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Review

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A review of current adjuvant and neoadjuvant systemic treatments for cholangiocarcinoma and gallbladder carcinoma

Michael J. Allen, Jennifer J. Knox

Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, Toronto ON M5G 2M9, ON, Canada.

Correspondence to: Dr. Jennifer J. Knox, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, 610 University Avenue, Toronto M5G 2M9, ON, Canada. E-mail: Jennifer.Knox@uhn.ca

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Abstract

Biliary tract cancers are a relatively rare heterogenous group of malignancies, including gallbladder cancer, intrahepatic, perihilar, and distal cholangiocarcinoma. Most patients are diagnosed with locally advanced or metastatic disease, and survival outcomes remain poor. This is also the case in the relatively few who undergo curative surgery. Efforts to improve patient survival outcomes have focussed on adjuvant and neoadjuvant chemotherapy and chemoradiotherapy. Adjuvant trials investigating the efficacy of systemic chemotherapy have primarily been negative to date, with challenges including compliance, recruitment rate, percentage of node-positive and R1 resections, and tumor heterogenicity observed. As reported in BILCAP, adjuvant capecitabine is currently considered the standard of care in many countries and guidelines, while chemoradiotherapy improves R1 outcomes as observed in the phase II trial SWOG S0809. Trials are ongoing to elicit the ideal combination of adjuvant treatment. Evidence for neoadjuvant chemotherapy continues to be based on retrospective analysis and a few phase II trials, with observed downstaging to surgery and improved R1 resection rates documented. This review documents the current evidence for systemic chemotherapy in adjuvant and neoadjuvant treatment of biliary tract cancers and highlights the ongoing clinical trials.

Keywords: Cholangiocarcinoma, gallbladder carcinoma, neoadjuvant chemotherapy, adjuvant chemotherapy

INTRODUCTION

Cancers of the biliary tract include intrahepatic, perihilar, and distal cholangiocarcinoma (CCA) and gallbladder cancer (GBC). Intrahepatic CCA arises from epithelial cells distal to the second-order bile ducts, hilar CCA arises from epithelial cells at either the right and/or left hepatic duct or their junction, while distal CCA arises from epithelial cells within the common bile duct[1,2]. CCA is the second most common primary liver cancer after hepatocellular carcinoma accounting for 3% of all gastrointestinal cancers and 2% of all yearly global cancer-related deaths[2,3]. GBC is the most common biliary tract malignancy accounting for 1.2% of global cancer diagnoses[4-7].

The incidence of CCA and GBC varies between geographical regions owing to differences in genotype predisposition, environmental and modifiable risk factors, with 85 cases per 100,000 in north-east Thailand, 3.6 per 100,000 in Western Europe, and 1.6 per 100,000 in the United States of America[8,9]. However, the incidence of biliary tract cancers is steadily increasing in most western countries[10].

Identified risk factors leading to the development of intrahepatic and perihilar/distal CCA differ, with a Surveillance, Epidemiology, and End-Results-Medicare dataset suggesting an association between intrahepatic CCA and hepatitis B and C infection, tobacco smoking, alcohol consumption, and non-alcoholic fatty liver disease, while reporting that such associations do not exist with perihilar/distal CCA[11,12]. Factors associated with GBC include obesity, female gender, chronic inflammation of the biliary tracts as occurs in primary sclerosing cholangitis, cholelithiasis, cholecystitis, gallbladder polyps, smoking, and *Salmonella* and *Helicobacter* infections[13]. Alterations in up to 32 genes have been identified in approximately 70% of biliary tract cancers, with *TP53*, *KRAS*, and *SMAD4* the most common[14,15], while potentially targetable molecular mutations have been identified in approximately 39% of biliary tracts cancers. These include *ERBB2* amplification, *BRAF* substitution, *PIK3CA* substitution, *FGFR1-3* fusions, *CDKN2A/B* loss, *IDH1/2* substitution, *ARID1A* alteration, *MET* and *BAP1* mutations[16,17]. Molecular heterogenicity exists with *IDH1/2* mutations and *FGFR2* fusions predominately identified in intrahepatic CCA relative to perihilar and distal CCA and GBC[18]. A reported 8.6% of all biliary tract cancers exhibit high programmed death-ligand 1 (PD-L1) expression[19]. Biomarker selection and precision treatments are likely to play an increasingly important role in optimizing care for patients with biliary tract cancers, likely validated first in advanced disease and then studied in the earlier disease settings.

Most patients are diagnosed with advanced (unresectable/metastatic) biliary tract cancer, with only 20%-30% resectable at diagnosis[20-23]. The 5-year survival remains poor at approximately 10% for CCA and 19% for GBC[3,24]. Chemotherapy is the standard of care treatment for advanced disease, with the median overall survival (OS) of 11.7 months with first-line cisplatin and gemcitabine as demonstrated in phase III clinical trial ABC-02 (NCT00262769)[25]. This trial also reported an observed response rate (ORR) of 26.1% (CCA 19%; GBC 37.7%) with doublet chemotherapy. Comparable outcomes were observed in an Asian population in the BT22 clinical trial, with both ABC-02 and BT22 then analyzed in a metanalysis by Valle *et al.*[26], which demonstrated consistent outcomes[27]. Keynote-158 (NCT02628067) and Keynote-028 (NCT02054806) report an ORR with pembrolizumab of 6%-13%, with similar rates observed with nivolumab (NCT02829918) in chemotherapy-refractory disease, while an ORR of 24% has been reported with combination nivolumab and ipilimumab (NCT02923934)[28-32]. All of these were non-randomized trials. For the smaller subset presenting with the localized disease, the median OS following curative surgical resection is approximately 40 months[33]. Criteria for resectability include no local vascular invasion (hepatic artery, hepatic vein, or portal vein) or local vascular invasion amenable to reconstruction, an ability to reconstruct the bile duct or achieve an R0 resection, sufficient liver volume, and no distant metastases[34,35]. Outcomes are worse in lymph-node positive (N+) disease, while a negative resection margin (R0) achieves a

significantly increased median OS compared to a positive microscopic margin (R1)[36,37].

The rationale for adjuvant therapy, whether it be chemotherapy, chemoradiotherapy, or radiation therapy alone, has been presented in a metanalysis by Horgan *et al.*[38], which reported a significant benefit with any adjuvant therapy in R1 and N+ disease, of which the majority received chemotherapy. Meanwhile, neoadjuvant therapy has the potential benefit of improving the R0 resection rate, increasing the rate of receipt of systemic chemotherapy given the potential challenges of adjuvant chemotherapy, enhancing patient selection for major surgery, and facilitating *in vivo* assessment of chemotherapy efficacy[20]. Preoperative or "downstaging" therapy can also potentially downstage locally advanced inoperable tumors to enable resection to occur.

This review aims to report on the current evidence for adjuvant and neoadjuvant systemic therapy in biliary tract cancers and discuss ongoing clinical research.

ADJUVANT THERAPY

Due to the relative rarity of biliary tract cancers, most of the evidence regarding adjuvant therapy is from phase II clinical trials and retrospective analyses, which are detailed in Table 1 with just five phase III randomized-control clinical trials reported.

One of the earliest studies by Takada *et al.*[39] (2002) compared adjuvant mitomycin C plus fluorouracil followed by oral fluorouracil until recurrence to surveillance. Patients with stage II-IV adenocarcinoma of the pancreas, gallbladder, biliary tract, or ampulla of Vater were included. The primary outcome was OS. One hundred and eighteen (of 508) patients with CCA were included in the analysis, with 58 randomized to adjuvant chemotherapy and 60 to surveillance. One hundred and twelve patients with GBC were included. Sixty-nine received adjuvant chemotherapy, and 43 were randomized to surveillance. Seventy-two (61%) patients with CCA and 51 (46%) with GBC underwent curative surgery. There was no observed 5-year OS benefit in CCA patients with chemotherapy (26.7% *vs.* 24.1%) or disease-free survival (DFS). The 5-year OS in GBC was 26.0% *vs.* 14.4% ($P = 0.0367$) and the 5-year DFS 20.3% *vs.* 11.6% ($P = 0.021$). When stratified for curative surgery, the 5-year OS in GBC was not improved with adjuvant chemotherapy. This suggests that the observed OS benefit may result from chemotherapy administration in patients with advanced disease. This study was not powered to determine the standard of care specifically in respect to biliary tract cancers.

ESPAC-3 (2012; NCT00058201) compared fluorouracil to gemcitabine and surveillance[40]. Ninety-six of 434 patients included in this study had distal CCA, in what was a predominantly pancreatic cancer adjuvant trial conducted in Europe. The median OS with surveillance ($n = 31$) was 27.2 months (95%CI: 15.4-31.9), 18.3 months (95%CI: 12.9-28.7) in those who received fluorouracil ($n = 31$), and 19.5 months (95%CI: 16.2-36.1) in those who received gemcitabine ($n = 34$). No biliary-specific DFS data was presented. Multivariate regression analysis indicated a survival benefit with chemotherapy (fluorouracil and gemcitabine combined) compared to surveillance [hazard ratio (HR) = 0.75, 95%CI: 0.57-0.98, $P = 0.03$], although this did not differentiate based on tumor subtype. This trial was not powered to draw specific conclusions regarding survival benefits for biliary tract cancers alone and could not offer recommendations regarding the standard of care.

The Bile Duct Cancer Adjuvant Trial [BCAT (2017; UMIN000000820)] was a Japanese study comparing gemcitabine to surveillance[41]. Patients with stage I-III perihilar and distal CCA with either an R0 or R1 resection were included. The primary endpoint was OS. Two hundred and twenty-five patients were included in the analysis, with 117 patients randomized to gemcitabine and 108 to surveillance. Seventy-eight

Table 1. Select completed clinical trials of adjuvant chemotherapy in biliary tract cancers

Trial name/ID/author	Year	Trial type/name	Tumor site	No. of patients	Node positive *n* (%)	Margin positive *n* (%)	Study arms	Primary endpoint	DFS*	OS*
Takada *et al.*[39]	2002	Phase III	CCA	118/508	102 (86%)	NR	MMC + fluorouracil *vs.* surveillance	OS	5 year 20.7% *vs.* 15% (P = 0.8892) 5 year: 20.3% *vs.* 11.6% (P = 0.021)	5 year: 26.7% *vs.* 24.1% 5 year: 26% *vs.* 14.4% (P = 0.0367)
			GBC	112/508	105 (94%)	NR		OS		
ESPAC-3 Neoptolemos *et al.*[40] NCT00058201	2012	Phase III	dCCA	96 of 434	251/434 (57.8%)	68/434 (15.7%)	Fluorouracil or gemcitabine *vs.* surveillance	OS	NR	18.3 months *vs.* 19.5 months *vs.* 27.2 months (P > 0.05)
BCAT Ebata *et al.*[41] (UMIN000000820)	2017	Phase III	pCCA, dCCA	225	78/225 (34.7%)	25/225 (11.1%)	Gemcitabine *vs.* surveillance	OS	36 months *vs.* 39.9 months (P = 0.69)	62.3 months *vs.* 63.8 months (P = 0.96)
PRODIGE 12-ACCORD-18 Edeline *at al.*[42] (NCT01313377)	2019	Phase III	CCA, GBC	194	71/194 (36.6%)	25/194 (12.9%)	GEMOX *vs.* surveillance	DFS	30.4 months *vs.* 18.5 months (P = 0.48)	75.8 months *vs.* 50.8 months (P = 0.74)
BILCAP Primrose *et al.*[43] (NCT00363584)	2019	Phase III	CCA, GBC	447	210/447 (47%)	168/447 (37.6%)	Capecitabine *vs.* surveillance	OS	IIT: 24.4 months *vs.* 17.5 months (P = 0.693) PP: 25.9 months *vs.* 17.4 months (P = 0.0093)	IIT: 51.1 months *vs.* 36.4 months (P = 0.097) PP: 53.0 months *vs.* 36.0 months (P = 0.028)
Kobayashi *et al.*[62] (UMIN000001020)	2011	Phase II	pCCA, dCCA, GBC, PC	27	NR	NR	Gemcitabine: 4-weekly *vs.* 3-weekly	Completion rate	53% *vs.* 55% at 2 year (P = 0.83)	71% *vs.* 75% at 2 year (P = 0.59)
SWOG S0809 Ben-Josef *et al.*[45] (NCT00789958)	2014	Phase II	pCCA, dCCA, GBC	79	NR	25/79 (31.6%)	Gemcitabine + capecitabine → CRT (capecitabine)	OS	65% at 2 year	52% at 2 year
Cho *et al.*[63] (NCT00660699)	2014	Phase II	CCA, GBC	12 (of 50)	15/21 (71.4%)	NR	Gemcitabine + docetaxel → CRT (fluorouracil) → gemcitabine + docetaxel	AEs	16.3 months	27.6 months
Kainuma *et al.*[64] (UMIN000001294)	2015	Phase II (Feasibility study)	CCA, GBC, PC	29	14/29 (48.3%)	9/29 (31%)	Cisplatin + gemcitabine	Completion rate, AEs	37.4 months	60% at 4 year
Woo *et al.*[65] (NCT01043172)	2017	Phase II	CCA, GBC	72	32/72 (44.4%)	0	Gemcitabine	DFS	17.6 months	61.2 months
Siebenhüner *et al.*[66] (NCT01073839)	2018	Phase II	iCCA, pCCA, GBC	30	10/30 (33.3%)	2/30 (6.7%)	Cisplatin + gemcitabine	AEs	14.9 months	40.6 months
Nakachi *et al.*[67] (UMIN000004051)	2018	Phase II	CCA, GBC, PC	33	17/33 (51.5%)	3/33 (9.1%)	S-1	Completion rate	18.9 months	54.5% at 3 year

KHBO1208[68] (NCT01815307)	2019	Phase II	CCA, GBC	70	32/70 (45.7%)	12/70 (17.1%)	S-1 *vs.* gemcitabine	DFS	51.4% *vs.* 31.4% at 2 year (P = 0.094)	80% *vs.* 60% at 2 year (P = 0.07)
TOSBIC01 Itano *et al.*[69] (UMIN000009029)	2020	Phase II	pCCA/dCCA GBC iCCA Ampullary	19 10 8 9 (total 46)	20/46 (46%)	3/46 (7%)	S-1 for 1 year *vs.* surveillance	Completion rate	2 year 77.2%	2 year 80%

*Median unless stated otherwise. CCA: Cholangiocarcinoma; GBC: gallbladder carcinoma; iCCA: intrahepatic cholangiocarcinoma; pCCA: perihilar cholangiocarcinoma; dCCA: distal cholangiocarcinoma; PC: pancreatic carcinoma; MMC: mitomycin C; GEMOX: gemcitabine + oxaliplatin; OS: overall survival; DFS: disease-free survival; AEs: adverse events; IIT: intention-to-treat analysis; PP: per-protocol analysis; CRT: chemoradiotherapy; NR: no result.

(34.7%) were N+ and only 25 (11.1%) R1. No difference in median OS (62.3 months *vs.* 63.8 months; HR = 1.01, 95%CI: 0.70-1.45, P = 0.964) or DFS (36 months *vs.* 39.9 months; HR = 0.93, 95%CI: 0.66-1.32, P = 0.693) was observed. Subgroup analysis of pN0 *vs.* pN1, R0 *vs.* R1, and tumor location (hilar *vs.* distal) did not demonstrate survival differences between adjuvant gemcitabine and surveillance.

PRODIGE 12-ACCORD 18 by Edeline *et al.*[42] (2018; EudraCT 2008-004560-39) compared gemcitabine plus oxaliplatin (GEMOX) to surveillance in localized biliary tract cancers with either an R0 or R1 resection. Ampullary cancers were excluded. The primary endpoint was DFS. One hundred and ninety-five patients were included in the analysis, 95 of whom received GEMOX, with 99 randomized to surveillance. Fifteen percent were R1 and 37% N+, with numbers balanced between both arms. Approximately 45% of those included in this trial were intrahepatic CCA. There was no observed statistical difference in DFS between the two arms, with the median DFS 30.4 months (95%CI: 15.4-43.0) with GEMOX and 18.5 months with surveillance (95%CI: 12.6-38.2) (log-rank P = 0.47). No difference in DFS was observed between GEMOX and surveillance in both R0 (HR = 0.881, 95%CI: 0.599-1.296) and R1 (HR = 0.833, 95%CI: 0.352-1.972) subgroup analysis. The median OS was 75.8 months (95%CI: 34.4-not estimable) *vs.* 50.8 months (95%CI: 38.0-not estimable) (HR = 1.08, 95%CI: 0.7-1.66, P = 0.74). The 2-year OS was 69% *vs.* 76%, respectively. No difference was observed regarding OS between GEMOX and surveillance in both R0 (HR = 1.03, 95%CI: 0.635-1.671) and R1 (HR = 1.203, 95%CI: 0.446-3.244) subgroup analysis. Subgroup analysis did not suggest any anatomical site benefited from GEMOX, with DFS (HR = 2.559, 95%CI: 1.037-6.318, P = 0.034) and OS (HR = 3.39, 95%CI: 1.169-9.83, P = 0.017) worse in GBC. The number of metastatic recurrences recorded was 41 (75%) and 43 (71%), respectively. N+ (HR = 2.31, 95%CI: 1.53-3.5, P < 0.001) and R1 (HR = 1.99, 95%CI: 1.13-3.5, P = 0.017) were both identified as independent predictors of worse survival in a multi-variate analysis. Despite a numerical benefit, the authors argued that this was a negative trial rather than underpowered and that with an OS hazard ratio of 1.08, the results did not suggest a trend towards benefit.

BILCAP (2019; EudraCT 2005-003318-13) is the largest phase III study completed, registering 430 patients with CCA or muscle-invasive GBC[43]. Patients were randomized to either capecitabine (n = 210) or surveillance (n = 220). Seventeen patients were excluded after randomization. Thirty-eight percent of patients were R1 and 47% N+. In the intention-to-treat analysis the median OS was 51.1 months (capecitabine) *vs.* 36.4 months (HR = 0.81, 95%CI: 0.63-1.04, P = 0.097) while the median DFS was 24.4 months *vs.* 17.5 months (adjusted HR = 0.75, 95%CI: 0.58-0.98, P = 0.033). The per-protocol analysis median OS was 53.0

(capecitabine) *vs.* 36.0 months (adjusted HR = 0.75, 95%CI: 0.58-0.97, *P* = 0.028) and the median DFS 25.9 months *vs.* 17.4 months, respectively (adjusted HR = 0.70, 95%CI: 0.54-0.92, *P* = 0.0093). No OS benefit was observed with adjuvant capecitabine compared to surveillance in patients with an R1 resection (HR = 0.90, 95%CI: 0.63-1.29) in the intention-to-treat analysis, while R0 had an HR = 0.73 (95%CI: 0.51-1.04). Fifty-five percent of patients receiving capecitabine completed eight cycles, and 46% of those who commenced treatment had at least one dose reduction. It was argued that despite the intention-to-treat analysis not achieving statistical significance regarding OS, the secondary analyses suggested that capecitabine improved survival outcomes. Adjuvant capecitabine is today accepted as a standard of care in many countries and guidelines[44] and has become the control arm on most newer randomized trials.

The phase II trial SWOG S0809 investigated gemcitabine plus capecitabine followed by chemoradiotherapy with capecitabine, and while only a single arm has been influential[45]. Seventy-nine patients received chemotherapy, with 69 completing the subsequent chemoradiotherapy. The median OS was 34 months for R0 and 35 months for R1, with the 2-year OS 67% and 60%, respectively. Median DFS was 26 months for R0 and 23 months for R1, with the 2-year DFS 54% and 48%, respectively. Thus, this trial suggested that survival outcomes of the poor prognostic R1 disease group may be improved in-line with R0 survival outcomes with the addition of chemoradiotherapy. Unfortunately, a search of clinicaltrials.gov and clinicaltrialsregister.eu using the search terms "cholangiocarcinoma" or "biliary" and "adjuvant" did not identify this specific trial design has progressed to an active or completed phase III clinical trial.

Ongoing adjuvant clinical trials

There are presently 15 ongoing clinical trials investigating adjuvant chemotherapy in biliary tract cancers [Table 2]. Four separate trials are comparing cisplatin plus gemcitabine to capecitabine [NCT02778308 (India), NCT02548195 (China), NCT02170090/EudraCT 2012-005078-70 (ACTICCA-1) (global), and NCT03079427 (Korea)]. These trials compare cisplatin plus gemcitabine, the current standard-of-care treatment in advanced/metastatic biliary tract cancers, as per ABC-02 to capecitabine. ACTICCA-1also includes a second randomization in R1 patients whereby chemoradiation is introduced to the treatment, replacing the final two (of eight) cycles of chemotherapy. This design has the potential to answer the chemo-intensification question and whether more tailored treatment for R1 cases improves outcomes. It has the distinction of being the largest adjuvant trial planned in biliary cancers and should give us clear answers. Also ongoing is a single phase II study investigating gemcitabine plus nab-paclitaxel (NCT04077983), a phase III study comparing gemcitabine plus capecitabine to single-agent capecitabine (NCT03779035), a Japanese trial is investigating adjuvant S-1 (UMIN000011688), and a trial investigating the benefit of adjuvant gemcitabine following liver transplantation is being performed in Germany (EudraCT 2010-020480-21). Additionally, following the observed results from SWOG S0809, a phase III clinical trial is proposed in China comparing adjuvant gemcitabine plus capecitabine with or without chemoradiotherapy in perihilar/distal CCA and GBC (NCT02798510). However, it is unclear if this trial has proceeded to recruitment. Three trials are investigating the combination of an anti-PD-1/PD-L1 monoclonal antibody with chemotherapy(s) (NCT04333927, NCT04782804, and NCT04295317). Clarity on the best approach awaits the completion and review of several of these important trials.

NEOADJUVANT AND DOWNSTAGING THERAPY

There has been a steady shift to neoadjuvant and perioperative chemotherapy in some gastrointestinal malignancies, including gastric[46] and locally advanced rectal carcinoma[47]. While improved OS is yet to be determined with neoadjuvant chemotherapy in pancreatic adenocarcinoma, an improved R0 rate, DFS, and locoregional failure-free interval have been observed with neoadjuvant FOLFIRINOX in borderline resectable pancreatic cancer[48]. Evidence supporting neoadjuvant chemotherapy as opposed to adjuvant

Table 2. Adjuvant chemotherapy clinical trials in progress

Trial ID/name	Location	Trial type	Tumor site	No. of patients	Intervention	Primary outcome	Status
NCT02170090; EudraCT 2012-005078-70 (ACTICCA-1)	Germany	Phase III	CCA, GBC	781	Cisplatin + gemcitabine + *vs.* capecitabine	DFS at 2 year	Recruiting
NCT03779035	China	Phase III	CCA, GBC	460	Gemcitabine + capecitabine *vs.* capecitabine	DFS at 2 year	Recruiting
UMIN000011688 (JCOG1202: ASCOT)[70]	Japan	Phase III	CCA, GBC, ampulla of Vater	440	S-1 24 weeks *vs.* surveillance	OS	Recruiting
NCT02548195	China	Phase III	iCCA	286	Cisplatin + gemcitabine *vs.* capecitabine	DFS	Unknown
NCT02798510	China	Phase III	GBC, pCCA, dCCA	140	Gemcitabine/capecitabine → CRT (capecitabine) → gemcitabine/capecitabine *vs.* gemcitabine/capecitabine	OS at 2 year	Unknown
NCT03079427	Korea	Phase II	pCCA + dCCA with regional LN metastases	100	Cisplatin + gemcitabine *vs.* capecitabine	2 year DFS	Recruiting
EudraCT 2010-020480-21	Germany	Phase II	iCCA	45	Gemcitabine post liver transplantation	Completion rate	Recruiting
NCT04333927	China	Phase II	CCA, GBC	92	Camrelizumab + CRT(capecitabine) *vs.* surveillance	OS 2 year	Active, not recruiting
NCT04295317	China	Phase II	iCCA	65	Anti-PD-L1 (SHR-1210) + capecitabine	DFS 2 year	Recruiting
NCT04077983	China	Phase II	iCCA	40	Gemcitabine + Nab-paclitaxel	DFS	Not yet recruiting
NCT04782804	China	Phase I-II	iCCA	30	Tislelizumab + capecitabine	DFS	Recruiting
NCT02778308	India	N/A	GBC	100	Cisplatin + gemcitabine *vs.* surveillance	DFS	Completed, not reported

As per clinicaltrials.gov and clinicaltrialsregister.eu on July 5 2021. CCA: Cholangiocarcinoma; GBC: gallbladder carcinoma; iCCA: intrahepatic cholangiocarcinoma; pCCA: perihilar cholangiocarcinoma; dCCA: distal cholangiocarcinoma; LN: lymph nodes; OS: overall survival; DFS: disease-free survival; AEs: adverse events; CRT: chemoradiotherapy.

chemotherapy is detailed in a retrospective series of 72 patients with resected intrahepatic CCA that indicated that as few as 35% of patients received adjuvant chemotherapy[49]. Furthermore, a review of 1450 patients with stage I-III CCA in the United States National Cancer Database by Yadav *et al.*[50] indicated that those who received neoadjuvant chemotherapy were more likely to attain an R0 resection compared to those who had upfront surgery followed by adjuvant chemotherapy (71.2% *vs.* 61.6%, $P = 0.02$).

There are no completed phase III randomized-control trials determining the survival benefit of neoadjuvant or downstaging chemotherapy, with evidence predominately obtained from retrospective analyses [Table 3]. All but two analyses assessed outcomes in patients with CCA considered unresectable at diagnosis. In addition, there are three reported non-randomized prospective studies. McMasters *et al.*[51] (1997) reported 9 patients who received external-beam radiation (EBRT) concurrently with fluorouracil prior to resection. An R0 resection was achieved in all patients, with a pathological complete response (pCR) reported in three[51], while Katayose *et al.*[52] (2015) reported on 24 patients with perihilar/distal CCA who received EBRT plus gemcitabine. An R0 resection was achieved in 80.9%. No survival outcomes were reported. The largest cohort is reported by Chaudhari *et al.*[53] (2018), who analyzed 160 patients with GBC treated at Tata Memorial Hospital in India between 2010 and 2016. All patients had locally advanced or borderline-resectable GBC and were treated with gemcitabine plus cisplatin or GEMOX. The median number of cycles administered was 4 (2-12) with an ORR of 52.5% (pCR 10.6%). Sixty-six (41.2%) patients

Table 3. Selected completed clinical trials of neoadjuvant or downstaging chemotherapy in biliary tract cancers

Study author	Year	Study type	Study arms	Tumor site	No. of patients	Resectability status presentation	Results			
							% R0	ORR	DFS	OS
McMasters *et al.*[51]	1997	Prospective (non-randomized)	EBRT (fluorouracil)	dCCA pCCA	4 5 (total 9)	Unresectable	100%	3 pCR	NA	NA
Nelson *et al.*[71]	2009	Retrospective	EBRT (fluorouracil) +/- brachytherapy	pCCA, dCCA	12	Unresectable	91.7%	3 pCR	NA	34 months
Jung *et al.*[72]	2017	Retrospective	Fluorouracil/gemcitabine + EBRT	pCCa	12	Unresectable	83.3%	NA	NA	NA
Katayose *et al.*[52]	2015	Prospective (non-randomized)	Gemcitabine + EBRT	dCCA, pCCA	24	Resectable	80.9%	NA	NA	NA
Kobayashi *et al.*[73]	2017	Retrospective	EBRT (gemcitabine) → surgery v surgery	pCCA, dCCA, GBC	106 (27 neoadjuvant CRT)	Resectable	NA	70%	3 year DFS 78% *vs.* 57%	3 year OS 85% *vs.* 69%
Kato *et al.*[35]	2013	Retrospective	Gemcitabine	iCCA	22	Unresectable	18%	37%	NA	45 months (resected)
Kato *et al.*[74]	2015	Retrospective	Cisplatin + gemcitabine	iCCA	39	Unresectable	26%	23%	NA	NA
Le Roy *et al.*[75]	2018	Retrospective	Gemcitabine + oxaliplatin	iCCA	74 (39 received surgery)	Unresectable	31%	24%	NA	24.1 months
Lunsford *et al.*[76]	2018	Prospective case series	Gemcitabine → liver transplant	iCCA	6	Unresectable	NA	NA	1 year 50%	5 year 83.3%
Chaudhari *et al.*[53]	2018	Prospective (non-randomized)	Cisplatin + gemcitabine OR gemcitabine + oxaliplatin	GBC	160	Unresectable	95% (63/66)	52.5%	25 months	49 months
Sumiyoshi *et al.*[34]	2018	Retrospective	IMRT (S-1)	iCCA pCCA	7 8	Unresectable	9/11 (both) (82%)	57% 37%	mDFS 21.5 months (4-40)	mOS 37 months (surgical pt)

CCA: Cholangiocarcinoma; GBC: gallbladder carcinoma; iCCA: intrahepatic cholangiocarcinoma; pCCA: perihilar cholangiocarcinoma; dCCA: distal cholangiocarcinoma; CRT: chemoradiotherapy; OS: overall survival; DFS: disease-free survival; AEs: adverse events; pCR: pathological complete response; EBRT: external-bean radiotherapy; IMRT: intensity-modulated radiotherapy.

were offered surgery, with an R0 resection achieved in 63. The remaining 94 patients either declined surgery or their tumors progressed. The median OS was 49 months, and median DFS 25 months in those who underwent curative surgery. In addition, 61 patients (92%) received adjuvant chemotherapy, with details regarding which chemotherapy prescribed was not provided.

The "Mayo protocol" included highly selected patients with unresectable perihilar CCA. Patients received neoadjuvant chemoradiotherapy followed by an orthotropic liver transplant. Chemoradiotherapy involved 45-55 Gy with concurrent fluorouracil for five weeks with maintenance capecitabine until transplant[54]. Analyses indicate improved locoregional control and a 5-year DFS of 60%-70% and OS of 82%[55].

Ongoing neoadjuvant and downstaging clinical trials

Currently, there are ten ongoing clinical trials identified investigating neoadjuvant and downstaging chemotherapy in biliary tract cancers, with these listed in Table 4. Four trials investigate outcomes in resectable intrahepatic CCA. NCT04546828 is a phase II study investigating cisplatin plus gemcitabine plus nab-paclitaxel, with the primary outcome the R0 rate. NCT04669496 is a phase II-III trial investigating GEMOX plus lenvatinib plus toripalimab, a PD-1 monoclonal antibody, with all patients receiving adjuvant capecitabine following resection. This is yet to commence recruitment. NCT04727541 is a phase II study investigating bintrafusp-alfa, a bivalent PD-L1/TGFβ trap fusion protein, with the primary outcome pathological response rate. NCT04523402 is a phase II study investigating GEMOX in intrahepatic CCA with high-risk lymph node metastases, with the primary outcome DFS. NCT03603834 is investigating modified FOLFOXIRI in resectable or potentially resectable CCA with ORR as the primary outcome.

There are three phase III trials currently underway. NCT04559139 is a global trial comparing neoadjuvant cisplatin plus gemcitabine prior to re-resection in patients with an incidentally identified GBC following cholecystectomy to adjuvant cisplatin plus gemcitabine. GAIN (NCT03673072/EudraCT 2017-004444-38) is a phase III trial comparing perioperative cisplatin plus gemcitabine prior to re-resection of incidentally diagnosed GBC following cholecystectomy or in patients with CCA, to surgery, with all patients receiving adjuvant chemotherapy (investigators choice)[56].

There are two clinical trials underway investigating downstaging chemoradiotherapy in upfront unresectable disease. POLCAGB (CTRI/2016/08/007199/NCT02867865) is a phase II-III clinical trial comparing neoadjuvant cisplatin plus gemcitabine to five weeks of chemoradiotherapy (45 Gy EBRT plus gemcitabine) followed by two cycles of cisplatin plus gemcitabine[57]. In addition, NCT04378023 is investigating chemoradiotherapy (50-54 Gy EBRT plus capecitabine) followed by cisplatin plus gemcitabine until liver transplant in unresectable hilar CCA.

There is currently one phase II trial (NCT04308174) investigating the addition of durvalumab, a PD-L1 monoclonal antibody, to cisplatin plus gemcitabine in patients with localized CCA or GBC.

DISCUSSION

Cancers of the biliary tract are relatively rare, and consequently, it has been a challenge to perform phase III clinical trials investigating adjuvant and neoadjuvant therapy. Of the five phase III trials assessing the efficacy of adjuvant chemotherapy, four were considered negative. Both ESPAC-3 and the early phase III clinical trial by Takada *et al.*[39] investigating mitomycin C and fluorouracil were underpowered to draw significant conclusions regarding adjuvant therapy, specifically in biliary tract cancers. BCAT did not demonstrate a benefit with adjuvant gemcitabine in perihilar or distal CCA despite efficacy in metastatic biliary tract cancers. One explanation is that treatment completion was approximately 50%, with an average dose-intensity of 80%. Additionally, despite retrospective analyses and metanalyses suggesting a definite benefit in R1 and N+ cancers, this was not observed in BCAT, although the trial was not powered to demonstrate significance in this subgroup analysis. PRODIGE 12-ACCORD 18 has been the only phase III clinical trial to investigate a combination of gemcitabine and platinum chemotherapy as adjuvant treatment. With ABC-02 and BT22 demonstrating that combination gemcitabine and cisplatin improved ORR, progression-free survival, and OS in metastatic disease, the theory was that GEMOX would result in improved outcomes. Despite a numerically improved DFS and OS of 12 and 25 months, respectively, neither met statistical significance. The calculated HR for DFS was 0.88, well above the pre-planned 0.6, and the OS HR was greater than 1. This supports the argument that this was a truly negative trial as opposed to being underpowered. It is concerning that this randomized trial evaluating a chemotherapy dose intensity

Table 4. Neoadjuvant and downstaging clinical trials in progress

Trial ID/name	Location	Trial type	Tumor site	Resectability status	No. of patients	Intervention	Primary outcomes	Status
NCT03673072; EudraCT 2017-004444-38 (GAIN)[56]	Germany	Phase III	GBC, CCA	Incidental diagnosis post cholecystectomy	300	Cisplatin + gemcitabine v nil (×3 cycles) → surgery → +/- adjuvant cisplatin + gemcitabine (×3 cycles)	OS	Recruiting
CTRI/2016/08/007199; NCT02867865 (POLCAGB)[57]	India	Phase II-III	GBC	Unresectable without evidence of distant metastases	314	Cisplatin + gemcitabine v CRT (gemcitabine) → cisplatin + gemcitabine	OS	Recruiting
NCT03603834	Thailand	Phase II	CCA	Resectable OR potentially resectable	25	mFOLFOXIRI	ORR	Recruiting
NCT04308174 (DEBATE)	Korea	Phase II	CCA, GBC	Resectable	45	Durvalumab + cisplatin + gemcitabine v cisplatin + gemcitabine	R0 rate	Recruiting
NCT04546828	Korea	Phase II	iCCA with high risk recurrence features	Resectable	34	Cisplatin + gemcitabine + nab-paclitaxel	RO rate	Not yet recruiting
NCT04669496	China		iCCA with high risk recurrence features	Resectable	178	Gemcitabine + oxaliplatin + lenvatinib + toripalimab → surgery → adjuvant capecitabine	Event-free survival	Recruiting
NCT04559139	USA	Phase II-III	Incidental GBC	Incidental diagnosis post cholecystectomy	186	+/- neoadjuvant cisplatin + gemcitabine → revision surgery → adjuvant cisplatin + gemcitabine	OS (5 year)	Recruiting
NCT04727541	Germany	Phase II	CCA, GBC	Resectable	24	Bintrafusp-alfa ×2 doses	Pathologic response rate	Not yet recruiting
NCT04378023	Spain	Phase IV	pCCA	Unresectable	34	EBRT + capecitabine → cisplatin + gemcitabine until transplant	OS at 1, 3 and 5 year	Recruiting
NCT04523402	China	Phase II	iCCA with high-risk LN metastases	Resectable	100	Gemcitabine + oxaliplatin	Event-free survival (24 months)	Not yet recruiting

As per clinicaltrials.gov and clinicaltrialsregister.eu on July 5 2021. High risk LN features include tumor > 5 cm, vascular invasion, multiple tumor nodules, and hilar lymph node metastases. CCA: Cholangiocarcinoma; GBC: gallbladder carcinoma; iCCA: intrahepatic cholangiocarcinoma; pCCA: perihilar cholangiocarcinoma; OS: overall survival; CRT: chemoradiotherapy; EBRT: external-beam radiotherapy; mFOLFOXIRI: fluorouracil + oxaliplatin + irinotecan; ORR: overall response rate; LN: lymph node.

strategy was negative. Significant clinical and genetic heterogenicity exists between tumors of the biliary tract[15,24]. The results of PRODIGE 12-ACCORD 18 may reflect this heterogenicity across biliary tract cancer subsites with differing benefits to systemic therapies not appreciated in the subgroup analysis of this smaller trial.

BILCAP, while not achieving its primary outcome in the intention-to-treat population, did demonstrate an improved OS effect size of 14.7 months and statistically significantly improved survival in the per-protocol analysis. Like BCAT, treatment compliance was a challenge, with only 55% of patients completing the proposed eight cycles and 46% requiring at least one dose reduction. This completion rate is significantly lower than that observed in adjuvant

colorectal trials highlighting the potential changed pharmacokinetics and chemotherapy tolerance following partial hepatectomy[58]. BILCAP included all biliary tract cancers except ampullary carcinomas and mucosal GBC, with this heterogenicity again potentially blunting the observed effect of adjuvant capecitabine. While there was an equal distribution between treatment arms, there are relative differences in biliary subtypes compared to some other trials, as detailed in Table 1 that may be important. Pending further data, adjuvant capecitabine has been adopted as the standard of care in many guidelines. With the current standard of care in metastatic biliary tract cancers cisplatin plus gemcitabine, the outcomes of large trials comparing cisplatin plus gemcitabine to capecitabine are eagerly awaited.

In all described adjuvant trials, anatomical subtypes were combined for analysis. BILCAP and BCAT had a relatively even distribution amongst all eligible anatomical subtypes, whereas PRODIGE 12-ACCORD 18 was predominately intrahepatic CCA, with 20% GBC. Subgroup analysis in these trials demonstrated differences in survival relative to anatomical subtype, particularly in PRODIGE 12-ACCORD 18, in which GBC exhibited a poorer survival with chemotherapy than surveillance. Therefore, it is likely that the mixing of distinctly different histological and genetic subtypes limits the interpretation of survival benefits with adjuvant chemotherapy.

Consistently across all trials, patients with R1 resections were observed to have poorer survival outcomes. In PRODIGE 12-ACCORD 18, the DFS and OS hazard ratios for R1 patients who received GEMOX were similar to that of surveillance, an observation reiterated for OS in BILCAP. SWOG S0809 demonstrated that with the addition of chemoradiotherapy, R1 tumors could potentially achieve comparable DFS and OS to that in R0 tumors. This suggests that R1 tumors specifically may benefit from adjuvant chemoradiotherapy in addition to chemotherapy. The ACTICCA-1 trial, which is currently recruiting with an estimated study completion early 2023, may go some way to answer this.

In respect to neoadjuvant chemotherapy, current evidence is sourced from retrospective analyses and three phase II trials. The population is highly selected in these analyses and is generally considered unresectable at diagnosis. With satisfactory R0 resection rates reported, there is a suggestion that systemic chemotherapy may have a role in downstaging a tumor to enable an attempt at curative resection. However, completion of the neoadjuvant trials currently underway is required to draw any further conclusions. The benefit of neoadjuvant chemotherapy on survival outcomes in those considered resectable at diagnoses remains less clear.

The survival benefits of anti-PD-1 and PD-L1 monoclonal antibodies in both adjuvant and neoadjuvant treatment remain unanswered. While there is minimal evidence of a significant ORR in metastatic biliary tract cancers, particularly with single agent treatment, the IMbrave150 clinical trial demonstrated a significantly improved OS in hepatocellular carcinoma with atezolizumab plus bevacizumab, offering hope that immunotherapy, particularly in combination with other targeted agents or chemotherapy may improve outcomes[59,60]. Furthermore, at this point, while targeted therapies such as FGFR inhibitors show promise in metastatic intrahepatic CCA[61], evidence is lacking to support their use in either adjuvant or neoadjuvant treatment. Targeted treatment is attractive but establishing the optimal standard of care with chemotherapy remains an unanswered and more pertinent question. Chemotherapy should then also serve as the backbone on which to add or compare with targeted agents.

CONCLUSION

Biliary tract cancers are a heterogenous group of cancers. Few phase III adjuvant trials have been completed, with only BILCAP suggesting a survival benefit with capecitabine. Several trials are ongoing, including

ACTICCA-1 comparing capecitabine to gemcitabine and cisplatin, the current standard of care in advanced and metastatic disease. This trial has the added possibility of demonstrating benefit with chemoradiotherapy in R1 disease. While evidence exists suggesting systemic chemotherapy, either alone or in combination with radiotherapy, may downstage unresectable biliary tracts cancers resulting in surgery, the benefit of neoadjuvant therapy in resectable tumors is less clear. What is evident in reviewing the literature is that significant improvements in the management of potentially curable biliary tract cancers have not been eventuated and that more work needs to be done. Given the rarity and difficulty in performing large, statistically powered clinical trials, collaborations between research groups around the world are necessary to drive an improvement in patient outcomes.

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