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# The Pathomorphological Substrate of Sonographic Signs in Gallbladder Disease: A Sign-Based Narrative Review

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**ABSTRACT:** Ultrasonography is the first-line and, in most settings, the only imaging modality applied to the gallbladder, yet its findings are habitually taught disease-first: a diagnosis is named and its sonographic appearance described. At the machine the operator faces the inverse problem — an echo pattern is present and its tissue meaning must be inferred. This review reorganises the evidence accordingly. We first set out the histological architecture of the gallbladder wall, emphasising two features that govern everything downstream: the absence of a submucosa and of a muscularis mucosae, and a total mural thickness of 1–3 mm that lies at or below the axial resolution of conventional transabdominal probes. We then work through the principal sonographic signs — diffuse and focal wall thickening, the striated or layered wall, loss of layering, comet-tail reverberation, intramural anechoic spaces, polypoid lesions, intraluminal membranes, intramural gas and mural calcification — and for each specify the tissue substrate, the differential range of substrates that can generate the same appearance, and the resulting diagnostic ceiling. Three systematic reasons why sono-pathological correlation fails are identified and discussed: substrate non-specificity, the mismatch between acoustic and histological scale, and verification bias arising from the fact that histology is available almost exclusively for gallbladders selected for resection. We consider what high-resolution ultrasound, contrast-enhanced ultrasound, elastography and radiomic analysis add to each of these three problems, and we trace the persistent disagreement between international guidelines on gallbladder polyps back to a histological fact: the great majority of small polypoid lesions are cholesterol polyps, and size is a weak surrogate for neoplasia. A structured reporting template derived from the sign-substrate analysis is proposed.

## 1. INTRODUCTION

Gallbladder disease is among the most frequent indications for abdominal ultrasonography, and in most health systems ultrasound is not merely the first-line examination but the only cross-sectional assessment the organ ever receives. The consequences of a sonographic report are therefore substantial: it determines whether a patient is operated on urgently, followed with repeat imaging, or discharged.

The standard literature approaches this task disease-first. A condition is named — acute cholecystitis, adenomyomatosis, carcinoma — and its characteristic appearances are enumerated. Excellent reviews of this kind exist for gallbladder wall thickening [1–4], for benign gallbladder disease and its malignant mimics [5], for the hyperplastic cholecystoses [6,7] and for gallbladder carcinoma [8]. The format is well suited to revision and to teaching a differential list.

It is not, however, the problem the operator actually faces. At the machine the diagnosis is unknown and the echo pattern is given; what is required is an inference from acoustic appearance to tissue state. That inference is only as good as the operator's model of what generates the appearance — and that model is pathomorphological. A striated wall is not a diagnosis; it is a statement about the distribution of fluid within mural connective tissue, and its diagnostic value depends entirely on which processes can produce that distribution.

This review is organised on that principle. Section 2 establishes the histological baseline and the physical limits within which any correlation must operate. Section 3, the substance of the paper, proceeds sign by sign: for each sonographic finding we state the tissue substrate, the full range of substrates capable of producing it, and the diagnostic ceiling that follows. Section 4 identifies three systematic reasons why sono-pathological correlation fails, one of which — verification bias in the correlation literature itself — is rarely made explicit. Section 5 asks what newer techniques contribute against each of those three problems. Section 6 traces the disagreement among international guidelines on polyp management back to its histological root and proposes a structured reporting template.

The review is narrative rather than systematic. Its aim is interpretive: to supply a framework within which the substantial existing evidence can be applied at the point of scanning.

## 2. THE HISTOLOGICAL BASELINE AND ITS ACOUSTIC LIMITS

### *2.1 Wall architecture*

The gallbladder wall comprises a mucosa of a single layer of tall columnar epithelium resting on a lamina propria; a muscularis of irregularly arranged smooth muscle bundles; a perimuscular (subserosal) connective tissue layer containing vessels, lymphatics and nerves; and, on the peritoneal aspect, a serosa. Where the gallbladder abuts the liver there is no serosa: the perimuscular connective tissue continues directly into the hepatic bed.

Two features of this architecture govern everything that follows, and both are peculiar to the gallbladder among hollow viscera. First, there is no submucosa and no muscularis mucosae. The lamina propria therefore sits directly on the muscularis, and a neoplasm that breaches the mucosa reaches the perimuscular tissue — and hence the lymphatics and the hepatic bed — after crossing a single muscular layer. This is the anatomical reason why gallbladder carcinoma so often presents at an advanced stage, and why T-category thresholds for the gallbladder do not map onto those of the stomach or colon. Second, the normal wall is thin: 1–3 mm in the fasting, adequately distended organ.

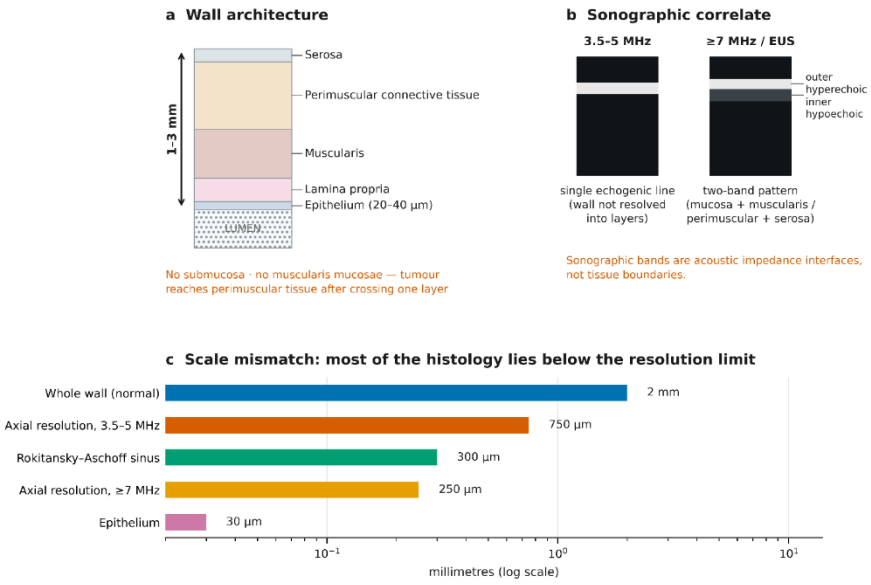


**Figure 1.** Architecture of the gallbladder wall and its sonographic correlate. (a) Histological layers in cross-section, with the lumen below. The gallbladder possesses neither a submucosa nor a muscularis mucosae, so a neoplasm reaches the perimuscular connective tissue — and hence the lymphatics and the hepatic bed — after crossing a single muscular layer. Total mural thickness in the fasting, distended organ is 1–3 mm. (b) The same wall as rendered by conventional transabdominal ultrasound

at 3.5–5 MHz, where it appears as a single echogenic line, and by high-frequency or endoscopic ultrasound, where a two-band pattern emerges. Sonographic bands correspond to acoustic impedance interfaces rather than to tissue boundaries. (c) Logarithmic comparison of the dimensions involved: the epithelium and the individual Rokitansky–Aschoff sinus lie at or below the axial resolution of the transducers in routine use.

The mucosa forms folds, and invaginations of mucosal epithelium into and through the muscularis — Rokitansky–Aschoff sinuses — are a normal or near-normal finding that becomes pathologically prominent in adenomyomatosis [6,7,9]. Their presence, contents and rupture account for several of the most characteristic sonographic signs discussed below.

### *2.2 What ultrasound can and cannot resolve*

Axial resolution is approximately half the spatial pulse length and thus improves with frequency. A 3.5–5 MHz curvilinear transducer, the standard for transabdominal abdominal survey in an adult, offers axial resolution of roughly half a millimetre to a millimetre. Set against a total mural thickness of 1–3 mm, this means that the normal wall occupies only two or three resolution elements, and that the histological features of interest — an epithelial layer measured in tens of micrometres, an inflammatory infiltrate, the individual sinus of Rokitansky and Aschoff — lie one to two orders of magnitude below the resolution limit.

It follows that conventional transabdominal ultrasound does not image the layers of the gallbladder wall. It images an acoustic composite, usually rendered as a single thin echogenic line, or as a two-component structure when an acoustic interface within or adjacent to the wall becomes sufficiently reflective. High-frequency linear transducers and endoscopic ultrasound resolve more, at the cost of depth of penetration, and the layered patterns they demonstrate correspond only approximately to histological layers [10–12].

Table 1 sets out the correspondence, and the caution it requires.

**Table 1.** Histological layers of the gallbladder wall and their sonographic correlates

| Histological layer | Typical thickness | Conventional transabdominal US (3.5–5 MHz) | High-resolution US / EUS (7–12 MHz and above) |
|---|---|---|---|
| Epithelium (single columnar layer) | 20–40 μm | Not resolved | Not resolved as a discrete layer |
| Lamina propria | Sub-millimetre | Not resolved | Contributes to the inner hypoechoic band |
| Muscularis (irregular smooth muscle; no muscularis mucosae) | Variable, sub-millimetre to ~1 mm | Not resolved separately | Contributes to the inner hypoechoic band |
| Perimuscular (subserosal) connective tissue | Variable; expands markedly with oedema | The principal source of the striated or "halo" appearance when oedematous | Outer hyperechoic band |
| Serosa (absent at the hepatic bed) | Very thin | Not resolved; contributes to the outer echogenic interface | Outer hyperechoic band |
| Whole wall, fasting and distended | 1–3 mm | Single echogenic line or two-component structure | Two- or three-layer pattern |

*Note: the correspondence between sonographic bands and histological layers is approximate. Sonographic layering reflects acoustic impedance interfaces, not tissue boundaries, and the number of bands visible varies with frequency, gain, angle of insonation and degree of gallbladder distension.*

### *2.3 Measurement conditions*

Because the normal range is narrow and the measurement is at the resolution limit, technique determines the result. Three conditions should be satisfied before a wall thickness is reported. The patient must be fasting and the gallbladder adequately distended: a physiologically contracted postprandial gallbladder has an apparently thick wall, and this pseudo-thickening is one of the commonest sources of a spurious report. The measurement should be taken on the anterior wall, perpendicular to it, because posterior acoustic enhancement through the bile-filled lumen artefactually brightens and obscures the far wall. And the site of measurement should be stated, since focal and diffuse thickening carry entirely different differential ranges.

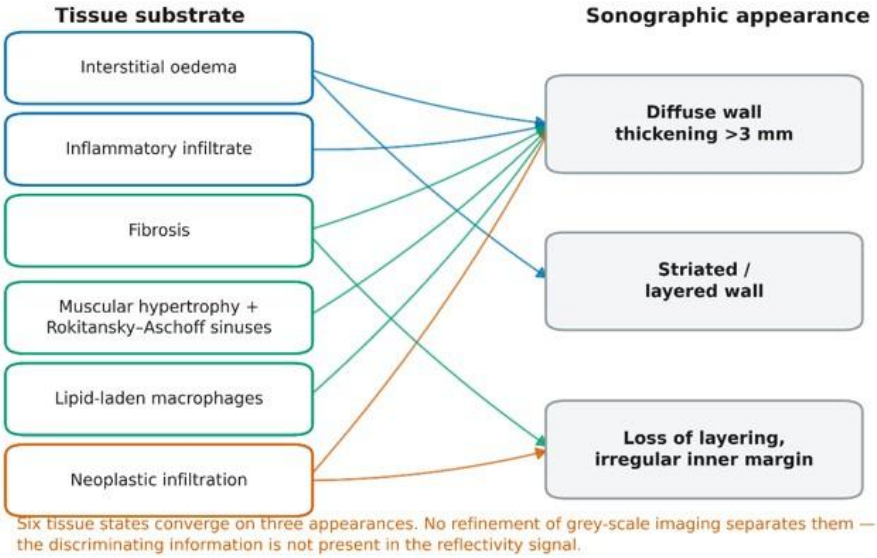


**Figure 2.** The many-to-one mapping from tissue substrate to sonographic appearance. Six distinct tissue states converge on three grey-scale appearances. Because the discriminating information is not present in the reflectivity signal, no improvement in image quality resolves the ambiguity; separation requires a different physical property, such as perfusion kinetics or tissue stiffness. Colour denotes the general character of the substrate: blue, acute inflammatory or oedematous; green, chronic, fibrotic or hyperplastic; orange, neoplastic.

## 3. SIGN BY SIGN: APPEARANCE, SUBSTRATE, CEILING

This section works from the sonographic finding to the tissue. Table 2 summarises; the text develops the reasoning.

### 3.1 Diffuse wall thickening

Diffuse thickening beyond 3 mm is the single most frequently reported abnormality of the gallbladder wall, and it is also the least specific. Its recognised substrates fall into three groups. Intramural inflammation contributes oedema, vascular congestion and cellular infiltrate in acute cholecystitis, and fibrosis with chronic inflammatory infiltrate and muscular hypertrophy in chronic cholecystitis. Intramural hyperplasia contributes epithelial and muscular proliferation with prominent Rokitansky–Aschoff sinuses in adenomyomatosis, and lipid-laden macrophages in the lamina propria in cholesterolosis. And a large group of extramural and systemic conditions produces mural oedema with no primary gallbladder pathology at all: hypoalbuminaemia from any cause, right heart failure and systemic venous congestion, cirrhosis with portal hypertension, acute viral hepatitis, renal failure and generalised anasarca [1–4].

The clinical importance of the third group is difficult to overstate. A thickened gallbladder wall in a patient with decompensated cirrhosis is not evidence of cholecystitis, and the pattern of misinterpretation this generates has been recognised in the sonographic literature for four decades [3]. Two features usually separate systemic oedema from primary inflammation: the gallbladder is not distended and is often small, and there are no stones, no focal tenderness and no pericholecystic inflammatory change.

The diagnostic ceiling is therefore explicit. Diffuse wall thickening establishes that the mural compartment is expanded. It does not establish by what, and no manipulation of grey-scale imaging alone will make it do so.

### 3.2 The striated or layered wall

A wall composed of alternating hypoechoic and hyperechoic bands reflects fluid accumulating preferentially in the perimuscular connective tissue, which is loose and expands readily, while the denser muscularis and the mucosal surface remain comparatively echogenic. The substrate is therefore interstitial oedema with the mural architecture preserved.

Two consequences follow. Preserved striation is a reassuring finding with respect to malignancy, because transmural tumour infiltration destroys the layered arrangement it depends on; the same logic underlies the emphasis on layered patterns in magnetic resonance correlation studies [2]. But striation is not specific for acute cholecystitis, because any cause of mural oedema, including all of the systemic causes listed above, produces it. Striation tells the operator about the mechanism of thickening, not about its cause.

### 3.3 Loss of layering and an irregular inner margin

The complementary finding — a wall that is thickened, echo-poor, structurally featureless and bounded internally by an irregular rather than a smooth line — corresponds to replacement of the normal mural architecture. The substrate of greatest concern is infiltrating adenocarcinoma, in which tumour crosses the muscularis into the perimuscular tissue, obliterating the acoustic interfaces on which layering depends and disrupting the mucosal surface [8,13,14].

The inference is not exclusive. Severe chronic cholecystitis with dense transmural fibrosis, and xanthogranulomatous cholecystitis in particular, can produce a comparably disorganised wall; this overlap is the origin of one of the most consequential diagnostic problems in the field and is treated separately below. What raises concern beyond wall texture alone is the combination of asymmetric or focal thickening, an irregular mucosal line, loss of the interface with the hepatic bed, regional lymphadenopathy and, on Doppler or contrast-enhanced study, disorganised intramural vascularity [8,14,15].

### 3.4 Comet-tail reverberation and intramural anechoic spaces

The V-shaped comet-tail artefact arising from within the gallbladder wall is generated by reverberation between highly reflective microscopic interfaces — in practice, cholesterol crystals and inspissated bile within Rokitansky–Aschoff sinuses. It is one of the few sonographic findings with a well-defined and near-specific microscopic substrate, and its presence in a thickened wall supports adenomyomatosis over carcinoma [6,7,9,16].

Two qualifications are required. The artefact reflects crystal content rather than the sinus itself, so its absence does not exclude adenomyomatosis; and its reliability as a marker of benign disease has been questioned, since comparable reverberation can arise from other intramural reflectors [17]. Directly visualised anechoic intramural spaces, corresponding to fluid-filled sinuses, are the more structurally specific finding, and their demonstration remains the anchor of the imaging diagnosis of adenomyomatosis across modalities [9,18].

### 3.5 Polypoid lesions

A polypoid lesion is an immobile, non-shadowing projection from the wall into the lumen, and it must first be distinguished from adherent sludge or a small stone, which are mobile with change of position and, in the case of a stone, shadowing.

The histological range is wide but the distribution is not. The overwhelming majority of small polypoid lesions are cholesterol polyps: aggregations of lipid-laden macrophages within the lamina propria beneath intact epithelium, typically multiple, pedunculated, homogeneously echogenic, and frequently under 10 mm [6,19,20]. Adenomas — true epithelial neoplasms and the recognised precursor of a proportion of carcinomas — are usually solitary, often larger, and hypo- or isoechoic relative to hepatic parenchyma [21,22]. Adenocarcinoma tends to be sessile rather than pedunculated, larger still, internally heterogeneous, and associated with disruption of the underlying wall [13,14].

The sonographic descriptors that carry most information are therefore attachment (pedunculated versus sessile), number (multiple favours cholesterol polyps), echogenicity relative to liver, and internal vascularity. Size, on which management guidelines principally depend, is a genuine but weak correlate of neoplasia, and the reason is histological: cholesterol polyps are so much more common than neoplastic ones that even a threshold with reasonable discriminatory properties yields a low positive predictive value [19,20,23,24]. Reproducibility compounds the problem, since interobserver agreement on sonographic polyp measurement is imperfect [25].

### 3.6 Signs of transmural necrosis

Gangrenous cholecystitis has a distinct substrate — mural necrosis with mucosal sloughing, intramural haemorrhage and microabscess formation — and a correspondingly distinct set of signs. Intraluminal membranes represent detached necrotic mucosa; asymmetric or irregular wall thickening reflects unevenly distributed necrosis; pericholecystic fluid indicates transmural inflammation or contained perforation [26,27].

The most instructive finding is a negative one. The sonographic Murphy sign, reliable in uncomplicated acute cholecystitis, is frequently absent in gangrenous disease, because necrosis of the wall interrupts its innervation. An operator who requires focal tenderness before diagnosing cholecystitis will therefore preferentially miss its most dangerous form — an inversion of the usual relationship between severity and detectability, and one that follows directly from the pathology. Contrast-enhanced ultrasound addresses this specifically by demonstrating mural perfusion defects corresponding to necrotic segments [27].

### 3.7 Intramural gas and mural calcification

Echogenic foci within the wall producing dirty shadowing or ring-down reverberation, and shifting with patient position, indicate intramural gas, the substrate of emphysematous cholecystitis. The finding warrants urgent management independently of other features.

Dense mural echogenicity with clean posterior acoustic shadowing indicates dystrophic calcification — the porcelain gallbladder. Its clinical significance has been revised: the strong association with carcinoma asserted in older series has not been sustained by later analyses, and the pattern of calcification appears to matter, with selective mucosal calcification treated as more concerning than diffuse intramural calcification [5,28].

### 3.8 Xanthogranulomatous cholecystitis: the instructive failure

Xanthogranulomatous cholecystitis deserves separate treatment because it is where the sign-substrate approach both explains the difficulty and offers what discrimination is available. The process begins with rupture of a Rokitansky–Aschoff sinus and extravasation of bile into the wall, provoking a granulomatous reaction in which lipid-laden histiocytes — xanthoma cells — accumulate together with fibrosis. The wall becomes markedly and often irregularly thickened, and it may invade the adjacent liver.

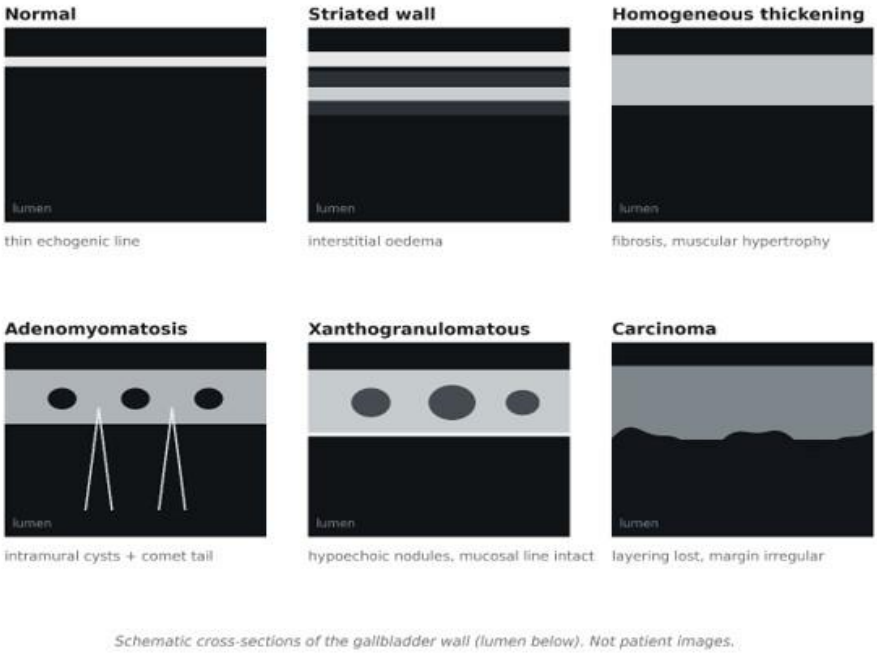


**Figure 3.** Schematic cross-sections of the principal mural patterns, with the lumen below in each panel. Normal wall: a thin echogenic line. Striated wall: interstitial oedema of the perimuscular connective tissue with mural architecture preserved. Homogeneous thickening: fibrosis and muscular hypertrophy. Adenomyomatosis: intramural anechoic spaces corresponding

to Rokitansky–Aschoff sinuses, with comet-tail reverberation arising from cholesterol crystals within them. Xanthogranulomatous cholecystitis: hypoechoic intramural nodules corresponding to xanthogranulomatous foci, with the mucosal line preserved. Carcinoma: loss of layering and an irregular inner margin. These are diagrams, not sonograms.

Every one of those features also characterises infiltrating carcinoma, and the two are misdiagnosed for one another in both directions, with real consequences: unnecessary radical resection on the one hand, inadequate surgery on the other [29–32]. The features reported to favour xanthogranulomatous disease are hypoechoic intramural nodules or bands corresponding to the xanthogranulomatous foci, diffuse rather than focal thickening, and — most usefully — a continuous, preserved mucosal line, since the process is centred on the wall rather than on the epithelium [30,31]. Contrast-enhanced ultrasound has been examined specifically for this distinction and reported to add discriminatory information [29], although the comparative accuracy of imaging modalities for this differential remains modest [32].

**Table 2.** Sonographic signs, their tissue substrate and the resulting diagnostic ceiling

| Sonographic sign | Tissue substrate | Range of substrates producing it | Diagnostic ceiling |
|---|---|---|---|
| Diffuse wall thickening >3 mm | Expansion of the mural compartment | Oedema; inflammatory infiltrate; fibrosis; muscular hypertrophy; hyperplasia; systemic oedema with normal gallbladder | Establishes expansion only; cannot identify its cause |
| Striated / layered ("halo") wall | Interstitial oedema of perimuscular connective tissue with architecture preserved | Acute cholecystitis; hypoalbuminaemia; heart failure; cirrhosis; hepatitis; renal failure | Indicates mechanism (oedema), not aetiology; argues against transmural tumour |
| Loss of layering; irregular inner margin | Replacement of mural architecture | Infiltrating adenocarcinoma; severe fibrosing chronic cholecystitis; xanthogranulomatous cholecystitis | Raises concern; does not establish malignancy |
| Comet-tail reverberation from the wall | Cholesterol crystals / inspissated bile in Rokitansky–Aschoff sinuses | Adenomyomatosis; cholesterolosis; other intramural reflectors | Supports benign hyperplastic disease; absence does not exclude it |
| Anechoic intramural spaces | Fluid-filled Rokitansky–Aschoff sinuses | Adenomyomatosis (segmental, fundal or diffuse) | The most structurally specific sign of adenomyomatosis |
| Pedunculated, multiple, echogenic polyps | Lipid-laden macrophages in lamina propria under intact epithelium | Cholesterol polyps predominantly | Strongly favours benign disease; does not exclude a coexisting neoplasm |
| Solitary sessile hypoechoic polypoid mass with vascularity | Epithelial neoplasm | Adenoma; adenocarcinoma | Cannot distinguish adenoma from early carcinoma on grey-scale alone |

| Sonographic sign | Tissue substrate | Range of substrates producing it | Diagnostic ceiling |
|---|---|---|---|
| Intraluminal membranes; asymmetric wall; absent Murphy sign | Mucosal necrosis and sloughing; interrupted mural innervation | Gangrenous cholecystitis | Highly suggestive; absence of Murphy sign must not be read as reassurance |
| Intramural echogenic foci with dirty shadowing | Intramural gas | Emphysematous cholecystitis | Effectively diagnostic; demands urgent management |
| Dense mural echogenicity with clean shadowing | Dystrophic calcification | Porcelain gallbladder | Malignant risk lower than historically asserted; pattern matters |
| Hypoechoic intramural nodules or bands with continuous mucosal line | Xanthoma cells and fibrosis following sinus rupture | Xanthogranulomatous cholecystitis | Favours benign disease but overlaps substantially with carcinoma |

## 4. THREE SYSTEMATIC REASONS THE CORRELATION FAILS

The limitations identified above are not a list of individually remediable shortcomings. They reduce to three structural problems, and distinguishing them matters because each responds to a different remedy.

### *4.1 Substrate non-specificity*

The first is a many-to-one mapping from tissue state to acoustic appearance. Oedema, cellular infiltrate, fibrosis, smooth-muscle hypertrophy and neoplastic infiltration all increase mural thickness, and several of them alter echogenicity in the same direction. No improvement in image quality resolves this, because the information is not present in the grey-scale signal. The remedy, if any, must come from a different physical property: perfusion kinetics, tissue stiffness, or a statistical texture signature not perceptible to the eye. This is precisely the rationale for contrast-enhanced ultrasound, elastography and radiomics, considered in Section 5.

### *4.2 Scale mismatch*

The second is that the histological features that define the diagnoses of interest are one to two orders of magnitude smaller than the resolution of the instrument. The wall is 1–3 mm thick; the epithelium is measured in tens of micrometres. Reports that describe sonographic "layers" as corresponding to histological layers should be read with this in mind: what is imaged is an acoustic impedance interface, and its coincidence with a tissue boundary is approximate. This problem does respond to technology, and higher-frequency transabdominal transducers and endoscopic ultrasound demonstrably improve mural characterisation and staging accuracy [10–12] — at the cost of depth of penetration, which in a patient of ordinary body habitus is a real constraint on the transabdominal approach.

### *4.3 Verification bias in the correlation literature*

The third problem is methodological and is the least often stated explicitly. Histological verification of a gallbladder requires that the gallbladder be removed. Sono-pathological correlation studies are therefore, with rare exceptions, studies of gallbladders selected for cholecystectomy — and selection is driven substantially by the imaging findings under evaluation.

The consequences are systematic and predictable. Lesions judged benign on ultrasound and left in situ contribute no histology, so false negatives are undercounted and sensitivity for malignancy is overestimated. The spectrum of disease in a resected series

is shifted towards the severe and the symptomatic, so the prevalence of the target condition in the study population exceeds that in the population to which the test will be applied, inflating positive predictive value. And a proportion of studies compare imaging with a histological report generated by a pathologist who had access to the imaging, introducing incorporation bias.

This bias affects almost every accuracy figure in the field, and it operates in a single direction: it flatters the test. It cannot be corrected retrospectively. It can, however, be reduced prospectively — by consecutive rather than selected enrolment, by blinded and independent reporting of imaging and histology, by explicit documentation of the proportion of imaged gallbladders that never reach histology, and by reporting accuracy separately for the subgroup in whom surgery was indicated on clinical rather than imaging grounds. Correlation studies that do not address it should be interpreted as upper bounds rather than as estimates.

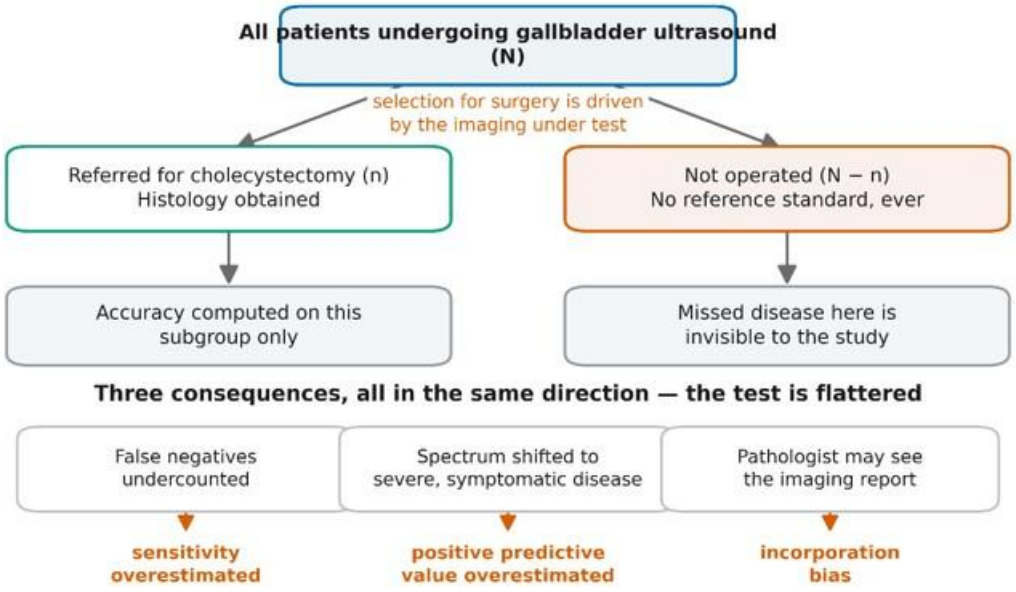


**Figure 4.** Verification bias in sono-pathological correlation studies. Histological verification requires resection, and referral for resection is driven substantially by the imaging findings under evaluation. Gallbladders judged benign and left in situ therefore contribute no reference standard. The three consequences all operate in the same direction and flatter the test: false negatives are undercounted, so sensitivity is overestimated; the spectrum of disease is shifted towards the severe and symptomatic, so positive predictive value is overestimated; and where the pathologist has access to the imaging report, incorporation bias is introduced.

## 5. WHAT THE NEWER TECHNIQUES CONTRIBUTE

The value of a new technique is best judged against which of the three problems it addresses.

High-resolution transabdominal ultrasound and endoscopic ultrasound attack the scale problem directly, and the evidence supports them: both improve differentiation of neoplastic from non-neoplastic polypoid lesions and assessment of depth of mural invasion relative to conventional transabdominal imaging and to computed tomography [10–12,33,34]. They do nothing for substrate non-specificity — a better-resolved oedematous wall is still an oedematous wall of unknown cause — and endoscopic ultrasound is invasive and unavailable in most settings where the diagnostic burden is greatest.

Contrast-enhanced ultrasound attacks substrate non-specificity, by substituting a perfusion measurement for a reflectivity measurement. Its reported contributions are consistent with that logic: demonstration of mural perfusion defects in gangrenous cholecystitis, where the question is tissue viability [27]; discrimination of xanthogranulomatous cholecystitis from wall-thickening carcinoma, where the question is whether an expanded wall is inflammatory or neoplastic [29]; and differentiation of adenoma from cholesterol polyp and of adenoma from malignant transformation, where the question is whether a lesion has a neoplastic vascular supply [21,22,35].

Elastography and radiomic or machine-learning analysis represent the more speculative attempt to extract substrate information from signal properties that are present but not perceptible. Early work applying texture analysis to high-resolution images of polyps larger than 10 mm, and radiomic analysis of dual-modality studies to separate neoplastic from cholesterol polyps, is encouraging [24,36]. The appropriate caution is that these methods are trained and validated on exactly the resected, selected series described in Section 4.3, and therefore inherit its verification bias in full. Reported performance should be understood accordingly until prospective, consecutively enrolled validation exists.

## 6. IMPLICATIONS: GUIDELINES AND REPORTING

### *6.1 Why the polyp guidelines disagree*

Several international bodies have issued recommendations on incidentally detected gallbladder polyps, including the joint European guidelines of the ESGAR, EAES, EFISDS and ESGE and their subsequent update [23,37], the consensus of the Society of Radiologists in Ultrasound [38,39] and further national recommendations [40]. Comparative analyses have documented substantial divergence in thresholds, follow-up intervals and stopping rules, and correspondingly large differences in the volume of imaging and surgery generated [40].

The divergence is usually described as unresolved evidence. It is better understood as a predictable consequence of the histology. All the documents converge on lesion size as the principal triage variable, and on a threshold in the region of 10 mm as the usual trigger for cholecystectomy, with an intermediate band in which additional risk factors decide. But size is a surrogate for neoplasia, and a weak one, for the reason set out in Section 3.5: cholesterol polyps outnumber neoplastic lesions by a wide margin, so at any plausible threshold most positives are false. Where the true positive rate is low and the cost of a false negative is a missed carcinoma, the position of the threshold is not determined by the data; it is determined by how the guideline group weighs an unnecessary cholecystectomy against a delayed cancer diagnosis. Different groups weigh them differently, and that is why the documents differ.

Two practical implications follow. First, no reconciliation of these guidelines is achievable by accumulating more size-outcome data; what would change the position is a discriminator that tracks neoplasia rather than volume, which is what the contrast-enhanced and radiomic work is attempting to supply. Second, because the operating characteristics of any size threshold depend on the local prevalence of gallbladder carcinoma — which varies by an order of magnitude between populations — a guideline calibrated in one setting should not be transplanted into another without explicit consideration of that difference. This is of direct relevance to Central Asia, where population-level data on gallbladder disease are sparse and where the applicability of European or North American thresholds has not been examined.

### *6.2 A structured report*

The sign-substrate analysis translates directly into what a gallbladder report should contain. Each element below exists because it changes the substrate inference, not because it completes a form.

Fasting state and degree of distension, since a contracted gallbladder cannot yield a valid wall measurement. Wall thickness with the site of measurement stated, taken on the anterior wall. Whether thickening is diffuse or focal. Whether mural layering is preserved, striated or lost, and whether the inner margin is smooth or irregular. Presence of intramural anechoic spaces or comet-tail reverberation. For any polypoid lesion: size on the longest axis, number, attachment (pedunculated or sessile), echogenicity relative to hepatic parenchyma, and vascularity where assessable. Calculi, with number and size. Pericholecystic fluid. Sonographic Murphy sign, reported as elicited, absent, or not assessable — and never treated as excluding disease when absent. The interface with the hepatic bed, stated as preserved or lost. Regional lymphadenopathy.

A report constructed on these lines communicates a substrate hypothesis rather than a list of observations, and it allows a subsequent reader to reconstruct the reasoning.

## 7. LIMITATIONS

This is a narrative review. It was not conducted according to a pre-registered protocol, the literature search was not exhaustive, and the selection of cited work reflects editorial judgement about what best illustrates the sign-substrate relationships; publication bias and language bias are therefore not excluded. The evidence base itself is heterogeneous, comprising individual correlation series, expert reviews and consensus documents rather than pooled analyses, and the verification bias described in Section 4.3 affects the primary studies on which the review draws. Quantitative performance figures have deliberately been

avoided in the text where the underlying studies are not methodologically comparable. Finally, the framework proposed here is interpretive: its claim is that reasoning from sign to substrate is a more faithful account of the diagnostic task than reasoning from disease to appearance, and that claim is argued rather than demonstrated.

## 8. CONCLUSION

The sonographic appearances of gallbladder disease are not diagnoses; they are acoustic consequences of tissue states, and their diagnostic value is bounded by how many tissue states can produce the same appearance. Reading them accordingly clarifies what ultrasound can be asked to do. Diffuse wall thickening establishes mural expansion and no more. A striated wall identifies oedema as the mechanism, not its cause. Comet-tail reverberation and intramural anechoic spaces are among the few findings with a near-specific microscopic substrate. The absence of a sonographic Murphy sign is a warning rather than a reassurance, because necrosis abolishes the very innervation the sign depends on.

The residual failures of correlation are structural: a many-to-one mapping from tissue to echo, a resolution limit an order of magnitude coarser than the histology, and a correlation literature systematically biased by the fact that only resected gallbladders yield a reference standard. The first two are being addressed, partially, by perfusion-based and higher-frequency techniques. The third is a matter of study design, and it will not improve until correlation studies are built to consecutive, blinded, prospectively enrolled protocols that report how many imaged gallbladders never reached histology at all.

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