

## Prevalence of Gallbladder Malignancy in Gallstone Diseases

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### ABSTRACT

**Background & objective:** Carcinoma (Ca) of the gallbladder is a rare disease. But its prognosis is poor. Early diagnosis of Ca gallbladder, though important, is rarely achieved due to lack of symptoms and physical signs. However, it is frequently associated with gallstone diseases. It is, therefore, of utmost importance to do a routine histopathological examination of all gallbladder specimens after cholecystectomy is done for gallstone diseases. The present study was undertaken to find the prevalence of Ca gallbladder in gallstone diseases.

**Methods:** This descriptive study was conducted in the Department of Surgery, BSMMU Hospital, and in the Public Medical College Hospitals of Dhaka over a period of eight months from July 2011 to February 2012. A total of 1012 specimens of gallbladder were taken from the patients who underwent either laparoscopic or open cholecystectomy for gallstone diseases in the above-mentioned hospitals during the study period. Following the operation, the resected specimens or the biopsies taken from the gallbladder were collected in 10% formaldehyde solution and were sent to the Histopathology Departments of the respective hospitals, for confirmation of diagnoses as well as for histological grading and typing.

**Result:** Of the 1012 cases of operated gallbladder for cholelithiasis, 28(2.7%) cases were histopathologically diagnosed as having Ca gallbladder. The age incidence of Ca gallbladder varied from 43 – 71 years. The highest incidence was observed in the 6<sup>th</sup> decade (53.6%) followed by the 5<sup>th</sup> decade of life (28.5%). Out of 28 cases of Ca gallbladder, 15(53.6%) exhibited increased wall thickness. All 28 cases were adenocarcinoma; of them, 25(89.3%) were poorly differentiated and 3(10.7%) were well-differentiated carcinoma. Non-squamous cell carcinoma or other variants were found. The majority (82.1%) of the cases was of infiltrative scirrhous (a hard slow-growing malignant tumor having a preponderance of fibrous tissue) type and the rest (17.9%) fungating type. Staging of the disease stratified 4(14.3%) cases as Stage-IV, 3(10.7%) cases as Stage-III, 8(28.6%) cases as Stage-II, and 13(46.4%) cases of Stage-I.

**Conclusion:** The study concluded that the prevalence of malignancy in gallstone disease is rare. The incidence is highest in the 6<sup>th</sup> decade of life and females are more often affected than males. As older people with gallstone diseases are at increased risk of having gallbladder malignancy, it is imperative that older patients with gallstone diseases should be routinely examined for evidence of carcinoma.

**Keywords:** Gallbladder, prevalence, malignancy, gallstone diseases etc.

### INTRODUCTION:

Gallstones are the most common biliary pathology and cholecystectomy is one of the most common operations performed by general surgeons.<sup>1</sup> Gallbladder malignancy is a lethal disease and is the fifth most common malignancy in the gastrointestinal tract.<sup>2</sup> It is the most common malignancy of the gastrointestinal tract in females.<sup>3</sup> Although the youngest reported case of gallbladder carcinoma was

found in an 11 years old Navajo girl,<sup>4</sup> the peak incidence of gallbladder carcinoma is observed in the 6<sup>th</sup> and 7<sup>th</sup> decades of life. Clinical presentation of gall bladder malignancy and benign gall bladder disease is almost similar and most of the time it is masked by chronic cholecystitis.<sup>5</sup> Sometimes it may be asymptomatic.

Carcinoma of the gallbladder is a rare disease, but most aggressive with a poor prognosis.<sup>6-8</sup> Early diagnosis of

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Ca gallbladder, though important, is rarely achieved due to lack of symptoms and physical signs.<sup>9</sup> The aetiology of the disease is unknown, but there may be an association with preexisting gallstone disease. Calcification of the gall bladder is associated with cancer in 10-25% of cases. The Ca gallbladder is associated with gallstones in 70% of cases, and the risk of malignancy correlates well with the length of time gallstones have been present. The majority of Ca gallbladder cases are adenocarcinoma (90%). The tumor is most commonly nodular and infiltrative, with thickening of the gall bladder wall.<sup>10,11</sup> Preoperative radiological and biochemical investigations are not helpful, but an isolated elevation in serum alkaline phosphatase level in the absence of any biliary obstruction or hepatic dysfunction was noticed in some patients with carcinoma gallbladder.<sup>12</sup> Occasionally, the diagnosis is made by histological examination of a gall bladder removed for 'benign' gallstone disease. The disease has a very poor prognosis with a median survival of < 6 months.<sup>13</sup> Radiotherapy and chemotherapy are not effective palliative measures.<sup>14</sup>

Surgery is the only treatment of choice if localized carcinoma is recognized at operation en-block. Wedge resection of adjacent 3-5 cm normal liver is also advised. If small invasive carcinoma is overlooked during cholecystectomy for gallstone diseases, consideration should be given to the re-operation and wedge resection of the liver bed with regional lymphadenectomy. There is little benefit with any form of treatment offered, for the overall mean survival rate for patients with gallbladder cancer is 6 months, with a 5-year survival rate of 5%.<sup>15</sup> So, early diagnosis is very important for carcinoma gallbladder as in other malignancies. Therefore, it should be a routine practice to do a histopathological examination of all gallbladder specimens after cholecystectomy is done for gallstone diseases. This will also give us an idea about the association of malignancy with gallstone diseases. However, limited studies have so far investigated the presence of gallbladder malignancy in gallstone diseases. Moreover, the studies were done with small sample sizes. The present large-scale study is, therefore, intended to find the prevalence of Ca gallbladder in gallstone diseases.

## METHODS:

Having obtained ethical clearance from the Ethical Review Committee of Bangabandhu Sheikh Mujib Medical University (BSMMU), this descriptive study was carried out in the Department of Surgery, BSMMU Hospital, and in the Public Medical College Hospitals of Dhaka over a period of eight months from July 2011 to February 2012. A total of 1012 specimens of gallbladder were taken from the patients who underwent either laparoscopy or open cholecystectomy for gallstone diseases in the above-mentioned hospitals during the study period. The purpose of the study was discussed in detail with the patients or their attendants before taking their consent to enroll in the study. The patients were subjected to general anesthesia with muscle relaxants as per the protocol followed in the institute. Intravenous prophylactic antibiotics were given on induction of anesthesia. After the operation, the resected specimens or the biopsies taken from the gall bladder were collected in 10% formaldehyde solution to send to the respective Histopathology Departments, for final diagnoses as well as for histological grading and typing. Data were processed and analyzed using SPSS (Statistical Package for Social Sciences), version 16.0. The test statistics used to analyze the data were descriptive statistics (frequency and its corresponding percentage, mean and standard deviation).

## RESULTS:

The age distribution of the patients of gallstone diseases varied from 16 to 75 yrs with the highest prevalence (38.3%) being observed in the 4<sup>th</sup> decade of life. The disease was more prevalent (82%) in middle-aged people (31-60 years) and was rarely (5%) found in extreme-aged cohorts (below 20 and above 70 years). Two-thirds (67.8%) of patients were female (female-to-male ratio: 2:1) and obesity was present in about 18% of cases (Table I). The majority (78.6%) of the cases presented with chronic cholecystitis followed by asymptomatic gallstone diseases (14%), acute cholecystitis (3.7%), perforation choledocholithiasis (1.9%), mucocele of the gall bladder, empyema gall bladder, and gangrene in decreasing frequencies. Out of 1012 specimens of operated gallbladder for cholelithiasis, 28(2.7%)

were histopathologically confirmed as harboring carcinoma gallbladder (Table II).

The age incidence of carcinoma gallbladder varied from 43-71 years. The highest incidence was observed in the 6<sup>th</sup> decade (53.6%) followed by the 5<sup>th</sup> decade of life (28.5%) (Table III). A female predominance (75%) was observed among Ca gallbladder cases giving a female-to-male ratio of 3:1. The cases were predominantly middle class (57.1%) followed by lower class (32.2%) and upper class (10.7%). Four cases (14.3%) were smokers and 5(17.8%) were obese. Out of 28 cases of Ca gallbladder, 15(53.6%) exhibited increased wall thickness. All 28 cases were adenocarcinoma; of them, 25(89.3%) were poorly differentiated & 3(10.7%) were well-differentiated carcinoma. Non- squamous cell carcinoma or other variants were found. The majority (82.1%) of the cases was of infiltrative scirrhous (a hard slow-growing malignant tumor having a preponderance of fibrous tissue) type and the rest (17.9%) fungating type. None of the growths involved the entire gallbladder (the neck, body, and fundus). However, growth involving the fundus and body was found in 23(82.1%) cases. Only 2(7.1%) cases exhibited growth in the neck and 3(10.7%) cases had isolated early growth. Staging of the disease stratified 4(14.3%) cases as Stage IV (growth involving the cystic lymph node only), 3(10.7%) cases as Stage III (growth invading all the layers of the gallbladder), 8(28.6%) cases as Stage II, (growth extended beyond the mucosa but not the fibromuscular coat) & 13(46.4%) cases as Stage I (Table III).

**Table I: Distribution of the cases by demographic characteristics (n=1012)**

Characteristics	Frequency	Percentage
<b>Age* (years)</b>		
≤ 20	40	3.9
21-30	100	10.0
31-40	388	38.3
41-50	283	27.9
51-60	160	15.9
61-70	30	2.9
71-80	11	1.1
<b>Sex</b>		
Male	325	32.1
Female	687	67.9
<b>Obesity</b>	5	17.8

\*Mean age : 41.4 ± 1.6 years; range : 16 – 75 years.

**Table II: Distribution of patients by mode of clinical presentations (n = 1012)**

Presentations	Frequency	Percentage
Asymptomatic	142	14.0
Chronic Cholecystitis	796	78.6
Acute cholecystitis	38	3.7
Mucocele	8	0.8
Empyema	6	0.6
Gangrene	2	0.2
Perforation Choledocholithiasis	20	1.9
Gall-stone disease with Ca Gallbladder	28	2.7

**Table III: Characteristics of the patients having gallbladder malignancy (n = 28)**

Characteristics	Frequency	Percentage
<b>Age (years)</b>		
41 – 50	8	28.5
51 – 60	15	53.6
61 – 70	4	14.3
71 – 80	1	3.6
<b>Sex incidence</b>		
Female	21	75.0
Male	7	25.0
<b>Social Class</b>		
Upper class	3	10.7
Middle class	16	57.1
Lower class	9	32.2
<b>Smoking Habit</b>	4	14.3
<b>Obesity</b>	5	17.8
<b>USG findings of the hepatobiliary system</b>		
No specific findings for Ca gallbladder	12	42.8
Thick-walled gallbladder	15	53.6
Thick-walled and fibrosed gallbladder	1	3.6
<b>Morphological type</b>		
Infiltrative	23	82.1
Fungating	5	17.9
<b>Histological category of Ca gallbladder</b>		
Well-differentiated carcinoma	3	10.7
Poorly-differentiated carcinoma	25	89.3
<b>Site of growth</b>		
Neck	2	7.2
Fundus & body	23	82.1
Fund us	3	10.7
<b>Staging of carcinoma gallbladder</b>		
Stage I	13	46.4
Stage II	8	28.6
Stage III	3	10.7
Stage IV	4	14.3

## DISCUSSION:

By far, it is the largest study in the context of our country to find the prevalence of gallbladder malignancy in gallstone diseases. So, this study may have some epidemiological significance. The study revealed a prevalence of 2.7% malignant gallbladder in patients with gallstone diseases. The most common malignant lesion of the biliary tract is primary carcinoma of the gallbladder, which is the third most common and aggressive cancer of the gastrointestinal tract. The prevalence of gallbladder carcinoma in any population varies widely from 1-23 per 100000 population. Doherty<sup>9</sup> reported that 70% of the cases of gallbladder malignancy to associate with gallstones. The age incidence of carcinoma gallbladder varied from 43-71 years with the highest incidence being observed in the 6<sup>th</sup> decade of life (53.6%). Of the 28 cases of gallstone disease that harbored gallbladder malignancy, only 17.8% were obese. Although obesity is thought to play an indirect role in the Ca gallbladder, the present study does not support so.

Over half (53.6%) of the patients with carcinoma gallbladder exhibited thickened walls, and only 1(3.6%) thickened fibrotic gallbladder on preoperative USG. Daly & associates<sup>16</sup> demonstrated that the most frequent finding in Chinese patients with gallbladder carcinoma was abnormal thickening of the gallbladder wall (44%). All patients of gallbladder malignancy in the present series were of adenocarcinoma; of them, 25(89.3%) were poorly differentiated and 3(10.7%) were well-differentiated carcinoma. Yalcin showed that the majority (85%) of gallbladder carcinoma was adenocarcinoma usually well or moderately differentiated & the remaining 15% are adenosquamous, squamous, or undifferentiated carcinoma.<sup>17</sup> In our series, no squamous cell carcinoma or other variety was found.

## CONCLUSION:

Gallstone diseases are fairly common in our country. But the prevalence of malignancy in gallstone disease is rare. The incidence is highest in the 6<sup>th</sup> decade of life and females are more vulnerable than males to be affected with the disease. A frequent

association of carcinoma with gallstone diseases in the advanced age group makes it imperative that older patients with gallstone diseases should be examined carefully for evidence of carcinoma. Surprisingly though, it is thought that gallstones may be responsible for the pathogenesis of Ca gallbladder in which all cancers should be of squamous variety. But it is not the case. All the reports of different grades were of adenocarcinoma of intestinal type. So, other causes are there to be considered.

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