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Review Article

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Abstract: Gallbladder cancer is the fifth most common cancer involving gastrointestinal tract, but it is the most common malignancy of the biliary tract, accounting for 80-95% of biliary tract cancers. This tumor is a highly lethal disease with an overall 5-year survival of less than 5% and mean survival mere than 6 months. An early diagnosis is essential as this malignancy progresses silently with a late diagnosis. The percentage of patients diagnosed to have gallbladder cancer after simple cholecystectomy for presumed gallbladder stone disease is 0.5-1.5%. Patients with preoperative suspicion of gallbladder cancer should not be treated by laparoscopy. Epidemiological studies have identified striking geographic and ethnic disparities—inordinately high occurrence in American Indians, elevated in Southeast Asia, yet quite low elsewhere in the Americas and the world. Environmental triggers play a critical role in eliciting cancer developing in the gallbladder, best exemplified by cholelithiasis and chronic inflammation from biliary tract and parasitic infections. Improved imaging modalities and improved radical aggressive surgical approach in the last decade has improved outcomes and helped prolong survival in patients with gallbladder cancer. The overall 5-year survival for patients with gallbladder cancer who underwent R0 curative resection was from 21% to 69%. In the future, the development of potential diagnostic markers for disease will yield screening opportunities for those at risk either with ethnic susceptibility or known anatomic anomalies of the biliary tract.

Keywords: Gallbladder carcinoma; gallstones; laparoscopic cholecystectomy; liver resection

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Introduction

Biliary tract cancers are invasive adenocarcinomas that arise from the epithelial lining of the gallbladder and intrahepatic and extra hepatic bile ducts. Although anatomically these malignancies are related and have similar metastatic patterns, each has a distinct clinical presentation, molecular pathology, and prognosis (1).

Gallbladder cancer is the most common malignancy of the biliary tract, representing 80-95% of biliary tract cancers worldwide (2,3). It ranks fifth among gastrointestinal cancers.

The global rates for gallbladder cancer shows differences, reaching epidemic levels for some regions and ethnicities. Gallbladder cancer has a particularly high incidence in Chile, Japan, and northern India (2).

The basis for this variance likely resides in differences in environmental exposure and intrinsic genetic predisposition to carcinogenesis. For gallbladder cancer, several conditions associated with chronic inflammation are considered risk factors, which include gallstone disease, porcelain gallbladder, gallbladder polyps, chronic *Salmonella* infection, congenital biliary cysts, and abnormal pancreaticobiliary duct junction (1,2).

The percentage of patients diagnosed to have gallbladder cancer after simple cholecystectomy for presumed gallbladder stone disease is 0.5-1.5% (4-6).

In most instances, gallbladder cancer develops over 5 to 15 years, when metaplasia progresses to dysplasia, carcinoma *in situ*, and then, invasive cancer (1).

A satisfactory outcome depends on an early diagnosis and surgical resection. Despite this potential for cure, less than 10% of patients have tumors that are resectable at the time

of surgery, while nearly 50% have lymph node metastasis (4). Even with surgery, most progress to metastatic disease, highlighting the importance of improving adjuvant therapies (5).

This tumour is traditionally regarded as a highly lethal disease with an overall 5-year survival of less than 5% (5). The overall mean survival rate for patients with gallbladder cancer is 6 months (6).

Risk factors

The identification of risk factors is critical, providing insight into the pathogenetic mechanism that drives geographic and ethnic variance, and yielding strategies for prevention and treatment.

Gallbladder cancer rates tend to increase with advancing age. The median age was 67 years in a Memorial Sloan-Kettering report of 435 gallbladder cancer patients (5).

Gender differences demonstrate a marked predominance of women over men worldwide (7). Women are affected 2-6 times more often than men (8).

There is a widely variable geographic pattern for gallbladder cancer, Asia is a high risk continent, while the United States and most western and Mediterranean European countries (e.g., UK, France, and Norway) represent low risk areas (5,6,9,10).

Ethnicity plays a role even in different geographic locations. The Korean people have the highest incidence rate (per 100,000) of gallbladder cancer in Asia. Korean males living in Los Angeles County, California also carry the highest US ethnic incidence rate (10).

Gallstones represent a most important association for this malignancy, being present in most (~85%) patients with gallbladder cancer. The incidence of gallbladder cancer in a population with gallstones varies from 0.3% to 3% (11). The higher risk of gallbladder cancer development in larger stones possibly reflects the greater duration and intensity of mucosal irritation causing chronic inflamation (12,13). Prophylactic cholecystectomy would appear reasonable in these individuals (14).

Chronic inflammation causing deoxyribonucleic acid (DNA) damage, provoking repeated tissue proliferative attempts at restoration, releasing cytokines and growth factors, and thus, predisposing cells to oncogenic transformation (15). Chronic inflammation can also result in calcium being deposited in the gallbladder wall. When calcium deposits become extensive, the gallbladder acquires a bluish hue and becomes fragile, even brittle—hence the term "porcelain gallbladder" (16). The porcelain gallbladder is frequently (average 25%, range, 12-61%) associated with gallbladder cancer (17,18).

Chronic bacterial cholangitis poses a clear risk for biliary tract malignancy. The organisms that have been most implicated are *Salmonella* (e.g., *S. typhi and S. paratyphi*) and *Helicobacter* (e.g., *H. bilis*) spp (19,20). Bacterial colonization may induce hydrolysis of primary bile acids forming. Malignant transformation is further implicated via chronic inflammation itself and alterations of tumor suppressor genes [such as *tumor protein 53* (*p53*)] or proto-oncogenes [such as mutations of *Kirsten ras oncogene homolog* (*K-ras*)] (15,21).

Primary sclerosing cholangitis (PSC) is a chronic fibroinflammatory syndrome linking chronic inflammation to carcinogenesis (22). Facilitating a metaplasia-dysplasia-carcinoma sequence (23,24).

Various environmental exposures have been hypothesized to contribute to gallbladder cancer, such as: heavy metals, tobacco, radon (25-28).

Obese people have an increased risk of developing gallbladder cancer (29-31). The risk of developing gallbladder cancer in those with diabetes mellitus is increased (32).

Almost 5% of adults harbor gallbladder polyps (33,34). Most of them are pseudopolyps, without neoplastic potential (35). Features that predict malignancy are: large polyps (>10 mm), a solitary or sessile mass, associated gallstones, the patient's age over 50 years old, and most importantly, rapid polyp growth (7,29).

Anomalous junction of the pancreaticobiliary duct is a congenital malformation in which the pancreatic duct drains into the biliary tract outside the papilae Vateri. Such a long common channel defeats the gatekeeper function of the sphincter of Oddi, potentially allowing pancreatic secretions to regurgitate into the bile ducts and gallbladder, thus leading to malignant changes in the mucosa (36).

Gallbladder cancer seems to result from a combination of genetic predisposition and exposure to environmental risk factors (37). One proposed carcinogenic pathways suggest that: gallstone mediated inflammation → *p53* mutation (↓) → *K-ras* mutation (↑) (21).

Diagnosis

Clinical presentation is similar to biliary colic or chronic cholecystitis. The most common symptoms are: persistent right upper quadrant pain, jaundice, nausea and weight loss. In some patients palpable mass is present (38,39).

Imaging can detect malignancy. Transabdominal ultrasound is a useful initial modality for investigating patients with upper abdominal pain and jaundice (40).

Endoscopic ultrasound (EUS) is currently the definitive modality for staging gallbladder cancer. EUS also offers sampling via fine needle aspiration (41).

Computerized tomography (CT) helps identify any extension to lymph nodes, liver involvement, or distant metastases, performed preoperatively, determines gallbladder resectability with a high accuracy (up to 93%) (42) .

Standard magnetic resonance imaging (MRI) is generally less valuable. Magnetic resonance (MR) cholangiography and MR angiography quite accurately detects bile duct or vascular invasion, with sensitivity and specificity approaching 100%.

Positron emission computed tomography (PET) scans are useful in differentiating malignant from benign disease, in preoperative staging, and in detecting postoperative residual disease (43).

Staging system

Gallbladder cancer staging, based on the American Joint Committee on Cancer (AJCC) guidelines, focuses on tumor invasion and the extent of spread (44).

Adenocarcinoma is the most frequent histologic type, accounting for 98% of all gallbladder tumors (45). The other histopathologic variants include the papillary, mucinous, squamous, and adenosquamous subtypes. The disease stage determines the treatment options. The best outcomes are reserved for patients who qualify for cholecystectomy. In stage I disease, according to AJCC criteria, tumor invades the lamina propria or the muscle layer. Stage II is designated by the perforation of the serosa and/or involvement of adjacent organs or structures. T1 to T3 tumor invasion with any nodal involvement is automatically classified as stage II. Both stage I and II are potentially resectable with curative intent. Stage III generally indicates locally unresectable disease, as a consequence of vascular invasion or the involvement of multiple adjacent organs. Stage IV represents nonresectability because of distant metastases (46).

Surgical management

Primary tumor invasion (T) is the most important factor in the AJCC staging criteria; it determines the surgical approach (44). The overall 5-year survival for patients with gallbladder cancer who underwent R0 curative resection was reported to range from 21% to 69%, and 0% for patients who did not get R0 resection. So the R0 curative resection is objective of surgical management for gallbader cancer (40).

Type of liver resection for carcinoma of the gallbladder varies from atipical resection of segments IVb at V to right hepatectomy.

By the Union for internatonal Cancer Control (UICC)/ AJCC are two types of regional lymphadenectomy for gallbladder cancer:

N1—lymphnodes of hepatoduodenal ligament (cystic duct, pericholedochal and hilar lymph nodes);

N2—peripancreatic, periductal, periportal, common hepatic artery, coeliac and superior mesenteric artery lymph nodes.

Laparoscopic cholecystectomy is absolutely contraindicated when gallbladder cancer is known or suspected pre-operatively. Patients with a pre-operative suspicion of gallbladder cancer should undergo open exploration and cholecystectomy after proper pre-operative assessment, or immediately with suspicion made during laparoscopy. If the diagnosis is confirmed on frozen section radical surgical resection should be performed in the same session (5).

Incidental gallbladder cancers are detected histologically after the fact in 0.3-3% of laparoscopic cholecystectomies performed for cholelithiasis. For these patients a second radical resection is indicated after adequate diagnostic and treatment preparation, except for Tis and T1a disease.

Port-site recurrences can follow laparoscopic cholecystectomies in up to 17% of cases where unsuspected gallbladder cancer is discovered (47). Here, accidental bile spillage implants tumor cells at the trocar or incision site, leading to recurrence so the excision of the port sites are indicated during the radical reoperation.

Tis and T1a gallblader cancer (tumor is limited to mucosa) are usually diagnosed after cholecystectomy. There is consensus that simple cholecystectomy is an adequate treatment which offers a surgical cure with 100% 5-year survival (47).

In T1b gallbladder cancer (tumor invades the muscular layer) there is still controversy for the optimal management. Reported incidence of occult lymphatic metastasis is 15-25% in this stage with 10% incidence of residual disease in liver bed (47,48). Given the frequency of positive lymph nodes and residual disease in this stage, recommended procedure is cholecystectomy with radical resection which encompasses 3 cm of liver parenchyma segment IVb and V,

plus adequate lymphadenectomy (48,49). The outcome after simple cholecystectomy in this stage is 75% 10-year survival *vs*. 100% for radical operation.

T2 lesions of gallbladder cancer invade perimuscular connective tissue with no extension beyond the serosa or into the liver. The reported 5-year survival for patients with this stage of disease treated with simple cholecystectomy where 10-61% and 54-100% after radical resection. Yamaguchi reported that over 40% of these patients had positive margins after simple cholecystectomy with rate of positive lymph nodes of 19-62%. So radical resection is the method of choice for these patients. This often requires a more formal resection of segments IVb and V (48-50).

In T3 disease, the tumor may extend to the serosa, liver, and/or adjacent organs/structures. Under these circumstances, resection becomes more radical, including an extended right hepatectomy with possible caudate lobectomy (47), regional lymphadenectomy, and extirpation of other affected structures (46). Some centers further advocate pancreaticoduodenectomy to improve outcomes (47). There is 45-70% incidence of lymph node dissemination with 36% of residual disease (51).

T4 disease is widely disseminated through vascular invasion and/or metastasis. Lesions here are commonly unresectable and it is impossible to achieve R0 resection in this stage. Consequently palliative therapy which includes adequate pain control, surgical or non-surgical biliary drainage is more appropriate in this stage.

The goal of surgical intervention is to obtain R0 resection. Surgical resection for advanced gallbaldder cancer is recommended only if a potentially curative R0 resection is technically possible (46,47,52).

Adjuvant therapy

Patients with gallbladder cancer often present in advanced stage of disease. In these patients adjuvant therapy with palliative therapy is the only way to treat though there is still no effective adjuvant therapy for gallbladder cancer.

Three classes of chemotherapeutics may be used: gemcitabine, fluoropyrimidine, and platinum compounds. Monotherapy has limited effect (43). Combination chemotherapy using gemcitabine and cisplatin offers a significant survival advantage for patients with advanced disease (51).

Radiotherapy has proven to be marginally useful in the setting of advanced disease.

Therapeutic agents, targeting cellular and molecular pathways, can impede tumor growth. Targeted therapy against epidermal growth factor receptor (EGFR) has demonstrated an antiproliferative effect *in vitro* and provides some optimism for a changing treatment paradigm in the future (53).

Unfortunately, the data supporting the use of adjuvant or neoadjuvant chemoradiotherapy is largely based on Phase II trials, with no conclusive evidence favoring benefit (46).

Prognosis

The most important prognostic factors that can predict survival after resection are: T staging of the original lesion; extent of nodal involvement; metastasis; and jaundice (which can signify biliary invasion and possible obstruction) (46).

The advent of gallbladder cancer staging has witnessed an improvement in overall 5-year survival rates, what is the merit of radical and successful surgical curing and advances in diagnosis (2). Further improvement in the treatment of this disease is expected from the progress of chemotherapy (53).

The AJCC "Cancer Staging Manual" assessed 10,000 patients diagnosed with gallbladder cancer from 1989 to 1996. The 5-year survival rates start at 80% for stage 0, then progressively fall to 50% for stage I, 28% for stage II, 8% for stage IIIa, 7% for stage IIIb, 4% for stage IVa, and finally, 2% for stage IVb (44).

Conclusions

Gallbladder cancer is the fifth most common cancer involving gastrointestinal tract, but it is the most common malignancy of the biliary tract with a highly variable prevalence in different parts of the world. Histopathological type is almost always adenocarcinoma.

This distinctive malignancy has disastrous outcomes with an overall 5-year survival of less than 5% and mean survival mere than 6 months.

Chronic inflammation caused with cholelithiasis is the most important risk factor.

Diagnosis may come at the time of cholecystectomy for gallstones, although preoperative imaging with transabdominal and EUS, multisliced computed tomography (MSCT) and MR is providing an important advance.

Surgery represents the only potential cure. Unfortunately, the usual late presentation means an advanced stage with potential nodal involvement and leads to recurrences despite attempted resection.

Laparoscopic cholecystectomy is contraindicated when gallbladder cancer is suspected preoperatively. After incidental finding of gallbladder cancer on pathohistological review following cholecystectomy for cholelithiasis, a second radical resection is indicated except for T1a stage.

There is still no effective adjuvant therapy for gallbladder cancer so R0 surgical resection is the only treatment with potential cure. Aggressive surgical approach should be based on a balance between the risk of surgery (morbidity, mortality) and the outcome.

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