Gallbladder cancer: Past, present and an uncertain future

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ABSTRACT

Although gallbladder cancer (GBC) is the most common malignancy of the biliary tract, its relatively low incidence and confounding symptomatology result in advanced disease at the time presentation, contributing to the poor prognosis and decreased survival associated with this disease. It is therefore increasingly important to understand its pathogenesis and risk factors to allow for the earliest possible diagnosis. To date, gallbladder cancer is poorly understood compared to other malignancies, and is still most commonly discovered incidentally after cholecystectomy. Moreover, while much is known about biliary neoplasms as a whole, understanding the clinical and molecular nuances of GBC as a separate disease process will prove a cornerstone in the development of early intervention, potential screening and overall more effective treatment strategies.

The present work reviews the most current understanding of the pathogenesis, diagnosis, staging and natural history of GBC, with additional focus on surgical treatment. Further, review of current adjuvant therapies for unresectable and advanced disease as well as prognostic factors provide fertile ground for the development of future studies which will hopefully improve treatment outcomes and affect overall survival for this highly morbid, poorly understood malignancy.

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Introduction

Gallbladder cancer (GBC) was first described by Maximillian de Stoll in two autopsy cases in 1777, with the first documented cancer resection performed by Keen in 1891 [1]. In the 21st century GBC is the fifth most commonly occurring gastrointestinal cancer in the US. According to data from the Surveillance, Epidemiology, and End Results (SEER) program (1992–2000) the incidence of GBC is estimated at 2.5 per 100,000 persons; it is the most common primary biliary tract malignancy, representing 46% of all such malignancies.

The pathogenesis of GBC is poorly understood compared to other neoplasms [2]. Diagnosis of GBC commonly occurs as an incidental finding in the setting of operative intervention for cholelithiasis, resulting in advanced disease at the time of initial diagnosis [3]. In addition, symptoms associated with GBC can be vague and nonspecific, further complicating early detection. Finally, symptoms of GBC mirror those due to cholelithiasis and cholecystitis, making it difficult to differentiate (in the absence of family history) from benign pathology.

Several risk factors have been associated with GBC including age, sex, parity, race/ethnicity, and obesity. In one retrospective series, the majority of GBC patients were of low socioeconomic status and rural background [4].

Epidemiology and pathogenesis

Chronic inflammation and GBC

Chronic inflammation may result from a wide and multifactorial range of etiologies: mechanical obstruction via gallstones, infectious and environmental exposure, polyps and adenomas, autoimmune disease, as well as anatomic variations including pancreatobiliary maljunction. Studies implicate each of these as a contributing factor to the development of GBC [4–6]. The exact role of inflammation in the molecular progression leading to the development of GBC has been poorly understood. However, recent studies may elucidate potential mechanisms and provide targets for therapeutic intervention. These will be discussed in further detail later in this work.

Gallstones and risk of GBC

Gallstones are present in about 80% of patients with GBC. Stones can lead to chronic inflammation, promoting metaplasia and adenocarcinoma by either mechanical irritation of the gallbladder mucosa or mechanical obstruction of the gallbladder leading to cholestasis [2]. The presence of stones alone is insufficient; gallstones remain asymptomatic in 66–77% of the general population [7]. Freidman et al. [8] reported that only 1–2% of patients with gallstones become symptomatic per year to warrant a cholecystectomy, and over a 20 year period 2/3 of asymptomatic patients with gallstones remain symptom free. The study reported as well that the longer the stones remain quiescent, the less likely they are to produce symptoms. As with nonmalignant cholecystic disease, cholesterol is the predominant component of gallstones, with greater than 75% being cholesterol [9].

The relationship between gallstone size and the risk of GBC has been studied. The relative risk of gallbladder carcinoma rises from 2.4× for stones size of 2–2.9 cm, to 10× for stones larger than 3 cm [10]. However, another study reported that gallstone weight and volume, not just size, were significantly higher in patients with gallbladder carcinoma. In their study a total stone volume greater than 10 mL had an odds ratio 11 times higher than the control group for the development of GBC [11].

The associated increase in number and size of gallstones in patients with GBC could be simply an effect of aging, or a reflection of the long term presence of the stones on the gallbladder rather than a chemical or physical influence [12].

Other gallstone-associated patient factors may act as confounding variables as well. One prospective case–control study of 37 patients with GBC identified typhoid carrier state, age, and smoking as three independent risk factors for the development of GBC in patients with concomitant gallstones [13].

Infection, chronic inflammation and GBC

The relationship between bacterial infection and oncogenesis has been characterized for many different types of cancers. Exploring the contribution of infection to the development of this malignancy continues to be an area of ongoing investigation, particularly in endemic regions where GBC is more prevalent. The proposed mechanism of action involves persistent infection leading to chronic inflammation, along with production of toxins and metabolites which may result in malignant transformation of gallbladder epithelium [14].

Chronic bacterial infection has also been associated with GBC, and even specific pathogens have been implicated [15,16]. Organisms recovered from bile are typically concomitantly present in large bowel flora; these include Escherichia coli, streptococcus, klebsiella and enterobacter. Anaerobic colonization by clostridium and bacteroides is observed in 48% of gallbladder specimens collected in one series [17,18]. Bacterial DNA were isolated in 78% of GBC tissue specimens using only a single round of amplification, however the causal association between bacterial presence and gallbladder carcinogenesis needs to be evaluated in depth.

Salmonella typhi has become a model for understanding this relationship. The first report of carcinoma of the gallbladder associated with typhoid carriage was in 1971 by Axelrod et al. [19]. Long term cohort studies after the Aberdeen typhoid outbreak in 1964 and from Central American typhoid patients, report a 6% lifetime risk of developing GBC and a 12-fold increase in this population, respectively [20,21].

Chemical and environmental (causes of chronic inflammation)

Exposure to carcinogenic agents represents a contributory etiology to the development of many types of cancers. Historical studies have shown that chemical pollution via pesticides, excessive exposure to heavy metals, radiation and vinyl chloride, as well as industrial/occupational exposures (e.g. rubber, textile, petroleum, and shoe factories) increase the risk of gallbladder cancer. A California Tumor Registry review of 1808 cases of gallbladder and bile duct cancers found a significant association between GBC and workers in rubber, automobile, wood furnishing and metal fabricating industries [22]. Interestingly, results from a study of biliary tract cancers in Akron, Ohio, a site of four major rubber manufacturing companies in the US demonstrated that 27.6 percent of the patients with GBC in their study were employed by rubber industries [23]. Clearly validation studies are necessary to
corroborate these epidemiologic findings and validate the association between caustic agents and GBC; indeed, population, in vivo and in vitro studies are ongoing.

Increased risk for the development of GBC has also been associated with ingestion of some medications (e.g., isoniazid and oral contraceptives) [24]. In a population-based case-control study in Shanghai, China examined the role of oral contraceptives. A group consisting of 411 biliary tract cancer patients, 893 biliary stone patients and 786 healthy Shanghai residents, were evaluated for single-nucleotide polymorphisms (SNPs) in 9 genes involved in steroid hormone synthesis. Among women taking oral contraceptives, polymorphisms present in this cohort possessed hormone related gene alterations linked to increased risk of biliary tract cancers [25]. Increased estrogen levels have been implicated in biliary tract neoplasia by multiple mechanisms including decreased gallbladder motility, thereby increasing the formation of gallstones and the risk of infection and inflammation in the biliary tract [26,27].

Autoimmune and hereditary syndromes

The association between ulcerative colitis (UC) and biliary disease—benign and malignant, has been well documented. Less clear is the more specific role of UC in the development of GBC, specifically. However, beginning in the 1950s there have been several reports of GBC arising in patients with both UC and primary sclerosing cholangitis (PSC), and the suggestion has been made that UC confers an increased risk in the development of GBC up to 10 times that of the general population [28,29]. Though still an area of interest and controversy, review of the available literature suggests that length of symptomatic colitis plays an active role in the development, further fueling the discussion of inflammation as an important etiologic factor in the progression of malignancy within the gallbladder [30].

Gallbladder polyps and risk of GBC

Gallbladder polyps are not an infrequent finding; ranging from 0.3% to 12.3% in healthy adults [31–34], several studies reported the relationship of gallbladder polyp size and the risk of GBC. All found that approximately 45% and 67% of polyps larger than 10 and 15 mm, respectively, harbored malignancy [35–38], supporting the current recommendation for cholecystectomy for polyps larger than 10 mm. In addition to polyp size, advanced age [36,37,39,40], sessile polyps [41], concurrent gallstones [42] and the presence of symptoms [42] have all been implicated as factors associated with an increased risk of malignancy in the polyp.

The exact sequence of molecular events taking place during the pathogenesis of GBC within polyps remains to be elucidated. K-ras and p53 alterations are likely to take part in the de novo pathway of gallbladder carcinogenesis [43].

A recent Cochrane review of the role of cholecystectomy in the management of gallbladder polyps was unable to identify any randomized clinical trial comparing cholecystectomy with observation; thus the management of gallbladder polyps remains controversial [23].

Radiological evaluation

Ultrasound (US) can detect suspicious lesions for GBC; concerning characteristics include a wide polyp base and irregular borders. US accuracy to determine the non resectability of a gallbladder carcinoma is between 63% [44] and 38% [45]. However, the depth of the invasion is better appreciated with an endoscopic ultrasound (EUS) than with trans-abdominal ultrasound.

Fujita et al. [46] studied 39 GBC patients with preoperative EUS and classified the tumor morphology into four categories. Type A implied a pedunculated mass with a fine-nodular surface and intact neighboring wall. Type B was a broad-based mass with an irregular surface and intact outer hyperechoic layer of the adjacent wall. In type C, the outer hyperechoic layer was irregular due to the mass, whereas, in type D, the outer hyperechoic layer was completely disrupted. Each of the four categories of EUS images correlated well with the histologic depth of invasion and was found to be useful to T staging.

Endoscopic retrograde cholangiopancreatography (ERCP) has utility when bile can be retrieved for cytological examination. Although the yield for biliary cytologies is notoriously low, if they are positive in the setting of suspicion for GBC, the likelihood of the diagnosis is high as 73% in one study [47].

Computed tomography scan (CT) is valuable because of its ability to detect local invasion of the liver, lymph nodes, and the presence of hepatic and peritoneal metastasis [48]. Spiral CT scan with thin slices has up to 93% accuracy for determining resectability of gallbladder carcinoma [49].

The role of positron emission tomography (PET) in GBC is still to be determined. Since most patients are diagnosed with after cholecystectomy, postoperative inflammation limits the value of PET scan [50]. The potential use of PET scan will be to preoperatively identify patients with advanced locoregional or metastatic disease, who will not benefit from any surgical exploration. In a recent series, PET had the sensitivity to detect primary tumor, residual disease and metastatic disease of 86%, 86% and 87% respectively, Corvera et al. [50].

Magnetic resonant imaging (MRI) may be helpful in identifying bile duct invasion and vascular invasion. A small cohort study (n = 18) utilizing magnetic resonant imaging, angiography and cholangiography reported a combined sensitivity of 100% for detecting biliary and vascular invasion [32]. However, the sensitivity for detecting lymph node metastasis was only 56%.

Staging

The staging of GBC is based on the depth of penetration and extent of spread. In 1976, Nevin et al. [51] reported a series of 66 patients with GBC and described a method combining staging and histological grading of this cancer (Table 1). Currently the staging systems of the American Joint Committee on Cancer (AJCC), is the most widely used (Table 2).

The most important prognostic factor is depth of invasion, Fong et al. [52] reported a progressive increase of distant and nodal metastasis from 16% to 79% and from 33% to 69%, respectively in going from T2 to T4 tumors.

Histologically, GBC is graded according to its cellular differentiation into four grades. Henson et al. [53] found that the majority of GBC patients presented with grade 3, poorly differentiated tumors.

Surgical options

The goal of surgical resection is to achieve a complete resection and obtain negative margins (R0 resection); unfortunately this can only be achieved in about half of cases. In one series, R0 status was obtained in only 43% of patients even with an extended resection [37]. The extent of the required surgical resection varies from simple cholecystectomy to a more complex surgery that may involve liver, bile duct and pancreatic resections.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Nevin’s staging for gall bladder carcinoma [51].</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Intramucosal tumor</td>
</tr>
<tr>
<td>Stage II</td>
<td>Tumor extends to the muscularis</td>
</tr>
<tr>
<td>Stage III</td>
<td>Tumor extends to the serosa</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Transmural involvement and cystic lymph node involvement</td>
</tr>
<tr>
<td>Stage V</td>
<td>Direct extension to the liver and/or distant metastasis</td>
</tr>
</tbody>
</table>
Table 2
AJCC staging classification of gallbladder carcinoma, 7th edition [104].

<table>
<thead>
<tr>
<th>Primary tumor (T)</th>
<th>Regional Lymph nodes (N)</th>
<th>M1 Distal metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX Primary tumor can not be assessed</td>
<td>NX Regional lymph nodes can not be assessed</td>
<td>M0 No distant metastasis</td>
</tr>
<tr>
<td>T0 No evidence of primary tumor</td>
<td>N0 No regional lymph node metastases</td>
<td>M1 Distal metastasis</td>
</tr>
<tr>
<td>Tis Carcinoma in situ</td>
<td>N1 Metastases to nodes along the cystic duct, common bile duct, hepatic artery, and or portal vein</td>
<td></td>
</tr>
<tr>
<td>T1 Tumor invades lamina propria or muscle layer</td>
<td>N2 Metastases to peri-aortic, pericaval, and/or celiac artery lymph nodes</td>
<td></td>
</tr>
<tr>
<td>T1a Tumor invades lamina propria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1b Tumor invades muscle layer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 Tumor invades perimuscular connective tissue, no extension beyond the serosa or into the liver</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3 Tumor perforates the serosa and/or directly invades the liver and/or one other adjacent organ or structure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4 Tumor invades main portal vein or hepatic artery or invades two or more intrahepatic organs or structures</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The only role of laparoscopic surgery in a case of known or suspected gallbladder carcinoma is to determine resectability. Laparoscopy can detect unresectable disease in 39–48% of patients, sparing them an unnecessary laparotomy [38,39]. Aside from staging, laparoscopic surgery is felt to have no role in the definitive resection due to the risk of dissemination.

Lymphatic route of spread is defined by different stations, starting with the primary cystic lymph node and pericholecodal nodes to the secondary group of regional lymph nodes, including the common hepatic and pancreatico-duodenal nodes. Metastasis to these lymph nodes are currently considered N1 disease according to the 7th edition of the AJCC classification.

Lymph node metastases in the celiac, superior mesenteric and para-aortic lymph nodes (N2) represent unresectable disease [54]. The management of T1b lesions is still controversial. These tumors have positive nodes in 3–28% of cases, potentially leading to locoregional failure after simple cholecystectomy [84,86]. Results from selected studies are reported on Table 3, suggesting that an extended cholecystectomy could be beneficial in patients with T1b lesions.

Extended liver wedge resection for early gall bladder cancer has been studied. In one series, there was no statistically significant difference in survival after extended or simple cholecystectomy in stage I disease; however, local recurrence was less after extended than after simple cholecystectomy (7% versus 17%) [58].

Surgical options for T1 GBC

Curative resection can be generally obtained for T1 lesion by simple cholecystectomy. In a series of 39 patients with T1a disease, a 100% 5-year survival was reported after simple cholecystectomy [44]. The management of T1b lesions is still controversial. These tumors have positive nodes in 3–28% of cases, potentially leading to locoregional failure after simple cholecystectomy [84,86]. Results from selected studies are reported on Table 3, suggesting that an extended cholecystectomy could be beneficial in patients with T1b lesions.

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Surgical options for T2 GBC

Extended cholecystectomy is required for tumors invading the perimuscular connective tissue (pT2) since the subserosal dissection in routine laparoscopic cholecystectomy results positive margins.

Extended cholecystectomy is defined as wedge resection of a two cm liver margin at the gall bladder bed (segment 4/5) as well as N1 lymphadenectomy. The lymphadenectomy is performed by skeletonizing the portal vein, hepatic artery and the porta hepatitis with excision all lymphatic tissue surrounding these structures. In Japan this dissection also includes the nodes behind the head of the pancreas, the second part of the duodenum, and celiac axis.

There is definitely a survival benefit in favor of extended cholecystectomy for pT2 lesions over simple cholecystectomy, with 5-year survival of 90% and 40%, respectively [44]. Other series have confirmed this observation.Muratore et al. [59] reported a 5 year survival of 60–80% for T2 gall bladder carcinoma with extended cholecystectomy.

Various other approaches and opinions exist regarding the role of extended cholecystectomy. Bartlett et al. reported 3 year survival of 90–100% for patients with T2 tumors after resection of segments IVb and V with aggressive lymph node dissection including N2 aortocaval lymph node lymph nodes [55]. On the other end of the spectrum, a Japanese report found that the long term survival benefit of the

Table 3
Likelihood of lymph node metastasis (LNM), and lymphatic invasion (LI) in pT1b lesion.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients with pT1b</th>
<th>% LNM/LI</th>
<th>Locoregional recurrence</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>You et al. [105] (2008)</td>
<td>25</td>
<td>3.8% LNM</td>
<td>1.9% LI</td>
<td>96% 5-year survival after extended cholecystectomy</td>
</tr>
<tr>
<td>Wagholikar et al. [106] (2002)</td>
<td>12</td>
<td>–</td>
<td>50%</td>
<td>–</td>
</tr>
<tr>
<td>De Aretxaballa et al. [80] (1992)</td>
<td>9</td>
<td>20% LNM</td>
<td>11%</td>
<td>100% 5-year survival after extended cholecystectomy</td>
</tr>
<tr>
<td>Oguera et al. [79] (1991)</td>
<td>165</td>
<td>15.6% LNM</td>
<td>–</td>
<td>72.5% 5-year survival (45% of patients had simple cholecystectomy)</td>
</tr>
<tr>
<td>Ouchi et al. [107] (1987)</td>
<td>7</td>
<td>28% LNM</td>
<td>60%</td>
<td>–</td>
</tr>
</tbody>
</table>
extended cholecystectomy in T2 lesions applied only to patients in whom a positive margin was obtained during the initial surgery \[46\]. General consensus at this time is that patients with T2 GBC benefit from an extended cholecystectomy.

The overall extent of hepatic resection still remains controversial. Yoshikawa et al. \[60\], in a retrospective clinicopathological study of 201 patients operated for advanced GBC, suggested that segmental hepatic resection may be beneficial in patients with liver bed type invasion >20 mm in depth.

In a study comparing simple vs. extended cholecystectomy for all stages of GBC, stage II patients with extended cholecystectomy (with 2 cm liver wedge resection) had a longer postoperative survival. There was no difference between extended and simple cholecystectomy in stage III and IV disease \[48\].

Though lymph node metastasis to N2 lymph nodes (para-aortic) is present in 19–25% of patients with locally advanced disease \[59\]; there is no survival benefit for N2 dissection for these patients. Surgical morbidity after an extended cholecystectomy ranges from 5 to 26% and surgical mortality ranges from 0% to 4% \[61–63\].

**Surgical options for T3–T4 GBC**

For more advanced disease (T3 and T4) the Japanese have reported extended hepatectomy, and pancreatoduodenectomy \[64,65\].

Since the 5-year survival of non-surgically treated locally advanced GBC is generally 0% (median survival 8 months), room for improvement exists. One Japanese study reported a 5-year survival of 50% (median survival 58.5 months) in those undergoing a potentially curative resection with non anatomic hepatectomy or pancreatoduodenectomy \[52\]. Another group compared the outcomes of patients undergoing radical hepato-pancreato-cholecysto-duodenectomy (HPD) vs no surgery. The HPD group had 1- and 2-year survival rates of 57% and 28.6%, respectively, with a median survival time of 12 months. In contrast, the 1-year survival rate of non-surgically treated patients was 5.8%, with a median survival of 2 months \[66\].

In the western world the management of advanced GBC is controversial. Some series suggest that aggressive surgery with hepatic resection prolongs survival even in the >70 year old population provided that an R0 resection is performed \[55,56\]. A series of patients with T4, N0 tumors reported long term survival with no surgical mortality \[51\]. Aggressive resection in this subset with advanced T-stage and negative nodes is almost certainly justified.

The opposing view is that though radical cholecystectomy may benefit individual patients and can be accomplished with low morbidity, there may be no overall survival advantage compared with simple cholecystectomy (5-year survival rate 33% versus 32%) \[61\].

The role of lymph dissection has been debated, with varying levels of aggressiveness being practiced throughout the world. Dixon et al. \[67\] described a skeletonization of the portal structures including suprapyloric lymph node overlying the hepatic-gastroduodenal junction. A more aggressive lymph node dissection is described in the Japanese literature where the node baring adipose tissue located within the hepatoduodenal ligament, postero-superior to the head of pancreas, and around the portal vein and common hepatic artery is removed en bloc with the gall bladder and adjacent liver tissue \[68\]. However, there has also been an absence of randomized controlled studies showing benefit for extended lymph node dissection \[69\].

**Role of surgery in locally invasive disease**

Advanced GBC can infiltrate as well surrounding structures such as the omentum, colon, stomach and abdominal wall. In general the prognosis of these patients is better than those with hepatic or hilar invasion \[70\]. hepatopancreatoduodenectomy though technically feasible carry a high morbidity and mortality and should be reserved to selected cases \[65,71\].

Although bile duct infiltration can be present in up to 54.2% of patients with GBC, \[72\], a routine bile duct resection in patients with advanced GBC is not recommended. Kosuge et al. \[73\] reported that bile duct resection did not confer any survival advantage in stages I, II, and III, and only a survival benefit was noted in stage IV where bile duct resection improve resection of nodal tissue or connective tissue deposits in the hepatoduodenal ligament. In case of cancer involving the neck of the gallbladder frozen section of the bile duct should be obtained to assure a negative resection margin.

Vascular involvement of the right hepatic artery should be included with right or extended right hepatectomy, while involvement of the left hepatic artery is considered a marker of unresectability \[74\].

Portal vein involvement is usually managed by either segmental resection or wedge resection of the wall with reconstruction. Though technically feasible, portal vein resection does not affect long-term survival. It should be only selectively used in few cases to achieve R0 resection \[71,75\].

In locally advanced disease where gall bladder cancer invades the duodenum and cause gastric outlet obstruction, a gastrojejunostomy, or gastroduodenal stenting may be applied as a palliative treatment \[76\], to be noted that malignant gastroparesis without real obstruction will not be relieved by these measures \[77\]. For unresectable cases based on radiological preoperative tests, a tissue diagnosis can be obtained by percutaneous biopsy \[78\] prior to chemotherapy.

Surgical morbidity for radical cholecystectomy (including hepato-pancreatectomy, hepatic lobectomy, and or other major liver resection) ranges from 22% to 100% and the mortality ranges from 2 to 28% \[65,71,79,80\].

**The role of chemotherapy and radiation**

There is no reported benefit of neoadjuvant therapy for advanced GBC, and to date, only few published studies have assessed its role in long term survival. Most of these studies were not sufficiently powered to show any statistically significant benefit \[81,82\]. One study found that combining neoadjuvant 5-fluorouracil continuous infusion and radiation (4500 cGy) did not improve survival \[72\].

Studies examining the benefit of adjuvant upon GBC specifically are inconclusive and often underpowered. Most published series are a heterogeneous mix of all cholangiocarcinomas including small cohorts of GBC pts, and are unable to take into account the variable response to chemoradiotherapy due to differences in tumor biology. A recent review of the genetic alterations in gallbladder cancer \[83\] has provided insight into the molecular mechanisms associated with the pathogenesis of GBC, to hopefully provide promising targets for therapeutic chemo-intervention.

Systemic chemotherapy has been shown to have (albeit marginal) superior impact on survival, versus supportive care alone. Gemcitabine and 5-FU as monotherapy or in combination are first line therapy for treatment of unresectable GBC. As a single agent, the clinical benefit of gemcitabine ranges from 15 to 60 percent, and median survival averages 11 months. Data from clinical trials combining gemcitabine with capecitabine report increased survival times of 13–16 months \[84–86\].

There is Grade 2B evidence that combination therapy using gemcitabine and cisplatin has (albeit marginally) superior impact on disease progression, resulting in prolonged survival when
compared with basic supportive care alone. In a randomized trial of 81 pts with unresectable GBC, gemcitabine plus oxaliplatin (GEMOX), 5-FU/leucovorin and supportive measures were compared; median overall survival of GEMOX was approximately twice that of supportive care at 9.5 and 4.5 months, respectively. 5-FU gave no survival advantage [87].

Other studies evaluating the effects of 5-FU on survival for patients with GBC show better overall averages, although still less than one year [88–91]. When infusional 5-FU was combined with cisplatin in two clinical trials, median survival ranged from 10 to 11.5 months [88–91]. The ECF regimen (epirubicin cisplatin and 5-FU) was shown to confer remission in some patients, with a median survival time of 11.5 months [88]. In a phase III trial of ECF versus 5-FU, leucovorin and etoposide, the median overall survival was twelve months with ECF infusion compared with 5months, and had less associated toxicity [92].

Adjuvant chemoradiotherapy results are mixed and include a number of underpowered series. Kresel et al. [93] reported that 21 patients with R0 resection of GBC followed by adjuvant radiotherapy (median dose of 54 Gy in 1.8–2.0-Gy fractions) plus 5-FU had 5-year survival rate of 64% compared to 33% with surgical resection only.

Another study examined 5-year overall survival, disease-free survival, and local-regional control in 22 patients with primary GBC treated with radiation therapy after surgical resection as 37%, 33%, and 59%, respectively. The patients received a median radiation dose of 45 Gy. Eighteen patients received concurrent 5-fluorouracil (5-FU) chemotherapy [94].

Currently there are no published studies examining the benefit of radiofrequency ablation (RFA) or transarterial chemoembolization (TACE) for unresectable GBC.

Prognostic factors

Several factors influence the prognosis of GBC that can be summarized into the ability to perform a curative resection. The most important of these factors are the depth of the invasion, which is directly proportional with the odds of lymphatic invasion, and the histological grade [95].

Pardeep et al. [96] in analyzing prognostic factors in 87 patients with GBC found that the presence of palpable mass, the type of surgical treatment, and age were also a significant predictor of survival by multivariate analysis. Interestingly, they reported that multivariate analysis of patients with Stage IV disease revealed the same three factors to be significant. These findings suggested that resectional surgery was associated with better survival compared with biliary and/or gastric bypass or laparotomy alone for patients with all stages of the disease, including those with advanced carcinoma of the gallbladder. Other studies failed to identify age as a risk factor, as well as serum bilirubin [63,97,98].

Long term result after surgical resection

GBC was usually considered a deadly disease, with poor five year survival that spreads between 0% and 10% in most studies [99]. This dismal picture partially changed in more recent studies probably due to the advance of the diagnostic tools allowing detection of the disease at early stages where a surgical cure can be achieved, and the more aggressive surgical approach adopted by many surgical centers.

Gagner et al. [100] reviewed the American experience with the use of radical operations for carcinoma of the gallbladder. The five year survival rate for patients was 95%, 40%, 9%, 7% and 1% with Nevin stage I, II, III, IV, and V disease, respectively. Other studies reported almost similar results [95].

Cubertafond et al. [101] reported the results of the French surgical association survey on 724 patients surgically treated for gallbladder carcinoma. The overall median survival was 3 months, and long term survival correlated with cancer stage. >60 months, >22 months, and 8 months for Tis, T1–2, and T3–4 tumors, respectively. Five year survival for cancer limited to the gallbladder and treated with simple cholecystectomy was 93%, 18%, and 10% for Tis, T1 and T2 respectively. For T3 lesions and above no difference was observed among different surgical procedures.

The Japanese literature reported better long term results. Tashiro et al. [102] reported a large series including 2269 patients surgically treated out of 2567 patients with gallbladder carcinoma. The five year survival was 97%, 58%, 25% and 20% for Nevin stage I, II, III and IV, respectively.

Ogura et al. [79] reported similar results in a multicentric Japanese study including 1686 patients treated surgically for gallbladder carcinoma. The five year survival was 82.6% for tumors limited to the gallbladder mucosa, 72.5% for tumors involving the lamina propria. These numbers dropped significantly with tumor invasion being 37% with extension to the subserosal layer, 14.7% with serosal invasion, and only 7.5% when the tumors invaded adjacent organs.

The primary cause of death from GBC is the local progression of the disease. Perputo et al. [103] found in reviewing GBC patient at the time of their death, that most of these patients have peritoneal carcinomatosis, one third of them had lung metastasis, and only few (5%) had brain metastasis.

Multimodal management and potential for new therapeutic options

Similar to other malignant process, modern practice management of GBC relies on multidisciplinary approach. Though the only hope for cure is surgical resection of early disease, a large group of patients are diagnosed with advanced disease beyond surgical resection. As previously discussed there are limited studies reporting the role of neoadjuvant or adjuvant chemotherapy or radiation therapy for GBC. The main limitation of these studies are being underpowered as per the low number of patients and the potential beneficial effect of the chemotherapeutic management carries a high risk for toxicity.

New chemotherapy molecules or treatment strategy may carry a potential role, however, to date very few studies discussed these potentials.

Expression of EGFR is increased in a majority of gallbladder and bile duct cancers and may be associated with a worse outcome. Unlike other GI malignancies, there is very limited experience with the use of monoclonal antibodies in GBC. Given the popularity of the double pathway blocking approach, early results of the combination of bevacizumab and erlotinib in previously untreated advanced gallbladder cancer or cholangiocarcinoma are interesting. The preliminary data were presented at the 2008 ASCO annual meeting and showed that bevacizumab and erlotinib produced partial response (PR) in 3 out of 17 (17.6%) evaluable patients [108].

This was followed by a full report in a recently published phase II multi-institutional trial of bevazcizumab and erlotinib combination therapy for patients with advanced biliary cancers. In this study 53 patients were included including 10 patients with GBC. The results of this report showed that the combination of bevacizumab and erlotinib produced partial response (PR) in 3 out of 17 (17.6%) evaluable patients [108].
regimen was not associated with prolonged neutropenia or GI adverse effects [109]. In a different track, liver targeted therapy using internal radiation therapy using 90 yttrium (Y90) had evolved as a safe and effective alternative or adjunct to systemic therapy for unresectable liver and biliary cancer. Y90 radioembolization has been investigated mainly for treatment of hepatocellular carcinoma and secondary liver tumors. So far, little is known on treatment of tumors originating from the gallbladder with radioembolization. A single published case report suggested that Y90 radioembolization can be a feasible palliative treatment option for patients with locally advanced gallbladder carcinoma [110]. As per the increasing experience of the use of radioembolization as liver targeted therapy for different primary and secondary hepatic malignancies, we believe that this modality merits more investigation for patients with unresectable GBC.

Summary
GBC is a rare but challenging disease. The most important prognostic factor is the depth of tumor invasion. Most cancers are discovered incidentally after cholecystectomy, which is considered curative treatment for early stage cancer limited only to the lamina propria (pT1a). For tumors that infiltrate the gallbladder muscle layer (pT1b), there may benefit in selected patients to perform an extended cholecystectomy. For more advanced disease extended or radical cholecystectomy is needed to achieve negative margins. The classically dismal prognosis of GBC has only partially improved in more recent years due to earlier detection and a more aggressive surgical approach adopted by many surgical centers for advanced disease. Although adjuvant therapy is prolonging life, much work remains to be done to develop solidly efficacious regimens. Given that the primary cause of death is mainly local progression of the disease, surgical resection remains the mainstay of treatment for GBC.

Conflict of interest statement
All authors have no conflict of interest to disclose.

References


