Review Article

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Carcinoma Gallbladder: A Review of Literature

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Abstract

Carcinoma of gallbladder is a very aggressive disease with poor outcomes. In spite of newer and advanced imaging techniques and better understanding of the disease even at the molecular level there is increased the incidence of mortality seen with this disease. This magnitude of the cancer problem in the Indian sub-continent (sheer numbers) is increasing due to, the poor to moderate living standards and inadequate medical facilities. The prevalence of gallbladder cancer in India is estimated to be around 2.5 million, with about 800,000 new cases and 550,000 deaths/annum. Women are more commonly affected than men. The disease commonly occurs in the age group ranging from 29 to 90 years with a peak incidence in their 60's with great geographic and ethnic variation. Carcinoma gallbladder a disease, which was a disease of old age, is now also found commonly in the younger age group also where it presents with greater ferocity.

Keywords: Age, Carcinoma, Gallbladder, Surgery, Women

INTRODUCTION

Every year in India there is about 800,000 new cases and 550,000 deaths per annum.[1] It has been reported that during 2008, there were 145,662 gallbladder cancer cases globally with an age-standardized rate of 2.0 per 105 person years.[2] Gallbladder cancer is the most common abdominal malignancy in the northern India.[3] The Indian Council of Medical Research Cancer Registry has reported incidence rate of 4.5% in males and 10.1% in females per 100,000 population in northern India.[4] Globally this incidence varies geographically with higher rates in certain areas of Latin America (Colombia, Peru, and Ecuador), North America (Hispanic and American Indian populations), Eastern Europe (Poland, the Czech Republic, Slovakia, Hungary, and the former East Germany) and Japan.[5]

Gallbladder carcinomas are associated with gallstones (80%), porcelain (calcified) gallbladder (10-20%) and abnormal choledochopancreatic duct junction. Anomalous pancreaticobiliary duct junction is a rare congenital malformation of the biliary tract, in which the pancreatic duct drains into the biliary tract outside the duodenal wall.[6] More prevalent in Asians (particularly Japanese patients), this anomaly carries a heightened risk of developing biliary tract cancer; 3-18% develop gallbladder cancer.[6,7] Size of the gallstones is an important risk factor. The patients with gallstones larger than 3 cm have a significantly greater risk of developing carcinoma.[8] About 0.3-3.0% of patients with gallstones develop gallbladder cancer. Chronic inflammatory state of the gallbladder usually as a result of gallstones is a significant risk factor for gallbladder cancer.[9] Gallbladder polyps are also associated with a risk of malignancy.[10] Choledochal cyst has been implicated as a risk for malignancy.[11]

The occurrence of carcinoma gallbladder has a direct correlation with the length of time that the gall stones reside in the gallbladder. A long duration provides the necessary time for such chronic trauma to the mucosa to initiate a sequence of pathologic changes that culminate in cancer. This also explains the inverse correlation that exists between cholecystectomy rates and gallbladder cancer; socioeconomic issues can delay access to cholecystectomy for cholelithiasis, increasing gallbladder cancer rates.[12] In patients with carcinoma gallbladder, the incidence of cholelithiasis ranges from 54% to 97%. Carcinoma gallbladder is more common in patients with Mirizzi's syndrome, and typhoid carriers are a high-risk group.[13,14] *Salmonella typhi* (~6% of carriers develop gallbladder

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cancer: A 12-fold risk increase) and *Helicobacter bilis* have been implicated in gallbladder cancer.[15,16] Bacterial colonization often accompanies chronic cholecystitis it has been proposed that bacteria may play a significant role in carcinogenesis.[17] Gallbladder polyps are considered a risk factor. Polypoidal masses of the gallbladder affect 5% of adults (range, 0.3-7%), depending upon the population studied. Most gallbladder polyps (over two-thirds) are composed of cholesterol esters, the common composition of those under 5 mm, yet they are not particularly associated with cholesterol gallstones. Other polypoidal lesions are adenomas, leiomyomas, or inflammatory polyps. The majority of these immobile hyperechoic shadows are incidental findings discovered on abdominal ultrasound performed for other purposes. Most polyps do not grow or change in size. Features predicting malignancy of polypoidal gallbladder masses include large polyps (>10 mm; one-quarter are malignant); a solitary lesion; a sessile polyp; polyp growth; age over 50-60 years; or associated gallstones. Features are suggesting a malignant polyp, or when accompanied by gallbladder symptoms (biliary-type pain), warrant cholecystectomy.[18] Polyps over 18 mm must be removed, as they are likely malignant.[19]

Gallbladder cancer appears to develop from dysplastic mucosa that progress to carcinoma *in situ* and then to invasive carcinoma.[20]

Other factors, that increase the risk for gallbladder cancer, include obesity, a high-carbohydrate diet, smoking, and alcohol use.[21] Adequate intake of fruits and vegetables has been shown to be a protective factor. Findings from various studies on the adequate consumption of vegetables indicate an inverse association with gallbladder cancer risk.[22,23] Several large population-based and observational epidemiological studies have highlighted the importance of vegetables and fruits in reducing the risk of cancer in a variety of organs and tissues.[23]

There are many other factors which are associated with gallbladder cancer though their exact role in the pathogenesis of gallbladder cancer is not proven such as high concentrations of free radical oxidation products.[24] Some chemicals have been implicated in the gallbladder cancer including methyldopa, oral contraceptives, isoniazid and occupational exposure in the rubber industry.[25]

Approximately 60% of tumors originate in the fundus of the gallbladder, 30% originate in the body, and 10% originate in the neck. Gallbladder cancers can be categorized into infiltrative, nodular, combined nodular infiltrative, papillary, and combined papillary-infiltrative forms. Infiltrated tumors cause thickening and induration of the gallbladder wall. They spread easily in a subserosal plane, which is the same plane used for routine cholecystectomy. Nodular types show early invasion through the gallbladder wall into the liver or neighboring structures and may be easier to surgically control than the infiltrative form. Papillary carcinomas have the best prognosis and exhibit a polypoid cauliflower-like appearance. These may completely fill the lumen of the gallbladder, with only minimal invasion of the gallbladder wall. Histologically, the most common type of gallbladder cancer is adenocarcinoma. Other types, such as adenosquamous carcinoma, oat cell carcinoma and sarcomas are also seen. In 92% of invasive carcinomas, 86% of carcinomas *in situ*, and 28% of dysplastic epithelia p53 protein is identifiable.[26]

In 39% of gallbladder cancers, K-ras mutations are identified.[27] Allele-specific deletions of the p53, deleted in colon cancer, and 9p genes play an important role in the pathogenesis of gallbladder cancer.[28] In some studies, p53 and p21 have been found to be abnormally expressed in the mucosa of gallbladders harboring chronic cholecystitis.[28] Other genetic abnormalities, that have been documented, include overexpression of c-erbB-2 gene[29] and decreased expression of the nm23 gene product.[30] In cholesterol stones, the factors best identified are the genes responsible for specific biliary lipid transporters in the canalicular membrane - The adenosine triphosphate-binding cassette (ABC) transporters. These transporters include ABCG5/ABCG8 for cholesterol secretion, ABCB11 as the bile salt export pump, and ABCB4 for phospholipids and lecithin.[15] Mutations in the gene ABCG5/G8, as the variant D19H, result in increased cholesterol secretion into bile, making it an important susceptibility factor.[31] Defective ABCB4 leads to decreased lecithin secretion and stone formation. In gallbladder cancer, variants of the apolipoprotein B (APOB) gene is responsible for APOB function which influences cholesterol handling by the liver, has been associated with an increased risk for gallbladder cancer.[32] One comprehensive explanation for the association of gallbladder cancer with cholesterol gallstones suggests an interdependent disposal pathway for cholesterol and environmental toxins exported into bile, linked by the activity of hepatic nuclear receptors and ABC transporter pumps.[33] Female sex hormones increase the secretion of cholesterol and xenobiotics into bile. Furthermore, prolonged gallbladder residence time (stasis due to impaired contractility) results from progesterone and the excessive cholesterol secreted in bile. Such protracted exposure allows environmental carcinogens such as aflatoxin B, possibly the culprit in some endemic areas.[15] Total parenteral nutrition is a well-known risk factor for developing microlithiasis (biliary sludge) and gallstone disease, in addition to acute acalculous cholecystitis in critically ill-patients.[34]

Gallbladder cancer can spread by direct invasion through the gallbladder wall into the liver or peritoneal cavity. The gallbladder has a narrow wall consisting of a thin lamina propria and a single muscle layer. Once a gallbladder cancer penetrates this muscle layer, it has access to major lymphatic and vascular channels as well as the liver or peritoneal cavity by penetration through the wall. Gallbladder cancer can also spread via lymphatic, hematogenously and along biopsy tracks or surgical wound tracks. Hematogenous spread originates from the small veins extending directly from the gallbladder into the portal venous system of the gallbladder fossa leading to segments IV and V of the liver or via large veins to the portal venous branches of segments V and VIII.[35] Boerma reviewed the literature and determined that at the time of presentation only 10% of gallbladder cancers were confined to the gallbladder wall, 59% invaded the liver, 45% invaded regional lymph nodes, 34% had distant hepatic metastases, and 20% had extrahepatic hematogenous metastases.[35,36]

The most common site of extra-abdominal metastases is the lung which occurs in cases of advanced intra-abdominal disease. The stage of disease is the most reliable predictor of outcome and ultimately outweighs histology, grading, or other biological parameters. The main staging systems over the past 5 years include the modified Nevin system,[36] Japanese Biliary Surgical Society System,[37] American Joint Commission on Cancer/Union Internationale Centre le Cancer tumor-node-metastasis staging system (Table 1).[38]

Gallbladder cancer is either detected early as an incidental finding when cholecystectomy is performed for symptomatic cholelithiasis or late, when the tumor has invaded the bile ducts or has metastasized intra-abdominally.[31] The clinical presentation of gallbladder cancer is difficult to separate from that of biliary colic. Advanced symptoms such as persistent pain, weight loss, and jaundice are often signs of unresectability. Elderly patients with a history of biliary colic that changes to a persistent, unrelenting, dull pain should be suspected of having gallbladder cancer, especially in the presence of weight loss or a right-upper quadrant mass. Any new right-upper-quadrant symptoms should prompt a work-up. The presence of jaundice is a particularly ominous finding. The median survival of patients with jaundice was 6 months as compared to patients without jaundice where the survival was 16 months.[39,40] Laboratory examination generally is not very helpful expect for the typical signs of advanced disease such as anemia, hypoalbuminemia, leukocytosis and elevated alkaline phosphate or bilirubin. Tumor markers may be of help and should be considered if gallbladder cancer is suspected. Serum carcinoembroynic antigen >4 ng/mL is 93% specific and 50% sensitive for detecting gallbladder cancer in the presence of appropriate symptoms[41] and a CA 19-9 serum level >20 U/mL is 79.4% sensitive and 79.2% specific.[42] Increased epidermal growth factor receptor (EGFR) expression has been noted in various cancers such as colon, squamous cell of the head and neck, non-small cell lung and breast cancers several small studies from Asia, Europe and Australia have examined the expression of EGFR in gallbladder cancer. The improved understanding of EGFR's role in oncogenesis has made it an attractive target for therapeutic intervention in several cancers. In a study by Kaufman *et al.* they found that EGFR was overexpressed in their patients of carcinoma gallbladder, they found that 3+ EGFR correlated with poorly differentiated carcinoma and patients with 1+ EGFR correlated with well-differentiated carcinoma.[43]

Table 1: AJCC staging system for gallbladder cancer (Seventh Edition)

T-stage	N-stage	M-stage
Tis=Carcinoma *in situ* T1=Tumor invades lamina propria (T1a) or muscle layer (T1b) T2=Tumor invades perimuscular connective tissue T3=Tumor perforates serosa and/or invades the liver and/or one adjacent organ T4=Tumor invades main portal vein or hepatic or multiple extrahepatic organs	N0=No regional nodal metastases N1=Metastases to nodes along cystic duct, hepatic artery, common bile duct, and/or portal vein N2=Metastases to pericaval, periaortic, superior mesenteric artery, and/or celiac artery nodes	M0=No distant metastases M1=Distant metastases

AJCC: American Joint Committee on Cancer

Early carcinoma gallbladder may be detected on abdominal ultrasonography (USG) as a fixed polypoidal mass projecting into the lumen of the gallbladder with absence of acoustic shadowing or as an asymmetric thickening of the gallbladder wall.[44] Signs of malignant disease on ultrasound examination include discontinuous mucosa, echogenic mucosa, and submucosal echolucency.[40] Diffuse thickening of the gallbladder is also common in gallbladder cancer but is also found in a benign condition.[41] The diagnostic accuracy of USG is over 80% in detecting carcinoma gallbladder (Chijiiwa *et al.* 1991).[44] A helical computed tomography scan with fine cuts through the liver may provide improved imaging over USG and should be examined carefully for evidence of liver metastases and enlarged celiac, perihepatic, and interaortocaval lymph nodes. A magnetic resonance (MR) scan with MR cholangiography is an ideal study.

Carcinoma gallbladder is incidentally discovered during cholecystectomy for benign diseases in 12-36% of patients (Bergdahl 1980).[45] If carcinoma gallbladder is discovered

intraoperatively the surgeon has to decide whether curative surgery is possible after determining the extent of disease. If the disease is so extensive as to preclude curative resection then a biopsy along with the appropriate palliative procedure may be carried out. Sometimes the probability of carcinoma gallbladder becomes evident only after the gallbladder is opened up after removal hence it is important to examine the opened gallbladder carefully before closing the abdomen. A difficult gallbladder at surgery usually raises the suspicion of cancer. Unusual findings at surgery such as a gallbladder mass, dense adhesion of the organs which are adjacent to the gallbladder and a difficult dissection of the gallbladder from the liver-bed are all pointers to the presence of a possible malignancy. Surgery is the only curative form of treatment with results depending upon the stage of the disease. Patients with disease confined to the gallbladder are treated by an extended or radical cholecystectomy (Gall *et al.* 1991).[46] Definitive resection for gallbladder cancer depends on the stage and location of the tumor as well as whether it is a repeat resection after the previous simple cholecystectomy. T1 (Stage lA) tumors can be treated with simple cholecystectomy. Stage IB, II, and selected Stage III (T4NO) tumors should be treated with en bloc resection of the gallbladder, segments IVb and V of the liver and regional lymph node dissection.[47] Donohue *et al.* (1990) reported a 5 year survival of 29% after extended cholcecystectomy in patients with transmural (T3, T4) tumor invasion and lymph node involvement.[48] Nakamura *et al.* (1989), Ogura *et al.* (1991) and Ouchi *et al.* (1994) advocate more extensive surgery such as excision of bile ducts, more extensive liver resections and even pancreaticoduodenectomy to further increase survival rates.[49,50] The criteria for resectability can vary, but presence of multiple peritoneal or liver metastases, distant metastases, extensive involvement of hepatoduodenal ligament, encasement or occlusion of major vessels and poor performance status are contraindications for surgical resection. Recommendations for liver resection for gallbladder cancer have ranged from a limited wedge excision of 2 cm of liver around the gallbladder bed to routine extended right hepatic lobectomy. The goal is to achieve a negative margin on the tumor, encompassing cells that have directly infiltrated the liver.[47]

In patients not fit for tumor resection, some form of palliative procedure such as a surgical bilioenteric bypass or endoscopic/percutaneous stenting in patients with obstructive jaundice may be done (Baxter and Garden, 1999).[51] Advances during the past decade in both endoscopic and radiologically guided percutaneous stenting of the biliary tract have made operative bypass, in cases of unresectable cancers, largely unnecessary. Non-operative stenting is the preferred approach. Duodenal or intestinal bypass may be done as a palliative procedure if gastric outlet or intestinal obstruction is present. In addition, patients may require palliation of pain, which is a major problem in advanced carcinoma of the gallbladder.[52] The incidence of gallbladder cancer is low compared with the incidence of gallstones in the population, so prophylactic cholecystectomy for asymptomatic cholelithiasis to prevent the development of carcinoma is not indicated Studies have suggested that the prognosis is different for pT1a and pT1b tumors after simple cholecystectomy.[53] T1a staging, no extended cholecystectomy is indicated, and simple cholecystectomy should result in a 100% 5-year survival. These tumors are recognized incidentally at the time of pathologic review, and as long as the cystic duct margin is negative, no further surgery is indicated. T1b staged tumors, an extended cholecystectomy is indicated as these tumors have been reported to recur after simple cholecystectomy. Patients with Stage II disease (T2NO) are best treated with an extended cholecystectomy. When an extended cholecystectomy is performed for T2 disease, the 5-year survival has been reported to be as high as 100% but probably falls in the range of 70-90%. Simple cholecystectomy alone is associated with a 5-year survival rate of 20-40.5%.[54] For patients with Stage T1b disease (T3 N1), an extended cholecystectomy is the recommended treatment approach. This should include en bloc resection of the common bile duct for the grossly positive periportal lymph nodes in order to improve periportal lymph node clearance. The 5-year survival ranges from 45% to 63% for patients having metastatic disease to N1 nodes. The 3-year survival has ranged from 38% to 80% in various trials. Stage III gallbladder cancer represents an advanced malignancy that is generally beyond surgical treatment. However, patients with T4NO disease, representing a mass-forming gallbladder cancer, may achieve long-term survival after an extended resection.[55] Patients with nodal metastases beyond the hepatoduodenal ligament have a poor prognosis, and in general for these cases the authors advocate palliative care.

Chemotherapy has not been widely successful in the treatment of gallbladder carcinoma fluorouracil is the most extensively used drug and fluorouracil-based combinations such as fluorouracil, adriamycin, and mitomycin C have been used without much success. The best responses were obtained by use of combined gemcitabine and cisplatin - survival was significantly improved. Ben-David *et al.* reported 14 patients with gallbladder cancer treated at the University of Michigan with resection followed by radiotherapy or chemoradiotherapy. The median radiation dose was 54 Gy and approximately half the patients received concurrent chemotherapy.[56] The median survival was 23 months, interestingly there was no difference in survival between RO and R1 resection patients. Wang *et al.* analyzed the SEER data and identified 4180 patients who underwent

resection between 1988 and 2003. The authors constructed a multivariate Cox proportional hazards model for overall survival. Age, gender, papillary histology, stage, and adjuvant radiotherapy were significant predictors of survival. The model predicts that adjuvant radiotherapy provides a survival benefit in node-positive or T2 or higher disease. The unadjusted median overall survival in patients who received radiotherapy was 15 months compared to 8 months in those who did not receive radiotherapy ($P < 0.0001$).[57] In another study, Balachandran *et al.* reported 117 patients with gallbladder cancer, of whom 80 underwent simple cholecystectomy, and 37 underwent extended resections. 73 patients received adjuvant chemoradiotherapy and 44 did not. No details were provided regarding this therapy or the selection criteria for adjuvant therapy. The median survival of all 117 patients was 16 months. On multivariate analysis, T-stage and the use of adjuvant therapy were the only statistically significant independent predictors of survival. Median survival was 24 months, 11 months in patients with or without adjuvant chemoradiotherapy ($P = 0.001$), and this difference was most pronounced for patients with T3, node-positive disease or after a simple cholecystectomy.[57] The high risk of systemic spread and loco-regional failure associated with gallbladder cancer that extends beyond the mucosa has led most cancer centers to recommend consideration of adjuvant chemotherapy and radiotherapy.

CONCLUSION

Carcinoma gallbladder is a devastating disease with dismal results. There is an increase in the number of cases of carcinoma gallbladder, may be due to better imaging techniques and more awareness among the patients due to better facilities. The progression of the disease is rapid with low 5-year survival. Key to survival is early detection of the disease and aggressive treatment strategy. Surgery is the only curative form of treatment which can achieve its intended goal if done at an early stage (T1) otherwise with the loco-regional spread, and jaundice survival is barely 6 months. Resection of hematogenous metastasis is not justified nor is resection of distant nodal disease. Radiotherapy and chemotherapy are the adjuvants to treatment but still the gold standard treatment is surgical resection (Ro) at an early stage.

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