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Carcinoma of Gallbladder

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Abstract

Gallbladder cancer is the most common malignancy of the biliary tract, accounting for 80%−95% of biliary tract cancers. An early diagnosis is essential as this malignancy progresses silently often proving fatal. This comprehensive review focuses on and explores the epidemiologic aspects including risk factors, clinical presentation, imaging studies, management, and outcomes for primary gallbladder carcinoma. Epidemiological studies have identified striking geographic and ethnic disparities. Age, female sex, congenital biliary tract anomalies, and a genetic predisposition represent important immutable risk factors. Environmental triggers play a critical role in gallbladder cancer development, best exemplified by cholelithiasis and chronic inflammation from biliary tract infections. Mortality rates closely follow incidence; those countries with the highest prevalence of gallstones experience the greatest mortality from gallbladder cancer. Vague symptoms quite often delay the diagnosis of gallbladder cancer, leading to poor outcome. Surgery represents the only potential for cure. Some individuals are fortunate to be incidentally found to have gallbladder cancer at the time of cholecystectomy performed for cholelithiasis. Such an early diagnosis is imperative as a late presentation connotes advanced staging, nodal involvement, and possible recurrence following attempted resection. Overall mean survival is a mere 6 months, while 5-year survival rate is only 5%. The dismal prognosis, in part, relates to the gallbladder lacking a serosal layer adjacent to the liver, enabling hepatic invasion and metastatic progression. Improved imaging modalities are helpful to diagnose patients at an earlier stage. The last decade has witnessed improved outcomes as aggressive surgical management and adjuvant therapy has helped prolong survival in patients with gallbladder cancer. Clarification of the value of prophylactic cholecystectomy should provide an opportunity for secondary prevention. Primary prevention will arrive once the predictive biomarkers and environmental risk factors are more clearly identified.

Keywords: Gallstones; Cholelithiasis; Epidemiology; Cholecystectomy; Gallbladder polyp; Anomalous junction of the pancreaticobiliary duct

Introduction

Gallbladder cancer is notoriously lethal. Because early symptoms are vague and anatomically the gallbladder lacks a serosa to limit cancer spread, the diagnosis of gallbladder cancer frequently occurs at an advanced stage, typically with an abysmal prognosis. Its 5-year survival rate is less than 5% for more advanced stages. The overall mean survival rate for patients with gallbladder cancer is 6 months [1-5]. Gallbladder cancer spreads locally to the liver and adjacent organs, and it disseminates by lymphatics, blood (even directly via gallbladder veins to the liver), and the peritoneum. Cholecystectomy offers a possible cure in early gallbladder cancers when the malignancy is confined to the mucosa (stage I or T1/T2) [5-7].

Prevalence Studies

Gallbladder cancer is the most common malignancy of the biliary tract, representing 80-95% of biliary tract cancers worldwide [8,9]. It ranks fifth among gastrointestinal cancers. The global rates for gallbladder cancer show differences, reaching epidemic levels for some regions and ethnicities. Gallbladder cancer has a particularly high incidence in Chile, Japan, and northern India [8]. In the United States, gallbladder cancer accounts for only 0.5% of all gastrointestinal malignancies; less than 5,000 cases occur yearly (1–2.5 per 100,000) [3]. Among Chilean women, gallbladder cancer is the leading cause of cancer death, exceeding breast, lung, and cervical cancers [10,11]. Intermediate frequencies of 3.7–9.1 per 100,000 occur elsewhere in South Americans of Indian descent (9). Other high-risk regions include Eastern Europe (14/100,000 in Poland), northern India (as high as 21.5/100,000 for women from Delhi), south Pakistan (11.3/100,000), Israel (5/100,000), and Japan (7/100,000) [12]. The incidence is rising in China and has doubled over the past 20 years in Shanghai [13]. In these areas, gallbladder cancer is the most frequent gastrointestinal malignancy and a significant cause of death. Elsewhere in the world, the occurrence of gallbladder cancer is low (<2/100,000).

Every year in India there are about 800,000 new cases and 550,000 deaths per annum [14]. Gallbladder cancer is the most common abdominal malignancy in the northern India [15]. 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 [16].

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. Gender differences demonstrated a marked predominance of women over men worldwide. Women are affected 2-6 times more often than men [12].

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% [12]. This association with cholelithiasis may explain why female gender, multiparity, or elevated body mass indices (which are risk factors for cholesterol gallstone formation) are also associated with a higher risk of developing gallbladder cancer. The higher risk of gallbladder cancer development in larger stones possibly reflects the greater duration and intensity of mucosal irritation causing chronic inflammation [17,18]. Prophylactic cholecystectomy appear reasonable in these individuals [18]. The larger the gallstones (>2–3 cm in diameter), the greater is the association with gallbladder carcinoma [19-22]. The link appears to be contingent upon the length of time that the 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 would explain the inverse correlation that exists between cholecystectomy rates and gallbladder cancer; socioeconomic issues can delay access to cholecystectomy for cholelithiasis, increasing gallbladder cancer rates [9,23,24]. The latter may also contribute to the heightened risk that occurs in patients belonging to lower socioeconomic groups. The logical consequence of a decrease in the cholecystectomy rate is an augmented number of gallstone carriers in the population and hence older stones with an increased diameter, resulting in higher incidence and mortality rates from gallbladder cancer [24-27]. Although gallstones are an associated risk factor, likely facultative rather than causative, studies of their natural history and decision analysis do not favor prophylactic cholecystectomy for clinically silent gallstones [28-30]. The exceptions are very large stones (≥3 cm), which carry a relative risk of 10.1 (4% over 20 years) [19], and perhaps elderly Indian women with cholelithiasis [6].

Chronic inflammation causes deoxyribonucleic acid (DNA) damage, provoking repeated tissue proliferative attempts at restoration, releasing cytokines and growth factors, and thus, predisposing cells to oncogenic transformation. Chronic inflammation can also result in calcium deposition in the gallbladder wall. With extensive calcium deposits, the gallbladder acquires a bluish hue and becomes fragile, even brittle, the "porcelain gallbladder" [31]. The porcelain gallbladder is frequently (12-61% in various studies) associated with gallbladder cancer [31,32]. Chronic bacterial cholangitis poses a clear risk for biliary tract malignancy. The organisms that have been implicated the most are Salmonella (e.g., *S. typhi* and *S. paratyphi*) and Helicobacter (e.g., H. bilis) [33,34]. 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)] [35,36].

Almost 5% of adults harbor gallbladder polyps; most of them are without any neoplastic potential. The vast majority are not associated with symptoms, though they occasionally cause biliary colic. 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. 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 that predict malignancy are: large polyps (>10 mm), solitary or sessile mass, associated gallstones, the patient's age more than 50 years, and most importantly, rapid polyp growth [12]. Features suggesting a malignant polyp, or when accompanied by gallbladder symptoms (biliary-type pain), warrant cholecystectomy. Differentiating gallbladder sludge from a potentially malignant polyp can be assisted by Doppler ultrasound, which has the ability to show blood flow in polyps.

Anomalous junction of the pancreaticobiliary duct is a congenital malformation in which the pancreatic duct drains into the biliary tract outside the papilla of Vater. Such a long common channel compromises 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. More prevalent in Asians (particularly Japanese patients), this anomaly carries a heightened risk of developing biliary tract cancer; 3-18% develop gallbladder cancer [3,37,38]. This association occurs particularly in relatively young women and is not associated with gallstones. The presence or the absence of associated bile duct dilatation must be taken into account before making the choice of the surgical treatment because the incidence of gallbladder cancer is different with or without biliary duct dilatation. Resection of the common bile duct followed by biliary diversion is recommended in case of bile duct dilatation. In the absence of biliary duct dilatation, prophylactic cholecystectomy alone is performed, except in case of gallbladder cancer or dysplasia on histology of the gallbladder. In such cases, a biliary diversion is recommended in addition to common bile duct resection.

Gallbladder cancer seems to result from a combination of genetic predisposition and exposure to environmental risk factors [39-41]. Carcinoma of the gallbladder is a multistep process involving cumulative genetic and epigenetic alterations that include activation of oncogenes and inactivation of tumor suppressor genes [39]. A unifying hypothesis consolidates the epidemiology and molecular pathogenesis into two pathways for the development of gallbladder cancer [4]. In most cases associated with cholelithiasis, the chronic inflammation leads to missense p53 mutations. Such loss of p53 function allows genetically damaged cells to survive inappropriately. This sequence predominates in older (>65 years) Chilean women. In the second pathway, associated with anomalous pancreaticobiliary duct junction and seemingly more common in Asian populations, the molecular aberration is a K-ras point mutation leading to an atypical epithelium and eventually to carcinoma. Similar malignant transformation, likely from atypical epithelium, can also develop in congenital bile duct dilation (choledochal cysts) that may be accompanied (in 70% of cases) by an anomalous pancreaticobiliary duct [40]. One proposed carcinogenic pathways suggest that: gallstone mediated inflammation → p53 mutation (↓)→ K-ras mutation (↑) [36].

Genetic factors account for approximately 25% of gallstone formation. In cholesterol stones, the factors best identified are the genes responsible for specific biliary lipid transporters in the canalicular membrane-the ATP-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. Mutations in the gene ABCG5/G8, as the variant D19H, result in increased cholesterol secretion into bile, making it an important susceptibility factor [42]. Defective ABCB4 leads to reduced lecithin secretion and stone formation. In gallbladder cancer, variants of the ApoB gene responsible for apolipoprotein B function, which influences cholesterol handling by the liver, have been associated with an increased risk for gallbladder cancer. Yet, this is independent of the presence of gallstones [43]. 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 [44]. This explanation also proposes that 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 [45]. Such protracted exposure allows environmental carcinogens such as aflatoxin B, possibly the culprit in some endemic areas, to then cause malignant transformation. In this scenario, the cancer phenotype results from gene variants that control key metabolic pathways, which then interact with environmental triggers to yield carcinogens.

The role of dietary factors in gallbladder carcinogenesis is now well defined. The regions of Eastern Uttar Pradesh and Western Bihar in India where carcinoma gallbladder is highly prevalent lie downstream of the river Ganges which is the main source of drinking and irrigation water. The Gangetic delta receives untreated domestic sewage and industrial effluents and it is possible that certain environmental pollutants may act as carcinogens. Other factors, that increase the risk for gallbladder cancer, include obesity, a high-carbohydrate diet, smoking, and alcohol use [46]. 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 [47,48].

Clinical Presentation

The clinical presentation of the gallbladder cancer is difficult to separate from that of biliary colic. 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 duct or has metastasized intraabdominally. Indeed, in 15-20% of patients, carcinoma of the gallbladder is discovered in patients operated for cholelithiasis, either intraoperatively or postoperatively on histology. In only 20% of the patients, the disease is confined to gallbladder at diagnosis. The majority of the patients thus have locoregionally advanced or metastatic disease at first presentation [49,50].

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 a study by Cunningham et al in 2002, 48.2% of patients of carcinoma gallbladder had a preoperative diagnosis of symptomatic cholelithiasis (49]. 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. 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 [51,52].

Laboratory examination generally is not very helpful expect for the typical signs of advanced disease such as anemia, hypoalbuminemia, leukocytosis and elevated alkaline phosphate, gamma glutamyl transpeptidase 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 [53] and a CA 19-9 serum level >20 U/mL is 79.4% sensitive and 79.2% specific [54]. A study by Kaufman et al. found that EGFR was overexpressed in patients of carcinoma gallbladder. They found that patients with 3+EGFR correlated with poorly differentiated carcinoma and patients with 1+EGFR correlated with well-differentiated carcinoma [55]. The improved understanding of EGFR's role in oncogenesis has made it an attractive target for therapeutic intervention.

Imaging Studies

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 [56]. Signs of malignant disease on ultrasound examination include discontinuous mucosa, echogenic mucosa, and submucosal echolucency [52]. Diffuse thickening of the gallbladder is also common in gallbladder cancer but is also found in benign conditions [53]. The diagnostic accuracy of USG is over 80% in detecting carcinoma gallbladder [56]. 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 as it helps in planning operative procedures because it can demonstrate the level and extent of tumour infiltration into extrahepatic/intrahepatic ducts.

USG or CT guidance greatly enhances the diagnostic accuracy of fine needle aspiration cytology (FNAC) in comparison to a blind FNAC [57]. The reported sensitivity of guided FNAC is 88% [58]. Endoscopic ultrasonography (EUS) delineates the depth of invasion fairly accurately. EUS is currently the definitive modality for staging gallbladder cancer. It also offers sampling via fine needle aspiration [59].

The most common extraabdominal site of metastasis in gall bladder cancer is the lung. Hence, it is imperative to screen for lung metastasis in patients who present with advanced gallbladder cancer. This can be achieved by a plain radiograph of the chest and in selected cases by a CT of thorax. Imaging studies may reveal nodular shadows or cavitary lesions in lungs.

Staging

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 direct 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 [60]. 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 [60,61].

The stage of disease is the most reliable predictor of outcome and outweighs histology, grading, or other biological parameters. The main staging systems in use over the past 5 years include the modified Nevin system [61], Japanese Biliary Surgical Society System [62] and American Joint Commission on Cancer (AJCC) / Union Internationale Centre le Cancer (UICC) tumor-node-metastasis staging system (Table 1) [63].

T stage	N stage	M stage
Tis-Carcinoma in situ	N0-No regional nodal metastases	M0-No distant metastases
T1-Tumor invades lamina propria(T1a) or muscle layer(T1b)		
T2-Tumor invades perimuscular connective tissue	N1-Metastases in cystic duct, pericholedochal and/or hilar lymph nodes (ie; in the hepatoduodenal ligament)	
T3-Tumor perforates serosa and/or invades the liver(extension ≤2 cm into liver) and/or one adjacent organ		M1-Distant metastases
T4-Tumor extends >2 cm into liver and/or invades main portal vein and/or multiple extrahepatic organs	N2-Metastases in peripancreatic(head only), periduodenal, periportal, superior mesenteric artery, and/or celiac artery nodes	
Stage	TNM status	
0	Tis N0 M0	
I	T1 N0 M0	
II	T2 N0 M0	
III A	T3 N0 M0	
III B	T1-3 N1 M0	
IV A	T4 N0 M0	
IV B	Tx Nx M1, Tx N2 Mx, T4 N1 M0	

Table 1: AJCC TNM staging of gallbladder cancer.

Pathological Features

Approximately 60% of tumors originate in the fundus of the gallbladder, 30% in the body, and 10% in the neck. Gallbladder cancers are 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, the same plane employed for routine cholecystectomy. Nodular types show early invasion through the gallbladder wall into the liver or neighbouring structures and may be easier to control surgically 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, but with minimal invasion of the gallbladder wall. Histologically, the most common type of gallbladder cancer is adenocarcinoma [64]. Other types, such as adenosquamous carcinoma, oat cell carcinoma and sarcomas are also seen.

Surgical Management

Primary tumor invasion (T) is the most important factor in the AJCC staging criteria; it determines the surgical approach [65,66]. 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 [65].

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 [65]. Type of liver resection for carcinoma of the gallbladder varies from atypical resection of segments IVb and V to right hepatectomy (Table 2).

Stage	Recommendation
Tis (confined to mucosa) or T1a (lamina propria)	Simple cholecystectomy
T1b (invading the muscular layer)	Radical cholecystectomy is recommended, although some
	series support simple cholecystectomy
T2 tumors (invading the perimuscular connective tissue)	Radical en bloc resection including liver bed

T3 tumors (those that perforate the serosa and/or directly invade the liver and/or one other adjacent organ)	Radical resection selectively
T4 tumors (those that invade the main portal vein or hepatic artery, and/or those that invade two or more extrahepatic organs or structures)	Generally unresectable

Table 2: Surgical treatment of gallbladder cancer.

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 appropriate pre-operative assessment, or immediately if suspected during laparoscopy. If the diagnosis is confirmed on frozen section, radical surgical resection should be performed in the same session [66].

Incidental gallbladder cancers are detected histologically in 0.3-3% of laparoscopic cholecystectomies performed for cholelithiasis. For these patients, a subsequent radical resection is indicated after adequate pre-operative 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 [67]. Since accidental bile spillage implants tumor cells at the trocar or incision site leading to recurrence, excision of the port sites are indicated during the subsequent radical surgery.

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 and 100% 5-year survival [67].

In T1b gallbladder cancer (tumor invades the muscular layer) there is still controversy regarding the optimal management. Some investigators recommend not going further than simple cholecystectomy, whereas others recommend subsequent radical resection. Reported incidence of occult lymphatic metastasis is 15-25% in this stage with 10% incidence of residual disease in liver bed [67,68]. Given the frequency of positive lymph nodes and residual disease in this stage, recommended procedure is cholecystectomy with radical resection that encompasses 3 cm of liver parenchyma segment IVb and V, plus adequate lymphadenectomy [68,69]. For this stage, the 10-year survival after simple cholecystectomy is 75% vs. 100%, if a radical resection is performed.

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 a positive lymph node rate to the tune of 19-62%. Hence, a radical procedure encompassing a more formal resection of segments IVb and V is indicated in this stage [68-70].

In T3 disease, the tumor may extend to the serosa, liver, and/or adjacent organs/structures. Hence, resection must be more radical, with an extended right hepatectomy and possible caudate lobectomy (67), regional lymphadenectomy, and extirpation of other affected structures [65]. Some centers further advocate pancreaticoduodenectomy to improve outcomes [67]. There is 45-70% incidence of lymph node dissemination with 36% of residual disease [71].

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

The goal of surgical intervention is to obtain R0 resection. Hence, surgical resection for advanced gallbladder cancer is recommended only if a potentially curative R0 resection is technically possible [65,67,72].

Gallbladders removed for presumed gallstone disease and its complications should be routinely examined grossly as well as microscopically as gross morphological changes of malignancy may be indistinguishable from benign conditions like chronic cholecystitis and xanthogranulomatous cholecystitis [73]. Potentially curable gallbladder cancer may be discovered on histological examination in gallbladder specimens which are macroscopically indistinguishable from gallbladders without cancer. Re-operation and liver resection with lymph node clearance at the earliest opportunity would provide the same survival benefit as primary curative surgery in these patients [74], while missing these cancers would mean sure death from disease recurrence and progression. In a disease as aggressive and lethal as gallbladder cancer this is a chance of cure that cannot and should not be denied to the patient. Hence, all gallbladders removed for presumed gallstone disease should be opened up by the surgeon in the operating room for a careful gross examination. If changes suspicious of malignancy are seen, the gallbladder should be subjected to a frozen section examination and if it is positive, an extended cholecystectomy should be performed. Moreover, it is ideal that gallbladders removed for presumed gallstone disease and its complications be routinely examined grossly as well microscopically after any cholecystectomy, even in geographical areas with a low incidence of gallbladder cancer, in order to detect early gallbladder cancers and to offer the patient a chance to be cured surgically.

Adjuvant Chemoradiotherapy

Clinical data for radiation therapy suffer from heterogeneous clinical characteristics. In a series published by Czito and colleagues, 22 patients at Duke with nonmetastatic GBC were treated with chemoradiation [75]. Whereas 20 of 22 patients first had a simple cholecystectomy, 11 patients subsequently underwent a radical reresection. Patients were then treated with 45 Gy to the tumor bed and regional lymphatics followed by a boost of 5.4-10.8 Gy. Eighteen patients received concurrent 5-FU chemotherapy. The 5-year overall survival rate was 37%. No single factor was found to significantly predict survival, including nodal status and margins. However, the strongest trend was seen in terms of the benefit of a radical procedure versus simple cholecystectomy (5-year overall survival rate, 51% versus 15%; p=0.10). The use of adjuvant therapy hence cannot compensate for inadequate surgery. Obtaining an R0 resection with radical surgery appears to be associated with the best survival. Radiation therapy

should be viewed as a means to improve upon optimal surgical management, rather than making up for inadequate surgery.

Adjuvant Chemotherapy

Two classes of chemotherapeutics may be used- gemcitabine and platinum compounds. Monotherapy has limited effect (76). Although most clinical trials in gallbladder cancer have included all biliary tract cancers, there have been three trials exclusively enrolling gallbladder cancer patients—one evaluating gemcitabine alone and two gemcitabine–cisplatin combination studies (Table 3).

Chemotherapy	Number of patients	Response rate (%)	Median overall survival	Reference
Gemcitabine	26	36	30 weeks	77
Gemcitabine + cisplatin	42	48	7 months	78
Gemcitabine + cisplatin	30	36.6	20 weeks	79

Table 3: Studies on chemotherapy in gallbladder cancer.

In one trial, 26 patients with metastatic or unresectable gallbladder cancer and no prior chemotherapy received single-agent gemcitabine. Of the 25 evaluable patients, an overall response rate of 36% (95% confidence interval [CI], 17.1%–57.9%) and median survival time of 30 weeks were observed [76,77]. Because of the single-arm nature of these small phase II studies, the survival values presented in Table 3 are observational in nature and not statistically valid. Gemcitabine and cisplatin were evaluated in 44 patients. Among 42 evaluable patients there were four complete responses and 16 partial responses, for a response rate of 48% (95% CI, 32%–71%). The median survival time was 7 months (95% CI, 6–8.5 months) and toxicity was reasonable [78]. A second experience with this combination demonstrated an overall response rate of 36.6% and moderate hematologic toxicity [79]. The recent studies showing longer survival with gemcitabine and cisplatin than with gemcitabine alone has set a new standard for this disease.

Molecular Targeted Therapies in Gallbladder Cancer

Characteristic molecular features in gallbladder cancer include mutation of Kras, INK4a and p53 as well as human epidermal growth factor receptor (HER)-2/Neu amplification [80-83]. Rare mutations in PI3K are described apart from a relatively high rate of BRAF hotspot mutations (33%) that are mutually exclusive of Kras mutation [84,85]. Activating epidermal growth factor receptor (EGFR) mutations have also been identified in a subset (13.6%–15%) of biliary tract cancer cases, including one case of gallbladder cancer [86,87], as have EGFR amplifications. EGFR gene amplification as well as case reports of the efficacy of cetuximab in combination with either gemcitabine or gemcitabine and oxaliplatin have also been published, further prompting investigation of EGFR inhibitors in biliary tract cancers [88,89]. Malka and colleagues reported their experience with a randomized phase II study comparing gemcitabine plus oxaliplatin alone with the same chemotherapy regimen in combination with cetuximab and demonstrated a higher 4-month progression-free survival rate with the addition of cetuximab (44% versus 61%, respectively) [90].

The expression of vascular endothelial growth factor (VEGF), a key mediator in tumor angiogenesis, has been detected in biliary tract cancer, with higher VEGF expression correlated with advanced stage of disease and poor prognosis [91]. Bevacizumab, a humanized monoclonal antibody against VEGF, was tested in combination with gemcitabine and oxaliplatin in biliary tract cancer patients, including a significant number of gallbladder cancer patients, in a multicenter phase II trial [92]. Of the 35 patients enrolled, 40% of patients had a partial response, the median overall survival time was 12.7 months (95% CI, 7.3–18.1 months), and the median progression-free survival time was 7.0 months (95% CI, 5.3–10.3 months). Sorafenib, that targets VEGF receptor (VEGFR-2, VEGFR-3) and platelet-derived growth factor receptor and less potently on B-RAF and C-RAF kinases, was tested as a single agent in a phase II trial involving 31 patients [93]. Significant toxicities affected about two thirds of the patients, and two patients (6%) had an unconfirmed partial response while nine patients (29%) had stable disease.

Molecularly targeted agents that inhibit angiogenesis and EGFR pathways are entering clinical trials. Further understanding of the molecular mechanism of carcinogenesis coupled with more extensive genetic profiling of gallbladder cancer patients will help to assess the therapeutic relevance of targeting a specific pathway.

Conclusion

Gallbladder cancer is a devastating disease with very dismal results. Originating in a small organ that functions merely for the storage of bile in anticipation of a meal, this malignancy is distinctive because of its demographic profile. Advancements that clarify the genetics of biliary tract diseases and develop unifying hypotheses to explain gallbladder cancer's unusual epidemiology not only will define its etiology but would also improve management. Of late, there has been an increase in the number of cases of carcinoma gallbladder due to better imaging techniques, better medical facilities and better awareness among the patients. Key to survival is early detection and aggressive treatment strategy. Surgery is the only curative treatment and can achieve its intended goal if done at an early stage. With loco-regional spread, and jaundice survival is barely 6 months. Secondary prevention should follow clarification of the value of prophylactic cholecystectomy in endemic areas and in patients at risk. Primary prevention will arrive once high-risk genes and environmental toxins are clearly identified.

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