

## GALL BLADDER CANCER ETIOPATHOLOGY AND TREATMENT

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Carcinoma gall bladder has an unusual geographic distribution. While it is uncommon in Europe and the United States, it is more frequent in Chile, Bolivia and Israel (Orth and Berger, 2000). The incidence of carcinoma gall bladder in India ranges from 1.01 per 100000 for males to 10.1 per 100000 for females (ICMR 1996) but the actual number may be much more in the endemic zones of Western Bihar and Eastern Uttar Pradesh where it is the third commonest malignancy of the alimentary tract (Shukla et al. 1985). Due to its non specific clinical presentation, it is seldom diagnosed preoperatively except in advanced cases. Survival depends on the ability to achieve a curative resection depending upon the stage of the disease. The overall surgical resection rates range from 10% to 30% only thereby indicating a poor prognosis. The aetiology of carcinoma gall bladder is poorly understood. Chronic cholecystitis and gallstones, choledochal cysts, female gender, age and exposure to carcinogens are some of the factors implicated in the causation of gall bladder cancer but a definite cause - effect relationship has yet to be established for any of these factors (Dixit et al 2001). The following article will discuss the evidence in support of the various aetiological factors and the management of patients with gallbladder cancer.

### I. CHOLELITHIASIS

Cholelithiasis is frequently associated with carcinoma gallbladder in up to 40%-100% patients and is the most common associated factor independent of age or sex (Hart et al, 1971). The risk of carcinoma gall bladder in patients with gall stones may be increased 4 to 7 times (Nervi et al, 1988) and patients with gallstones >3cm in diameter have a much higher risk (Diehl 1983). Gallstones were found in 45% of our cases of carcinoma gallbladder (Shukla et al, 1985). Carcinoma gallbladder is known to develop in patients with gallbladder preserving therapies for cholelithiasis. However, the mode of carcinogenesis is not clear.

Experimental studies have demonstrated chronic irritation of gallbladder mucosa by using different materials such as gallstones, pebbles, pitch,

linonin, glass beads etc. (Piehler et al, 1978). It has been shown that chronic trauma and inflammation can induce epithelial dysplasia, carcinoma in situ and invasive cancer (Kijima et al, 1989, Dowling & Kelly, 1986) but a cause and effect relation has not been unequivocally proved. Furthermore, one would expect squamous carcinoma to develop as a result of chronic irritation whereas it is adenocarcinoma which is the commonest histological type of carcinoma gallbladder seen in over 90% of cases. In about 10-40% of patients, carcinoma gallbladder is not associated with gallstones. Moreover only a small proportion (1-3%) of all cholelithiasis patients develop carcinoma gallbladder (Piehler et al, 1978). Certain ethnic and racial groups have a higher incidence of carcinoma gallbladder in population where cholelithiasis is uncommon (Strom et al 1995) suggesting that other environmental and/or genetic factors may also have a contributory role in gallbladder carcinogenesis. Comfort et al followed patients with silent gallstones for 10-25 years and only 1% of them developed carcinoma gallbladder. In another prospective study none of the 123 patients with gallstones who were followed from 1000 patient years developed carcinoma. Therefore there is insufficient clinical data to irrefutably support this association, yet, the frequent association suggests common antecedents.

#### *Chronic Cholecystitis:*

Approximately 50% patients of carcinoma of the gallbladder have a history suggestive of chronic cholecystitis (Silk et al, 1989). It has been reported that carcinoma gallbladder may develop in 10% of patients with xanthogranulomatous cholecystitis, (Houston et al, 1994, Benbow 1989) a variant of chronic cholecystitis but in our own series there has been a low association between xanthogranulomatous cholecystitis and carcinoma gallbladder suggesting that this is a coincidental finding (Dixit et al, 1998).

#### *Porcelain gallbladder:*

There is a 20% risk of developing carcinoma gallbladder in patients with calcified or porcelain

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gallbladder making this an absolute indication for cholecystectomy (Berk et al, 1973).

**Gallbladder polyp:** Even though a definitive evidence similar to the adenoma carcinoma sequence in colonic cancer is lacking in carcinoma gallbladder, recent studies suggest that polyps greater than 10mm in diameter have a strong malignant potential. In one study all the adenomas showing malignant change were larger than 12mm in diameter (Kozuka et al, 1982). If diagnosed in asymptomatic patients, cholecystectomy is recommended even in the absence of stones (Aldridge & Bismuth, 1990). However, for polyps < 10mm in diameter cholecystectomy is only recommended in the presence of stones and/or symptoms.

## II. CONGENITAL ANOMALIES

Recent studies have suggested that anomalous pancreaticobiliary duct junction (APBDJ) is a risk factor for carcinoma gallbladder (Kimura et al 1985, Chijiwa et al 1995, Mishra et al 1998). Gallbladder carcinoma occurred in 25% of the 65 patients with an anomalous union of the 2 duct systems as compared with 1.9% among 635 consecutive patients with a normal duct union. Anomalous duct union is seen in approximately 17% patients with carcinoma gall bladder as compared with less than 3% among patients with other hepatobiliary disorders. It is thought that this anomalous junction allows the free reflux of pancreatic juice into the gallbladder, the stasis of which damages the gallbladder mucosa and causes precancerous changes (Mori, 1993). Choledochal cysts are also associated with malignant transformation if they are left or incompletely excised during surgery.

**Inflammatory bowel disease:** Though the association of sclerosing cholangitis with long standing ulcerative colitis is well known, carcinoma gallbladder has been uncommonly reported in patients with chronic inflammatory bowel disease (O'Connor 1986). Polyposis coli also has been rarely associated with carcinoma gallbladder (Willson et al, 1987).

**Chemical Carcinogen:** Methylcholanthrene, a known chemical carcinogen is derived from deoxycholic acid which aroused suspicion about the possible role of bile acids as precursors of carcinogenic aromatic hydrocarbons in gallbladder carcinogenesis. Recently many studies have shown bile acids as co-mutagens as they can cause dysplastic changes in colonic and gastric mucosa. We have found a significantly high concentration of secondary bile acid in patients with carcinoma of the gallbladder (Shukla et al, 1993). Chemicals such as O-aminoazotoluene, aflatoxin B and

various other nitrosamines have been implicated in carcinogenesis in experimental studies (Klamer & Max, 1983). This observation is further supported by the high risk of carcinoma gallbladder occurring in rubber, automobile, wood finishing and metal fabricating industry workers who are exposed to nitrosamines (Kelly & Chamberlain 1982).

## III. DIETARY FACTORS

The role of dietary factors in gallbladder carcinogenesis is now well defined. The regions of Eastern UP, and Western Bihar where carcinoma gallbladder is highly prevalent lie downstream of the river Ganges which is the main source of drinking and irrigation water. It also receives untreated domestic sewage and industrial effluents and it is possible that certain environmental pollutants may act as carcinogens. We have shown the protective effect of vegetables on gallbladder carcinogenesis while consumption of red meat was associated with increased risk of gallbladder cancer (Pandey et al, 2002). Other studies have also shown protective effect of fat and protein rich diet and consumption of fiber, vitamin C and vitamin E (Tominaga et al, 1979, Zatonski et al, 1992).

## IV. REPRODUCTIVE FACTORS

Increased frequency of carcinoma gallbladder in females suggests a possible role of hormonal factors (Silk et al 1989, Plesko et al 1985). An increased risk has also been seen in women taking oral contraceptive pills. Khan et al (1999) reported post menopausal status to be a risk factor for carcinoma gall bladder. Singh et al (1997) reported a high risk of carcinoma gallbladder in women having early menarche, late marriage, late pregnancy and prolonged reproductive phase. Epidemiological studies have demonstrated a strong association between carcinoma gallbladder, obesity and oestrogens.

## V. FAMILIAL AND GENETIC FACTORS

Several members of two Spanish American families were affected by carcinoma of the gallbladder. Trajber et al (1982) reported carcinoma gallbladder in two siblings from Brazil. Recently Pandey et al (1995) have shown increased frequency of carcinoma gallbladder in patients with A+ and AB+ blood groups. Allele specific mutations in pathogenesis of carcinoma gallbladder were reported in 25 patients by Wistuba et al (1995).

## VI. BILE AND BACTERIA

Primary bile acids are degraded to the secondary bile acids by anaerobic organisms in the large bowel, some of which are thought to be implicated in colonic carcinogenesis (Lowenfels, 1978). Fox et al (1998) identified the presence of *Helicobacter* species in bile and gallbladder tissue from patients with cholelithiasis and cholecystitis but its relevance in carcinoma of the gallbladder is not yet established. A study from one centre has clearly shown significantly higher secondary bile acid in carcinoma of the gallbladder with positive culture (Shukla et al, 1993). Among the different microbial agents salmonella typhi has been implicated frequently. Mellemsgaard et al (1988) reported a six fold higher risk for hepatobiliary cancer among typhoid carriers but the exact mechanism of carcinogenesis is yet to be established. We found that 10.7% of our cholelithiasis patients were typhoid carriers. There was an 8.5 times higher risk of carcinoma in culture positive carriers as compared to culture negative carriers (Pandey et al, 1995, Shukla VK et al, 2000).

## VII. FATTY ACIDS

The fatty acid saturation index is found to be decreased in patients with recurrent cancer as compared to cancers without recurrence (Wood et al, 1985). The erythrocyte stearic and oleic acid ratio (Erythrocyte saturation index) changes in patients with cancers as compared to cholelithiasis, a finding which is however, not specific for neoplasia (Pandey et al, 1995, Kelly et al, 1990).

### *Lipid peroxidation and cytochrome P-450*

Free radicals, which are highly reactive chemical intermediates, are being implicated in a wide range of neoplastic transformations. Lipid peroxidation is a free radical mediated chemical reaction which damages polyunsaturated fatty acids and results in liberation of genotoxic and tumorigenic peroxidation products (Southorn et al, 1988). Increased concentration of a lipid peroxidation product 4-hydroxynoneal (HNE) was reported in the bile of patients with carcinoma of the gallbladder (Shukla et al 1994). NADP cytochrome P-450 acts as an electron donor and thus promotes generation of free radicals which initiate lipid peroxidation (Rosen & Rauchkan 1982). Significantly higher levels of this enzyme have been associated with carcinoma of the gallbladder (Singh et al 1998).

## VIII. HEAVY METALS AND METALLOTHIONEIN

Heavy metals as environmental pollutants have been implicated in carcinogenesis. In our study

significantly higher biliary concentration of cadmium, chromium and lead was seen in patient with carcinoma gallbladder as compared to those with gallstones alone (Shukla et al, 1998). Recently metallothionein, a low molecular weight, metal binding protein which also acts as a free radical scavenger has been shown to play a protective role against heavy metal toxicity. We have observed significantly higher metallothionein expression in carcinoma gallbladder (70.3%) as compared to controls and cholelithiasis (Shukla et al, 1998). Metallothionein expression has also been shown to be associated with resistance to anticancer drugs (Kelly et al, 1988).

## IX. DIAGNOSIS OF CARCINOMA GALLBLADDER - CLINICAL PRESENTATION

Early carcinoma gallbladder has no specific clinical presentation and preoperative diagnosis is rarely possible. Most of these patients are asymptomatic while a few present with clinical features suggestive of benign disease such as right upper abdominal pain interspersed with occasional attack of nausea and vomiting. In one study (Cunningham et al, 2002), 48.2% of patients of carcinoma gallbladder had a preoperative diagnosis of symptomatic cholelithiasis. About 1% of patients operated for acute cholecystitis are found to have carcinoma gallbladder. Jaundice, presence of a lump and features of malignant cachexia such as anorexia and weight loss are a feature of extensive disease as is the presence of repeated attacks of vomiting which suggests gastric outlet obstruction due to tumour infiltration. The presence of a hard nodule in the liver and ascites indicates disseminated disease. In 15-20% of patients, carcinoma gallbladder is discovered either intraoperatively or postoperatively on histology, which in only 20% of the patients is the disease confined to gallbladder at diagnosis. The majority of the patients thus have locoregionally advanced or metastatic disease on first presentation.

## X. INVESTIGATIONS

Early carcinoma gallbladder may be detected on abdominal USG as a fixed polypoidal mass projecting in to the lumen of the gallbladder with absence of acoustic shadowing or as an asymmetric thickening of the gallbladder wall. However differentiation from cholecystitis is difficult because wall thickening can be seen in both diseases (Hederstrom et al, 1987). Advanced tumours also show loss of interface between gallbladder and liver indicating tumour invasion, lymph node and hepatic metastases, dilated bile ducts and ascites. USG will also show associated gallstones.

The diagnostic accuracy of USG is over 80% in detecting carcinoma gallbladder (Chijiwa et al 1991). Endoscopic ultrasonography delineates the depth of tumour invasion fairly accurately. The diagnostic accuracy of CT scan at 60% (Araki et al, 1988) is lower than that of USG. Its main advantage lies in showing tumour infiltration into adjacent viscera or vessels, lymph node and distant metastases. The morphologic appearances of carcinoma gallbladder are similar on MRI and CT. The tumour appear hypointense on T1 weighted images and hyperintense on T2 weighted images. It is useful for delineating tumour invasion in hepatoduodenal ligament, portal vein encasement and lymph node involvement. There are no large series comparing CT and MRI (Kersting - Sommerhoff et al 1993). Even though cholangiography does not help in diagnosis of carcinoma gallbladder, it is helpful in planning operative procedures because it can

demonstrate the level and extent of tumour infiltration into extrahepatic/intrahepatic ducts. US or CT guidance greatly enhances the diagnostic accuracy of fine needle aspiration cytology (FNAC) in comparison to a blind FNAC (Shukla et al 1997). The reported sensitivity of guided FNAC is 88% (Akosa et al 1995). Biochemical investigations being non specific have little diagnostic value. Elevated serum bilirubin and alkaline phosphatase suggests biliary tract obstruction. Tumour markers such as CEA and CA 19-9 are only occasionally elevated (Yamaguchi et al, 1988).

## XI. STAGING

TNM and Nevin's staging of gallbladder carcinoma

<i>Nevin's stage</i>	<i>TNM Staging</i>	<i>Definition</i>
Stage I - Intramucosal only	0	T1s - Carcinoma in situ N0 - No lymph node metastases M0 - No distant metastases
Stage II- Extends to the muscularis	I	T1a - Tumour invades mucosa T1b - Tumour invades muscularis N0 - No lymph node metastases M0 - No distant metastases
Stage III - extends through the liver	II	T2 - Tumor invades perimuscular connective tissue extension beyond serosa or into liver N0 - No lymph node metastases M0 - No distant metastases
Stage IV - transmural involvement	III	T3 - Tumour invades beyond serosa or into on adjacent organ or both (extension 2cm or liver) N1- regional lymph node metastases M0 - No distant metastases or T1N1M0 or T;
Stage V - Direct extension and/or distant metastases	IV	T4 - Tumour extends more than 2cm into liver and/or into two or more adjacent organs (between stomach, duodenum, liver, omentum etc). N0 or N1 M0 or Any T1 any N1 M1 - distant metastases

## XII. TREATMENT

The treatment depends primarily upon the stage of the disease at presentation. The only potentially curative therapy is surgical resection. Unfortunately the overall resection rates at presentation range from 10%-30% only. Broadly management guidelines can be divided into three clinical groups.

1. Incidentally discovered carcinoma gallbladder during laparotomy or after cholecystectomy for benign disease.
2. Carcinoma gallbladder suspected or confirmed preoperatively on diagnostic workup
3. Advanced carcinoma gallbladder diagnosed clinically or by preoperative investigations.

### *Incidentally discovered carcinoma gallbladder:*

Carcinoma gallbladder is incidentally discovered during cholecystectomy for benign diseases in 12-36% of patients (Bergdahl 1980, Pehler & Crichlow 1978). 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. More commonly, however it is only after histopathological examination of the cholecystectomy specimen that the diagnosis is made. Further treatment of such cases remain controversial. While most authors feel that simple cholecystectomy is adequate if the tumour has not invaded beyond the muscle layer reporting 5 year survival rates of nearly 100%. (Wanebo et al 1980, Donohue et al 1990, Gagner & Rossi 1991, Cubertafond et al 1994) other authors notably Ouchi et al (1993, 1994) argue against this approach. They have reported a 100% 5 year survival for lesions confined to mucosa and muscularis treated by extended cholecystectomy as against 71% and 92% 5 year survival rates respectively for patients treated by simple cholecystectomy alone ( $p < 0.05$ ). A large number of patients in this situation have been reoperated for more extensive surgical procedures but long term survival in this group is almost entirely limited to only those who have no residual tumour in the resected specimen (Morrow et al 1983, Yamaguchi et al 1992, Shirai et al 1992, de-Aretxabala et al 1992, Toyonaga et al 2003). These authors have showed that occult carcinoma gallbladder which penetrates only the

mucosa or muscle coat carries a 100% 5 year survival whereas if the serosal layer is invaded the 5 year survival decreases to 91% if resection margins are negative on reexploration and to 43% with positive resection margins. At present there is no irrefutable evidence to recommend a uniform guideline for reexploration in all occult carcinoma gallbladder detected by the pathologist subsequently. The morbidity and mortality of reexploration has to be weighed against the lack of demonstrated efficacy of subsequent surgery. This underlines the importance of a preoperative or at least a peroperative diagnosis. In a resectable carcinoma recognized intraoperatively, extended resection including a wedge of liver and hepatoduodenal lymphatic tissue may improve the duration of survival for patients with gallbladder cancer invading beyond the mucosa (stage I & II) but not invading contiguous structure (Stage III & IV). This extended or radical cholecystectomy means enbloc removal of the gallbladder bed. The lymphatics surrounding the portal vein, hepatic artery, porta-hepatis and the nodes behind the 2nd part of duodenum, head of pancreas and coeliac axis are also dissected. The extent of liver resection ranges from a nonanatomical wedge resection to removal of segments IV & V (Bismuth et al 1982, Blumgart 1984), Segments IV, V and VIII and even right hepatic lobectomy.

The surgical management of carcinoma gallbladder diagnosed preoperatively depends upon the extent of the disease determined either by investigations or at laparotomy. Patients with disease confined to the gallbladder are treated by extended or radical cholecystectomy (Gall et al 1991) but for disease extending beyond the gallbladder extended or radical cholecystectomy offers little, if any, survival advantage. Donohue et al (1990) reported a 5 year survival of 29% after extended cholecystectomy in patients with transmural (T3, T4) tumour invasion and lymph node involvement as compared to no survivors after simple cholecystectomy in this group of patients. Matsumoto et al (1992), 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. Although some long term survivors have been reported, the morbidity and mortality of these procedures is high (48-54% and 15-18% respectively) especially in patients with obstructive jaundice. Nakamura et al (1989) reported 54% 1 year survival, 23% 2 year survival and 15% 5 year survival rate for patients with TNM stage IV carcinoma gallbladder. 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. Direct involvement of colon, duodenum or liver however, are not absolute contraindications for resectional surgery.

In patients not fit for tumour resection, some form of palliative procedure such as a surgical bilio-enteric bypass or endoscopic/percutaneous stenting in patients with obstructive jaundice may be done (Baxter & Garden, 1999). Since the level of tumour obstruction is usually at the common hepatic duct or above, the round ligament approach to the segment III duct along with a biliary enteric anastomoses provides good palliation. In the presence of tumour invasion of the umbilical fissure of the liver, segment III bypass is not possible and recourse has to be taken for an alternative approach such as the Longmire procedure (Blumgart & Thompson 1987). Advances in endoscopic and radiologically guided percutaneous stenting have made operative bypass procedures in patients with unresectable cancer largely redundant. For patients with distal common bile duct obstruction an endoscopically placed stent provides good palliation whereas the percutaneous approach does the same for more proximal obstructions. These patients rarely live long enough to require stent replacement.

Duodenal or intestinal bypass can also be performed as a palliative procedure if gastrointestinal obstruction is present.

### **Radiotherapy**

Radiotherapy has been used primarily as an adjuvant treatment following surgery. The 3 year cumulative survival rate was 10.1% for patients receiving intraoperative radiotherapy after resectional surgery whereas it was nil for a similar group of patients undergoing resection alone (Todoroki et al, 1991). External radiotherapy has also shown some survival benefit (Houry et al 1989). However carcinoma gallbladder is not only relatively radioresistant but also the proximity of sensitive normal tissues limits the delivery of large doses of radiotherapy.

### **Chemotherapy**

5-Fluorouracil (5-FU) either alone or in combination has been widely used but without much success. It offers no survival benefit (Falkson et al, 1984), however hepatic arterial infusion of mitomycin C with or without systemic 5FU was associated with

increased survival rates (Smith et al, 1984). Further studies are required before chemotherapy can be recommended in patients with carcinoma gallbladder wither as an adjuvant or as a palliative therapeutic strategy.

### **Prognosis and survival**

The stage at presentation is the most important prognostic determinant. Presently, the overall survival I carcinoma gallbladder is extremely discouraging. Hension et al (1992) have shown 2 year survival is 45% for stage I, 15% for stage II, 4% for stage III and 2% for stage IV. Medical survival is 19, 7, 4 and 2 months for stage I, II, III and IV disease respectively.

The aetiology of carcinoma of the gallbladder is not known. However in region where the incidence of carcinoma of the gallbladder is high, cholelithiasis should be considered as a risk factor.

Most of the case present with advanced disease. In early carcinoma of the gallbladder sign and symptoms mimic benign disease.

Right upper quadrant pain, hard irregular lump in the right hypochondrium and jaundice, are the commonest symptoms.

The diagnosis is established by ultrasonography or computerised tomography and a guided fine needle aspiration cytology.

Biochemical tests are of very little value in making a diagnosis.

The treatment depends upon the clinical stage at presentation. Surgery offers the best chances of cure.

The exact role of chemotherapy and radiotherapy in management of carcinoma of the gallbladder is unclear for accidentally diagnosed carcinoma gallbladder.

Resurgery is required only in those cases where tumour has invaded the adjacent liver bed. Reoperation does not significantly improve the prognosis in early carcinoma gallbladder (T1).

A multicenter, phase II trial preliminary results indicate the efficacy of the combination of gemcitabine and cisplatin in gallbladder cancer in association with modest toxicity.

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