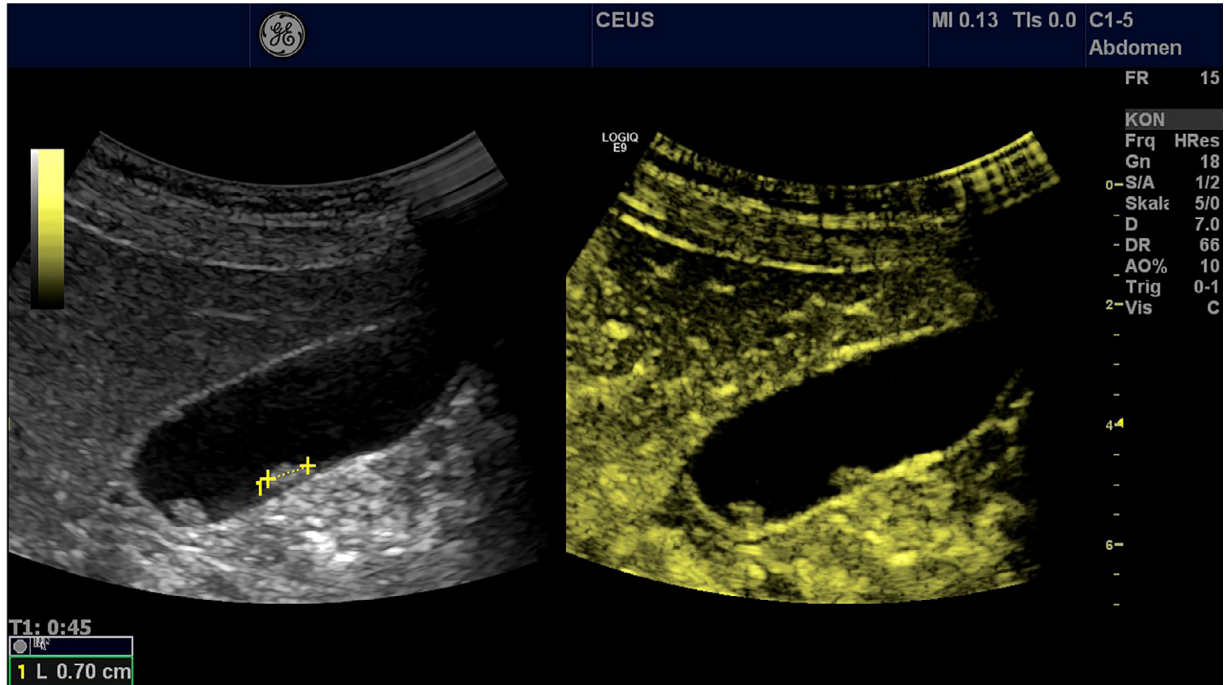
characterizing GBPs has only been evaluated in small studies (Behzadmehr and Salarzaei 2021). CEUS can definitely discriminate between polypoid-appearing sludge/debris and GBPs resulting from the absence or presence of vascularity (Serra *et al.* 2018). CEUS has revealed tumor enhancement and tortuous vessels in GBCs >10 mm; the diagnostic criteria are still subject to research (Numata *et al.* 2007; Zheng *et al.* 2013; Wang *et al.* 2016; Cheng *et al.* 2018; Zhang *et al.* 2018; Liang and Jing 2020). A wide vascular stalk and a fast and intense enhancement pattern seem to be predictive of IPTNs (“adenomas”), whereas heterogeneous enhancement and an irregular vascular pattern predict malignancy (Sidhu *et al.* 2018; Miwa *et al.* 2019; Dong *et al.* 2020a; Fei *et al.* 2021; Zhu *et al.* 2021b) (Figs. 3 and 4). In a recent meta-analysis of studies with an overall prevalence of IPTNs (“adenomas”) of 16% among GBPs, the pooled PPV and NPV of CEUS for the diagnosis of IPTNs (“adenomas”) were calculated to be 86% and 85%, respectively (Behzadmehr and Salarzaei 2021). However, according to EFSUMB guidelines, the role of CEUS in the differential diagnosis of GBPs is not yet well established (Sidhu *et al.* 2018).

Ultrasound elastography may reveal increased stiffness in large and superficially located GBC (Badea *et al.* 2014), whereas benign GBPs are characterized by low stiffness (Teber *et al.* 2014). However, elastographic US techniques need to be evaluated prospectively in larger cohorts.

Endoscopic ultrasound. Because of the proximity of the gastric antrum and duodenum to the GB and higher US frequencies (5–13 MHz), EUS can characterize the morphology of GBPs with very high resolution (Sugiyama *et al.* 2000; Azuma *et al.* 2001; Jang *et al.* 2009; Tanaka *et al.* 2021) (Fig. 5).

In a small surgical cohort, EUS correctly distinguished between true and pseudopolyps in 97% of cases (Sugiyama *et al.* 2000). A lower accuracy of 40% was reported for GBPs <10 mm compared with GBPs >10 mm (88.9%) (Cheon *et al.* 2009). A Cochrane analysis did not report sufficient evidence of the superiority of EUS over transabdominal US in differentiating GBPs (Choi *et al.* 2013; Wennmacker *et al.* 2018). With color Doppler-EUS and contrast-enhanced harmonic EUS (CEH-EUS), a high vascularity was predictive of neoplastic GBPs, whereas an irregular vessel pattern and perfusion defects aided in the diagnosis of malignant polyps (Liang and Jing 2020). A recent guideline of the Asian Federation of Societies for Ultrasound in Medicine and Biology (AFSUMB) suggested that CEH-EUS may be used for characterization of GBPs, but the quality of evidence was rated low (Kitano *et al.* 2021).

a



b

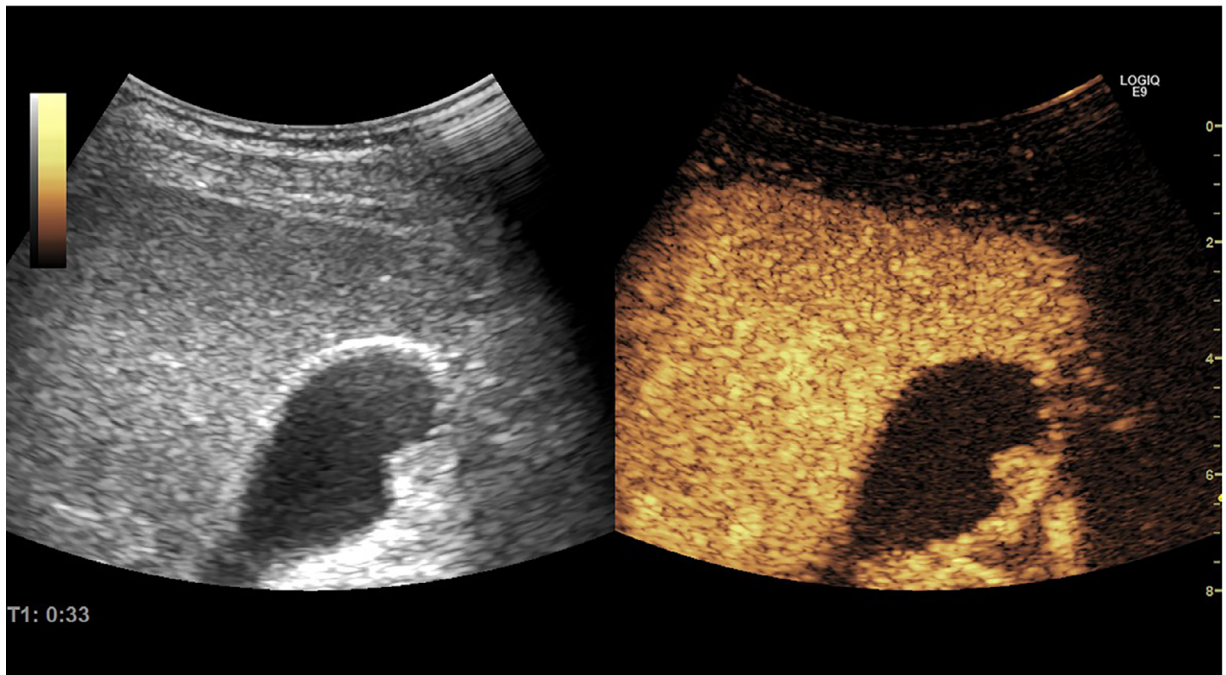


Fig. 2. Contrast-enhanced ultrasound image of small cholesterol polyps of the gallbladder. Note that cholesterol polyps typically exhibit homogeneous enhancement (a, b). Figures provided by the authors: C.F.D. (a), T.L. (b).

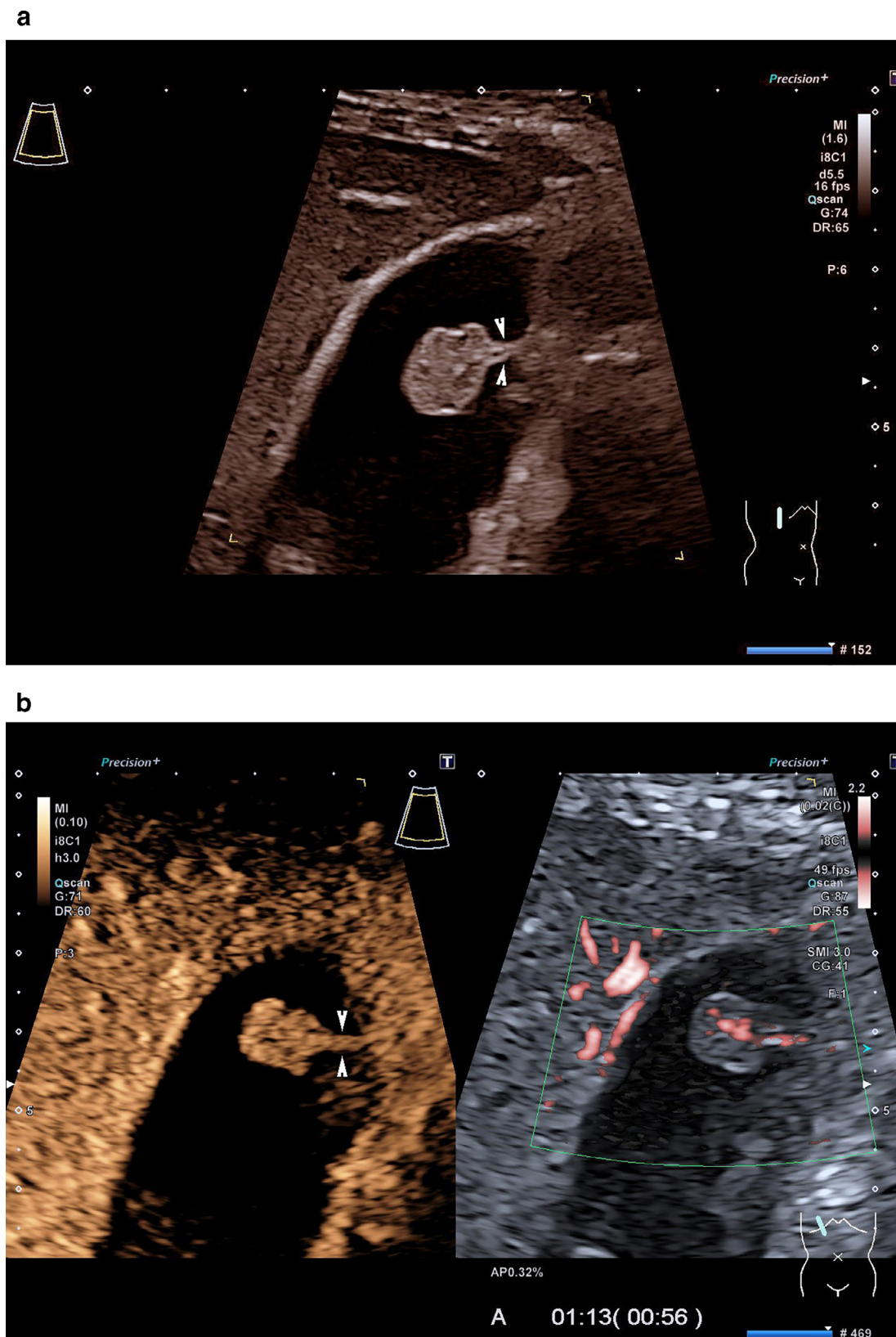


Fig. 3. (a) Multiparametric ultrasound characterization of the 12-mm gallbladder polyp seen in Figure 1d using a high-frequency linear probe. Slightly inhomogeneous echo pattern, lobulated outline, thin stalk (*arrowheads*). (b) Contrast-enhanced ultrasound combined with high-sensitivity color Doppler imaging (superb microvascular imaging) visualizes the rich vascularity of the GBP with a central feeding vessel. Figures provided by the authors: C.J. (a, b).

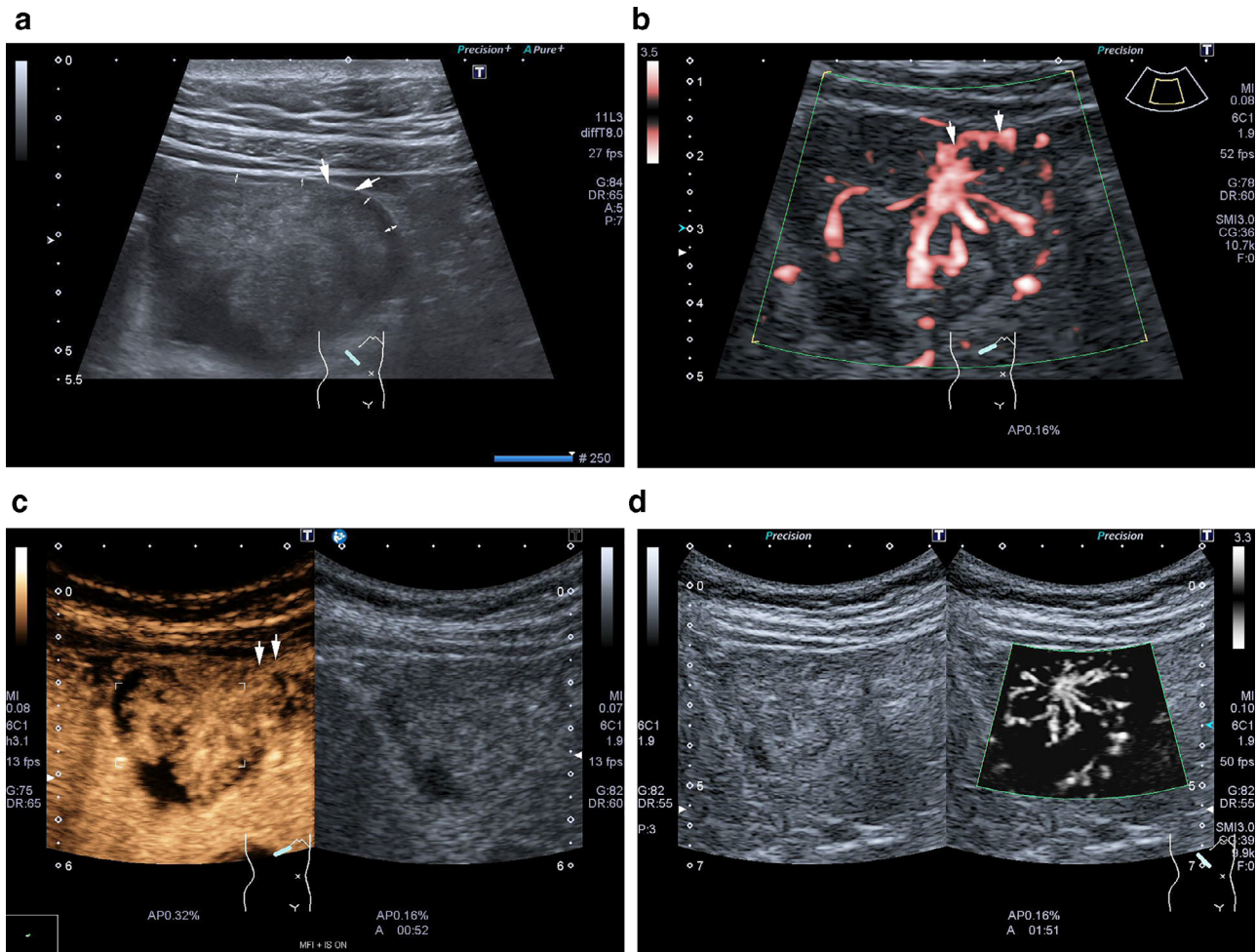


Fig. 4. (a) Multiparametric ultrasound characterization of the large gallbladder polyp depicted in [Figure 1e](#) using a high-frequency linear probe. Slightly inhomogeneous echo pattern, 4-mm base (*arrowheads*), but smooth echogenic outer contour of the gallbladder wall without focal thickening. (b) High-sensitivity color Doppler image (superb microvascular imaging [SMI]) visualizes a branching tortuous feeding vessel. (c, d) Contrast-enhanced ultrasound (c) and contrast-enhanced SMI (d) reveal the rich vascularity of the gallbladder polyp with the strong feeding vessel (*arrowheads*) without non-enhancing areas and a wheel-spoke vascular pattern. Laparoscopic cholecystectomy was performed, and a small-base mucosal polypoid adenocarcinoma without submucosal infiltration (pT1a) was described by the pathologist.

Figures provided by the authors: C.J. (a–d).

Other imaging modalities. CT, MRI and PET/CT have a role in the diagnosis and staging of GBP. Their value in diagnosing and characterizing small GBPs is, however, limited by spatial resolution and motion artifacts ([Jang et al. 2009](#); [Irie et al. 2011](#)). Diffusion-weighted MRI ([Irie et al. 2011](#); [Ogawa et al. 2012](#); [Kitazume et al. 2016](#); [Kuipers et al., 2021](#)) and dual-energy CT ([Yin et al. 2021](#)) have been described as helpful in discriminating between benign and malignant GBPs, but case numbers and experience are limited. Recently, [Wennmacker et al.](#) suggested a flowchart for GBP characterization based on a targeted abdominal US examination including high-frequency US and complementary MRI in selected cases (GBPs indeterminate with US and single homogeneous GBPs ≥ 10 mm) with limited

diagnostic gain. A high signal intensity in T1-weighted images was found to be a characteristic feature of cholesterol polyps, while foci of decreased apparent diffusion coefficient (ADC) values were found in one IPTN (“adenoma”) with high-grade dysplasia ([Wennmacker et al. 2021a](#)). The most recent European guidelines do not recommend the routine use of imaging modalities other than abdominal US for the diagnostic workup of GBPs, but suggest the use of CEUS and EUS in difficult cases in centers with appropriate resources and expertise ([Foley et al. 2022](#)).

Treatment and follow-up strategies for incidental GBPs

The diagnostic challenge is to identify the small group of patients with malignant and premalignant

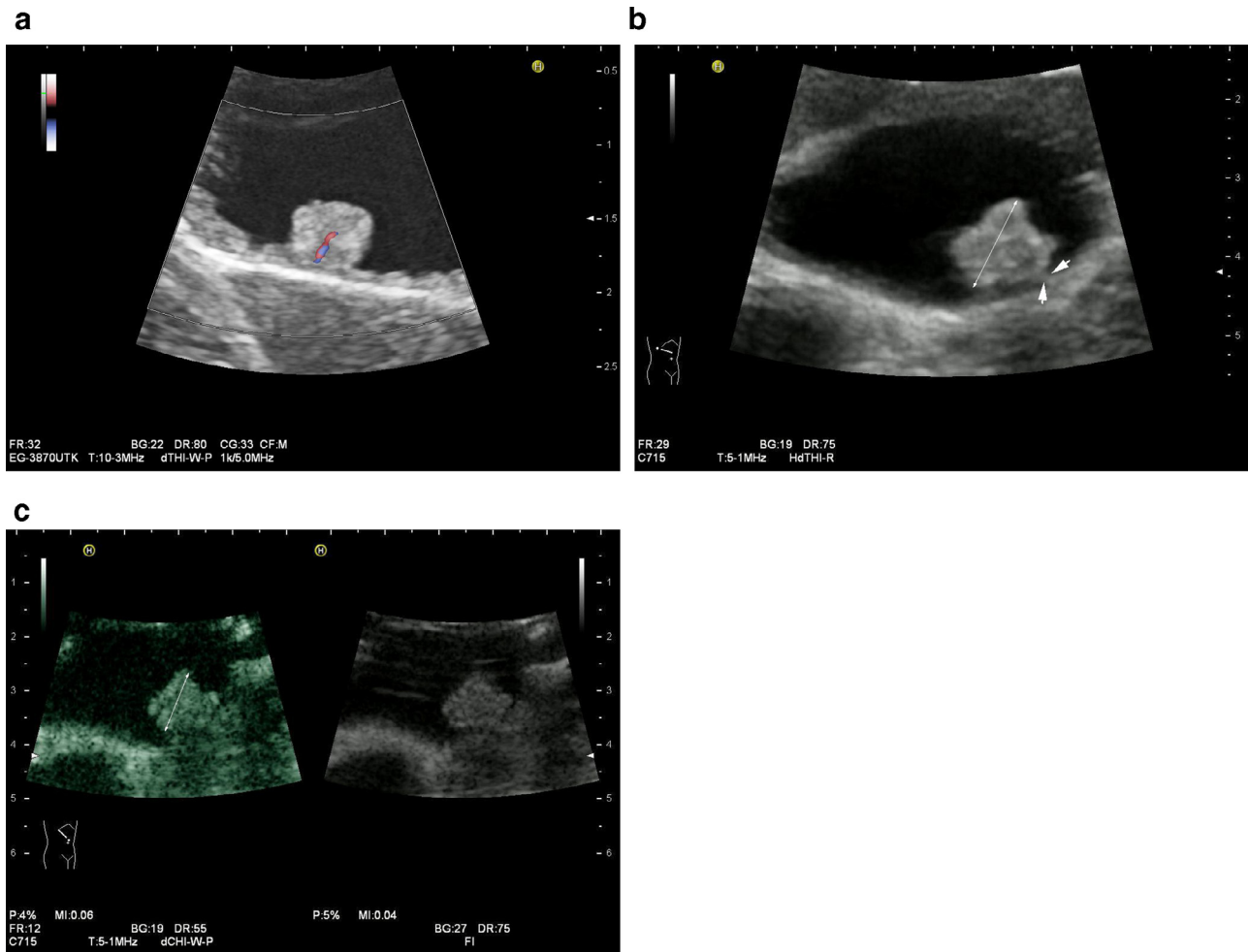


Fig. 5. Endoscopic ultrasound characterization of gallbladder polyps. (a) An echogenic 5-mm gallbladder polyp with a central feeding vessel revealed on color Doppler imaging (cholesterol polyp). (b, c) A slightly heterogeneous and lobulated gallbladder polyp 13 mm in diameter (marked with *double arrows*) and a thin stalk (*arrowheads*) (b) reveals enhancement after intravenous injection of 4.8 mL of the US contrast agent SonoVue (c) and was diagnosed as gallbladder adenoma without dysplasia. Figures provided by the authors: C.J. (a–c).

GBPs for whom cholecystectomy is indicated, spare the remaining large group of patients with non-neoplastic GBP unnecessary cholecystectomy and dispense with follow-up examinations to reduce the substantial economic cost and psychological implications.

Unfortunately, the level of evidence for guidelines on follow-up and treatment of GBP is low, and randomized controlled trials are lacking. The general consensus is that patients with GBPs ≥ 10 mm and patients with GBPs and possible biliary symptoms should be evaluated for cholecystectomy (Koga *et al.* 1988; Sebastian *et al.* 2013; Bhatt *et al.* 2016; Gutt *et al.* 2018; Bird *et al.* 2020; Foley *et al.* 2022). A 2013 white paper on incidental findings in the GB and biliary system by the American College of Radiology (ACR) (Sebastian *et al.* 2013) and a 2020 clinical practice guideline from the Canadian Association of Radiologists (CAR) (Bird *et al.* 2020)

both recommended abstaining from evaluation and follow-up of GBPs ≤ 6 mm and performing an annual US follow-up of GBPs of 6–9 mm for 5 y with surgical consultation in case of growth ≥ 2 mm (Sebastian *et al.* 2013; Bird *et al.* 2020). The first joint guidelines of the European Society of Gastrointestinal and Abdominal Radiology (ESGAR), European Association for Endoscopic Surgery and other Interventional Techniques (EAES), International Society of Digestive Surgery—European Federation (EFISDS) and the ESGE published in 2017 have recommended, in addition, monitoring of patients with GBPs < 6 mm (1, 3 and 5 y). For GBPs of 6–9 mm, an initial check at 6 mo was recommended in addition to annual follow-up. For the first time, patient-specific risk factors for malignancy (age > 50 y, diagnosis of PSC, Indian ethnicity, sessile polyp morphology, focal GB wall thickening > 4 mm) were

Table 1. Weighted US criteria useful for characterizing GBPs

US feature of GBP(s)	Typical of/ predictive of	Risk of malignancy
Number ^{*,†}		
Solitary	Neoplastic polyps and focal adenomyomatosis	Increased
Multiple	Cholesterol polyps	Low
Size and growth ^{*,‡}		
≥10 mm	Neoplastic polyps and focal adenomyomatosis	High
6–9 mm	Cholesterol polyps and other benign polyps	Low
<6 mm	Cholesterol polyps and other benign polyps	Very low
Growth ≥2 mm or >10 mm	Belongs to the natural history of benign GBPs	Ambiguous
Shape [*]		
Sessile with disruption and/or focal thickening of GB wall ≥4 mm	Malignant polyp	High
Sessile without wall disruption and without thickening of GB wall ≥4 mm	Neoplastic polyps and focal adenomyomatosis	Increased
Pedunculated	Cholesterol polyps and other benign GBPs	Low
Surface [*]		
Irregular/ lobulated	Neoplastic and benign fibromyoglandular polyps	Increased
Smooth	Cholesterol polyps	Low
Special US features [*]		
Small cysts	Focal adenomyomatosis	Low
Reverberation artifacts	Focal adenomyomatosis, cholesterol polyps	Low
Hyperechoic foci	Cholesterol polyps, focal adenomyomatosis	Low
Focal GB wall disruption	Malignant GBP, focal adenomyomatosis	Increased
Focal GB wall thickening ≥4 mm	Malignant GBP, focal adenomyomatosis	Increased
Echogenicity		
Hypo-echoic/ isoechoic	Neoplastic polyps, focal adenomyomatosis, several types of pseudopolyps	Ambiguous
Hyperechoic	Cholesterol polyps	Very low
Contrast-enhancement and high-sensitivity CDI techniques (microvascular imaging) [§]		
Arterial hyperenhancement	Neoplastic and malignant GBPs, but also non-neoplastic GBPs	Increased
Heterogeneous enhancement	Malignant GBPs	High
Irregular vessel pattern	Malignant GBPs	High
Late-phase hypo-enhancement	Malignant GBPs	High
Homogeneous enhancement	Benign GBPs	Low
Continuous mucosal layer enhancement	Benign GBPs	Low

CDI = color Doppler imaging; GB = gallbladder; GBP = gallbladder polyp; US = ultrasound.

* Adequate distension of the GB is required to allow complete evaluation of the wall and the lumen (Gupta et al. 2022).

† In the case of multiple GBPs, their number should be indicated. The measurement of the largest GBP is sufficient.

‡ Measurement in the long axis of the GBP is recommended, which can be supplemented by measurement perpendicular to the long axis (short axis) to give the height/width ratio as a parameter to describe polyp shape.

§ Settings of the US machine for performing CDI modalities or CEUS should be adjusted for detecting tiny vessels with low flow velocities, and US contrast agent dose should be adapted to the transducer frequency (Dietrich et al. 2018; Lowe et al. 2021).

included in the decision on management (Wiles et al. 2017). These European guidelines have been updated very recently, and now recommend the surveillance of GBPs ≤5mm only in the presence of risk factors for malignancy and of all GBPs 6–9 mm without risk factors for malignancy at 6 mo, 1 y and 2 y for all cases. For patients with GBPs of 6–9 mm in the presence of risk factors for malignancy, evaluation for cholecystectomy is recommended. Surveillance can be stopped after 2 y in the absence of growth. For growth ≥2 mm and an achieved diameter <10 mm, an individual decision is suggested, taking into account current GBP size and patient-specific risk factors (Foley et al. 2022).

All of the aforementioned recommendations for risk stratification and management of GBPs refrain from including US criteria beyond size, growth and sessile

morphology (Bird et al. 2020; Foley et al. 2022; Sebastian et al. 2013). Wennmacker et al. (2021a) recently evaluated a standardized US approach (“targeted trans-abdominal ultrasound”) based on an expanded set of criteria and including a high-frequency US examination and determined substantial increased diagnostic sensitivity compared with standard US. As combining different US and other imaging features within a decision algorithm may improve clinical management of GBPs (Wennmacker et al. 2019, 2021a), especially for patients with GBPs of intermediate size (7–9 mm), we suggest analyzing malignancy risk based not only on polyp size and risk factors for malignancy but including additional established US criteria (Table 1). We acknowledge that the association of US criteria, including CEUS features, with the risk of malignancy in GBPs is based on low-

Table 2. Recommendations for management of incidentally detected GBPs

GBP size	Management
≥10 mm*	Surgical treatment (cholecystectomy) is recommended. High-resolution EUS and CEUS may be performed prior to cholecystectomy to evaluate malignancy risk and potential infiltration. In the presence of signs of infiltration/local spread, surgery should be performed at a hepatobiliary center.
7–9 mm*	In patients without individual risk factors for malignancy or suspicious B-mode US features beyond size, follow-up after 6, 12 and 24 mo is recommended. [†] Evaluation using high-resolution and/or CEUS or EUS may be performed in patients with <ul style="list-style-type: none"> • Individual risk factors (Indian ethnicity, history of PSC, age > 50 y) OR • B-Mode US features beyond size associated with increased/high risk of malignancy (Table 1) OR • Growth ≥2 mm* Surgical treatment should be offered to patients with <ul style="list-style-type: none"> • Indian ethnicity • PSC AND/OR • US features (B-mode US, high-resolution EUS, CEUS) associated with high risk of malignancy (Table 1)
≤6 mm*	In patients without individual risk factors or suspicious B-mode US features beyond size, no evaluation, no follow-up and no treatment are recommended. Follow-up after 6, 12 and 24 mo [†] should be considered in: <ul style="list-style-type: none"> • Patients with Indian ethnicity OR • History of PSC AND/OR • Patients with B-mode US features beyond size associated with increased/ high risk of malignancy. Although not evidence-based this could involve applying additional expert-opinion based criteria listed in Table 1.

CEUS = contrast-enhanced ultrasound; EUS = endoscopic ultrasound; GBP = gallbladder polyp; PSC = primary sclerosing cholangitis.

* As size and growth of GBPs are essential for recommended management decisions, measurements must be standardized and reproducible. Measurement in the long axis of the GBP is recommended, which can be supplemented by measurement perpendicular to the long axis (short axis) to give the height/width ratio as a parameter to describe polyp shape. In the case of multiple polyps, their number should be indicated. Measurement of the largest GBP is sufficient.

† Follow-up can be stopped when GBPs disappear, there is no growth (≥2 mm to ≥10 mm), no US high-risk features (Table 1) are observed within 24 mo and no individual risk factors are present.

quality evidence so far and, therefore, suggest prospective studies to correlate pathomorphologic and US features of GBPs and to validate this concept.

Given the relatively high prevalence of GBPs and their concomitant extremely low malignant potential, we recommend management of patients with incidentally detected GBPs based on existing evidence, best clinical practice and the medical ethical principle of "first do no harm" as outlined in Table 2.

Several limitations exist with GBP surveillance programs. In two studies, the compliance with surveillance was not optimal with participation rates of only 15% (Pedersen *et al.* 2012) and 33% (Patel *et al.* 2019). The annual detection rate of (pre-)malignant GB pathology was 12 cases per 1000 GBPs surveyed (Patel *et al.* 2019). The study with the largest number of GBP cases and the longest follow-up reported considerably lower detection rates (Szapkowski and Tucker 2020).

FOCAL, SEGMENTAL AND DIFFUSE GALLBLADDER WALL THICKENING

Definition, risk assessment and epidemiology

Gallbladder wall thickening is a frequent and ambiguous imaging finding. It is defined as a GB wall diameter >3 mm (focally, segmental or general) in a fasted state (Dietrich and Braden 2009; Matcuk *et al.* 2014; Chavva and Karpur 2018).

In patients with right upper quadrant pain and findings of inflammation, GB wall thickening is most often related to acute cholecystitis, but in patients without clinical symptoms of cholecystitis, a large variety of causes must be considered (Kaftori *et al.* 1987; Lee *et al.* 2014a; Maudgal *et al.* 1984; Miyoshi *et al.* 2021; Setiawan *et al.* 1995; van Breda Vriesman *et al.* 2007; Wegener *et al.* 1987; Yamada and Yamada 2001):

- GB wall edema, for example, in hypoalbuminemia, liver cirrhosis with portal hypertension and right heart failure
- Involvement of GB wall in systemic and infectious disease, for example, acute hepatitis, Dengue fever, infectious mononucleosis and amyloidosis
- Chronic cholecystitis
- Adenomyomatosis and
- Gallbladder cancer.

In both acute hepatitis and Dengue fever, the extent of GB wall thickening is related to disease severity. The honeycomb pattern of GB wall edema is a relatively specific finding in severe Dengue fever (Setiawan *et al.* 1995; Kim *et al.* 2003; Colbert *et al.* 2007; Yoo *et al.* 2010; Ahn *et al.* 2015; Pothapregada *et al.* 2016; Tavares *et al.* 2019).

Chronic cholecystitis relatively often presents with non-specific complaints or may be detected incidentally.

Table 3. Weighted ultrasound criteria for assessment of gallbladder wall thickening

US feature	Typical of/predictive of	Risk of malignancy
Wall characteristics*		
Symmetrical wall thickening	Contraction, edema, cholecystitis	Low
Asymmetrical wall thickening	Malignant tumor and focal/segmental adenomyomatosis	Increased
Irregular inner or outer surface	Malignant tumor	High
Surface		
Smooth	Various benign conditions	Low
Irregular inner or outer surface	Malignant tumor	High
Layering		
Preserved two-layer stratification	Contraction, edema, inflammation	Low
Intramural membranes, honeycombing appearance	Edema, cholecystitis	Low
Focal/segmental disruption of inner or outer wall layer	Malignant tumor and focal/segmental adenomyomatosis	Increased
Infiltration into liver parenchyma	Malignant tumor	High
Bile duct obstruction at the hilum level	Malignant tumor	High
Special US features		
Small intramural cysts	Adenomyomatosis	Low
Intramural echogenic foci with reverberation artifacts and twinkling	Cholesterosis, adenomyomatosis	Low
Calcifications with shadowing	Porcelain gallbladder	Increased
Pericholecystic fluid (without general ascites)	Cholecystitis, edema	Low
Contrast-enhancement and high-sensitivity CDI techniques (microvascular imaging) [†]		
Integrity of the GB wall	Variety of benign lesions	Low
Homogeneous arterial hyperenhancement	Cholecystitis, adenomyomatosis	Low
Heterogeneous arterial enhancement	Malignant tumors, adenomyomatosis	Increased
Regular vessel pattern (linear vessels)	Various benign conditions	Low
Irregular vessel pattern (irregular branching, tortuous vessels)	Malignant tumor	High
Small focal areas of non-enhancement	Adenomyomatosis	Low
Late hypo-enhancement (>40 s)	Various benign conditions	Low
Early hypo-enhancement (<28 s)	Malignant GBPs	High

CDI = color Doppler imaging; GBP = gallbladder polyp; US = ultrasound.

* Adequate distension of the gallbladder is required to allow complete evaluation of the wall and the lumen (Gupta et al. 2022a, 2022b).

† Settings of the US machine for performing CDI modalities or CEUS should be adjusted for detecting tiny vessels with low flow velocities, and contrast agent dose should be adapted to the transducer frequency (Dietrich et al. 2018; Lowe et al. 2021).

It is characterized by fibrous transformation and shrinking of the GB wall and is almost always associated with GB calculi. A rare variant of chronic cholecystitis is xanthogranulomatous cholecystitis, characterized by proliferative fibrosis, inflammatory infiltration with macrophages and foamy cells. Because of these features, pre-operative differentiation from GBC with imaging techniques is challenging (Shlaer et al. 1981; Setiawan et al. 1995; Feng et al. 2020).

Gallbladder wall thickening is also the most common finding in early GBC (Zhu et al. 2015; Goussous et al. 2018). Whereas advanced GBC (in particular N2 and metastatic disease) has a dismal outcome with nearly no long-term survival, early detection (Tis or T1) is accompanied by 5-y survival rates >60% (Zhu et al. 2020). An intact hyperechoic outer layer of the GB wall on US was observed to be associated with a lack of cancerous infiltration of the serosa and a favorable prognosis after cholecystectomy (Iri et al. 2002).

Imaging features and diagnostic work-up. To avoid unnecessary surgical treatment, for example, of GB wall thickening associated with extrinsic disease and misdiagnosis of GBC as benign disease, the precise

characterization of GB wall thickening is crucial (Brook et al. 2011; Matsui et al. 2019). Standardized examination and description of GBs with mural thickening should include GB dimensions, luminal contents (calculi, sludge, solid tissue), maximum wall diameter from the inner to the outer hyperechoic layer, anatomic site, extent (focal, diffuse) and symmetry of wall thickening, presence of mural layering, intramural changes (echogenic foci, hypoechoic nodules, intramural cysts), the interface between GB wall and liver and GB wall vascularity (Gupta et al. 2020a, 2020b, 2022; Jenssen et al. 2019) (Table 3). Anamnestic, clinical and laboratory information should be included in differential diagnostic considerations. In a recently published meta-analysis, B-mode features suitable for differentiation between benign and malignant GB wall thickening were analyzed. Echogenic foci, lack of GB wall disruption and hypo-echoic nodules predicted benign diagnoses with sensitivities of 89%, 77% and 66% and specificities of 86%, 51% and 80%, respectively. Focal thickening and indistinct liver interface were significantly associated with malignancy (sensitivity = 75% and 55% and specificity = 64% and 69%, respectively) (Rana et al. 2022). On the basis of these data, a Gallbladder Reporting and

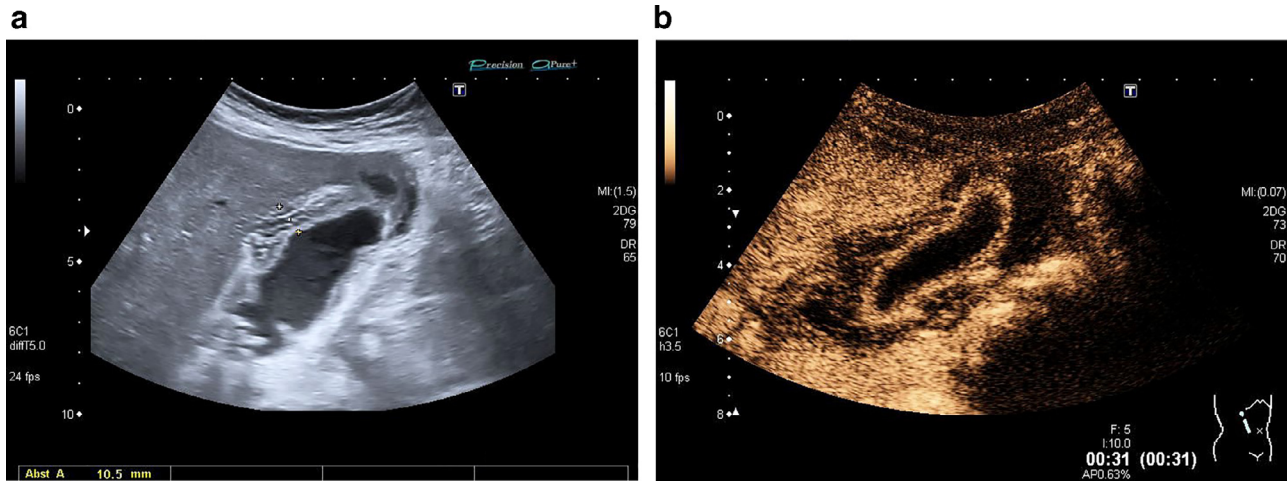


Fig. 6. Gallbladder wall thickening in a patient without any abdominal complaints and without clinical or laboratory signs of inflammation. (a) B-Mode ultrasound reveals small stones in the gallbladder infundibulum and thickening of the gallbladder wall (10.5 mm, between markers) with lamination corresponding to edema. (b) After intravenous injection of the ultrasound contrast agent SonoVue, there is enhancement only of the mucosal layer and the thin lamellae within the thickened wall, whereas intramural fluid is non-enhancing. The patient was diagnosed with nephrotic syndrome, and serum albumin was as low as 18 g/dL. Figures provided by the authors: C.J. (a, b).

Data System (GB-RADS) has been proposed for the description and risk stratification of GB wall thickening on B-mode US (Gupta *et al.* 2022). High-resolution US (Joo *et al.* 2013, 2014; Bang *et al.* 2014; Kim *et al.* 2015; Lee *et al.* 2017; Dong *et al.* 2020b) or EUS (Kim *et al.* 2003; Tanaka *et al.* 2021) is superior to standard abdominal US in evaluating the integrity and layering of the GB wall. GB wall vascularity can be assessed using CDI (Hirooka *et al.* 1996; Pradhan *et al.* 2002; Badea *et al.* 2014), CEUS and CEH-EUS (Cornell and Clarke 1959; Numata *et al.* 2007; Liu *et al.* 2012; Xu *et al.* 2014; Badea *et al.* 2014; Bang *et al.* 2014; Imazu *et al.* 2014; Chen *et al.* 2017; Tang *et al.* 2015; Wang *et al.* 2016; Cheng *et al.* 2018; Kamata *et al.* 2018; Kong *et al.* 2018; Serra *et al.* 2018; Sidhu *et al.* 2018; Yuan *et al.* 2018; Zhang *et al.* 2018; Zhuang *et al.* 2018; Dong *et al.* 2020b; Gupta *et al.* 2020a, 2020b; Kin *et al.* 2020; Kumar *et al.* 2020; Liang and Jing 2020; Yu *et al.* 2020) (Fig. 6). Tumefactive sludge is easily differentiated from solid GB wall lesions (Kim *et al.* 2017; Kamata *et al.* 2018; Serra *et al.* 2018; Kumar *et al.* 2020). CEUS and CEH-EUS improve characterization of GB wall thickening when used in addition to B-mode (pooled sensitivity = 81% and 92%, pooled specificity = 94% and 89% for CEUS and CEH-EUS, respectively) (Liang and Jing 2020). Discontinuity of the GB wall, heterogeneous enhancement, the presence of tortuous or branching vessels and fast wash-out (<28 s) indicate malignancy (Wang *et al.* 2016; Cheng *et al.* 2018; Liang and Jing 2020). A CEUS-based nomogram to differentiate between benign and malignant GB wall thickening turned out to be at least as effective as a CT-based nomogram (Chen *et al.*

et al. 2017). Data on elastography are sparse and preliminary (Kapoor *et al.* 2011; Badea *et al.* 2014).

In patients with equivocal or suspicious US-based risk assessment, contrast-enhanced CT (Kane *et al.* 1984; Jang *et al.* 2009; Bang *et al.* 2014; Hammad *et al.* 2016; Chen *et al.* 2017, 2019) and (diffusion-weighted) MRI (Ogawa *et al.* 2012; Bang *et al.* 2014; Hammad *et al.* 2016; Kitazume *et al.* 2016) are recommended for evaluation and staging (Gupta *et al.* 2020a, 2020b, 2022).

Calcification and porcelain gallbladder

Porcelain gallbladder (PGB) and multiple partial calcifications of the GB wall are rare conditions interpreted as resulting from a chronic inflammatory process and are traditionally considered pre-cancerous conditions. On the basis of pathological examinations, it was suggested that progressive calcification occurs in a particular type of chronic cholecystitis (“hyaline cholecystitis”) with fibrotic transformation, atrophy and loss of normal layering of the complete GB wall (Patel *et al.* 2011). The range of calcification ranges from focal mucosal or intramural plaques (“incomplete PGB”) to full-thickness wall involvement (“complete PGB”) with complete mucosal denudation (Patel *et al.* 2011). Autopsy studies report an incidence of PGB of 0.06%–0.08% (Polk 1966; Kane *et al.* 1984), while in large cholecystectomy series, PGB was observed in 0.2%–1.1% of specimens, with a female predominance of 5:1 (Stephen and Berger 2001; Khan *et al.* 2011; Chen *et al.* 2015). Hypercalcemia and hyperparathyroidism are risk factors, and in most cases, PGB is accompanied by GB calculi. PGB is asymptomatic in 18%–87% of cases

(Berger et al. 2020, Stephen and Berger 2001). Older studies report 12.5%–62.5% of PGB cases concomitantly harboring GBCs (Cornell and Clarke 1959; Ashur et al. 1978; Kane et al. 1984; Shimizu et al. 1989). This very high risk of malignancy is contradicted by recent studies, some of which reported no cases of GBC even in large surgical and non-surgical PGB cohorts (Towfigh et al. 2001; Kim et al. 2009; Khan et al. 2011; Chen et al. 2015). In their analysis of 25,900 cholecystectomy specimens from the years 1962 to 1999, Stephen and Berger (2001) found a prevalence of GBC among 44 cases with GB wall calcifications of 2 cases (5%). A review of seven published series that included 60,665 cholecystectomies revealed an overall prevalence of PGB of 0.2%, and GBC occurred in 15% of PGB cases (Khan et al. 2011). Another systematic review reported a GBP prevalence of 6% in 124 cases with calcified GB wall from 13 studies: Compared with a matched control group of patients without GB wall calcification, a relative risk of 8 was estimated (Schnelldorfer 2013). The largest study published so far included 1000 cases of PGB with a malignancy rate of 3%, which was sixfold higher than observed in cases without PGB (0.5%) (Berger et al. 2020). A remarkably concordant observation of several studies is that GBC was observed predominantly or solely in incomplete PGB, possibly because of the loss of mucosal epithelium with progress of the disease (Shimizu et al. 1989; Stephen and Berger 2001; Patel et al. 2011; Schnelldorfer 2013).

Diagnostic work-up and management. PGB is diagnosed mainly with US or CT. Both imaging techniques have a relatively high false-positive rate, due mainly to a GB lumen that is completely filled with calculi (Appel et al. 2021).

Because of the only slightly increased risk of GBP and the increased conversion rate and surgical risk in PGB, some authors question the indication for cholecystectomy in PGB (DesJardins et al. 2018). Because of the low risk of malignancy in patients with homogeneous wall calcification, the European Association for the Study of the Liver (EASL) guidelines limit the recommendation for preventive cholecystectomy to patients with homogeneous wall calcifications (Chen et al. 2015; EASL 2016). German guidelines suggest preventive cholecystectomy independently from distribution type of calcification (Gutt et al. 2018), whereas other guidelines abstain from giving recommendations. It should be taken into account that imaging diagnosis of GBP arising in “hyaline cholecystitis” and PGB may be challenging because of a lack of mass-forming features (Patel et al. 2011). Therefore, follow-up strategies seem to be questionable, and we recommend offering cholecystectomy to all patients with PGB.

Comet tail artifacts with and without gallbladder wall thickening (hyperplastic cholecystoses)

Cholesterosis and adenomyomatosis are grouped as hyperplastic GB wall disorders (hyperplastic cholecystoses) and were first described using oral cholecystography (Jutras 1960; Berk et al. 1983). Both cholesterosis and adenomyomatosis are frequent IFs in cholecystectomy specimens as well as in GB imaging. Cholesterosis (“strawberry gallbladder”) is an accumulation of cholesterol-containing macrophages within the lamina propria with or without thickening of the GB mucosa and was reported to have a prevalence of 12.5%–34.7% in autopsy studies (Mentzer 1925; Salmenkivi 1964; Feldman and Feldman 1954; Dairi et al. 2016). Cholesterol calculi are frequently associated with cholesterosis. A connection of cholesterosis to GB dyskinesia, chronic cholecystitis, non-calculous biliary pain and pancreatitis was discussed from a clinical point of view (Salmenkivi 1964; Jacyna and Bouchier 1987), but proof for this assumption is lacking (Dairi et al. 2016).

Adenomyomatosis of the GB is observed in 1%–9% of cholecystectomy specimens and is characterized by a localized, segmental or diffuse epithelial proliferation with infoldings into and through the hyperplastic muscularis propria. In diverticular pouches (Rokitansky–Aschoff sinuses) bile becomes increasingly concentrated with intra-diverticular cholesterol crystal precipitation, local chronic inflammation, and intramural calcifications. The localized type usually involves the GB fundus, the segmental type fundus and adjacent parts of the GB body (Jutras 1960; Ram and Midha 1975; Berk et al. 1983; Lee et al. 2020b). Adenomyomatosis is discovered incidentally in most cases but may present with symptoms of cholelithiasis. It is no longer regarded as a pre-cancerous lesion, but pre-existing adenomyomatosis may prevent timely diagnosis of GBC (Kim et al. 2010; Kai et al. 2011).

Diagnostic work-up and follow-up. Cholesterosis is characterized on US by multiple echogenic spots of the normal or slightly thickened GB wall with comet tail artifacts (Fig. 7).

As comet tail artifacts of the GB wall are associated with numerous, mostly benign GB wall conditions, careful examination of the complete GB searching for focal or diffuse thickening is mandatory (Shcherbinina et al. 2010; Oh et al. 2019).

Typical US findings of adenomyomatosis include focal, segmental or diffuse wall thickening with small cystic lesions of variable echogenicity (Rokitansky–Aschoff sinuses). Cholesterol precipitates result in intracystic echogenic foci with comet tail artifacts, whereas small calculi or calcifications cause shadowing.

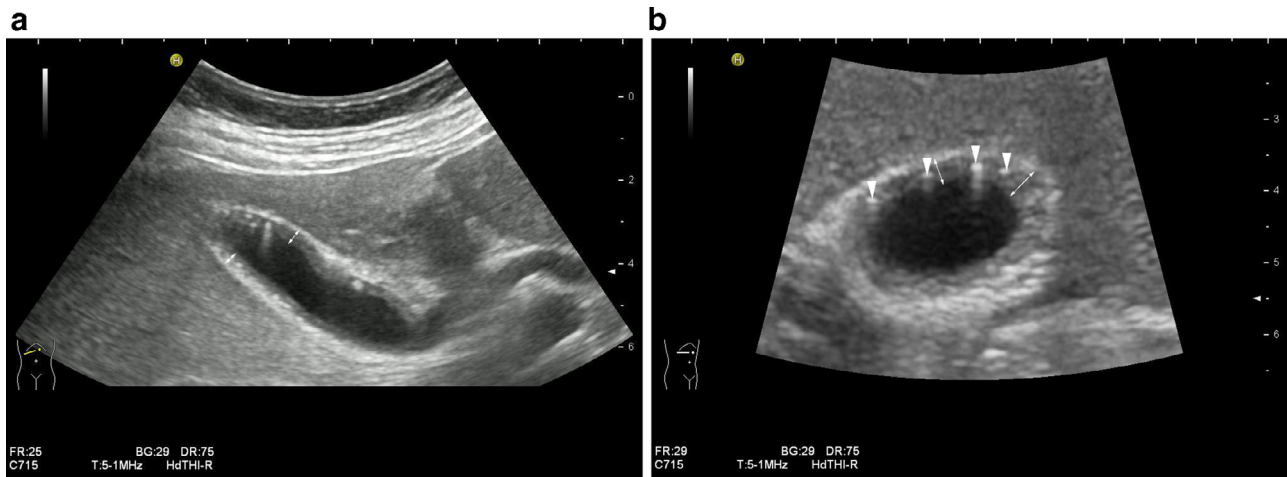


Fig. 7. Cholesterosis of the gallbladder wall. Slight thickening of the wall (*double arrows*) and multiple hyperechoic intramural spots with comet tail artifacts (*arrowheads*). (a) Longitudinal section. (b) Transverse section. Figures provided by the authors: C.J. (a, b).

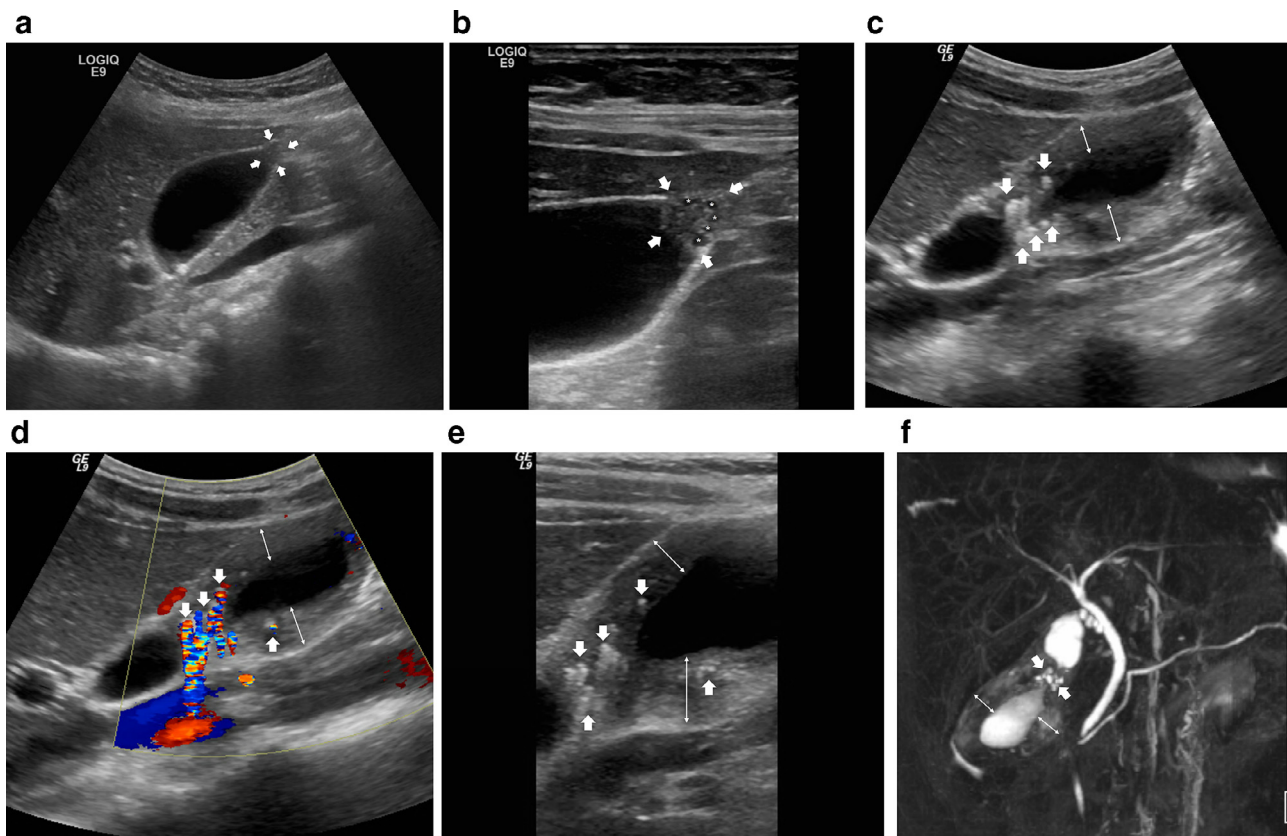


Fig. 8. Adenomyomatosis of the gallbladder wall, various types. Fundal type: (a) An ill-defined wall-thickening (*arrows*) is detected in the gallbladder fundus using a convex-type transducer (2–6 MHz). (b) High-resolution ultrasound (9–12 MHz) reveals multiple intramural cysts (*asterisks*) within the mass-like focal thickening (*arrows*), representing the presence of Rokintansky–Aschoff sinuses. Segmental type: (c, d) A bicameral gallbladder with hour-glass deformity is found with marked hypo-echoic wall thickening in the gallbladder body and fundus (*double arrows*). Multiple hyperechoic foci with comet tail artifacts (*arrows*) are detected in the region of luminal narrowing (c), generating twinkling artifacts on CDI (d), which represent the presence of cholesterol crystals in the thickened wall. (e) High-resolution ultrasound clearly depicts the presence of the hyperechoic foci (*arrows*) within the thickened muscle layer (*double arrows*). (f) The corresponding MRCP reveals the pearl-necklace sign (*arrows*) in the wall of the wall-thickened gallbladder body (*double arrows*), a diagnostic sign of adenomyomatosis. Figures provided by the authors: J.Y.L. (a–f).

Twinkling artifacts are observed with CDI (Hammad et al. 2016, Il'chenko et al. 2013, Yoon et al. 2006, Yu et al. 2012) (Fig. 8).

The presence of small intramural cysts or echogenic foci has a sensitivity of 80% and a specificity of 85.7% for diagnosis of adenomyomatosis (Joo et al. 2013). If possible, high-frequency US should be used for evaluation of the GB wall (Choi et al. 2013; Bang et al. 2014). However, differentiation of adenomyomatosis from early-stage GBC may be challenging, with more pre-operative misdiagnoses for GBC compared with adenomyomatosis (Moon et al. 2019). American Society of Anesthesiologists (ASA) stage, age and CA 19-9 (each higher in GBC) are helpful in differentiation (Liu et al. 2012; Chen et al. 2017, 2019; Moon et al. 2019). Recent studies have determined that CEUS and CEH-EUS may be helpful in the diagnosis of GB wall adenomyomatosis by revealing wall-integrity, heterogeneous enhancement, small non-enhancing spaces (corresponding to the avascular Rokitanisky–Aschoff sinuses) and slow wash-out (>40 s) (Liu et al. 2012; Imazu et al. 2014; Xu et al. 2014; Tang et al. 2015; Sugimoto et al. 2016; Chen et al. 2017; Kamata et al. 2018; Kong et al. 2018; Yuan et al. 2018; Zhuang et al. 2018; Dong et al. 2020b; Kumar et al. 2020).

SUMMARY: MANAGEMENT STRATEGIES

The work-up strategy for incidentally detected GB wall lesions (polyps, wall thickening) should include clinical risk factors for malignancy (*e.g.*, age, ethnicity, history of PSC), laboratory findings (CA 19-9) and B-mode US features. Their characterization can be improved with EUS and multiparametric US. Weighted ultrasound criteria are proposed to be used for characterization and risk stratification of incidental findings of the GB wall. Surgical therapy should always be pursued in the presence of high-risk imaging features. US features associated with increased risk of malignancy indicate the need for additional diagnostic procedures (CT and MRI, in carefully selected cases US-guided or EUS-guided sampling) or a systematic follow-up. As laparoscopic cholecystectomy is a low-risk procedure and GBC has an acceptable prognosis only in early stages, a primary surgical approach may alternatively be considered in such cases.

CONFLICT OF INTEREST DISCLOSURE

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All figures were provided by the authors, and data was acquired according to protocols approved by the

institutional review boards of the authors. According to these protocols, participants gave consent for the use of their fully anonymized data (ultrasound images) in this article.

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