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Role of dual energy CT in differentiation of benign and malignant gall bladder disease: A histopathological correlation.

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Abstract

Objective:

To evaluate the role of dual-energy CT (DECT) and contrast enhancement in differentiating benign from malignant gallbladder (GB) diseases.

Methods:

Ninety patients (21–70 years) with GB wall thickening >3 mm or GB mass on ultrasonography undergoing cholecystectomy were enrolled. CT was performed using a 384-slice Siemens SOMATOM Force dual-source DECT scanner. Non-ionic contrast (iopromide, Ultravist 370) was administered, and attenuation images were acquired at 80 and 140 kVp. Parameters assessed included wall thickening and its pattern, presence and extent of polypoidal mass, iodine uptake in GB wall and pericholecystic liver parenchyma, attenuation pattern, pericholecystic invasion, and lymphadenopathy. DECT diagnoses were made by consensus of two radiologists. Histopathological examination (HPE) served as the reference standard. Data were analyzed using SPSS 21.0, with chi-square and independent t-tests applied. Diagnostic performance indices of DECT were calculated.

Results:

On HPE, 51 cases (56.7%) were benign and 39 (43.3%) malignant. Malignant cases had significantly higher mean age (51.13±11.80 years) than benign (41.18±10.01 years) ($p<0.001$). Most patients were female (71.1%) and from rural areas (63.3%). No significant association of clinicodemographic factors with HPE diagnosis was noted. On DECT, focal irregular wall thickening, mass replacing GB, increased iodine uptake in GB wall and pericholecystic liver, invasion, and lymphadenopathy were significantly linked to malignancy, whereas regular circumferential thickening suggested benignity. DECT diagnosed malignancy in 36 cases (40%) and benign disease in 54 (60%). Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of DECT were 79.5%, 90.2%, 86.1%, 85.2%, and 85.6%, respectively.

Conclusion:

Dual-energy CT is a reliable tool for distinguishing malignant from benign GB diseases, with good diagnostic accuracy. Its wider application may improve early detection, though further exploration is warranted.

***Keywords**: Dual energy computed tomography, Gall bladder malignancy, pericholecystic invasion, regional lymphadenopathy, post-image processing.*
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Introduction

Owing to the high accuracy of USG in the detection of gall bladder malignancy, other advanced imaging techniques such as CT and MRI have not been extensively evaluated for their potential in the differentiation of benign and malignant diseases of the gall bladder.[1,2] Although some recent studies have shown that multidetector row CT with dual phase technique has also been studied and found to be more efficacious, having greater sensitivity and specificity in distinguishing benign and malignant causes of gall bladder wall thickening.[3] Newer imaging techniques, such as MRI and Real-time elastography, have also been used, but in developing countries, their use is limited due to high cost and availability at specialty centres only.

Interestingly, due to the variable appearance of gallstones on CT, gallstones and other gallbladder conditions can be difficult to detect at conventional MDCT. However, dual energy CT, which works on material-dependent x-ray absorption behavior of concurrently acquired high– and kilovolt-peak data and with its post-processing techniques, can add value in the visualization of gallbladder stones, detection of inflammatory and neoplastic causes of gallbladder thickening.[4]

Hence, the present study was done to evaluate the DECT findings of the Gall Bladder diseases, with special emphasis on contrast enhancement patterns of the gallbladder wall on DECT.

Material and method

The study was carried out at the Department of Radiodiagnosis in collaboration with the Department of Surgery and Department of Pathology, Era's Lucknow Medical College & Hospital, Lucknow, after getting approval from the Institutional Ethics Committee. A total of 90 patients aged 21 to 70 years with GB wall thickening >3 mm and gallbladder mass on USG scheduled to undergo cholecystectomy because of diagnosed gallbladder disease were enrolled in the study after getting informed consent. Pregnant women, patients with deranged renal function test, patients allergic to contrast, and cases with incomplete histopathological diagnosis were excluded from the study.

The sample size of the study was calculated at 95% confidence and 90% power with a type I error of 5% and error allowance of 3% based on a projected sensitivity of 89% and an estimated prevalence of 38.5% malignancy.[3]

After obtaining informed consent, demographic information, duration, and nature of complaints were noted on a separate case sheet for the individual. All patients were then subjected to imaging evaluation using Dual Energy CT and contrast as a modality.

All the 90 patients recruited in our study underwent CT examination on a Siemens SOMATOM Force Dual source dual energy CT scanner (384 slice) installed at the Radiology Department of our institution. Each patient received 60–80 mL (according to body weight) of a non-ionic contrast agent (iopromide [Ultravist 370]) through an 18-gauge catheter inserted into a forearm vein. The contrast was injected at a rate of 3–5 ml/second using an automatic power injector. DECT scans were obtained in supine position during full inspiration from the level of the lung bases and proceeded in a craniocaudal direction up to the lower pole of the kidney. Dual energy images were obtained at low energy (70-80 kVp) and high energy (100-140 kVp). Post-imaging processing was done with the built-in software provided by the manufacturer.

The DECT diagnosis was made by two trained and experienced radiologists, blind to histopathological diagnosis, based on criteria described by Ratanaprasatporn after mutual agreement.[4] The protocol of the study included a second-tier opinion of a third radiologist in case of a disagreement between two radiologists involved in the study; however, all the diagnoses were made by consensus of two radiologists engaged at the first tier itself.

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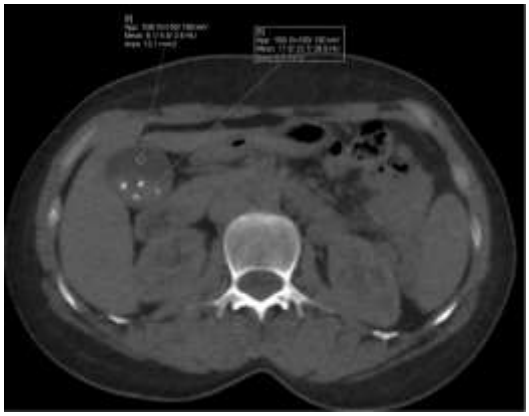
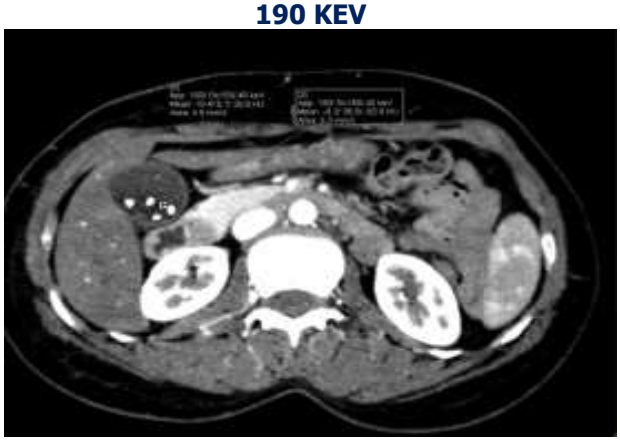


1 Fig: DECT 190 KEV: non-calcified cholesterol-containing calculi have higher hu than bile at 190 KEV



2 Fig.: DECT 40 KEV: non-calcified cholesterol-containing calculi have higher hu than bile at 40 KEV

Data analysis

The data was analyzed using the Statistical Package for the Social Sciences, Version 21.0. Chi-square and Independent samples' tests were used to compare the data.

Results

A total of 90 patients were enrolled in the study. Histopathologically, a total of 51 (56.7%) were diagnosed as benign, and the remaining 39 (43.3%) as malignant. Among 51 cases diagnosed as benign, the major findings were chronic cholecystitis with hyperplasia (n=11; 21.6%), followed by chronic cholecystitis with dysplasia (n=10; 19.6%), xanthogranulomatous cholecystitis (n=8; 15.7%), chronic cholecystitis with cholelithiasis and acute on chronic cholecystitis with cholelithiasis (n=5; 9.8% each). On the other hand, of the 39 cases diagnosed as malignant, 35 (89.7%) were adenocarcinoma, and the remaining 4 (10.3%) were adenocarcinoma with cholecystitis (Table 1) (Fig. 1).

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Table 1: distribution of benign and malignant gall bladder disease cases according to histopathological type

SN	Histopathological type	No. of cases	Percentage
The	Benign (n=51)		
1.	Chronic cholecystitis with hyperplasia	11	21.6
	Chronic cholecystitis with dysplasia	10	19.6
	Xanthogranulomatous cholecystitis	8	15.7
	Chronic cholecystitis with cholelithiasis	5	9.8
	Acute on chronic cholecystitis with cholelithiasis	5	9.8
	Adenomyomatosis	4	7.8
	Acute on chronic cholecystitis	4	7.8
	Chronic cholecystitis with polyp	2	3.9
	Acute on chronic cholecystitis with focal gangrenous changes	1	2.0
	Acute on chronic cholecystitis with cholelithiasis and hyperplasia	1	2.0
2.	Malignant (n=39)		
	Adenocarcinoma	35	89.7
	Adenocarcinoma with chronic cholecystitis	4	10.3

Mean age of malignant cases (51.13±11.80 years) was significantly higher than that of benign cases (41.18±10.01 years) ($p<0.001$). The majority of benign (68.6%) as well as malignant (74.4%) cases were females. Overall, there were 28.9% males and 71.1% females. Overall, there were 57 (63.3%) rural and 33 (36.7%) urban patients. Retired (50%) and students (23.3%) comprised the most common occupational groups. None of the cases had a history of gallbladder disease. Family history of gall bladder disease was revealed in 1 (1.1%) case only. A total of 3 (3.3%) patients had a diabetic history, too. Statistically, there was no significant difference in gender, residence, occupation, history, family history, and diabetic history of benign and malignant cases (Table 2).

Table 2: Comparison of demographic and clinical profiles and their correlation with histopathological diagnosis

SN	Variable	Benign (n=51)		Malignant (n=39)		Total (n=90)		Statistical significance	
1.	Mean Age±SD (Range)	41.18±10.01 (21-70)		51.13±11.80 (28-70)		45.49±11.80 (21-70)		't'=4.324; p<0.001	
		No.	**%**	**No.**	**%**	**No.**	**%**	**χ^2**	**'p'**
2.	Sex								
	Male	16	31.4	10	25.6	26	28.9	0.353	0.552
	Female	35	68.6	29	74.4	64	71.1		
3.	Place of residence								
	Rural	30	58.8	27	69.2	57	63.3	1.031	0.310
	Urban	21	41.2	12	30.8	33	36.7		
4.	Occupation								
	Business	4	7.8	4	10.3	8	8.9	4.172	0.653
	Professional	1	2.0	0	0.0	1	1.1		
	Housewife	7	13.7	4	10.3	11	12.2		
	Retired	22	43.1	23	59.0	45	50.0		
	Service	2	3.9	2	5.12	4	4.4		

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	Student	15	29.4	6	15.4	21	23.3		
5.	History	0	0	0	0	0	0	-	-
6.	Family history	0	0	1	2.6	1	1.1	1.322	0.250
7.	Diabetic history	3	5.9	0	0	3	3.3	2.37	0.123

On DECT evaluation, Diffuse wall thickening was present in significantly higher proportion of benign (90.2%) as compared to malignant (15.4%) cases (p<0.001) while focal irregular wall thickening was more common in malignant (23.1%) as compared to benign (7.8%) cases (p=0.042) **(Fig. 2)**. No significant difference between two groups was observed with respect to intraluminal polypoid mass. Finding of mass replacing the gall bladder was seen in the majority (54.4%) of malignant cases, as compared to none of the benign (0%) cases (p<0.001). Uptake of iodine was increased in only 49% of benign as compared to 94.9% of malignant cases (p<0.001) **(Fig. 3)**.

Table 3: CT findings and their correlation with histopathological diagnosis

SN	Finding	Benign (n=51)		Malignant (n=39)		Total (n=90)		Statistical significance	
		No.	%	No.	%	No.	%	χ^2	'p'
1.	Diffuse regular circumferential wall thickening.								
	Absent	5	9.8	33	84.6	38	42.2	57.55	<0.001
	<1 cm	43	84.3	2	5.1	45	50.0		
	>1 cm	3	5.9	4	10.3	7	7.8		
2.	Focal irregular wall thickening	4	7.8	9	23.1	13	14.4	4.15	0.042
3.	Intraluminal polypoid mass	2	3.9	3	7.7	5	5.6	0.599	0.439
4.	Mass replacing the gall bladder	0	0	22	54.4	22	24.4	38.1	<0.001
5.	Increased uptake of iodine in the GB wall	25	49.0	37	94.9	62	68.9	21.7	<0.001
6.	Increased Iodine uptake in the Pericholecystic liver parenchyma								
	Absent	27	52.9	3	7.7	30	33.3	26.65	<0.001
	Normal	16	31.4	12	30.8	28	31.1		
	Increased	8	15.7	24	61.5	32	35.6		
7.	Hypoattenuating nodules in the GB wall	12	23.5	4	10.3	16	17.8	2.664	0.103
8.	Pericholecystic invasion	0	0	33	84.6	33	36.7	68.1	<0.001
9.	Regional lymphadenopathy	20	39.2	38	97.4	58	64.4	32.7	<0.001

Similarly, increased uptake of iodine in pericholecystic liver parenchyma was seen in a significantly higher proportion of malignant (61.5%) as compared to benign (15.7%) cases (p<0.001) **(Fig. 4)**.

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Table 4: correlation between DECT and histopathological diagnosis for malignancy

DECT Diagnosis	Histopathological diagnosis		Total
	Malignant	Benign	
Malignant	31	5	36
Benign	8	46	54
Total	39	51	90

Sensitivity	Specificity	PPV	NPV	Accuracy
79.5%	90.2%	86.1%	85.2%	85.6%

Fig. 2: DECT iodine overlay image: no increased iodine uptake in gallbladder wall, consistent with benign disease

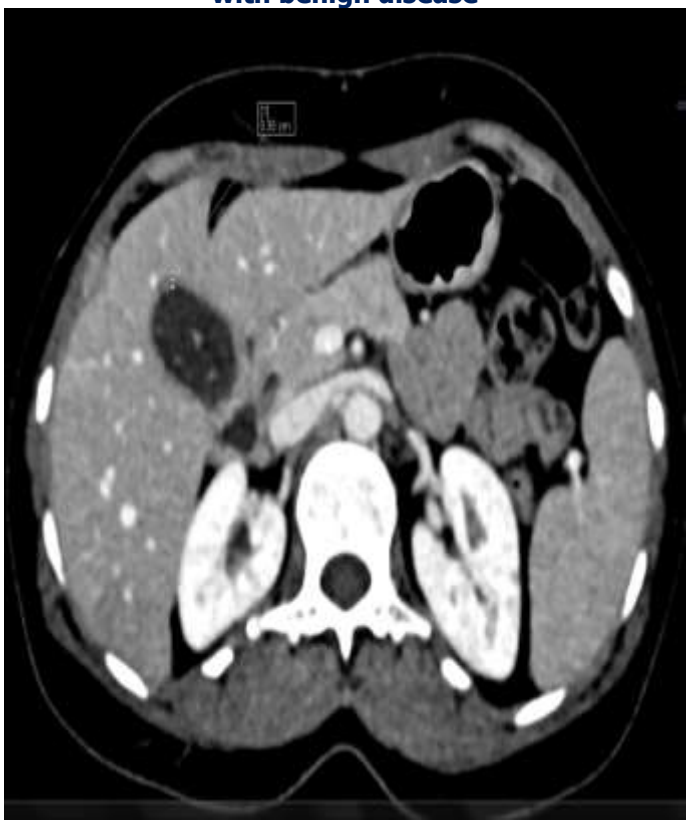

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Fig. 3: DECT hot gallbladder sign: increased iodine uptake in the gallbladder wall, typical of malignant cases

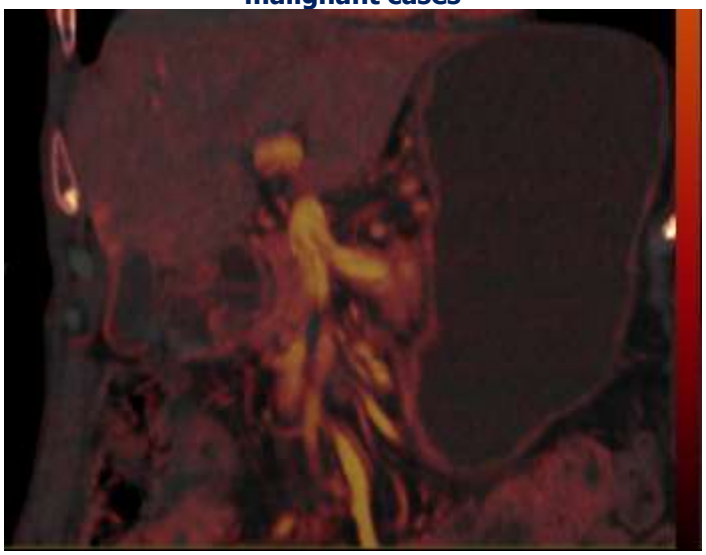
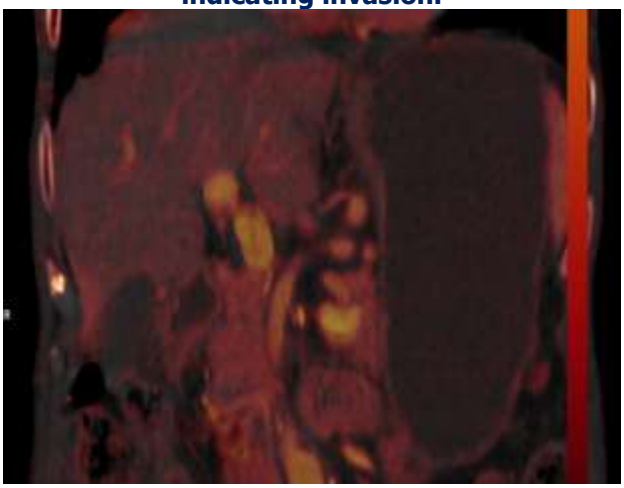


Fig. 4: DECT hot rim sign: increased iodine content in pericholecystic liver parenchyma, indicating invasion.



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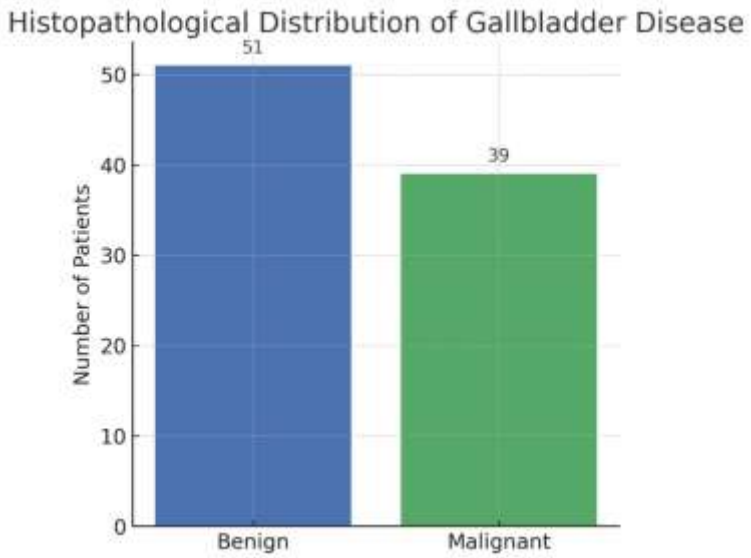

Fig. 1: histopathological distribution of gallbladder disease showing the proportion of benign (n=51) and malignant (n=39) cases among the study population.

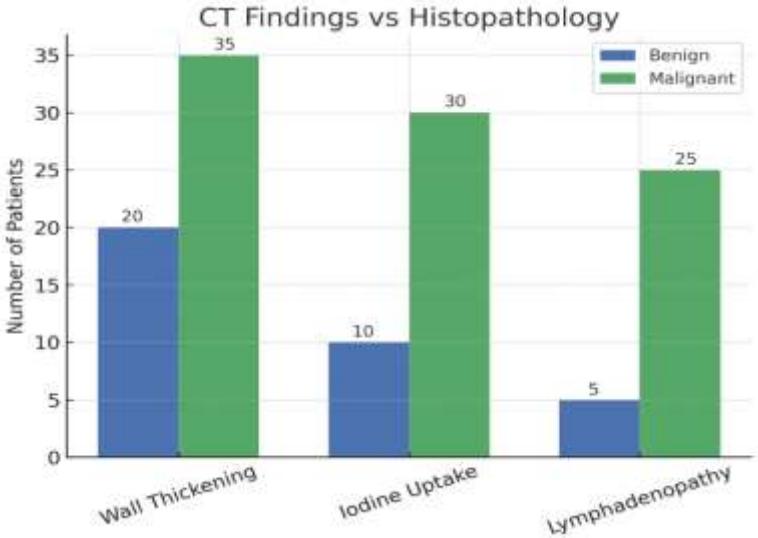

Fig. 5: correlation of CT findings with histopathological outcomes. Malignant cases demonstrated higher rates of wall thickening, iodine uptake, and lymphadenopathy compared with benign disease.

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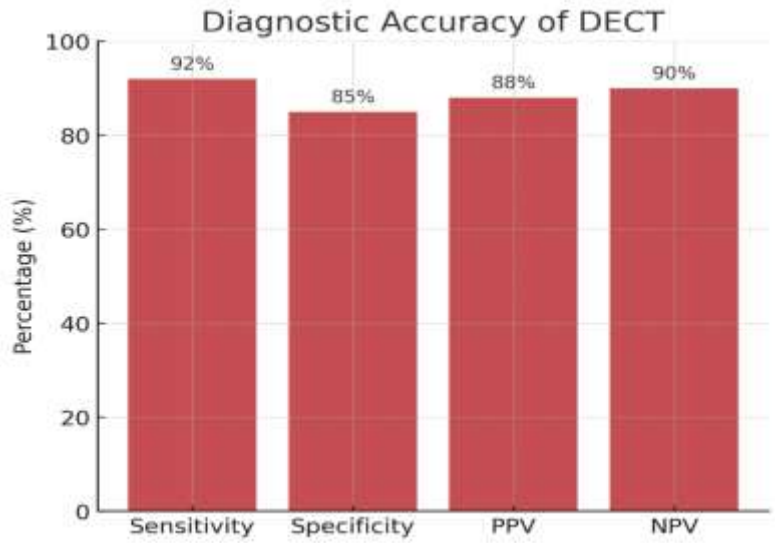

Fig. 6: diagnostic accuracy of dual-energy CT in differentiating benign from malignant gallbladder disease. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) are presented as percentages.

Hypoattenuating nodules in the gall bladder were seen in a higher proportion of benign (23.5%) as compared to malignant (10.3%) cases, but the difference was not found to be statistically significant (p=0.103). Pericholecystic invasion and regional lymphadenopathy were seen in 84.6% and 97.4% of malignant cases, respectively, as compared to 0% and 39.2% of benign cases, thus showing a significant difference for both the features between the two groups (p<0.001) (Table 3) (Fig. 5).

On DECT diagnosis, a total of 36 (40%) cases were diagnosed as malignant. There were 28 (31.1%) cases diagnosed as chronic cholecystitis, 10 (11.1%) as xanthogranulomatous cholecystitis, 10 (11.1%) as acute cholecystitis, and 6 (6.7%) as adenomyomatosis.

Out of 39 histopathologically diagnosed malignant cases, 31 were diagnosed as malignant and 8 as benign by DECT, whereas out of 51 histopathologically benign cases, a total of 46 were diagnosed as benign and 5 as malignant by DECT. The sensitivity, specificity, positive predictive, negative predictive, and accuracy values of DECT for malignant gall bladder masses were 79.5%, 90.2%, 86.1%, 85.2% and 85.6% respectively (Table 4) (Fig. 6).

Discussion

In the present study, the histopathologically detected malignancy rate was 43.3% (n=39/90). Compared to the present study, some studies have reported a malignancy rate as high as 77.3% in cases operated for suspected gall bladder carcinoma.[5,6] In the present study, the prevalence of gall bladder carcinoma is lower than in these studies, as the present study included all the patients who were undergoing cholecystectomy for benign as well as malignant diseases.

In the present study, among benign conditions, Chronic cholecystitis with hyperplasia (21.6%), dysplasia (19.l6%), and Xanthogranulomatous cholecystitis (15.7%) were the major diagnoses. In all, a total of 54.9% of cases had chronic cholecystitis. Compared to the present study, chronic cholecystitis has been reported to be the major diagnosis in most of the other series, and xanthogranulomatous cholecystitis is found only in up to 1.2% to 2.5% cases.[7-11] The profile of benign diseases in the present study thus varies from the previous studies and should be considered as a study-specific phenomenon.

In the present study, all the cases with malignancy had adenocarcinoma. Although malignant tumors of the gall bladder are not common yet in malignant cases,

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adenocarcinomas are most common, comprising>80% 80% of gallbladder cancers.[12,13]

In the present study, the mean age of patients was significantly higher in the malignant group. Gall bladder disease, particularly cholelithiasis, is generally common in middle age. Evolution and progression from non-neoplastic to neoplastic conditions generally takes 5 to 15 years; thus, malignant gall bladder disease is distinguished by a dominance of patients >50 years of age.[14,15]

In the present study, in both groups, the majority of patients were females. However, we did not find a significant association of gender with malignancy. Epidemiological studies show that women are at a greater risk of gall bladder disease (both benign and malignant). Several other studies from India have also shown advancing age and female dominance as the key features in gall bladder malignancy cases.[16,17]

In the present study, no rural/urban differences and occupational factors did not seem to be significantly associated with malignancy. As such, no such differences associated with malignancy have been reported elsewhere, either.

In the present study, on dual energy CT, diffuse regular circumferential wall thickening >1cm, focal irregular wall thickening, mass replacing the gall bladder, increased uptake of gangrenous GB wall, and iodine uptake in pericholecystic liver parenchyma, pericholecystic invasion, and regional lymphadenopathy were significantly associated with malignancy. Among different DECT features significantly associated with malignancy, pericholecystic invasion was 84.6% sensitive and 100% specific, while diffuse irregular circumferential wall thickening was 84.6% sensitive and 90.2% specific in the detection of malignancy. According to Ratanaprasatporn, irregular focal or diffuse gallbladder wall thickening, an intraluminal polypoid mass, and a mass obscuring the gallbladder wall or completely replacing the gallbladder are the characteristic morphological features that could be evaluated through DECT for the detection of gallbladder cancer.[4] However, in the present study, focal irregular wall thickening was seen in only 23.1% of malignant as compared to 7.8% of benign cases, and intraluminal polypoid mass was seen in only 7.7% of malignant and 3.9% of benign cases, thus showing that these features independently have a low diagnostic value. Increased iodine uptake in pericholecystic liver parenchyma was seen to have a better diagnostic value as it was present in 61.5% of malignant cases, as compared to only 15.7% of benign cases. Similarly, increased uptake of iodine in the GB wall, which was seen in 94.9% of malignant as compared to 49% of benign cases, was highly sensitive but less specific for the detection of malignancy. Both these findings are considered to be signs of a hot gall bladder and a feature of acute cholecystitis, secondary to hepatic arterial hyperemia[4]. Focal or diffuse gallbladder wall thickening of greater than 1 cm and asymmetric gallbladder wall thickening are highly suggestive of carcinoma. Additional imaging features that favor a diagnosis of malignancy include associated lymphadenopathy, extension of soft tissue into the adjacent liver, and hematogenous metastasis.[18]

As far as the potential of dual-energy CT iodine uptake is concerned, it helps to facilitate improved detection and characterization of gallbladder carcinoma. It helps in contrast enhancement, thus helping in easy visualization of malignancy, as the iodine uptake is higher in malignant conditions as compared to other benign conditions like Xanthogranulomatous cholecystitis and adenomyomatosis.[19] In a study by Jindal, the CT features of gall bladder malignancy were described as a mass replacing the entire GB was seen in 62.8% of patients, asymmetrical wall thickening of the GB in 45% of patients, and a polypoidal intraluminal mass in 11.4% of patients.[6] In the present study, the presence of all these features was relatively less, whereas the diagnostic value of pericholecystic invasion and regional lymphadenopathy was more conclusive. Pericholecystic scarring/invasion is a characteristic finding of adenocarcinoma.[19] In the present study, all the malignant cases were histopathologically confirmed as adenocarcinoma. DECT, in fact, offers a better contrast and, with the help of dual-energy, helps to differentiate the pericholecystic invasion in an effective manner, thus helping in the diagnosis of invasive malignancy from benign disease.

As far as regional lymphadenopathy is concerned. It is quite frequent in gall bladder carcinoma [20]. DECT has a high accuracy in the evaluation of regional lymph node metastasis as described in different other conditions, such as colorectal cancer and hepatocellular carcinoma, and has been shown to have a high sensitivity and specificity of nearly 85%. [21,22,23]

In the present study, on the basis of the correlation of DECT findings, we evolved a diagnosis for different malignant and

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benign conditions as per the description provided by Ratanaprasatporn and made the diagnosis of malignancy in 36 (40%) cases.[4] There were 28 (31.1%) cases diagnosed as chronic cholecystitis, 10 (11.1%) as xanthogranulomatous cholecystitis, 10 (11.1%) as acute cholecystitis, and 6 (6.7%) as adenomyomatosis. As compared to the histopathological diagnosis of different benign diseases, the detection rate for chronic cholecystitis was the same for both conditions. DECT failed to diagnose one case out of eleven cases of acute cholecystitis, but overdiagnosed two cases of adenomyomatosis and two cases of xanthogranulomatous cholecystitis. As such, the characteristic DECT features of these diagnoses have not been well described in the literature and need further study separately. Owing to the limited number of these conditions and the primary focus of the study being on the broad differentiation between malignant and benign conditions, we could not do so in the present study.

In the present study, we found the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy values of DECT for malignant gall bladder masses were 79.5%, 90.2%, 86.1%, 85.2% and 85.6% respectively. The present study is the first such study that has assessed the diagnostic efficacy of DECT for the diagnosis of gall bladder malignancy. As such, the diagnostic efficacy of MDCT in the evaluation of resectability of gall bladder carcinoma had been studied by Kalra *et al.*, who found it to be 72.2% and 100%, thus showing a higher specificity as compared to sensitivity.[25] In another study, Kim *et al.* described the sensitivity and specificity of MDCT in gall bladder carcinoma diagnosis to be 82.8% and 87.8% and 75.9% and 91.8% respectively, for two different observers.[3] The benefit of DECT is that, owing to the use of quantified iodine uptake patterns, it has a higher objectivity and could perform even better if proper standardization is done on a larger sample size and with the help of a multicentric study. The present study would like to thrust more research in that direction.

Conclusion

To date, DECT has remained almost unexploited in the characterization of benign and malignant diseases of the gall bladder; however, in view of its high imaging characteristics, it could be recommended as a diagnostic tool of choice for determining resectability and clinical management of gall bladder diseases more effectively.

Source of funding

This study did not receive any external funding. It was conducted as part of routine academic and clinical practice.

Conflict of interest

The authors declare no conflicts of interest.

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