

Can gallbladder wall thickness by gross examination predicts its carcinoma before histopathological study?

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Abstract

Background: The gallbladder lesions are often underappreciated. Though gallbladder carcinomas are less in incidence, it is important to examine all gallbladders on removal so that carcinomas are not missed. In this regard, this study is about predicting the risk of carcinoma gallbladder on gross examination, so that no carcinoma cases are missed and also unnecessary histopathological examination of non-neoplastic conditions which forms the major bulk of gallbladder pathology can be avoided.

Objectives: 1) To study gross and microscopic features of gallbladder in cholecystectomy specimens. 2) To study association of gross features and carcinoma of gallbladder. **Methods:** A 4 years study was conducted on 316 specimens of cholecystectomy in KIMS, Hubballi from June 2014 to May 2018. Gallbladder specimens were processed by standard procedures and histopathological patterns were studied. **Results:** The present study included patients from 7 to 87 years of age with Male: Female ratio 1:1.8 and majority were in 5th and 7th decade. Chronic cholecystitis (78.6%) was most common gallbladder lesion. Incidence of gallbladder carcinoma was 1.89% and majority were in 7th decade. Statistically significant association was found between carcinoma and increased thickness of gallbladder wall.

Keywords: Carcinoma, Cholecystitis, Gallbladder, Gall bladder wall thickness.

Introduction

Gallstones are the commonest biliary pathology and more than 95% of biliary tract disease is attributable to cholelithiasis (gallstones). The current changes in lifestyles of individuals pertaining to indulgence in unhealthy fat-rich food, lack of exercise, obesity, sedentary lifestyles and various other factors have once again focused our attention to gall stones and diseases of the gall bladder [1].

Obstruction caused due to gallstones leads to development of chronic cholecystitis which, in turn predisposes to carcinoma of gallbladder. Gallstones present for a longer period predispose for carcinoma of gall bladder. Cholelithiasis is found in approximately 85% of people with gallbladder cancer. The association between cholelithiasis and gallbladder cancer ranges from 2.3 to 34.4 in case control studies [1].

Gall bladder carcinoma ranks 5th in the gastrointestinal malignant tumours [2] and due to non-specific clinical presentation, it is rarely diagnosed at an early stage. Pre-operative imaging techniques fail to identify the

pre-malignant and malignant lesions. Incidental gallbladder cancer is found in up to 1% of cholecystectomy specimens for gallstone disease, which recommend routine histopathology of all cholecystectomy specimens [3]. But if it is possible to predict the risk of carcinoma by gross examination of specimen, it will guide in taking adequate samples for further microscopic examination and also will reduce the burden on histopathologists.

Objectives

1. To study gross and microscopic features of gallbladder in cholecystectomy specimens.
2. To study association of gross features and carcinoma of gallbladder.

Carcinoma of the gallbladder: Carcinoma of the gallbladder is the most common malignancy of the extrahepatic biliary tract [4] Female to male ratio is 1.77, seen mainly in 6th-7th decade of life [5].

Incidence rates are more in American Indians, Hispanic Americans and people of Mexico, Central and South America, eastern Europe and in parts of Asia [6].

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Grossly, gallbladder carcinoma may present as a diffusely growing (70%) or polypoidal (30%) mass. Usually it will be infiltrating grey-white mass, may be associated with diffuse thickening and induration of the entire gallbladder wall. Carcinoma arising in association with intracystic papillary neoplasms may be sessile or polypoid. Mucinous and signet ring cell carcinomas have a mucoid or gelatinous cut surface [7].

Microscopically, most gallbladder cancers are adenocarcinomas showing varying degrees of differentiation. Most tumours have a morphologic appearance that is common to adenocarcinomas of the pancreaticobiliary region: well-formed glands with wide lumina lined by one or a few rows of highly atypical cuboidal cells, surrounded by a cellular stroma often arranged concentrically. It is characteristic for these glands to be well differentiated at an architectural level but poorly differentiated at cytological level [8].

Methodology

Setting: The present study was conducted in the Department of Pathology, Karnataka Institute of Medical Sciences, Hubballi.

Duration: Four years extending from June 2014 to May 2018

Type of study: Descriptive study

Results

Spectrum of overall lesions of gallbladder in the present study. Out of total 316 cases, majority of the study population were having chronic cholecystitis (248 cases, 78.6%), followed by acute cholecystitis (27 cases, 8.6%), acute on chronic cholecystitis (26 cases, 8.2%), adenocarcinoma of gallbladder (6 cases, 1.9%), xanthogranulomatous cholecystitis, tubular adenoma, eosinophilic cholecystitis (each group had 2 cases each, 0.6%) and least reported were cholesterol polyp, cholecystitis glandularis proliferans and empyema of gallbladder (1 case in each group, 0.3%), as shown in Table 1.

Table-1: Distribution of various histopathological lesions of gallbladder in the present study.

Histopathological lesions	No. of patients	Percentage
Acute cholecystitis	27	8.6
Acute on chronic cholecystitis	26	8.2
Adenocarcinoma of gallbladder	6	1.9
Chronic cholecystitis	248	78.6
Cholecystitis glandularis proliferans	1	0.3
Cholesterol polyp	1	0.3
Empyema of gallbladder	1	0.3
Eosinophilic cholecystitis	2	0.6
Tubular adenoma	2	0.6
Xanthogranulomatous cholecystitis	2	0.6
Total	316	100

Out of 316 cholecystectomy specimens, there were 6 cases of adenocarcinoma gallbladder. The frequency of gallbladder adenocarcinoma was 1.89% (Figure1).

Sampling methods: All the cholecystectomy specimens were studied which satisfied inclusion and exclusion criteria

Sample size calculation: 316 cholecystectomy specimens

Inclusion criteria: All cases of cholecystectomy were included in the study.

Exclusion criteria: Autolysed and gangrenous specimens were excluded from this study.

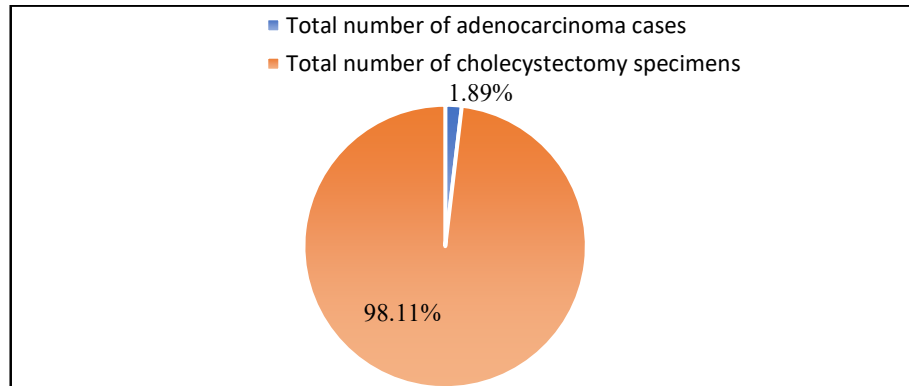
Data collection procedure: The gall bladder specimens were collected in 10% formalin following scrutinizing the patient details and identity. The gallbladder specimens were cut and fixed in fresh formalin for 24 hours. Detailed gross examinations were carried out and descriptions of the specimens were noted. Tissue bits were taken from representative areas of the fundus, body and neck of the gall bladder and additional tissue bits were taken from abnormal appearing areas. This was followed by processing with routine histopathological examination.

Data analysis: Statistical analysis was done using SPSS software. Chi square test was used wherever necessary.

Ethical consideration & permission: Patient's consent and ethical clearance was obtained before starting the study.

Any scoring system: No

Surgical procedure: Included both open and laparoscopic cholecystectomies

Adenocarcinoma of Gallbladder**Fig-1: Pie chart showing percentage of gallbladder adenocarcinoma cases in the present study.**

Out of 6 adenocarcinoma gallbladder cases, 4 cases were associated with calculi (66.7%), which constituted majority of cases and in 2 cases (33.3%) calculus was not found, as shown in Table 2.

Table-2: Association of adenocarcinoma gallbladder with gallstones in the present study

Adenocarcinoma of gallbladder	Number of patients	Percentage (%)
Associated with calculi	4	66.7%
Not associated with calculi	2	33.3%
Total	6	100%

In the present study for the data obtained, the Chi-square statistic was 0.2657. The p-value was 0.606233. This result was not significant at $p < 0.05$. Therefore, according to the present study there was no statistical significance between the malignancy and gallbladder calculi. Hence the association of presence of gallstones with carcinoma gallbladder could not be considered (Table 3).

Table-3: Statistical association of gallstones with gallbladder carcinoma in the present study

		Adenocarcinoma gallbladder		Total	Chi square test
		Present	Absent		
Calculi	Present	4	174	178	$\chi^2=0.26$ P=0.606233 (not significant)
	Absent	2	136	138	
Total		6	310	316	

Gross features: External surface of all 6 cases of adenocarcinoma gallbladder were congested, enlarged in 2 cases and perforation was seen in one case. On cut section lumen was filled with bile in 2 cases, sludge in 3 cases and grey white, firm, granular mass was seen in all cases of adenocarcinoma gallbladder. Mucosa was congested in 4 cases, granular in 2 cases and diffuse thickening of gallbladder wall was seen in 5 cases. (Figure 2)

**Fig-2: Gross photograph of adenocarcinoma of the gallbladder. Cut surface showing grey-white, granular, firm, diffuse thickening of the gallbladder wall at the fundus measuring 3*3 cm.**

Gross features of mass: Out of 6 cases of adenocarcinoma gallbladder, mass was seen in fundus in 4 cases (66.66%), in body in one case (16.67%) and involving both fundus and body in one case (16.67%); fundus was the most common site involved. All of them were showing mass which was grey white in colour, granular and firm in consistency. Five cases had grey white irregular growth (5 cases, 83.34%) and only one case (16.66%) had polypoidal growth. Out of 6 cases, one case showed focal mucoid areas (17%), as shown in Table 4, Figure 3 A and B.

Table-4: Gross features of mass in adenocarcinoma gallbladder in the present study

Nature of the mass in the gallbladder	Number of carcinoma gallbladder	Percentage
Grey white irregular growth	5	83.34%
Polypoidal growth	1	16.66%
Total	6	100%

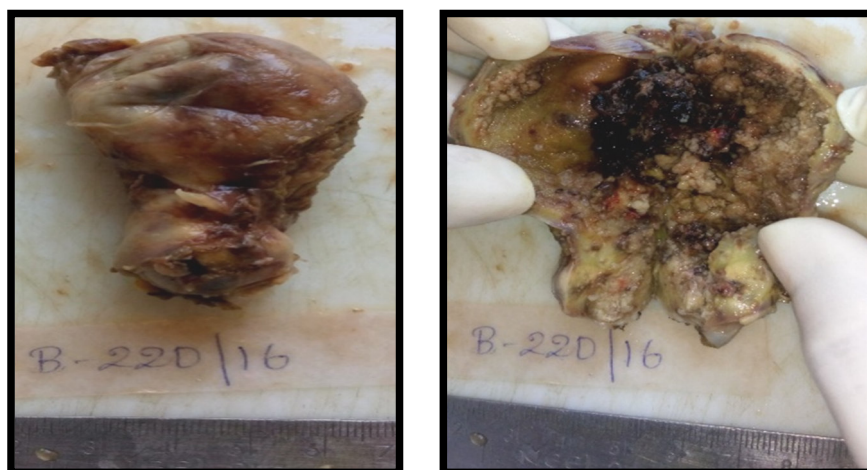


Figure 3: A. Gross photograph of adenocarcinoma of the gallbladder showing congested external surface. B. Cut surface showing grey-white to grey-brown, granular mucosa showing tiny papillary projections involving neck, body and fundus of the gallbladder measuring 4*3.5 cm. There also found firm, diffuse thickening of the gallbladder wall.

In the present study for the data obtained, the Chi-square statistic was 5.625. The p-value was 0.017706. This result was significant at $p < 0.05$. Therefore, according to the present study there was statistically significance between the malignancy and thickness of gallbladder. Hence the association of presence of thickened gallbladder with carcinoma gallbladder could be considered. And also, gross examination of thickened gallbladder should alert both the surgeon and the pathologists to rule out carcinoma gallbladder (Table 5).

Table-5: Statistical association of thickness of gallbladder with gallbladder carcinoma in the present study.

		Adenocarcinoma gallbladder		Total	Chi square test
		Present	Absent		
Gall bladder wall thickness (>3mm)	Present	5	112	117	$\chi^2 = 5.625$ P=0.017706 (Significant)
	Absent	1	198	199	
Total		6	310	316	

Microscopy: Out of 6 cases of gallbladder carcinoma, 4 (66.67%) cases were found to be well differentiated adenocarcinoma, 1 case (16.67%) was mucin secreting adenocarcinoma and another one (16.66%) was poorly differentiated adenocarcinoma. In 4 cases tumour cells was invading muscularis propria but no extension into serosa and in 2 cases tumour cells were seen infiltrating serosa (Figure 4).

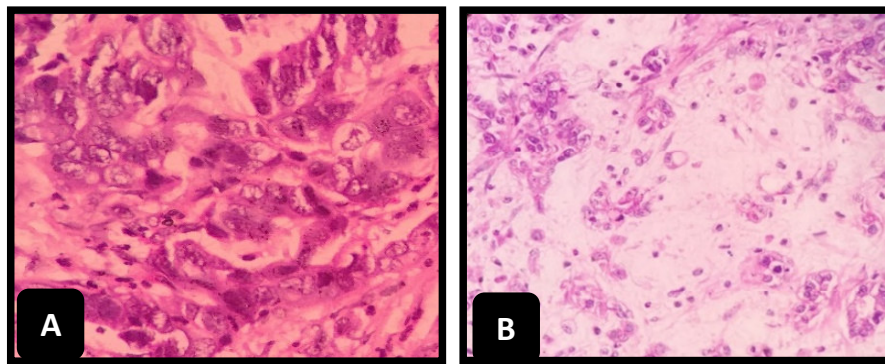


Fig-4: A: Photomicrograph of adenocarcinoma of the gallbladder showing dysplastic mucosa, complex branching of the glandular structures and infiltration of tumour cells into muscularis propria. These tumour cells are highly pleomorphic, hyperchromatic, irregular nucleus and moderate amount of cytoplasm (A: H&E stain-40x). B: Photomicrograph of mucin secreting adenocarcinoma of the gallbladder showing tumour cells arranged in glandular pattern with nuclear pleomorphism, coarse nuclear chromatin, prominent nucleoli with moderate amount of eosinophilic cytoplasm, some showing vacuolation. Tumour cells seen floating in mucinous pool in singles and in groups. (H&E stain-40x).

Discussion

Carcinoma of gallbladder: Gallbladder carcinoma is the fifth most common malignancy of the gastrointestinal tract, which is found incidentally in 1% to 3% of cholecystectomy specimens [9]. Due to lack of early or specific symptoms, it is often detected at later stage. Though cholecystitis, adenomyomatosis, congestive right heart failure and hepatitis etc, causes gallbladder wall thickening; carcinoma gallbladder causing wall thickness should not be neglected. And it has to be differentiated from benign lesions by histopathological examination. Grossly, gallbladder carcinoma may present as a diffusely growing (70%) or polypoidal (30%) mass. Usually it will be infiltrating grey-white mass, associated with focal or diffuse thickening and induration of the entire gallbladder wall [7].

Comparison of incidence of gallbladder carcinoma in the present study with other studies: Incidence of carcinoma gallbladder found in the present study was 1.89% (6 cases), which correlated very well to the incidence found in the study conducted by Murmu S et al [10] (2 cases, 1.88%), Kumar H et al [11] (North Indian data- 8 cases, 2%, South Indian data- 5 cases, 1.25%) and the study by Kumari G et al [12] (7 cases, 1.27%). A lower incidence was observed in studies done by Beena D et al [13] (1 case, 0.5%), Mondal B et al [14] (5 cases, 0.6%), Sharma I et al [15] (3 cases, 0.86%) and H Mohan et al [16] (12 cases, 1.09%).

Comparison of characteristics of growth in gallbladder carcinoma of the present study with other studies: In the present study, 5 cases of gallbladder carcinomas were having grey white irregular mass (83.34%) and remaining one case had polypoidal growth (16.66%). Majority of them were seen in the fundus (83.4%). These results were comparable to the study done by Levy DA et al [17] in

which 68% cases were grey white irregular mass lesions and 60% of the tumour originate in fundus of the gallbladder. Also comparable to the study done by Kumari G et al [12] where 90% of the cases were grey white irregular mass lesions.

Comparison of wall thickness in gallbladder carcinoma of the present study with other studies: According to the present study, statistical analysis revealed significant association of thickness of gallbladder wall grossly and carcinoma gallbladder (at $p < 0.05$). 83.4% of the gallbladder carcinomas were associated with thickened gallbladder wall ($>3\text{mm}$) [12]. Hence the association of thickened gallbladder wall with carcinoma gallbladder could be considered. (Table 5).

This result holds good for correlation with the study done by Mittal R et al [18], where 70% (9 cases) of gallbladder carcinomas had thickened wall macroscopically. Also, different studies done by Kumari G et al [12], Haq N et al [19], Romero-Gonzalez RJ et al [20], Levy DA et al [17] had observed increased gallbladder thickness as one of the risk factor for gallbladder carcinoma and advised for thorough gross examination.

Kim et al. conducted the study which explained MDCT findings of hyper enhancing thick inner wall $\geq 2.6\text{ mm}$ during the portal venous phase, weakly enhancing or non-enhancing thin outer wall $\leq 3.4\text{ mm}$, and irregular and focal wall thickening indicate a malignant cause of flat gallbladder wall thickening rather than benign disease [21].

A new technique real-time elastography using acoustic radiation force impulse (ARFI) uses high intensity focused ultrasound to evaluate the tissue stiffness in the liver, breast,

and other organs [22]. It has also been shown to differentiate between benign and malignant nodules in various organs [23]. The likely reason for this difference is that malignant tissues have much higher stiffness due to increased cell density compared to tissues with chronic inflammation and fibrosis [24].

In the study done by Jha V et al showed out of 20 cases of gallbladder carcinoma, preoperative USG detected an increase in wall thickness in six cases (30%) in contrast to gross examination which revealed the same in 55% (11/20) cases. Therefore, gallbladder carcinoma being a clinical masquerade often evades the eye of a radiologist and comes as pathological surprise. Histopathological examination of cholecystectomy specimens remains the gold standard for the detection of this occult, yet notorious malignancy [25].

Indeed, when gallbladder cancer manifests as wall thickening, it is challenging to diagnose because it mimics the appearance of more common acute and chronic inflammatory conditions of the gallbladder [17]. But the results obtained from the present study emphasised the necessity to gross examine all the cholecystectomy specimens, in order to avoid missing gallbladder carcinoma cases. And histopathological examination is mandated in cases with thickened gallbladder wall.

Conclusion

Gall bladder diseases have a spectrum of presentation histopathologically. In the present study an attempt was made to demonstrate the association of gross features and carcinoma of gallbladder.

Incidence of gallbladder carcinoma was 1.89% in the present study. The observations from this study indicated statistical association between increased thickness of gallbladder wall and carcinoma of gallbladder.

What this study adds to existing knowledge?

The present study emphasised the need of thorough gross examination of all the cholecystectomy specimens and sampling of thickened portion as well as any suspicious area in the gallbladder specimen should be done, in order to avoid missing gallbladder carcinoma cases.

Author's contributions

Dr. Sujata S Giriyan: Concepts, manuscript review and guided the research work.

Dr. Navyashree N: Literature search, data acquisition, statistics and manuscript preparation.

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Conflict of interest: None declared

Ethical Approval: This study was approved by the Institutional Ethics Committee

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