



Updates on Gallbladder Cancer Management

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Abstract

Purpose of Review We will review the current standard of care management for metastatic gallbladder cancer (GBC), recommendations for resection of incidentally or non-incidentally diagnosed GBC, and developments in preoperative risk stratification and adjuvant chemotherapy.

Recent Findings Gemcitabine-cisplatin is the standard of care therapy for advanced-stage disease. Patients with incidentally diagnosed GBC should undergo re-resection for T1b, T2, or T3 disease. The presence of residual disease is associated with decreased survival. Diagnostic laparoscopy should be used in select patients to avoid unnecessary laparotomy. Major hepatectomy and common bile duct excision should only be performed in select cases. Current standard of care for adjuvant therapy includes 6 months of oral capecitabine.

Summary Gallbladder cancer continues to carry high mortality rates due to its aggressive course and early spread. Recent developments in preoperative risk stratification, surgical resection, and chemotherapy have greatly shaped management of this malignancy in the current era.

Keywords Gallbladder cancer · Staging of gallbladder cancer · Gallbladder cancer management · Incidental gallbladder cancer

Introduction

Gallbladder carcinoma (GBC) is the sixth most common gastrointestinal malignancy in the USA, characterized by an aggressive course with early spread to regional lymph nodes and distant sites, resulting in high mortality rates. The incidence of GBC is low in North America, but in countries like Chile, India, and Japan, incidence of the disease is relatively high [1]. Most GBCs in the USA are discovered incidentally after laparoscopic cholecystectomy for presumed benign conditions, and many patients, although asymptomatic, are found to have advanced disease at the time of diagnosis without any options for curative therapy [2]. The cornerstone of therapy is curative-intent surgical resection, but the extent of resection

has only recently been well defined. This review will cover the standard of care management for metastatic GBC and recent developments regarding recommendations for resection in patients with either incidentally or non-incidentally diagnosed GBC, as well as developments in preoperative risk stratification and adjuvant chemotherapy.

Metastatic Gallbladder Cancer

When GBC is discovered, most cases are in advanced stages with 40–75% of patients diagnosed with metastatic disease [2]. Systemic symptoms such as abdominal pain, jaundice, weight loss, and malaise often indicate advanced disease; incurable disease is often associated with pruritus, cholangitis, and gastrointestinal obstruction due to local infiltration [3]. Although palliative surgical procedures are available, they are associated with high morbidity and variable success in relieving biliary and intestinal obstruction [4]. Any efforts at palliation, often performed in order to enable receipt of chemotherapy, should ideally be pursued via endoscopic or percutaneous techniques. Prior to 2010, although there was no standard chemotherapeutic regimen to treat advanced-stage

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biliary cancer, the experience with pancreas cancer using gemcitabine monotherapy was extrapolated and applied to biliary tract malignancies. Published in 2010, the Advanced Biliary Cancer-02 trial (ABC-02) was a randomized phase III trial conducted in 37 centers in the UK comparing cisplatin plus gemcitabine versus gemcitabine alone for patients with metastatic biliary tract cancer [5]. Of the 410 patients participating in the trial, 88.3% of patients had tumor progression at 8 months, but the overall median survival in the cisplatin-gemcitabine group was 11.7 months compared to 8.1 months in the gemcitabine only group. Further studies have validated this improvement in survival, thus making cisplatin-gemcitabine the standard of care first-line therapy for advanced biliary tract cancers [6–8]. There are recent reports published from Japan demonstrating efficacy of S1/cisplatin chemotherapy in unresectable advanced biliary tract carcinoma, but these data require further investigation [9, 10].

Incidentally Diagnosed Gallbladder Cancer

The majority of localized GBC is diagnosed incidentally on pathologic examination after simple cholecystectomy for presumed benign disease. We will review the updated staging system from the American Joint Committee on Cancer (AJCC) 8th edition and the current standard of care recommendations for further treatment.

Staging and Indications for Re-resection

GBC is staged according to the depth of invasion of the tumor, regional spread, and distant disease [11]. Tumor (T), nodal (N), and metastasis (M) factors stratify patients into AJCC prognostic stages and can be used to define further therapeutic strategies (Tables 1 and 2). For incidentally diagnosed gallbladder cancer, assuming there is no distant disease, i.e., M0, the T stage is used to guide decisions for further therapy, particularly re-resection.

T1a tumors, confined to the lamina propria, are considered adequately treated with simple cholecystectomy with negative surgical margins. T1b tumors penetrate into the submucosa, but do not traverse the full thickness of the gallbladder wall [12]. In the 8th edition of the AJCC, T2 tumors, which have grown into perimuscular connective tissue, are divided into T2a and T2b: T2a tumors invade on the peritoneal side of the gallbladder while T2b tumors invade on the hepatic side of the gallbladder. Principles for resection for T2 tumors also apply to T3 tumors, which are tumors that have grown through the gallbladder serosa into the liver or a single nearby organ. T4 tumors have invaded a major hepatic blood vessel or two nearby organs and are not diagnosed “incidentally” given their extensive nature. Once the specimen is reviewed, GBC is confirmed, and distant disease is ruled out with cross-

Table 1 Gallbladder cancer: AJCC 8th edition prognostic stage groups

T	N	M	Stage
Tis	NO	MO	0
T1	NO	MO	1
T2a	NO	MO	2A
T2b	NO	MO	2B
T3	NO	MO	3A
T1–3	N1	MO	3B
T4	NO-1	MO	4A
Any T	N2	MO	4B
Any T	Any N	M1	4B

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sectional imaging; the decision to re-resect is currently primarily based on T stage. Patients with T1b, T2, or T3 tumors are usually recommended for re-resection as long as there are no performance status contraindications to resection. The rationale for re-resection is based on the fact that the presence of residual disease ranges from 10–70% with progressing T stage. Given the lower incidence of residual disease, T1b disease is a bit controversial as to whether re-resection should be performed but is still usually offered to fit patients.

Residual Disease

The rationale for re-resection is to remove any residual disease that may be present after an incomplete resection for T1b, T2, or T3 disease. The incidence of residual disease varies predominantly by T stage. Pawlik et al. reported that in 115 patients from 6 major hepatobiliary centers who underwent a second-staged surgery for incidentally discovered GBC, 46% of patients had residual disease [13]. In this series, T stage was the strongest predictor of finding residual disease (T1b 37.5%, T2 56.7%, and T3 77.3%). Residual disease in the common bile duct (CBD) was found in 21.4% of patients, with a positive cystic duct margin status at the time of initial cholecystectomy being the strongest predictor of finding residual disease in the CBD. In a Memorial Sloan-Kettering Cancer Center (MSKCC) series of 435 patients over a 10-year period, 136 patients were re-explored, and 76% of patients had residual disease. The presence of residual disease was associated with a decreased median survival compared to those without residual disease (15 months versus 72 months; p value < 0.0001) [2]. In fact, the presence of residual disease may be a more important negative prognostic factor than T stage as patients with advanced T stage but no residual disease

Table 2 Gallbladder cancer: definitions of AJCC 8th edition TNM

T category	T criteria
TX	Primary tumor cannot be assessed
TO	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades lamina propria or muscular layer
T1a	Tumor invades lamina propria
T1b	Tumor invades muscular 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 one other adjacent organ or structure
T4	Tumor invades the main portal vein or hepatic artery or invades two or more extrahepatic organs or structures
N category	N criteria
NX	Regional lymph nodes cannot be assessed
NO	No regional lymph node metastasis
N1	Mets to 1–3 regional lymph nodes
N2	Mets to 4+ regional lymph nodes
M category	M criteria
MO	No distant metastasis
M1	Distant metastasis is present

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may have improved outcomes compared to those with lesser T stage but positive residual disease [14].

Gallbladder Risk Score

Given the prognostic importance of residual disease, attention has been directed towards better risk-stratifying patients after initial cholecystectomy by a more accurately predicting residual disease [15•]. Although T stage is used to primarily dictate management in these patients, Ethun et al. developed a gallbladder risk score to calculate the odds of discovering locoregional and distant disease at the time of re-exploration based on several pathologic factors [16•]. Using information routinely available from the initial cholecystectomy specimen (T stage, grade, presence of lymphovascular and perineural invasion), patients were stratified into low-, intermediate-, and high-risk groups. Intermediate- and high-risk patients

had a 4.5× and 12.2× higher odds, respectively, of finding locoregional and distant disease at time of reoperation compared to low-risk patients. The intermediate- and high-risk patients also had a lower median overall survival (OS) compared to low-risk patients (low-risk: median OS not reached; intermediate-risk: 67 months; high-risk: 16 months; $p < 0.001$). Patients at increased risk for residual disease may be good candidates for staging laparoscopy and even receipt of preoperative chemotherapy prior to re-resection.

Conduct of Surgery

Staging Laparoscopy

A staging laparoscopy prior to re-resection for incidentally discovered GBC is intended to detect any contraindications to resection prior to subjecting a patient to a non-therapeutic laparotomy. Specifically, the goal of laparoscopy is to discover peritoneal and/or hepatic metastatic disease, tumor invasion into major vascular structures, or distant lymphatic disease that may be missed by CT scan or MRI. In a 2011 series from the MSKCC of 136 patients with incidental gallbladder cancer who underwent re-exploration, 46 patients underwent restaging by laparoscopy [17]. In this study, patients who had disseminated disease at time of re-exploration were more likely to have a higher incidence of gallbladder wall thickening on pre-cholecystectomy ultrasound, higher incidence of an open cholecystectomy, T3 tumors, poorly differentiated tumors, and a positive cholecystectomy margin compared to patients with localized disease on re-exploration. The sensitivity of staging laparoscopy to detect hepatic metastases can further be enhanced by intraoperative ultrasound [18]. Practice patterns may differ from performing routine versus selective laparoscopy but patients with these preoperative factors may benefit from laparoscopic evaluation prior to laparotomy.

Extent of Resection: Hepatectomy, Bile Duct, and Lymph Nodes

For T1a tumors, simple cholecystectomy is curative in over 90% of cases. For non-metastatic T1b or greater tumors, more extensive resection is required: partial hepatectomy incorporating portions of segments 4b and 5, an extended right hepatectomy, excision of the extrahepatic bile duct, and resection of adjacent organs are all potential options. The extent of resection does not have a significant impact on survival. T/N stage and histologic differentiation, however, were shown to be independent predictors of survival, thus emphasizing the importance of tumor biology [19]. Importantly, achieving a negative margin is associated with improved survival compared to a microscopic positive margin [12, 20, 21]. Thus, a partial hepatectomy of segments 4b and 5 is the standard

recommended procedure. An extended resection, or a major hepatectomy, is only indicated if needed to obtain a negative margin. Similarly, a common bile duct resection is only indicated if needed to clear a positive cystic duct margin at the time of the original resection. Routine common bile duct resection is not indicated nor recommended, as it only increases postoperative morbidity, does not increase the number of lymph nodes removed, and is not associated with improved overall survival [22]. The extent of lymph node dissection should be limited to the porta hepatis region as distant lymph node disease, such as celiac or para-aortic, should be considered M1 disease, and retrieval of these lymph nodes is not associated with improved survival [23].

Port Sites

There have been reports of port-site recurrences after laparoscopic cholecystectomy for an incidentally discovered gallbladder cancer, leading some groups to advocate for routine port-site excision at the time of re-resection [24, 25]. Port-site recurrences are thought to be caused by direct physical contact of the specimen during extraction, gallbladder perforation with bile spillage, or tumor seeding secondary to increased abdominal pressure from pneumoperitoneum associated with laparoscopy [26]. A recent series of 113 patients who presented for re-resection after incidentally diagnosed GBC showed that only patients with T2 and T3 tumors developed metastases at the port sites, and resection of the port sites was not associated with improvement in overall survival or recurrence-free survival [27]. Port-site recurrence, rather, was a surrogate for distant disease as these patients developed diffuse peritoneal disease soon after. This was further validated by a multi-institutional study evaluating 193 patients demonstrating port-site excision was not associated with improved overall survival [28]. Due to the increased morbidity of performing port-site resections, including increased incisional hernia rates, without an improvement in survival or recurrence, routine port-site resection is not recommended at the time of re-resection for incidentally discovered gallbladder cancer [29].

Non-incidentally Diagnosed Gallbladder Cancer

Ultrasound and advanced imaging techniques are able to identify suspicious gallbladder masses prior to surgery. GBC on ultrasound may appear as an obvious infiltrative mass or an irregularity of the gallbladder wall. On CT and MRI, GBC may appear as an irregularity and disruption of the gallbladder wall with invasion into segments 4b/5 of the liver. When GBC is suspected, an algorithmic approach to assess the mass is

necessary to distinguish it from benign conditions and to assess for evidence of locoregional or distant spread.

Approach to a Suspicious Gallbladder Mass Prior to Resection

Key radiographic features can discriminate benign lesions, like cholesterol polyps and adenomyomatosis, from potentially neoplastic lesions of the gallbladder. Patients with symptomatic radiographically benign-appearing lesions can undergo simple cholecystectomy alone, while those that are asymptomatic can be monitored. Patients with radiographic calcifications of the gallbladder wall, or a “porcelain gallbladder,” were historically thought to have an increased risk of cancer, but multiple studies have confirmed there is no association with increased risk of malignancy in these patients [30]. Adenomatous polyps larger than 1 cm in size on preoperative imaging have a 25 times greater risk of developing into malignant lesions than those smaller than 1 cm [31]. Due to this increased risk, such patients are referred for surgical resection, often with intraoperative frozen section analysis. Results from real-time histologic evaluation can guide further operative management; if malignancy is confirmed, then a radical cholecystectomy is performed with a regional lymph node dissection. As with incidental GBCs undergoing re-resection, non-incidentally operative management should aim for an R0 resection, and major hepatectomy and/or bile duct resection should only be performed if necessary to achieve that goal.

Relevance of Bile Duct Obstruction at Presentation

Jaundice as a presenting symptom of GBC often signals progression to advanced or unresectable disease. In a recent series of 240 patients with GBC treated over a 7-year time period, 34% presented with jaundice mainly due to tumor invading nearby structures of the porta hepatis, including the common bile duct and proximal biliary tree [32]. Jaundice was found to be an independent predictor of poor outcome, with median disease-specific survival significantly worse in patients presenting with jaundice compared to those without jaundice (6 months versus 16 months). There were also fewer R0 resections reported in patients with jaundice on presentation compared to non-jaundiced patients (5% versus 39%). There were no 2-year survivors in patients who presented with jaundice. A subsequent multi-institutional series of 400 patients demonstrated that of the 108 patients presenting with jaundice, patients with low CA 19–9 levels (<50) and without lymphovascular invasion on surgical pathology had favorable survival [33]. Preoperative jaundice remains an ominous presenting sign in patients with GBC and is considered a relative contraindication to radical resection, although may be performed in well-selected patients.

Recurrence Patterns and Survival

Previous reports have described disease recurrence in patients who underwent curative-intent resection as high as 66% at 2 years, with regional lymph node recurrences in 28% of patients and distant recurrences occurring in 85% of patients [34, 35]. In 2016, the US Extrahepatic Biliary Malignancy Consortium published data on 217 patients who underwent curative-intent surgical resection for GBC at ten academic institutions [36]. The most common sites of recurrence were in the liver and peritoneum, and median recurrence-free survival for this cohort was only 11.2 months. Higher T stage, presence of residual disease at the time of re-resection, and poorly differentiated tumors were all independent risk factors for recurrence, and the 5-year survival for patients who developed a recurrence was only 16% compared to 76% in patients who did not recur. Given these significant recurrence rates, postoperative surveillance strategies are essential for detecting tumor recurrence, but must be coupled with more effective treatment regimens. Currently, the survival rates for patients with resected GBC remain dismal (1-, 3-, and 5-year survival at 56, 30, and 21%, respectively) [37].

Adjuvant Therapy

Even after surgical resection, the overall survival for patients with GBC is poor suggesting the role for adjuvant systemic chemotherapy. Takada et al. performed a phase III prospective randomized control trial in 112 patients with gallbladder carcinoma with 69 patients treated with mitomycin C and 5-fluorouracil and 43 patients treated with surgery alone; the 5-year overall survival and 5-year disease-free survival were higher in the treated groups compared to the control group [38]. Ma et al. performed a meta-analysis in 2015 of 10 retrospective studies involving 3191 patients and reported improvement in overall survival in patients treated with adjuvant chemotherapy with greatest benefit in patients with non-curative surgical resection, lymph node-positive disease, and AJCC stage greater than 2 [39]. Recently, Edeline et al. reported in the PRODIGE 12-ACCORD 18 phase III trial that patients with biliary tract cancer treated with gemcitabine and oxaliplatin did not have a statistical difference in median relapse-free survival compared to placebo [40]. Finally, the recently reported BILCAP trial was a phase III randomized control study of 447 patients conducted in the UK which demonstrated an improvement in median overall survival in per protocol analysis (53 months versus 36 months; $p = 0.028$) and recurrence-free survival (25 months versus 18 months; $p = 0.03$) in patients treated with adjuvant capecitabine compared to observation alone [41]. This regimen has now become the recommended standard of care for resected gallbladder cancer, regardless of the method of diagnosis. The role of

adjuvant radiation therapy for gallbladder cancer is controversial, with some previous studies suggesting a benefit with radiation after resection. A recent multi-institutional analysis from 2015, however, found that in 112 patients with resected gallbladder cancer, the delivery of adjuvant radiation was not associated with improved overall survival, although there was an association with a decreased risk of local recurrence [42]. The value of radiation after re-resection for incidentally discovered gallbladder cancer in particular is limited as the margin positive rate is only approximately 5% and the majority of recurrences are distant. The exact conditions in which adjuvant radiation therapy confers clinical benefit remains to be determined.

Conclusion

Gallbladder cancer remains an ominous diagnosis for patients, as mortality rates continue to be high despite current treatments. Gemcitabine-cisplatin is the standard of care therapy for advanced-stage disease. Patients with incidentally diagnosed gallbladder cancer should undergo re-resection for T1b, T2, or T3 disease, which entails a partial hepatectomy and lymph node dissection. Major hepatectomy and/or bile duct resection should only be performed if needed to obtain a negative margin resection. The same surgical principles apply to non-incidentally diagnosed gallbladder cancer. Current standard of care for adjuvant therapy includes 6 months of oral capecitabine. Future trials assessing the value of preoperative therapy and chemotherapy intensification regimens in the adjuvant setting are underway.

Compliance with Ethical Standards

Conflict of Interest Mohammad Yahya Zaidi and Shishir K. Maitheal declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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