

# Incidence of Gallbladder Carcinoma in Thick Walled Gallbladder in Comparison with that of Normal Thickness – A Study of 300 Cases

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## Summary:

**Background:** Gall bladder carcinoma (GBC) is the most common biliary tract cancer. Delayed presentation and early spread of tumor made it one of the lethal tumors with poor prognosis.

**Objective:** The objective of this study is to find out the incidence of GBC in thick walled gall bladder (GB) in comparison with that of normal wall thickness.

**Methods:** This prospective study was carried out in Combined Military Hospital (CMH) Dhaka, CMH Momenshahi and CMH Ghatail during the period of June 2007 to June 2014. A total 300 patients underwent cholecystectomy were studied retrospectively. Diagnosis was confirmed by histopathological examination.

**Results:** Out of 300 patients 254 (84.88%) were female (male : female = 1:5.52), age range 28 to 79 years. Maximum

number of the patients fall into fourth and fifth decades. 42 (14%) patients were found to have thick walled GB by pre-operative sonography and during surgery. Histopathologically 13 (4.33%) patients were diagnosed as GBC. Maximum patient (52.33%) had chronic cholecystitis. Incidence of malignancy were higher (84.62%) in patients having thick walled GB.

**Conclusion:** GBC may present as focal or diffuse asymmetric wall thickening or even in GB having normal wall thickness. As early diagnosis and effective treatment can significantly reduce the mortality and morbidity all specimen should be examined histopathologically.

**Key words:** Cholecystectomy, Gall bladder carcinoma, Thick walled gall bladder.

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## Introduction:

Gallbladder carcinoma (GBC) is the most common biliary tract cancer, accounting for 3% of all tumors.<sup>1</sup> GBC is hard to detect and diagnose in its early stages because it usually has very slight symptoms or is asymptomatic. But once the diagnosis is confirmed, most of these patients often have metastasis and invasion. Furthermore, GBC is not sensitive to radiotherapy and chemotherapy. All of these characteristics made GBC a highly lethal tumor with a 5 years survival rate of less than 5%<sup>2</sup> and a median survival of only 3 months.<sup>3</sup>

Globally, there is a prominent geographical inconsistency in GBC incidence that draws a parallel with the prevalence of cholelithiasis.<sup>4</sup> Numerous reports propose an association between chronic *S. typhi* carriage and elevated risk of GBC.<sup>5</sup>

Incidental gallbladder carcinoma (IGBC) is defined as GBC suspected for the first time during cholecystectomy or accidentally found on histological examination of the gallbladder (GB).<sup>6</sup> With the increase of cholecystectomies since the wide acceptance of laparoscopic cholecystectomy (LC), the incidental diagnosis of GBC is more frequent.<sup>7</sup> Unsuspected GBC can be discovered incidentally following 1% of routine cholecystectomies<sup>8</sup> diagnosed either intra-operatively or subsequent to histological analysis following cholecystectomy.<sup>9</sup>

Diffuse GB wall thickening may be caused by a wide range of GB diseases and extracholecystic pathologic conditions. It can result from a broad spectrum of pathologic conditions, including surgical and nonsurgical diseases. In most cases it's cause can be determined by correlation of the clinical presentation and associated imaging findings. GBC has various

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imaging appearances, ranging from a polypoid intraluminal lesion to an infiltrating mass replacing the GB, and it may also present as diffuse mural thickening.<sup>10</sup> In this study we tried to find out the incidence of GBC in relation with wall thickness.

#### Materials and Methods:

This observational study has been carried out in Combined Military Hospital (CMH) Dhaka, CMH Momenshahi and CMH Ghatail during the period of June 2007 to June 2014. A total 300 patients underwent cholecystectomy were studied retrospectively. Diagnosis confirmed by histopathological examination. Patients with clinically suspected or diagnosed malignancy and intraoperatively obvious growth with or without signs of metastasis were excluded from the study.

A detailed history was taken from the patients. Physical findings were recorded properly.

Patients diagnosed as GBC received further treatment under hepatobiliary surgeon and oncologist. All the patients were followed up regularly during their stay in the hospital and as out patient.

#### Results:

The youngest patient of this series was 28 years and oldest was of 79 years. Male 46 (15.12%) and Female:

254 (84.88%); Male: Female is 1: 5.52. A total 42 (14%) patients had thick walled GB and 258 (86%) patients GB had normal wall thickness (Table – 1).

All patients were evaluated by sonography to determine the wall thickness. Thirty six (12%) patients were found to have thick walled GB. And in 10 (3.33%) patients contracted GB was found (Table – 2).

All resected specimen were examined histopathologically. Incidence of GBC were 4.33%. Maximum 157 (52.33%) patients had features of chronic inflammation. 54 (18%) specimens revealed nonspecific findings (Table – 3).

Incidence of malignancy was higher (84.62%) in patients with thick walled GB. Out of 13 cases 10 (76.92%) were female. Incidence were more in patients of >60 years of age group (46.15%) irrespective of wall thickness (Table -4).

In all 13 malignant cases the initial diagnosis was GB stone in 11 (84.62%) and GB polyp in 2 (15.36%) patients (Table – 5).

Out of the all 13 GBC, maximum 7 (53.85%) were well differentiated adenocarcinoma, 4 (30.77%) were moderately differentiated. Only 1 (7.96%) patient each had poorly differentiated and non-specific adenocarcinoma. Invasion was pT<sub>1</sub> in 11 (84.62%) and pT<sub>2</sub> in 2 (15.38%) patients (Table – 6).

**Table-I**

<i>Age and Sex distribution in relation with GB wall thickness (n=300)</i>								
Condition of	Sex		Age (years)				Total	Percentage
	Male	Female	<40	41–50	51 – 60	>60		
GB Wall								
Thick	07 (16.67%)	35 (83.33%)	13 (30.95%)	18 (42.56%)	09 (21.43%)	02 (4.76%)	42	14%
Normal	39 (15.12%)	219 (84.88%)	79 (30.62%)	105 (40.70%)	59 (22.87%)	15 (5.81%)	258	86%
Total	46 (15.12%)	254 (84.88%)	92 (30.62%)	123 (40.70%)	68 (22.87%)	17 (5.81%)	300	100

M:F = 1:5.52

**Table-II**

<i>Sonographic findings of GB wall (n=300)</i>		
Sonographic findings	No. of patients	Percentage %
Normal wall thickness	254	84.67
Thick wall (>3mm)	36	12
Contracted GB	10	3.33

\* 6 patients had thick walled GB found during surgery

**Table-III***Histopathological Diagnosis: (n=300)*

Histopathological Diagnosis	Total	Percentage (%)
Chronic Cholecystitis	157	52.33
Cholesterosis	05	1.67
Acute Cholecystitis	11	3.67
Epithelial Hyperplasia	59	19.67
Tuberculosis	01	0.33
Carcinoma GB	13	4.33
Non specific findings	54	18
Total	300	100

**Table-IV***Incidence of Ca in comparison to wall thickness (n=13)*

Condition of GB Wall	Sex		Age (years)				Total	Percentage %
	Male	Female	30-40	41-50	51-60	>60		
Thick	03	08	-	02	05	04	11	84.62
Normal	-	02	-	-	01	01	02	15.38
Total	03 (23.08%)	10 (76.92%)	-	02 (15.38%)	05 (38.46%)	06 (46.15%)	13	100

**Table-V***Clinical diagnosis in the 13 cases of gallbladder carcinoma (n=13)*

Clinical Diagnosis	No. of patients	Percentage (%)
GB stone	11	84.62
GB polyp > 1 Cm	02	15.38

**Table-VI***Histopathological Characteristics of Ca (n=13)*

Histopathological Characteristics	No. of patients	Percentage (%)
Type		
Well differentiated adenocarcinoma	07	53.85
Moderately differentiated adenocarcinoma	04	30.77
Poorly differentiated adenocarcinoma	01	7.69
Non-specific adenocarcinoma	01	7.69
Invasion		
pT <sub>1</sub>	11	84.62
pT <sub>2</sub>	02	15.38

**Discussion:**

Cancer of the GB is uncommon, although it is the fifth most common gastrointestinal malignancy<sup>11</sup> and is found incidentally in 1% to 3% of cholecystectomy specimens.<sup>12</sup> 2.5 new cases detected per 100,000 inhabitants per year. It has a high mortality rate as its diagnosis is most of times achieved at advanced stages of the disease, because of the scarcity of symptoms.<sup>13</sup>

Countries with a high incidence of GBC include Chile, Poland, India, and Japan. There is also a very high incidence of this cancer among women in Northern India (21.5/100,000) and female Native American Indians (14.5/100,000).<sup>14</sup> Our patient was of Bangladeshi (ie, the Indian subcontinent) origin.

The majority of reports suggest that GBC is two to six times more prevalent in women and the incidence peaks in the seventh decade of life<sup>15,16</sup> In this study out of 13 malignant cases 10 (76.92%) were female. Incidence were more in patients of >60 years of age group (46.15%) irrespective of wall thickness.

There is a strong association between cholelithiasis and GBC, with gallstones found in nearly 80% of all cases. Other risk factors for GBC include a calcified GB (known as porcelain gall-bladder), a long common channel, and a chronic typhoid carrier state. Adenomas figure less prominently or not at all in the list of precursors.<sup>17</sup> Majority of GBC patients have associated gallstones. With the advent of ultrasonography more patients are being diagnosed with gallstones and are being subjected to cholecystectomy. IGBC is found in 0.2–2.9 % of all cholecystectomies done for gallstone disease.<sup>18</sup> A common characteristic is the presence of gallstones and chronic GB inflammation.<sup>19</sup> Cholelithiasis is found in approximately 85% of people with GBC. The association between cholelithiasis and GBC ranges from 2.3 to 34.4 in case control studies.<sup>20</sup> In our study 84.62% patients of GBC had cholelithiasis which is almost similar to this.

Clinical presentation of the disease is often vague or delayed relative to pathologic progression, contributing to advanced staging and dismal prognosis at the time of diagnosis.<sup>21</sup> Unfortunately, the preoperative diagnosis of early-stages of gallbladder carcinoma is difficult due to its non-specific symptoms. The symptoms of GBC overlap with the symptoms of gallstones and biliary colic. Sonography is a routinely requested technique for investigating patients with

gallbladder symptoms<sup>22,23</sup> has a relatively high sensitivity for the detection of GBC at advanced stages, but it is limited in the diagnosis of early lesions. Although CT scan is a valuable investigation for suspected cases of GBC with a reported sensitivity of 80% and 100%, it is not routinely used to investigate patients with GB disease symptoms. Pre-operative diagnosis depends mainly on a high index of clinical suspicion especially in elderly patients with gallstones. Some authors<sup>24</sup> suggested criteria for early diagnosis of GBC in presence of the combination of female sex, old age, silent gallstones presenting at late age, abnormal liver function test and thickened wall of the GB on ultrasonic examination (plus criteria), but these criteria are not yet critically evaluated.<sup>25</sup>

GBC may present as focal or diffuse asymmetric wall thickening in 20–30% of cases.<sup>2</sup> Diffuse GB wall thickening is a frequently detected finding on cross-sectional imaging in clinical practice; this finding can result from a broad spectrum of pathologic conditions. Among these conditions, acute cholecystitis, chronic cholecystitis, GBC, and adenomyomatosis are common diseases that cause diffuse or focal GB wall thickening.<sup>26</sup> When GBC manifests as wall thickening, it is challenging to diagnose because it mimics the appearance of more common acute and chronic inflammatory conditions of the GB.<sup>27</sup>

According to several authors, the upper limit for normality of the GB wall thickness is 3 mm. However, in patients under inappropriate fasting, the parietal thickness may exceed such a limit because of the organ's smooth muscle contraction.<sup>13</sup> GB wall thickening is classified as mild (between 4 and 7 mm), marked (> 7 mm), and in focal or diffuse. As a rule, systemic diseases such as heart, renal or hepatic failure cause diffuse and less marked thickening, contrary to tumor lesions that cause focal and more exuberant thickening, frequently greater than 10 mm.<sup>26</sup>

Ultrasonography is the method of choice for the study of the GB, with a high sensitivity in the detection of wall thickening.<sup>13</sup> Real-time elastography using acoustic radiation force impulse (ARFI) is a new emerging technique, which uses high intensity focused ultrasound to evaluate the tissue stiffness in the liver, breast, and other organs.<sup>28</sup> It has also been shown to differentiate between benign and malignant nodules in various organs.<sup>29</sup>

Magnetic resonance imaging has been shown to be valuable in the evaluation of GB wall thickening, but it still plays a small diagnostic role.<sup>30</sup> Because of its high cost and low specificity, MRI is not used to diagnose chronic cholecystitis.<sup>31,32</sup> In our study 42 (14%) patients had thick walled GB out of them 36 were diagnosed sonographically and 6 cases were found during surgery. On histopathological examination 11 (84.62%) GBC cases had thick walled GB which is very high.

GBC is associated with macroscopic abnormalities in all cases. Therefore histopathology should be restricted to only those specimens which reveal a macroscopic abnormality.<sup>33</sup> The question of a selective approach to sending all GBs for histology following cholecystectomy has been postulated in many journals but as yet no guidelines have been published in light of such concern.<sup>3, 33</sup>

The only effective treatment for GBC is operative resection, and an open technique is preferred. Unfortunately, as is often the case, the lack of presurgical differential diagnosis hampers the planning of surgery.<sup>34</sup> Evidence has emerged that suggests early GBC (pT1) need not be treated further than the cholecystectomy that was previously performed in order to obtain the tissue sample. In other words, although early macroscopic findings indicative of GBC could theoretically be missed in a selective method, no further treatment is necessary in such early pathogenic stages.<sup>35</sup> In this study 84.62% cases were in pT<sub>1</sub> stage.

According to this study incidence of GBC is very high on thick walled GB. But we found two patients of GBC having normal wall thickness. So we recommend all resected specimen should be examined histopathologically.

#### Conclusion:

Diffuse GB wall thickening can result from a broad spectrum of pathological conditions, including surgical and non-surgical diseases. GBC may present as focal or diffuse asymmetric wall thickening or even in GB having normal wall thickness. Combined with well known risk factors such as increasing age, female sex, ethnicity and working on a when-in-doubt policy whereby if there are any suspicions whether small or large, all GB should be sent for histology, thus clinicians will be able to put into action a more evidence-based approach to send specimens to pathology.

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