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REVIEW

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Clinical approach to patients with thick wall gallbladder

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Abstract

Background Thick wall gallbladder (TWGB) is not an uncommon finding on ultrasonography especially in region with high prevalence of gall stones disease like north India. On most occasion, these thickening could be because of benign disorders but malignancy are not a rare cause of it. Preoperative distinction between benign and malignant causes of TWGB is important as the surgical treatment entirely differ. Despite after thorough evaluation with various imaging modalities, a definitive diagnosis cannot be reached on many occasion. The aim of our study was to review the literature for the diagnosis and management approach in patients with TWGB.

Methods We perform a thorough online search of full text articles related with thick wall GB published in English literature. After doing a critical appraisal of available literature, a comprehensive narrative review was described.

Conclusions In this review, the authors have described a clinical algorithmic approach by detailing the diagnostic utility of various imaging modalities and also different surgical options for treatment especially in cases of ambiguity.

Keywords Thick wall gallbladder, Xanthogranulomatous cholecystitis, Chronic cholecystitis, Gallbladder carcinoma, Gallbladder diseases

Background

Technological advances have enabled us to diagnose most benign and malignant biliary tract disorders and provide an appropriate treatment to our patients. However, diagnosis and an appropriate treatment of patients with a thick-walled gallbladder (TWGB) is still challenging. The normal thickness of the gallbladder (GB) is considered up to 3 mm, and a thickness beyond 3 mm is considered TWGB [1]. TWGB may be caused by various disorders as enumerated in Table 1 [2–5]. An evidence-based methodical approach is necessary to avoid over and under treatment in these patients. Aim of our study was to review the literature for the diagnosis and management approach in patients with TWGB. We perform a thorough online search of full text articles related with thick wall GB published in English literature. After doing a critical appraisal of available literature, a comprehensive narrative review was described.

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Blood Investigations

Hematological investigations may help to support or refute a diagnosis. Leukocytosis is usually present in patients with inflammatory disorders like acute cholecystitis (AC) and Xanthogranulomatous cholecystitis (XC). Rajaguru et al., [6] reported leukocytosis in 90% patients with XC versus 40% patients with gallbladder cancer (GBC) ($p < 0.01$). Patients with non-biliary inflammatory diseases like acute pancreatitis (AP) and peritonitis also show leukocytosis.

Hyperbilirubinemia due to bile duct infiltration is more prevalent in GBC than XC; however, association of bile duct stones should be considered foremost biliary disorder causing hyperbilirubinemia [6]. Depending upon etiology and severity, patients with hepatitis, presents with raised transaminases, hyperbilirubinemia, and/or

Table 1 Surgical and medical causes of thick-walled gallbladder

Surgical causes	Benign	Acute cholecystitis
		Chronic cholecystitis
		Xanthogranulomatous cholecystitis
		Adenomyomatosis
		Sclerosing cholecystitis (IgG4)
	Extracholecystic inflammation	Pancreatitis
		Pyelonephritis
		Peritonitis
	Malignant	Gallbladder carcinoma
		Lymphoma
Medical causes		Hepatitis
		Cirrhosis
		Portal hypertension
		Congestive heart failure
		Sepsis
		Hypoalbuminemia

other features hepatic dysfunction/failure [7]. Patients with typical presentation of AP show significantly raised serum amylase and/or lipase along with other features of AP [8]. IgG4-related cholecystitis show deranged liver function test, raised serum IgG4 levels (> 135 mg/dl) and increased IgG4/IgG ratio [9].

Carbohydrate antigen 19-9 (Ca 19-9) and carcinoembryonic (CEA) antigen are commonly utilized markers but due to low specificity, these are not useful in making diagnosis [10, 11]. Lin et al., [12] reported a significantly higher Ca 19-9 levels in malignant than benign GB thickening (826.83 ± 557.34 versus. 401.92 ± 483.92 U/mL, $P = 0.005$); the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for Ca 19-9 were 100%, 76.9%, 33.33% and 47.47%, respectively; therefore, it cannot alone be utilized for the diagnosis.

Imaging modalities

Differentiating benign and malignant thick-walled GB usually require multimodal approach including ultrasonography (US), contrast-enhanced US (CEUS), endoscopic US, computed tomography, etc.

Ultrasonography (US)

Asymmetric and irregular wall thickening, discontinuity in mucosal lining is typical of GBC, whereas alternate hypoechoic and hyperechoic layers with a distinct specular mucosal lining are seen in benign thickening [13] (Table 2). The use of color Doppler helps in assessing vascularity and improves diagnostic accuracy with a sensitivity and specificity of 100% and 96%, respectively. A higher peak systolic velocity is also seen in malignant conditions [14–16]. USG can also point toward other causes of wall thickening like pancreatitis, pyelonephritis, hepatitis, portal hypertension or cirrhosis, etc., by identifying signs of inflammation in these organs like pericholecystic fat stranding, mural thickening and bowel wall edema. Patients with cirrhosis will show shrunken liver with nodular parenchyma along with the absence of GB wall inflammation; however, signs of portal hypertension may also be seen like splenomegaly, dilated portal vein, reversal of flow, collaterals, etc. A diffusely thickened and edematous gallbladder wall in conjunction with a diffusely hypoechogenic liver with prominent portal triads ("starry sky" appearance) hints acute hepatitis as a cause of GB wall thickening [2].

Contrast-enhanced ultrasonography (CEUS)

Benign wall thickening show washout time of more than 40 s and dotted linear vascularity. In GBC arterial phase irregular intralesional vascularity, late phase hypoenhancement are seen [17, 18]. The specificity for detection of malignant GB wall thickening has been found to be 92.4% [19].

Contrast-enhanced computed tomography (CECT)

Malignant lesions show wall irregularity or focal thickening, discontinuity in mucosal lining and direct invasion into an adjacent organ (Table 3) [2, 5]. CT has moderate sensitivity (67–78%) and poor specificity

Table 2 USG characterization of benign and malignant GB wall thickening

USG features	Benign	Malignant
Thickening	Diffuse and symmetrical	Focal and asymmetrical
GB wall layered pattern	Preserved	Absent
Mucosal continuity	Intact	Breached
Parenchymal infiltration	Absent	Present
Color Doppler (Mean & Peak Flow Velocities)	Low	High
Elastography	Low velocity	High velocity
Contrast-enhanced US	Homogeneous enhancement Delayed washout	Heterogeneous enhancement Early washout

Table 3 CT characterization of benign and malignant GB wall thickening

CT findings	Benign	Malignant
Thickening	Diffuse, symmetrical	Focal, asymmetrical
Enhancement	(a) Single layer: Homogenous (b) Two layered patterns: Inner layer iso-attenuating to liver	(a) Thick one layer with heterogeneous enhancement (b) Two layers: Strongly enhancing thick inner layer (≥ 2.6 mm) with weakly enhancing or non-enhancing thin outer layer
Bile duct obstruction	Uncommon	More common
Lymphadenopathy	Usually absent	Mostly present
Adjacent organ infiltration	Not seen commonly	Present in advanced disease

(22–33%) in differentiating GBC from benign GB pathologies (AC and XC) [20]. Kim et al., [21] have proposed five patterns of wall enhancement in diffuse GB wall thickening. The two-layer pattern showing strongly enhancing thick inner layer (≥ 2.6 mm) and a weak enhancement of outer layer (≤ 3.4 mm) and the one-layer pattern of heterogeneously enhancing thick wall are significantly associated with malignant thickening (Fig. 1).

In Xanthogranulomatous cholecystitis, intramural hypoattenuating nodules have been reported which represent xanthogranulomas or microabscesses depending on the phase of inflammation (Fig. 2). The presence of nodules occupying > 60% area of diffusely thickened wall is a more specific indicator of XC rather than just the presence of nodules [22, 23]. An enhanced continuous mucosa together with gallstones are highly suggestive of XC. In addition, pericholecystic fat stranding, blurring of the interface with liver, edema, transient hepatic attenuation differences or early enhancement may be appreciated in the adjacent liver parenchyma [21, 24]. CT also help in picking up other causes of GB wall thickening like pancreatitis, cirrhosis, pyelonephritis, etc.

Magnetic resonance imaging (MRI)

A normal GB wall is hypointense on T2- weighted images, isointense on T1-weighted images and has homogenous post-contrast enhancement [25]. Benign GB wall thickening are hyperintense on both T1- and T2-weighted images and relatively slow enhancement. Malignant thickening shows moderate T2 hyperintensity with papillary appearance, diffusion restriction and early enhancement [26]. On diffusion-weighted images (DWI), a lower ADC value ($0.8–1.8 \times 10^{-3}$ mm^2/s) is seen in malignant, whereas a higher value ($2.60 \pm 0.54 \times 10^{-3}$ mm^2/s) is associated with benign thickening [27]. With a cutoff value of 1.2×10^{-3} mm^2/s, combined with morphological patterns such as substantial thickening, interrupted mucosal line and the absence of a two-layered pattern, the reported sensitivity and specificity of DWI is 73.0% and 96.2%, respectively [28].

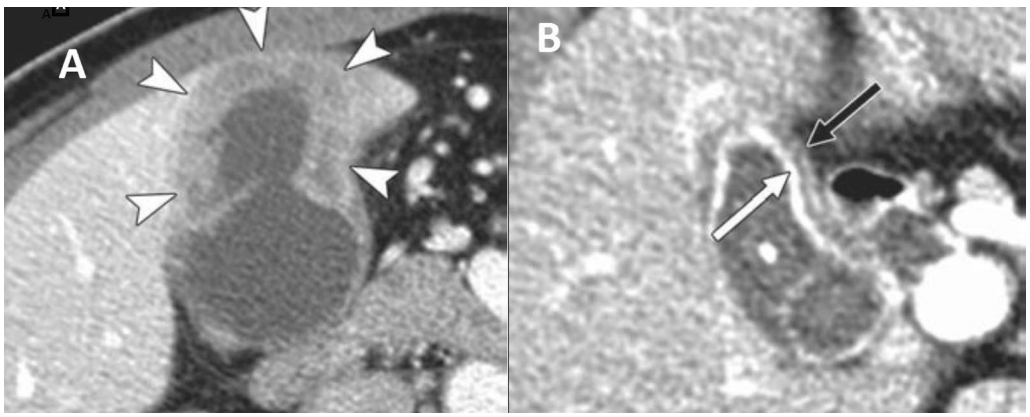

Fig. 1 Axial CECT images of malignant GB thickening **a** showing heterogeneously enhancing thick one-layer pattern (arrowheads, type 1pattern). **b** Type 2 pattern-intense enhancement of inner layer (white arrow) and weakly enhanced or unenhanced outer layer (black arrow) on portal phase (quoted from Kim et al. [21]

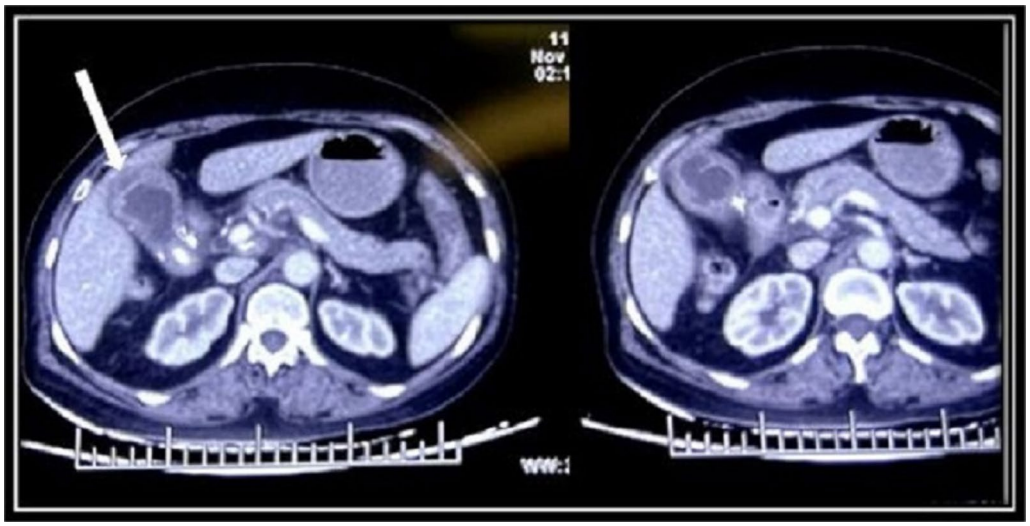

Fig. 2 Axial CECT images in a 42-year female who presented with complaint of pain in upper abdomen showing GB stone (hyperdense content) with diffuse GB wall thickening and intramural nodule (arrow) favoring Xanthogranulomatous cholecystitis

Fluorodeoxyglucose (FDG) Positron emission tomography-computed tomography (PET-CT)

The uptake value (SUV max) along with wall thickness are helpful in differentiation. Malignant thickening has a higher SUV max than benign, but sometime due intense inflammatory changes, XC can show a higher value. When the cutoff of both wall thickness of 8.5 mm and SUV max of 5.98 are taken together, the sensitivity, specificity and positive and negative predictive values were reported to be 58.33%, 94.44%, 87.5% and 77.27%, respectively [29, 30].

Endoscopic ultrasound (EUS)

It is useful for determining the invasion depth of gallbladder cancer [31]. EUS can obtain higher-resolution images than trans-abdominal US because the transducer can be positioned closer lesion and gives a detailed view of the changes in the layered structure of GB wall and the internal echoes of the tumor. The characteristic findings of malignancy include wall thickening (> 10 mm), inhomogeneous internal echo pattern, and disrupted wall layering [32]. In the differentiation of malignant from GB lesions, EUS showed sensitivity, specificity, and accuracy of 90% and 91.1%, respectively [33]. EUS can also be utilized for cytological diagnosis by taking guided FNAC. It is usually a safe procedure with minimal risk of bleeding and tumor seeding. EUS-FNA has a sensitivity of 91.7% and specificity of 100% [34, 35]. EUS has limited availability, and being operator-dependent, good results can be obtained in expert hands only.

Table 4 Diagnostic accuracy of various imaging tests (quoted from Bo et al. [36])

Tests	Sensitivity	Specificity	PPV	NPV
USG	0.80 (0.70–0.88)	0.86 (0.77–0.92)	0.85 (0.75–0.91)	0.81 (0.72–0.88)
CEUS	0.90 (0.68–0.99)	0.93 (0.80–0.98)	0.86 (0.63–0.96)	0.94 (0.81–0.99)
CECT	0.71 (0.54–0.85)	0.92 (0.83–0.97)	0.82 (0.64–0.92)	0.86 (0.75–0.92)
MRI	0.75 (0.60–0.86)	0.90 (0.79–0.97)	0.88 (0.74–0.95)	0.78 (0.65–0.87)
PET-CT	0.55 (0.32–0.76)	0.90 (0.73–0.98)	0.80 (0.51–0.95)	0.73 (0.56–0.86)

In clinical practice, a combination of various imaging modalities are used to clinch a diagnosis as none of these is ideal in differentiating a benign thickening from malignant. The diagnostic accuracy of different imaging techniques are mentioned in Table 4 [36].

Differentiating specific causes of TWGB

Acute cholecystitis (AC) is the first clinical presentation in 10–15% of patients with cholelithiasis [37]. Patients of AC have history of recent onset pain and/or fever, tenderness in right upper abdomen. Leukocytosis with a normal liver function can be found on routine blood examination. US can reveal an obstructing gallstone, distended GB, a positive sonographic "Murphy's" sign, pericholecystic fluid and hyperemia of the GB wall [5].

Chronic cholecystitis (CC) almost always occurs in the setting of GB stones causing low-grade inflammation and fibrosis. Patients are usually asymptomatic or have mild

pain in abdomen. Blood investigations are usually unremarkable. The ultrasound findings include lucency of the wall and a distended GB containing stone(s)/sludge without pericholecystic fluid/edema. Fibrotic changes may result in contracted and TWGB [2, 5].

Xanthogranulomatous cholecystitis is a variant of chronic cholecystitis with variable prevalence ranging from 1.3% to 1.9% in Western societies, while in India, the reported prevalence reaches up to 9% [38]. It is a chronic, focal or diffuse, destructive, fibro-inflammatory disease of the GB that results from intramural accumulation of foamy macrophages and inflammatory cells, with proliferative fibrosis in later stages. XC is characterized by GB wall thickening along with wall perforation, fistula formation and adjacent organs invasion. Patients can present as a case of CC with no abdominal signs or as a mass forming GB lump. In about 2–15% of cases, XC can coexist with GBC [38, 39]. XC patients with associated GBC were more likely to present with anorexia, weight loss, palpable lump and jaundice [4, 10].

Rammohan et al. [4] found that incidences of abdominal pain, cholelithiasis, choledocholithiasis and acute cholecystitis were significantly higher in patients of XC, while anorexia and weight loss were higher in GBC cases ($p < 0.01$). On imaging, patients with XC were more often had a diffuse thickening of gallbladder wall, submucosal hypoattenuated nodules and continuous mucosal line enhancement.

Rajaguru et al. [6] formulated a simple preoperative scoring system for diagnosis of XC using preoperative clinical and imaging parameters. They concluded that a high value scores ($\geq 11/13$) helps in diagnosing XC in preoperative setting with a sensitivity and specificity of 81% and 95%, respectively, thereby avoiding intra-op frozen analysis in these patients.

Adenomyomatosis (ADM) of the gallbladder is a benign condition seen in up to 9% of cholecystectomy specimens as an incidental findings. It is characterized by epithelial proliferation, muscular hypertrophia and intramural diverticula (Rokitansky-Aschoff sinuses), which may segmentally or diffusely involve gallbladder. Ultrasonography features of cholesterol crystals as comet-tail reverberation artifacts within a thickened wall of the gallbladder strongly suggests this diagnosis [2, 5].

Gallbladder carcinoma (GBC) is one of the leading cancers among women of north and northeast India. The age standardized rate for GBC in women of north and northeast India are 11.8/100,000 population and 17.1/100,000 population, respectively [40]. GBC most often manifests as a diffusely infiltrating lesion that replaces the gallbladder and extends into the liver. Sometime, it can also present as asymmetric wall thickening or polypoidal mass projecting into lumen. Gallstones are present in about 80% of cases. The CT or ultrasound visualization of pronounced wall thickening (> 10 mm) along with mural irregularity and enlarged lymphnodes should raise suspicion of malignancy [1, 2, 5].

Mathur et al. [24] evaluated TWGB cases using enhancement pattern of GB wall on CECT and found that the one-layered pattern with a heterogeneously enhancing thick layered pattern (Type 1) was significantly associated with gallbladder cancer ($p < 0.001$). The sensitivity, specificity, positive and negative predictive values of type 1 enhancement pattern on CT for predicting malignancy were 90.476%, 97.43%, 95% and 95%, respectively.

Discussion

Despite after thorough preoperative evaluation, a definitive diagnosis cannot be reached on many occasion. TWGB especially XC put a surgical challenge as at times it could be malignant so simple cholecystectomy (SC) will not only result in inadequate treatment but will also breach tumor plane thus compromising survival. Performing extended cholecystectomy (EC) in TWGB will be an over-treatment as most of the times these are benign and will add to morbidity and mortality. To counter this difficulty, different approaches have been described.

Kapoor et al. [1] advised anticipatory extended cholecystectomy (AEC) approach (Lucknow approach) in doubtful TWGB cases. AEC includes removal of the GB with a non-anatomical 2-cm wedge of liver in segments IVB and V (without lymph node dissection) and frozen section histopathological examination. Standard lymphadenectomy was added if frozen examination reports suggested malignancy, thus avoiding EC in benign cases and adding little morbidity.

Performing staging laparoscopy and assessment is another option. If the suspicion of GBC is negligible, a simple cholecystectomy is enough. The GB should be opened to examine the mucosa and any suspected area can be sent for frozen analysis or imprint cytology. If a malignancy is found, a completion EC should be performed during the same operation. Patkar et al. [41] evaluated the utility of intra-operative frozen examination in suspected GBC cases and found the sensitivity, specificity, PPV, NPV and accuracy to be 88.3%, 99.6%, 99.4%, 92.7% and 95.1%, respectively. They also found that with routine use of frozen analysis, only 2% of patients need a revised surgical strategy. Denge et al. [42] have reported 93% diagnostic accuracy of intra-op frozen analysis for XC in suspected GBC cases. If, after simple cholecystectomy, the histology reveals GBC, it should be treated as an incidental GBC and should be treated accordingly [43].

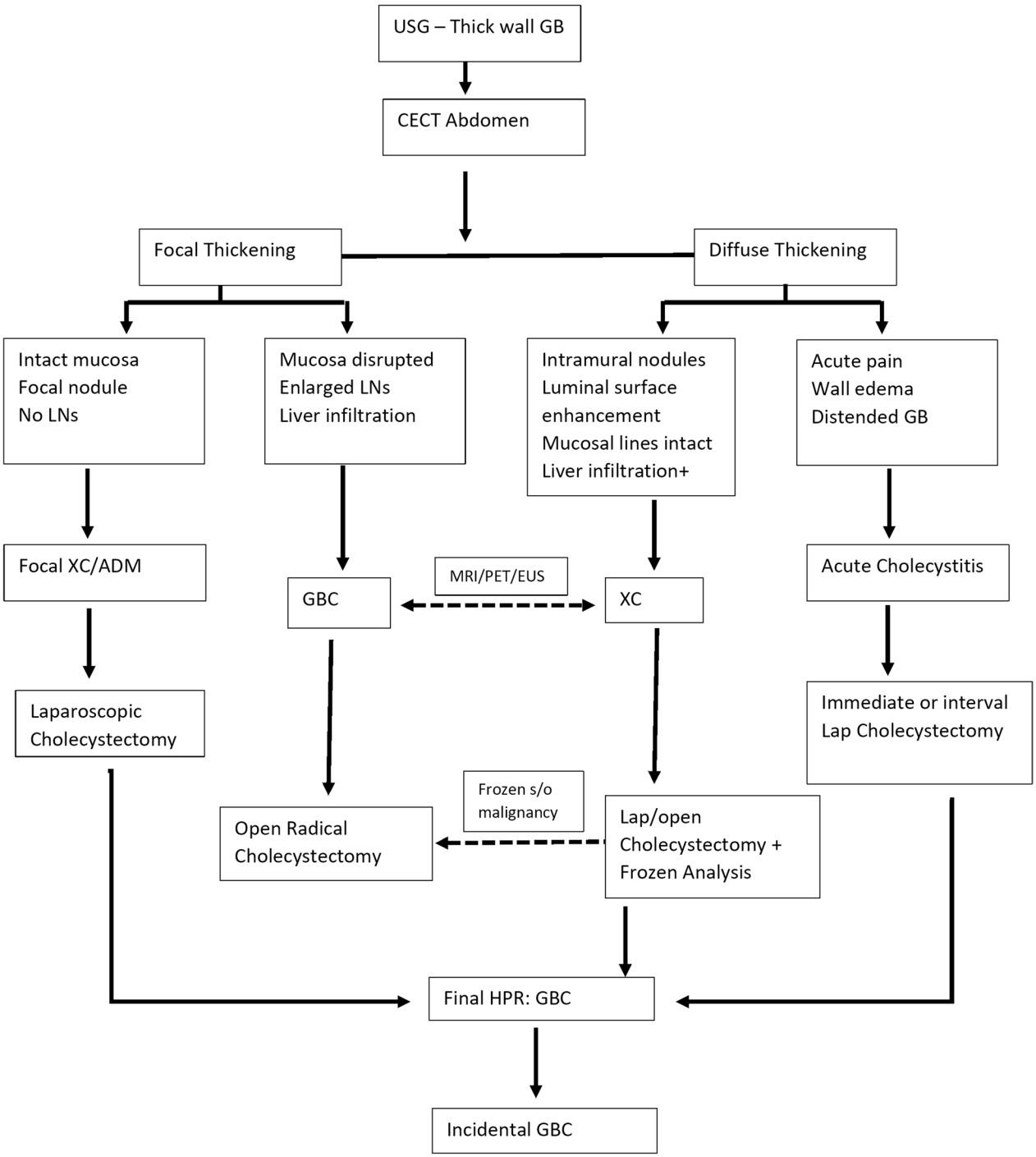

Fig. 3 Flow diagram showing approach in cases of thick wall GB

Shirai et al. [44] have described a less radical procedure "full-thickness cholecystectomy with limited lymphadenectomy" in 12 elderly patients of GBC without distant metastases or nodal diseases. This procedure comprises full-thickness resection of the gallbladder including entire cystic plate and removal of the pericholedochal and cystic duct lymph nodes (the first-echelon node groups). They found no in-hospital mortality or recurrent disease and a median overall survival 229 months with a cumulative 5-year survival

of 100%. This could be another approach in TWGB cases.

Another area of debate is open versus laparoscopic approach in patients of TWGB. Earlier studies have raised the concern of dissemination and port site metastases if a laparoscopic cholecystectomy is done for GBC. A TWGB is an independent predictor of difficult laparoscopic cholecystectomy requiring subsequent conversion to open surgery and is also related with higher postoperative morbidity and longer hospital stay. Open conversion rate of 34–53% has been noted in different series [3, 45]. Recent studies have favored laparoscopic approach due to less blood loss, low morbidity rate, shorter hospital stay and early commencement of adjuvant chemotherapy. Navarro et al. [46] have found no significant difference in terms of 5-year overall survival rate (64.6% vs 80.4%, P = 0.214) and disease-free survival rate (77.1% vs 82.2%, P = 0.641) between the laparoscopic and open-surgery groups in GBC patients. Several prospective studies have also demonstrated a favorable oncological outcome of laparoscopic radical cholecystectomy for GBC [46, 47].

Patients with GB wall thickening detected on US should be evaluated with contrast-enhanced CT of abdomen before proceeding for surgery. Focal thickening with disrupted mucosal lining and enlarged LNs suggests malignant thickening, and a radical approach should be adopted in treatment. For CT features showing benign thickening (XC/AC), a laparoscopic or open simple cholecystectomy should be done. Cases indistinguishable on CT can be sorted out by MRI or FDG-PET. EUS can also be utilized for the assessment of GB, loco-regional lymphadenopathy and if needed FNA cytology can also be done. All these cases should be tested for CEA/Ca 19–9 levels which not only help in diagnosis, but also needed for future follow-up. Intra-operative frozen (IOF) analysis is the pivotal step in surgical management of TWGB. The definitive treatment can be decided based on the result of IOF analysis following either a simple or a full-thickness cholecystectomy. For benign diagnosis, this is sufficient but for malignant thickening, a completion radical surgery can be added during the same surgery (Fig. 3).

Conclusions

Patients of TWGB should be managed with a detailed preoperative evaluation at a specialized center preferably by expert hepatobiliary surgeons. Intra-operative frozen analysis is the key step in surgical management. Laparoscopic or open cholecystectomy followed by intra-operative frozen analysis is a preferred approach at most of the centers.

Abbreviations

TWGB	Thick wall gallbladder
GBC	Gallbladder cancer
AC	Acute cholecystitis
CC	Chronic cholecystitis
XC	Xanthogranulomatous cholecystitis
ADM	Adenomyomatosis
AP	Acute pancreatitis
IOF	Intra-operative frozen

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Author contributions

MA involved in data acquisition; interpretation; and drafting and final approval. PM involved in revising and drafting of manuscript. HHN involved in conception and drafting and final approval. All authors have read and approved the final manuscript.

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Declarations

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Consent for publication

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Competing interests

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