

## RESEARCH ARTICLE

# Clinicopathological Study of Gall Bladder Carcinoma with Special Reference to Gallstones: Our 8-year Experience from Eastern India

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### Abstract

Gallbladder carcinoma (GBC) is the commonest cancer of the biliary tree and the most frequent cause of death from biliary malignancies. The incidence of GBC shows prominent geographic, age, race, and gender-related differences and is 4-7 times higher in patients with gallstones. This prompted us to study the clinicopathological aspects of the disease and the incidence of gallstones in gallbladder carcinoma patients, in this part of India. In this, combined retrospective (Jan 2004-March 2010) and prospective study (April 2010-Dec 2011) of eight years, 198 patients of gallbladder carcinoma (50 males and 148 females), (range 28-82 years; mean 55 years) were studied. Most of the patients were poor and presented with abdominal pain and mass, with abnormal lab parameters. Gallstones were present in 86% of patients. Surgical exploration was performed in 130, with gallbladder resection in 60 (including 7 incidental GBC). Adenocarcinoma (87.7%) was the commonest histological type. The study indicates that GBC is common in our scenario. It is a disease of elderly females, has a strong association with gallstones and every cholecystectomy specimen should be examined histopathologically.

**Keywords:** Gallbladder carcinoma - gallstone - Calcutta - India

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### Introduction

Carcinoma of the gallbladder (GBC), although it has a low overall prevalence, is the most common cancer of the biliary tree and one of the most highly malignant tumors with poor prognosis (Pavlidis et al., 2012). It is the fifth most common gastrointestinal malignancy following colon, pancreas, stomach and oesophagus (Kapoor et al., 2003).

Gallbladder carcinoma is two to six times more common in women than men. Incidence increases with age and more than 75% of patients with this malignancy are older than 65 years. GBC is more common in Caucasians than in blacks and there is some evidence that the incidence is increasing in younger individuals (Mishra et al., 2012).

Globally, there is a prominent geographic variability in gallbladder carcinoma incidence. High rates of GBC are seen in South American countries, particularly Chile, Bolivia, and Ecuador, as well as some areas of India, Pakistan, Japan and Korea. In Chile, mortality rates from GBC are the highest in the world, where it constitutes the most common cancer affecting women and is the leading cause of death from cancer among women (Kapoor et al., 2003; Mishra et al., 2012). The United Kingdom, Denmark, and Norway have the lowest international incidence rates.

The etiology of gallbladder cancer has been a source of speculation. The incidence of GBC parallels the prevalence of gallstone disease; large and longstanding gallstones being associated with a higher risk of GBC. The risk of GBC in patients with gallstones has been reported to have increased four to seven times (Tyagi et al., 2008). The association between an abnormal pancreaticobiliary duct junction, a porcelain gallbladder, and other biliary disorders such as choledochal cyst, primary sclerosing cholangitis, Mirrizi's syndrome and gallbladder cancer has also been recognized (Pandey et al., 2003). About 1% of all elective cholecystectomies performed for cholelithiasis harbor an occult gallbladder cancer (Pandey et al., 2001).

The objectives of the present study were: 1) To study the clinicopathological aspect of the disease in patients of gallbladder carcinoma. 2) To know the incidence of gallstones in these patients of gallbladder cancer in this part of Eastern India.

### Materials and Methods

This was a combined retrospective (Jan 2004-March 2010) and prospective study (April 2010-Dec 2011) carried over a period of eight years at The Calcutta Medical Research Institute which serves as a tertiary care

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referral institute for the Eastern Indian states (including West Bengal, Orissa, Bihar and parts of Uttar Pradesh) and even the neighboring countries like Bangladesh. All the patients diagnosed with primary carcinoma of gallbladder including incidentally diagnosed gallbladder carcinomas were studied. Patients without a confirmed histological diagnosis and patients with history of any previous malignancy were excluded from the study.

A total of 198 patients were selected. All the relevant clinical details of patients selected during retrospective study were retrieved using e-medicare™, Birla Software, India. During the prospective study period, all selected patients were subjected to a detailed history taking and physical examination followed by routine laboratory tests and other investigations including ultrasonographic (US) and computed tomography (CT) scan of whole abdomen. The results were analyzed using SPSS 11.

**Results**

During this 8-year study period a total of 198 patients with gallbladder carcinoma and 13,876 patients with gallstone diseases were observed (Table 1). Males contributed 50 cases (25.3%) and females 148 cases (75.5%), with a male to female ratio of 1:3. The age of the patients ranged from 28-82 years (mean 55 years). The peak age of presentation was the fifth decade of life (Table 2). On the basis of economic status, patients were divided into three groups: Poor (124 cases, 62.6%), Middle class (44 cases, 22.2%) and Upper class (30 cases, 15.2%). The most common presenting features were pain in right hypochondrium and epigastrium in 176 patients (88.9%) and abdominal mass in 151 patients (76.3%) (Table 3). The symptoms were present for an average duration of 4.8 months prior to presentation. Laboratory investigations revealed anemia, (Hb<10g/dl) in most of the patients and

**Table 1. Year-wise Distribution of Patients (N=198)**

Year	GSD cases	GBC cases		
		GSD +	GSD -	Total
2004	1135	6 (60%)	4	10 (0.9%)
2005	948	11 (80%)	4	15 (1.6%)
2006	1216	17 (85%)	3	20 (1.6%)
2007	2513	28 (90%)	3	31 (1.2%)
2008	1802	23 (92%)	2	25 (1.4%)
2009	2511	30 (90%)	3	33 (1.3%)
2010	1864	22 (81%)	5	27 (1.4%)
2011	1987	34 (92%)	3	37 (1.9%)
Total	13876	171 (86.4%)	27	198 (100%)

**Table 2. Distribution of Age of Patients (N=198)**

Age	No.	Percentage	Male	Female
10-20	-	-	-	-
21-30	1	0.50%	1	-
31-40	24	12.10%	5	19
41-50	32	16.20%	7	25
51-60	105	53.00%	26	79
61-70	28	14.10%	8	20
71-80	4	2.00%	1	3
81-90	4	2.00%	2	2
Total	198	100%	50	148

**Table 3. Distribution of Symptoms and Signs (N=198)**

	No. of cases	Percentage	
Symptoms:	Abdominal pain	176	88.9
	Anorexia	119	60.0
	Dyspepsia	106	53.5
	Weight loss	89	44.9
	aundice	65	32.8
	Nausea and vomiting	61	30.8
	Malaise	53	26.8
	Pruritus	51	25.7
Signs:	Abdominal mass	151	76.3
	Tenderness	103	52.0
	Icterus	72	36.4
	Ascites	44	22.2
	Cachexia	32	16.2
	Fever	22	11.1

**Table 4. Lab Parameters of Patients in the Study (N=198)**

Lab parameter	Mean±SD	Range
Hb (g/dl)	8.1±3.2	4.2-12.8
Sr. Bilirubin (mg/dl)	2.8±4.8	0.4-25.3
Sr. ALP (IU/L)	938.6±456.7	79.0-2255.0
Total protein (g/dl)	6.9±1.0	4.8-8.3
Serum albumin (g/dl)	3.5±0.9	1.9-5.2

**Table 5. Gross Morphology in 60 Resected Specimens**

Site	Number (n)	Percentage (%)	
GB mass lesion	48	80.00%	
	Body	19	31.70%
	Fundus	15	25.00%
	Infundibulum/Neck	9	15.00%
	Whole GB	5	8.30%
GB Wall Thickening only	8	13.30%	
Area couldn't be specified	4	6.70%	
Total	60	100%	

leucocytosis (TLC>10,000/mm<sup>3</sup>) in 21.2% patients (Table 4). Preoperative imaging of abdomen (including US and CT) performed in all the patients showed: Gallstones in 159 patients (80.3%), gallbladder mass in 184 patients (92.9%) which was associated with gallstones in 145 patients (73.2%). There was evidence of lymph node enlargement in 52 patients (26.3%) and involvement of liver in 105 patients (53%).

*Surgical exploration was performed in 130 patients*

Gallbladder resection was done in 60 patients (including incidentally diagnosed gallbladder carcinomas in 7 patients, 3.5%) and only biopsy, with or without bypass and biliary drainage in 70 patients. In 60 patients, (88.2%) diagnosis of malignancy was achieved by fine needle aspiration cytology (FNAC), both direct and image guided. FNAC was inconclusive in 8 patients due to inadequate material or presence of necrotic material only. Findings on gross and histopathological examination of the resected surgical specimens are shown in Table 5 and Table 6 respectively. Staging of the patients was done according to AJCC TNM 6<sup>th</sup> edition: Stage I in 25 patients (12.6%), stage II in 32 patients (16.2%), stage III in 28 patients (14.1%) and stage IV in 113 patients (57.1%).

**Table 6. Histopathological Findings in 130 Surgical Specimens**

Histopathological variants	Number (n)	Percentage (%)
Adenocarcinoma (not otherwise specified)	114	87.70%
Moderately differentiated	68	52.30%
Poorly differentiated	36	27.70%
Well differentiated	10	7.70%
Papillary adenocarcinoma	9	6.90%
Mucinous adenocarcinoma	5	3.80%
Squamous cell carcinoma	1	0.80%
Adenosquamous carcinoma	1	0.80%
Total	130	100%

**Table 7. Various Studies of GBC Patients Reported from India**

Study	Place	Zone	Period	No. of patients
Prakash et al.	New Delhi	North	1959-73	100
Gupta et al.	Varanasi	North	1967-76	328
Talwar et al.	Chandigarh	North	not mentioned	209
Shukla et al.	Varanasi	North	1963-79	315
Chattopadhyay et al.	New Delhi	North	5 years	143
Pal et al.	Calcutta	East	1984-88	201
Zargar et al.	Kashmir	North	3 years	98
Kapoor et al.	Lucknow	North	1989-94	297
Chaudhary et al.	New Delhi	North	1987-96	196
Present Study	Calcutta	East	2004-2011	198

Surgical resection of gallbladder (cholecystectomy/radical cholecystectomy) was performed in all the stage I patients (25 cases) and in 16 stage II patients. Eleven stage II patients and 15 stage III patients were given chemotherapy besides surgical resection. In 67 stage III and IV patients, surgical exploration with only biopsy and chemotherapy, with or without bypass and biliary drainage was done. Diagnostic laparoscopy was performed in 31 patients, among them 18 were found to be inoperable. In 61 patients with inoperable disease, either chemotherapy or symptomatic treatment only was given. Three patients died before receiving any treatment.

## Discussion

Gallbladder cancer is the most common cause of death from biliary malignancies (Khan et al., 2010). It is usually detected at an advanced stage due to its non-specific symptoms (Le et al., 2011). In India, cancer of gallbladder shows varying geographic distribution, as the incidence is much higher in Delhi population as compared to South India. Gallbladder cancer ranks among the first five common cancers in females in Delhi, India (Tyagi et al., 2008). In the endemic zone of West Bihar and Eastern Uttar Pradesh, it is the third most common malignancy of the alimentary tract (Shukla et al., 1985) (Table 7).

It was found that increasing numbers of patients were being referred to our hospital in recent past, thus increasing the number of cases per year. This fact may be attributed to the increasing awareness of this disease amongst general physicians and general surgeons working in the peripheral areas and small medical facilities within the city. This is in contrast to the study (Kapoor et al., 2003) in which global trends for GBC reveal falling incidence rates, probably

as a result of increasing rates of cholecystectomy for gall stone disease. Some European studies (Levi et al., 2003) also noted declining rates of GBC incidence and mortality. However, no such inverse relationship was observed in another study (Le et al 2011).

The commonest factor implicated in the gallbladder carcinogenesis is gallstones. In our study, gallstones were present in 86% of cases with gallbladder cancer which is comparable to a study from MD Anderson Hospital (Perpetuo et al., 1978) in which 51 (88%) patients had gallstones. Other study from India (Pandey et al., 2001) reported presence of gall stones in 70% gallbladder cancer patients. In a study (Hart et al., 1972) from United States, it was found that 74% females and 26.7% males had a previous history of gallstone disease, while on pathological examination of resected specimens gallstones were found in 69% males and 83% females, suggesting a high incidence of silent gallstones among male carcinoma patients. Another study (Black et al., 1977) found gallstones in 41 out of 56 patients of southwestern American Indian origin, an incidence of 73.2%. In a study (De Aretxabla et al, 1990) from Chile, an area of high incidence of GBC, gallstones were found in 53 out of 54 potentially resectable GBC patients. The above studies favor a casual association between gallstones and GBC. However, some other studies favor the argument against stone as a possible cause of carcinogenesis: i) In an epidemiological study (Maringhini et al., 1987) 2,583 patients with documented cholelithiasis were followed for a mean of 13.3 years. Only 5 (0.19%) patients developed gallbladder cancer. Thus, an overall cumulative incidence of GBC was found to be 1% for 20 years after the initial diagnosis of gallstone disease in patients who do not undergo cholecystectomy. ii) Silent gallstone patient were followed in a study (Comfort et al., 1948) from 10-20 years with only 1% patients developed carcinoma. When these results were clubbed with another study (Wenekert et al., 1976), the incidence of carcinoma in silent gallstone patients dropped to 0.4%.

The clinical data doesn't establish a causative role for the gallstone in carcinogenesis, although the association is quite frequent to suggest a common antecedent or at least a facilitative role, the controversy over the cause and effect still exists.

The present study revealed the mean age of the patients to be 55 years, with a range of 28-82 years and fifth decade as the peak age of presentation. Similar results were observed in other studies from India (Shukla et al., 1985; Pandey et al., 2001; Kapoor et al., 2003). In contrast, studies from west reported the mean age of 67 years (Beltz et al., 1974) and the peak age of incidence in 7<sup>th</sup> decade of life (Perpetuo et al., 1978).

Results from our study showed that gallbladder cancer is predominantly a disease of elderly females; with an overall male to female ratio of 1:3. These results were consistent with the results of other studies (Beltz et al., 1974; Shukla et al., 1985; Pandey et al., 2001) where it was reported to be 1:3, 1:3 and 1:2.5 respectively. In another study, a male to female ratio of 1:1 was seen (Liang et al., 2008).

Most of the patients in our study had a poor

socioeconomic background, similar to that of one study (Shukla et al., 2008). Was this relation contributory in etiology or only because of the fact that patients from low socioeconomic strata harbor gallstones for a longer duration of time and neglect their disease, needs further evaluation.

GBC either remains asymptomatic for a long time or presents with very non-specific symptoms. Commonly, symptoms are related to associated gallstones (Shiwani et al., 2005). In our study, abdominal pain (88.9%) followed by abdominal mass (76.3%) and anorexia (60%) were the most common presenting features. Consistent results were reported in other studies (Gupta et al., 2004; Khan et al., 2010). Clinical signs mimic benign gallbladder diseases until the invasion of surrounding structures give clue to correct diagnosis (Piehler et al., 1978).

The laboratory investigations in our study revealed anemia (hemoglobin, <10 g/dl) in 172 (86.9%) patients; hyperbilirubinemia (serum bilirubin, >2 mg/dl) in 37.4%; and elevated levels of alkaline phosphatase (>100 IU/ml) in 64.5% of the patients. Comparable findings were reported in other studies (Shukla et al., 1985; Pandey et al., 2001). Abnormal serum alkaline phosphatase and gamma glutamyltransferase may be elevated in the absence of jaundice (Shiwani, 2007).

CT is better at detecting lesions than US. CT has a low sensitivity for detecting lymph node metastasis, although its positive predictive value is more than 90%. Both US and CT may fail to show local gastrointestinal and omental infiltration and peritoneal deposits (Shiwani, 2007). In our study, preoperative imaging of the abdomen (both US and CT) showed the presence of gallstones in 159 (80.3%) cases and a mass in the gallbladder was evident in 184 patients (92.9%). Hepatic involvement was picked up accurately in almost all the patients; however, the pickup rate for lymph nodes was rather low; peritoneal deposits were not picked up in any case. There were no false positive cases in our study. Similar results were observed in other studies (Piehler et al., 1978; Pandey et al., 2001). FNAC (direct as well as image guided) suggested malignancy in 88.2% of cases. The sensitivity of image guided FNAC was higher than that of direct FNAC. Other studies (Zargar et al., 1991; Pandey et al., 2001) found similar results.

Adenocarcinomas are the most frequent histological subtype of the malignant gallbladder neoplasms, representing approximately 90-95% of all cases. In contrast, squamous cell or 'epidermoid' carcinomas and adenosquamous carcinomas are rare (Roa et al., 2011). Adenocarcinoma, not otherwise specified, constituted the most common (87.7%) histological type followed by papillary (6.9%) and mucinous (3.8%) adenocarcinoma. One case, each of squamous cell carcinoma and adenosquamous carcinoma were also seen. Histopathology revealed comparable findings in other studies (Beltz et al., 1974; Liang et al., 2008). Seven cases of incidental GBC (3.5%) were observed in the current study: three cases had polypoidal mass, 2 had wall thickenings only and 2 cases mucosal irregularity, with gall stones in three cases. All of the cases were report as adenocarcinomas. Our results were comparable with a study from Malaysia (Khoo et

al., 2008) where 9 cases of incidental GBC were reported. (Malik et al., 2009) reported 6.15% incidental carcinomas whereas (Shreshtra et al., 2010) found the frequency of incidental primary gallbladder carcinoma to be 1.4% (i.e. 8/570 cases).

In conclusion, GBC is not an uncommon clinical entity in our Indian scenario, unlike western countries. It is predominantly a disease of females. Therefore, a female especially in forties and fifties with a history of recent onset of constant pain in the right hypochondrium or change in the character of pain should be thoroughly evaluated. Though the association between gallstones and GBC is strong, the causal relationship between them is not clear. In spite of the advances made in the field of gallbladder imaging, the detection of carcinoma of the gallbladder in early stages remains low. Therefore, every gallbladder should be subjected to routine histopathological examination because with identification of an early gallbladder carcinoma a curative resection may be possible and these patients have a good long term survival.

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