

# Predictors of long term survival after surgical resection in carcinoma gall bladder

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## Abstract

**Background-**Carcinoma of the gallbladder is known to be associated with a dismal prognosis, with majority of patients presenting at late stages. Controversies still exist regarding the optimal management and the extent of surgery. **Methods-** This study was done at a tertiary hospital in an endemic region for cancer gallbladder (north Indian Gangetic belt). All patients operated for cancer gallbladder between January 2006 and January 2011 were included, with details of clinical presentation, survival analysis and identification of prognostic factors. **Results-** Of the total 252 patients of carcinoma gall bladder identified during the study period, 71 patients were explored surgically. Curative resection was achieved in 27 patients with 10 long term survivors (disease free interval >3years). Nodal status, TNM stage and bilirubin levels affect survival. Majority of patients presented late in the course of disease (Mean of 44 days from the onset of symptoms). **Conclusion-**Majority patients with carcinoma gallbladder in our region have advanced unresectable disease. Bilirubin levels at presentation predict resectability. Nodal involvement implies a worse prognosis; however the extent of lymphadenectomy to be done is still debatable. Community screening programs and sensitization of local physicians for early referral can improve survival in endemic areas.

**Keywords:** Cancer, Gallbladder, Nodes, Bilirubin, Surgery

## Introduction

Carcinoma of the gallbladder is known to be associated with an overall dismal prognosis [1-3]. Majority of patients are diagnosed at late stages of the disease resulting in poor surgical results [4-6]. Five year survival rates can range from 5 to 75 per cent [5-8] and the prognosis is stage dependent [9-11]. Patients with early gallbladder carcinoma may have survival rates greater than 70 per cent at 5 year [5, 9-11].

Despite increased understanding, controversies regarding the type of curative surgical treatment for each stage of the disease remain [12]. Reports suggest that aggressive resections like hepato-pancreaticoduodenectomy can have a possibility of

better outcome than usual in patients with advanced gallbladder cancer [13-17]; nevertheless advantages of radical surgery for cancer of the gallbladder still remain controversial.

A review of 4770 patients in Japan did not support any advantage for aggressive surgical resection and adjuvant chemotherapy [18].

Surgical morbidity and mortality rates continue to remain high after radical surgery [19, 20].

This study was under taken to analyse the clinical presentation and surgical outcomes of patients of cancer gallbladder at a tertiary care University hospital in north Indian Gangetic belt with a known high prevalence for carcinoma gall bladder [21].

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## Methods

This study was carried out at the Department of Surgical Gastroenterology, King George's Medical University, Lucknow, India. All patients diagnosed with gallbladder carcinoma from January 2006 to January 2011 were included in this study.

Relevant data was obtained from our prospectively maintained digital database as well as review of patient's records. Multiple parameters were analysed including clinical history, examination findings, complete blood count, coagulation profile, liver and renal function, radiological findings and interventions performed (Surgical, radiological and endoscopic).

As a part of routine workup all patients suspected to have carcinoma gall bladder underwent contrast enhanced CT scan of abdomen as well as abdominal ultrasound correlation to determine the extent of disease.

Further tests including MRI, PET scan and chest CT were done if required for staging or surgical planning. Radiological findings were recorded in detail, including the number and size of gall stones, gallbladder wall thickening, mass, contiguous or non contiguous spread, bile duct diameter, regional lymph nodes, ascites and intraperitoneal spread.

The cancers were classified by using the staging criteria of the American Joint Committee on Cancer 2010, 7<sup>th</sup> edition<sup>22</sup>. Tis, carcinoma in situ; T1, tumor invades the lamina propria or muscle layer; T2, tumor invades perimuscular connective tissue, with no extension beyond the serosa or into the liver; T3, tumor invades beyond the serosa into liver and/or one adjacent organ; T4, tumor involves hepatic artery or main portal vein or multiple extrahepatic organs; N0, Nodes absent; N1, involvement of nodes in the hepatoduodenal ligament and N2, nodes in the celiac axis, superior mesenteric axis or aortocaval region.

After pre-op work up patients were divided into operable and non-operable groups. The criterion for unresectability being: malignant lymphadenopathy along the celiac axis, superior mesenteric axis or aortocaval region, malignant ascites, multiple hepatic metastasis or distant metastasis. T4 lesion per se was not taken as suggestive of unresectability. Contrast enhanced CT scan abdomen was relied upon for the preoperative staging. If the intraoperative findings were

found to be different from the CT findings and these were recorded and the procedure was modified accordingly.

Patients with obstructive jaundice selectively underwent preoperative biliary drainage procedure if major hepatic resection was planned or if serum bilirubin was more than 15 mg/dl. Cholangitis was another indication for drainage. Percutaneous transhepatic biliary drainage or ERCP stent placement was done depending on the level of block. A biopsy was usually not performed unless in inoperable cases, before starting chemotherapy. A variety of resection procedures were applied, ranging from extended cholecystectomy, with or without common bile duct resection, extended right hepatectomy, gastric and colonic resections. Prophylactic resection of surrounding organs without apparent tumor invasion was not employed.

Regional lymphadenectomy was performed routinely which involved nodes in the hepatoduodenal ligament (N1) and nodes behind the head of the pancreas. Radical resection was abandoned when gallbladder carcinoma was found to be associated with multiple hepatic metastasis, peritoneal seeding, and celiac or para-aortic lymph node metastasis that could not be identified pre-operatively.

Patients in unresectable group were offered palliation of various sorts mainly chemotherapy. Biliary stenting or surgical bypass (segment 3 bypass, left duct bypass, hepaticojejunostomy) with or without gastrojejunostomy were done to relieve jaundice or gastric outlet obstruction. Radiotherapy was not offered either as palliation or adjuvant therapy by our centre. Patients who refused any further treatment after counseling were offered effective pain relief and general palliative care. Follow-up data were obtained by reviewing hospital visits as well as telephonically. Survival was estimated by the Kaplan-Meier analysis. There was a minimum follow up of 5 years and a maximum of 10 years in this study.

Patients who survived for more than 3 years were compared with those who died of recurrent disease within 3 years to identify factors associated with long term survival. The prognosis was calculated stage wise. The differences among groups were tested by the log rank test, Chi square test and Mann Whitney U test as appropriate (SPSS-Software).

## Results

A total of 252 patients with a diagnosis of carcinoma gallbladder were identified from January 2006 to January 2011. Patients had a mean age of 48.7yrs and a female predominance (76.1%, n=192). The main physical findings at presentation seen in these patients were pain (87.6% n=221), gallbladder mass (75.7%, n=191), icterus (42%, n=106), anemia (38.2%, n=96) and ascites (13.4%, n=34). On radiological evaluation gallbladder wall thickening/irregularity with or without mass lesion was seen in 97.2% patients (n=245), contiguous spread (75%, n=189), non contiguous metastasis (32%, n=82), nodal involvement (78.1%, n=197), ascites (23%, n=58) and gall stones were present in 74.2% of patients (n=187). Mean duration of presenting to our institute after the onset of symptoms was 44 days.

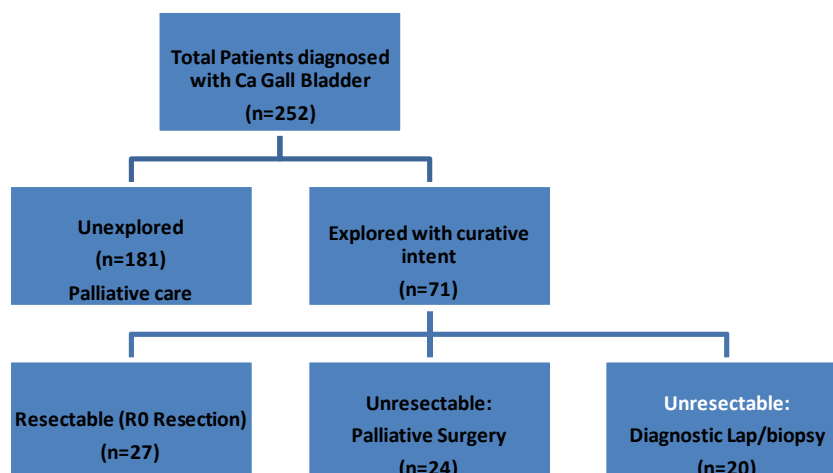
Out of the 252 patients, majority 181(71.8%) were found to have advanced malignancy beyond any possibility of surgical cure based on the previously mentioned criterion for unresectability and were offered palliative or symptomatic treatment as chosen in consultation with the patient (CHART-1). Palliative treatment involved use of chemotherapy, biliary stenting or biliary bypass (seg.3 bypass/ left duct drainage) and gastrojejunostomy for patients with gastric outlet obstruction. Effective pain relief in the form of celiac axis blocks was also considered. Thirty eight patients refused any further treatment after counseling and were offered pain relief and general palliative care.

Seventy one patients underwent surgical exploration with curative intent. TABLE 1 gives the details of the AJCC [22] staging of 71 patients explored. None of the patients in our series had a stage I or II lesion. Out of the 71 patients, it was possible to successfully remove the entire tumor and node burden (R0 resection) in 27 patients only. The rest 44 had either an unresectable disease on intra-operative evaluation, which was underestimated by radiology scans or the tumor involved the surgical margin as confirmed by biopsy (R1/R2 resection). Duodenum was the most common extrahepatic organ involved in the operated patients (n=13). Two patients underwent duodenal sleeve resections; however hepatopancreatoduodenectomy as a means of curative resection was not employed in this series of patients. Gastrojejunostomy was performed as a palliation in 11 patients of duodenal involvement. 12 patients underwent a palliative surgical procedure to relieve jaundice (Segment 3/Left duct bypass). Biopsy alone was done in 11 patients (CHART1). The most common surgical procedure carried out was an extended cholecystectomy. The list of all procedures is shown in TABLE 2. Three patients were referred to us after the pathologist identified the disease in the biopsy specimen (Incidental carcinoma gallbladder). CT was done to stage these patients in which one patient was found to have unresectable disease. Two patients underwent surgery however diagnostic laparoscopy revealed multiple peritoneal deposits in both patients and biopsy only was taken.

There were overall 2 mortalities in immediate postoperative phase out of 27 operated patients. Morbidity rate was 25.9% (7 patients) and included respiratory infections, biliary leak, liver abscess, wound dehiscence etc. In our series, we did not encounter any patient with stage I or II disease. At a follow up of three years post surgery, 3 out of 6 patients with Stage IIIA; 9 out of 14 patients with stage IIIB and 5 out of 7 patients with stage IVA had died of recurrence. At last follow up 4 patients had died due to unrelated cause while 4 were healthy till date. There was no death due to disease recurrence after three years of surgery. One of the long term survivors had a multivisceral resection (Extended cholecystectomy with colonic and abdominal parietal wall resection). Kaplan Meier and log rank test was applied for survival analysis. The median survival time was 1.79 years. Stage wise difference in survival based on AJCC stage (CHART 2) was not found significant in this study probably owing to the small no of patients (n=27).

8 patients had N0 disease with 5 long term survivors while 19 patients had N1 disease also with 5 long term survivors (Log rank test p=0.07). This p value is close to significance and our experience also makes us believe that nodal involvement defines a subset of patients which has a worse prognosis (CHART 3). Difference in survival based on T staging did not reach significant level in this study. Fundal lesions even if advanced (T4) tend to involve colon and hence may be more resectable than the lesions situated in gall bladder neck involving hilar structures and duodenum. Pre operative bilirubin levels had a direct implication on prognosis and the difference in the mean bilirubin levels of patients between survivors and non survivors was significant p=0.02. Age of the patient had no influence on the overall survival in this study (p=0.717). There was no significant difference noted between survivors and non survivors based on sex (p=0.59) or the presence or absence of gall stones (p=0.952); however it has been our keen observation that younger

patients tend to have more aggressive disease. This hypothesis is still to be proved by larger trials. The two prognostic factors identified in our study were nodal status (AJCC 7<sup>th</sup> edition) and the preoperative bilirubin levels.



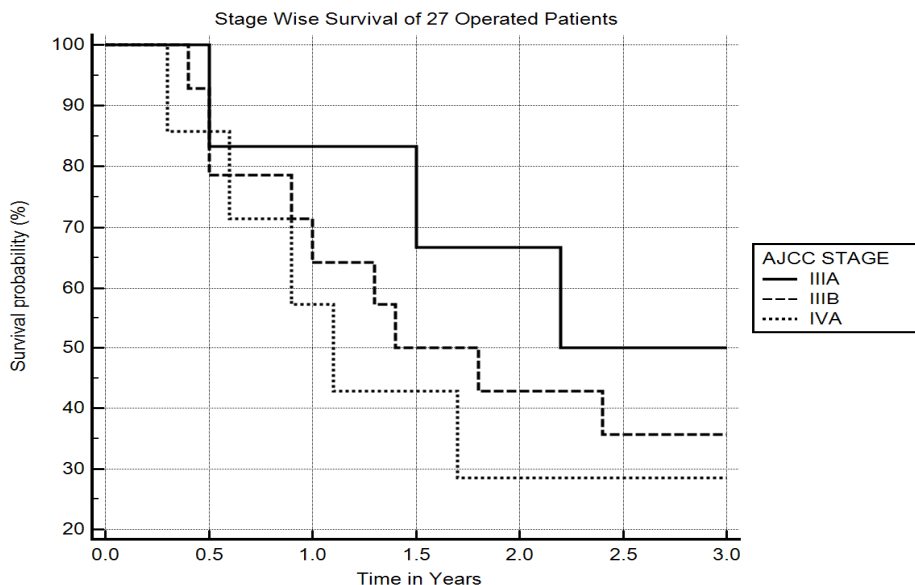
**Chart-1: Outline of the management of 252 patients of carcinoma gall bladder enrolled in the study.**

**Table-1: AJCC staging (7<sup>th</sup> edition) of 27 patients of carcinoma gall bladder who underwent successful R0 resection.**

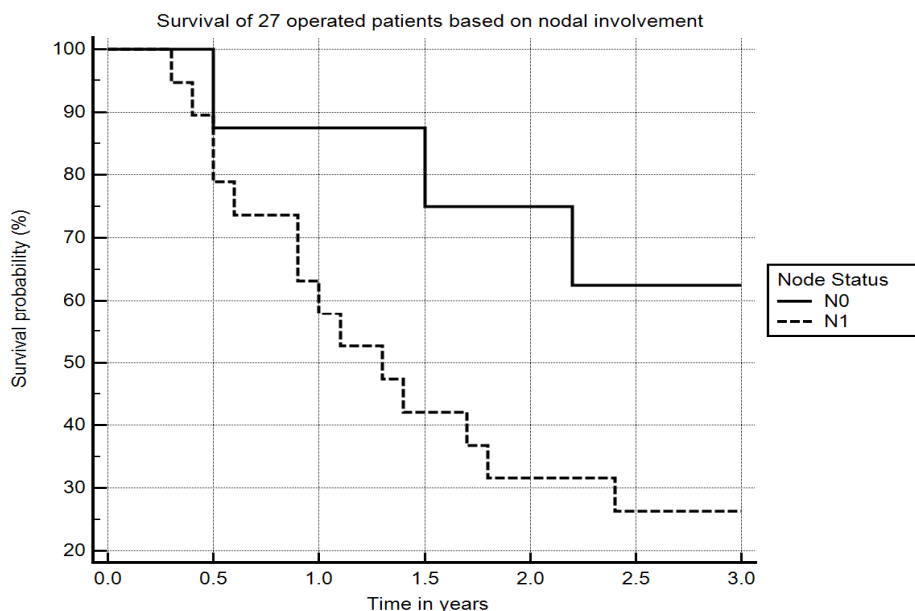
Stage	TNM	Total Number	Curative(R0) Resection Achieved	Survival > 3 yrs
<b>0</b>	Tis, N0, M0	<b>0</b>	<b>0</b>	<b>N/A</b>
<b>I</b>	T1, N0, M0	<b>0</b>	<b>0</b>	<b>N/A</b>
<b>II</b>	T2, N0, M0	<b>0</b>	<b>0</b>	<b>N/A</b>
<b>III A</b>	T3, N0, M0	<b>6</b>	<b>6</b>	<b>3</b>
<b>III B</b>	T 1-3, N1, M0	<b>21</b>	<b>14</b>	<b>5</b>
<b>IVA</b>	T4, N0, M0	<b>3</b>	<b>2</b>	<b>2</b>
	T4, N1, M0	<b>8</b>	<b>5</b>	<b>0</b>
<b>IVB</b>	Any T, N2, M0 (15)	<b>15</b>	<b>0</b>	<b>N/A</b>
	Any T, Any N, M1 (18)	<b>18</b>	<b>0</b>	<b>N/A</b>
<b>Total</b>		<b>71</b>	<b>27</b>	<b>10</b>

**Table-2: Details of surgical procedures performed on 71 patients of carcinoma gallbladder.**

<ul style="list-style-type: none"> <li>▪ <b>Resectable patients (n=27):</b> Extended cholecystectomy done in all patients along with</li> <li>▪ Right Lobe Hepatectomy (n=3)</li> <li>▪ Excision of CBD (n=9)</li> <li>▪ Multivisceral Resection (n=6) Partial Gastrectomy and duodenal Wedge (1) Colonic wedge resection (4) Duodenal wedge resection (1)</li> </ul>
<ul style="list-style-type: none"> <li>▪ <b>Unresectable Patients (n=44):</b></li> <li>▪ Segment III bypass (n=7)</li> <li>▪ Left duct bypass (n=5)</li> <li>▪ Gastric bypass (n=11)</li> <li>▪ Colonic bypass (n=1) to relieve colonic obstruction.</li> <li>▪ Inoperable – biopsy only (n=11)</li> </ul>



**Chart-2: Kaplan Meier survival curve of 27 patients of surgically treated carcinoma gallbladder divided into stages based on AJCC-7<sup>th</sup> edition**



**Chart-3: Kaplan Meier survival curve of 27 patients of surgically treated carcinoma gallbladder divided based on nodal status - AJCC-7<sup>th</sup> edition**

**Discussion**

The majority of patients with Gallbladder cancer in India have advanced unresectable disease. As noted in our study, only 28.2% patients had apparently resectable disease at initial presentation and finally curative resection could only be achieved in only 10.7% patients. Gallbladder malignancies are still diagnosed too late. In a review of 724 cases done by the French surgical association 77% of the patients had lesions

beyond the possibility of any curative treatment [23]. This finding is not surprising when we consider that improved diagnostic imaging techniques cannot be applied until late in the disease course. Majority of patients with gallbladder carcinoma present at late stages of the disease resulting in a dismal overall prognosis [4-6, 24, 25]. More so this is especially true in our patient population from rural and Gangetic plains

of India where people prefer alternate form of medication and are referred to us much later. Community screening programs and sensitization of local physicians for early referral can improve survival in endemic areas.

The prognosis of carcinoma of gallbladder has always been presented as dismal [1-8]. This is essentially the result of the slow and asymptomatic growth of the neoplasm that infiltrates the surrounding structures such as the portal vein and hepatic artery, making surgical treatment almost impossible. Several prognostic factors influence the clinical course of patients with gallbladder carcinoma: depth of tumor invasion, presence or absence of lymph node metastasis, histological type, surgical margin and TNM stage [26-28]. In our study nodal status was more important than the tumor size or conjugate spread in predicting the outcome.

The difference in the bilirubin levels between survivors and non survivors was statistically significant ( $p < 0.02$ ). Biliary tract carcinoma accompanied by obstructive jaundice is associated with increased surgical morbidity and mortality rates [13,19]. Higher pre operative bilirubin levels in this series of patients indicate a probability of advanced unresectable disease. Disease spectrum seems to be distributed into two patterns. An elderly age group  $\geq 68$  years appears to have a more indolent and resectable disease with increased survival, while another group of younger patients (onset  $\leq 50$  years) is characterized by more aggressive disease and poor survival outcomes. This difference needs to be statistically proven in further studies.

Satisfactory results can be achieved by simple or radical cholecystectomy in patients with stage I or II disease. Extensive surgery is not necessary in these patients [29-31]. In contrast, the results of surgical treatment of stages III and IV gallbladder carcinoma have been reported to be extremely poor [2, 5]. Recently, the results have improved as a result of the introduction of extensive resection [32-34], including en bloc resection of involved organs especially by Japanese surgeons. The role of resectional surgery for T<sub>3</sub> and T<sub>4</sub> lesions is controversial as most authors report that patients with serosal involvement do not survive for 5 years even when major resections, including hepatectomy are performed [35-37].

Glenn and Hays had proposed the importance of lymph node dissection in surgery for GBC as early as 1954.

The procedure was referred to as "skeletonization of the lesser Omentum." [38] Radical resection with nodal dissection for GBC has been widely accepted with some surgeons including extensive dissection of lymph nodes in the peripancreatic portion, coeliac axis and paraaortic region [11, 17], however our experience is pessimistic about the radical procedure as once the N2 nodes are involved, radical surgery did not seem to improve outcomes. In our patient population the issues concerning the indications and limitations of lymph node dissection still need to be resolved. RO resection is required for the long-term survival of the patient with GBC. Direct invasion of the liver can be treated with liver resection. Wedge resection of the gallbladder bed (segment IV-V) can control limited liver invasion but extended right hepatic lobectomy has to be undertaken for a massive invasion of the liver or the invasion of the right main branches in the hepatic pedicle. A combined resection of the involved organs (pancreatoduodenectomy, colectomy, etc.) can achieve RO resection for T3 or T4 lesions. Combined resection and reconstruction of large blood vessels should be considered to obtain RO resection only in selected cases. A multidisciplinary approach, which includes neoadjuvant radiochemotherapy, may allow us to increase the rate of curative RO resection [11, 34].

As such there is still no consensus among the surgeons worldwide for a common protocol to manage carcinoma gallbladder. However all early stage cancers should be offered curative resectional surgery. Involvement of N2 node stations generally implies a grave prognosis.

The extent of lymphadenectomy is debatable, as is extensive surgery in the form of hepatopancreatoduodenectomy for advanced lesions. Despite best efforts the prognosis of cancer gallbladder remains grim in this part of the world.

## Conclusion

Majority patients with carcinoma gallbladder in our region have advanced unresectable disease. Bilirubin levels at presentation predict resectability. Nodal involvement implies a worse prognosis however the extent of lymphadenectomy to be done is still debatable. Community screening programs and sensitization of local physicians for early referral can improve survival in endemic areas.

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