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Chapter

Gallbladder Cancer: Diagnosis and Surgical Management

Asmita Chopra and Alessandro Paniccia

Abstract

Gallbladder cancer (GBCa) is a biliary tract malignancy that is common in South America and Southeast Asia, where patients often present with abdominal pain and jaundice. However, most cases of GBCa in the United States are diagnosed incidentally following cholecystectomy. The pre-operative diagnosis and evaluation involves imaging with ultrasound, CT, MRI, and PET. In patients with incidental GBCa, the histopathology directs further management. The surgical management of GBCa ranges from a simple cholecystectomy to liver resection with lymphadenectomy. Bile duct and vascular resections are reserved to obtain negative margins. To date, multiple controversies remain in the management of GBCa. The determination of type of surgery is based predominantly on T stage. The need for liver resection for tumor on the peritonealized surface continues to be debated. The added value of neoadjuvant and peri-operative therapy is being actively investigated. Systemic therapy has greatly evolved encompassing the use of capecitabine, gemcitabine-cisplatin, with recent addition of taxanes, HER2 inhibitors, and immunotherapy using PD-L1 inhibitors including Durvalumab. This chapter describes current diagnosis and treatment practices for GBCa especially determinants of surgical management and the benefits of peri-operative systemic therapy highlighting the recent advances and shortcomings.

Keywords: gallbladder cancer, radical cholecystectomy, incidental cancer, neoadjuvant, PD-L1 inhibitors

1. Introduction

Gallbladder cancer (GBCa) is the most common form of biliary tract cancer and is associated with a particularly insidious course coupled with an aggressive biological behavior. While GBCa constitutes 40% of diagnosed biliary tract malignancies, the incidence has been reported to be as high as 80–95% in autopsy studies [1, 2]. Gallbladder cancer has the worst prognosis of all bile duct malignancies with a 5-year relative survival of 19% [1]. While rare in the developed world, including the United States, incidence of GBCa is high in South America and Southeast Asia, and is highest in women of North India [3]. The most important risk factor of GBCa is chronic cholelithiasis, with more than 85% cases of gallbladder cancer being associated with gallstones. Conversely, less than 3% of patients with gallstones, eventually develop gallbladder cancer. As such, there is no role for prophylactic cholecystectomy in patients with asymptomatic gallstone disease in the absence of high risk features

such as associated polyps measuring more than 10 mm, and gallbladder wall thickening [4]. Females are two times more likely to develop GBCa compared to their male counterparts [5]. Additional risk factors of gallbladder cancer include: chronic inflammation, porcelain gallbladder, infections including bacterial (most commonly Salmonella and Helicobacter) and parasitic (Clonorchis and Opisthorchis), primary sclerosing cholangitis, smoking, obesity, gallbladder polyps, and family history of gallbladder cancer [4]. Additionally genetic mutations associated with other gastrointestinal malignancies—including TP53 mutation (47.1–59%), ERBB2/3 amplification (9.8–19%), CDKN2A/B loss (5.9–19%), ARID1A mutation (13%), KRAS mutation (4–13%), PIK3CA mutation (5.9–12.5%), NRAS mutation (6.3%) and BRAF mutation (1–5.9%)—have also been reported in GBCa [6]. In this chapter, we discuss the diagnosis of GBCa in patients with clinical symptoms as well as asymptomatic patients who are incidentally diagnosed on imaging or following pathological evaluation of a cholecystectomy specimen. We also discuss the various determinants of surgical and medical management of patients with GBCa, as well as the recent advances in treatment strategies.

2. Diagnosis of gallbladder cancer

2.1 Clinical presentation

Patients with gallbladder cancer may present with constitutive symptoms of weight loss and anorexia, and in advanced cases with abdominal pain, abdominal mass and jaundice. These symptoms are more commonly reported in areas with high incidence of gallbladder cancer, including South America and North India. In developed countries, including the United States, most cases of gallbladder cancer are found incidentally after cholecystectomy. While incidental gallbladder cancer is seen in less than 2% of the routine cholecystectomies done for benign disease, it accounts for more than 50% of all gallbladder cancer diagnosis [7, 8]. The current indications for cholecystectomy in asymptomatic patients have partly been dictated by the presence of risk factors predictive of malignancy. These include patient age more than 60 years with GB polyp less than 10 mm, history of primary sclerosing cholangitis and presence of GB polyp, Asian race, GB wall thickening more than 4 mm, and polyp more than 10 mm [9, 10].

2.2 Imaging

Imaging plays an important role in diagnosing a gallbladder cancer. Ultrasound is the first imaging modality used for gallbladder pathologies. It comes with the advantage of lack of ionizing-radiation exposure, cost-effectiveness, and real-time imaging of the gallbladder (e.g., assessment of intraluminal mass mobility). Ultrasound findings of gallbladder wall thickening, mass, or polyp (measuring more than 10 mm in size) are most suggestive of malignancy [11, 12]. The presence of gallstones and the absence of pericholecystic fluid as seen with acute cholecystitis—in the presence of asymmetric gallbladder thickening—is associated with an increased risk of GBCa [11]. However, routine transabdominal ultrasound is hindered by the observer bias as well as by the negative impact of body habitus and bowel interposition. In recent years, advancement in ultrasound using contrast-enhanced ultrasound imaging (CEUS) and high-resolution ultrasound (HRUS),

have greatly enhanced the ability of ultrasound to differentiate between benign and malignant diseases [13, 14]. Endoscopic ultrasound (EUS) is increasingly utilized to improve diagnosis of gallbladder neoplasms. EUS may have a theoretical advantage over traditional transabdominal ultrasound, as it utilizes higher frequency waves and benefits from reduced intervening tissue between the probe and the target of interest [14, 15]. However, direct comparison of endoscopic ultrasound (EUS) and high-resolution transabdominal ultrasound has shown similar rates of diagnosis of gallbladder cancer and neoplastic polyps, with no added benefits obtained by EUS [16, 17]. With these findings, the non-invasive aspect of HRUS makes it preferable over an EUS.

Cross sectional gallbladder imaging may be performed with computed tomography (CT) or magnetic resonance imaging (MRI). Common CT imaging findings for GBCa include GB wall thickening, evidence of an isolated hypodense intraluminal mass, GB wall calcification, and porcelain GB. CT imaging is also especially helpful in identifying infiltration of surrounding organs, LN involvement, peritoneal nodules, and distant metastasis [18, 19]. MRI of the abdomen can also be used to diagnose GBCa, which is seen as an irregular, hypointense lesion on T1-weighted images and hyperintense lesion on T2-weighted images. GBCa often demonstrates early enhancement during MRI performed with gadolinium contrast [20, 21].

GBCa is an FDG-avid malignancy, and thus can be diagnosed with a PET (positron emission tomography) scan [22]. Nonetheless, the low negative predictive value of this test limits its utility [23]. However, the application of FDG PET in the evaluation of residual disease after diagnosis of incidental gallbladder cancer is increasing. While CT scan is the primary imaging to evaluate residual disease, PET has been shown to detect residual disease and LN metastasis in patients with otherwise normal CT scans, in about 25% of the patients [24, 25].

Diagnostic laparoscopy plays a paramount role in confirming pre-operative imaging findings with high applicability in identifying peritoneal disease and/or disseminated solid organ disease. Diagnostic laparoscopy has been shown to identify occult disseminated disease in more than 25% patients of GBCa, who are otherwise found to have localized disease on imaging studies [26]. However, this rate is much lower in patients with incidental GBCa, with benefits noted only in patients with T3/T4 tumors, positive resection margin and poor differentiation on final histopathology evaluation [27].

2.3 Biopsy

Biopsy of suspicious gallbladder masses is not recommended, due to fear of tumor dissemination and bile peritonitis. While previous studies have noted transhepatic route to be safer in terms of GB perforation and peritonitis, the concern for tumor seeding remains. Current NCCN guidelines recommend against biopsy and recommend resection of suspicious masses [28]. Biopsy is however required for patients with unresectable disease to establish diagnosis prior to starting treatment. This has been done percutaneously, laparoscopically or via EUS, however, a core biopsy is preferred for diagnosis [28–30]. Bile cytology obtained through ERCP has also been used to identify GBCa in patients with suspicious lesions. However, recent studies investigating the potential role of liquid biopsy of the bile to identify tumor DNA reported higher predictive value than bile cytology in identifying GBCa [31]. None of these methods are currently indicated in patients who have a potentially resectable tumor and are good surgical candidates.

2.4 Tumor markers

Various tumor markers have been evaluated for gallbladder cancer, and currently, the most used tumor marker in clinical practice is CA19-9. The other tumor markers include CA242, CEA and CA125 [32]. While none of these markers are diagnostic, or specific to GBCa, their levels alone or in combination have been shown to have prognostic implications and may be used to monitor response to therapy [32, 33].

In addition to the tumor markers, various other hematological markers have been shown to have diagnostic and prognostic importance in GBCa. Inflammatory markers have been shown to have prognostic significance with neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio negatively impacting survival and monocyte-lymphocyte ratio predicting response to chemotherapy [34–36]. Recent studies also note the prognostic potential of red cell distribution width and calreticulin in predicting tumor burden [37, 38].

Additionally liquid biopsies identifying circulating free DNA (cf-DNA) and micro-RNA (miRNA) have been shown to have both diagnostic as well as prognostic potential [39, 40]. Identification of certain miRNA mutations may also guide therapeutic interventions [41].

3. Incidental gallbladder cancer and determinants of surgical resection

Incidental GB cancer identified on pathology after routine cholecystectomy, accounts for more than half of the cases of GBCa [7, 8]. Evaluation and management of patients with incidental GBCa is vastly different from patients diagnosed pre-operatively. Since incidental GBCa are identified on pathological evaluation of grossly benign gallbladders, they are identified at an earlier stage and often with no surrounding invasion. As such, patients with incidental GBCa have increased rates of complete resection and better survival than patients who are diagnosed with GBCa pre-operatively [42]. **Table 1** depicts the most recent tumor staging by the AJCC 8th edition classification.

Pathological evaluation of the operative specimen, importantly the depth of invasion (T-stage), involvement of cystic duct margin and in some cases involvement of hepatic or peritoneal surface of the gallbladder, ultimately dictates further management. Re-resection is warranted in most patients to excise residual disease or to obtain adequate margins [8]. Approximately 75% of patients with incidental GBCa—for whom re-resection is performed—demonstrate residual disease which is an independent predictor of poor prognosis. A noteworthy exception—where re-resection is not recommended- is represented by patients with T1a tumors confined to the mucosa—where a simple cholecystectomy is considered an oncologically adequate resection. In addition, resection is not recommended for T4 tumors which are unresectable due to loco-regional invasion and for patients with distant metastatic disease [44, 45]. Re-resection is warranted once the cancer invades through the muscular layer. It is typically described as hepatectomy of segment 4b and 5 with lymphadenectomy of at least six lymph nodes and is associated with improved disease-free survival and overall survival in patients with T1b, T2 and T3 tumors [46, 47]. T2 tumors, where cancer invades the peri-muscular connective tissue without invading the serosa, have been a great area of interest. In this group of patients, the location of the tumor, specifically hepatic surface versus peritoneal surface, has been shown to significantly impact recurrence rates and overall survival [48]. This led to the modification of the

	Stage	Description
T-stage	Tx	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	T1a	Tumor invades the lamina propria
	T1b	Tumor invades the muscular layer
	T2a	Tumor involves perimuscular connective tissue on the peritoneal side without involving the serosa
	T2b	Tumor involves perimuscular connective tissue on the hepatic side without extension into the liver
	T3	Tumor perforates the serosa (visceral peritoneum) or invades the liver and/or invades one of the adjacent structures or organs (stomach, duodenum, colon, pancreas, omentum, extrahepatic bile duct)
	T4	Tumor invades the main portal vein or hepatic artery or invades two or more extrahepatic structures
N-stage	Nx	Regional lymph nodes cannot be assessed
	N0	No regional lymph nodes
	N1	Metastasis to 1-3 regional lymph nodes
	N2	Metastasis to 4 or more regional lymph nodes
M-stage	M0	No distant metastasis
	M1	Distant metastasis present

T: Tumor; N: Nodal; and M: Metastasis.

Table 1.
TNM staging of gallbladder cancer (AJCC 8th edition) [43].

AJCC staging in the 8th edition to subclassify T2 tumors into T2a where the tumor is located on the peritoneal side and T2b where the tumor is located on the hepatic side [43]. Data suggest that T2b tumors have worse prognosis compared to T2a tumors; in addition, some authors reported improved outcomes when T2b tumors are diagnosed pre-operatively (prior to formal oncological resection) compared to patients who undergo re-resection [48, 49]. Recent studies suggest that hepatic resection only impacts survival in patients with T2b tumors but not T2a [50]. However, the later findings need to be further validated, and the current practice continues to include hepatic resection in all T2 tumors.

Lymph node positivity is an important negative prognostic factor in GBCa. While lymph node (LN) involvement is an important prognostic factor of gallbladder cancer, routine cholecystectomy specimens do not include formal lymphadenectomy [51]. Routine cholecystectomy occasionally includes excision of the cystic node. The positivity of the cystic node has not been shown to be predictive of loco-regional disease, nor is predictive of survival in patients with GBCa [52]. Lymphadenectomy of the pericholedochal, the peri-portal lymph nodes up to the superior-posterior pancreatoduodenal lymph nodes is recommended for complete oncological resection [29]. The presence of positive lymph nodes around the aorta, celiac axis or the SMA constitutes a very poor prognostic factor, with 0% survival noted at 5 years [53]. CBD resection does not improve the quality of the lymph node dissection nor the lymph node yield [54]. In addition, various studies have led to the determination of what constitutes an adequate lymphadenectomy for staging purpose and the current recommendation is

for a minimum harvest of six lymph nodes [43]. Bile duct resection is not routinely recommended for gallbladder cancer unless a positive cystic duct margin is noted on final pathology [45].

Residual disease is another important predictor of prognosis in patients with GBCa. Found in more than half of the patients with incidental GBCa, it represents an independent poor prognostic factor, with survival rates similar to patients with metastatic disease [55]. However, recent studies from Japan suggest that the location of residual disease may impact prognosis, with disease in the extrahepatic bile duct or distant sites having worse prognosis compared to disease in the gallbladder bed [56]. While some residual disease may be identified on imaging, specifically PET CT, there are now attempts to develop scoring systems that utilize tumor stage and grade to predict residual disease in patients with GBCa [57].

Lymphovascular invasion and perineural invasion noted in the pathological specimen are also poor prognostic factors [58, 59]. Despite their impact on survival the presence of residual disease, lymphovascular invasion and perineural invasion have no impact on the decision-making for re-resection versus systemic therapy in patients with GBCa. Current attempts on developing additional scoring systems inclusive of these factors remain modest at best [60].

Timing to definitive surgery is a very important determinant of prognosis. Most studies suggest the best outcomes are noted in patients who undergo re-resection between 4 and 8 weeks after the initial cholecystectomy [61].

Intra-operative diagnosis of gallbladder cancer—when resectable—may be ideal, as it would allow the surgeon to perform radical resection during the primary surgery. However multiple concerns remain regarding this approach. Frozen section analysis of suspicious gallbladder lesions remains inconsistent with false positive and false negative results seen in up to 25% of the patients [62]. Additionally, the identification of tumor at the cystic duct margin, which would mandate the need for further biliary duct resection, may be inaccurate in many cases [63]. Thus, current practice for patients undergoing routine cholecystectomy with concerning intra-operative findings remains final histopathology based treatment planning.

4. Systemic therapy in gallbladder cancer

Gallbladder cancer is an aggressive malignancy with early recurrence and metastasis even after complete surgical resection. There is an unmet need for effective systemic therapy and reliable biomarkers specifically for GBCa. Due to the rarity of this disease, most studies investigating systemic therapeutic options often encompass all biliary tract malignancies—including intra and extrahepatic cholangiocarcinoma—which have distinct genetic features and clinical behaviors thus confounding data interpretation and applicability.

4.1 Neoadjuvant therapy

While surgical resection is the mainstay of treatment of GBCa, the high rate of early recurrence after complete resection supports the undeniable need for more effective patient selection strategies for surgical resection and systemic perioperative therapy. Peri-operative therapy and multimodality treatments have been shown to improve outcomes in patients with extrahepatic biliary tract cancers including GBCa [64]. While neoadjuvant therapy has been advantageous in patients with locally

advanced disease, there is mounting interest in the use of chemotherapy even in patients with resectable disease [65, 66]. However, data to support this approach are limited, and mostly obtained from studies encompassing all biliary tract cancers, with limited dedicated studies focusing solely on GBCa.

Neoadjuvant chemotherapy for GBCa has evolved significantly over the last two decades. Currently the first line neoadjuvant therapy consists of Gemcitabine-Cisplatin (Gem-Cis) based chemotherapy, which has been shown to improve overall survival and progression free survival compared to both gemcitabine and 5-Flurouracil (5-FU) based chemotherapy [67, 68]. Recently, higher response rates—up to 40–50%—were reported with the use of combination chemotherapy by combining "gemcitabine- nab-paclitaxel- cisplatin" [69]. Additional studies conducted on patients who have disease refractory to Gem-Cis have shown improved progression free survival with the administration of FOLFOX or FOLFIRI, justifying the use of these regimens as second line therapy in GBCa [70, 71] (**Table 2**).

There is currently no clear evidence supporting the use of neoadjuvant chemoradiation in patients with GBCa [72]. However, a phase III randomized trial—POLCAGB—is currently underway comparing the survival outcomes of neoadjuvant chemotherapy versus chemoradiotherapy in patients with GBCa [73].

Immunotherapy has been shown to improve response to chemotherapy and impact survival in patients with GBCa in patients with locally advanced—unresectable or metastatic disease. PD-L1 is a known target for immunotherapy that is present in about a quarter of pathological specimens of biliary tract cancer [74, 75]. Studies have shown improved response rates to neoadjuvant therapy when PD-L1 inhibitor, Durvalumab is combined with Gem-Cis [76]. The TOPAZ-1 trial confirmed the safety and efficacy of Durvalumab plus Gem-Cis, demonstrating improved overall survival versus placebo plus chemotherapy (estimated 24-month was 24.9% vs. 10.4%). Moreover, it showed improvements in prespecified secondary end points including objective response rate up to 26.7% vs. 18.7% (OR 1.6; 95% CI, 1.11–2.31). It is important to note that the

Publication	Study	Patients	Comparison	Result
Valle et al., 2010 (ABC-02) [68]	RCT	410 (LA, metastatic)	Gemcitabine vs. Gem-Cis	Gem-Cis: Improved OS & PFS
Phelip et al., 2022 (PRODIGE 38 AMEBICA) [67]	RCT	191 (LA, metastatic)	Gem-Cis vs. FOLFIRINOX	No advantage
Shroff et al., 2019 [69]	RCT	62 (LA, metastatic)	Gem-Cis- nab-Paclitaxel vs. Gem-cis	Gem-Cis- nab-Paclitaxel: Improved OS & PFS
Lamarca et al., 2021 (ABC 06) [70]	RCT	162 (LA, metastatic, progression with Gem-Cis)	FOLFOX vs. ASC	FOLFOX: Improved PFS
Yoo et al., 2021 (NIFTY) [71]	RCT	174 (metastatic progression with Gem-Cis)	FOLFIRI vs. 5FU and leucovorin	FOLFIRI: Improved PFS

ABC: advanced biliary cancer; RCT: randomized control trial; Gem-Cis: gemcitabine- cisplatin; LA: locally advanced; FOLFIRINOX: 5-flurouracil- irinotecan-oxaliplatin; FOLFOX: 5-flurouracil-oxaliplatin; FOLFIRI: 5-flurouracil-irinotecan; 5FU: 5-flurouracil; OS: overall survival; and PFS: progression free survival.

Table 2.
Trials evaluating chemotherapy use in gallbladder cancer.

TOPAZ-1 trial was designed to address a locally advanced-unresectable or metastatic population of biliary tract cancer—among which approximately 25% represented GBca—with previously untreated disease but included patients who developed recurrent disease more than 6 months after surgery with curative intent and more than 6 months after the completion of adjuvant therapy [77].

4.2 Adjuvant therapy

Due to the low incidence of GBCa, most of the data on the impact of adjuvant therapy on survival of patients with GBCa are derived from studies done on patients with any biliary tract cancer. While initial randomized control trials with gemcitabine-based adjuvant therapy failed to show a survival benefit in biliary tract cancers, examination of adjuvant capecitabine (BILCAP trial), suggested positive trends towards survival when adjusted for nodal positivity and tumor grade [78–80]. These studies also prompted dedicated examination of patients with GBCa. Retrospective analysis of large cohorts, including two studies that utilized National Cancer Database and a subsequent meta-analysis of more than 20,000 patients have shown an association between adjuvant chemotherapy and prolonged survival in patients with GBCa, especially in the presence of node positive disease [81–84].

There is also an increased interest in the use of adjuvant chemoradiotherapy in gallbladder cancer. Recent studies including propensity matched analysis of patients receiving adjuvant chemoradiotherapy versus chemotherapy have noted improved survival and reduced local recurrence associated with the use of adjuvant chemoradiation. These findings are especially noted in patients with tumor stage T2 or lymph node positive disease [85, 86]. In addition, a secondary analysis of the phase II intergroup trial, SWOG S0809—that evaluated adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine—demonstrated improved OS in patients with extrahepatic cholangiocarcinoma and GBCa compared to historical controls. Furthermore, the data suggested that adjuvant chemoradiation positively impacted local control in patients with node positive disease [87].

4.3 Peri-operative chemotherapy

There is now a great interest in the use of peri-operative therapy in patients with incidental GBCa (i.e., prior to formal oncological resection in patients who are diagnosed with incidental GBCa after a cholecystectomy). It may be hypothesized that timing of systemic therapy prior to formal resection would allow downstaging of the residual disease, allowing complete resection of the tumor. While no definitive data exist to suggest the superiority of either regimen (i.e., peri-operative versus adjuvant) there are currently two randomized control trials underway to ascertain the merits of the two approaches. Both the OPT-IN trial and the ACO-GAIN trial are examining the difference in oncological outcomes of patients treated with peri-operative gemcitabine- cisplatin therapy compared to those who undergo radical resection without any intervening systemic therapy [88, 89].

5. Surgical resection of GBCa

All GBCa with T-stage including T1b to T3 warrant a radical cholecystectomy after having ascertained the absence of distal lymphadenopathy (i.e., periaortic, celiac, and

retropancreatic) and metastatic disease. Similar to the operative principles used in patients undergoing re-resection, patients diagnosed pre-operatively and those found to have GBCa on intra-operative frozen section should undergo cholecystectomy with hepatic resection of segment 4b and 5, along with lymphadenectomy with bile duct resection reserved only for obtaining negative margins [45]. Additional aspects of the surgery may include bile duct resection, vascular resection and extended hepatectomy, all of which are performed with the single goal of obtaining negative resection margins. There is currently no role of port site resection in patients who were diagnosed following a previous laparoscopic cholecystectomy, as this practice does not impact disease-free or overall survival [90].

Traditionally, the concern for port site seeding, chimney effect and concern for peritoneal dissemination, led to radical cholecystectomy being done as an exclusively open procedure [91–93]. However, studies comparing minimally invasive and open radical cholecystectomies have noted no oncological differences between laparoscopic and open surgery, with improved intra-operative and peri-operative outcomes in patients undergoing laparoscopic resection [94, 95]. Thus this procedure is now performed both laparoscopically and robotically. While most of the data on robotic oncological safety is derived from studies on laparoscopic radical cholecystectomy, there is an increasing trend of utilization of the robotic platform for this surgical procedure [96, 97].

6. Conclusion

Gallbladder cancer, although rare, is an aggressive malignancy and the most common biliary tract cancer. With the increased cholecystectomy rate, most patients in the western world are diagnosed incidentally. Pathological evaluation of the gallbladder not only establishes diagnosis, but also guides further treatment planning, based on the accurate knowledge of the T-stage and of the cystic duct margin. The early systemic recurrence and poor overall survival—even after complete resection—warrant the use of multimodality treatment with chemotherapy and immunotherapy. Systemic therapy is currently the first line treatment in patients unable to undergo surgical resection, moreover, it is increasingly being advocated in the neoadjuvant and perioperative period to improve resection rates and possibly disease-free survival.

Conflict of interest

The authors declare no conflict of interest.

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