

Carcinoma of the gallbladder

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Abstract

Carcinoma of the gallbladder is the most common biliary tract tumor and the fifth most common gastrointestinal tract cancer. Women are two to three times more commonly affected than men. The risk is significantly higher in cholelithiasis. Congenital malformations of the biliary tract (more frequent in Japan and possibly China than in western countries) are considered to be a risk factor for gallbladder carcinoma. TP53 and KRAS mutations have been found associated with the pathogenesis of gallbladder carcinoma. The symptoms of gallbladder carcinoma are nonspecific. More than 85% of gallbladder cancers are adenocarcinomas. Gallbladder carcinoma is staged using the American Joint Committee on Cancer TNM Staging System. Radical surgery including segmental liver resection, bile duct resection and extensive lymphadenectomy should be performed. The role of adjuvant treatment including radiation, chemoradiation or chemotherapy alone has not been proven. Patients with unresectable disease have poor prognosis. Some patients will benefit from nonsurgical palliative procedures such as biliary drainage and stenting. External radiation therapy may provide palliative benefit. 5-Fluorouracil (5-FU) has been the most active single agent with a 10-20% response rate. Gemcitabine is a promising agent. Addition of cisplatin may increase the response rate. Other agents with reported activity in biliary tract cancers are capecitabine, docetaxel, mitomycin-C, doxorubicin and nitrosureas.

Keywords

Gallbladder cancer, KRAS, TP53, BCL-2, 5-Fluorouracil, Cisplatin, Gemcitabine

Disease name

Carcinoma of the gallbladder

Definition/Diagnostic criteria

Carcinoma of the gallbladder is an aggressive malignancy occurring predominantly in the elderly

with a mean age of 65.2 years. It constitutes nearly two-thirds of the biliary tract cancers, making it the most common biliary tract tumor and the fifth most common gastrointestinal tract cancer (1,2).

Epidemiology

Women are two to three times more commonly affected than men. Ethnic background and geographic location are important in the incidence of gallbladder cancer. In United States gallbladder cancer is seen 5-6 times more in Southwestern American Indians, Mexicans, Hispanics and Alaskans. The rate of gallbladder cancer is higher in Poland, Hungary, former Czechoslovakia, Japan, Peru, Ecuador, Colombia, Costa Rica and interestingly, highest in Chile where the mortality rate (5.2%) is the highest in the world. Gallbladder cancer is the fourth leading cause of cancer deaths in Chile. Marked geographic differences seen in the frequency of gallbladder carcinoma suggest a possible environmental cause besides race or ethnicity (3-6).

Etiology/Risk factors/Molecular biology

There is a strong association between gallbladder cancer and cholelithiasis. Cholelithiasis is present in up to 90% of the cases (4-6). The risk of developing gallbladder cancer is significantly higher in patients with cholelithiasis, calcified/porcelain gallbladders, anomalous pancreatic duct-biliary duct junction and typhoid carriers. Congenital malformations of the biliary tract are more frequent in Japan and possibly China than in western countries. Incidental gallbladder cancer is detected in approximately 1-2% of all elective cholecystectomies (6). The risk of gallbladder cancer correlates with increasing gallstone size. The relative risk is 2.4 times higher in patients with gallstones 2.0-2.9 cm in diameter, while the risk is 10.1 times higher when the gallstone diameter size is greater than 3.0 cm (7). Other risk factors include adenomatous polyps, partial gastrectomy, obesity, exposure to azotoluene, estrogen, methyldopa, isoniazide or nitrosamine. Workers in rubber and metal fabrication industries are also at increased risk of developing gallbladder cancer. Strong dietary association has also been reported. While increased intake of total carbohydrates is associated with increased risk, a significant reduction in the risk has been observed with increased intake of vitamin B6, vitamin E. Increased intake of fat, vitamin C and dietary fibers has also been found to be protective (5).

There seems to be a chronic inflammation-hyperplasia (adenomatous polyp)-dysplasia-carcinoma *in situ* and invasive carcinoma sequence in the development of gallbladder cancer. *RAS* mutations especially *KRAS* were noted in high grade hyperplasia, suggesting that proto-oncogen activation was an early event in gallbladder carcinogenesis (8). In majority of invasive carcinomas, tumor suppressor gene *p53* (*TP53*), the genes encoding cyclin D1 and/or cyclin E, and apoptosis regulator gene *BCL-2*, were found to be mutated (9).

Sign and Symptoms

Gallbladder carcinoma is usually asymptomatic in the early stages, later symptoms such as right upper quadrant pain, nausea, vomiting, intolerance of fatty foods, jaundice, and weight loss occur. The non-specificity of symptoms is responsible for delayed diagnosis resulting low curability of the disease. Physical examination may reveal right upper quadrant tenderness, a palpable mass, hepatomegaly and ascites.

Diagnosis

Gallbladder carcinoma is usually diagnosed at an advanced stage. The tumor is usually unresectable at the time of diagnosis. The laboratory findings are also non specific and may include anemia, leukocytosis, and elevated bilirubin and alkaline phosphatase levels. Tumor markers Carcinoembryogenic antigen (CEA) and CA 19-9 may be elevated but are not usually helpful in diagnosis. Ultrasonography (US) is usually the first diagnostic modality. US may show gallbladder wall thickening, replacement of gallbladder with a heterogeneous mass or tumor extension into the liver. Computed tomography (CT) is superior to US in assessing lymphadenopathy and spread of the disease into liver, porta hepatis or other adjacent structures. Magnetic Resonance Imaging (MRI) maybe used to evaluate intrahepatic spread, portal vein involvement and biliary obstruction. Endoscopic retrograde cholangiopancreatography (ERCP) or transhepatic cholangiography (THC) may be useful in the presence of jaundice to determine the location of biliary obstruction and involvement of the liver but MR cholangiopancreatography (MRCP) seems to replace these techniques.

Pathology

More than 85% of gallbladder cancers are adenocarcinomas, usually well or moderately differentiated and the remaining 15% are adenosquamous, squamous or undifferentiated carcinoma. Sarcomas, neuroendocrine carcinomas or lymphomas constitute less than 1% of all gallbladder tumors.

Route of spread

The major route of spread of gallbladder cancer is locoregional rather than distant, with 25% of patients having lymphatic involvement and 70% having direct extension of disease into liver. Lymphatic drainage from the gallbladder occurs in a predictive fashion and correlates with the pattern of lymph node metastases seen in gallbladder cancer. Initially the cystic duct and pericholedochal nodes are involved, followed by more distant metastases to nodes posterior to the head of the pancreas and then to inter aortocaval lymph nodes. This primary route is called

cholecysto-retropancreatic course. Secondary route of lymphatic drainage includes the retroportal and right celiac lymph nodes through the gastrohepatic ligament, called cholecysto-celiac pathway. The third one is called cholecysto-mesenteric route consisting of a pathway from the gallbladder posterior to the pancreas to aortocaval lymph nodes (10). Commonly, the gallbladder cancer also extends directly into the liver and porta hepatis resulting in narrowing or obstruction of the common hepatic or right hepatic duct.

Staging

Gallbladder carcinoma is staged primarily at the time of surgery and staging is determined by the depth of invasion, extension of disease into adjacent structures, involvement of lymph nodes and presence of metastasis using the American Joint Committee on Cancer TNM Staging System (11,12) (Table 1).

Treatment

Relatively few patients with gallbladder cancer are diagnosed prior to surgery. Only 25% of the gallbladder cancer are resectable.

Surgery

Surgical management of gallbladder carcinoma is based on the local extension of the tumor. At early stage when the tumor invades mucosa but does not penetrate into the muscularis and those that penetrates full thickness but does not abut the liver or muscularis, cholecystectomy alone is required. If there is direct extension of disease to or through the serosa, radical surgery including segmental (segments 4b and 5) or wedge liver resection, bile duct resection and extensive lymphadenectomy should be performed. Radical surgery appears to increase survival. Median survival is improved in patients who have undergone a curative resection, as compared with those who have had palliative procedures or no surgery (17 months vs 6 and 3 months respectively). Resection should be particularly tried in cases with involvement limited to the gallbladder node where cure can be achieved. Nodal disease beyond pericholedochal nodes, however, is considered as surgically incurable (13-16).

Adjuvant therapy

Local recurrence after cholecystectomy has been reported to occur up to 86% of patients who die within 5 years after surgery. Data show that radiation therapy dose of more than 54 Gy is needed for improved local control of gallbladder cancer (17). In a study investigating the role of adjuvant chemotherapy in patients with resected pancreaticobiliary carcinomas, patients with gallbladder cancer benefited from an adjuvant chemotherapy regimen including 5-Fluorouracil

(5-FU) and mitomycin-C. At the end of 5-year follow-up 26% of the treated patients were alive while the survivors were only 14% in the follow-up group (18). However, there are not enough data to define the exact role of adjuvant treatment including radiation, chemoradiation or chemotherapy alone (17,18).

Treatment of unresectable disease

These patients have poor prognosis. Some patients will benefit from nonsurgical palliative procedures such as biliary drainage and stenting. External radiation therapy may provide palliative benefit. Radiation at the dose of 45 Gy has been shown to produce responses in 20-70% of the patients. Chemotherapy trials are scarce because of the relative rarity of the disease. Responses to chemotherapy are infrequent and of short duration. 5-FU has been the most active single agent with a 10-20% response rate (19). Gemcitabine is a promising agent. A phase II study reported 7/19 response rate in biliary tract cancer. In another trial with gemcitabine, 14/39 patients most of whom had gallbladder cancer, responded. Addition of cisplatin may increase the response rate. Other agents with reported activity in biliary tract cancers are docetaxel, capecitabine, oxaliplatin, mitomycin-C, doxorubicin and nitrosureas (20).

In the absence of a clinical trial patients should be offered 5-FU with or without folinic acid (leucovorin) or gemcitabine. Combination of cisplatin and gemcitabine may be synergistic. However, these combination regimens do not clearly improve survival, therefore they still should be considered as investigational.

Prognosis

Survival of gallbladder carcinoma is directly related to the disease stage. The 5-year survival rate is 83% for tumors that are confined to the gallbladder mucosa; this rate decreases to 33% if the tumors extends through the gallbladder. For patients who have involvement of the lymph node or metastatic disease, 5-year survival rates range 0%-15%. The median survival of patients with metastatic disease is around 6-12 months (8,9,19,20).

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Table 1. American Joint Committee on Cancer (AJCC) TNM staging of gallbladder cancer.

Primary Tumor			
Tx	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma <i>in situ</i>		
T1	Tumor invades the lamina propria or muscularis		
	T1a	Invasion of lamina propria	
	T1b	Invasion of muscularis	
T2	Perimuscular connective tissue invasion		
T3	Tumor perforates the serosa or invades adjacent structures		
T4	Tumor invades portal vein, hepatic artery, or 2 or more extrahepatic structures		
Regional lymph nodes (N)			
Nx	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis present		
Distant metastasis (M)			
Mx	Metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis present		
Staging grouping			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any M	M1

Greene FL, Fleming ID, et al (eds), AJCC Cancer Staging Manual (6th ed), New York: Springer-Verlag, 2002.