

Clinicopathological study of gall bladder carcinoma: Our experience from Patan Hospital, Patan Academy of Health Sciences

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Abstract

Introduction: Gall bladder carcinoma is not a common disease. The overall prevalence is low worldwide. It is a highly malignant tumor with a poor prognosis. The outcome of gallbladder carcinoma is poor, and the overall 5-year survival rate is less than 5%. The carcinoma gall bladder is 2-6 times more common in females compared to males and its incidence increases with increasing age. Aggressive surgical management and preoperative adjuvant therapy have helped to prolong survival in patients with gallbladder cancer. We conducted a study with an aim to evaluate the clinicopathological aspect of the disease in patients of gall bladder cancer managed in our surgical department.

Methods: Data were recorded retrospectively by reviewing the charts of the patients who were diagnosed and treated for carcinoma gall bladder in Patan hospital from Aug 2017 to Aug 2019.

Results: Thirty patients were included in the study. Twenty (66.7%) were female and ten (33.33%) were males. Age ranged from 36 to 83 years with the median age of presentation at 63.5 yrs. Curative treatment was possible in 43.33% of the patient, among them 12 had radical surgery and one had cholecystectomy alone for the T1a stage. All other (56.6%) required palliative treatment. One patient developed liver metastasis within six months of radical excision.

Conclusions: The majority of the patients present with an advanced disease which makes it less chance for curative surgical resection. Since only palliative care is possible in an advanced stage, early detection and curative treatment are advisable.

Keywords: Extended cholecystectomy; Gall bladder carcinoma; Radical Cholecystectomy

Introduction

Gall bladder carcinoma (GBC) is not a common disease. Overall prevalence is low worldwide, but it is still the most common cancer of the biliary system. After colon cancer, the carcinoma gall bladder is the 5th most common gastrointestinal malignancy.¹ It is a highly malignant tumor with a poor prognosis. The overall 5-year survival rate is less than 5%. In early-stage disease, a 5-year survival rate of 75% can be achieved if stage-adjusted therapy is

performed.² Seventy percent are incidentally discovered by the pathologist incidental gallbladder carcinoma (IGBC). Preoperative recognition or suspicion of GBC is difficult and only a third of them are recognized preoperatively. Aggressive surgical management and preoperative adjuvant therapy have helped prolong survival in patients with gallbladder cancer.³ Radical re-resection (completion extended cholecystectomy) in cases of incidental or occult GBC is important to achieve surgical clearance and proper staging.⁴

The carcinoma gall bladder is 2-6 times more common in females compared to males and its incidence increases with increasing age. More than 75% of the patients suffering from GBC are older than 65 years.⁵

The etiology of carcinoma is still not clear. Incidence is high among patients with gallstone disease, especially patients with large and longstanding gallstones are at higher risk.⁶ Reports have shown an association between a porcelain gallbladder, abnormal pancreaticobiliary junction (APBJ) and other biliary disorders including choledochal cyst, primary sclerosing cholangitis, Mirrizi's syndrome.⁷ Adenocarcinoma is the most common histological subtype (90-95%) of the gallbladder carcinoma. In contrast, squamous cell carcinomas and adenosquamous carcinomas are rare.⁸

We conducted a study with an aim to evaluate the clinicopathological aspect of the disease in patients of gall bladder cancer managed in our surgical department.

Methods

An institution-based retrospective study was performed by reviewing the data from Aug 2017 to Aug 2019 in patients having GBC. Institutional review committee approval was obtained. Medical records were retrieved by searching hospital-based computer databases using ICD 10 code "C3". Data were recorded in a pre-formed Performa by reviewing the charts retrospectively. Patient demographics, duration of symptoms, presenting symptoms, associated symptoms, Pre-treatment diagnostic methods, findings on USG and CT, FNAC if done in advanced diseases, level of Ca 19.9 and CEA, record of unsuspected / incidental / missed GBC, presence of gallstones or choledochal cyst, histological tumor type, Surgical clearance in case of surgery with curative intent, pathological details, type of surgery, postoperative adjuvant treatment, palliative treatment, recurrence and follow up were recorded.

Patients were included if they had a preoperative diagnosis of overt carcinoma gall bladder by ultrasonogram (USG) and contrast-enhanced computerized tomogram(CECT), or preoperative Fine needle aspiration cytology (FNAC) if the tumor is deemed unresectable on the basis of radiology. Other patients with unsuspected GBC who were diagnosed intraoperatively or incidentally at the histopathological examination were included in the study.

All the patients were managed at the department of surgery, Patan hospital, Nepal.

Last follow up was recorded and duration was calculated

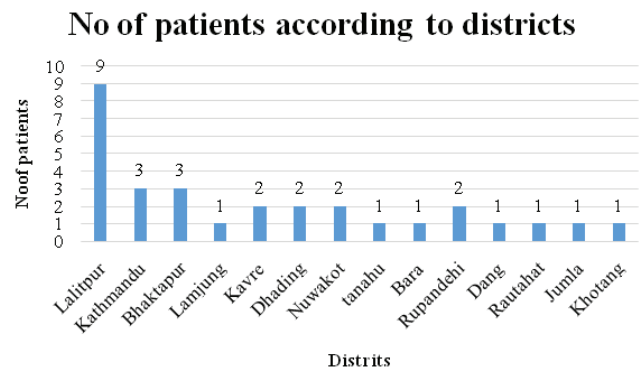
after the date of initial diagnosis. Recurrence of the operated patients was said if there was an obvious diagnosis of recurrence at the time of the last follow up.

Data were analyzed using SPSS 20. Continuous data were presented as mean/median with range and categorical data were presented as a percentage.

Results

A total of 30 patients were analyzed. According to the political divisions of Nepal, the majority of the patients were from Lalitpur district (30%) and according to geographical distribution, most patients were from the Hilly region (76.6%) (Figures 1 and 2). Twenty (66.7%) were female and 10 (33.3%) were male. Age ranged from 36 to 83 years with a median age of presentation at 63.5 yrs.

Figure 1: Patients distribution according to districts



Geographical distribution of patients

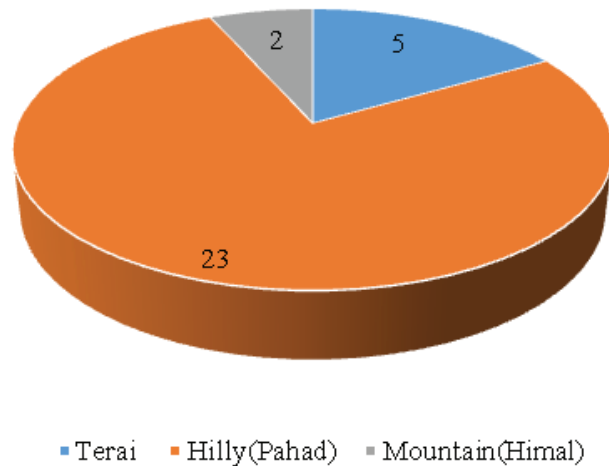


Figure 2: Patient distribution according to geographical regions.

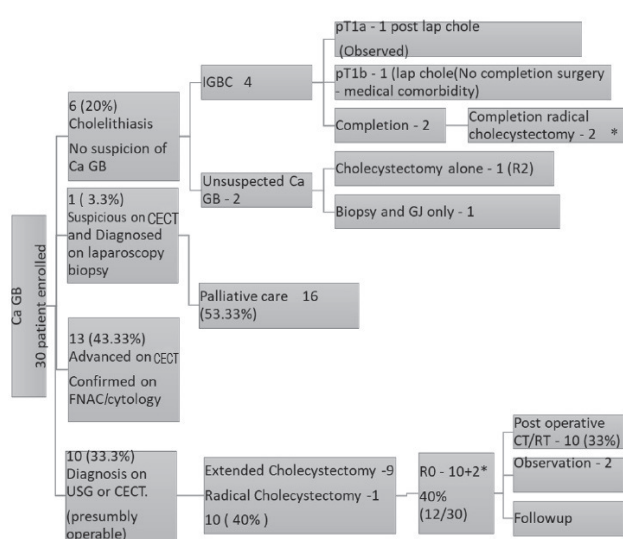
The mean duration of symptoms before presenting to our institute was 115 days (5 days to 1 year). The patients' presentations were very varied with combinations of various symptoms and findings (Table 1).

Table 1: Presenting symptoms

Symptoms	No of patients	Percentage
Pain abdomen	18	60%
Pain abdomen with a palpable mass	6	20%
Weight loss	3	10%
Jaundice	2	6.7%
Ascites	1	3.3%
Weight loss and jaundice	7	23.3%
Weight loss and ascites	1	3.3%

Figure 3 shows the management flowchart of the patients enrolled in this study.

Figure 3: Flow chart of patient management



CECT- Contrast Enhanced Computed Tomography, CT-chemotherapy, RT-radiotherapy, *= patients included in R0 resection

Ten (33.33%) patients had overt diagnosis by means of radiological findings mostly USG and CT scans and were resectable radiologically. Thirteen patients (43.33%) who had an advanced disease on the basis of CT scan, underwent FNAC for diagnosis and malignant cells were confirmed on cytological examination. One patient (3.33%) was diagnosed as an advanced disease by CT and staging laparoscopy.

Six patients (20%) did not have any obvious preoperative diagnosis of GBC by clinical and radiological examination. Among these, two had unsuspected GBC detected intraoperatively and confirmed later on biopsy findings. Incidental gall bladder carcinoma (IGBC) was found in 4 patients of routine cholecystectomy, among them two patients underwent completion extended cholecystectomy.

Out of 30 patients, 27 have been tested for Ca 19.9 and CEA. Ca 19.9 was found to be elevated (more than 37 U/ml) in 18 (66.6%). Seven patients had CEA elevation. Both of these markers did not correlate with the disease stage; however, it was observed that Ca 19.9 was elevated in most of the advanced cases.

Gall stones were associated with 19 (63.3%) of the patients. Among 30, only 17 (56.6%) patients had undergone surgery, of which only 12 (40%) patients underwent radical resection. The other 13 patients (43.33%) got non-surgical treatment. Types of surgery are tabulated in Table 2.

Table 2: Types of surgery

Types of surgery	No of patients (17)
Extended cholecystectomy	9 (60%)
Radical extended cholecystectomy (Extrahepatic bile duct excision with HJ)	1(6.6%)
Completion extended cholecystectomy for IGBC	2(13.3%)
Non-curative surgery (R2) (To palliate symptoms)	2(13.3%)
Cholecystectomy alone (T1a and T1b on biopsy)	1(6.6.3%)
Open and close with biopsy only (Locally advanced)	1(6.63%)
Staging Lap and biopsy only for peritoneal metastasis	1(6.63%)

Thirteen patients who underwent curative resection had R0 resection including the case of ICGB pT1a. Complete histopathological detail was available in 15 patients. The most common histological type was adenocarcinoma of biliary type 11/15 (73.33%) followed by adenocarcinoma of intestinal type 3/15 (20%). One patient had adeno-squamous type and there was no histological description on 15 patients because they were diagnosed on the basis of radiological findings with FNAC or biopsy only in advanced disease.

In patients who had undergone surgery, pathological T stage (pT) were evaluated. pT stage was available in 15 out of 17 patients. Three patients were excluded in

whom, two had biopsy only and one patient had palliative surgery (gastrojejunostomy and biopsy). Table 3. Out of 15 histopathology examinations, 4 had a positive lymphovascular invasion and 3 had a perineural invasion.

Table 3: Pathological T stage

T stage	No of patient (n=15)	Percentage
pT1a	1	6.66%
pT1b	1	6.66%
pT2	8	53.33%
pT3	4	26.66%
PT4	1	6.66%

The mean number of lymph nodes harvested during radical surgery was 6.2 (ranging from 3- 10). The positivity of nodes was reported on the basis of the number of lymph nodes involved in histopathology. The complete nodal staging was available in a patient who underwent curative surgery. Results of 12 patients with curative surgery were analyzed. Table 4.

Table 4: Pathological N (pN) stage among 12 patient who had extended cholecystectomy

Nodal stage (pN)	No of Patients (n=12)	Percentage
N0 (No nodal involvement)	9	75
N1 (1-3)	1	8.3
N2(more than 4)	2	16

M (Metastatic) stage was evaluated on the basis of either radiology and FNAC or on the pathological specimen if available. Table 4. All 30 patients were analyzed.

Table 5: Metastasis (M stage)

M stage	No of patient	Percentage
M0	14	46.66 70%
M1 (liver)	4	13.3%
M1 (peritoneal)	3	10%
M1(distant)	2	6.7%
MX	7	23.33

Ten (33.3%) got post-operative adjuvant treatment (Chemoradiation) after evaluation by the oncologist. Sixteen(53.33%) had palliative treatment among which 3

patients had palliative percutaneous transhepatic biliary drainage (PTBD) for deep jaundice and itching. Rest of the patient were kept only on follow-up. One patient of IGBC who had T1b stage did not go for radical surgery because of medical co-morbidity and old age.

Recurrence was evaluated for the patient who underwent resection with curative intent. One out of 14 developed liver metastases within six months of surgery. Follow up duration ranged from 1 week to 2 years. (median was 8 weeks only). Patients sent for palliative treatment and for adjuvant treatment had short follow up because of a short stay in hospital with few visits in Outpatient Clinic after discharge.

Discussions

Gallbladder carcinoma is the most common cancer of the biliary tract. Simple cholecystectomy is adequate for mucosal disease (T1a) and it is found in 0.2%-3% of all cholecystectomies.^{9,10} Ghimire P reported 10 (1.28%) of GBC out of 783 cases of routine cholecystectomy for gallstones in Nepal.¹¹ Gallbladder carcinoma is suspected preoperatively in only 30% of all patients.⁹ The other 70% of cases are either suspected in the intraoperative period and/or confirmed postoperatively in histopathological examination. These cancers are termed incidental gallbladder carcinomas (IGBC). Only 15-47% of the preoperatively known gallbladder carcinomas are suitable for resection.¹² The majority of symptomatic patients with GBC have an incurable tumor.

Mortality related to GBC is very high with an overall 2-year survival rate of 39.58% and it is the most common cause of death from biliary malignancies.¹³ It is usually detected at an advanced stage due to its non-specific symptoms.¹⁴

In India, cancer of gallbladder shows varying geographic distribution. The incidence is higher in Delhi as compared to South India. GBC ranks among the first five common cancers in females in India.⁶

Shukla et al in his report stated that Northern India falls in the endemic zone (West Bihar and Eastern Uttar Pradesh) where it is the third most common malignancy of the alimentary tract. ¹⁵ Terai region of Nepal has similar geography and culture in comparison to northern India but we were unable to compare our results with their report as most of our patients are not from the Terai region. This may be because our institute is located in Kathmandu valley and we cater most of the patients from the surrounding hilly region. Our study shows 76.6% of patients are from the hilly region.

In this study, females were predominantly affected by a male: female ratio of 1:2. Elderly females were mostly affected with an overall median age of 63.5 years. Mishra et al in 2012 reported that GBC is two to six times more common in women than men.⁵

GBC either remains asymptomatic for a long time or presents with very non-specific symptoms. Commonly, symptoms are related to associated gallstones. In our study, 63.3% of diagnosed GBC had concomitant gall stones. The study done by Hamdani et al reported the presence of gallstones in 159 (80.3%) in initial radiological evaluation.¹⁶ We found that the most common presenting symptom was abdominal pain mostly located in the epigastrium and right upper quadrant in 60 % of patients, followed by abdominal mass along with pain in 20% and weight loss in 36 % patients. Few advanced diseases presented with jaundice and ascites. This was consistent with results reported in other studies.^{13,17,18}

In the current study, USG and CT scan were able to elench diagnosis or suspect GBC in 24 (80 %) patients. The majority of USG findings were increased wall thickness. These patients were subjected to CT examination. The accuracy of preoperative diagnosis on conventional computed tomographic (CT) imaging alone has ranged from 52.6% to 71.7%.¹⁹ The majority of our patients had been tested for CA 19.9. Yunfeng reported that the sensitivity of CA 19.9 was 71.7% for the diagnosis of GBC and he stated that CA19.9 expression level were independent prognostic factors.²⁰ In our study, CA 19.9 was elevated in 18 out of 27 (66%).

Surgery is the mainstay of treatment and only chance of cure in gall bladder carcinoma because of its high recurrence and poor prognosis. In our study, only 12 patients (40%) had undergone radical resection with curative intent and others were either metastatic or locally advanced who required palliative treatment. Among curative resection, 60 % of patients had extended cholecystectomy and 6.6% of patients had radical extended resection with R0 resection achieved in all. Eun Hong in his report of 106 patients, curative resection was conducted in 75 patients (70.8%), in which 61 patients required extended cholecystectomy, bile duct resection and choledochojunostomy in 5 patients, and major hepatectomy and other organ resection in 11 patients.²¹

The most common type of GBC was adenocarcinoma of biliary and intestinal-type (93.33% together) in this study, which is in accordance with reports from other studies.⁸ In our study, 4 had lymphovascular and 3 had a perineural invasion. Various studies have reported that the presence of

this finding correlates with poor prognosis. Kohei Shibata in his study stated that lymphatic invasion well reflects the malignant phenotype of stages T1b–T3 Gall bladder cancer. This is the basis to advocate additional radical resection for Incidental gall bladder carcinoma.²² Perineural invasion is common in advanced gallbladder carcinoma and has a significant negative impact on patient survival. Yamguchi reported that the overall incidence of perineural invasion was 71 % and extrahepatic bile duct invasion was the only significant factor correlated with perineural invasion.²³

Our study results showed that among curative resection, 66.66% of patients were in stage T1 & T2 and 26.66% in stage T3. All of them had curative surgery with R0 resection. Average nodal harvest was 6. Among the patient who had undergone nodal dissection, 75 % did not show nodal metastasis. The pathological evaluation of a minimum number of 6 lymph nodes is critical for stratifying recurrence risk and cancer-specific survival.²⁴

We noticed that the majority of patients with metastasis either had liver involvement or ascites. The overall advance disease was detected in 53.33%. These patients only had a chance for palliative treatment. Among them, many required palliation for pain and ascites. Three patients required PTBD to palliate their itching. Amit Gupta in his study reported that the most common symptom that needed palliation was a pain (92%) and obstructive jaundice (46.7%).¹⁷

Although our follow-up was not optimal, we identified one recurrence with liver metastasis within six months of extended cholecystectomy who had a histopathology report of T2N0M0 with R0 resection. This patient had also received postoperative adjuvant treatment. Our study had limitations in regards to follow up to identify recurrence. The patient who had gone for chemoradiation therapy had poor follow up in our institute. Antonious reported in his study of 76 patients, 35.0% had experienced a recurrence (locoregional 15.8%; distant 65.8%; locoregional and distant 18.4%). The median time to recurrence was 9.5 months.²⁵

Overall 33% of the patients received adjuvant treatment in our study. Mohamad in his study of 251 patients who underwent surgical resection for stage I-III, concluded that patients who underwent extended radical resection had better overall survival. Adjuvant therapy had no statistically significant effect on overall survival or disease-free survival on the overall population. However, in stage IIIB, patients receiving adjuvant therapy had better overall survival and disease-free survival.²⁶ Tae hyun kim in their study of resected 151 patients concluded that adjuvant

chemoradiotherapy may improve the loco-regional recurrence-free survival and recurrence-free survival and subsequently improve overall survival in lymph node-positive resected GBC.²⁷

Conclusion

Patients with GBC present late due to non-specific abdominal symptoms and association with gall stones. The majority of the patients present with an advanced disease which results in less chance for curative surgical resection. Since only palliative care is possible in an advanced stage, early detection and curative treatment are recommended.

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Conflicts of interest: None

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