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Original Research Article

Computed tomography derived imaging surrogates as pre-operative predictors of gall bladder pathologies in cases of cholecystic mural thickening

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ABSTRACT

Background: Diffuse or focal wall thickening wall is a common manifestation of most gall bladder pathologies. Identification of features to differentiate malignant from benign causes is hence of prime importance in clinical practice.
Methods: Contrast enhanced computed tomography (CT) scan was performed on 100 patients who revealed a gallbladder wall thickening (>5 mm) on screening sonography. The imaging features were charged with the intent of radiomic analysis and post-operative histopathologic correlation was done.
Results: The average wall thickness was 22.28±12.51 mm in malignancies and 13.5±6.6 mm in benign conditions with the difference being highly significant ($p<0.05$). The gallbladder wall thickening was a common feature (76.2%) in benign group while wall thickening with associated focal mass lesion was common (59.5%) in malignant group. Morphologically inhomogeneous lesions were more prone to develop malignancy (53%) compared to benign lesions in which homogeneous wall thickening (52.4%) was common. Type I (39.2%) and type II (39.2%) was seen in malignant conditions, while type I pattern was also seen in xanthogranulomatous cholecystitis (66.7%). Type V was common in benign cases (23.8%).
Conclusions: Amongst the charted radiomic features wall thickening and pattern of wall thickening were the most significant with sensitivity and specificity of 59.49% and 76.19% respectively. The next most common feature was pattern of enhancement on post contrast CT scan.

Keywords: Gall bladder carcinoma, Mural thickening, Computed tomography, Enhancement pattern

INTRODUCTION

Gallbladder (GB) pathologies have a high incidence (10-22/100,000 population) and prevalence (6.2%) in the Gangetic basin of northern India.[1] The spectrum of disease varies from benign gallbladder pathologies like acute cholecystitis, chronic cholecystitis, xanthogranulomatous cholecystitis to neoplastic pathologies most of which are malignant.[2] Most clinical practice-oriented protocols consider a screening sonography as the most logical initial diagnostic modality, whereby most of these pathologies present as a cholecystic mural thickening.[3]

A wall thickening in excess of 5 mm makes the differentiation between benign and malignant lesions difficult. The intent of this study was to systematically analyse and assign statistical significance to the imaging features used commonly for differentiation between benign and malignant lesions in cases showing cholecystic mural thickening on screening sonography.

METHODS

This is an institutional review board approved prospective observational study carried out in Department of General Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi between August 2017 to July 2019. Patients presenting to the surgical out-patient unit with upper abdominal symptoms were subjected to an initial screening sonography, out of a total of 550 patients a total of 83 patients reported back with a gallbladder wall thickening more than 5 mm on ultrasonography and were recruited in the study. Further 17 patients were referred to us from certain other medical and surgical units fulfilling the criteria and were also included. A total of 100 patients were hence recruited based on pre-decided criteria and were further evaluated by contrast enhanced computed tomography (CECT) of abdomen as a pre-standardized protocol.

Inclusion criteria

Patients were recruited for study when they met the following criteria: GB mass or GB wall thickening found at primary sonography examination, patient age 20 to 70 years old, absence of severe cardiopulmonary disease, not pregnant or lactating, and diagnoses confirmed by pathological examination.

Exclusion criteria

Patients having severe cardiopulmonary diseases, ascites, patients not having appropriate histopathological examination, and patients not giving consent were excluded. Informed consent from all the patients was taken prior to the examination and ethical approval taken for the study.

At the time of recruitment, all the data regarding clinical details, investigation reports were also collected. After due pre-surgical work-up to ensure resectability, the patients underwent surgical extraction of gall bladder with lymph node dissection wherever indicated. The surgical specimen was evaluated by a histopathologist blinded to the imaging impression and the data was correlated for accuracy of imaging features as pre-operative predictors of histopathology.

CT scans were performed on a multidetector row helical scanner (Discovery®VCT 128 slice scanner, GE Medical systems, Milwaukee, WI, USA) following a patient fasting of 4-6 hours. A total of 100 ml low-osmolar non-ionic iodinated contrast media iohexol with an iodine content of 300 mg/ml (Omnipaque®, GE medical systems, Milwaukee, WI, USA) was injected through an 18-gauge cannula in the median ante-cubital vein of left arm at the rate of 3-5 ml/min, to give a dosage of 500 mg of iodine/kg body weight. The contrast was injected using an automated dual head pressure injector (Optistar LE, Covidien, MA, USA) synchronized with the scanner, followed by a saline bolus chase of 20 ml. After an initial localizer and non-contrast scan from dome of diaphragm to iliac crest, three-phases of post-contrast scans were acquired (viz. arterial, portal venous and hepatic venous) using bolus tracking technique. The scanning was performed at 120 Kv, 350 mAs, with an increment of 5 mm and a pitch of 1.0, post contrast scanning was done to include the region from mid portion of the xiphisternum to the pubic symphysis. Multi-planar imaging reconstruction and analysis was done on an off-line work-station (ADW 2.0, GE Medical systems, Milwaukee, WI, USA). The CT imaging was analysed by trained radiologist with more than 5 years of experience. All examinations were read and reported by an experienced abdominal radiologist with 15 years of experience, who was blinded to the sonographic findings. Compilation and charting of features was done to systematically evaluate each feature and to retrospectively correlate each with post-operative gross pathological/ histopathological examination findings.

Statistical analysis was performed on a statistical package for the social sciences (SPSS) version 21.0 software (IBM Corporation, Chicago, IL, United States). The diagnostic accuracy of multiphasic CT scan was assessed in terms of sensitivity, specificity, positive predictive value, negative predictive value and accuracy and was compared using chi-square test and Fisher's exact test. $P<0.05$ was considered for statistical significance of each parameter.

RESULTS

The mean age of the patients in gallbladder cancer group was 53.56±12.11years and in benign group 59.24±12.8 years.

Out of 79 patients with malignancy, 14 (17.7%) were male and 65 (82.3%) were female with ratio 1:5, while, in benign, out of 21 patients, 15 (71.4%) were male and 6 (28.6%) were female with ratio 2.5:1.

The most common symptom was pain in right upper quadrant, both in cancer group (91.1%, n=72) and benign group (81%, n=17) followed by vomiting (cancer- 21.5%; benign 38.1%).

The most common sign was tenderness in right upper quadrant (malignant 43.0%; benign 23.8%) followed by palpable lump (malignant 26.6%; benign 4.8%).

Surgery was performed in majority of the patients. After surgical procedure, detailed histological evaluation of specimens were done. The patients were categorized as malignant and benign based on histology. Out of 100 specimens, 79 cases came out to be malignant and remaining 21 were of benign histology.

Wall thickening

Wall thickening was noted in 48 patients with the mean wall thickness in gallbladder carcinoma was 22.28±12.51 mm while in benign group it was 13.5±6.6 mm (p=0.002).

An associated focal mass lesion was seen in 4 patients. Conversely, in malignant group, wall thickening was seen in 32 (40.5%) cases, while wall thickening with associated mass were seen in 47 (59.5%) patients. In benign group, 16 (76.2%) patients showed wall thickening, while wall thickening with associated mass were seen in only 5 (23.8%) patients. The difference in both cases was significant.

A receiver operating characteristic (ROC) curve plotted between gallbladder wall thickness and nature of lesion, i.e., benign and malignant lesion showed a cut-off value of 15.65 mm for malignancy with sensitivity of 70%, specificity of 53% with p value of 0.018 (Figure 1).

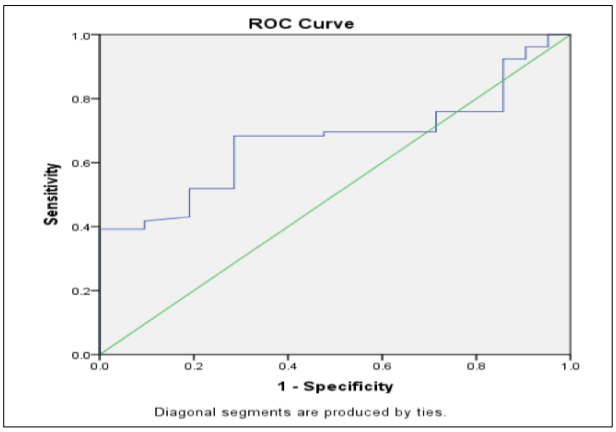

Figure 1: ROC curve showing relation of gallbladder wall thickness with incidence of malignancy in the present study.

Gall bladder dimensions

Distension of gallbladder was measured in terms of long axis diameter (LAD) and short axis dimension (SAD). In malignancy, 45.6% cases had LAD ≤50 mm and 54.5% cases ≥50 mm whereas, 34.2% cases had SAD ≤25 mm while 65.8% cases more than 25 mm. Contrary to this, in benign cases, 57.1% cases had LAD ≤50 mm and 42.9% cases ≥50 mm whereas 85.7% had SAD ≤25 mm while only 14.3% cases had SAD more than 25 mm.

Table 1: Gallbladder distension in LAD and SAD on CT scan (malignant versus benign).

CT GB distension	Malignant, N (%)	Benign , N (%)
LAD (mm)		
≤50	36 (45.6)	12 (57.1)
>50	43 (54.5)	9 (42.9)
Total	79 (100)	21 (100)
SAD (mm)		
≤25	27 (34.2)	18 (85.7)
>25	52 (65.8)	3 (14.3)
Total	79 (100)	21 (100)

Wall attenuation and enhancement

Homogeneity of wall attenuation on CT among malignant and benign conditions was compared. In malignant group, 53.2% patients had inhomogeneous lesion, 24.1% patients had borderline lesions and 22.8% cases had homogenous lesion. In benign lesions, these data were 38.1, 9.5% and 52.4% respectively.

Table 2: Homogeneity of gallbladder wall attenuation on CT scan (malignant versus benign).

CT homogeneity of wall attenuation (scale of 3)	Malignant, N (%)	Benign, N (%)
1 (Inhomogenous lesion)	42 (53.2)	8 (38.1)
2 (Borderline lesion)	19 (24.1)	2 (9.5)
3 (Homogenous lesion)	18 (22.8)	11 (52.4)
Total	79 (100)	21 (100)

χ^2=7.432; p=0.024

Enhancement patterns of thickened gallbladder wall on CT scan were compared between malignant and benign cases. In malignancy, type 1 and type 2 enhancement pattern was seen in 31 (39.2%) patients each (Figures 2 and 3).

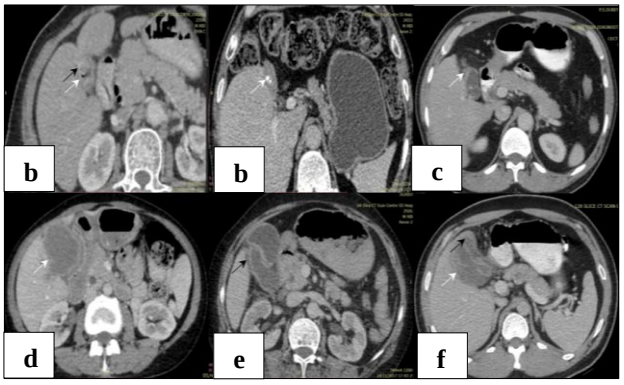

Figure 2: Contrast enhanced CT scan showing type I enhancement pattern in a thickened gall bladder wall, with various accompanying pathologies (a) homogenously enhancing one layered wall or indistinguishable layer (white arrow) with associated focal mass lesion (black arrow), (b) with calculi inside the lumen (white arrow), (c) a homogenous wall enhancement and thickening (white arrow), (d) an inhomogeneous lesion in wall (white arrow), (e) presence of pericholecystic fluid (black arrow,) and (f) presence of pericholecystic fluid (black arrow) and non- visualised pericholecystic fascia (white arrow).

None of the patients had type 3 pattern. Type 4 pattern was present in 2 (2.5%) cases (Figure 4) while type 5 pattern was seen in 15 (19%) cases (Figure 5).

In benign lesion, type 1 pattern was seen in 14 (66.7%) patients, 1 (4.8%) patient showed type 2 pattern, type 4 pattern was present in 1 (4.8%) case while type 5 pattern was seen in 5 (23.8%) cases. Based on histology, in

adenocarcinoma NOS, type 2 pattern was the most common enhancement pattern (n=24) followed by type 1 and type 5 (n=15, each). In xanthogranulomatous cholecystitis, type 1 was most common enhancement pattern (n=11). In chronic cholecystitis, type 5 pattern was the most common pattern present (n=4) followed by type 1 pattern (n=3). In papillary adenocarcinoma, type 1 was the most common pattern (n=7) followed by type 2 pattern (n=5). In diffuse infiltrative adenocarcinoma, only type 1 pattern was seen (n=3) (Table 3).

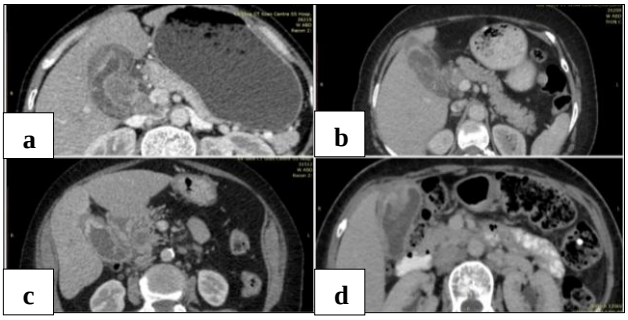

Figure 3: Contrast enhanced CT scan showing type II enhancement pattern in a thickened gall bladder wall [strongly enhancing thick inner layer (>2.6 mm) with a weakly enhancing or non-enhancing thin outer layer (>3.4 mm)], with various accompanying pathologies (a) thickened two layered wall with maintained pericholecystic fascia, (b) inhomogeneous lesion and thickened pericholecystic fascia, (c) inhomogeneous lesion and maintained pericholecystic fascia, and (d) with associated focal mass lesion.

Pericholecystic fascia/hepato-cholecystic plane

As far as condition of pericholecystic fascia on CT scan was concerned, in malignancy, 11.5% cases had normal pericholecystic fascia, 47.4% cases had thickened fascia while in 41% patients it was not visualised. In benign cases, these data were 4.8%, 71.4% and 23.8%, respectively (Figures 2f, 3c, and 5c).

Extra-cholecystic features

Various baseline characteristics were seen on CECT and USG in malignant and benign lesions. On CECT, liver infiltration was present in 67.1% (n=53) patients in malignant group and 61.9% (n=13) patients in benign group. Lymph nodes enlargement was seen in 86.1% (n=68) in malignancy while 42.9% patients (n= 9) had this feature in benign condition. Homogeneity of thickened gallbladder wall was maintained in 22.8% patients (n=18) in case of malignancy, while in patients with benign lesion, it was maintained in 57.1% patients (n=12). Pericholecystic fluid was present in 33 patients in malignant group and 14 cases in benign group (Figures 2e and f). Hepatocholecystic plane was maintained in 27.8% (n=22) patients in malignancy and in 61.9% patients (n=13) in benign group (Figures 3a and c).

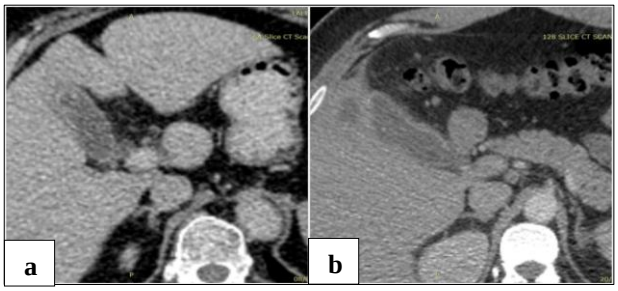

Figure 4: Contrast enhanced CT scan showing type IV enhancement pattern in a thickened gall bladder wall, which is weakly enhancing, thin inner layer with a non-enhancing thin outer layer. The enhancement pattern is shown in (a) and (b).

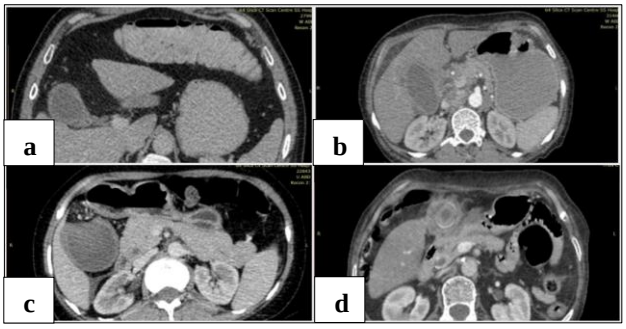

Figure 5: Contrast enhanced CT scan showing type V enhancement pattern in a thickened gall bladder wall, which is weakly enhancing, thin inner layer with a non-enhancing thin outer layer. The enhancement pattern is shown in (a) and (b). Various accompanying pathologies which are shown (c) a non-visualized pericholecystic fascia, and (d) presence of pericholecystic fluid.

Table 3: CT Enhancement pattern of thickened gallbladder wall.

CT enhancement pattern	Malignant % (N)				Benign % (N)		
	Total	AC NOS	Papillary AC	Diffuse infiltrative AC	Total	XGC	CC
Type 1	39.2 (31)	18.9 (15)	8.9 (7)	3.8 (3)	66.7 (14)	52.4 (11)	14.3 (3)
Type 2	39.2 (31)	30.4 (24)	6.3 (5)	0	4.8 (1)	4.8 (1)	0
Type 3	0	0	0	0	0	0	0
Type 4	2.5 (2)	2.5 (2)	0	0	4.8 (1)	4.8 (1)	0
Type 5	19.0 (15)	18.9 (15)	0	0	23.8 (5)	4.8 (1)	19.0 (4)

χ^2=9.404; p=0.024

Table 4: Pericholecystic fascia on CT scan (malignant versus benign).

CT pericholecystic fascia	Malignant, N (%)	Benign, N (%)
Normal	9 (11.5)	1 (4.8)
Thickened	37 (47.4)	15 (71.4)
Not visualized	32 (41.0)	5 (23.8)
Total	78 (100)	21 (100)

χ^2=3.878; p=0.144

Table 5: Other associated features as markers of differentiation of malignant from benign pathologies.

Baseline characteristics on CT scan		Malignant (n=79), N (%)	Benign (n=21), N (%)	P value
CECT	Wall thickening	32 (42.5)	16 (76.2)	0.004
	Wall thickening with associated mass	47 (59.5)	5 (23.8)	
	Liver infiltration	53 (67.1)	13 (61.9)	0.656
	LN enlargement	68 (86.1)	9 (42.9)	<0.001
	GB distension	61 (77.2)	17 (81)	0.713
	Ascites	9 (11.4)	0	0.105
	Homogeneity of wall attenuation	18 (22.8)	12 (57.1)	0.024
	Calcification	28 (35.4)	12 (57.1)	0.071
	Other hyperattenuating foci	29 (36.7)	11 (52.4)	0.193
	Necrosis	19 (24.1)	6 (28.6)	0.671
	Pericholecystic fluid	33 (41.8)	14 (66.7)	0.051
	Calculus/sludge	72 (91.1)	21 (100)	0.157
	Mucosal breach	47 (59.1)	12 (57.1)	1.00
	Hepatocholecystic plane	22 (27.8)	13 (61.9)	0.008

DISCUSSION

Wall thickening

Among all patients who had malignancy, 40.5% patients (n=32) showed only wall thickening while wall thickening with associated focal mass lesion was seen in 59.5% cases (n=47). In benign group, 76.2% patients (n=16) showed gallbladder wall thickening while only 23.8% patients (n=5) had wall thickening with an associated focal mass. The gallbladder wall thickening was common feature (76.2%) in benign group while wall thickening associated with mass lesion was common feature (59.5%) in malignant group which was similar to study by Yun et al where thicker and more irregular wall thickening was more frequent in patients with gallbladder carcinoma (20 of 35, 57.1%) than in those with chronic cholecystitis (13 of 47, 27.7%).[4] Focal thickening of the gallbladder wall indicated malignancy. In study by Jeffrey et al, it was seen that focal thickening was difficult to differentiate from an area of fibrosis associated with chronic cholecystitis or an area of adenomatous hyperplasia.[5] Lane et al said that gallbladder wall infiltrated by malignancy was thicker and more irregular than one thickened by inflammation.[6] They concluded that the thicker and more irregular wall would suggest malignancy. Contrarily, Rooholamini et al showed diffuse thickening of the gallbladder wall secondary to uniform infiltration by a tumour can be similar in appearance to chronic cholecystitis which was nonspecific.[7] Smathers et al also reported that smoothness versus irregularity of the gallbladder wall was not a reliable differentiating feature between carcinoma and benign conditions.[8]

The mean wall thickness in gallbladder carcinoma was 22.28±12.51 mm while in benign group it was 13.5±6.6 mm (p<0.05). In study by Yun et al, the mean wall thickness in carcinoma gallbladder was 12.6 mm and in chronic cholecystitis was 6.9 mm.[4] While in study by Sandhu et al, mean thickness of wall in gallbladder malignancy and in chronic cholecystitis as 14.31 mm and 10.91 mm respectively.[9] In our study, higher mean wall thickness in benign gallbladder condition is due to large number of xanthogranulomatous cholecystitis patients in comparison to other studies.

In our study, a ROC curve (Figure 1) plotted for gallbladder wall thickness showed the cut off value of 15.65 mm for malignancy with sensitivity of 70%, specificity of 53% and p value 0.018. In study by Sandhu et al, the mean thicknesses of the wall in gallbladder malignancy group and cholecystitis group were 14.31 mm and 10.91 mm respectively.[9] A cut off value of 13.45 mm for malignancy yielded sensitivity of ~85% and a specificity of ~75%.

Gall bladder dimensions

Distension of gallbladder in terms of SAD (mm) was studied. In malignancy, 34.2% cases had SAD ≤25 mm while 65.8% cases more than 25 mm. Contrary to this, in benign lesions, 85.7% cases had SAD ≤25 mm while only

14.3% cases had SAD more than 25 mm. The difference was statistically significant (p value <0.001). This shows that chronically distended gallbladders are more prone to develop malignancy. This was a new finding in our study and no literature has ever mentioned the importance of GB distension in terms of SAD.

Wall attenuation and enhancement

Homogeneity of wall attenuation on CT scan among malignant and benign conditions were studied. 53.2% patients (n=42) in malignant group had inhomogeneous lesion and 24.1% patients (n=19) had borderline lesions whereas, in benign disease group, 52.4% patients (n=11) had homogenous lesions. This showed that inhomogeneous lesions were more prone to develop malignancy (present in 53% of the cases) as opposed to benign lesions in which homogeneous wall thickening was a salient feature. Our findings were coherent with the findings given by Yun et al.[4] In study by Chen et al, on MDCT, most gallbladder carcinomas showed inhomogeneous high enhancement in the arterial phase, irregular wall thickening and interruption of the gallbladder wall.[3]

The contrast enhancement of thickened gallbladder wall in porto-venous phase of CECT was compared to that of attenuation shown by adjacent liver bed. In our study, enhancement patterns described by Kim et al was used.[10] In this, a single phase MDCT in porto-venous phase was used to classify thickened gallbladder wall lesions.[10] In carcinoma gallbladder, the most common enhancement pattern was type 1 and type 2 with 31 cases each (39.2%) followed by type 5 pattern (n=15, 19%). However, in adenocarcinoma NOS, type 2 was the most common pattern of enhancement (n=24, 30.4%). In xanthogranulomatous cholecystitis, type 1 was the most common enhancement pattern, present in 11 (52.4%) cases. In chronic cholecystitis, type 5 enhancement was most common (n=4, 19.0%) followed by type 1 (n=3, 14.3%) enhancement pattern.[10]

Kim et al has reported high prevalence of gallbladder cancer in type 2 and type 1 pattern, i.e., two layered wall thickening showing a strongly enhancing thick inner layer and weakly enhancing or non-enhancing thin outer layer and one-layer thickening showing heterogenous enhancement respectively.[10] They too have concluded that thickened gallbladder wall with disruption or obliteration of normal layered pattern suggests carcinoma. Similar findings were reported by Tongdee et al and Mathur et al.[11,12] The type 5 pattern was reported in 6.9% and 3.4% cases of carcinoma gallbladder by two observers respectively in Kim et al, however, in our study type 5 pattern was reported in 19% cases (n=15) in malignant group.[10]

Kim et al, also reported, type 1 and 2 patterns in chronic granulomatous cholecystitis including xanthogranu-lomatous cholecystitis. Type 3 is considered to be borderline enhancement pattern including adenomyomatosis; type 4 as chronic cholecystitis and type 5 as acute cholecystitis.

In our study, type 5 pattern was mainly found in chronic cholecystitis. This difference could be explained by the fact that a minimum cut off value of 5 mm thickness of gallbladder wall was taken into this study and so to have a thin non enhancing outer layer (type 4) was not as common as to have a thick non enhancing outer layer (type 5).

Our results were similar in some aspect to a previous report by Jung et al, regarding the layered patterns of gallbladder wall on MRI.[13] In that study, Jung and colleagues classified thickened gallbladder wall into four patterns on T2-weighted images on the basis of the presence of striation, the features of the inner and outer layers, and the signal intensity of each layer. In their results, acute and chronic cholecystitis showed two layers with an ill-defined or discrete margin, whereas gallbladder cancer showed diffuse nodular wall thickening without layering.

Pericholecystic fascia/hepato-cholecystic plane

On CT scan pericholecystic fascia was studied and in around 88% cases of malignancy, pericholecystic fascia was either thickened or not visualised, while majority of the patients (71%) with benign disease showed thickened pericholecystic fascia owing to inflammatory lesions like xanthogranulomatous cholecystitis.

CONCLUSION

The present study suffers with the limited numbers of subjects due to which many characteristics which are statistically significant could not give accurate measurements like presence of liver infiltration in malignancy, distension of gallbladder, presence of ascites, presence of calcification or other hyperattenuating foci, presence of necrosis, presence of calculus/sludge, mucosal breach and biliary dilatation. Further, study of enhancement patterns of gallbladder wall thickening, the dynamic contrast enhanced study for various phases of wall enhancement could have added more information on the subject.

In conclusion, the differential diagnosis of gallbladder wall thickening can be both malignant and benign lesion of gallbladder. However, the gallbladder wall thickening was more marked in malignant lesion. The inhomogeneous wall attenuation and non-visualization of pericholecystic fascia are in favour of malignant lesion. The enhancement pattern may also help in differentiating malignant from benign pathology.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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