

The Enigma of Gall Bladder Cancer

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SUMMARY

A review of 107 cases of histologically proven carcinoma of the gall bladder managed over seven and a half years period at Department of General Surgery, Sheikh Zayed Hospital Lahore is presented. Gall bladder cancer is the second most common malignant tumor of the gastrointestinal tract. A steady increase in the operative incidence is observed. Mean age at presentation is 52 years, a decade younger than the Western figures. The disease is 4 times more common in females. Upper abdominal pain with a recent change in the character is the most frequent and significant complaint (77.5%). A palpable gall bladder was found in 61.6% cases. 41% patients presented with obstructive jaundice. Raised serum alkaline phosphatase level was the most common derangement in liver functions in anicteric patients (46%). Abdominal ultrasonography is the most important diagnostic tool with an accuracy of 79.4%. Cholelithiasis and chronic cholecystitis are associated findings in 89.6% and 78.3% cases respectively. 79.4% patients presented in Nevin's stage IV & V. Overall resectability is 60.3% with a postoperative morbidity of 27.3% and thirty day hospital mortality of 1.38%. The importance of early diagnosis (by US, CT) is emphasized.

INTRODUCTION

Carcinoma of the gall bladder is the most common malignancy of the biliary tract and is the fifth most frequent malignant tumor of the gastrointestinal tract. Since the original description by Maximillian deStoll of Vienna in 1777, the reports have established a characteristic pattern of late diagnosis, ineffectual treatment and poor prognosis¹. Keeping in view the dismal outcome, Blalock suggested that an operation be avoided if a preoperative diagnosis of carcinoma of the gall bladder has been made². Gall bladder cancer is a disease of elderly females with a peak incidence in 6th and 7th decade in the world literature. In spite of the development and availability of the modern imaging techniques the disease still poses a diagnostic challenge. Seventy-five percent of patients have unresectable disease at first presentation with a median survival of 5.2 months from diagnosis and a 5-year survival of 1 to 6 percent³. Carcinoma of the gall bladder remains the commonest malignancy of biliary tract in Pakistan with an operative incidence of 6 to 12% in various studies⁴⁻⁸. The disease is prevalent in relatively younger age group and a

worrying increase in the incidence is being reported from this region of the world^{9,10}. A preliminary report comprising of 30 cases of carcinoma of the gall bladder was published in 1989⁷. On account of the uniformly reported poor results, we have reviewed our experience to know the changing pattern in the clinicoepidemiological presentation, diagnostic efficacy of various modern modalities and outcome of surgery at this center.

PATIENTS AND METHODS

During the period January 1988 to June 1995, 14370 patients were admitted to the Department of General Surgery, Shaikh Zayed Hospital, Lahore. Out of these, 1961 (13.6%) patients had gall bladder disease and 1939 (13.5%) were operated upon. Carcinoma of the gall bladder was found in 123 (6.34%) of the operated patients. Complete medical record of 107 patients is available with a variable follow up. Various parameters examined were age and sex incidence, clinical features at presentation, positive yield of various diagnostic modalities, the surgical procedures and the outcome of surgery. Abdominal ultrasound was used as the main

diagnostic tool supplemented by more sophisticated investigations like computed tomography, ERCP, PTC, HIDA scan and barium studies whenever indicated. All patients except one underwent exploration. Cholecystectomy with or without wedge excision of gall bladder bed was performed in all resectable cases. An internal biliary drainage procedure was carried out wherever possible in advanced disease. The external drainage was employed only in desperate situations where no other option could be availed. The tumor was staged according to the Nevin's staging for carcinoma of the gall bladder¹¹. For the purpose of review and follow up the patients were divided into three groups: Group A, patients with Nevin's stage I, Group B, patients with Nevin's stage II and III, and Group C, patients with advanced Nevin's stage IV and V. The follow up was initially performed at one month interval for six months and then every 3 months. Clinical examination and various hematological, biochemical and radiological examinations including an abdominal ultrasound were employed in the follow up.

RESULTS

Epidemiology

During the seven and a half years period under review, a total of 957 patients (6.65%) were admitted to the Department of General Surgery with various malignancies. Out of these 561 (58.6%) patients had malignant tumors of the gastrointestinal and hepatopancreaticobiliary tract. Carcinoma of the gall bladder comprised 12.8% of all the malignant tumors and 21.9% of the gastrointestinal malignancies. A steady rise in the operative incidence from 5.7% in 1988 to 7% till 1994 has been observed as a remarkable feature (Fig. 1). Overall it was the second most common gastrointestinal cancer, superseded only by colorectal cancer (27.2%). A strong family history of the disease was available in 3 patients (2.8%).

Sex and age (Fig. 2)

Out of 107 patients under evaluation, 85 were females and 22 were males with a 3.8:1 ratio, showing marked female preponderance. The age ranged between 30 to 80 years with a mean incidence at 52 years. The mean age for females was 51.3 years (range 30 to 70 years) and for males was

54 years (range 48 to 80 years). 29 patients (27%) were younger than 45 years.

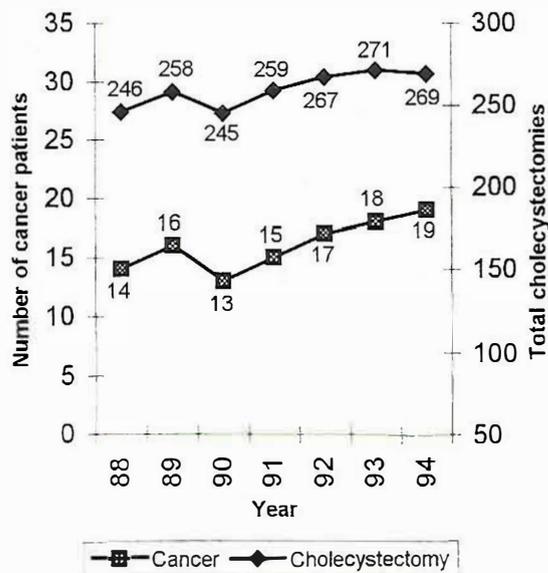


Fig. 1: Yearly operative incidence of carcinoma gall bladder.

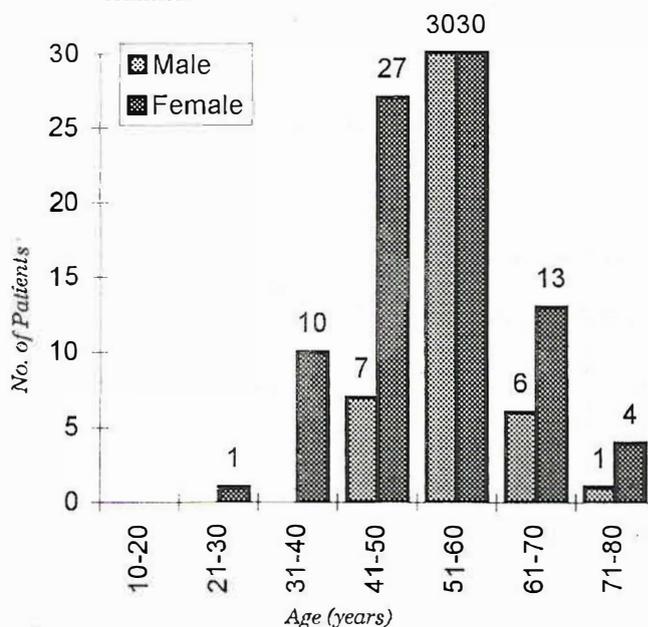


Fig. 2: Age and sex distribution in 107 cases of gall bladder.

Clinical presentation (Tables 1 & 2)

Pain upper abdomen was the commonest symptom observed in all cases (100%). 83 patients (77.5%) gave a history of change in the frequency and severity of the pain during the past one year at presentation. Flatulent dyspepsia was present in 60 patients (56%). Jaundice was the presenting feature

in 44 patients (41%) whereas 43 patients (40%) presented with syndrome of chronic gall bladder disease and unexplained weight loss. Gastric outlet obstruction was present in another 9 patients (8.4%). Upper abdominal tenderness was observed in 80 patients (74.7%). 66 patients (61.6%) had a palpable mass in the region of gall bladder. Malignant ascites, jaundice and hepatomegaly were found in 48 (44.8%), 44 (41.1%) and 41 (38.3%) cases respectively.

Table 1: Clinical presentation (n=107)

Presentation	Duration	No.	%
Pain upper abdomen	1-15 yrs	24	22.4
	1-12 mth	71	66.3
	< 1 mth	12	11.2
Biliary colic	1-5 yrs	07	06.4
	< 1 Yr	11	10.3
Dyspepsia	1-7 yrs	38	5.5
	< 1 Yr	22	20.5
Anorexia & weight loss	1-18 mths	43	40.1
Mass upper abdomen	1-6.5 mths	17	15.8
	< 1 mth	11	10.3
Jaundice	1-4 mths	27	25.3
	< 1 mth	17	15.9
Gastric outlet obstruction	1-4.8 mths	09	08.4

Table 2: Clinical signs (n=107).

Sign	No	%
Upper abdominal tenderness	80	74.7
Palpable gall bladder/mass	66	61.6
Malignant ascites	48	44.8
Jaundice	44	41.1
Hepatomegaly	41	38.3
Cholangitis/fever	11	10.2
Gastric outlet obstruction	09	08.4
Clinical suspicion of cancer gall bladder	62	58.0

Diagnosis

17 patients (15.8%) were anemic (Hb <10 gm%). A raised ESR of more than 75 in first hour was seen in 85 patients (79.4%). Raised alkaline phosphatase level of more than 250 units/L was seen in 80 cases (74.7%) and was the most frequent derangement in liver function tests in anicteric

patients (58%). 75 patients (70%) had severe hypoalbuminemia (<3 gm%) whereas 19 patients (17.7%) had deranged clotting profile. Abdominal ultrasound was the main stay of diagnosis and was diagnostic of malignancy in 85 patients (79.4%). Table 3 shows various ultrasonographic findings observed in 107 patients whereas Table 4 reflects the diagnostic yield of various other radiological procedures carried out in selective patients. Computed tomography was diagnostic in 84.2% and ERCP in 63.6% cases. Preoperative diagnosis of carcinoma of gall bladder was established in 81 patients (75.7%).

Table 3: Ultrasonographic findings.

Findings	No.	%
Gall bladder		
Irregular thickening of wall	17	15.8
Thickened walls + intraluminal growth	28	26.1
Mass gall bladder	62	58.0
Gall bladder fossa infiltration by mass	57	53.2
Associated stones	95	88.8
Multiple	76	71.0
Solitary	19	17.7
Hepatomegaly	47	43.9
Ascites	17	13.9
Cystic/coeliac/perportal lymph nodes	41	38.3
Dilated intra/extra hepatic ducts	45	42.0
Multiple liver metastases	29	27.1
Gall stones + common duct stones	07	06.5

Table 4 Additional radiological procedures

Procedure	No.	Diagnostic/suspicious	%
C.T. scan	19	16	84.2
ERCP	11	07	63.6
PTC	07	04	57.1
HIDA	07	01	57.1
Barium meal	06	05	83.3

Surgical procedures

Various surgical procedures carried out in 106 patients according to the Nevin's stage of the tumor are shown in Table 5. One patient presenting with deep jaundice and advance disease diagnosed on ultrasound-guided fine needle aspiration cytology of

a tumor replacing the gall bladder with multiple secondaries in the liver and malignant ascites was not subjected to exploration. Overall resectability rate (potentially curative/palliative) is 60.3%. 36 (34%) patients had cholecystectomy alone with (5.6%) or without (28.3%) wedge excision of the liver. An internal (6.5%) or external (19.8%) drainage procedure was added in another 29 patients (27.3%), 10 patients (9.4%) had some palliation only for jaundice with internal or external drainage procedures along with a biopsy of the tumor. In 32 patients (30.1%) presenting with advanced disease only a biopsy was possible to establish the diagnosis.

Table 5: Surgical procedures according to the Nevin's staging (n= 106).

Procedure	CIS	I	II	III	IV	V	Total
Cholecystectomy	02	03	05	08	17	01	36
Cholecystectomy + Int. biliary drainage	-	-	-	01	04	02	07
Cholecystectomy + Ext. biliary drainage	-	-	-	03	04	14	21
Biopsy + internal biliary drainage	-	-	-	-	-	03	03
Biopsy + external drainage procedure	-	-	-	-	-	07	07
Biopsy only	-	-	-	-	-	32	32
FNAC	-	-	-	-	-	01	01
Total	02	03	05	12	25	60	107

Histology and staging

Cholelithiasis was associated feature in 95 specimens (89.6%). Chronic cholecystitis was found in 83 (78.3%) and acute on chronic cholecystitis was found in 17 patients (16%). Porcelain gall bladder was associated in 39 cases (36.7%). Six patients (5.6%) were explored on the diagnosis of empyema gall bladder. 16 tumors (15%) were diagnosed on postoperative histopathology. Histologically 2 patients (1.9%) had carcinoma in situ as histological surprise. Adenocarcinoma was found in 99 patients (92.5%) whereas 5 patients (4.6%) had squamous cell carcinoma. Table 6 shows various histological features and grading of the tumor. 85 patients (79.4%) presented in Nevin's stage IV and V (Group C). Only 5 patients (4.67%) presented in Group A (stage I) whereas 17 patients (15.8%) belonged to Group B (Stage II and III). Table 7 gives

the Nevin's staging of the tumor along with the sex distribution.

Table 6: Histological features of 107 cancers of gall bladder.

Histology	No.	%
CIS*	02	01.9
Adenocarcinoma	99	92.5
Well differentiated	12	12.1**
Moderately differentiated	46	46.4**
Poorly differentiated	30	30.3**
Undifferentiated	11	11.1**
Squamous cell carcinoma	05	4.6
Adenosquamous carcinoma	01	0.9

*Carcinoma in situ

**Percentage of adenocarcinoma (99)

Table 7: Nevin's staging in 107 cases of carcinoma gall bladder.

Stage	Male	Female	Total	%
CIS*	-	02	02	01.9
I	-	03	03	02.8
II	-	05	05	04.6
III	01	11	12	11.2
IV	04	21	25	23.3
V	17	43	60	56.0
Total	22	85	107	100

*Carcinoma in situ

Morbidity and mortality

Twenty nine patients (27.3%) had various complications. Chest infection requiring antibiotic treatment was the commonest complication observed in 19 patients (17.9%). Wound infection and acute cholangitis was observed in 3 patients each (2.8%). Two patients (1.9%) developed small bowel fistula and wound dehiscence requiring re-exploration. Eleven patients died during the hospital stay with an operative mortality of 10.3% in a mean period of 11.5 days. Table 8 depicts various causes of mortality along with the time period and sex distribution.

Follow up (Table 9)

Complete follow up of 77 patients is available for a variable period. Two patients (2.6%) diagnosed

as having carcinoma *in situ* are still alive after a mean follow up of 5.5 years and are therefore not included in the follow up of remaining 75 patients with invasive carcinoma. Only 1 patients (1.3%) with stage I who had wedge excision of the gall bladder bed on account of preoperative ultrasonographic suspicion of gall bladder cancer survived for four years. The remaining two in Group A died of extensive nodal recurrence and multiple liver secondaries causing proximal obstructive jaundice leading to fatal hepatorenal failure within 3 to 3.5 years period. Seven patients (50%) in Group B developed multiple liver secondaries and extensive portal and periportal lymph node recurrence, 4 patients (28.5%) developed local recurrence involving duodenum and large bowel along with multiple liver secondaries, 3 patients (21.4%) developed portal and periportal lymph node recurrence causing proximal malignant jaundice. All these patients died within 2 years of palliative cholecystectomy. As 58 patients (77.3%) belong to Group C (stage IV & V) the mean survival is 9.6 ± 7.8 months.

Table 8: Hospital mortality with the cause.

Cause	No.	Sex	Period
Acute renal failure	03	F(1) M(2)	7-13 days
Acute hepatic failure	02	F	9-22 days
Coagulopathy (DIC)	02	F	2-5 days
Ac.renal + hepatic failure	01	F	28 days
DVT + pulmonary embolism	01	F	12 days
Uncontrolled haemorrhage	01	M	09 hours
Duodenal fistula	01	F	07 days
Total	11	F(8) M(3)	11.5 days (Mean)

DISCUSSION

Cancer of the gall bladder is one of the lethal malignancies of the gastrointestinal tract. Though the exact incidence of the disease remains unknown, an incidence of 1 to 9 per 100,000 has been reported in the general population^{1,12,13}. The true incidence of this disease in general population is unknown in Pakistan. In a multi tumor study by Pakistan Medical Research Council, carcinoma of the gall

bladder was found to be one of the ten most common malignancies in the females¹. Gall bladder cancer is known to occur more frequently in populations with high incidence of benign gall bladder and biliary tract diseases. In Pakistan cholelithiasis and other benign biliary tract diseases are quite common with an expected high prevalence of gall bladder cancer. The behaviour of this malignancy in our population appears to be similar to those ethnic groups who have higher incidence of gall bladder disease and carcinoma of the gall bladder like American Indians and Hispanics¹.

Table 9: Follow-up of 75 patients with invasive gall bladder cancer.

Group	Stage	No.	%	Survival (range)	Mean
A	I	03	04.0	3.2-4.0 yrs	3.5 ± 0.3 yrs
B	II+III	14	18.6	11 mths-2 yrs	1.2 ± 0.2 yrs
C	IV+V	58	77.3	4-11 mths	0.4 ± 1.2 mths
Overall mean survival months					9.6 ± 7.8

Carcinoma of the gall bladder remains the commonest malignancy of biliary tract and is the second most common malignant tumor of the gastrointestinal tract at this institute. The steady rise observed in the prevalence during the past seven and a half years may be due to increased referrals from various other institutes to us or may be a true increase in the incidence of this lethal malignancy. Multicentre studies from various institutes from all over the country are required with the establishment of a cancer formulary to document the true increase in the incidence. The mean age of 52 years reflects a high occurrence in the younger age group than the Western figure¹ but is in accordance with other studies from IndoPak^{5,7,10,15}. A high female preponderance of 3.8:1 in this study is a general feature of this disease all over the world^{1,3,12-15}. The presenting symptoms usually mimic those of benign gall bladder disease which make the early diagnosis difficult. However the common symptoms observed in this study are similar to those described in the literature^{1,3,5}. All patients with benign gall bladder disease who complain of a recent change in the character of pain which becomes more severe

and persistent losing its periodicity and mild to moderate nature should be aggressively investigated and even advised cholecystectomy. The diagnosis of carcinoma of the gall bladder in early stage is still a challenge. Laboratory investigations are of little help and add only minimally to the diagnostic armamentarium. 70% of our patients had severe hypoalbuminemia, 17% were markedly anemic whereas raised serum alkaline phosphatase levels were found in 58% of anicteric patients. These findings are similar to those of Strauch¹³ and Collier and Blumgart¹⁶. An unexplained weight loss with laboratory findings of anemia, hypoalbuminemia and raised serum alkaline phosphatase levels in a patient with biliary symptoms should arouse the possibility of malignancy with a vigilant workup to diagnose carcinoma of the gall bladder. Abdominal ultrasonography remained the most important radiological investigation with a diagnostic efficacy of 79.4% which is higher than the published reports of 44 to 75%¹⁶⁻¹⁹. Computed tomography diagnostic in 84.2% of our cases is another very reliable and sensitive modality but is expensive and not available everywhere. The contrast studies used in localizing the level of obstruction in jaundiced patients with carcinoma of the gall bladder have the disadvantage of being invasive and nonspecific. A preoperative diagnosis of gall bladder cancer was established in 75.7% of the cases which is partly on account of a high diagnostic yield of ultrasonography and partly because more than two third of our patients presented with an advanced disease. Saving the two patients with carcinoma in situ as histological surprise in which cholecystectomy can be considered as a curative procedure, all patients with resectable disease had palliative cholecystectomy (60.3%). Three patients (2.8%) in Group A in whom cholecystectomy with wedge excision of the gall bladder bed of the liver was also performed on preoperative ultrasonographic suspicion of gall bladder cancer, the mean survival was 3.5 years which is in accordance with the reported figures. This subscribes to the view that wedge excision of the liver is the minimum desirable operative procedure if a preoperative suspicion of carcinoma of the gall bladder is made. In Group B most of the patients developed nodal recurrence causing proximal obstructive jaundice within a mean period of 1.5 years. Hence an extended cholecystectomy which includes lymph node clearance along free edge of lesser omentum is desirable if a preoperative

diagnosis of cancer gall bladder is made or preoperative suspicion of cancer arises. Recently some authors from Japan are reporting more radical procedures including segmentectomy and/or partial hepatectomy both for early as well as advanced gall bladder cancers with long survival figures^{20,21}. Shirai and colleagues even recommended a radical second operation for advanced unapparent carcinoma of the gall bladder²¹. These advanced procedures claimed to be curative in expert hands are probably not feasible in our country as yet on account of late patient presentation and lack of ancillary help in the form of advanced nursing care and critical units facilities. This is reflected in this study as 79.3% of the patients presented in an advanced stage (IV & V). Establishing the specialist referral centers is desirable to provide a potential chance of cure to these patients. Whenever possible an internal biliary drainage procedure (22.7% in this study) is the best palliation for obstructive jaundice in patients with advanced disease. An external drainage (26% in present study) can only be recommended in desperate conditions like carcinomatosis peritonii, high obstruction at porta hepatis or malignant lymphadenopathy occluding the extrahepatic biliary tract. Histologically the associated presence of benign diseases like cholelithiasis (89.6%) and chronic cholecystitis (78.3%) in this study is consistent with the reported figures^{1,3,16}. Similarly the finding of porcelain gall bladder 36.7% of patients is within the reported range of 12.5% to 61%^{1,3}. Adenocarcinoma was the most common malignancy found in 92.5% of the cases followed by squamous cell carcinoma seen in 4.6% patients. This is also in accordance with international data^{1,3,11-13,16}. Keeping in view the advanced stage of the disease at presentation with approximately one third of patients having obstructive jaundice, the morbidity figure of 27.3% and thirty day hospital mortality of 1.38% are remarkably low. This is on account of good preoperative preparation, safe anesthetic cover, surgical expertise and better postoperative care of our patients. As more than two thirds of our patients (79.3%) presented in stage IV and V, the mean survival of 77 patients with complete follow up is 9.6 months which is similar to the reported figures^{1,11,13,16}.

Surgery, whether curative or palliative, is still the treatment of choice for carcinoma of the gall bladder. However, the prognosis in patients with advanced lesions remains poor. A high index of

suspicion is required in all patients of benign gall bladder disease presenting with a recent change in the character of pain. Multicentre studies with the development of a cancer registry and formulary is recommended to determine any true rise in the prevalence of this highly lethal malignancy. However, a high association with cholelithiasis and chronic cholecystitis may justify the indication for cholecystectomy in our country till the development of an efficient screening programme to pick up the lesion at an early stage.

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