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Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Guido Giordano, MD, Research Assistant Professor, Department of Medical and Surgical Sciences; Unit of Medical Oncology and Biomolecular Therapy, University of Foggia, Policlinico Riuniti, Foggia 71122, Italy. giordano.guido81@gmail.com

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Gallbladder cancer: Historical treatment and new management options

Kenji Okumura, Shekhar Gogna, Mahir Gachabayov, Daniel Moritz Felsenreich, Matthew McGuirk, Aram Rojas, Luis Quintero, Ramanathan Seshadri, Katie Gu, Xiang Da Dong

ORCID number: Kenji Okumura 0000-0002-7751-2624; Shekhar Gogna 0000-0002-4075-9674; Mahir Gachabayov 0000-0002-9200-1304; Daniel Moritz Felsenreich 0000-0002-5229-5096; Matthew McGuirk 0000-0003-3830-9380; Aram Rojas 0000-0001-6984-6731; Luis Quintero 0000-0002-5220-705X; Ramanathan Seshadri 0000-0003-0136-4562; Katie Gu 0000-0002-5952-7478; Xiang Da Dong 0000-0001-9324-1281.

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Kenji Okumura, Shekhar Gogna, Mahir Gachabayov, Matthew McGuirk, Aram Rojas, Department of Surgery, Westchester Medical Center, Valhalla, NY 10595, United States

Daniel Moritz Felsenreich, Division of General Surgery, Department of Surgery, Vienna Medical University, Vienna 1090, Austria

Luis Quintero, Department of Surgery, New York Medical College, Valhalla, NY 10595, United States

Ramanathan Seshadri, Katie Gu, Xiang Da Dong, Division of Surgical Oncology, Nuvance Health, Norwalk, CT 06856, United States

Corresponding author: Xiang Da Dong, FACS, MD, Chief Doctor, Division of Surgical Oncology, Nuvance Health, 34 Maple Street, Norwalk, CT 06856, United States. eric.dong@nuvancehealth.org

Abstract

Gallbladder cancer is a rare, aggressive malignancy that has a poor overall prognosis. Effective treatment consists of early detection and surgical treatment. With the wide spread treatment of gallbladder disease with minimally invasive techniques, the rate of incidental gallbladder cancer has seen an equitable rise along with stage migration towards earlier disease. Although the treatment remains mostly surgical, newer modalities such as regional therapy as well as directed therapy based on molecular medicine has led to improved outcomes in patients with advanced disease. We aim to summarize the management of gallbladder cancer along with the newer developments in this formidable disease process.

Key Words: Gallbladder cancer; Radical cholecystectomy; Cholangiocarcinoma; Epidemiology; Gallbladder disease

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Core Tip: Gallbladder cancer is a rare, aggressive malignancy that has an overall poor

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INTRODUCTION

Gallbladder cancer (GBC) is an uncommon malignancy (1.2%) accounting for about 220000 cases worldwide in 2018[1]. Although the incidence of the malignancy is low, there is significant geographic variability with cases concentrated in Latin America such as Bolivia and Peru, and Southeast Asia such as Thailand. It is also the only gastrointestinal malignancy that is more common in women than men[1]. Being the most common biliary tract malignancy, it accounts for 1.7% of all cancer mortalities reflecting the poor prognosis associated with this diagnosis. Adenocarcinoma of the gallbladder is also significant from management standpoint due to the technical challenges in surgical treatment as well as lack of significant breakthroughs in adjuvant therapies.

In this review, we will examine the causes of GBC along with new innovative treatments in the management of GBC. The various genetic predispositions are examined in detail in terms of their particular risks.

NOMENCLATURE, ETIOLOGY, BIOLOGY, AND INCIDENCE OF GBC

GBC is a rare disease with a worldwide incidence of 2/100000 individuals[2], and females are 2-3 times more likely to develop this disease than males[3]. While GBC is a very rare disease in western countries, the numbers are particularly high in some regions of the world (*e.g.*, South America, Eastern Europe, India, Pakistan, *etc.*). Overall, GBC is the fifth most common cancer of the gastrointestinal tract[2].

GBC as well as cholangiocarcinoma (CCA) are both different types of biliary tract cancer, which includes all tumors originating from the biliary tract epithelium. GBC is the most common biliary tract cancer (equaling 80%-90% of all biliary tract cancers), followed by CCA[4]. CCA can be categorized by its anatomical origin into intra- and extrahepatic CCA. Special types of extrahepatic CCA are the Klatskin tumor and distal CCA[5].

The etiology of GBC is multifactorial. So far, various genetic variants as well as different environmental factors have been associated with a higher risk of developing GBC[6] (Table 1). To name a few: Chronic infections of the gallbladder, gallstones, polyps of the gallbladder, obesity, various dietary factors, exposure to special chemicals or metals and infections with salmonella are risk factors for GBC[7-9]. Furthermore, GBC is known to be more frequent in women than in men, which may be caused by hormonal influences that increase the levels of cholesterol in the bile. This, in turn, is postulated to lead to development of gallstones[10]. On a genetic level, using either a candidate gene study approach or a genome-wide association approach, multiple gene candidates have been identified as possible candidates for GBC[6]. Genetic alterations including KRAS, TP53, and c-ERB-B2 are associated with poor prognosis with GBC[6]. Several other factors, such as those involved in lipid movement through the liver, gallbladder and bile ducts are still under discussion and are focuses of a few ongoing studies.

Over 90% of GBC are adenocarcinomas. Histopathological types include papillary, mucinous, squamous or adeno-squamous carcinomas. The most common type of differentiation is the biliary type, followed by the intestinal and the gastric-foveolar

Table 1 Risk factors for gallbladder cancer[35]

Patient predisposition	Environmental factors	Patient factors/conditions
Female sex	Chronic bacterial infections	Diabetes
Age	Aflatoxins	High body mass index
Race/ethnicity	Ochratoxin	Primary sclerosing cholangitis
Genetics (variants)	Arsenic	Porcelain gallbladder
	Liver fluke	Gallbladder polyps
	Geography	Crohn's disease
		Anomalous biliary ductal insertion
		Gallstones
		Sjogren's syndrome

type[2]. In terms of the location of GBC, it is isolated to the fundus in 60%, in the body in 30%, and in the neck of the gallbladder in 10% of times[4].

CLINICAL PRESENTATION OF GBC

Incidental finding during surgery

Due to the rare nature of the disease, GBC is often discovered incidentally. This occurs either during routine cholecystectomy or post-operatively on final pathology performed for other indications. Intra-operative diagnosis is found to be as low as 0.28% by Glauser *et al*[11], with the majority discovered on pathology post-operatively. Re-operative surgery needs to be contemplated to achieve an R0 resection, improve adequacy of margin resection, and/or to perform concurrent lymphadenectomy[12].

The tumor depth of invasion is the single biggest factor in determining the need for further surgical intervention. For GBC with Tis or T1a on pathology, no further surgery is required as the initial cholecystectomy is frequently curative. For GBC with T1b and above, re-operation is recommended[12] (Figure 1). Re-operation with extended re-resection of the gallbladder bed and lymph nodes increases survival for patients with T2 and T3 lesions. Interestingly enough, for patients with T1b lesions, extended re-resection does appear to increase survival over simple cholecystectomy alone[11]. Goetze and Paolucci[13] suggested that with each increasing tumor depth, more radical resection was needed. For T1b lesions a wedge-resection of 2-3 cm margins had superior survival compared to radical re-resection, while for patients with T2 and T3 tumors, survival was better with segment IVb and V resection with lymph node dissection around the hepatoduodenal ligament[13]. In fact, with radical re-resection, survival is comparable to the survival of patients who have primary resection rather than re-resection for incidental disease[14]. While re-resection increases survival, resection of the common bile duct has not been shown to increase survival or margin-free resection[15].

Although these re-resections have shown survival benefits, particularly in T1b or stage II-III, GBC with T4 or N1 Lesions still have very poor prognosis. For GBC overall, neoadjuvant therapy and clinical trials are more important for survival than radical re-resection[14]. For these patients, a re-operation with radical resection may provide some palliation if biliary compression is causing secondary sequelae[16]. With each increasing tumor grade, the chance of having curative re-operation decreases[17]. Re-operation appears to have the best survival rates if done within 4-8 wk following the initial cholecystectomy[18].

Historically, there were concerns that laparoscopic cholecystectomy increased the risk of intra-peritoneal metastases in cases of occult GBC. This is no longer felt to be the case. Survival rates have now been shown to be similar between laparoscopic and open cholecystectomy, with no differences in recurrence of cancer in the abdominal wall[19,20]. What is important, however, is the tumor stage and whether or not bile spillage occurred during the index surgery[19].

One of the biggest questions during re-operative surgery following an incidental GBC is whether or not to perform a port site resection. In a large meta-analysis of 26 studies, Choi *et al*[21] found that 8.1% of patients had positive cancer cells at the port

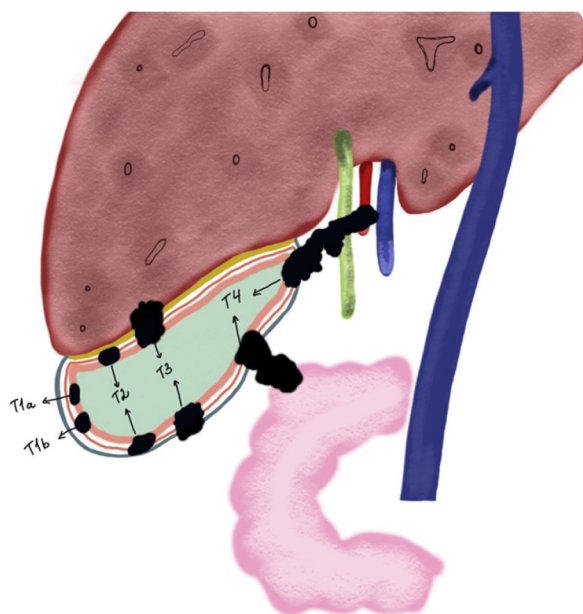


Figure 1 Diagram of gallbladder cancer based on depth of tumor invasion is shown.

sites. Despite the fact that port site metastases are associated with decreased survival, Maker *et al*[22] determined that port site resection should not be a mandatory step in management, as it did not improve survival or disease-free recurrence. Ethun *et al*[23] reached the same conclusion, with no increase in survival with port site excision and the same rate of distant recurrence of GBC despite port-site resection. In a study of 218 patients with incidental GBC, port-site excision was not associated with improved survival[24].

Interestingly enough, patients with GBC found incidentally have been found to have better survival than patients with known cancer going into a cholecystectomy. D'Hondt *et al*[25] found that curative surgery and five-year survival rates were both higher in patients who had incidental GBC. This is potentially due to lower tumor stages in patients with incidentally discovered GBC.

Clinical presentation

GBC is relatively asymptomatic in its early stages. The presentation of GBC has been divided into three common scenarios: (1) Identification by final pathology following a routine cholecystectomy; (2) Discovery during the index surgery; and (3) Suspicion before surgery due to atypical symptomatology[26].

In a United States population-based study of incidental GBC, Pitt *et al*[27] showed that four factors are strongly associated with the finding of cancer at cholecystectomy: Age ≥ 65 years, female, Asian or African American race, and elevated alkaline phosphatase preoperatively.

The diagnosis of GBC should be considered in an elderly patient with constant right upper quadrant abdominal pain with weight loss or anorexia. Weight loss, anorexia and particularly jaundice are signs of advanced disease[28]. Hawkins *et al*[29] showed that the presence of jaundice with localized GBC are associated with worse outcome.

Tumor makers such as carcinoembryonic antigen (CEA) and carbonic anhydrase 19-9 (CA 19-9) may be associated with GBC, but are unreliable screening tools. An elevated CEA can be specific for presence of gastrointestinal malignancy (90%) but lacks sensitivity (50%) when CEA was used as a screening test for cancer in patients presenting with gallbladder diseases[30]. CA 19-9 is another tumor marker used in patients with pancreato-biliary tumors with up to 75% sensitivities and specificities when the level exceeds 20 U/mL[31]. Due to their limitations, serum tumor markers are useful in the setting of follow up, for earlier detection of recurrent disease. The use of tumor markers in the form of CEA and CA 19-9 has been useful in the diagnostic algorithm for GBC although they pertain to a larger group of pancreatic biliary associated malignancies and not specific to the GBC alone[32].

When the clinical presentation is worrisome for a GBC, ultrasonography (US) is frequently the first imaging modality of choice. These findings on the US are worrisome: Calcification, a mass protruding into the lumen, loss of interface between gallbladder and liver, direct liver infiltration, gallbladder polyps ≥ 10 mm, or an

abnormal thickened gallbladder wall[33]. The overall accuracy of US to diagnose and stage the local and distant extent of suspected GBC is limited[34]. Additional imaging such as computed tomography (CT) or magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP) is necessary to complete staging work up for GBC (Figure 2). Subsequent biopsy, either percutaneous or endoscopic, may guide therapeutic interventions.

On cross sectional imaging, we need to evaluate the potential for resectability by the extent of invasion into liver parenchyma, vascular involvement (hepatic artery and portal vein) and suspected nodal involvement[35]. Once the diagnosis is established, based on the staging of GBC, the extent of surgical resection and regional lymphadenectomy is determined. Endoscopic ultrasound (EUS) is an emerging modality to assess GBC. EUS is more accurate than trans-abdominal US and EUS is useful both detection and staging of tumor extension[36,37].

The role of a positron emission tomography (PET) scan is controversial in patients with potential resectable disease[12]. PET scanning may help to distinguish between benign and malignant diseases. Furthermore, although PET has been reported to have low sensitivity of extrahepatic disease, particularly peritoneal carcinomatosis, it is still a useful adjunct to detect metastatic disease[38]. The recent study from Goel *et al*[39] showed that up to 23.4% patients had a change in the management following PET-CT and they suggested PET-CT should be included in preoperative work up.

Staging

Over the years, a variety of staging systems for GBC has been proposed. Realizing that the histological grade of the tumor impacted survival, Nevin *et al*[40] reported a series of 66 patients with GBC and described a method combining staging with histological grading of this cancer. This staging method was modified and later used[41]. Currently, the Tumor, Node, Metastasis (TNM) staging system of the combined American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) is the standard classification scheme[35] (Tables 2 and 3).

In AJCC staging system, GBC is classified into four stages based on the depth of invasion into the gallbladder wall and the extend of spread to surrounding organs and lymph nodes (Figure 3). In the revised 8th edition of the AJCC staging system, T2 gallbladder carcinoma was divided into two groups: tumors on the peritoneal side (T2a) and tumors on the hepatic side (T2b)[35]. This revision was made based on two retrospective studies showing that invasion into the hepatic side carries with worse prognosis, compared to tumors located on the peritoneal side[42,43]. However, it is important to note that it can be difficult to determine the exact location of the tumor, contributing to difficulty in predicting patient outcome. In the most updated edition, staging of lymph nodes was also changed. Regional lymph node involvement is now staged according to number of positive nodes, instead of staging based on anatomic location of involved lymph nodes.

SURGICAL MANAGEMENT OF GBC

Rationale for surgery

GBC requires a multimodal approach to its management. Surgery remains the gold standard for curative intent. Several factors need to be taken into account when choosing surgical management in patients with GBC: health of the patient, extent of surgical intervention needed, and post-operative outcomes anticipated. Extent of the disease and location of the tumor are important factors determining the extent of surgery in addition to the type of procedure need to ensure radical excision of the cancer with no residual disease. The location of the cancer influences surgical procedure because tumors located closer to the cystic plate have a propensity to invade the liver whereas those located in the inferior wall may spread to the peritoneum early (Figure 1).

Types of surgical interventions

Table 4 summarizes the types of surgical procedures performed for GBC, ranging from simple cholecystectomy to multi-visceral resection. These surgical procedures can be divided into curative and palliative procedures. In early stages of GBC (T1a or less), a simple cholecystectomy, regardless of whether the approach is open or minimally invasive (laparoscopic or robotic), is sufficient with almost 100% 5-year survival rate, as the current evidence supports[44,45]. In general, open approach rather than laparoscopy is recommended by most experts to minimize the risk of bile spillage.

Table 2 Staging of gallbladder cancer

T stage	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 muscular layer
T1a	Tumor invades lamina propria
T1b	Tumor invades muscle layer
T2	Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum) or tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver
T2a	Tumor invades the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (visceral peritoneum)
T2b	Tumor invades the perimuscular connective tissue on the hepatic side, with no extension into the liver
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4	Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures
N stage	Regional lymph nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to one to three regional lymph nodes
N2	Metastasis to four or more regional lymph nodes
M stage	Distant metastasis
M0	No distant metastasis
M1	Distant metastasis

Table 3 Cancer stage grouping

Stage	T	N	M	Description
0	Tis	N0	M0	Cancer <i>in situ</i>
I	T1	N0	M0	Tumor is only in the gallbladder and has not spread
II	T2	N0	M0	Tumor has extended to the perimuscular connective tissue but has not spread elsewhere
IIIA	T3	N0	M0	Tumor has spread beyond the gallbladder but not to nearby arteries or veins. It has not spread to any lymph nodes or other parts of the body
IIIB	T1-3	N1	M0	Tumor of any size has spread to nearby lymph nodes but not to nearby arteries and/or veins or to other parts of the body
IVA	T4	N0 or N1	M0	Tumor has spread to nearby arteries, veins, and/or nearby lymph nodes, but it has not spread to other parts of the body
IVB	Any T	Any N	M1	Any tumor that has spread to other parts of the body
	Any T	N2	M0	Any tumor that has distant lymph node spread, even if it has not spread to distant organs

Nonetheless, laparoscopy has a key role in staging, especially in patients with preoperatively diagnosed GBCs with elevated CA 19-9 levels[46]. Agarwal *et al*[47] studied the role of diagnostic laparoscopy for GBCs and found that 23.2% of patients had disseminated disease and could avoid laparotomy. Currently, routine port-site excision is not recommended after laparoscopic cholecystectomy as we discussed above. In fact, the data from the US Extrahepatic Biliary Malignancy Consortium found no difference in distant recurrence rates and 3-year overall survival (OS) rates between patients who

Table 4 Surgical procedures performed for gallbladder cancer

Procedure	Description	Indications
Curative procedures		
Simple cholecystectomy	Dissection, ligation, and transection of cystic duct and artery at the level of Calot triangle and dissection of the cystic plate	Benign gallbladder conditions, gallbladder polyps, porcelain gallbladder, GBC (T0, Tis, and T1a)
Extended cholecystectomy	Simple cholecystectomy + hepatic wedge resection at the level of gallbladder fossa (2-3 cm in depth)	T1b and higher GBC
IVb/V hepatic bisegmentectomy	Resection of liver segments IVb and V <i>en bloc</i> with the gallbladder with intra-parenchymal transection of the middle hepatic vein	GBC invading liver parenchyma
Extended liver resections	Most commonly right hepatectomy, rarely left hepatectomy	GBC invading structures of porta hepatis
Bile duct resection	Resection of the extrahepatic bile duct + Roux-en-Y hepaticojejunostomy	GBC invading extrahepatic bile ducts or positive cystic duct margin at frozen section pathology
Lymphadenectomy	Removal of lymph nodes from N1 and N2 zones	T1b and higher GBC, N+ GBC
Multivisceral resection	May involve right colectomy, pancreaticoduodenectomy, resection of abdominal wall, <i>etc.</i>	Locally advanced GBC
Palliative procedures		
Biliodigestive anastomoses	Roux-en-Y hepaticojejunostomy	Locally advanced unresectable GBC presenting with jaundice
Digestive anastomoses	Gastro-enteric anastomosis, ileo-transverse colon anastomosis	Locally advanced unresectable GBC presenting with intestinal obstruction

GBC: Gallbladder cancer.



Figure 2 Typical gallbladder cancer on computed tomography scan is shown. Contrast enhanced tumor is seen in the gallbladder.

underwent port-site excision and those who did not[23].

In GBC with the T stage of T1b or higher, more radical procedures are required. The extent of radical cholecystectomy may vary from extended cholecystectomy, when liver margin at the gallbladder fossa is resected, to right hepatectomy or multi-visceral resection[12,48] (Figure 3). Contraindications for curative surgery include the following: Distant metastases (M1) including liver and peritoneal metastases and metastases to paraaortic lymph nodes (N2); malignant ascites; extensive invasion of hepatoduodenal ligament and major vascular involvement[12]. Advanced GBC may require palliative procedures such as bilio-digestive anastomoses performed to relieve biliary obstruction and digestive anastomoses performed to bypass intestinal obstruction.

Surgical approaches to preoperatively detected GBC

In patients with preoperatively detected GBC with no distant metastases, laparotomy is the traditional treatment of choice as it allows for extended resections. This was historically due to suboptimal accuracy in radiologic staging. More recently, current evidence suggests laparoscopy to be the feasible with advances in minimally invasive surgery[44,45]. Simple cholecystectomy is usually sufficient in T1a cancers when

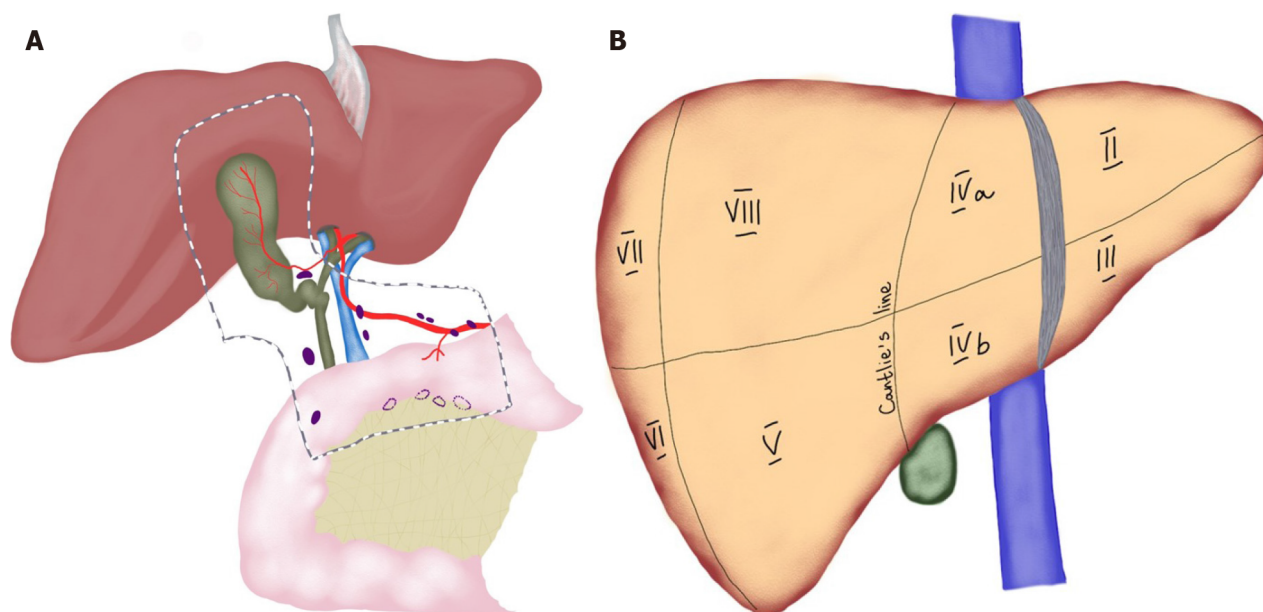


Figure 3 A key anatomy for gallbladder cancer. A: Lymphatic drainage pattern for gallbladder cancer; B: Liver segments along with Cantlie's line. Segments IVB and V are frequently involved with gallbladder cancer.

muscular layer is not involved and is associated with 73%-100% OS[49,50]. Intraoperative frozen section pathology of the cystic duct is a decisive factor for bile duct resection, if positive. In a recent study, bile duct resection was not found to improve lymph node harvest or OS[51]. Moreover, bile duct resection was associated with increased rates of postoperative morbidity in the AFC-GBC-2009 cohort[15]. Therefore, it should be reserved for cases with positive cystic duct margin. In T1b GBCs when the muscular layer is involved, extended cholecystectomy is indicated due to higher rates of lymph node metastases (15% *vs* 2.5%), higher loco-regional recurrence rates (60% *vs* 50%), and higher rates of liver invasion (13% *vs* 0%)[48]. Nonetheless, a recent SEER database study did not find the survival benefit of extended cholecystectomy to be as significant as the number of harvested lymph nodes more than six[52]. In T2 GBCs when peri-muscular connective tissue is involved, extended cholecystectomy with lymphadenectomy in N2 zone (hepatoduodenal ligament, along proper hepatic artery, and posterior superior pancreatic lymph nodes) is indicated as T2 cancers are associated with a higher rate of liver invasion (10%), higher rate of lymph node involvement (up to 60%), and higher risk of residual disease (up to 76%)[53] (Figure 1). It is known that survival in patients with T2 GBC correlates with the number of lymph nodes harvested[54]. In fact, data from previous reports suggested that a minimum of six lymph nodes should be removed in order to consider the nodal status negative [55]. With regard to resectable T3 and T4 cancers, surgeons were reluctant in the past to operate on these patients due to high postoperative morbidity and poor survival outcomes[56]. However, data from Japan indicating improved survival in these patients (15%-63% in T3 and 7%-25% in T4 cancers) advocated for surgical management[57]. Moreover, some authors have advocated for even more extensive multivisceral resections involving hepatectomy, colectomy, pancreaticoduodenectomy, or nephrectomy in potentially resectable disease and have reported a median survival of 17 mo in such patients[58]. Nonetheless, postoperative morbidity (in half of the patients) and mortality (in every fifth patient) were significant. Dissimilarly, D'Angelica *et al*[59] in the United States did not find any survival benefit in patients undergoing multivisceral resection. In general, lymph nodes outside the hepatoduodenal ligament are usually not subject to resection since outcomes following radical lymphadenectomy are even worse than with N2 disease[12].

CHEMOTHERAPY AND LOCOREGIONAL THERAPY FOR GBC

Surgery is the only curative treatment option in GBC, but recurrence is very common despite curative resection[60]. Therefore, considerable interest exists in applying neoadjuvant[61] or adjuvant therapy in the multi-modal management of GBC.

Although there is a paucity of high-quality prospective studies, several chemotherapy regimens are recommended by NCCN in the neoadjuvant setting. These include gemcitabine/cisplatin, gemcitabine/oxaliplatin, capecitabine/oxaliplatin, and combinations of gemcitabine, capecitabine, and 5-FU[12].

American Hepato-Pancreato-Biliary Association (AHPBA) sponsored consensus meeting advocated for neoadjuvant therapy in patients with clinical T3/T4/N1 disease [62]. Patients receiving neoadjuvant treatment can potentially downsize their tumor or avoid unnecessary surgery in those with occult metastases. However, the latest meta-analysis on 8 studies totaling 474 patients found that there was insufficient data to support the routine use of neoadjuvant therapy for advanced GBC[12]. Only one-third of all the patients were down-staged completely to be able to achieve an R0 resection. There is a need for multicenter prospective studies on this topic.

After complete resection, locoregional and/or distant recurrences are very common. The burden of disease recurrence rate at locoregional sites is 33.9%-79.2%, distant sites, 52.6%-79.8%, and at both sites is 18.9%-50%, respectively[63]. Adjuvant chemoradiotherapy seems to offer a potential solution to improve OS, but high-quality data seems to be lacking. The literature supporting gemcitabine and fluoropyrimidine based adjuvant chemotherapy comes from four randomized control trials (RCT)[64-67]. More recently, the 3 phase III RCTs trial BILCAP trial deserves special mention. This trial is considered pivotal in updating international treatment guidelines, in defining the role of capecitabine based ACT as a reference regimen in resectable GBC. These results set the benchmark for subsequent phase III trials testing other combination chemotherapy regimens in the adjuvant setting[68]. Intra-arterial chemotherapy (IAC) has a well-established role in decreasing liver metastases from colorectal cancer and is known to improve long-term survival[69]. More recently, IAC (based on oxaliplatin and gemcitabine regimen) has been shown to effectively and safely improve 3-year disease-free survival, OS, and hepatic metastases-free survival of stage 2-3 GBC[69].

Unfortunately, the majority of patients present with unresectable or metastatic disease when palliative treatment is the only option[70]. However, the emergence of targeted therapies is rapidly changing the treatment paradigm for biliary tract cancer [71].

RECENT ADVANCES IN MANAGEMENT OF GBC

In recent years, 'precision medicine' for advanced or refractory advanced GBC is an exciting area of research and clinical trials. Essentially, it involves targeting specific molecular alterations with immunotherapy[72]. Figure 4 shows that alterations in genes such as IDH1/2, FGFR2, FGFR4, EGFR, ERBB2, and PIK3CA are frequent in biliary tract cancer and can be targets for treatment[71]. It is important to note that immunotherapy for GBC is still in infancy as compared to options for intrahepatic CCA.

Management of metastatic disease and unresectable begins with preoperative evaluation and biopsy to confirm the diagnosis[12]. With biopsy specimen, microsatellite instability and or mismatch repair testing should be routinely performed. The GBCs with MMR deficiency benefit from PD-1 receptor blockade such as pembrolizumab[73]. Pembrolizumab is a monoclonal antibody against PD-1, which has been shown to have a long-lasting antitumor activity and low toxicity in several advanced cancers[74]. A recent study has shown that high PD-L1 expression was associated with a better response to pembrolizumab based therapy[75]. The combination of pertuzumab and trastuzumab was also investigated in 11 patients with previously treated biliary tract cancer, with HER2 amplification (8 patients) or HER2 mutations (3 patients). Risk reduction of 7.5% and 33.3% were achieved in these patients, respectively[76]. For patients with BRAF (V600E) mutations, dual inhibition with dabrafenib and trametinib have been investigated[77]. Within the biliary tract cancer subgroup (33 patients) in that study, partial response rates of 42% and 36% with a dual inhibitor were achieved, respectively. However, none of the studies so far has shown the superiority of immunotherapy over first or second-line systemic chemotherapy. Therefore, clinical investigations of neoadjuvant, adjuvant chemotherapy and immunotherapy must continue.

NEWER APPROACHES TO MANAGEMENT

Given the severity of GBC, new surgical approaches and techniques are constantly

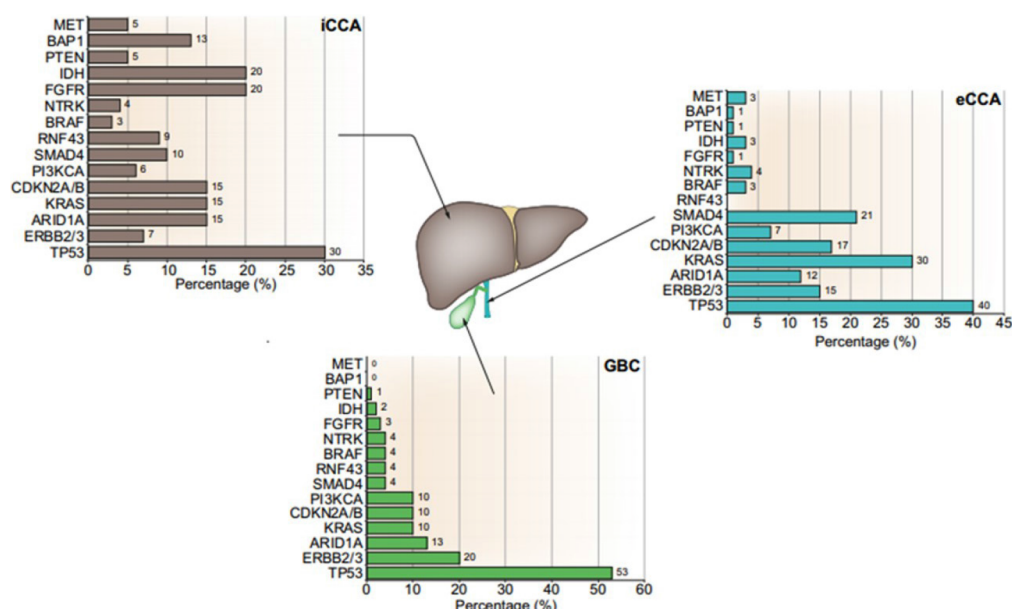


Figure 4 Molecular profiling of biliary tract cancers. Percentage of main targetable and non-targetable genetic alterations are summarized for intrahepatic cholangiocarcinoma (iCCA), extrahepatic cholangiocarcinoma (eCCA), and gallbladder cancer (GBC). Within targetable alterations, there are clear variations within the molecular profiling of these tumors with a predominance of IDH and FGFR alterations in iCCA and ERBB2/3 (HER2/3) in eCCA and GBC[71]. Citation: Lamarca A, Barriuso J, McNamara MG, Valle JW. Molecular targeted therapies: Ready for "prime time" in biliary tract cancer. *J Hepatol* 2020; 73(1): 170-185. Copyright ©2020 European Association for the study of the Liver. Published by Elsevier B.V.[71]. CCA: Cholangiocarcinoma; eCCA: Extrahepatic cholangiocarcinoma; GBC: Gallbladder cancer; iCCA: Intrahepatic cholangiocarcinoma.

being explored. Innovations in how these patients are treated are sought to decrease morbidity, and hopefully, eventually decrease mortality as well.

Minimally invasive surgery

Laparoscopic and robotic surgical management of GBC greatly could reduce morbidity with decreased estimated blood loss and length of hospital stay[78,79]. Initially, laparoscopic approaches raised further questions due to increase in port site cancer occurrences in addition to the lack of dexterity of laparoscopic instruments[49]. Current consensus for minimally invasive surgery approach is still controversial among hepatobiliary/pancreas surgeons, especially in advanced GBCs[80]. Yoon *et al* [81] showed that laparoscopic extended cholecystectomy including lymphadenectomy for GBC achieved compatible outcomes with that of open surgery over long-term follow-up. Development of robotic surgery overcame some of the limitations of laparoscopic surgery and demonstrated equivalent outcomes to open approaches while retaining the benefits of minimally invasive approach[78,79]. Laparoscopic surgery for liver resection or bile duct resection showed comparable oncological outcomes for the experts and the instrumentation in the robotic platforms would be expected to show similar outcomes. The robotic installment allows increased dexterity required for proper lymphadenectomy and 3D high-definition visualization which could possibly aid in better visualization of anatomical structures.

Recent studies on robotic surgery for GBC have shown favorable results in several limited case series[79,82,83]. As such, there is a need for larger studies. While a randomized trial for a rare pathology is not feasible, larger cohort studies could still be conducted[82,83]. At present, the technical approach for the robotic surgery of GBC has been described in the literature, such as that of Belli *et al*[84]. Similar to the laparoscopic approach, the patient is positioned in reverse-Trendelenburg, with five ports being used which include the 3 ports for robotic instrumentation, 1 for the camera and 1 Laparoscopic port for an assistant surgeon[84].

Fluorescent visualization

Indocyanine green (ICG) is a fluorescent molecule that is water soluble and injected intravenously. ICG is taken up by the liver and excreted in biliary system allowing visualization of liver perfusion and imaging of the extrahepatic biliary tree. The use of ICG is not limited to the robotic surgery, however, it has been used widespread in the laparoscopic surgery prior to its adoption in robotic surgery. In the literature, its use has been described for GBC to identify the biliary system and lymph nodes[85]. ICG is

useful to identify anatomical border of liver sections and ICG allows to perform anatomical resections in minimally invasive surgery setting. Yu *et al*[86] showed no difference between anatomical resection and non-anatomical resection in GBC. Si *et al* [87] reported anatomical resection for intrahepatic CCA had similar complication rates, but showed better survival outcomes in tumors with stage IB or II without vascular invasions. Hepatocellular carcinoma might have benefit from anatomical resection[88,89]. For oncology prospective, it is better to perform anatomical resection and ICG makes anatomical resection easier. Current evidence showed that no difference in outcomes, however, we need to study using ICG and compare the outcomes.

Minimally invasive ablative therapy

Several ablative therapies have been utilized for management of GBC when it is isolated to the liver parenchyma. Modalities such as microwave ablation, radiofrequency ablation (RFA), alcohol ablation all have had limited success. Ablative therapies work by destruction of liver parenchyma through targeted tissue necrosis. Because of the need to avoid injury to the central biliary tree, these modalities have been mostly limited to local regional recurrence or metastatic sites for GBC[90,91]. Microwave ablation, RFA and alcohol ablation may also be useful to treat palliative purposes for advanced stage GBC, however, the literature is limited on this topic and further research is needed to better understand the benefits of such an approach.

Augmented reality

With improvements in preoperative imaging, augmented reality allows precise preoperative planning for surgical resections with superimposed intraoperative imaging. This technology takes multiple preoperative images, integration into a 3D reconstruction, followed by preoperative planning and incorporation intraoperatively to improve identification of structures and precision of resections. Several software systems have been developed to generate such simulations which can simulate surgical resections[92]. Intraoperatively, the images are superimposed directly over the patient's anatomy and the technology has been used in a case series by Peterhans *et al*[93]. Augmented reality has also been used as an aid in visualization by helping to see through structures, aiding in port placement, and identification of intrahepatic vasculature. Additionally, artificial intelligence, while still in its infancy, may also assist in locating and identifying structures in complex surgeries[94]. Such technology could lead to improved margins of resection and preservation of unaffected and critical structures in patients.

PROGNOSIS

The prognosis of GBC remains guarded. Most GBC are diagnosed as advanced conditions. Surgical resection is an important factor for management of GBC. According to SEER database between 2000 and 2016, five-year survival is 17.9%[95] (Figure 5). The age-adjusted incidence of gallbladder has remain unchanged around 1.2 per 100000, however the mortality has been decreasing significantly over the last 2 decades ($P < 0.01$)[95].

We have reviewed the outcomes of previous published studies for GBC (Table 5). The overall five-year survival for all patients with GBC is around 20 percent (SEER 19.2%, Figure 5)[95]. Patients with localized disease who are amenable to surgical treatment have over 65% survival in five years[95]. However, survival of patients with distant metastasis remains dismal at 2%-13%. Therefore, potentially resectable patients have a significant advantage over patients without surgical options.

CONCLUSION

GBC remains a formidable disease. Surgical management has traditionally been challenging due to the technical difficulties associated with liver resection and biliary reconstruction. In addition, effective cytotoxic agents were limited. However, newer developments in management are leading to significant changes in the prognosis of this disease. Minimally invasive techniques in management such as robotic surgery coupled with ablative techniques offer quicker recovery for patients undergoing surgery for loco-regional disease. Perioperative management for incidentally

Table 5 Historical prognosis of gallbladder cancer

Ref.	n	Year	Status	Survival time (mo)
Gall <i>et al</i> [96], 1991	113	1970-1989	Curative resection	42
			Non-curative resection (metastasis +)	12.5
Cuberta <i>et al</i> [97], 1994	724	1980-1989	Curative resection 25%	Overall 3
			Non-curative resection 75%	
Jarnagin <i>et al</i> [98], 2003	97	1990-2001	Curative resection	31.3
Hawkins <i>et al</i> [29], 2004	240	1995-2002	Curative resection	34
			Non-curative resection	8
Nishio <i>et al</i> [99], 2007	166	1977-2004	Curative resection	12
			Non-curative resection	6
Duffy <i>et al</i> [28], 2008	206	1995-2005	Overall	10.3
			Incidental GBC	15.7
			Curative surgery	30.3
			Curative surgery + adjuvant therapy	23.4
D'Hondt <i>et al</i> [25], 2013	102	1998-2008	Overall	7.2
			Incidental GBC	25.8
			Non-Incidental GBC	4.4
Butte <i>et al</i> [100], 2011	261	1999-2007	Overall	DSS 16.97
Ito <i>et al</i> [55], 2011	122	1992-2007	R0 resection	DSS 41
Butte <i>et al</i> [101], 2014	135	1998-2009	Overall	DFS 25.9
			Residual disease	11.2
			Non-residual disease	93.4
Ethun <i>et al</i> [18], 2017	449	2000-2014	Incidental GBC	27.6
Zhang <i>et al</i> [102], 2018	1422	2010-2014	Resection	13
Yu <i>et al</i> [86], 2019	81	2006-2015	T3 Anatomical resection	54
			T3 Wedge resection	49
Ref.	n	Year	Status	Survival rate (%)
Ogura <i>et al</i> [103], 1991	1686	1979-1988	Radical resection	66.2 (3 yr) 50.7 (5 yr)
			Non-radical resection	14.1 (3 yr) 6.2 (5 yr)
Cuberta <i>et al</i> [97], 1994	724	1980-1989	Curative resection 25%	Overall 14 (1 yr) 5 (5 yr)
			Non-curative resection 75%	
Carriaga and Henson[104], 1995	4412	1973-1987	Overall	12.3 (5 yr)
Bartlett <i>et al</i> [105], 1996	149	1985-1993	Resection	51 (5 yr)
Fong <i>et al</i> [17], 2000	410	1986-2000	Resection	38 (5 yr)
			Non-resection	4 (5 yr)
Nakeeb <i>et al</i> [106], 2002	140	1990-2001	Resection	31 (5 yr)
Pawlik <i>et al</i> [107], 2007	115	1984-2006	Resection	12 (5 yr)
Kayahara and Nagakawa[57], 2007	4770	1988-1997	Overall	39 (5 yr)
Shih <i>et al</i> [108], 2007	107	1995-2004	Overall	15 (5 yr)
			Incidental GBC	33 (5 yr)
D'Angelica <i>et al</i> [59], 2009	109	1988-2002	Overall	42 (5 yr)
Fuks <i>et al</i> [15], 2011	218	1998-2008	Incidental GBC	41 (5 yr)

Hari <i>et al</i> [109], 2013	1115	1988-2008	Cholecystectomy	50 (5 yr)
			Cholecystectomy + LN dissection	70 (5 yr)
			Radical cholecystectomy	79 (5 yr)
Barreto <i>et al</i> [110], 2014	163	2003-2010	Overall	DFS 79.6 (2 yr)
Shindoh <i>et al</i> [42], 2015	252	1981-2011	T2	42.6 (5 yr)

DSS: Disease specific survival; DFS: Disease free survival; LN: Lymph node.

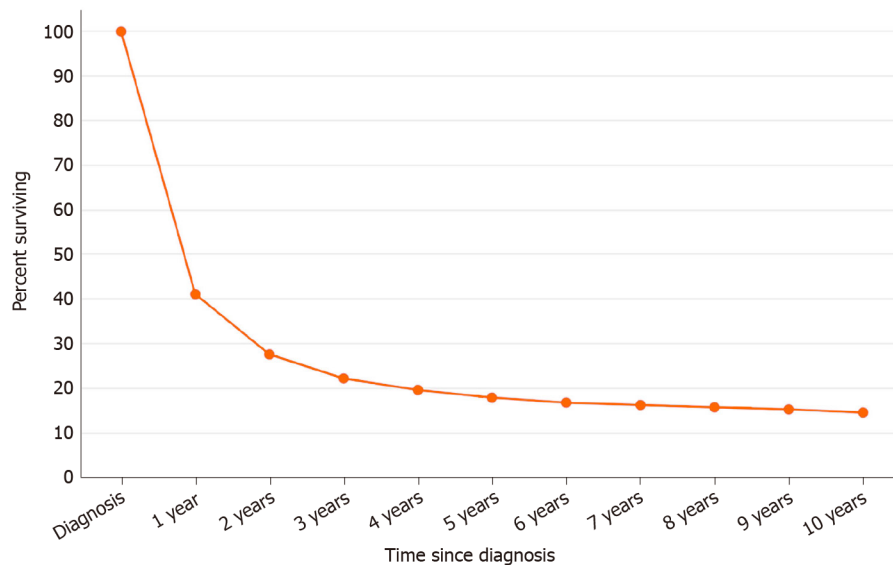


Figure 5 Overall survival for gallbladder cancer based on SEER database.

discovered GBC is being better defined based on more accurate pathologic staging. Targeted therapies are offering renewed enthusiasm among oncologists with its rapidly evolving landscape. Nonetheless, much remains undefined in management of GBC and further studies are urgently needed in this malignancy.

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