

Treatment outcomes of gall bladder cancer, 10 years experience

Abstract

Background: Gallbladder cancer (GBC) represents the most common and aggressive biliary tract cancer with overall 5-year survival being only 5%–10%. Survival following resection, especially in early stages, has shown some improvement due to advances in surgical treatment. Advanced stages, however, continue to have dismal outcome. Complete surgical resection offers the only chance for cure, which extended from simple cholecystectomy to major hepatectomy or en bloc resection of adjacent organs. The aim of this study was to examine the predictors of longterm survival in patients with gall bladder cancer.

Methods: We retrospectively evaluated 38 patients who underwent curative (R0) resection for GBC between January 2001 and December 2010 in Surgical Oncology Department, South Egypt Cancer Institute, Assiut University, Egypt. Surgical procedures included simple cholecystectomy (10.5%), radical cholecystectomy (75.4%), bile duct resection (33.8), and right hepatectomy (7.8%). Adjacent organ resection was performed in (23.4%), duodenal sleeve resection (10.4%), segmental colectomy (5.2%), segmental gastrectomy (2.6%), Hepatopancreatico-duodenectomy (5.3 %). Adjuvant chemotherapy was given for (68.4%) of patients and adjuvant radiotherapy for (36.8%) of patients. Median follow up period of the patients was 38 months (0.5-69 months).

Results: The median disease free survival (DFS) for GBC patients was 38 months. Univariate analysis revealed that patient's age, comorbidities, weight loss, jaundice, tumor differentiation, organ invasion, lymph node metastasis, perineural invasion, tumor stage and chemotherapy were associated with the patient's survival. Of these, weight loss, jaundice, lymph node metastasis and tumor stage were found to influence the overall survival on the multivariate Cox Hazard Regression analysis. First year overall survival estimate was 86.84% \pm 5.5%, 2nd year = 71.05% \pm 7.4%, Third year 60.53% \pm 7.9% fifth year = 15.79% \pm 5.9%.

Conclusion: Curative surgical resection remains the only effective approach for treatment of GBC. This study confirms that jaundice, weight loss and aggressive tumor (advanced stage and regional lymph nodes metastasis) are predictors of poor prognosis.

Keywords: cholecystectomy, gallbladder neoplasms, hepatectomy, prognosis, retrospective studies

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Abbreviations: GBC, gallbladder cancer; SECI, South Egypt cancer institute; CT, computed tomography; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; AJCC, American joint committee on cancer; SC, simple cholecystectomy; ELR, extended liver resection; HPD, hepatopancreatico-duodenectomy; RC, radical cholecystectomy; BD, bile duct resection; DVT, deep venous thrombosis

Introduction

Gallbladder cancer (GBC) is the most common malignancy of the biliary tract and the fifth cancer of the gastrointestinal tract that is frequently diagnosed at an advanced stage due to non specific symptoms, anatomic location and aggressive biologic behavior, with a poor prognosis and 5-year survival rate of 5 to 15%.¹⁻⁴ GBC is characterized by local invasion, extensive regional lymph node metastasis, vascular encasement and distant metastases, mode of spread are direct, lymphatic, vascular, neural, intraperitoneal and intraductal.⁵ Gallbladder carcinomas (T1 and T2) which are found incidentally in 0.2–2.9 % after surgery for symptomatic gallstones, representing anywhere from 40 to 70 % of all gallbladder cancer diagnoses.^{6,7} Gallbladder cancer is curable if treated at an early stage

but notoriously difficult to cure, especially when it is associated with lymph node metastasis and/or liver metastasis. Because surgical resection represents the only modality offering potential cure, aggressive surgery is advocated.^{2,3,7-10} It affects more females with a male to female ratio of 1:2 and commonly diagnosed in the seventh decade of life.⁷ Gallstones have been associated as a risk factor.¹¹ Symptoms such as jaundice, palpable mass, changes in the bowel habit and ascites invariably represent the disease in the end-stage with low curability.¹² Lymphatic metastasis from gallbladder cancer spreads widely through hepatoduodenal ligament towards peripancreatic region and beyond strongly influenced by the depth of the primary tumor, so complete resection of the regional lymph nodes is important.^{3,13} Curative resection ranging from simple cholecystectomy to combined extended hepatectomy with common bile duct resection in the same stage. Radical surgery is advocated for patients in stages II and III. However considering the particularly poor prognosis of stage IV patients, radical resection appears less favorable than palliative resection in those who were complicated with hepatic invasion.¹⁴ Simple cholecystectomy is sufficient for T1a gallbladder cancer, but careful attention to the surgical margin of the cystic duct is essential because there is no difference in survival or recurrence rates between radical and simple cholecystectomy.^{7,11,15} Segment IVB

and V hepatic resection and bile duct resection is usually indicated for T2 and /or T3 gallbladder cancer^{11,16} If the gallbladder cancer invades the hepatic hilar confluence, right hemihepatectomy or extended right hepatectomy should be considered.^{11,15-17} Hepatopancreaticoduodenectomy (HPD) has been performed to achieve radical resection.¹⁸ Organs in proximity such as the duodenum, the hepatic flexure of the colon and pancreas, bring up with technical challenges in achieving a negative margin and potentially curative resection.¹⁹ Gender, age, hepatic resection, and adjuvant chemotherapy did not influence postoperative survival. In contrast, tumor differentiation, hepatic invasion, choledochal invasion, lymph node metastasis, surgical margin status, and stage were significant predictors of survival of GBC patients.^{3,20}

In the current study, we aimed to examine factors influencing the patient's survival following radical gall bladder cancer resection.

Patients and methods

Patients' selections

From January 2001 to December 2010 medical records of 38 patients underwent curative surgery for gall bladder carcinoma, who admitted to Surgical Oncology Department, South Egypt Cancer Institute (SECI), Assiut University, were retrospectively reviewed. Curative surgery was defined as complete resection of all macroscopic and microscopic tumors. Patients' demographic, clinical and diagnostic data were collected from chart review and office visits. Data included age, sex, clinical history, co-morbidity, preoperative investigation, as well as type of operation ,surgical morbidity and mortality, chemotherapy, radiotherapy, follow up data, survival, diagnostic procedures (ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), or magnetic resonance cholangiopancreatography (MRCP)) and tumor markers (CA19-9 & CEA). Clinical staging of the disease was according to the American Joint Committee on Cancer (AJCC) staging system (7th edition). The criteria established in patients with GBC as an indication for radical resection at our institute comprise the absence of distant metastasis, peritoneal dissemination, liver or para-aortic lymph node metastasis, invasions on both sides of the portal vein or common hepatic artery, severe comorbidities or chronic liver disease. This study was conducted in accordance with the Helsinki Declaration and after the study had been approved by SECI Ethics Review Board. Median follow up period of the patients was 38 months (0.5-69 months).

Surgical procedures

Surgery for GBC ranged from simple cholecystectomy (whole gall bladder removed nothing else) for T1a tumor with negative cystic duct stump to radical cholecystectomy with partial resection of the adjacent liver tissue within 2.0 cm around the gallbladder bed/resection of segment V and IVB for T2 and/or T3 disease and with regional lymphadenectomy (enbloc clearance of cystic duct, pericholedochal, hepatic artery, portal vein, periduodenal and peripancreatic lymph nodes). Enbloc resection of adjacent organs was done if direct invasion occurred. Biliary continuity was restored by a Roux-en-Y biliary-enteric anastomosis when extra hepatic bile ducts were resected.

Statistical analysis

Univariate analysis for the most important factors regarding patients, tumor and operation carried out using chi-square and Mann-Whitney test analysis. Factors with proven statistical significance from

the univariate analyses were further included in the multivariable Cox proportional hazard regression models. All non significant variables from the initial model were included in the final model one at a time to test for their effect on the model. Kaplan's Meier method with the log-rank test for statistical significance was used for survival analysis of individual prognostic factors. All statistical analyses were performed using STATA v.12 (STATA Corp., Texas, USA). A p-value <0.05 was considered significant.

Results

Demographic and clinicopathological data

During the study period of 10years, 38 patients with gall bladder cancer (GBC) underwent curative resection at Surgical Oncology Department, South Egypt Cancer Institute, Assiut University with median follow-up 38 months. The clinicopathological features were analyzed and summarized in (Table 1). 16 patients (42.1%) were males and 22 (57.9%) were females, with average age at presentation was 63 years old (38-86 years). 16 patients (42.1%) had co-morbidities and Diabetes Mellitus had been the commonest (13.2%).

Table 1 Demographic and clinicopathological data for patients presented with gall bladder cancer

Variables	Number	Percentage (%)
Age (≥75)	21	54.60%
Gender (Female)	22	57.90%
Co-Morbidity	16	42.10%
Presentation		
-Abdominal Pain	29	75.40%
-Weight Loss	20	52%
-Jaundice	14	36.40%
-Abdominal Mass	4	10.40%
-Gall Stones	33	85.80%
Preoperative Biliary Drainage	11	28.60%
Tumor Differentiation		
-Well Differentiation	15	51%
-Moderate Differentiation	13	37%
-Poor Differentiation	10	26%
Organ Invasion	9	23.40%
Lymph vascular Invasion	15	39%
Perineural Invasion	11	8.60%
Tumor Size		
T1/T2	12	31.20%
T3/4	26	67.60%
Co-Morbidity		
Cardiac	4	10.50%
Cirrhosis	3	7.90%
COPD	4	10.50%
Diabetes	5	13.20%
Radiotherapy	14	36.80%
Chemotherapy	26	68.40%

The most common symptom was pain in 29 patients (75.4%) and the least common was abdominal mass. Most of the patients had a gall

stones (85.8%), 14 patients presented with obstructive jaundice, and of those 11 patients needed preoperative biliary drainage. Fifty-two percent of patients presented with weight loss.

About two third (67.6%) of the patients had a large tumor size (T3/T4). The tumor histology was dominantly adenocarcinoma. Tumor differentiation was classified as well differentiated (51%), moderately differentiated (37%), and poorly differentiated (26%). Perineural invasion was detected in only 2 cases, adjacent organ invasion was detected in 9 cases, and lymph vascular invasion was detected in 15 cases.

The surgical procedures, morbidity, mortality and recurrence for gall bladder cancer patients were illustrated in (Table 2). All patients underwent exploratory laparotomy for potentially curative resection and R0 resection (microscopic negative margin) performed. Radical cholecystectomy (RC) was performed in 34 patients while simple cholecystectomy (SC) was adequate in only 4 patients. In addition to radical cholecystectomy, concomitant resection of different nearby organs done in 23 patients, involving extended liver resection (ELR) in 3 patients, biliary tree resection in 2 patients, duodenal resection in 4 patients, colonic resection in 2 patients and gastric resection only in 1 patient. Concurrent pancreatoduodenectomy was performed in 2 patients due to doubtful distal biliary margins.

Table 2 Surgical procedures, morbidity, mortality and recurrence for gall bladder cancer patients

Surgical procedures	Frequency	Percent
ELR	3	7.90%
HPD	2	5.30%
RC	11	28.90%
RC + BD	12	31.60%
RC + BD + Duodenal Sleeve Resection	1	2.60%
RC + segmental Colonic Resection	1	2.60%
RC + Gastric Sleeve Resection	1	2.60%
RC + Sleeve Duodenectomy	2	5.30%
RC + segmental Colectomy + Duodenal Sleeve	1	2.60%
SC	4	10.50%
Total	38	100.00%
Morbidity		
-Liver Dysfunction	2	5.20%
-Pneumonia	3	7.80%
-Liver Abscess	1	2.60%
-Bleeding	1	2.60%
-Surgical Site Infection	4	10.40%
-Dvt	2	5.20%
-Biliary Leak	1	2.60%
Total	14	36.40%
Hospital Mortality	1	2.60%
Tumor Recurrence	13	37%

ELR, extended liver resection; HPD, hepatopancreatico-duodenectomy; RC, radical cholecystectomy; BD, bile duct resection; SC, simple cholecystectomy; DVT, deep venous thrombosis

Hospital mortality only occurred in 1 patient due to liver failure following extended liver resection. The morbidity rate in our study was 36.4%. The general post-operative complications included pneumonia (7.8%), surgical site infection (10.4%) and deep venous thrombosis DVT (5.2%). The specific complications included liver dysfunction (5.2%), bleeding (2.6%), liver abscess (2.6%), and biliary leak (2.6%).

Adjuvant chemotherapy was received in 26 patients (67.6%) while 14 patients (36.4%) received radiotherapy.

Survival analysis

First year overall survival estimate was $86.84\% \pm 5.5\%$, 2nd year = $71.05\% \pm 7.4\%$, Third year $60.53\% \pm 7.9\%$ fifth year = $15.79\% \pm 5.9\%$ (Figure 1). Median DFS for GBC patients was 37 months.

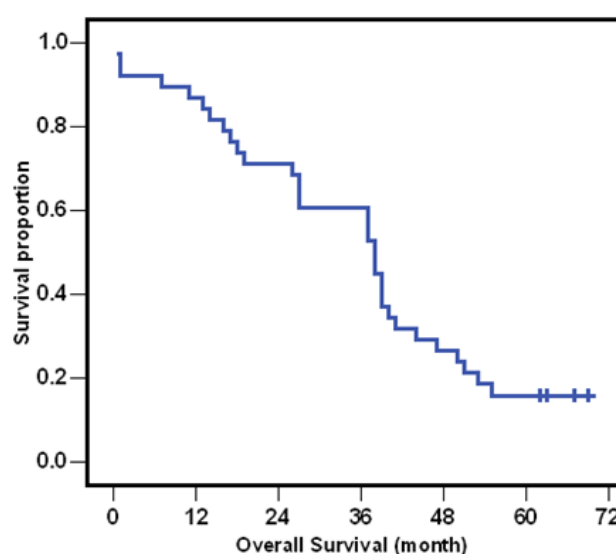


Figure 1 Overall survival of gall bladder cancer patients.

Factors found to have significance on survival of GBC patients upon univariate analysis underwent a multivariate analysis that revealed, tumor stage (p value=0.004), lymph node metastasis (p value=0.03) and both weight loss (p value=0.001) and jaundice (p value=0.03) at presentation to be statistically significant.

Median survival for those having lymph node metastasis versus those not having lymph node metastasis was 18 months and 50 months, respectively ($p=0.003$).

Median survival for those presenting with weight loss and jaundice was 15 months and 17 months, with significant p values (0.001, 0.003), respectively.

Patients with early stages (stage I&II) had better survival with median survival for those having early stages versus those having late stages (stage III&IV) 53 months and 27 months, respectively ($p=0.003$).

Tumor recurrence occurred in 13 patients (34.2%). The sites and nature of recurrence in these patients included peritoneal dissemination in 4 patients (10.4%), liver metastases in 5 patients (13%), lung metastases in 3 patients (7.8%) and local recurrence in one patient (2.6%) (Table 3).

Table 3 Univariate and multivariate analysis of predictors of overall survival of gall bladder cancer patients

	Univariate analysis (P value)	Multivariate analysis (P Value)
Age (≥ 70 / <70)	0.04	0.08
Gender (Female/Male)	0.12	
Co-Morbidity	0.03	
Abdominal Pain	0.14	
Weight Loss	0.0001	0.001
Jaundice	0.005	0.03
Abdominal Mass	0.066	
Gall Stones	0.071	
Tumor Differentiation		
Wd-Md/Pd	0.002	0.07
Organ Invasion	0.004	0.06
Lymph Node Metastasis	0.001	0.03
Perineural Invasion	0.05	
Tumor Size		
T1-T2/T3-4	0.06	
Tumor Stage		
I -Ii /Iii-Iv	0.003	0.004
Morbidity	0.23	
Radiotherapy	0.54	
Chemotherapy	0.008	

Discussion

Gallbladder cancer remains a disease with poor prognosis, with median DFS about 28 months.^{2,12,19} Non radical cholecystectomies had 5-year overall survival rate of 17% reported by Wang et al, while the expected 5-year overall survival rates after curative resection was 40%.^{2,12,19,21} In our study the median DFS was 38 months with a 5-year survival rate of 16 % after curative resection.

Gallbladder cancer has been reported as a disease of the elderly and females have a 40-60 % higher incidence than men (2). In our study, mean age at the time of diagnosis was 59 years with female to male ratio of 1.4. Gallstones are a well-known risk factor for GBC.^{11,22,23} In this study, 86.8% of gallbladder patients had gall stones.

While jaundice is a poor prognostic factor in patients with gallbladder cancer, this does not necessarily preclude operative intervention as long as negative margins may be achieved.^{24,25} In our study, curative surgery achieved in 14 patients (36.4%) presented with jaundice.

Although the rate of lymph node metastases has been reported to be less than 2.5 % in stage Ia, survival was significantly impacted by the extent of surgery (LN dissection and RC), so cholecystectomy alone is inadequate in stage I GBC.²⁶ In our study, 4 (10.4%) patients with stage Ia GBC underwent simple cholecystectomy only with 100% 5-year overall survival rate. So simple cholecystectomy with negative margins is sufficient and these patients with stage Ia GBC do not need further surgical intervention and lymphadenectomy is generally not warranted.

Insufficient wedge resection of the liver result in a recurrence, while excessive extended right lobectomy may cause postoperative liver failure.²⁷ In the current study, radical cholecystectomy was done in 29 patients (75.4%) with partial resection of the adjacent liver tissue within 2 cm around the gallbladder bed and /or resection of segment V and IVb in T2 and /or T3 tumors. For selected patients, extended hepatectomy may be necessary to achieve negative margins and has been shown to be safe.^{24,28} In our study extended liver resection (right hepatectomy) was done only in 3 patients (7.8%) due to gross liver invasion with reasonable morbidity.

Aggressive surgical resection including HPD was introduced to achieve curative surgical resection in patients with advanced GBC, although long-term survival was described by many surgeons but with high morbidity rates of 30.8- 91% (hepatic failure occurred in 10-46.8% of patients) and mortality rates of 0-41.0%,^{18,29,30} in current study, HPD was done in two patients (5.2%) one of them died from hepatic failure, to prevent this lethal complication, many authors have recommended preoperative biliary drainage.¹² In our study, preoperative biliary drainage was performed in 11 patients (28.6%) presented with obstructive jaundice (9 patients with endoscopic retrograde biliary drainage and 2 patients with percutaneous transhepatic biliary drainage).

Routine extra hepatic bile duct resection does not increase the nodal yield or survival, but is associated with increased postoperative morbidity. Hence, it should be selectively performed to ensure negative surgical margins.¹² In our study, resection of extra hepatic bile duct was selectively undertaken in patients with invasion of the bile duct by tumor (33.8% of patients).

Lymph node involvement is a poor prognostic sign and nodal-positive patients with radical resection always show a better survival rate than nodal-positive patients without radical resection, stage for stage,^{24,31,32} in our study Lymph nodes negative patients (47.4%) had median survival time of 50 months, while patients with positive lymph nodes metastasis (52.6%) had median survival time 19 month (p value =0.001).

Higher T Stage, predict poor outcome in patients with gallbladder cancer. According to the depth of invasion, 5-years survival was 86% (T1), 56% (T2), 45% (T3), and 5% (T4) (10, 12). Our study supports these findings as we detected significantly lower survival in stage (T3 and T4) disease, median survival was 27 months compared to 53 months for (T1 and T2).

Radical resection of GBC associated with a high morbidity (53%) and mortality (5%).³³ In our study, postoperative complications occurred in (36.4%) patients, and post operative mortality was seen in one patient (2.6%), while 12 patients (31.2%) died of recurrent disease. Para-aortic lymphadenectomy did not confer a survival benefit for patients with para-aortic disease, for whom the prognosis was as poor as that of distant metastases.⁸ Therefore, we did not perform formal para-aortic lymphadenectomy in patients with para-aortic lymph nodes metastasis.

Survival after surgical resection for patients with gallbladder carcinoma depends heavily on stage of disease. 5-year survival rate of patients with resected gallbladder carcinoma is 33-63% for patients at all disease stages and 9-20% for patients with stages III and IV (3). In our study 5 year survival was 16% this is may due to late presentation of most of our patients (stage III and IV 25 patients (65.8%) and stage I and II 13 patients (34.2%)). Patients with stage (I and II) had a median survival of 53 months while stage (III & IV) patients had median survival of 27 months.

Chemotherapy and radiation therapy are not effective in the treatment of gallbladder cancer, their survival benefits on patients with resected gallbladder carcinoma are controversial.³⁴ This is in agreement with our results which showed that, adjuvant chemotherapy was not received in 12 patients (31.6%) and had median survival of 51 months, while 26 patients (68.4%) received adjuvant chemotherapy and had median survival of 27 months with p value=0.0089. Also, 24 patients (63.2%) did not receive radiotherapy and had median survival of 39 months, while 14 patients (36.8%) received radiotherapy and had median survival of 27 months with P value=0.5464.

Tumor recurrence of GBC is high and chiefly intra-abdominal involving liver or retroperitoneal lymph nodes.^{12,35} In our study, tumor recurrence occurred in (34.2%) of patients including peritoneal dissemination, liver metastases, lung metastases, and local recurrence.

The prognosis is poor for most patients of GBC with direct invasion of the liver and/or one other adjacent organ or structure.²⁹ In current study, tumors with organ invasion had a median survival of 19 months compared to 39 months for patients with no organs invasion.

The limitations of this study were its retrospective design and the small number of patients studied. However, it did have few strong points as we studied a well annotated retrospective cohort of patients with clearly defined clinical, demographic, and pathologic variables along with distinct study outcomes. Hence, we recommend other studies on larger numbers of patients, including prospective studies to confirm the results of this study.

Conclusion

Curative surgical resection remains the only effective approach for treatment of GBC and can be done safely with a satisfying survival. This study confirms that jaundice, weight loss and aggressive tumor (advanced stage and regional lymph nodes metastasis) are poor prognostic factor. However, the presence of jaundice does not exclude resection, especially in highly selected patients.

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Conflicts of interest

The authors declare there is no conflict of interests.

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