

# Incidental Gall Bladder Carcinoma (IGBC) in Cholecystectomy Specimens Removed for Cholelithiasis- A Single Centre Experience

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## ABSTRACT

### BACKGROUND

Carcinoma of the gallbladder is the most common malignancy of the biliary tract. The indistinguishable clinical manifestations of cholelithiasis and cholecystitis may mask an underlying malignancy. The present study highlights the occurrence of Incidental gallbladder carcinoma (IGBC) detected during histopathological examination in cholecystectomy specimens removed for cholelithiasis.

### METHODS

This is a tertiary hospital based cross-sectional study of 2379 cholecystectomy specimens removed during cholelithiasis over a ten-year period. Relevant hospital records, histopathology slides and reports were reviewed, re-evaluated and studied.

### RESULTS

Eleven (11) cases of IGBC, constituting 0.46% were diagnosed. Females with IGBC were more than the males (M:F=1:4.5). Focally thickened wall (mean wall thickness of 0.57 cm) was the most common gross finding with 100% association with cholelithiasis. Moderately differentiated Adenocarcinoma was the most common histological type and more than 70% were in lower stage (3 cases in pT1 and 5 cases in pT2) while the remaining 3 cases were at a higher stage with positive margins.

### CONCLUSIONS

Early detection of IGBC by histopathological examination would have a favourable impact on prognosis and management thereby increasing the survival outcome.

### KEYWORDS

Cholelithiasis, Incidental Gall Bladder Carcinoma

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**BACKGROUND**

Gallbladder Cancer (GBC) accounts for 98% of all biliary tract malignancies and is the sixth most common malignancy of the gastrointestinal tract worldwide.<sup>1</sup> The incidence and prevalence of gall bladder cancer (GBC) is different in different parts of the world and also differs among different ethnic groups within the same country. The highest is found in Latin American and Asian countries.<sup>2</sup> The National Population Based Cancer Registry Programme of India shows that females of north-eastern states are more affected by GBC than other parts of the country, probably due to its different ethnicity, lifestyles, food-habits and tobacco consumption.<sup>3</sup> The preoperative diagnosis of GBC is less than 20% as the signs and symptoms are non-specific and the onset is insidious.<sup>4</sup>

Incidental Gall Bladder Carcinoma (IGBC) is defined as carcinoma of gall bladder suspected for the first time during cholecystectomy or accidentally found on histological examination of gall bladder.<sup>1,5</sup> The incidence of IGBC as given in literatures ranges from 0.19% to 3.13% of all cholecystectomies.<sup>4,6</sup> Gall bladder stones and chronic inflammation of the wall are common risk factors for this tumor. Around 90% of GBC have accompanying cholelithiasis, however only 0.5-3% of patients with cholelithiasis develop GBC.<sup>5-8</sup>

GBC is an aggressive and lethal malignancy with a dismal prognosis. The anatomic location, the non-specificity of signs and symptoms, the aggressive course of the malignancy all contribute to a late presentation at an advanced stage.<sup>5,6</sup> Thus, histopathological analysis of cholecystectomy specimens provide important information about the diagnosis for further line of management. The aim of the present study is to report our experience with incidental gall bladder carcinoma (IGBC) diagnosed during histopathological examination of cholecystectomy specimens removed for cholelithiasis.

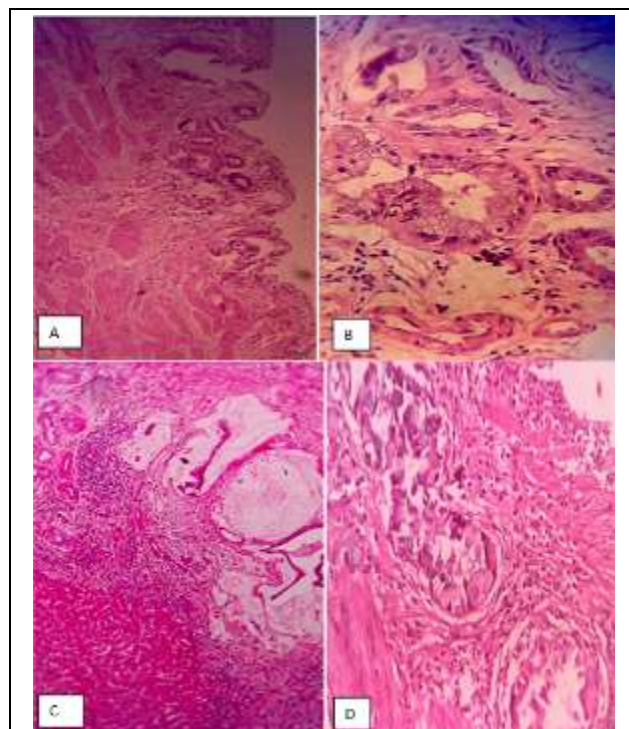
**METHODS**

In this cross-sectional study conducted in the Department of Pathology, RIMS, Imphal, Manipur, the clinical and histopathological records of patients who underwent cholecystectomy procedure for biliary diseases especially gall stone diseases during the period from January 2009 to October 2019 were reviewed. After excluding autolysed and clinically known cases of GBC cases, 2379 cases of cholecystectomy specimens were selected for the study.



**Figure 1.**  
**Cholecystectomy Specimen- Markedly Thickened Wall (Arrow)**

Study variables like age, gender, presence of gall stones, gall bladder wall thickness, grade and stage of IGBC were recorded and analysed. WHO (2010) classification of Tumours of the Gallbladder and Extrahepatic Bile Ducts<sup>9</sup> was followed for the histomorphological diagnosis of the tumours and pathological TNM Staging system of the American Joint Committee on Cancer (AJCC- 8<sup>th</sup> Edition, 2010) was used for staging incidental gall bladder carcinoma.<sup>10</sup> Relevant data were entered and analysed using SPSS (IBM) version 21.0 software database programme. Approval from the Institutional Ethics Committee (IEC) was taken prior to the study.



**Figure 2. (A). Photomicrograph of Sections (H & E, 40X) of Gallbladder Showing Metaplastic Change. (B) Dysplastic Change. (C) Section of Gallbladder Showing Malignant Glands Extending Towards the Hepatic Tissue Which was Adherent to the Cholecystectomy Specimen and (D) Another Section Showing Malignant Glands Infiltrating the Muscular Propria**

Case No.	Age / Gender	HPE Diagnosis / Grade	pTNM Stage
1	65/F	Moderately Differentiated Adenocarcinoma	pT3N1Mx
2	35/F	Well differentiated Adenocarcinoma	p T1bNxMx
3	65/M	Moderately Differentiated Adenocarcinoma	p T3N1Mx
4	56/F	Well differentiated Adenocarcinoma	p T2aNxMx
5	70/F	Moderately Differentiated Adenocarcinoma	p T1bNxMx
6	78/F	Moderately Differentiated Adenocarcinoma	p T2aNxMx
7	52/F	Moderately Differentiated Adenocarcinoma	p T2aNxMx
8	50/F	Moderately Differentiated Adenocarcinoma	p T1b NxMx
9	50/F	Moderately Differentiated Adenocarcinoma	p T2b NxMx
10	60/F	Moderately Differentiated Adenocarcinoma	p T2a NoMx
11	40/M	Poorly Differentiated Adenocarcinoma	p T3N1Mx

**Table 1. Age/Gender, Histological Diagnosis, Grade and Stage of IGBC (11 cases)**

Total no. of cholecystectomy cases	2379
No of Incidental gallbladder carcinomas	11
Frequency of occurrence	0.46%
M: F	1: 4.5
Mean Age	56.45 years
Sites	Body- 8 (72.7%), Fundus- 3 (27.3%)
Mean wall thickness	0.57 cm
Most common Histological Type	Adenocarcinoma
Tumour grade	Well differentiated- 2 (18.18%), Moderately differentiated- 8 (72.72%), Poorly differentiated- 1(9.09%)
Tumour extension	>70% show perimuscular connective tissue involvement
Margins	Cystic duct margin(+)-1 case Liver parenchymal margin (+)- 2 cases
Pathological Stage	pT1 (1b)- 3 (27.2%) pT2 (2a)- 4 (36.3%) (2b)- 1 (9.09%) pT3- 3 (27.2%)
Additional pathologic findings- Cholelithiasis with cholecystitis	100%

**Table 2. Summary of Findings**

## RESULTS

Eleven (11) cases of incidental gall bladder carcinoma (IGBC) were diagnosed from the histopathological evaluation (HPE) of 2379 cholecystectomy specimens, constituting 0.46% of gall bladder specimens received during the study period. Cholelithiasis was the indication for cholecystectomy for all the cases. The age of the patients with IGBC ranged from 35-78 years. (Table-1) More females were affected than males with a M:F ratio of 1:4.5. Gross examination of the gall bladder specimens revealed thickened wall (mean- 0.57 cm) in all the cases (Figure 1). Irregular, shaggy, ulcerative areas were identified in 50% of the cases however no definite mass could be identified. A minimum of 5 or more sections were taken for examination. Moderately differentiated Adenocarcinoma was the most common histological type, with more than 70% cases showing confinement to the perimuscular connective tissue (Figure 2). Two cases showed involvement of liver parenchymal margin and one case showed cystic duct margin and cystic lymph node involvement. Cholecystitis with antral and intestinal metaplasia were the most common additional pathologic findings (Table 2). Dysplasia of adjacent epithelium could be appreciated in 2 cases.

## DISCUSSION

GBC although relatively uncommon, is the most frequently encountered malignancy of the extrahepatic biliary tree occurring predominantly in elderly women. As per the Population Based Cancer Registry (PBCR-2016) report of our institute, GBC is the 5<sup>th</sup> leading site among females with a crude incidence rate of 3.3%. In the present study, the rate of occurrence of IGBC is 0.46% which is comparable (0.19%-3.13%) with the published literatures.<sup>5,6,11,12,13,14</sup> The incidence of GBC rises with age. The age range and the mean age of 56.45 years are comparable with other studies.<sup>6</sup>

GBC is 2-6 times more common in the female gender which is also found in our study with a M:F ratio of 1:4.5.

The role of increased oestrogen levels and multiple pregnancies with the increased risk of GBC in women has been evaluated in many studies.<sup>11,12,15</sup> All the cases of IGBC in our study are associated with cholelithiasis (100%) So, women aged 55 years and more with cholelithiasis are at increased risk of developing GBC.<sup>16,17</sup> Gall stones inducing chronic mechanical damage and hence chronic inflammation leading to chronic cholecystitis has been widely recognized. The role of carcinogens in bile and chronic inflammation as key players in carcinogenesis causing DNA damage and hence leading to tissue proliferation with cytokine and growth factor release, thus following the steps of carcinogenesis has been hypothesized by many workers.<sup>5,11,12,18</sup> Studies have found p53 mutations and other genetic aberrations in chronically inflamed gall bladders secondary to gall stones.<sup>19</sup> The increasing risk of gall bladder cancer with larger stones(>3 cm) as compared to smaller stones is about 10 times. Even though, microlithiasis is less symptomatic, Seretis C et al found increased prevalence of dysplastic changes, gall bladder wall thickening and metaplastic changes in cases with microlithiasis.<sup>18</sup>

In our study, no striking features like intraluminal growth suggestive of malignancy could be appreciated from the gross examination except for focal ulceration and thickened wall. However, the adventitial surface on the liver parenchymal margin in two male patients in our study, showed irregular and shaggy surface, which on HPE revealed tumour infiltration into the liver tissue adherent to the gall bladder wall. The unique anatomy of the gall bladder wall i.e. absence of muscularis mucosae and submucosa favours the growth and infiltration of tumours deeper into muscularis propria and beyond, especially into the liver parenchyma and this is the most common form of direct local spread.<sup>20,21</sup> 1 case of perimuscular connective tissue involvement on the hepatic side and 2 cases showed extension into the adherent liver tissue (1 case of pT2b and 2 cases of pT3, Table -2) Hepatic metastasis may also be due to portal tract involvement through lymphatic spread and is associated with a worse outcome.<sup>22</sup>

The most common histological type seen in our study is moderately differentiated adenocarcinoma (Grade-2) which is comparable to the study of Waghmare R. Only two cases of well differentiated adenocarcinoma were seen. As Rokitansky Aschoff Sinus (RAS) can extend deep into the perimuscular adipose tissue and throughout the gall bladder wall, distinguishing between invasive carcinoma and dysplastic RAS can be challenging in cases of well differentiated adenocarcinoma as RAS involvement has been reported as being an independent adverse prognostic factor.<sup>23</sup> The cytologically bland appearance of the glands, lack of desmoplasia, cystic dilations and connections with the luminal surface are important clues for benignity.<sup>24</sup>

Although histologic grade and stage of GBC have an impact on survival, however pathological stage is the most important prognostic factor for patient outcome. The extent of invasion correlates inversely with survival. Muscle destruction by invasive tumour has more adverse outcome

when compared to simple infiltration as found in some studies.<sup>10,20,21</sup>

Three cases in our study showed perineural invasion and 2 male patients when compared with the females showed a higher stage with cystic lymph node involvement. Studies have observed that perineural invasion and lymphovascular spread in GBC are regarded as adverse prognostic factors and also are associated with spread of carcinoma beyond the gall bladder to involve the biliary tree.<sup>25</sup> As IGBC detected by laparoscopic cholecystectomy has its risk of peritoneal dissemination and port site recurrence, open cholecystectomy has an advantage for better staging.<sup>26</sup>

In spite of the non-specific symptoms, incidentally discovered gall bladder carcinoma have better prognosis, significant curability rate and increased survival rate as these cases are detected at an earlier stage, when compared to pre-operatively diagnosed GBC.<sup>27,28</sup> Henceforth, as suggested by Kalita D et al,<sup>29</sup> HPE of every cholecystectomy specimen has the advantage of detecting this malignancy at an earlier stage, thus nipping this aggressive tumour at its bud stage. Further, larger studies on molecular markers of GBC would probably pave a way for targeted therapy.

## CONCLUSIONS

Cholelithiasis, especially asymptomatic cases, should not be taken lightly as it may harbor an occult malignancy. Incidental Gall Bladder Carcinoma (IGBC) does occur insidiously. So, histopathological examination of every cholecystectomy specimen is mandatory as early detection and prompt management at a potentially curable stage is very crucial for a better survival outcome.

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