

# Histopathologic Profile of Premalignant and Malignant Lesions of Gallbladder

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## ABSTRACT

### Introduction

Neoplastic lesions of gallbladder are less well defined than other lesions in gastrointestinal tract due to rarity of lesions and also poor accessibility of this site. More than fifty percent cases of cancer are clinically missed. This study was aimed to see the histopathologic spectrum of premalignant and malignant lesions, compare clinical diagnosis with histopathological diagnosis and see association between gross morphology and missed clinical diagnosis.

### Methods

This study was conducted on 56 consecutive cases of premalignant and malignant lesions of gallbladder received in study period of 10 years from January 2011 to December 2020.

### Results

Age of the patients ranged from 13 – 84 years with a mean±SD of 56.8±13.7 years with maximum 17 (30.4%) cases in 41 – 50 years age group. There were 14 (25.0%) males and 42 (75.0%) females with a male female ratio of 1:3. 10 (17.9%) cases were premalignant lesions and 46 (82.1%) cases were malignant lesions. 93.5% malignant cases were adenocarcinoma. 41.3% cases were clinically not suspected to be malignant. There was no association between gross morphology and missed clinical diagnosis ( $p > 0.05$ ).

### Conclusions

Routine histopathologic examination of all the resected gallbladder specimens is mandatory as important diagnosis can be missed.

**Keywords:** gallbladder; gallbladder cancer; malignant; premalignant

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## INTRODUCTION

Gallbladder is a pear shaped muscular sac attached to the posterior aspect of right lobe of liver.<sup>1,2</sup> Between meals bile is stored in the gallbladder where it is concentrated.<sup>3</sup> During and after a fatty meal, it contracts delivering the bile through the bile ducts into the intestine to help with digestion.<sup>4</sup>

Gallbladder can be a site of various disease processes like congenital anomalies, acute and chronic inflammation, cholelithiasis, benign and premalignant conditions and cancer.<sup>3,5</sup> More than ninety five percent of biliary tract diseases are attributed to gall stone disease. Though uncommon, gallbladder cancer (GBC) is most common cancer of extrahepatic biliary tract.<sup>3</sup> According to Global cancer statistics (GLOBOCAN 2020) GBC accounts for age standardized incidence rate of 1.2% and mortality rate of 0.84% and Asia has the highest burden comprising 70.8% of new cases and 73.6% deaths due to GBC.<sup>6</sup>

Two distinct epithelial lesions, adenoma and dysplasia, also termed as biliary intraepithelial neoplasia (Bil IN) are considered premalignant conditions in gallbladder carcinogenesis.<sup>7,8</sup> Intracholecystic papillary neoplasm (ICPN) is a relatively new entity encompassing all neoplastic polyps, preinvasive adenomas and intracystic papillary neoplasms  $\geq 1$  cm in diameter irrespective of phenotype of tumor cells and is considered a premalignant condition.<sup>9-11</sup>

Only 1 in 5 cases of GBC are diagnosed at an early stage in United States and median survival of advanced stage cancer is not more than a year.<sup>4</sup> Approximately fifty percent of gallbladder carcinomas are diagnosed incidentally in cholecystectomy specimens with gall stone disease and even when found incidentally, tend to present at a late stage.<sup>12</sup> If the protocol of routine histopathological examination of

all gallbladder specimens is not followed, subclinical malignancies may be missed with disastrous results.<sup>13</sup>

Hence, this study is conducted to see spectrum of various premalignant and malignant conditions of gallbladder, compare their clinical diagnosis with histopathological diagnosis and see association between gross morphology and missed clinical diagnoses.

## METHODS

This retrospective chart review was carried out in Department of Pathology, College of Medical Sciences and Teaching Hospital. Ethical approval from the Institutional Review Committee was obtained (reference no. COMSTH-IRC/2021-39). 56 consecutive cases of premalignant and malignant lesions of gallbladder received in cholecystectomy specimens in histopathology section of Department of Pathology of College of Medical Sciences and Teaching Hospital during a time period of 10 years from January 2011 to December 2020 were included in the study. All the premalignant and malignant lesions were included. Inflammatory and other non-neoplastic polyps and conditions were excluded. Tumors of biliary tree were excluded. Recurrent tumors were also excluded. Malignancies were classified and staged according to World Health Organization Classification of Tumors (fourth edition).<sup>12</sup> All the cases of premalignant and malignant lesions received in the study period were reviewed from the departmental records. Data was initially entered in MS-Excel, refined and finally analyzed by SPSS 20.0. Variables like age at presentation, gender, site, gross type, histological type, differentiation and extent of tumor invasion were analyzed. Continuous variables were expressed as mean  $\pm$  standard deviation (SD) and categorical variables were expressed as frequencies and percentages. Histological diagnosis was compared with

clinical diagnosis. Association between clinical diagnosis and gross morphology were sought for malignant cases using Pearson chi square test and likelihood ratio was calculated and level of significance was calculated at 95% confidence interval.

## RESULTS

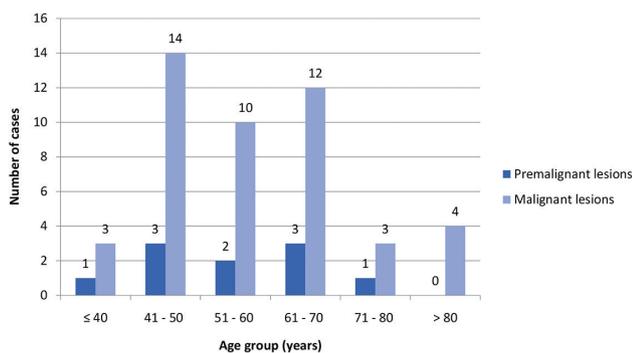
Altogether 56 cases of premalignant and malignant lesions were received in the study period. Age of the patients ranged from 13 – 84 years with a mean±SD of 56.8±13.7 years with maximum 17 (30.4%) cases in 41 – 50 years age group. There were 14 (25.0%) males and 42 (75.0%) females with a male female ratio of 1:3 (Table 1). 10 (17.9%) cases were premalignant lesions and 46 (82.1%) cases were malignant lesions with maximum 14 (30.4%) malignant cases in 41 – 50 years age group (Figure 1).

**Table 2.** Histological diagnoses of premalignant and malignant lesions (n = 56)

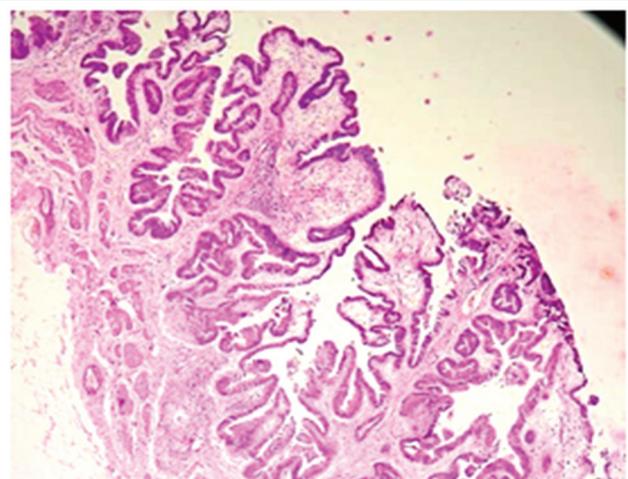
S.N	Histological diagnoses	Number (%) of cases
<b>Premalignant lesions</b>		
	Billin	4 (7.1)
	Adenoma	3 (5.4)
	ICPN (Fig 2)	3 (5.4)
<b>Malignant lesions</b>		
	Adenocarcinoma	39 (69.6)
	Intracholecystic papillary neoplasm with invasive carcinoma	4 (7.1)
	Undifferentiated carcinoma (Fig 3)	2 (3.6)
	Adenosquamous carcinoma (Fig 4)	1 (1.8)
Total		56 (100)

**Table 1: Age and gender distribution of cases (n = 56)**

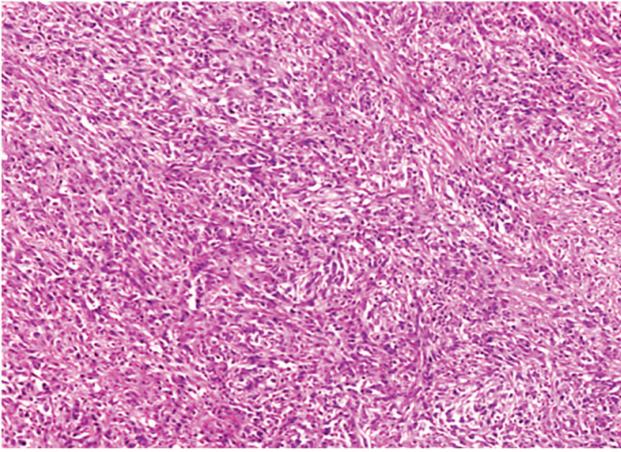
Age group (years)	Male n (%)	Female n (%)	Total n (%)
≤ 40	2 (3.6)	2 (3.6)	4 (7.1)
41 – 50	5 (8.9)	12 (21.4)	17 (30.4)
51 – 60	0 (0)	12 (21.4)	12 (21.4)
61 – 70	4 (7.1)	11 (19.6)	15 (26.8)
71 – 80	1 (1.8)	3 (5.4)	4 (7.1)
>80	2 (3.6)	2 (3.6)	4 (7.1)
Total	14 (25)	42 (75)	56 (100)



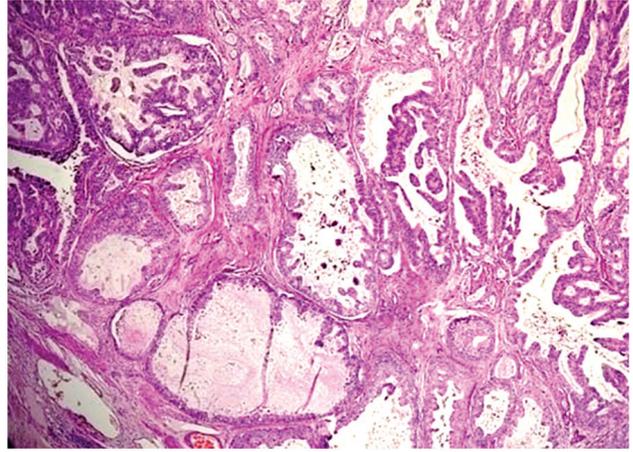
**Figure 1.** Bar diagram showing age distribution of premalignant and malignant lesions (n = 56)



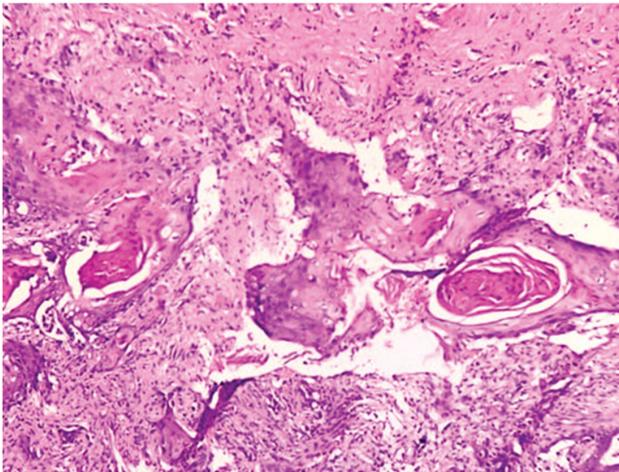
**Figure 2.** ICPN with low grade dysplasia (Haematoxylin and Eosin (H and E) x40X)



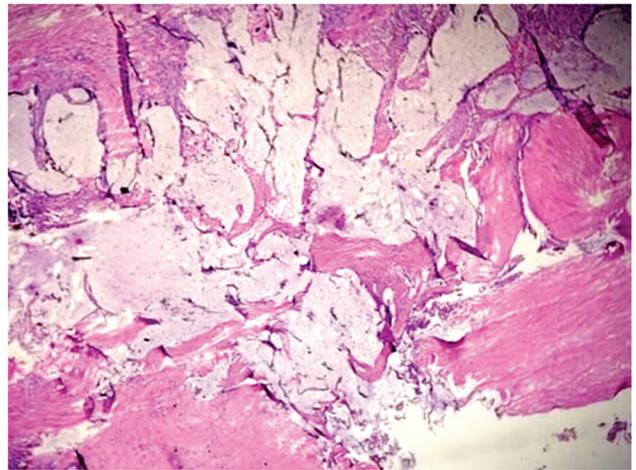
**Figure 3.** Undifferentiated carcinoma (H and E x40X)



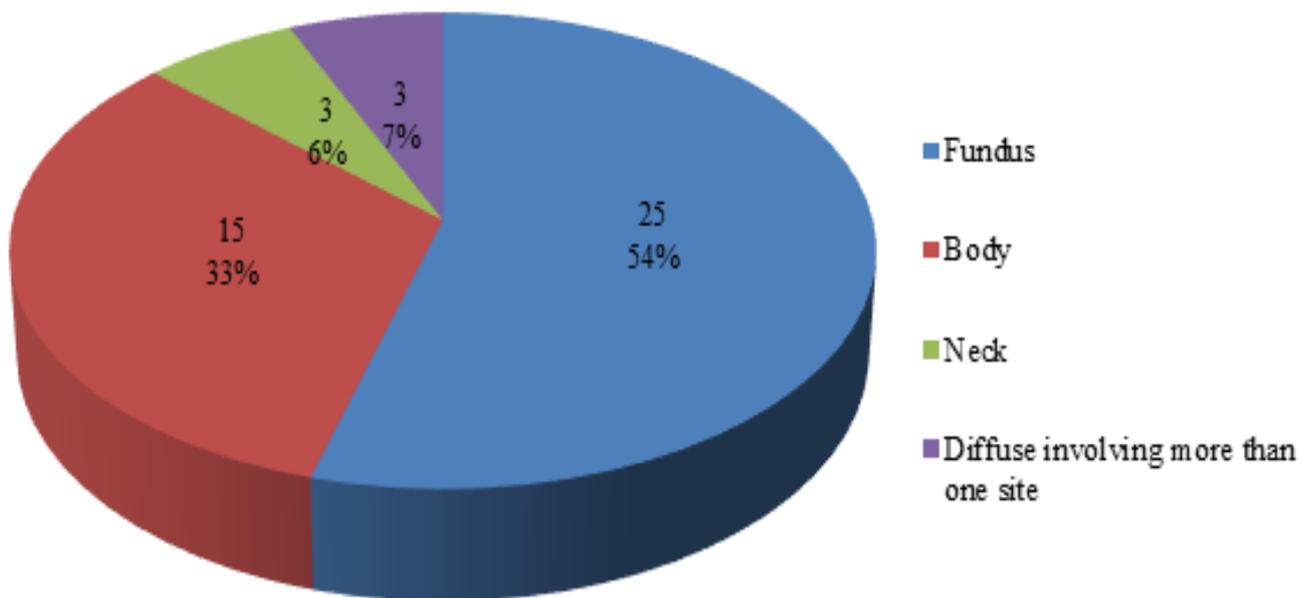
**Figure 5.** Intestinal type adenocarcinoma (H and E x 40X)



**Figure 4.** Squamous component in adenosquamous carcinoma (H and E x40X)



**Figure 6.** Mucinous adenocarcinoma (H and E x40X)



**Figure 7.** Pie chart showing site of lesion in malignant cases (n = 46)

Histological diagnoses of premalignant and malignant conditions are presented in Table 2. BilIN cases were 3 (5.4%) cases of high grade dysplasia or biliary intraepithelial neoplasia 3 (BilIn-3) and 1 (1.8%) case was low grade dysplasia or biliary intraepithelial neoplasia 1 (BilIn-1). All cases of ICPN had low grade dysplasia. All the adenomas were pyloric gland type with 2 (3.6%) having tubular architecture and 1 (1.8%) having

(Figure 7). Grossly, 29 (63.0%) cases were diffusely infiltrating, 13 (28.3%) cases were exophytic growths and 4 (8.7%) cases had papillary growths.

Twenty (43.5%) cases were moderately differentiated followed by 17 (37.0%) cases which were well differentiated. 15 (32.6%) cases had invaded muscularis propria only followed by 15 (32.6%) cases extending up to serosa (Table 3).

**Table 3.** Histological differentiation and extent of tumor invasion in malignant cases (n = 46)

Tumor extension	Histological differentiation				Total
	Well differentiated	Moderately differentiated	Poorly differentiated	Undifferentiated	
Muscularispropria	8 (17.4)	5 (10.9)	2 (4.3)	0 (0)	15 (32.6)
Serosa	6 (13.0)	6 (13.0)	1 (2.2)	2 (4.3)	15 (32.6)
Liver	2 (4.3)	7 (15.2)	3 (6.5)	0 (0)	12 (26.1)
CBD	0 (0)	1 (2.2)	1 (2.2)	0 (0)	2 (4.3)
Gut	1 (2.2)	1 (2.2)	0 (0)	0 (0)	2 (4.3)
Total	17 (37.0)	20 (43.5)	7 (15.2)	2 (4.3)	46 (100)

tubulopapillary architecture. Out of 39 (69.6%) cases of adenocarcinoma, 33 (58.9%) cases were biliary type, 3 (5.4%) cases were intestinal type (Figure 5), 2 (3.6%) cases were signet ring type and 1 (1.8%) case was mucinous type (Figure 6)

Out of 46 malignant cases, fundus was the most common site involved in 25 (54.3%) cases followed by body in 15 (32.6%) cases

Malignancy was clinically not suspected in 19 (41.3%) cases. Missed clinical diagnosis was not associated with gross morphology ( $p > 0.05$ ) (Table 4). Out of 19 cases not clinically suspected as malignancy, 10 (52.6%) had extended till muscularispropria, 5 (26.3%) had extended till serosa and 4 (21.1%) had extended till liver.

**Table 4.** Comparison of gross morphology with clinical suspicion of malignancy (n = 46)

Gross morphology	Clinical diagnosis		Total
	Malignant	Non malignant	
Diffusely infiltrating	15 (32.6)	14 (30.4)	29 (63.0)
Exophytic	9 (19.6)	4 (8.7)	13 (28.3)
Papillary	3 (6.5)	1 (2.2)	4 (8.7)
Total	27 (58.7)	19 (41.3)	46 (100)

Likelihood ratio = 1.656,  $p = 0.473$

## DISCUSSION

Diseases of the gallbladder are often underappreciated, though it is affected by variety of pathological processes which have specific clinical correlates. Metaplasia from normal columnar absorptive epithelium to mucinous epithelium may occur in few cases which may progress to dysplasia and further invasive carcinoma. Most adenocarcinomas of gallbladder present at late stage and therefore, highly lethal.<sup>14</sup>

In the present study 17.9% cases were premalignant and rest were malignant. These were 7.1% cases of dysplasia (BillIN), 5.4% cases of adenoma and 5.4% cases of ICTPN. In a study conducted by Kocaoz et al, dysplasia and adenomas were seen in 1% and 0.5% of total 5026 cholecystectomies respectively.<sup>15</sup> In gallbladder, dysplasia-carcinoma or metaplasia-dysplasia-carcinoma sequence is considered more important than adenoma-carcinoma sequence as evidenced by presence of metaplasia, dysplasia and carcinoma in situ in 66%, 81.3% and 69% cases of mucosa adjacent to GBC as compared to presence of adenomatous remnants in only 3% cases adjacent to GBC in a study conducted by Roa et al.<sup>8, 9</sup> ICPN is a relatively new entity first described by Adsay et al in 2012 for grossly visible non invasive epithelial neoplasm arising from mucosa and projecting into lumen measuring  $\geq 1$  cm and was recognized by WHO as preinvasive neoplasm under the name of intracholecystic papillary neoplasm.<sup>11, 12</sup> In a study conducted by Hazarika et al, ICPN comprised 23.5% of all gallbladder neoplasms.<sup>10</sup> Compared with other organs of the gastrointestinal tract, clinical features, morphology and diagnostic criteria of precursor lesions of gall bladder and biliary tract are less well characterized due to rarity of cancerous lesions and also poor accessibility of this site.<sup>16</sup>

More than 90% cases of GBC are seen in patients older than 50 years of age with most patients

in sixth or seventh decade of life.<sup>1, 12</sup> In a study conducted by Henson et al in 2665 patients with GBC, 63% of GBC occurred in patients 70 years or older.<sup>17</sup> In the present study, GBC was most commonly seen in 41 – 50 years age group comprising 30.4% cases. A study conducted in North America has also observed increasing incidence of obesity related cancers including GBC in younger individuals.<sup>18</sup> Females were three times more commonly affected than males in present study. In study conducted by Makhdoomi et al, females were twice more commonly affected.<sup>19</sup> In study done by Henson et al female male ratio was 2.7:1.<sup>17</sup> Literature also suggests that GBC is 2 – 4 times more common in females.<sup>1, 3, 12</sup> This disparity in gender may be because gall stones and gallbladder inflammation are more common in females which are known risk factors for GBC.<sup>20</sup> 60% cases of GBC occur in fundus, 30% in body and 10% in neck.<sup>21</sup> In the present study also, fundus was the most common site involved in 54% cases, followed by body in 33% cases, neck in 6% cases and 7% cases were diffuse involving more than one site.

Approximately, 84% of GBC are adenocarcinomas and 16% are others like adenosquamous, squamous and other rarer types.<sup>22</sup> In the present study, 93.5% of total malignant cases were adenocarcinoma. In study done by Pavani et al, all the malignant cases were adenocarcinoma.<sup>23</sup> In study done by Makhdoomi et al, 87.5% cases were adenocarcinoma.<sup>19</sup> In study done by Henson et al, 94% cases were adenocarcinoma.<sup>17</sup> 84.6% cases of total 39 cases of adenocarcinoma were biliary type. Well to moderately differentiated adenocarcinomas of biliary type are the most common epithelial neoplasms of gallbladder.<sup>12</sup> Well differentiated adenocarcinomas were most common (50%) in study done by Pavani et al.<sup>23</sup> Whereas, moderately differentiated tumors were most common in present study comprising 43.5% cases. In study

conducted by Henson et al, poorly differentiated tumors were most common (42.4%) and authors had observed linear association between grade and survival.<sup>17</sup> 7.7%, 5.1% and 2.6% out of total 39 cases of adenocarcinoma were intestinal type, signet ring cell type and mucinous type respectively. All three, intestinal type, signet ring cell type and mucinous type histology are associated with an aggressive clinical course and poor outcome.<sup>24-26</sup>

Intracholecystic papillary neoplasm with invasive carcinoma was seen in 8.7% of total 46 malignant cases. Previously known by various now not recommended terminologies like intracystic papillary neoplasm with invasive carcinoma and papillary carcinoma in the WHO 2019 edition, it has good prognosis and better prognosis than conventional gallbladder adenocarcinoma.<sup>11, 12, 16</sup> 4.3% cases out of total malignant cases were undifferentiated carcinoma. Undifferentiated carcinoma of gallbladder is a rare malignant neoplasm which shows a significantly larger tumor size and poorer survival than conventional gallbladder adenocarcinoma.<sup>27</sup> 1 (2.2%) case was adenosquamous carcinoma. In a study conducted by Roa et al, adenosquamous carcinoma comprised 4.3% of total 606 GBC and they found a worse prognosis as compared to conventional GBC.<sup>28</sup>

More than 50% of GBC is diagnosed in cholecystectomy specimens presumed to have

benign disease. Remaining which are clinically diagnosed, also present at late stage due to lack of early clinical features.<sup>29</sup> Out of total malignant cases, 41.3% cases were clinically not suspected malignant in present study. In studies conducted by Ghimire et al and Poudel et al in Nepal, incidental GBC in routine cholecystectomies was found in 1.28% and 1.67% of total cholecystectomies.<sup>30, 31</sup>

Grossly, 70% of GBC may present as diffusely infiltrating growth and 30% as polypoid mass. When diffuse, distinction from chronic cholecystitis may be difficult.<sup>1</sup> 63.0% of GBC was diffusely infiltrating in present study and 48.3% of these diffusely infiltrating growths were clinically not suspected to be malignant. However, statistical association between gross morphology and missed clinical diagnosis was not observed. Hence, routine microscopic examination of all cholecystectomy specimens is mandatory.<sup>1</sup>

## CONCLUSION

GBC though rare, often presents late and hence carries a poor prognosis. Routine histopathological analysis of all the cholecystectomy specimens is mandatory in all the centers as malignancy may be clinically missed. There is no significant association between gross morphology of tumor and clinical suspicion in missed clinical diagnoses.

**Conflicts of interest:** None declared.

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