



INVESTIGATING GALLBLADDER FOCAL WALL THICKNESS AS AN EARLY INDICATOR FOR MALIGNANCY: EXPLORING ITS SIGNIFICANCE IN EARLY DETECTION THROUGH HISTOPATHOLOGICAL ANALYSIS

Medical Science

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ABSTRACT

Background: Gallbladder cancer often goes undetected until surgery for non-cancerous gallbladder conditions. Different patterns of thickening are observed, with gallbladder cancer manifesting in diffuse, segmental, or focal forms, frequently resulting in thickened walls. Imaging aids in evaluation, but distinguishing cancerous thickening from benign causes remains challenging. Histopathological analysis is crucial for accurate diagnosis, allowing for early detection and informed clinical decisions. **Methods:** This prospective observational study was conducted at Darbhanga Medical College and Hospital from August 2023 to March 2024, analyzing 60 cases. Inclusion criteria involved patients aged 18-50 with gallbladder focal wall thickness exceeding 3.5mm on ultrasonography. Exclusion criteria included contraindications to imaging procedures, prior gallbladder surgery after age 50, unwillingness for surgery, and suspicion of metastatic disease. Eligible patients received counseling, provided consent, and underwent documentation of demographics and clinical parameters. Cholecystectomy was performed for qualifying patients, with post-surgery specimens examined histopathologically. Data integration and statistical analysis adhered to ethical standards, with a p-value of ≤ 0.05 considered significant, and ongoing collaboration among the research team was maintained. **Results:** In our study of 60 cases, patient demographics revealed a majority in the age range of 51-60 years, with females comprising 34 cases and males 26. USG proved effective as a screening tool for gallbladder pathology, highlighting cholesterosis as the most common condition and gallbladder tumefactive sludge as the least frequent. CECT emerged as superior in confirming suspicious malignant pathology. A significant association (p-value < 0.0001) between gallbladder wall thickness observed on USG and HPE indicated a higher risk of malignancy with increased thickness. A similar association was noted with CECT findings (p-value < 0.0001), with thicker gallbladder walls suggesting a greater risk of malignancy. **Discussion:** In a prospective observational study at Darbhanga Medical College, 60 cases with gallbladder focal wall thickness over 3mm on USG were examined, correlating with HPE reports. Various conditions were identified, including chronic cholecystitis (16.6%), parasitic granuloma (3.33%), adenocarcinoma (11.6%), xanthogranulomatous cholecystitis (25%), gallbladder polyps (11.6%), and cholesterosis (31.6%). Reference studies highlighted alternative surgical approaches for gallbladder cancer, with significant findings in xanthogranulomatous cholecystitis cases. The study emphasizes the importance of early detection in improving prognosis. Moreover, gallbladder polyps and wall thickening patterns were explored, with imaging modalities aiding in diagnosis. Notably, the Gallbladder Reporting and Data System (GB-RADS) facilitates consistent assessment of malignancy risk. Statistical analysis revealed a significant association between gallbladder wall thickening and malignant potential. Overall, the study underscores the complexity of distinguishing benign and malignant gallbladder conditions, advocating for comprehensive diagnostic approaches. **Conclusion:** Gallbladder cancer, though rare, is highly lethal, often asymptomatic initially but discovered incidentally. Abnormalities indicating gallbladder cancer require comprehensive assessment and potential surgical intervention. Our study establishes a significant correlation between radiological patterns and histopathological findings, facilitating early detection and potentially improving survival rates.

KEYWORDS

BACKGROUND

The majority of gallbladder cancer cases (70%) are discovered incidentally during surgery for non-cancerous gallbladder conditions. The survival rate after 5 years for those with gallbladder cancer is 80% when the cancer is localized. However, this rate drops significantly to 8% when the cancer spreads to nearby lymph nodes and further to only 2% for those in advanced stage 4b.(1) These statistics underscore the importance of early detection to prevent progression. Gallbladder cancer can manifest in three main forms: diffuse, segmental, and focal. The most common type involves a mass replacing the gallbladder, while around 20% to 30% of patients exhibit thickening of the gallbladder wall. Numerous individuals diagnosed with gallbladder cancer (GBC) are identified at a late stage, leading to poor outcomes. Unlike other gastrointestinal structures, the gallbladder lacks muscularis mucosa and submucosa, making it particularly vulnerable to early spreading of cancer cells. Typically, gallbladder cancer causes thickening of the gallbladder wall, which often appears focal, uneven, and irregular. However, in certain cases such as acute cholecystitis, chronic cholecystitis, and xanthogranulomatous cholecystitis, the thickening may present as diffuse, uniform, and regular. The thickening patterns observed in gallbladder cancer (GBC) can be classified into three main types: A) Symmetrical circumferential thickening, which involves the gallbladder (GB) and infiltrates into the adjacent liver parenchyma. B) Asymmetrical mural thickening involving the GB, often accompanied by multiple calculi, and infiltrating the liver parenchyma. C) Asymmetrical mural thickening specifically affecting the fundus of the GB while maintaining an interface with the adjacent liver surface.(2) A thickened GB wall, typically measuring more than 3 mm, usually exhibits a layered

appearance on sonography, although this may not always be the case. Such thickening can stem from inflammatory, neoplastic, or systemic causes. Focal thickening of the gallbladder can occur in the fundus, body, or neck regions, with thickening in the neck region often posing a challenge in diagnosis, particularly in distinguishing it from other biliary tract malignancies like cholangiocarcinoma. The use of cross-sectional imaging alongside angiography and cholangiography aids in evaluating vascular and biliary involvement, thereby assisting in distinguishing between these two conditions. Additionally, it is crucial to differentiate wall thickening in the fundus region from normal variations such as a mucosal fold or a Phrygian cap, which are present in about 4% of cases. Inflammatory causes encompass conditions such as acute cholecystitis, chronic cholecystitis, and a-calculus cholecystitis.(3) Systemic diseases, on the other hand, include conditions like heart, renal, or hepatic failure, acute pancreatitis, and viral hepatitis. These conditions typically result in diffuse and less pronounced wall thickening. In contrast, tumor lesions tend to cause focal and more pronounced thickening, often exceeding 10 mm. The incidence of incidental gallbladder carcinoma is 5–10 times higher in thick-walled gallbladders compared to those with normal wall thickness.(4) Additionally, gallbladder malignancy can occur secondarily, most commonly due to melanoma. Given the clinical symptoms' non-specific nature, often resembling those of chronic cholecystitis, having an imaging tool for early gallbladder cancer detection is crucial. This is because the management and prognosis of gallbladder carcinoma differ from benign causes. While ultrasound (USG) serves as a screening tool, computed tomography (CT), with its high spatial resolution, offers a detailed assessment of gallbladder wall thickening and aids in staging the disease. However, despite numerous

technical advancements in these imaging modalities, accurately predicting the nature of focal gallbladder wall thickening remains challenging.(5) The histopathological analysis of the specimen, which serves as the final step in diagnosing the nature of focal wall thickness, can be utilized to evaluate the accuracy of radiological investigations. By integrating these diagnostic methods, a deeper understanding of gallbladder pathologies can be attained, thereby enabling early detection, precise diagnosis, and timely clinical decision-making. This study aims to enhance existing knowledge by extensively examining focal gallbladder wall thickness alongside robust histopathological correlation.

METHODS

This prospective observational study was conducted at Darbhanga Medical College and Hospital in Bihar, spanning from August 2023 to March 2024. A total of 60 cases were included in the analysis. Inclusion Criteria: Patients with gallbladder focal wall thickness exceeding 3.5mm on ultrasonography, aged between 18 and 50 years. Exclusion Criteria: Individuals with known contraindications to imaging procedures, prior history of gallbladder surgery after the age of 50, patients unwilling to undergo surgery, and those suspected of having metastatic disease. Procedure: Following the selection criteria, all eligible patients received counseling about the study, provided informed written consent, and underwent documentation of relevant demographics and clinical parameters. Necessary investigations were conducted. Patients meeting clinical and radiological criteria were scheduled for cholecystectomy, and post-surgery specimens were subjected to histopathological examination. Data integration, statistical analysis, and comprehensive interpretation of the integrated data were conducted, adhering to ethical standards throughout the study. A p-value of ≤ 0.05 was considered statistically significant. Regular communication and collaboration among the research team, including clinicians, radiologists, and pathologists, were maintained.

RESULTS

In our study, 10 (20.0%) patients were ≤ 50 years old, 34 (53.3%) patients were 51-60 years old, 12(20.0%) patients were 61-70 years old and 4 (6.7%) patients were 71-80 years old. Out of 60 cases , the females were 34 and male were 26.

Table 1: Distribution: USG findings

Findings on USG	Frequency	percentage
Adenomyomatous GB	11	18.33
Heterogenous Calcified Lesion In GB	15	25
Gall bladder tumefactive sludge	5	8.33
GB polyp	9	15
Cholesterolosis	20	33.3
TOTAL	60	100

The USG being the good screening tool for gall bladder pathology. Among 60 cases the largest number of cases were of cholesterosis and lowest were of gall bladder tumefactive sludge.

Table 2 : Distribution: CECT findings

Findings on CECT	Frequency	Percentage
Adenomyomatous GB	10	16.6
Heterogenous Calcified Lesion In GB	16	26.6
Gall bladder tumefactive sludge	4	6.66
GB polyp	10	16.6
Cholesterolosis	20	33.3
TOTAL	60	100

The cect is the better imaging to confirm suspicious malignant pathology. Among cases 10 were Adenomyomatous gall bladder and heterogenous calcified lesion were seen in 16 cases.

Table 3: Distribution: HPE Final report

HPE Final report	Frequency	Percentage
Benign	53	88.3
Malignant	7	11.6
Total	60	100

On final HPE report 7 cases were found to be malignant pertaining to be 11.6 percent of cases included.

Table 4: Distribution: HPE

HPE findings	Frequency	Percentage
Chronic Cholecystitis	10	16.6

Parasitic granuloma	2	3.33
Adenocarcinoma	7	11.6
Xantho-Granulomatous Cholecystitis	15	25
GB polyp	7	11.6
Cholesterolosis	19	31.6
Total	60	100

The hsitopathological diagnosis of 6 cases which were malignant was adenocarcinoma and 2 rare cases of parasitic granuloma were also identified.

Table 5: Association between USG findings: HPE

HPE findings	Wall thickness on USG		P -VALUE
	MEAN	SD	
Benign	4.037	1.241	<0.0001
Malignant	7.314	1.361	

The mean wall thickness of gall bladder of malignant cases were 7.314 with SD 1.361 with reference of benign cases having mean wall thickness 4.037 and SD 1.241. and the association of wall thickness of gall bladder seen on USG with HPE reference to be higher thickness of gall bladder having higher risk of malignancy and this association is statistically significant with p value <0.0001

Table 6: Association between CECT findings: HPE

HPE findings	Wall thickness on CECT		P -VALUE
	MEAN	SD	
Benign	3.663	0.574	<0.0001
Malignant	7.543	1.270	

The mean wall thickness of gall bladder of malignant cases were 7.543 with SD 1.270 with reference of benign cases having mean wall thickness 3.663 and SD 1574. and the association of wall thickness of gall bladder seen on CECT with HPE reference to be higher thickness of gall bladder having higher risk of malignancy and this association is statistically significant with p value <0.0001.

DISCUSSION

This prospective observational study took place at Darbhanga Medical College from August 2023 to March 2024. It involved 60 cases where the gallbladder exhibited focal wall thickness exceeding 3mm on ultrasonography. These cases were then correlated with the final histopathological report of the specimens. The histopathological examination revealed various conditions: chronic cholecystitis in 10 cases (16.6%), parasitic granuloma in 2 cases (3.33%), adenocarcinoma in 7 cases (11.6%), xanthogranulomatous cholecystitis in 15 cases (25%), gallbladder polyp in 7 cases (11.6%), and cholesterosis in 19 cases (31.6%). Reference studies provided additional insights: Rammohan et al. reported that out of 77 patients undergoing Extended Cholecystectomy for suspected Gallbladder Carcinoma, 15 were diagnosed with Xanthogranulomatous Cholecystitis upon final histology. Jain et al. noted 22 cases of Xanthogranulomatous Cholecystitis, with radical (extended) cholecystectomy performed in 11 patients.(6) Shirai and colleagues recently described a surgical approach involving full-thickness cholecystectomy (removal of the gallbladder with the cystic plate) along with limited lymphadenectomy of the first echelon lymph nodes (cystic and pericholedochal) as an alternative to extended cholecystectomy . They applied this method in 12 elderly patients with gallbladder cancer.(7) Han reported utilizing cholecystectomy with a wedge resection of the liver in only 4 out of 39 patients with xanthogranulomatous cholecystitis. Agarwal et al reported a large experience involving 556 cases of gallbladder masses identified on imaging, with 167 being diagnosed as Gallbladder Cancer and 31 as Xanthogranulomatous Cholecystitis. In our study, we applied this knowledge to 60 selected patients with focal gallbladder wall thickness and low suspicion of malignancy, identifying 15 cases of xanthogranulomatous cholecystitis.

Miyazaki and colleagues (2008) discovered that a gallbladder polyp with specific characteristics such as being sessile, having a diameter larger than 10 mm, and/or exhibiting rapid growth is highly indicative of cancer and should be surgically removed. While there appears to be a strong correlation between gallstones and gallbladder cancer, there is no direct evidence of a causal relationship between gallstones and the development of gallbladder cancer. In our study, 7 cases of gallbladder polyps were identified upon histopathological examination.

In their study, Gupta and colleagues (2020) discovered that the pattern

of gallbladder wall thickening in gallbladder cancer (GBC) is frequently mistaken for benign conditions, particularly chronic cholecystitis, xanthogranulomatous cholecystitis, and adenomyomatosis. Early identification and differentiation of these conditions can lead to improved prognosis.(8) In their mini-review, the authors outline the various abnormalities observed on different imaging techniques (both conventional and advanced) for diagnosing gallbladder wall thickening and its correlation with malignant potential. Suspicious lesions in the gallbladder are typically initially detected through transabdominal ultrasound, which assesses dimensions and characterizes abnormal findings. Gallbladder wall abnormalities are categorized as either protuberant or diffuse/focal wall thickening. Protuberant lesions like gallbladder polyps are found in up to 7% of healthy individuals. Gallbladder polyps less than 5 mm in size are unlikely to indicate gallbladder carcinoma. Patients with polyps between 6 and 10 mm should undergo surveillance ultrasound every 6–12 months. In cases of primary sclerosing cholangitis (PSC), where polyps of any size are identified, cholecystectomy is recommended due to the heightened risk of malignancy. Symptomatic polyps should also be removed via cholecystectomy. Certain sonographic findings suggest a benign diagnosis for polyps less than 10 mm.(9) For instance, cholesterol polyps typically have a thin attachment to the wall, are highly echogenic, and may display punctate foci indicating cholesterolosis. Gallbladder adenomas often exhibit multiple hypoechoic microcystic spaces.

Distinguishing between benign and malignant gallbladder wall thickening is generally challenging due to similar imaging characteristics. Certain features, such as the presence of intramural echogenic foci on ultrasound (US) and intramural cysts, are highly specific for adenomyomatosis diagnosis. Intramural cysts are most clearly observed in magnetic resonance cholangiopancreatography (MRCP) images. The existence of intramural hypodense (CT) or hyperintense (MRI) nodules diffusely involving the gallbladder suggests xanthogranulomatous cholecystitis (XGC). However, distinguishing XGC from gallbladder cancer (GBC) is exceptionally challenging due to overlapping findings. Mural thickening associated with extracholecystic conditions like liver and cardiac disease tends to be diffuse and exhibits mural layering. A recent systematic review reported ultrasound features of benign and malignant gallbladder wall thickening. Some innovative imaging techniques, including dual-energy computed tomography (DECT) and texture analysis, have been explored to enhance the accuracy of detecting malignant gallbladder wall thickening. The Gallbladder Reporting and Data System (GB-RADS) for ultrasound (US) aims to enhance the consistency of interpretations, reporting, and evaluation of the risk of malignancy associated with gallbladder wall thickening in non-acute scenarios.(10) The association between gallbladder wall thickening exceeding 3 mm and malignant potential was found to be statistically significant (p-value = 0.0001). In summary, radiographic findings suggesting a higher risk of malignant potential include focal wall thickening and polypoid lesions exceeding 10 mm in size.

CONCLUSION

Gallbladder cancer, while rare, poses a significant threat due to its potential lethality. Often asymptomatic in its initial stages, gallbladder cancer is frequently discovered incidentally. Any abnormalities suggestive of gallbladder cancer, whether incidental findings or detected during diagnostic imaging, warrant thorough evaluation, including consideration for surgical intervention when appropriate. Our study concludes that there is a statistically significant correlation between the enhancement pattern observed on radiological imaging and the histopathological findings of gallbladder specimens. Therefore, the radiological observation of gallbladder wall thickening patterns aids in recognizing early signs of gallbladder cancer, potentially altering the prognosis and enhancing survival rates.

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