Ann Surg Oncol (2020) 27:2846–2858
https://doi.org/10.1245/s10434-020-08654-9

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

REVIEW ARTICLE – HEPATOBILIARY TUMORS

The Landmark Series: Gallbladder Cancer

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ABSTRACT Given the rarity of gallbladder carcinoma, level I evidence to guide the multimodal treatment of this disease is lacking. Since 2010, four randomized phase III clinical trials including ABC-02, PRODIGE-12/ACCORD-18, BILCAP, and BCAT, and a single-arm phase II trial (SWOG0809) have been reported on the use of adjuvant strategies for biliary malignancies. These trials have led to the recommendation that patients with resected biliary tract cancer should be offered adjuvant capecitabine chemotherapy and those with R1 margins could be considered for chemoradiotherapy. Because there is no level I evidence to guide neoadjuvant therapy or surgical management, current consensus is based on strong retrospective data. The following review summarizes available trials and highlights the best available evidence that form the basis of consensus statements for the multimodal management of gallbladder carcinoma.

EPIDEMIOLOGY

Gallbladder cancer is the sixth most common gastrointestinal malignancy in the United States with an estimated incidence of 1.13 cases per 100,000.[1,2] This incidence, however, has been in decline since the 1960s potentially as an unintended consequence of increased rates of cholecystectomy secondary to gallstones.[3] The mean age of diagnosis falls in the seventh decade with a female predominant incidence pattern representing the only gastrointestinal cancer that is more common in women.[1] Recent evidence suggests that the carcinogenesis of gallbladder carcinoma (GBC) may be mediated by estrogen and progesterone and that estrogen/progesterone receptor expression correlates with an early stage of tumor, whereas nonexpression usually correlates with inoperable or metastatic disease.[4] Gallstones represent the most important risk factor and are present in approximately 85% of patients with gallbladder cancer.[5,6] Furthermore, increasing stone size augments the risk for gallbladder cancer; stones > 3 cm have a tenfold increased risk compared with smaller stones.[7,8] This association likely can be explained by the resultant chronic mucosal irritation and inflammation associated with gallstones, a factor that has been linked repeatedly to carcinogenesis. Modifiable risk factors include obesity, poor diet, and chronic infections with *Salmonella* or *Helicobacter* species.[9] The exact mechanism of this infectious association remains elusive but could be related to bacterial degradation of bile constituents, or alterations of tumor suppressor genes or proto-oncogenes.[5,10]

There is substantial geographic variation in the incidence of primary gallbladder cancer worldwide (Fig. 1). Rates are high in Bolivia, Colombia, and India with the highest rates seen in females in Chile at 20.1 per 100,000 in 2018.[11] Incidence also is high in Eastern Europe, particularly Poland, Hungary, and the Czech Republic. In addition to geographic variation, there are striking ethnic disparities. In the United States, GBC is one of the few cancers with a low incidence among black individuals but high incidence among American Indian, Alaska Native, and Hispanic persons.[1] Recent evidence demonstrates that Hispanic women in the United States have shown 3- to 5-fold higher incidence rates than non-Hispanic white women in the same areas.[5] This variation in both geographic and ethnic incidence patterns is indicative of an interaction between environmental and genetic etiologic factors. Currently, diagnosis of gallstones and cholecystectomy represents the only prevention strategy in high-risk populations. Routine

First Received: 14 March 2020;
Published Online: 30 May 2020

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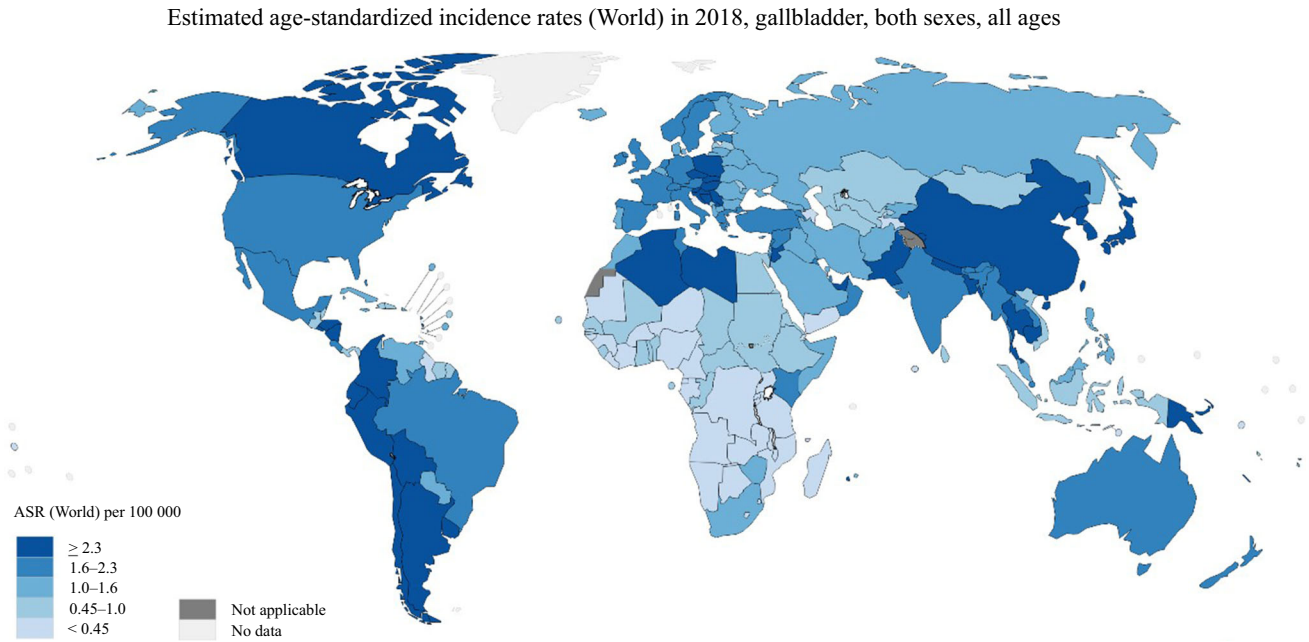

FIG. 1 Estimated age-standardized gallbladder cancer incidence rates in 2018 for both sexes. Data source: GLOBOCAN 2018. WHO, IARC: https://gco.iarc.fr/today/

cholecystectomy is not warranted in low-risk populations due to the low incidence of this disease and the associated potential morbidity of a cholecystectomy.

Incidental versus Per Primum Gallbladder Cancer

Gallbladder cancer is diagnosed in one of two scenarios: either incidentally during routine cholecystectomy for benign indications, or in advanced stages after symptomatic presentation often with jaundice or weight loss.[12] In a multi-institutional retrospective review of 445 patients treated with curative resection, 60% of patients were diagnosed with GBC as an incidental finding after laparoscopic cholecystectomy.[13] The remainder of cases are discovered at an advanced stage with rates of metastatic disease in 30–40% of patients depending on the reported series.[14] Given that the majority are diagnosed incidentally after initial cholecystectomy, there is no preoperative evaluation undertaken for this cohort of patients and appropriate staging is only fully ascertained after removal of the gallbladder.

Compared with primary GBC, incidental GBC tends to be associated with more favorable pathologic characteristics, such as earlier T-stage, and lower tumor grade.[13] As such, incidental GBC carries a better median survival of 21 months compared with 8 months for primary GBC.[13,15]

Current Era of Management

Gallbladder carcinoma has a universally poor outcome with an overall estimated 5-year survival rate of 5–13% due to its late presentation, early invasion into adjacent structures, and lack of effective therapy.[16–18] Additionally, as a result of its low incidence, existing data to guide the specific management of this disease remains limited to retrospective reviews and a few trials on adjuvant therapy, which also have included other biliary tract malignancies. Importantly, there have been no trials on neoadjuvant therapy or the surgical management of GBC. Given the paucity of level I evidence, the current article aims to highlight the best available evidence from large series and review the consensus statements that have been published for this disease.

DIAGNOSIS AND STAGING

As mentioned above, the diagnosis and staging for incidental GBC is made postoperatively but prior to re-resection. For per primum GBC, the tools listed below facilitate diagnosis for patients with a visualized mass that is suspicious for gallbladder cancer. To date, however, there are no reliable preoperative tools for early diagnosis of GBC. Laboratory studies may demonstrate an obstructive biliary pattern with elevated bilirubin and alkaline phosphatase, but there are no tumor markers that are highly sensitive or specific for the diagnosis of GBC. The use of CEA or CA 19-9, however, can be considered as part of a

baseline assessment.[19] Similarly, currently available imaging techniques cannot reliably distinguish between benign processes and early malignant disease. Right upper quadrant ultrasound remains the standard diagnostic modality where GBC may appear as hypo- or isoechogenic intraluminal masses with or without entrapped gallstones, irregular wall thickening, or intraluminal polyps > 10 mm in diameter.[20] Even in the setting of advanced disease, however, the rate of detection using this modality can be as low as 37%.[21] CT may aid in accurate detection of GBC with a sensitivity of 90%, and it is more useful than ultrasound in detecting lymph node involvement.[22] Findings may include a heterogenous mass replacing the gallbladder with variable enhancement, wall thickening, or a fungate tumor.[22] Contrast-enhanced MRI remains the preferred modality for evaluating masses within the gallbladder and demonstrating bile duct involvement and invasion into the liver parenchyma.[23] Additional workup includes evaluation for the presence of distant disease with high-quality, contrast-enhanced, cross-sectional imaging with CT or MRI of the chest, abdomen, and pelvis. Lastly, in patients with suspected GBC, 28-FDG positron emission tomography (PET)-CT has been shown to detect occult peritoneal, omental, and/or lymph node metastases with a sensitivity of 56%.[24]

For patients with presumed or known GBC, staging laparoscopy has been shown to identify radiographically occult peritoneal and/or hepatic disease or involvement of major vascular structures. In an analysis of 44 patients with GBC at Memorial Sloan-Kettering Cancer Center (MSKCC), almost half of the patients had disseminated disease at laparoscopy.[25] In an effort to prevent a non-therapeutic laparotomy, staging laparoscopy is therefore recommended before laparotomy for all cases of suspected or proven GBC.[26] The sensitivity of staging laparoscopy to detect hepatic metastasis can be further aided by the use of intraoperative ultrasound.[27] In select cases of primary GBC in which diagnosis is not clear with preoperative imaging or at staging laparoscopy, a frozen-section analysis may be considered at the time of cholecystectomy followed by immediate definitive resection if pathology confirms cancer.

Following resection, the AJCC staging system remains the standard for staging GBC and is based on the depth of invasion of the tumor, regional spread, and distant disease (Table 1). Notably, in the eighth edition of the manual, T2 GBC was divided into two groups, including tumors that invade the peritoneal side (T2a) and tumors invading the hepatic side (T2b). This is supported by data from two retrospective studies, which demonstrated that tumors invading the hepatic side have a worse prognosis.[28,29] Tumor stage remains the strongest prognostic factor with a median survival of 12.9 months for those presenting with stage IA-III disease and 5.8 months for those presenting with stage IV disease.[30]

EXTENT OF RESECTION

Incidentally Diagnosed Gallbladder Cancer

Once a pathologic diagnosis is confirmed and distant disease is ruled out with high-quality, cross-sectional imaging, radical re-resection is recommended for patients with T1b, T2, or T3 tumors unless contraindicated by poor performance status.[26,31] This rationale is based on data demonstrating the presence of residual disease in a large proportion of patients. A 2007 study by Pawlik et al. found that 46% of patients had residual disease and that T stage was strongly associated with the risk of finding residual disease at any site (T1: 37.5%; T2: 56.7%; T3: 77.3%).[15] Additionally, several series have demonstrated improved survival with re-resection. In a retrospective study of 218 patients, Fuks et al. reported 1-, 3-, and 5-year survival rates of 76%, 54%, and 41%, respectively, for patients who underwent re-resection compared with 52%, 20%, and 15%, respectively, for patients who did not undergo re-resection. Furthermore, this improvement in survival was highly correlated with T-stage.[32] For tumors confined to the mucosa (Tis or T1a), no further resection is necessary if the cystic duct margin is free of tumor based on data demonstrating no improvement in survival with radical resection for this tumor stage.[33] For T1b-T3 tumors, the goal of re-resection is to achieve microscopic negative margins.[15,34] The role of a major hepatectomy versus wedge resection or anatomic resection of segments 4b and 5 has been the topic of several studies.[32,35,36] Across the literature, performance of a major hepatectomy is associated with increased morbidity but not survival and should only be pursued if necessary to achieve a negative-margin resection.[15,35]

Similar to the extent of hepatic resection, routine resection of the common bile duct also is not associated with improved survival and is not routinely indicated unless necessary to clear a positive cystic duct margin. This has been shown repeatedly across several retrospective studies.[15,35,37] A 2007 retrospective study by Shih et al. demonstrated that patients who underwent hepatic resection along with lymphadenectomy and extrahepatic biliary resection had similar survival compared with those who had a hepatic resection and lymphadenectomy alone.[37] Additionally, common bile duct resection has been shown to not increase lymph node yield.[38]

The previously mentioned 2007 study by Pawlik et al. also demonstrated that the incidence of lymph node

TABLE 1 American Joint Committee on Cancer (AJCC) TNM Staging for Gallbladder Carcinoma (8th edition, 2017)

T stage	Primary tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
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 one 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	Metastases to one to three regional lymph nodes
N2	Metastases to four or more regional lymph nodes

M stage	Distant metastasis
M0	No distant metastasis
M1	Distant metastasis

involvement varies by T-stage, approximately 12%, 31%, and 45% in patients with T1b, T2, and T3 tumors, respectively.[15] A 2009 SEER study of 4614 patients found that for patients with T1b-T3 disease pathologic evaluation of at least one lymph node was associated with a significant improvement in median overall survival (OS) compared with those who had no lymph nodes evaluated. Importantly, in the absence of lymph node evaluation, radical resection provided no benefit over cholecystectomy alone.[39] A subsequent 2011 study from MSKCC found that histologic evaluation of at least six lymph nodes improves risk-stratification after resection of GBC.[40] The extent of lymph node dissection, however, should be limited to the porta hepatis (cystic, pericholedochal, hilar) as para-aortic lymphadenectomy does not result in improved survival and nodal disease beyond the hepatoduodenal ligament portends similar outcomes to distant disease, such as hepatic or peritoneal metastasis.[41] Ultimately, lymph node dissection, although limited to the porta hepatis, is primarily a staging and prognostic tool and is likely not associated with improved survival.

Several series in the literature have reported port-site recurrence rates of up to 40% after laparoscopic cholecystectomy particularly in the setting of bile spillage secondary to gallbladder perforation.[42,43] As a result, these early series advocated routine port excision. This clinical practice was questioned in a 2012 MSKCC series by Maker et al., which demonstrated that port-site resection was not associated with OS or recurrence-free survival (RFS) when adjusted for T- and N-stage. Importantly, this study highlighted that the presence of port-site disease is associated with diffuse peritoneal disease, thus explaining why routine excision is unlikely to result in improved long-term outcomes.[44] These findings were further validated in a 2013 study by Fuks and colleagues, which showed similar findings with no improvement in OS for patients who underwent port-site excision. This study also found an associated hernia rate of 15% in patients who underwent routine port-site excision.[45] Lastly, a 2017 multi-institutional study by Ethun et al. highlighted the decreasing practice of port-site excision and again showed no association with improved survival when adjusting for other prognostic factors, including tumor stage and grade.[46]

Given the increased morbidity of this practice and the lack of improvement in long-term outcomes, routine port-site resection is not recommended at the time of re-resection of incidental gallbladder cancer.

In terms of optimal timing of re-resection of incidental gallbladder cancer, a 2017 retrospective study by Ethun et al. found that re-resection between 4 to 8 weeks from initial cholecystectomy best balanced both tumor biology and technical considerations.[47]

Per Primum Gallbladder Cancer

As previously discussed, for cases of nonincidental gallbladder cancer, there may be suspicion of disease on preoperative imaging but no tissue diagnosis before exploration. According to expert consensus, intraoperative core needle biopsy with immediate frozen-section analysis is recommended before committing to radical resection.[26] When malignancy is suspected, an open procedure should be performed, preceded by staging laparoscopy, which can prevent unnecessary surgical resection in up 37% of patients.[48] Surgical management is otherwise similar to that outlined for incidental gallbladder cancer.

Summary Statement

Patients with incidentally diagnosed gallbladder cancer with T1b, T2, or T3 disease should undergo re-resection and portal lymphadenectomy within 4 to 8 weeks of initial cholecystectomy with a goal of achieving microscopic negative margins. Major hepatectomy and/or bile duct resection should be performed only if needed to obtain negative margins. Routine port-site resection is not recommended. The same surgical principles apply to per-primum gallbladder cancer.

ADJUVANT THERAPY

Background

Despite surgical resection, nearly 70% of patients ultimately develop recurrent disease.[49] Given this high rate of recurrence, adjuvant strategies have been explored for many years, in the form of chemotherapy, radiotherapy, and chemoradiotherapy. Due to the rarity of GBC, however, trials assessing the effect of adjuvant chemotherapy and radiation regimens have been limited and often have included other biliary malignancies in an effort to achieve sufficient statistical power. The following section summarizes available literature to support the use of adjuvant therapy and concludes with recommendations according to the American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines.

Chemotherapy

Since 2010, four randomized phase III clinical trials have been reported that inform the use of adjuvant chemotherapy for biliary malignancies. The use of gemcitabine and cisplatin for advanced disease (ABC-02), adjuvant gemcitabine and oxaliplatin (PRODIGE-12/ACCORD-18), adjuvant capecitabine (BILCAP), and adjuvant gemcitabine (BCAT) have all been addressed and details of each trial are reviewed below and further summarized in Table 2. A fifth trial exploring the use of adjuvant S-1 (JCOG1202, Registration number: UMIN 000011688) has completed accrual but will not be formally discussed below as findings have not been published.[50]

ABC-02 (2010) The Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer trial (ClinicalTrials.gov number, NCT00262769) by Valle et al. was a randomized, phase III trial conducted by 37 centers in the United Kingdom that compared gemcitabine/cisplatin with gemcitabine alone in locally advanced or metastatic cholangiocarcinoma and GBC. The trial included patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 who were randomly assigned to receive cisplatin (25 mg/m^2) plus gemcitabine (1000 mg/m^2) on days 1 and 8 every 3 weeks or gemcitabine (1000 mg/m^2) alone on days 1, 8, and 15 every 4 weeks for up to 24 weeks. It was designed to have 80% power to detect an increase in median survival from 8 months in patients receiving gemcitabine alone to 11 months in patients receiving gemcitabine/cisplatin.

A total of 410 patients were randomized between February 2002 and October 2008 and were evaluable for a primary endpoint of OS and secondary endpoints of progression-free survival, tumor response, and adverse events. Among all patients, 204 received cisplatin plus gemcitabine, and 206 received gemcitabine alone (Fig. 2).

Results demonstrated clear superiority of the combination regimen, with significant improvements in OS (11.7 vs. 8.1 months, $p < 0.001$; Fig. 3a) and progression-free survival (8 vs. 5 months, $p < 0.001$; Fig. 3b). Tumor control was achieved in 81.4% of patients who received cisplatin plus gemcitabine compared with 71.8% of patients who received gemcitabine alone ($p = 0.049$). Adverse events were similar between the two arms aside from liver function, which was significantly worse in the gemcitabine-only group (27.1%) than in the cisplatin-gemcitabine group (16.7%).[51] These results have been extrapolated to the adjuvant setting, with many clinicians utilizing adjuvant gemcitabine and cisplatin after resection

TABLE 2 Characteristics of randomized controlled trials of adjuvant therapy for biliary tract carcinoma

Study characteristic	ABC-02	PRODIGE-12/ ACCORD-18	BILCAP	BCAT
Study design	Randomized phase III	Randomized phase III	Randomized phase III	Randomized phase III
Study arms	Gemcitabine/cisplatin versus gemcitabine alone	GEMOX versus surgery alone	Capecitabine versus surgery alone	Gemcitabine versus surgery alone
Recruitment period	February 2022–October 2008	July 2009–february 2014	March 2006–december 2017	September 2007–january 2011
Country	United Kingdom	France	United Kingdom	Japan
Number of sites	37	33	44	48
Sample size (ITT and PP)	ITT: 410	ITT: 196	ITT: 447	ITT: 226
	PP: 410	PP: 155	PP: 430	PP: 225
Primary endpoint	OS	RFS	OS	OS
Secondary endpoint(s)	PFS	OS	PP OS/RFS	RFS
	Tumor response	Toxicity	ITT RFS	Subgroup analysis
	Adverse events		Toxicity	Toxicity
			Health economics	
			Quality of life	
Disease site (%)	36% gallbladder cancer	46% intrahepatic CC	19% intrahepatic CC	45% hilar CC
	59% CC	8% perihilar CC	29% hilar CC	55% distal CC
	5% ampullary cancer	27% distal CC	18% gallbladder cancer	
		20% gallbladder cancer	35% distal CC	
Median follow-up (mo)	8.2	46.5	60	79.4
Results				
Primary endpoint	OS	RFS	OS	OS
	Gem/Cis: 11.7 mo	GEMOX: 30.4 mo	Cap: 51.1 mo	Gem: 62.3 mo
	Gem: 8.1 mo	Obs: 18.5 mo	Obs: 36.4 mo	Obs: 63.8 mo
	HR 0.64, $p < 0.001$	HR 0.88, $p = 0.48$	HR 0.81, $p = 0.09$	HR 1.01, $p = 0.96$
Secondary endpoint(s)	PFS	OS	PP OS	RFS
	Gem/Cis: 8 mo	GEMOX: 75.8 mo	Cap: 53 mo	Gem: 36 mo
	Gem: 5 mo	Obs: 50.8 mo	Obs: 36 mo	Obs: 39.9 mo
	HR 0.63, $p < 0.001$	HR 1.08, $p = 0.74$	HR 0.75, $p = 0.02$	HR 0.93, $p = 0.69$
	Tumor response:		PP RFS	
	Gem/Cis: 81.4%		Cap: 25.9 mo	
	Gem: 71.8%		Obs: 17.4 mo	
	$p = 0.049$		HR 0.70, $p = 0.009$	
			ITT RFS	
			Cap: 24.2 mo	
			Obs: 17.5 mo	
			HR 0.75, $p = 0.03$	

ITT intention-to-treat; *PP* per protocol; *CC* cholangiocarcinoma; *OS* overall survival; *PFS* progression-free survival; *RFS* relapse-free survival

as the standard-of-care in their clinical practice for many years. The use of gemcitabine-based regimens formed the basis of the PRODIGE-12/ACCORD-18 and BCAT trials, which are summarized below.

PRODIGE-12/ACCORD-18 (2017) Gemcitabine Hydrochloride and Oxaliplatin or Observation in Treating Patients with Biliary Tract Cancer that Has Been Removed by Surgery Trial (PRODIGE-12/ACCORD-18) by Edeline et al. was a multicenter, randomized, phase III trial conducted in 33 centers in France that compared adjuvant gemcitabine and oxaliplatin (GEMOX) to surveillance alone in patients with intrahepatic (46%), perihilar (8%), or distal (27%) cholangiocarcinoma or gallbladder

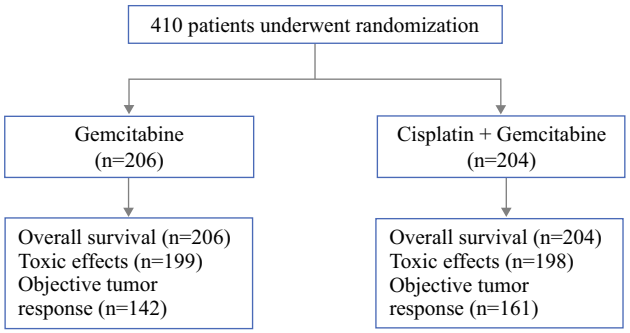

FIG. 2 ABC-02 trial schema

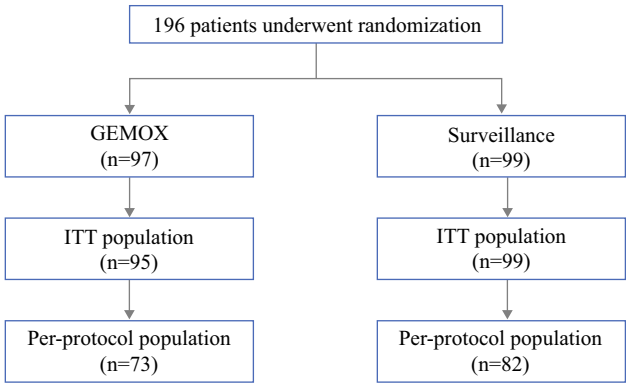

FIG. 4 PRODIGE-12/ACCORD-18 trial schema

adenocarcinoma (20%). The trial included patients with an ECOG performance status of 0, 1, or 2 within 3 months of a macroscopic negative resection (R0 or R1) who were randomized to receive either GEMOX (gemcitabine 1000 mg/m^2 on day 1 and oxaliplatin 85 mg/m^2 infused on day 2 of a 2-week cycle) for 12 cycles or surveillance. The trial was designed to detect a difference in median relapse-free survival from 18 months in the surveillance arm to 30 months in the GEMOX arm, corresponding to a hazard ratio (HR) of 0.6.

A total of 196 patients were randomized between July 2009 and February 2014 and 155 were evaluable for a primary endpoint of relapse-free survival and global health-related quality of life (Fig. 4). Importantly, 13% of patients had microscopic positive margins and 37% of patients had lymph node metastases.

Results demonstrated no significant difference between the two arms in the primary outcomes of relapse-free survival [hazard ratio (HR) 0.88, 95% confidence interval (CI) 0.62 to 1.25, p = 0.48; Fig. 5a] and global health-related quality-of-life scores at 12 months (GEMOX: 70.8 vs. Surveillance: 83.3, p = 0.18). There also was no difference in OS between the study arms (HR 1.08, 95% CI 0.70–1.66, p = 0.74; Fig. 5b). Subgroup analyses by lymph node status, margin status, and primary disease site did not suggest any subgroup who would benefit from adjuvant GEMOX.[52] This study has drawn criticism for its design to detect an effect size of HR 0.6, which resulted in the study being underpowered to identify smaller but still clinically relevant differences between the arms. Additionally, the trial included a low proportion of patients who are considered to be high-risk (only 13% had R1 resections, and 37% had lymph node metastases) and hence derive the most benefit from adjuvant therapy.

BILCAP (2017) Capecitabine or Observation after Surgery in Treating Patients with Biliary Tract Cancer (BILCAP; EudraCT, number 2005-003318-13) trial by

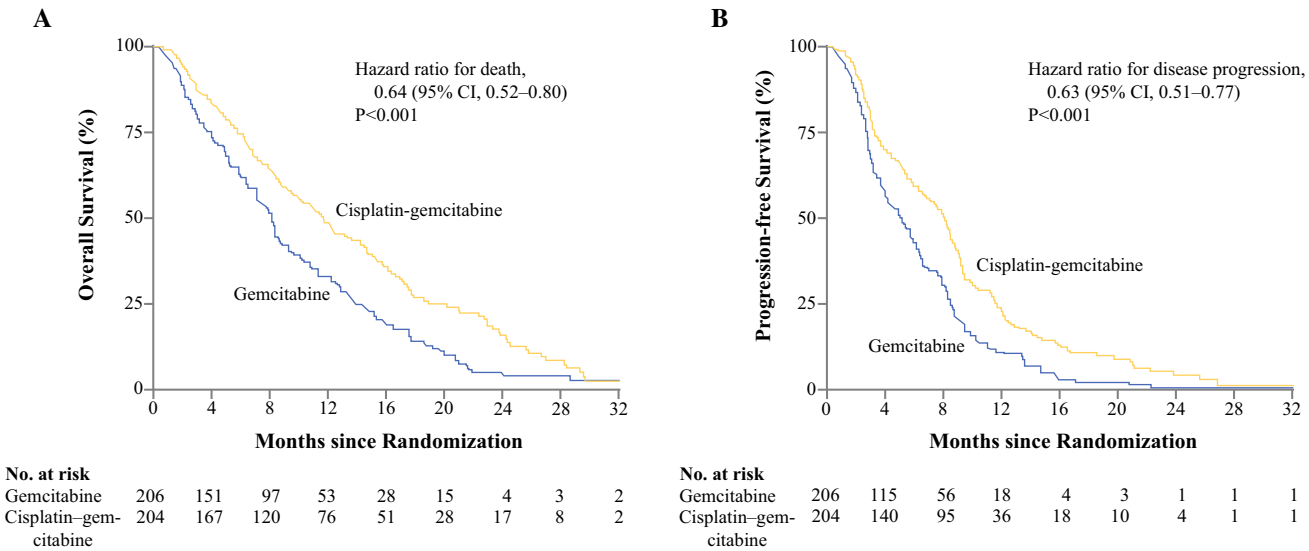

FIG. 3 ABC-02 trial survival plots. Overall survival (**a**) and progression-free survival (**b**) comparing patients who underwent adjuvant treatment with gemcitabine-cisplatin or gemcitabine alone. Reproduced from: *N Engl J Med.* 2010;362(14):1273–1281

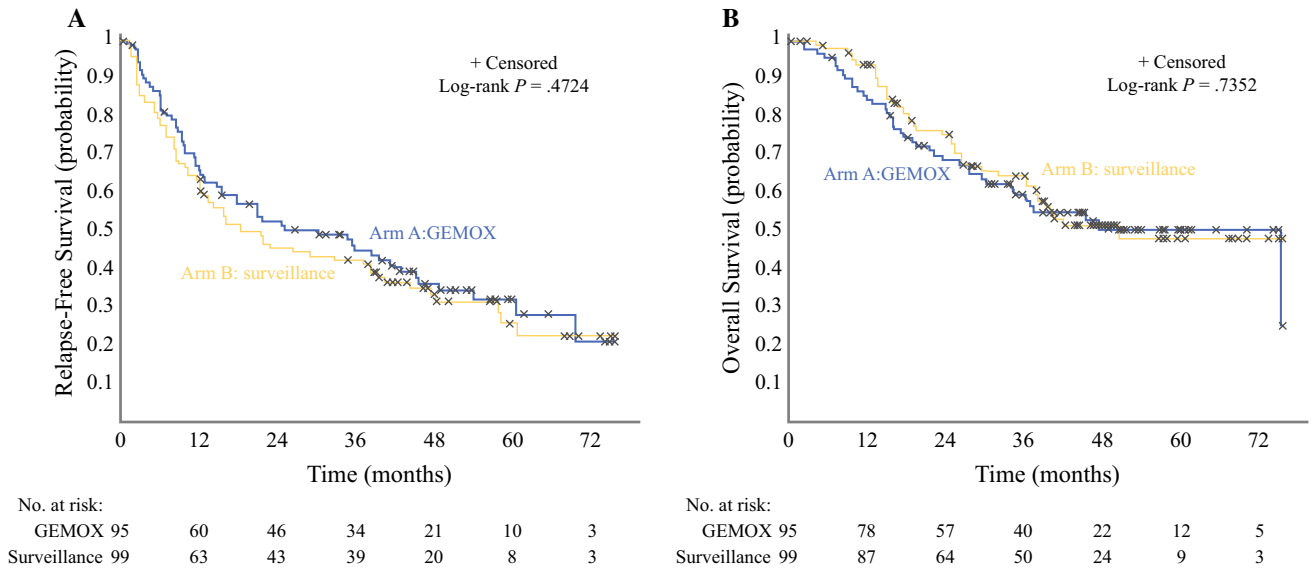

FIG. 5 PRODIGE-12/ACCORD-18 survival plots. Relapse-free survival (**a**) and overall survival (**b**) comparing patients who underwent adjuvant treatment with gemcitabine and oxaliplatin or surveillance alone. Reproduced from: *J Clin Oncol.* 2019;37(8):658–667

Primrose et al. was a phase III, randomized, controlled trial conducted in 44 centers in the United Kingdom, which sought to compare adjuvant capecitabine to observation alone after macroscopic complete resection in patients with intrahepatic cholangiocarcinoma (19%), hilar cholangiocarcinoma (29%), muscle-invasive gallbladder cancer (18%), or cholangiocarcinoma of the lower common bile duct (35%). Importantly, this study remains the first and only trial to demonstrate a benefit in adjuvant therapy for biliary tract malignancies.

The trial included patients with an ECOG performance status of 0, 1, or 2 who were randomized to receive capecitabine delivered at a dose of 1250 mg/m^2 twice a day on treatment days 1 to 14 of a 3-week cycle for 24 weeks (8 cycles) or observation alone 16 weeks after curative-intent resection. The trial was designed to detect an improvement in OS from 20% to 32%, corresponding to an HR of 0.71.

A total of 447 patients were randomized between March 2006 and December 2014 and 430 were evaluable for the primary endpoint of OS in the intent-to-treat population and secondary outcomes of OS in the per-protocol population, which excluded ineligible patients and patients failing to complete at least one cycle of capecitabine. Other secondary outcomes included RFS, toxicity, health economics, and quality of life (Fig. 6). Approximately 54% of patients had microscopic positive margins and 38% of patients had lymph node-positive disease.

Results failed to show a significant difference in unadjusted intention-to-treat OS (HR 0.81, 95% CI 0.63–1.04, p = 0.097; Fig. 7A). However, there was significant difference in OS in a prespecified intention-to-treat analysis

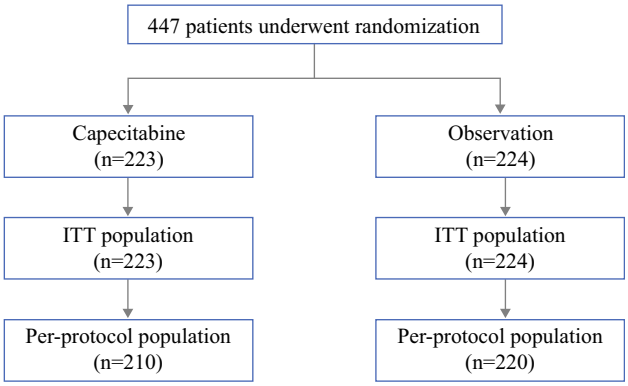

FIG. 6 BILCAP trial schema

adjusted for nodal status, disease grade, and sex (HR 0.71, 95% CI 0.55–0.92, p = 0.01). Additionally, a per-protocol analysis that excluded 17 patients who were either found to be ineligible or were randomly assigned to but did not receive capecitabine also found a significant difference in OS (HR 0.75, 95% CI 0.58–0.97, p = 0.028; Fig. 7B) in favor of capecitabine versus observation. RFS differed between treatment groups in the first 24 months (HR 0.75, 95% CI 0.58–0.98, p = 0.033), but not thereafter (HR 1.48, 95% CI 0.80–2.77, p = 0.21) raising the possibility that capecitabine only defers recurrence.[53] The 5-year survival data from the BILCAP trial is currently awaited. Despite its negative results on intention-to-treat analysis, the observed overall survival effect is large and clinically meaningful at 9%, and capecitabine is convenient and tolerable.[54] As a result, adjuvant capecitabine is currently recommended for all patients who undergo resection of GBC, as outlined in the *Summary Statement* below.

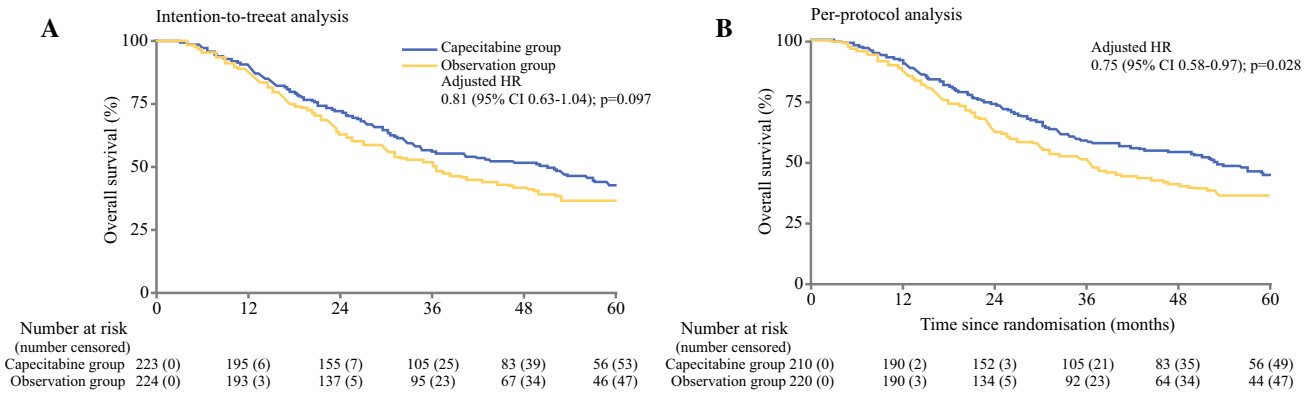

FIG. 7 BILCAP survival plots. Overall survival by intention-to-treat (**a**) and per-protocol (**b**) analyses comparing patients who underwent adjuvant treatment with capecitabine or observation alone. Reproduced from: *Lancet Oncol.* 2019;20(5):663–673

BCAT (2018) The Bile Duct Cancer Adjuvant Trial (BCAT, Registration number: UMIN 000000820) by Ebata et al. was a randomized, controlled, phase III trial conducted in 48 Japanese hospitals which aimed to test the hypothesis that adjuvant gemcitabine chemotherapy would improve survival probability in resected bile duct cancer. The trial included patients with histologically proven extrahepatic bile duct cancer (45% hilar, 55% distal) and ECOG performance status of 0 or 1 who were randomized to receive adjuvant gemcitabine at a dose of 1000 mg/m^2 administered on days 1, 8, and 15 every 4 weeks for six cycles or observation. It was designed to have 80% power to detect an HR of 0.85 in the gemcitabine group compared to the observation group.

A total of 226 patients were randomized between September 2007 and January 2011 and were evaluable for a primary endpoint of OS. Among all patients enrolled, 117 were assigned to the gemcitabine group and 109 to the observation group (Fig. 8). Approximately 11% of patients had microscopic positive margins and 54% and 35% had lymph node metastases. Median follow-up was 79.4 months. There were no significant differences in OS (HR 1.01, 95% CI 0.70–1.45, p = 0.964; Fig. 9a) or RFS (HR 0.93, 95% CI 0.66–1.32, p = 0.693; Fig. 9b). These results persisted in subgroup analyses according to lymph node status and margin status.[55] Although this study failed to accrue the planned number of patients which perhaps resulted in an underpowered analysis, the authors stated that this was unlikely to have affected the final results.

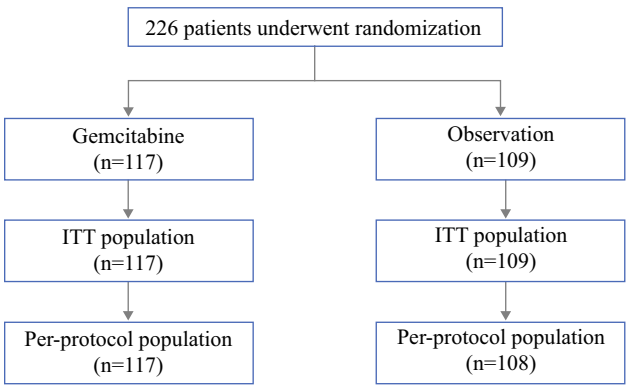

FIG. 8 BCAT trial schema

Chemoradiotherapy

Given a rate of locoregional recurrence of 15–62% in patients with GBC, there is considerable interest in exploring the benefit of adjuvant chemoradiotherapy.[49,56] This topic has been the subject of various retrospective series, but only one trial has been published on the use of adjuvant chemoradiotherapy.[57,58]

SWOG0809 (2015) The Adjuvant Capecitabine and Gemcitabine Followed by Radiotherapy and Concurrent Capecitabine in Extrahepatic Cholangiocarcinoma and Gallbladder Carcinoma (SWOG0809; ClinicalTrials.gov number, NCT00789958) trial by Ben-Josef et al. was a single-arm, phase II trial conducted in the United States that included patients with hilar cholangiocarcinoma (48%), distal cholangiocarcinoma (16%), or gallbladder cancer (32%) who underwent four cycles of chemotherapy with gemcitabine delivered at a dose of 1000 mg/m^2 on treatment days 1 and 8 and capecitabine delivered at a dose of 1500 mg/m^2 twice daily on treatment days 1 to 14 every 21 days. After reimaging, patients not experiencing progression received capecitabine (1330 mg/m^2/day, 7 days/week) concurrent with radiotherapy (45 Gy to regional lymph nodes [retropancreaticoduodenal, celiac, and portal vein nodes] and 54 to 59.4 Gy to tumor bed). The primary aim was to estimate stratum-specific (R0 and R1) and 2-year OS probabilities with a goal of demonstrating OS $\geq$ 65% for R0 and $\geq$ 45% for R1.

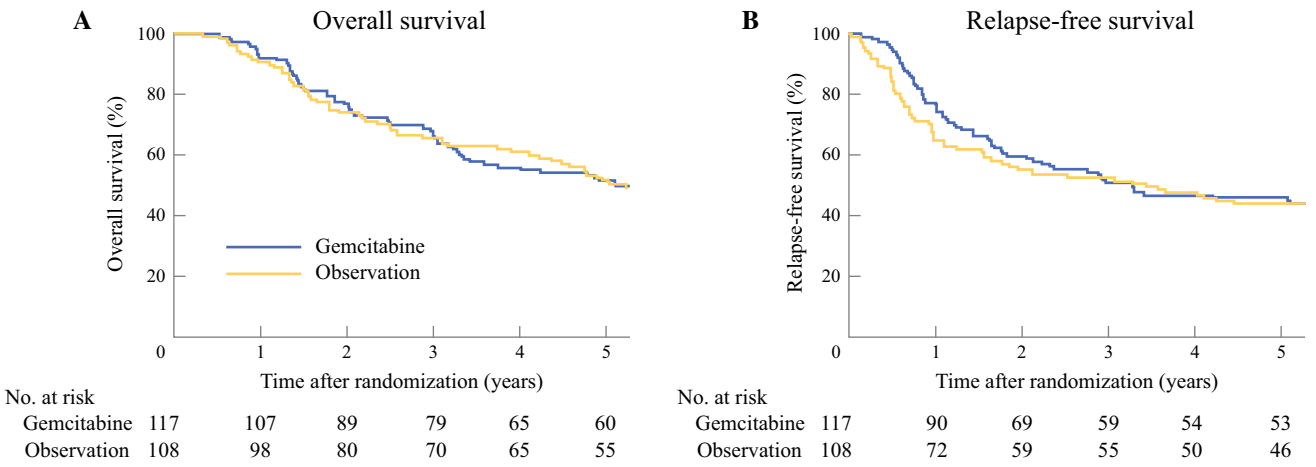

FIG. 9 BCAT trial survival plots. Overall survival (**a**) and recurrence-free survival (**b**) comparing patients who underwent adjuvant treatment with gemcitabine or observation alone. Reproduced from: *Br J Surg*. 2018;105(3):192–202

A total of 105 patients were recruited between December 2008 and October 2012 of whom 79 were eligible for analysis. With a median follow-up of 35 months, OS was 65% overall (Fig. 10a): 67% in the R0 group, and 60% in the R1 group (Fig. 10b). Local recurrence at 2 years was 11% overall, 9% for R0, and 16% for R1. Results exceeded predetermined thresholds, and the authors cautiously attribute the improvement in OS in the R1 stratum to the efficacy of chemoradiotherapy.[59] Although the lack of a control arm limits the interpretability of these findings, the favorable survival results compared with historical controls support consideration of this regimen. Importantly, this trial demonstrated the feasibility of accrual of patients with a rare diagnosis to a national trial.

Summary Statement

Based on a systematic review of the data presented here, the ASCO Clinical Practice Guidelines provide the following recommendations: (1) patients with resected biliary tract cancer should be offered adjuvant capecitabine chemotherapy for a duration of 6 months at a dose determined by institutional or regional practices, and (2) patients with extrahepatic cholangiocarcinoma or gallbladder cancer and a microscopically positive surgical margin resection (R1 resection) may be offered chemoradiotherapy.[60] Given the negative results of the BILCAP trial on intention-to-treat analysis, however, the combination of adjuvant gemcitabine and cisplatin is still commonly used in clinical practice. The multinational ACTICCA-01 trial from Germany (ClinicalTrials.gov number, NCT02170090) is investigating the superiority of this regimen versus capecitabine alone (the control arm was originally observation but was amended to capecitabine after results of the BILCAP trial), and results are eagerly awaited. At this time, the evidence regarding adjuvant chemoradiotherapy is not sufficiently well-developed to make a recommendation for optimal dosing of radiation therapy.

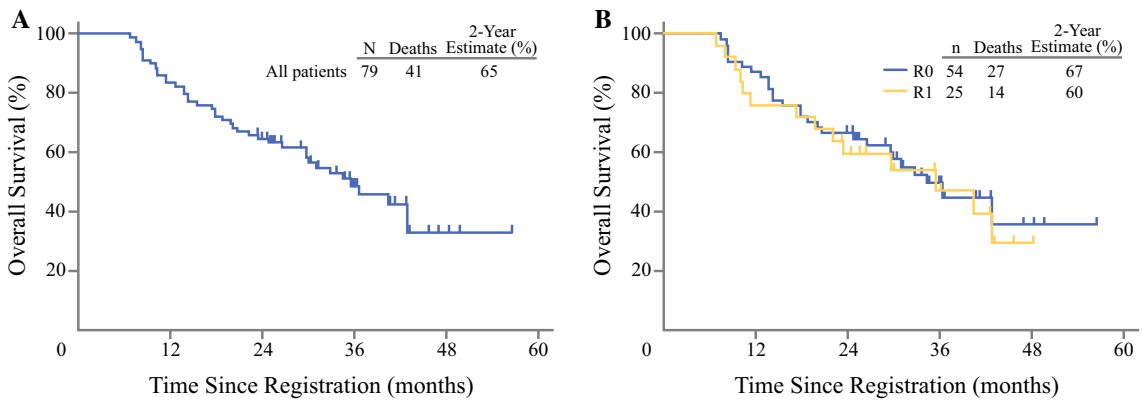

FIG. 10 SWOG 0809 trial survival plots. Overall survival in all patients (**a**) and by resection margin (**b**). Reproduced from: *J Clin Oncol*. 2015;33(24):2617–2622

NEOADJUVANT THERAPY

Background

The use of neoadjuvant therapy has demonstrated a number of benefits in other gastrointestinal malignancies, including ensured delivery of therapy, potential downstaging, and conversion to resectable disease, and most importantly improved identification of patients who would not benefit from resection due to occult, micrometastatic disease that becomes evident during therapy. Delays in surgical resection and potential for progression of disease, however, pose considerable concern. Additionally, as primary GBC is usually discovered in an advanced setting, the use of neoadjuvant therapy for these patients remains a challenging concept. As such, the most feasible implementation of neoadjuvant therapy in GBC would be in the situation of incidental diagnosis after simple cholecystectomy.

Despite the potential benefits, the role of neoadjuvant therapy for GBC remains ill-defined due to a paucity of high-level evidence. Indeed, no trials to date have explored its use in GBC. The section below summarizes available retrospective studies evaluating the use of neoadjuvant chemotherapy or chemoradiotherapy in locally advanced GBC.

Neoadjuvant Chemotherapy

A 2019 review of six retrospective and two prospective studies included 474 patients with locally advanced GBC of whom 84% were treated with neoadjuvant chemotherapy and 16% were treated with neoadjuvant chemoradiotherapy. Only 40% of patients who underwent neoadjuvant treatment were able to undergo curative resection, and of these, 92.5% had an R0 resection. The median OS for those patients who underwent curative resection following neoadjuvant therapy ranged from 18.5 to 50.1 months compared with 5.0 to 10.8 months in those patients who underwent neoadjuvant therapy but were unable to have surgery.[61] Notably, all of the included studies were deemed low quality due to the lack of comparison between treatments, and there was wide variation in the chemotherapy and chemoradiation protocols with no standardized timing of surgery following treatment completion. As a result, the authors of this review conclude that there are insufficient data to support the routine use of neoadjuvant chemotherapy or chemoradiotherapy for gallbladder cancer. A recently approved trial titled "EA2197: A Randomized Phase II/III Trial of Optimal Perioperative Therapy for Incidental Gallbladder Cancer (OPT-IN)" by Maithel et al. will seek to evaluate the role of neoadjuvant therapy in patients with T2 or T3 incidental GBC. This trial will be conducted through the National Cancer Trial Network (NCTN), and we eagerly its results.

Summary Statement

Although there is no definitive data to support its use, neoadjuvant therapy may allow for evaluation of tumor biology and prevent resection in patients who are unlikely to derive any benefit. According to the National Comprehensive Cancer Network (NCCN) guidelines, neoadjuvant therapy should be considered if there is evidence of locoregionally advanced disease, such as a mass invading the liver and or nodal involvement.[19] There is limited evidence to define a standard regimen but options include gemcitabine/cisplatin, gemcitabine/capecitabine, capecitabine/cisplatin, capecitabine/oxaliplatin, 5-fluorouracil/oxaliplatin, 5-fluorouracil/cisplatin, and the single agents gemcitabine, capecitabine, and 5-fluorouracil.

TARGETED THERAPY AND IMMUNOTHERAPY

Genomic profiling-guided targeted therapy has been widely applied in several types of cancers and recent studies also have demonstrated that gallbladder cancer harbors actionable genomic alterations. For patients with advanced GBC, HER2 overexpression has been found in 12% to 18% with an associated favorable response to HER2-directed therapy, including treatment with trastuzumab or lapatinib.[62,63] Furthermore, KRAS mutations in gallbladder cancer have been reported to occur at a frequency of 3% to 30%, and notably, KRAS mutations are known to predict clinical response to EGFR inhibitors in colorectal and lung cancer.[63] Other altered genes in gallbladder cancer include TP53, CDKN2A, and PIK3CA.[64] Lastly, a recent study found that high tumor mutational burden (defined as > 12.5 mutations/Mb) could serve as the cutoff value for determining the therapeutic benefit of a regimen of Lenvatinib plus a PD-1 inhibitor.[64] These studies highlight that genomic profiling-guided targeted therapy is feasible in this rare cancer, and this approach is currently being studied in several trials for advanced disease. As we begin to understand its efficacy in that subset of patients, we will be able to personalize therapy for patients with resectable disease.

CONCLUSIONS

Although multimodal management is paramount for patients with gallbladder carcinoma, the rarity of this cancer has posed a significant challenge in the development of meaningful clinical trials to further guide surgical management or neoadjuvant and adjuvant strategies. Five

clinical trials have been reported since 2010 to include all biliary malignancies and have led to the consensus statement that all patients with resected biliary tract cancer should be treated with 6 months of adjuvant oral capecitabine or adjuvant chemoradiotherapy in the setting of R1 margins. Future trials assessing the role of perioperative chemotherapy are underway, and the development of novel targeted and immunologic therapies based on genetic profiling is promising. Ultimately, international collaborations are needed to systematically improve survival for patients with gallbladder carcinoma. In the meantime, the multidisciplinary management of patients with gallbladder carcinoma remains the best way of optimizing long-term outcomes.

FUNDING Supported in part by the Katz Foundation.

DISCLOSURE None.

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