

Gallbladder Cancer: Experience of Managing Twenty Consecutive Cases

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Abstract

Background: Gall bladder cancer (GBC) is a burning topic of discussion in the recent era of laparoscopic cholecystectomy. In 1% of patients undergoing cholecystectomy for cholelithiasis, an incidental gallbladder carcinoma is discovered. Reports of laparoscopic cholecystectomies for cholelithiasis have resulted in earlier discovery of gallbladder cancer. So an increasing number of gall bladder cancer patients in earlier stage are now attending physicians and surgeons. These patients have an excellent chance of survival if aggressively and appropriately managed. Radical cholecystectomy is the only potentially curative therapy for this group of patients. It is crucial to make proper treatment decisions early, rather than after a cholecystectomy - an operation that is incomplete except for the earliest stage of the disease. Present study is a small document about the various presentations and management of gall bladder cancer. It will highlight the options available to patients in Bangladesh which is certainly in line with the internationally accepted standard treatment.

Methods: This observational study included patients with confirmed gall bladder malignancy (pre-operative, intra-operative or post-operative) presenting in Hepato-Biliary-Pancreatic Surgery unit (HBPS), of Bangladesh institute of Diabetes, Endocrine and Metabolic Disorders (BIRDEM) Hospital, in 2004-2005. The patients were diagnosed with detail history, proper clinical examinations and appropriate investigations. The disease status was staged and the patients were appropriately counselled. Patients presenting in stage Ib, II and a few stage III patients underwent loco-regional enblock resection of malignant gall bladder with regional hepatic segments (IVB & V), without violating the cystic plate, skeletonization of hepatoduodenal ligament, clearance of fascia, fat of hepatic hilum with/without excision of bile duct followed by Roux-en-Y hepatico/choleangio-jejunostomy, where necessary. Patients in advanced stages underwent some form of palliative procedure. All were regularly followed by a standard protocol.

Results: This study comprise of 20 consecutive cases of GBC. Three (15%) patients presented with histopathological report of gall bladder malignancy after cholecystectomy. Seven (35%) patients underwent curative enmass resection. Thirteen patients (65%) were offered, appropriate palliative procedure. In this study, 35% cases had a disease free survival of five years. These were the cases in stage Ib & II who underwent a curative radical resection (enmass resection or bisegmentectomy after cholecystectomy). The rest of the patients (65%) had very poor survival. They were the patients in Stage III & IV disease who underwent some sort of palliative procedure with or without chemotherapy. The mean survival in these patients was 7.2 months.

Conclusion: With improvements in imaging, staging and hepatic and biliary resection, there is now hope for patients with non-metastatic gallbladder cancer. Radical surgery has been shown to be effective in properly selected patients. It is very important to carry out a proper broad scale study of these cancers in our country. A detailed study will invariably strengthen our efforts to combat this killer disease. More studies need to be done in this context to draw any inference regarding the best way of handling this gloomy condition.

Key words: Gallbladder cancer, enblock resection, enmass resection, cystic plate, radical cholecystectomy.

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Introduction

Gallbladder cancer (GBC) is rare and had been considered as an incurable disease with an extremely poor prognosis. The gloomy outcome of GBC is due to its asymptomatic nature, late presentation, close relation of vital structures (junction of both lobes, portal vein, hepatic artery, bile duct, duodenum, pancreas), abundant lymphatics, multiple regional glands, direct venous drainage to liver, histological incomplete serosa, single muscle layer and lack of submucosa. Thus, GBC spreads early by lymphatic metastasis, haematogenous metastasis and direct invasion into the liver. In addition, it has a high propensity to seed the peritoneal surfaces after tumor spillage and cause tumor implants in biopsy tracts, abdominal wounds and peritoneal cavity.^{1, 2} However, there is good chance of survival for those who present in earlier stages (stage Ib, II, selective III). Early GBC needs radical cholecystectomy, which is the only option and can give patients a survival benefit. This study aims on the various presentations of GBC and the diverse options of surgical managements available in dealing with the condition.

Methods

This was an observational study, carried out in HBPS unit, BIRDEM Hospital, Dhaka. The patients were referred to this unit by different surgeons and physicians from various hospitals all over Bangladesh. They either received advice or treatment during the period of January 2004 to December 2005. Twenty patients with confirmed gall bladder malignancy (pre-operative, intra-operative or post-operative) were selected consecutively in this study irrespective of age, sex and status of diabetes.

Patients with radiological suspicion of early GBC were not attempted for histological confirmation preoperatively. Rather arrangements were made for frozen section biopsy/imprint cytology per-operatively, which confirmed the diagnosis. Enmass resection of seg IVB, V and gallbladder, without violating the cystic plate, skeletonization of hepatoduodenal ligament, with or without excision of bile duct and Roux-en-Y hepaticojejunostomy was done. Specimens were sent for histopathology.

Patients presenting after cholecystectomy, with histological report of GBC, presented 3 to 10 days after surgery. They were all carefully assessed by relevant

history, clinical examination and review of all previous investigations. Operation notes were thoroughly studied and where possible the initial operating surgeon was contacted to gather all information about any difficulty encountered during cholecystectomy, whether gall bladder was perforated during the procedure, which port was used for gall bladder extraction and if endobag was used for extraction. All these patients were investigated with computed tomography (CT) and any sign of metastasis looked for. These patients underwent resection of seg IVB and V together with full thickness excision of the port through which gall bladder was extracted. Specimen of the liver and port were sent for histopathology.

Patients in advanced stages (stage III or IV disease) underwent some sort of palliative procedure. Most of them underwent a triple bypass operation. There were several post-operative complications. Stage Ib patients were not sent for chemotherapy. All the rest were referred to oncologist for chemotherapy. Five of the advanced malignancy cases refused to take any further treatment considering the cost and poor outcome of treatment.

All the patients were followed-up regularly according to following schedule: 3 monthly – first year, 6 monthly – second year, yearly – upto 5 years. In each follow-up visit patient's detail history was taken, thorough physical examination was performed and few investigations suggested- liver function tests, CA 19.9, ultra sonogram of whole abdomen and other investigations if required. All data were analyzed and results shown below.

Results

Out of twenty patients, seven (35%) were male and thirteen (65%) female. Age range was 35 yrs to 73 yrs. They had various presentations (Table I). Most (50%) patients presented with palpable mass of variable size in right hypochondrium and/or epigastrium +/- obstructive jaundice +/- gastric outlet obstruction. These patients were all cases of advanced gall bladder malignancy.

Liver function tests were done in all patients (Table II). Interestingly, some non-icteric patients had raised alkaline phosphatase and prolonged prothrombin time. Ekeven patients (55%) had raised CA19.9 level, while 5 patients (25%) had raised CEA level. All the patients had an ultrasonogram done as their first imaging study.

Various findings were found (Table-III). In addition, 16 patients (80%) had associated gall stones. Computed Tomography (CT) was done in all the patients and decision, whether a patient is eligible for a possible curative surgery or not, was made depending on its findings. Nine patients (45%) showed no sign of extensive regional or distant metastases and were selected for curative resection. The rest of the eleven (55%) patients showed evidence of extensive regional or distant metastases in CT scan and were selected for image guided fine needle aspiration cytology (FNAC) to confirm the diagnosis. After confirmation, appropriate palliative procedure was offered to the patients. Details of management shown in Table IV.

Post-operative complications are shown in Table V. One patient (5%) developed hepatorenal shut down and expired on 8th POD, in spite of all efforts. The other complications were managed successfully. Histopathological examination of specimen showed different stages of disease (Table VI). Two third of the patients were in unresectable stage (Stage III and IV).

In this study, 35% cases had a disease free survival of five years. These were the cases in stage Ib & II who underwent a curative radical resection (enmass resection or bisegmentectomy after cholecystectomy). The rest of the patients (65%) had very poor survival (Table VII). They were the patients in Stage III & IV disease who underwent some sort of palliative procedure with or without chemotherapy +/- radiotherapy. The mean survival in these patients was 7.2 months.

Table I Clinical presentations of the patients (n=20)

Presentation of patients	Frequency	Percentage
Cholecystectomy specimen shows malignancy	3	15
Flatulent dyspepsia with suspicious USG findings of GB	7	35
Palpable epigastric/ hypochondriac mass+/- obstructive jaundice +/- gastric outlet obstruction	10	50

Table II Results of liver function tests of the patients (n=20)

Parameters	Frequency	Percentage
Hyperbilirubinaemia	7	35
Raised ALT	7	35
Raised AST	7	35
Raised alkaline phosphatase	10	50
Reduced albumin	7	35
Prolonged prothrombin time	8	40

Table III Ultrasonogram findings of the patients (n=20)

USG findings	Frequency	Percentage
Thick walled GB	1	5
Single gall bladder polyp (diameter- 13 mm)	1	5
Porcelain gall bladder	1	5
Polypoid mass in the lumen of GB	4	20%
Inhomogeneous mass replacing all or part of the gallbladder with variable extension into the liver & surrounding structures	13	65%

Table IV Management of the patients (n=20)

Procedure done	Frequency	Percentage
1. Hepaticojejunostomy & gastrojejunostomy & entero-enterostomy & biopsy	5	25
2. Enmass resection of seg IVB & V & gallbladder	4	20
3. Bisegmentectomy & port excision	3	15
4. Gastrojejunostomy & biopsy from gallbladder/ lymph node/ hepatic metastases	2	10
5. ERCP with endoscopic internal biliary drainage	1	5
6. MRCP guided percutaneous external biliary drainage	1	5
7. External biliary drainage & gastrojejunostomy & biopsy	2	10
8. Laparotomy & biopsy	2	10

Table V Post-operative complications and their management (n=20)

Post-operative complications	Frequency	Percentage	Management of complications
Hepatorenal shut-down	1	5	Haemodialysis
Bile leakage	2	10	-NPO, antibiotics, fluids-Relaparotomy & external biliary drainage followed by hepaticojejunostomy after 6 weeks
Wound infection	6	30	Regular dressing & appropriate antibiotics followed by secondary closure
Incisional hernia	2	10	Conservative

Table VI Histopathological Report (n=20)

Histopathological Report	Frequency	Percentage
Stage IV : Metastatic adenocarcinoma in liver or mesenteric nodes or para-aortic lymph nodes.	10	50
Stage III : Tumor cells have traversed the whole thickness of gall bladder wall and involved >2cm of liver tissue &/or involved hepatoduodenal lymph node.	3	15
Stage II : Tumor cells have infiltrated throughout the muscle coat and reached the serosa.	3	15
Stage Ib : Tumor cells have infiltrated the muscle coat but not reached the serosa.	4	20

Table VII Survival (n=20)

Survival	< 6months	> 6months< 1year	> 1year< 2years	> 2years
No. of patients	7	5	1	7

Discussion

D.E. Stoll first described GBC in 1778.³ It is the most common biliary malignancy and 5th common malignancy of gastrointestinal tract. It is also the most

common cause of malignant obstructive jaundice. The incidence of GBC parallels the prevalence of gall stones in the population and women are at 2- 4 fold increased risk. The incidence is extremely variable by

geographical, regional, racial and ethnic groups. Majority of the patients have locally advanced / metastatic disease at presentation.^{3, 4} This study comprises of 20 consecutive cases of GBC. Incidence in female was almost double. In a study by Lazcano et al, female preponderance was far higher (Male: Female ratio is 1:4).⁵ Stone is found in 75-90% of gallbladder cancer specimens.^{5, 6} Our series also showed 80% with associated gallstone. Whether gall stone and gall bladder cancer is simply an association or whether they have a cause effect relationship is still not established.⁵

In our study the most common symptom at presentation was jaundice (50%) compared to other American or Japanese studies where commonest symptom was abdominal pain.^{7, 8} Possibly, patients present with more advanced stage in our country. Two third of the patients presented in stage III and IV where there was no scope of curative surgery. Adson M reported that three fourth of patients present with cancer beyond the scope of resection due to metastatic or locally advanced disease.⁹ The difference is possibly due to the fact that many advanced GBC cases reported to us in out-patient department. But when counseled about the poor outcome, many refused to get admitted in hospital and so were not included in this study. In this series, 15% presented after laparoscopic cholecystectomy. This figure is comparable to study by Clair et al where approximately 15% of gallbladder carcinomas were detected incidentally at microscopic examination of cholecystectomy specimen.¹⁰

All the patients with advanced GBC had altered liver function tests. Those in stage Ib and II had normal liver function. Only 11 patients (55%) had raised CA19.9 level, while 5 patients (25%) had raised CEA level in this study. In comparison 26 out of 42 patients (62%) showed elevated CEA and CA 19.9 in a study from Berlin.¹¹

Ultrasonogram was the basic imaging done for all our patients. Patients in Stage III and IV showed gall bladder replaced by mass. Those in stage Ib and II mostly had polypoid mass in the lumen of gall bladder. Our findings were consistent with other large international studies where advanced cases (50%) were seen as an inhomogeneous mass replacing whole or part of the gallbladder^{12, 13} and often extending into the porta to produce features of obstructive jaundice. Resectable

GBC patients (27%) showed polypoid mass or diffuse thickening of the gallbladder wall.¹⁴

In this study, 7 patients (35%) underwent curative surgery. They were all either in stage Ib or stage II. All of these patients are well after 5 years of definitive resection and none have developed recurrence so far. Different studies performing an extended cholecystectomy in T1b patients have also shown a 5-year disease free survival of 100%.^{4, 15} According to publications, T2 tumors are those most likely to benefit from an extended cholecystectomy. Most large series showed a 5 year survivals of 60% - 100% of patients undergoing an extended resection.^{4, 16-18} In our study post laparoscopic cholecystectomy cases had a similar outcome corresponding to the stage of disease. But, in one study, GBC was seen to recur more rapidly after laparoscopic cholecystectomy than after open cholecystectomy.¹⁹ It is thought that inadvertent manipulation at cholecystectomy (open / lap) leads to stage migration. Grasping the fundus of GB (60% site for GBC) and dissection of the cystic plate during cholecystectomy lead to dissemination. Furthermore during laparoscopic cholecystectomy in GBC setting, increased exfoliation of malignant cells occur due to manipulation and traction of unsuspected impalpable malignancy, contact of tumour laden instruments to different abdominal organs, port site implantation (by instruments/ cancerous GB), accidental perforation of cancerous GB, physical effects of closed continuously circulating pneumoperitoneum, early peritoneal and abdominal spread – all leading to tumour dissemination giving poorer prognosis. So survival is less in post cholecystectomy diagnosis of GBC.²⁰ Tumor is also documented to recur in the laparoscopic port tracts even if surgical resection of the port site is performed at subsequent hepatic resection for attempted cure.¹⁴ Recurrent tumor may appear as a mass along the anterior abdominal wall with extension into the subsequent omental fat.²¹ These observations justify the need to identify correctly, findings suggestive of GBC on preoperative imaging when elective laparoscopic cholecystectomy is planned. All patients having muscle invasive adenocarcinoma were sent for adjuvant chemotherapy.

All studies show, most GBC patients are unresectable at presentation. The most common symptoms to palliate include pain, jaundice and bowel obstruction. In this

study, 13 patients (65%) were in stage III and IV and had some sort of palliative procedure. Palliation of jaundice is done by endobiliary prosthesis, Triple bypass operation (hepatico-jejunostomy, gastro-jejunostomy and entero-enterostomy) or external biliary drainage depending on the level and extent of biliary obstruction. Triple bypass can relieve the bowel obstruction as well. All the procedures were effective in relieving suffering from symptoms but gave no survival benefit. No attempt for a more extensive surgery for cure was taken. These patients had a median survival of 7.2 months in our study. Samuel PS et al reported a median survival of 7 months for stage III & IV in spite of all attempt for an extensive curative surgery (right hepatectomy with biliary tree resection, extended right hepatectomy with biliary tree resection, pancreaticoduodenectomy).²² Other studies showed the median survival for patients with unresectable disease is 2-4 months with a 1 year survival of less than 5%.²³ Cause of mortality are metastatic disease, roux loop blockage, abdominal seedling and systemic metastasis.

Conclusion

The overall picture of GBC is a dismal one, as almost 2/3 rd of the patients present at a late stage. All that can be done for these patients is a palliative procedure. However, there is now hope for patients with non-metastatic GBC. Radical surgery has now been shown to be effective in properly selected patients. Any physician, who encounters a patient with a soft tissue mass in the gallbladder, should further evaluate the patient with a CT scan. If no sign of metastases is found, a preoperative FNAC to confirm the diagnosis should never be advised. Rather, per-operative frozen section biopsy and imprint cytology arrangements should be made. On table tissue diagnosis and subsequent appropriate decision is the key factor for the management of early GBC (stage I and II) cases. During cholecystectomy (open / laparoscopic), if GBC is suspected, with no sign of metastases elsewhere, cholecystectomy procedure must be abandoned. No attempt should be taken to take a biopsy from the suspected lesion. Patients with incidentally discovered malignancy of cholecystectomy specimen should be properly counseled and sent promptly to a specialized center for definitive resection. In conclusion, all medical professionals treating gallbladder disease must have clear conception about diagnosis and proper surgical

treatment of GBC at the time of initial diagnosis. A rational approach from the time of encounter of patient can cure a GBC patient and save him from a death sentence.

Conflict of interest: Nothing to declare.

References

1. Fong Y, Brennan MF, Turnbull A, Colt DG, Blumgart LH. Gallbladder cancer discovered during laparoscopic surgery-potential for iatrogenic dissemination. *Arch Surg* 1993; 128:1054-56.
2. Merz BJ, Dodge GG, Abellera RM, Kiskan WA. Implant metastasis of gallbladder carcinoma in situ in a cholecystectomy scar: a case report. *Surgery* 1993; 114:120-24.
3. Michael DA, William RJ. Tumors of the gallbladder. In: Leslie HB, Jacques B, William RJ, Ronald PD, William CC, Markus WB, et al, editors. *Surgery of the Liver, Biliary Tract and Pancreas*. 4th ed. Saunders Elsevier; 2007. vol 1 p. 764-79.
4. Leslie HB, Lucy EH. Surgical and radiologic anatomy of the liver, biliary tract and pancreas. In: Leslie HB, Jacques B, William RJ, Ronald PD, William CC, Markus WB, et al, editors. *Surgery of the Liver, Biliary Tract and Pancreas*. 4th ed. Saunders Elsevier; 2007. vol 1 p. 12-14.
5. Lazcano-Ponce EC, Miquel JF, Muñoz N, Herrero R, Ferrecio C, Wistuba II, et al. Epidemiology and molecular pathology of gallbladder cancer. *CA Cancer J Clin* 2001; 51:349-64.
6. Serra I, Diehl AK. Number and size of stones in patients with asymptomatic and symptomatic gallstones and gallbladder carcinoma. *J Gastrointest Surg* 2002; 6:272-73.
7. North JHJ, Pack MS, Hong C, Rivera DE. Prognostic factors for adenocarcinoma of the gallbladder: an analysis of 162 cases. *Am Surg* 1998; 64:437-40.
8. Chao TC, Greager JA. Primary carcinoma of the gallbladder. *J Surg Oncol* 1991; 46:215-21.
9. Adson M. *Advances in Diagnosis and Surgical Treatment of Biliary Tract Diseases*. Chicago: Year Book Medical Publishers; 1983.
10. Clair DG, Lautz DB, Brooks DC. Rapid development of umbilical metastases after laparoscopic cholecystectomy for unsuspected gallbladder carcinoma. *Surgery* 1993; 113:355-58.
11. Frauenschuh D, Greim R, Krase E. How to proceed in patients with carcinoma detected after laparoscopic cholecystectomy. *Langenbecks Arch Surg* 2000; 385:495-500.
12. Bach AM, Loring LA, Hann LE, Illescas FF, Fong Y, Blumgart LH. Gallbladder cancer: can ultrasonography evaluate extent of disease? *J Ultrasound Med* 1998; 17:303-9.
13. Franquet T, Montes M, Ruiz de AY, Jimenez FJ, Cozcolluela R. Primary gallbladder carcinoma: imaging findings in 50 patients with pathologic correlation. *Gastrointest Radiol* 1991; 16:143-48.

14. Wibbenmeyer LA, Wade TP, Chen RC, Meyer RC, Turgeon RP, Andrus CH. Laparoscopic cholecystectomy can disseminate in situ carcinoma of the gallbladder. *J Am Coll Surg* 1995; 181:504-10.
15. Shirai Y, Yoshida K, Tsukada K, Muto T, Watanabe H. Radical surgery for gall bladder carcinoma: long term results. *Ann Surg* 1992; 216:565-68.
16. Fong Y, Jarnagin W, Blumgart LH. Gallbladder cancer: comparison of patients presenting initially for definitive operation with those presenting after prior non-curative intervention. *Ann Surg* 2000; 232:557-69.
17. Suzuki S, Yoshihiro Y, Kiyotaka K, Keisuke I, Shigeyasu O, Masaki A et al. Appraisal of surgical treatment for pT2 gall bladder carcinomas. *World J Surg* 2004; 28:160-65.
18. Toyonaga T, Chijiwa K, Nakano K, Noshiro H, Yamaguchi K, Sada M, et al. Completion radical surgery after cholecystectomy for accidentally undiagnosed gall bladder carcinoma. *World J Surg* 2003; 27: 266-71.
19. Winston CB, Chen JW, Fong Y, Schwartz LH, David M. Panicek DM. Recurrent gallbladder carcinoma along laparoscopic cholecystectomy port tracts: CT demonstration. *Radiology* 1999; 212:439-44.
20. Ciulla A, Romeo G, Genova G, Tomasello G, Agnello G, Cstronovo G. Gallbladder carcinoma late metastases and incisional hernia at umbilical port site after laparoscopic cholecystectomy. *G Chir* 2006 May; 27(5):214-16.
21. De Aretxabala X, Roa IS, Burgos LA. Curative resection in potentially respectable tumors of the gallbladder *Eur J Surg* 1997; 163:419-26.
22. Shih SP, Schulick RD, Cameron JL, Lillemoe KD, Pitt HA, Choti MA, et al. Gall bladder cancer: The Role of Laparoscopy and Radical Resection. *Ann Surg* 2007 ; 245:893-901.
23. Oertili D, Herzog U, Tondelli P. Primary carcinoma of the gallbladder: operative experience during a 16 year period. *Eur J Surg* 1993; 159:415-20.