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Computed tomography correlation with histopathology in cases of gall bladder cancer

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Abstract
Gallbladder carcinoma is the most common biliary system malignancy with females predominance. Clinically it presents with vague symptoms or remains clinically silent until it has spread to adjacent organs, which leads to delay in early diagnosis and treatment. It is frequently identified incidentally by final pathology after routine cholecystectomy or discovered intraoperatively or when complications occur due to invasion of adjacent organs, which is an advanced stage.
Ultrasonography is usually used as initial modality of investigation in a suspected gallbladder pathology but for accurate diagnosis, staging and management high resolution cross-sectional imaging like CT with contrast or magnetic resonance imaging (MRI) is recommended.
Settings and Designs: It is a prospective diagnostic study on 200 patients with sonographically/ clinically suspected gallbladder carcinoma. GE 32 slice Multi Detector Computed Tomography (MDCT) machine and non ionic iodinated water soluble contrast medium (Omnipaque TM) was used in the study.
Results: For gall bladder cancer (GB fossa mass) CT had 100% sensitivity, 73.08% specificity, 96.13% positive predictive value, and 100% negative predictive value. CT's gallbladder cancer diagnostic sensitivity was 100%, specificity 84.62%, positive predictive value 95.92%, and negative predictive value 100%.
Conclusion: Gall bladder carcinoma is sometimes misdiagnosed as symptomatic cholelithiasis or chronic cholecystitis with non-specific symptoms. With this study we would like to recommend screening for gall bladder carcinoma at least in endemic regions with ultrasonography followed by contrast enhanced CT to give patients early curative surgical resection and better prognosis.

Keywords: Cholelithiasis, cholecystitis, choledocholithiasis, gall bladder carcinoma

Introduction

Gallbladder carcinoma is the most common biliary system malignancy. It has wide geographic and ethic variations worldwide as well as in India. Its incidence is high in South America, East Asia and in Central Europe. In India, incidence of gallbladder carcinoma is higher in north and north eastern states compared to south India [1]. Women are more likely to develop gallbladder carcinoma as compared to men among all populations that have been studied [2]. Apart from geographic location, female gender and age other important risk factors for development of gallbladder cancer are genetic factors, obesity, cholelithiasis and chronic inflammation of gallbladder due to parasitic infestations and bacterial infections. Clinically it presents with very vague symptoms or remains clinically silent until it has spread to adjacent organs, which leads to delay in early diagnosis and treatment. It is frequently identified incidentally by final pathology after routine cholecystectomy or discovered intraoperatively or when complications occur due to invasion of adjacent organs, which is an advanced stage [3]. Gallbladder cancer spreads via lymphatics, haematogenous and into the peritoneal cavity or along biopsy or surgical wound tracts.

Cancers of the gallbladder seem to invade and metastasize relatively early; this may be attributable to the anatomy of the gallbladder. The gallbladder wall is considerably thinner than that of other hollow organs and lacks a submucosal layer. The layers of the gallbladder consist of mucosa, a single muscular layer, perimuscular connective tissue, and serosa on one side and serosa is lacking on the side of the gall bladder embedded in the liver. Tumors invade the liver at a thickness where in many organs a second muscular layer would be encountered. The thin wall of the gallbladder may be responsible for early hematogenous and lymphatic spread. Gallbladder tumors, once through the muscular layer, have access to major lymphatic and vascular channels, providing these tumors with early opportunities for dissemination. Though surgery is the only cure compared to chemotherapy or radiotherapy, as gallbladder cancer is frequently diagnosed at unresectable stage due to its silent spread, it has poor prognosis [4]. The overall 5- year survival rate of patients with gallbladder cancer is 20% with median survival of 16 months for resectable cases [5]. For Serum tumors markers are of minimal clinical value when compared to clinical suspicion and good quality imaging in appropriate cases.

Serum tumor markers are helpful in following a patient for recurrence if they are elevated before treatment and normalized after treatment. Before the era of ultrasonography (USG) and computed tomography (CT), gallbladder cancer is rarely diagnosed preoperatively. Usually, ultrasonography is used as initial modality of investigation for suspected gallbladder pathology but accurate diagnosis and staging may be difficult in case of gallbladder carcinoma. Therefore, high resolution, cross-sectional imaging like CT with contrast or magnetic resonance imaging (MRI) should be done for proper staging in patients who have suspected to have gallbladder cancer or incidentally detected gallbladder cancer after cholecystectomy.

These modalities provide crucial information about the local extent of disease and whether distant metastases are present. It is unclear whether MRI adds to the results obtained from CT scan. As most of the patients present in advanced stage, it is important to establish the diagnosis and to know the extent of disease with cross-sectional imaging to minimize nontherapeutic surgical exploration. Tissue diagnosis is not done for resectable cases due to propensity of seeding of malignant cell in the tract, and it is reserved only for unresectable tumours to guide the oncologist [7-10].

The aim of the present study is to assess spectrum of gallbladder fossa masses on CT with their histopathological correlation.

Materials and Methodology

This is a hospital based prospective diagnostic study on 200 patients with sonographically/clinically suspected gallbladder carcinoma who were referred to Department of Radio diagnosis. These patients underwent evaluation by multi detector computed tomography.

Patients with deranged renal parameters, those that are pregnant, those that have contrast allergy, on metformin and those with other systemic illnesses or malignancy were excluded.

GE 32 slice Multi Detector Computed Tomography (MDCT) machine, operating under 120 kvp, 250 mAs (varies according to the thickness of patient), 0.5mm reconstruction interval and 0.5 sec gantry rotation time were used in the study. The procedure was explained to the patient in detail including the chances for contrast reaction and a written consent was obtained from each patient before the procedure. 600-1000 ml of oral neutral contrast medium (water) given at regular intervals in divided doses were used for proper distension of stomach and bowel loops. Non ionic iodinated water soluble contrast medium (Omnipaque TM) containing 350mg iodine/ml will be used as i.v contrast medium. The patient was placed on the gantry table in supine position with both arms above the head and CT scan will be done. Pre contrast study of the whole abdomen will be performed initially then post contrast scan was done by injecting 1 ml/kg body weight of non ionic iodinated water soluble contrast manually via 18G angiocath place in ante cubital vein or via power injector.

Stage	Definition
Note.—Adapted from references 64, 65, 75. AJCC = American Joint Committee on Cancer.	
Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades lamina propria (T1a) or muscle layer (T1b)
T2	Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver
T3	Tumor perforates the serosa (visceral peritoneum) or directly invades one adjacent organ, or both (extension 2 cm or less into liver)
T4	Tumor extends more than 2 cm into liver, or into two or more adjacent organs (stomach, duodenum, colon, pancreas, omentum, extrahepatic bile ducts, any involvement of liver)
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in cystic duct, pericholedochal, or hilar lymph nodes (ie, in the hepatoduodenal ligament)
N2	Metastasis in peripancreatic (head only), periduodenal, periportal, celiac, or superior mesenteric lymph nodes
Distant metastasis (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis

Fig 1

Resectability criteria for gall bladder masses according to our institute are as follows:

1. Involvement of non regional lymphnodes
2. Distant organ metastasis except for drop metastasis in extra hepatic biliary radicles.
3. Bilateral hepatic hilar involvement either vascular or biliary or both
4. Involvement of main portal vein / common hepatic artery either by the mass lesion or due to extra nodal spread from involved lymphnodes

In non contrast and contrast enhanced portal venous phase studies, the region of interest is put over the lesion to calculate pre and post contrast HU.

After patient agreement, ultrasonography guided core cut biopsy of suspected gallbladder lesion was performed with Bard Biopsy Gun (diameter 18G and cutting length 20 mm) for histological evaluation. Histopathology will be performed on post-CT cholecystectomy specimens.

Statistical Method

Sensitivity, Specificity, Positive predictive value and Negative predictive value were used to evaluate the diagnostic value of MDCT in detecting malignant gallbladder fossa masses taking histopathological diagnosis as the gold standard test.

Percentage were applied to know how many cases of GB malignancy are operable at the time of CT imaging, to know the structural pattern, enhancement pattern of GB masses on Multi Detector CT imaging and associated findings noted in gallbladder malignancy on CT.

Results

Mean age of our study participants were 54.16 years with a standard deviation of 11.69 years. Minimum age was 25 years and maximum of 81 years. There was female preponderance in our study with 140 females (70%) and 60 (30%) males.

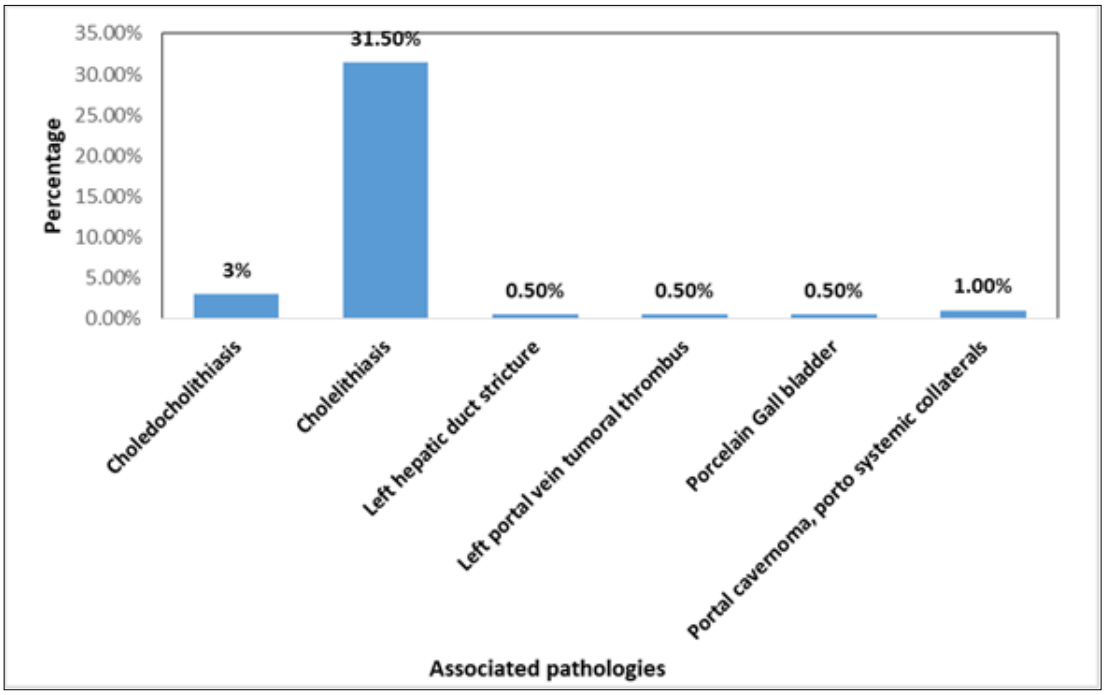

Fig 2: Distribution of structural pattern of gall bladder masses among the study participants (N=200)

In our study focal irregular wall thickening was found to be around 33.5% followed by sessile intraluminal polyp 27.5%, mass replacing GB fossa 24.5%, diffuse asymmetrical wall thickening 12%, pedunculated intraluminal polyp 3%, exophytic mass 2%, diffuse symmetrical wall thickening 1% and focal smooth wall thickening 1%. The diffuse symmetrical wall thickening with mild heterogenous enhancement turned out to be empyema gall bladder. Two cases with focal asymmetrical wall thickening turned out to be chronic cholecystitis and two cases with diffuse asymmetrical wall thickening turned out to be chronic cholecystitis, among these one has perforated gall bladder with minimal pericholecystic collection. Two cases of sessile intraluminal polyp turned out to be benign hyperplasia and hyaline degenetration.

36.5% of the gall bladder masses were situated on the entire gall bladder followed by 19% situated on the neck, 16% on the fundus, 10% on the body, 9% body, neck, 8.5% fundus, body; 1% on the left side of the body and, 0.5% on the fundus and neck.

Around 81% of the gall bladder masses had infiltrated into the liver, while 24% of the study participants had one extrahepatic organ involvement and 20.5% had two or more extrahepatic organ involvement.

About 2% of the study participants had infiltration of secondary confluence, while 55% had involvement of the primary confluence.

Infiltration of extra hepatic bile duct was present among 11.5% of the study participants. Intrahepatic bile radicle dilatation was present among 46% of the study participants.

Table 1: Distribution of vascular involvement in gall bladder carcinoma among the study participants (N=200)

Sl no	Blood supply	Frequency	Percentage
1	Portal vein involvement	30	15
2	Arterial involvement	20	10

Around 15% of gall bladder masses had portal vein involvement. Around 10% had hepatic artery involvement.

Table 2: Distribution of Arterial involvement in gall bladder carcinoma among the study participants (n=20)

Sl no	Arterial involvement	Frequency	Percentage
1	Right hepatic artery	13	65
2	Common hepatic artery	5	25
3	Left hepatic artery	1	5
4	Hepatic artery proper	1	5

Around 65% of them were right hepatic artery involvement followed by 25% common hepatic artery involvement, 5% left hepatic artery and 5% hepatic artery proper.

Metastasis of lymph node was seen in 44.5% of the study participants followed by 20% in liver, 6% in omentum, 5% in ovary, 4% in peritoneum, 4.5% in drop mets in common bile duct, 2.5% in pulmonary, 2% adrenals and 1% in bone.

Around 28% of the study participants had resectable gall bladder masses and around 73% of the study participants had unresectable gall bladder masses.

Table 3 : Distribution of Pre contrast HU and Post contrast HU among the study participants (N=200)

Sl no	Contrast HU	Mean±SD	t, (df), p
1	Pre	42.30±10.49	-12.765 (147) <0.001
2	Post	57.55±14.83	

There was mild enhancement of the lesion in post contrast study acquired in portal venous phase.

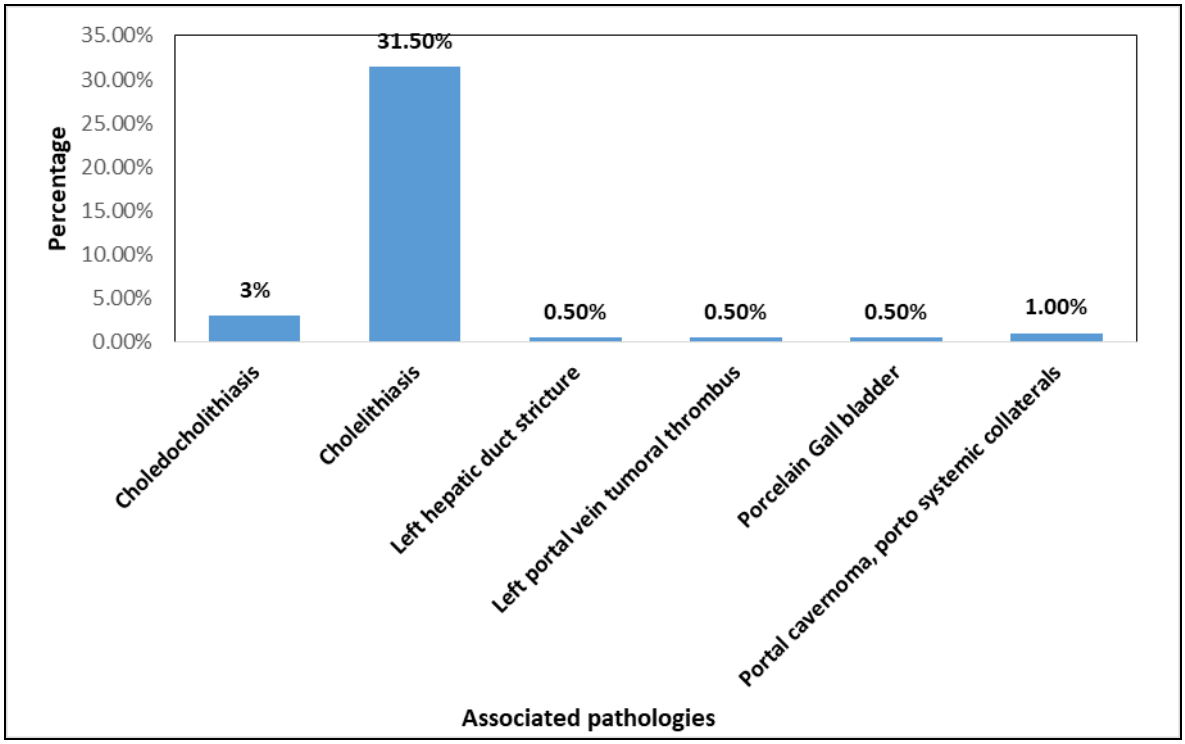

Fig 3: Distribution of associated pathologies among the study participants (N=200)

Around 31.5% of the study participants had cholelithiasis followed by 3% choledocholithiasis, 0.5% had left hepatic duct stricture, 0.5% had left portal vein tumoral thrombus, 0.5% porcelain gall bladder and 1% portal cavernoma.

Around 51.5% had moderately differentiated adenocarcinoma followed by 26% poorly differentiated adenocarcinoma and 6.5% well differentiated adenocarcinoma.

The sensitivity of CT in the diagnosis of gall bladder carcinoma (GB fossa mass) was found to be 100% with specificity of 73.08%, positive Predictive Value of 96.13% and negative predictive value of 100%.

Table 4

Sensitivity	100% (97.90% to 100.00%)
Specificity	73.08% (52.21% to 88.43%)
Positive predictive value	96.13% (92.96% to 97.91%)
Negative predictive value	100% (97.90% to 100.00%)
Accuracy	96.50% (92.92% to 98.58%)

Discussion

CT has never been important for gallbladder disease assessment. Doctors tested gallbladder illness with sonography or nuclear medicine. Because it can see the gallbladder regardless of disease, CT is the main imaging modality for acute abdominal evaluation. Advanced CT scanners can see bile, gallstones, cholecystitis, and cancer [10, 11].

Gallbladder cancer symptoms are nonspecific, and 60–85% of cholecystitis cases are unrelated.12 CT, the recommended imaging method for acute abdomen assessment, may be better than sonography's excellent sensitivity and specificity.

Our study participants averaged 54.16 years old with 11.69 SD. From 25 to 81. Our survey had 140 women (70%) and 60 men (30%). Singh *et al.* [13] examined 60 cases. The gender ratio was 2.16:1, 41 women to 19 men. They were 32–84. The most patients were 51–60 (36.67%). Participants averaged 55.73 years old. Most patients (85%) felt stomach pain and abdominal mass (45%). Twelve (20%) suffered stomach distension and seventeen (26.7%) lost weight.

We found focal irregular wall thickening at 33.5%, sessile intraluminal polyp 27.5%, mass replacing GB fossa 24.5%, diffuse asymmetrical 12%, pedunculated 3%, exophytic mass 2%, and focal smooth 1% Gore *et al.* (2002) [14], Hagga *et al.* (2003), and Afifi *et al.* (2012) reported that gallbladder replacement or obscuration with hepatic invasion is the most common presentation, with wall thickening of varying degrees being the least prevalent. (14-16) George *et al.* (2007) [17] found focal or diffuse wall thickening in 12 (24%) and 16.3% of individuals. (17)

Our study found 36.5% of gall bladder masses on the entire gall bladder, 19% on the neck, 16% on the fundus, 10% on the body, 9% body, neck, 8.5% fundus, body, 1% on the left side of the body, and 0.5% on the fundus and neck. Singh [13] discovered 63.3% gall bladder fossa masses. More than 50% of gall bladder tumours were fundus-based, according to Gore *et al.* [14].

George *et al.* (2007) [17] reported 10% intraluminal polypoidal mass in the GB, while Gore *et al.* (2002) [14] identified 25%. Uniform contrast enhancement was seen in polypoidal intraluminal mass images. Polypoid gallbladder cancer rarely necroses or calcifies. [14, 17] Lesion enhancement was varied in our study.

Singh *et al.* [13] detected liver infiltration in 37 of 49 (81.7%) gallbladder cancers on CT. Duodenum, pancreas, and omentum infiltration in 21, lymph node metastases in 26, and intrahepatic biliary enlargement in 12 (24.5%). Ascites and pleural effusion were observed in 15 (30.6%) of 28 (57.1%) and peritoneal involvement in 10 (20.4%). In another study, George *et al.* (2007) [17] revealed liver involvement in 36 (72%) cases and duodenum, pancreas, and omentum infiltration in 23 (46%) cases at diagnosis 21 (42%), lymph nodes involved.

Our investigation found metastases in 98.5% of gall bladder tumours. In 44.5% of cases, lymph nodes metastasized, followed by liver (20%), omentum (6%), ovary (5%), peritoneum (4%), common bile duct (4.5%), pulmonary (2.5%), adrenals (2%), and bone (1%).

In 46% of individuals, intrahepatic bile radicle dilation occurred. 11.5% of study participants had extra hepatic bile duct involvement. Gall bladder masses invaded liver 81% of the time. 20.5% of research patients had pylorus, duodenum, omentum, or hepatic flexure.

Localised mass lesion from GB (43.7%) followed extensive, uneven, increasing wall thickening in 49.4% (n = 43) with an intraluminal component, according to Pandey *et al*. 120. Further disease progression signs include biliary blockage and liver participation, which are commonly misinterpreted for pancreatic or liver cancer. Liver enlargement spreads gall bladder cancer, but lymph nodes are commonly involved. Our study demonstrated parenchymal liver invasion in 65 patients (74.7%). Portal and peripancreatic adenopathy reached 58.1% in our study. Vascular metastases are rare but conceivable. Pandey *et al*. [18] found portal vein invasion in 11 (12.6%). Lymphadenopathy or bile radicals can clog gallbladders. Direct biliary radical invasion was prevalent (13.8-18.4%). Intestinal, omentum, and pancreatic disease progresses. Many (41.4-48.3%) had duodenal invasion. The incidence of hepatic flexure invasion was 33.3%. Their examination indicated 19.5% peritoneal deposits and 31% ascites.

Our institute's gall bladder mass resectability criteria are non-regional lymphnodes, distant organ metastasis except for drop metastasis in extra hepatic biliary radicles, bilateral hepatic hilar involvement, and mass lesion or extra nodal spread from involved lymphnodes involving the main portal vein or common hepatic artery Our investigation found 28% resectable gall bladder masses and 73% unresectable ones.

Results must be examined for abdominal CT cholecystitis diagnosis. Singh *et al*. [13] found gallstones in 95% of acute cholecystitis patients despite CT sensitivity was 75%. Unlike biliary attenuation, cholesterol stones can be insulating or hypoattenuating, making them difficult to detect. Patients had 31.5% cholelithiasis, 3% choledocholithiasis, 0.5% adenocarcinoma, left hepatic duct stricture, left portal vein tumoral thrombus, 0.5% porcelain gall bladder, and 1% portal cavernoma.

For gall bladder cancer (GB fossa mass), CT had 100% sensitivity, 73.08% specificity, 96.13% positive predictive value, and 100% negative predictive value. CT's gallbladder cancer diagnostic sensitivity was 100%, specificity 84.62%, positive predictive value 95.92%, and negative predictive value 100%, according to Singh *et al*. 118. This improved gall bladder mass CT assessment.

Conclusion

Gallbladder cancer is sometimes misdiagnosed as symptomatic cholelithiasis or chronic cholecystitis with non-specific symptoms. Females predominate. Malignant and mildly enhancing gallbladder carcinoma (almost 90% have metastases at diagnosis). About 73% of research participants had unresectable gall bladder masses. To reduce non-therapeutic surgical exploration, cross-sectional imaging like Multi-detector CT is needed to diagnose and assess illness. According to this study, most sonographically/clinically suspected gallbladder carcinoma patients present in advanced stage at CT evaluation, making curative resection impossible. We recommend screening for gall bladder carcinoma at least in endemic regions (north and north eastern India) with ultrasonography followed by contrast enhanced CT to give early curative surgical resection and better prognosis.

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