CURRENT ONCOLOGY
A Canadian Cancer Research Journal

ORIGINAL ARTICLE

A systematic review and network meta-analysis of adjuvant therapy for curatively resected biliary tract cancers

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ABSTRACT

Background Recent randomized controlled trials (RCTs) have contributed high-quality data about adjuvant therapy in curatively resected biliary tract cancer (BTC); however, a standard approach to treating those patients still has not been developed.

Methods We conducted a systematic review of published studies and abstracts up to and including June 2018, choosing RCTs involving patients with BTC receiving adjuvant chemotherapy after complete surgical resection. Network meta-analysis methods were used for indirect comparisons of overall survival (OS) and relapse-free survival (RFS) for various adjuvant therapies.

Results Five RCTs were included in qualitative synthesis, and three RCTs (BILCAP, PRODIGE 12–ACCORD 18, and BCAT) had data sufficient for inclusion in the meta-analysis. Results from the indirect comparison demonstrated no significant improvement in OS for capecitabine compared with gemcitabine or with gemcitabine–oxaliplatin (GEMOX), the hazard ratios (HRs) being 0.82 [95% confidence interval (CI): 0.53 to 1.27] and 0.86 (95% CI: 0.56 to 1.34) respectively. Similarly, no significant improvement in RFS was observed for capecitabine compared with gemcitabine or GEMOX.

Conclusions Although in the present analysis, we found no statistically significant improvements in OS or RFS for capecitabine compared with GEMOX or gemcitabine, capecitabine can—until further prospective trials are completed—be considered the standard of care in the adjuvant setting based on a single randomized phase III study.

Key Words Biliary tract cancer, medical oncology, chemotherapy

Curr Oncol. 2020 February;27(1):e20–e26 www.current-oncology.com

INTRODUCTION

Biliary tract cancers (BTCs) are a rare group of cancers that include cholangiocarcinoma and gallbladder cancer. Cholangiocarcinoma can be further divided into intrahepatic, extrahepatic, or perihilar cholangiocarcinoma. The most common histologic type of BTC is adenocarcinoma, which arises from the epithelial cells of the biliary ducts and gallbladder. These tumours are aggressive malignancies that typically present at an advanced stage[1,2]. Prognosis is poor, the 5-year overall survival (OS) rate for BTC ranging from approximately 5% to 15% in the United States, with the survival rate for intrahepatic bile duct cancer being the lowest[3,4]. Although the BTC incidence is low (approximately 12,190 new cases in the United States annually), rates of bile duct cancer have been rising globally[3,5–7].

The mainstay of treatment for BTCs is surgical resection if possible, because surgery is the only curative treatment. However, few patients with BTC (<35%) are eligible for surgical resection because of anatomic limitations; and even after resection, relapse rates are high, with a 5-year survival rate of approximately 15%[6,8,9]. Available guidelines consider several options for patients after resection, including observation, adjuvant chemotherapy, or adjuvant chemoradiation[10]. However, because of the low incidence of BTC and the small percentage of patients eligible for resection, high-quality evidence to guide clinical decision-making for adjuvant therapy has been lacking, and guidelines are based largely on retrospective studies[6,11]. Consequently, no widely accepted standard adjuvant therapy for BTC is currently recommended.

Recently, results from a few phase III randomized trials evaluating the effect of adjuvant chemotherapy regimens

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Supplemental material available at http://www.current-oncology.com

compared with observation have been published. The phase III PRODIGE 12–ACCORD 18 trial found no significant difference in relapse-free survival (RFS) between adjuvant gemcitabine–oxaliplatin (GEMOX) and observation[12]. In an intention-to-treat (ITT) analysis, the BILCAP trial found no significant difference in OS for adjuvant capecitabine compared with observation in patients with resected BTC, but in a per-protocol analysis, found that, compared with observation, capecitabine was associated with a significantly improved OS[13]. A phase III trial in Japan also failed to show a significant difference in OS for adjuvant gemcitabine compared with observation in patients with resected BTC[14].

The foregoing studies have contributed high-quality data to the literature about adjuvant chemotherapy in resected BTC. However, the results of those randomized trials do not support a standard approach to patients with resected BTCs. The aim of the present study was therefore to use a network meta-analysis to compare the efficacy of chemotherapy regimens so as to help guide clinical decision-making and the design of future prospective randomized studies.

METHODS

Literature Search and Study Selection

For the systematic review, we searched the MEDLINE, EMBASE, and Cochrane databases; ClinicalTrials.gov; and American Society of Clinical Oncology meeting abstracts up to and including 28 June 2018. The systematic review is reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[15]. We searched "biliary tract cancer" and "adjuvant" and "chemotherapy" or "chemoradiation," and all relevant variations for those terms. Reference lists of pertinent articles were manually searched for additional studies. Two authors (MK, KP) independently examined the literature search results and included articles that met the eligibility criteria. If a discrepancy arose in the inclusion of an article, it was resolved by consensus between the 2 reviewers. If a consensus could not be reached, it was resolved by a 3rd reviewer. If articles were redundant, the most recent article was included in the meta-analysis.

Inclusion and Exclusion Criteria

Studies were included if they were phase III randomized controlled trials (RCTs) in patients with histologically proven BTC (including intrahepatic and extrahepatic bile duct cancer and gallbladder cancer) receiving adjuvant chemotherapy or chemoradiation after a complete surgical resection (R0 or R1). Trials were limited to those that included at least 1 of the outcomes of interest: OS and RFS. Any RCTs in patients with advanced or metastatic BTC, or in patients with other malignancies such as ampullary cancer, were excluded.

Data Extraction and Statistical Analysis

Data for OS and RFS were extracted. The primary outcome of interest was OS, defined as the time from randomization to death from any cause. The secondary endpoint was RFS, defined as the time from randomization to first clinical or radiologic sign of relapse. The hazard ratios (HRs) for OS and RFS, together with their 95% confidence intervals (CIs), were extracted from the articles if available. If HRs and CIs were not reported in the article, calculation of those values was attempted based on methods previously reported by Parmar *et al.*[16] and using the reported number of events and log-rank *p* values. For trials whose HRs and CIs could not be calculated, we requested further details from the first author.

The extracted CIs were used to calculate variance estimates. For the endpoints of OS and RFS, a random-effects model using HRs with 95% CIs measured the pooled effect[16]. Data were pooled using the Review Manager software application (RevMan 5.3: The Cochrane Collaboration, Copenhagen, Denmark) for pairwise direct meta-analysis (capecitabine vs. observation, GEMOX vs. observation, and gemcitabine vs. observation). For the indirect comparison (capecitabine vs. GEMOX), network meta-analysis methods to preserve within-trial randomization used the netmeta package for the R software application (version 3.3.1: The R Foundation for Statistical Computing, Vienna, Austria)[17–20]. The network meta-analysis was conducted in accordance with the good practice guidelines established by the International Society for Pharmacoeconomics and Outcomes Research[21]. The quality of the studies included in the meta-analysis was assessed using the Cochrane Risk of Bias tool[22].

RESULTS

Literature Search Results

Of 2014 records identified from the literature (Figure 1), 377 duplicates were removed. The remaining articles were then screened for relevancy. Based on pre-specified inclusion criteria, 1600 articles were excluded after titles and abstracts had been reviewed. A full-text assessment

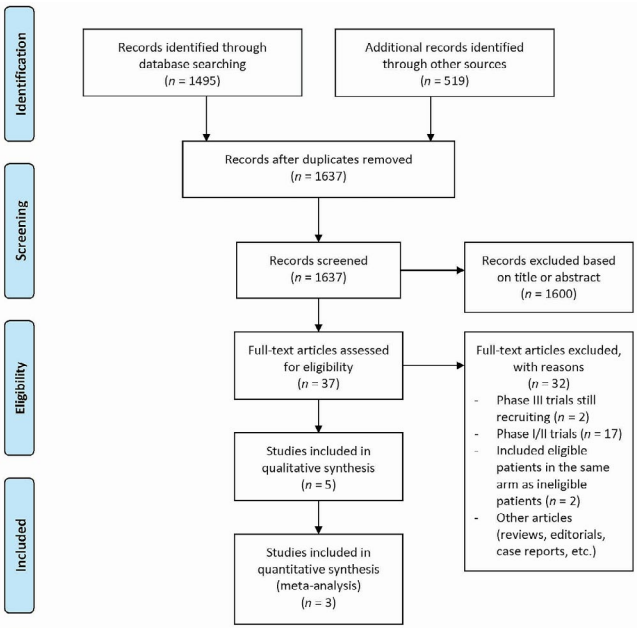

FIGURE 1 PRISMA flow diagram of the literature search.

was conducted for thirty-seven articles, of which two were excluded because they were phase III trials that had not yet reported data; seventeen, because they were phase I or II trials; two, because they included eligible patients in the same arm as ineligible patients; and eleven, because the article types were retrospective studies, reviews, and so on. The five RCTs that fulfilled the eligibility criteria were included in the review. Two of those studies lacked data sufficient to calculate the HRs for treatment effect in the eligible subgroups and were therefore eligible only for qualitative analysis. Three RCTs (the BILCAP, PRODIGE 12–ACCORD 18, and BCAT trials) contained data sufficient for inclusion in the meta-analysis. The studies included in the meta-analysis consisted of one full manuscript and two American Society of Clinical Oncology meeting abstracts.

Study Quality

Figure 2 shows the summary of the risk of bias for the included studies. All three studies included in the meta-analysis were centrally randomized, thereby minimizing selection bias. No studies explicitly mentioned allocation concealment. All three studies were open-label and not placebo-controlled, potentially introducing performance bias. It was not clear if any of the studies used blinded outcome assessors, and so detection bias for the endpoint of RFS could potentially be present. All trials performed ITT, minimizing attrition bias, but one trial (BILCAP) also reported a per-protocol analysis.

Trial Design and Characteristics

All three trials included in the meta-analysis included only patients who had histologically proven BTC and who underwent a curative resection (R0 or R1). All selected trials were superiority trials comparing an adjuvant chemotherapy regimen with observation (Table I). In the BILCAP and BCAT trials, the primary endpoint was OS. In the PRODIGE 12–ACCORD 18 trial, the co-primary endpoints were RFS and quality of life (QOL).

In the BILCAP trial, patients were either observed or received capecitabine 1250 mg/m^2 twice daily on days 1–14 of a 3-week cycle for a maximum of 8 cycles. In the PRODIGE 12–ACCORD 18 trial, patients were either observed or received gemcitabine 1000 mg/m^2 on days 1 and 8, and oxaliplatin 85 mg/m^2 on day 2 of a 2-week cycle for a maximum of 12 cycles. In the BCAT trial, patients were observed or received gemcitabine 1000 mg/m^2 on days 1, 8, and 15 of a 4-week cycle for maximum of 6 cycles. Overall, the trials enrolled 866 patients, of whom 431 underwent observation, 223 received capecitabine, 95 received GEMOX, and 117 received gemcitabine alone. Figure 3 shows the network of treatment comparisons.

Two additional trials met eligibility criteria for the present study, but were not included in the meta-analysis. The ESPAC-3 trial was a 3-arm open-label RCT comparing two chemotherapy regimens (fluorouracil–folinic acid or gemcitabine) with observation in patients with resected periampullary cancer[24]. Patients in the fluorouracil–folinic acid group received an intravenous bolus of folinic acid (20 mg/m^2) followed by an intravenous bolus of fluorouracil (425 mg/m^2) for 5 consecutive days of a 28-day cycle for a maximum of 6 cycles. Patients in the gemcitabine group received gemcitabine 1000 mg/m^2 once weekly for 3 weeks in a 4-week cycle for maximum of 6 cycles. In the study by Takada *et al.*[23], patients were observed or treated with rapid-infusion mitomycin C 6 mg/m^2 on the day of surgery and then 5 consecutive days of intravenous fluorouracil 310 mg/m^2 in weeks 1 and 3, followed by daily oral fluorouracil (100 mg/m^2) beginning in week 5 and continuing until disease recurrence.

Patient Characteristics

Baseline characteristics of patients in the BILCAP and PRODIGE 12–ACCORD 18 trials were similar, but in the BCAT trial, some differences were observed (Table II). The BILCAP and PRODIGE 12–ACCORD 18 trials included patients with intrahepatic and extrahepatic cholangiocarcinoma and gallbladder carcinoma; the BCAT trial included only patients with extrahepatic cholangiocarcinoma (distal bile duct and hilar). Compared with the other two trials, the BCAT trial had a greater proportion of men and a lower proportion of patients with an Eastern Cooperative Oncology Group performance status of 0. Median age of the patients was not explicitly stated in the BCAT trial.

Direct Analysis of Adjuvant Therapy Compared with Observation

The outcomes assessed in each of the trials were OS and RFS. The median OS and RFS durations reported in each of the included trials are presented in supplementary Table 1. Based on direct evidence in an ITT analysis, none of the trials found significant differences in OS. However, in a per-protocol analysis, the BILCAP trial found a significant improvement in OS in patients treated with capecitabine compared with those undergoing observation (HR: 0.75;

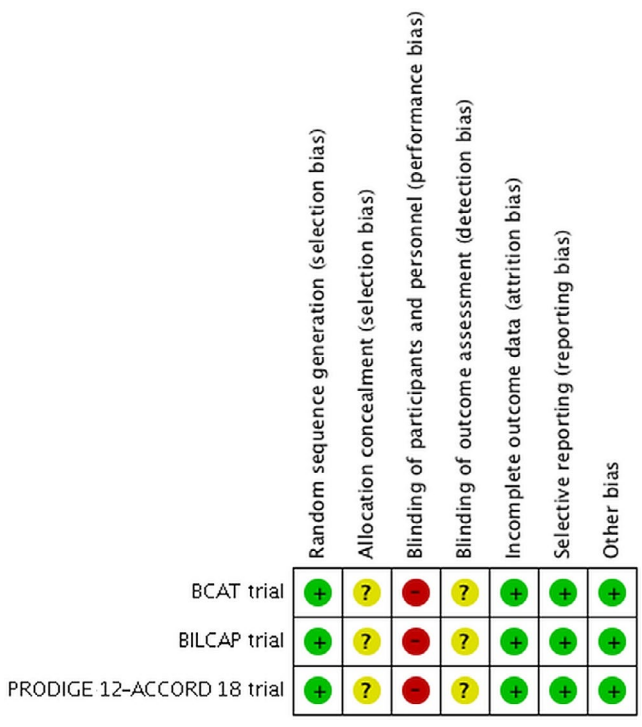

FIGURE 2 Risk-of-bias results for the trials included in the meta-analysis.

TABLE I Characteristics of the included randomized controlled trials

Trial	Outcomes		Trial type	Treatment	Eligible patients randomized
	Primary	Secondary			
BILCAP	OS	RFS, toxicity, QOL, health economics	Superiority	Capecitabine (1250 mg/m^2) twice daily on days 1–14 every 3 weeks for 8 cycles	223
				Observation	224
PRODIGE 12–ACCORD 18	RFS, QOL	OS, DFS, tolerance and toxicity, translational research	Superiority	Gemcitabine (1000 mg/m^2) day 1 and oxaliplatin (85 mg/m^2) day 2 every 2 weeks for 12 cycles	95
				Observation	99
BCAT	OS	RFS, subgroup analysis, and toxicity	Superiority	Gemcitabine (1000 mg/m^2) on days 1, 8, and 15 every 4 weeks for 6 cycles	117
				Observation	108
ESPAC-3	OS	Effect of the type of chemotherapy, toxicity, DFS, and QOL	Superiority	Folinic acid (20 mg/m^2) and fluorouracil (425 mg/m^2) for 5 days every 28 days for 6 cycles	31
				Gemcitabine (1000 mg/m^2) once weekly for 3 weeks of a 4-week cycle for 6 cycles	34
				Observation	31
Takada *et al.*, 2002[23]	Survival	DFS, ECOG PS, improvement in body weight, and adverse effects	Superiority	Mitomycin C (6 mg/m^2) on day of surgery, and intravenous fluorouracil (310 mg/m^2) for 5 consecutive days in weeks 1 and 3, followed by daily oral fluorouracil (100 mg/m^2) from week 5 until disease recurrence	65
				Observation	58

OS = overall survival; RFS = relapse-free survival; QOL = quality of life; DFS = disease-free survival; ECOG PS = Eastern Cooperative Oncology Group performance status.

95% CI: 0.58 to 0.97; Figure 4). Based on ITT and per-protocol analyses, the BILCAP trial also found a significant improvement in RFS, with HRs of 0.76 (95% CI: 0.58 to 0.99) and 0.71 (95% CI: 0.54 to 0.93) respectively. The other two trials did not demonstrate a significant improvement in RFS for adjuvant chemotherapy compared with observation (Figure 4).

In the ESPAC-3 trial, 31 patients with bile duct cancer were included in the observation group, 31 in the fluorouracil–folinic acid arm, and 34 in the gemcitabine arm. Median OS for patients with bile duct cancer was 27.2 months (95% CI: 15.4 to 31.9 months) in the observation group, 18.3 months (95% CI: 12.9 to 28.7 months) in the fluorouracil–folinic acid group, and 19.5 months (95% CI: 16.2 to 36.1 months) in the gemcitabine group.

In the study by Takada *et al.*[23], 34 patients had bile duct cancer, and 31 had gallbladder cancer. All underwent curative resection, followed by therapy with mitomycin C–fluorouracil (MF). The control group consisted of 38 patients with bile duct cancer and 20 patients with gallbladder cancer who underwent curative resection. For bile duct cancer, the 5-year survival rate was 41% in the MF group and 28.3% in the control group ($p = 0.4816$), and the 5-year disease-free survival rate was 32.4% in the MF group and 15.8% in the control group ($p = 0.2872$). For gallbladder cancer, the 5-year survival rate was 46.4% in the MF group and 30.9% in the control group ($p = 0.1517$), and the 5-year disease-free survival rate was 35.5% in the MF group and 25% in the control group ($p = 0.1179$).

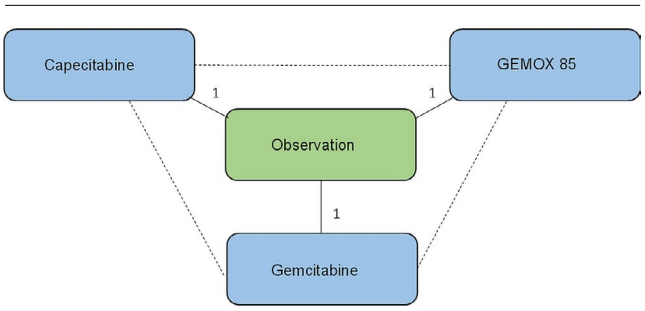

FIGURE 3 Network of treatment comparisons. Solid lines represent direct treatment comparisons; dashed lines represent indirect treatment comparisons. The numbers represent the number of studies included in the meta-analysis for each comparison.

Indirect Comparison of Adjuvant Therapies

The indirect comparison showed no significant difference in OS for capecitabine compared with gemcitabine or for capecitabine compared with GEMOX, with HRs of 0.80 (95% CI: 0.52 to 1.25) and 0.75 (95% CI: 0.46 to 1.24) respectively, based on the results of the ITT analysis from the BILCAP trial. Similarly, no significant difference in OS was demonstrated using the per-protocol analysis from the BILCAP trial (Figure 5).

No significant improvement in RFS was observed for capecitabine compared with either gemcitabine or GEMOX, with HRs of 0.82 (95% CI: 0.53 to 1.27) and 0.86 (95% CI: 0.56

to 1.34) respectively, based on the results of the ITT analysis from BILCAP (Figure 5). Similar results were observed using the per-protocol analysis from the BILCAP trial.

DISCUSSION

Our meta-analysis showed no statistically significant differences in OS or RFS between any of the analyzed adjuvant therapies. However, a trend was evident that favoured adjuvant capecitabine compared with either gemcitabine alone or GEMOX. We were not able to compare toxicity between the adjuvant regimens because of insufficient published toxicity data; however, all of the included trials reported manageable toxicity. Similarly, health-related QOL is an important goal of treatment, but we lacked data sufficient

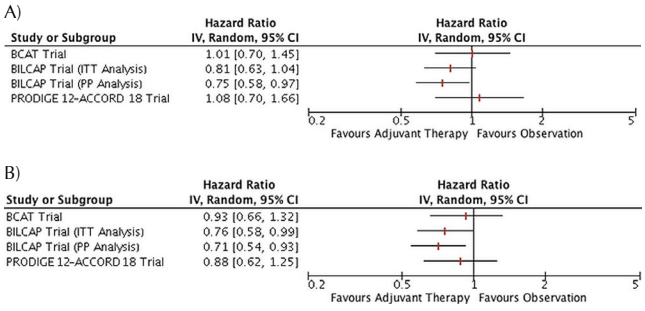

FIGURE 4 (A) Overall survival, direct analysis of adjuvant therapies compared with observation. (B) Relapse-free survival, direct analysis of adjuvant therapies compared with observation. IV = inverse variance; CI = confidence interval; ITT = intention to treat; PP = per-protocol.

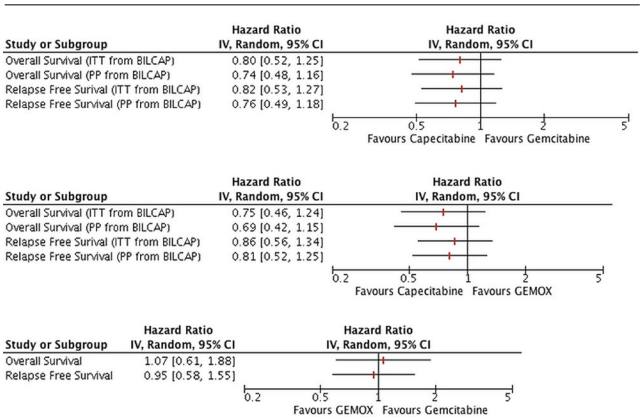

FIGURE 5 Overall survival and relapse-free survival, indirect analysis of adjuvant therapies. IV = inverse variance; CI = confidence interval; ITT = intention to treat; PP = per-protocol; GEMOX = gemcitabine–oxaliplatin.

TABLE II Baseline characteristics of the patients in the included randomized controlled trials

Characteristic	Trial					
	BILCAP		PRODIGE 12–ACCORD 18		BCAT	
	Capecitabine	Observation	GEMOX	Observation	Gemcitabine	Observation
Patients *(n)*	223	224	94	99	117	108
Sex [*n* (%)]						
Men	111 (50)	113 (50)	57 (60)	50 (50)	77 (65.8)	82 (75.9)
Women	112 (50)	111 (50)	38 (40)	49 (50)	40 (34.2)	26 (24.1)
Median age (years)	62	64	63	63	NR	NR
Tumour site [*n* (%)]						
Intrahepatic CC	43 (19)	41 (18)	41 (43)	45 (46)		
Hilar or perihilar CC	65 (29)	63 (28)	10 (11)	5 (5)	51 (43.6)	51 (47.2)
Muscle-invasive gallbladder carcinoma	39 (17)	40 (18)	17 (18)	21 (21)		
Lower common bile duct CC / distal CC	76 (34)	80 (36)	27 (28)	28 (28)	66 (56.4)	57 (52.8)
Resection status [n (%)]						
R0	139 (62)	140 (63)	82 (86)	88 (88)	106 (90.6)	94 (80.7)
R1	84 (38)	84 (38)	13 (14)	12 (12)	11 (9.4)	14 (13.0)
ECOG PS [*n* (%)]						
0	100 (45)	101 (45)	51 (54)	63 (64)	12 (10.3)	14 (13)
1	116 (52)	116 (52)	37 (39)	31 (31)	105 (89.7)	94 (87)
2	7 (3)	7 (3)	5 (5)	2 (2)		
Unknown			2 (2)	3 (3)		
Lymph node status						
N0	100 (45)	108 (48)	47 (49)	51 (51)	75 (64.1)	72 (66.7)
N+	108 (48)	102 (46)	35 (37)	36 (36)	42 (35.9)	36 (33.3)
Nx	15 (7)	14 (6)	13 (14)	12 (12)		

GEMOX = gemcitabine–oxaliplatin; NR = not reported; CC = cholangiocarcinoma; ECOG PS = Eastern Cooperative Oncology Group performance status.

to make indirect comparisons in QOL between treatments. The BILCAP and PRODIGE 12–ACCORD 18 studies both reported QOL scores that were similar in the adjuvant therapy and observation groups, and so the adjuvant therapies were unlikely to show a QOL difference.

In its per-protocol analysis, the BILCAP trial demonstrated improved OS with adjuvant capecitabine; however, in the ITT analysis, the improvement was not statistically significant. The PRODIGE 12–ACCORD 18, BCAT, ESPAC-3, and Takada *et al.*[23] trials all failed to show a significant improvement in OS or RFS with adjuvant chemotherapy in curatively resected cancers. The BILCAP trial is therefore considered to be the only positive phase III randomized trial in patients with resected BTC. Despite those findings, there is still no single recommended treatment plan for patients with BTC in the adjuvant setting. The European Society for Medical Oncology guideline states that adjuvant therapy—including radiotherapy, chemoradiotherapy, or chemotherapy—can be offered to patients with the understanding that the evidence is weak[10]. The National Comprehensive Cancer Network guideline suggests several options after R0 and R1 resections, including observation, fluoropyrimidine- or gemcitabine-based chemotherapy, fluoropyrimidine chemoradiation, and fluoropyrimidine- or gemcitabine-based chemotherapy with or without fluoropyrimidine chemoradiation[25]. The National Comprehensive Cancer Network guideline was revised after the BILCAP trial results were released; however, it notes that the OS improvement was observed only in the per-protocol analysis. Therefore, no consensus for optimal management has been achieved in the guidelines. Our network meta-analysis synthesized all available phase III data reported in the literature and confirmed that, based on the totality of the evidence, substantial uncertainty remains about the relative efficacy of capecitabine compared with gemcitabine or GEMOX in improving OS or RFS in patients with resected BTC. Those results highlight a need for further adequately powered prospective trials in such patients.

As outlined in a recent review of adjuvant therapy in BTCs, interpretation of the available data is difficult for a number of reasons, including heterogeneity of the study populations, varying chemotherapy regimens, and underpowered designs[26]. Certain subgroups might derive more benefit from adjuvant therapy. For example, in a meta-analysis of studies in patients with resected BTC, a significant increase in the survival benefit with adjuvant therapy was observed in patients with lymph node–positive disease[6]. An exploratory analysis of the BILCAP trial demonstrated that OS was worse in patients with nodal involvement than in patients without nodal involvement, although both groups derived a similar benefit from capecitabine[27]. The analysis also showed a trend of a lesser survival benefit from adjuvant capecitabine in female patients, patients who had an R1 resection, and patients with perihilar cholangiocarcinoma. Full publication of data from those trials will allow for further interpretation of subgroup data. In future prospective randomized trials, it would be useful to control for those prognostic factors.

More phase III randomized trials are being conducted to assess adjuvant chemotherapy regimens in patients with resected BTC, with results expected in a few years. The large, multinational ACTICCA-1 trial was originally designed to compare adjuvant gemcitabine–cisplatin with observation in patients after curative resection in BTC, but based on results from the BILCAP trial, it has since been amended to replace observation with adjuvant capecitabine in the control group[28]. That phase III trial will be the first to compare different chemotherapy regimens head-to-head, and it will help to guide clinical decision-making in the adjuvant setting. Additionally, a multicentre randomized phase III trial for patients with curatively resected BTC has been activated in Japan and will compare adjuvant S-1 therapy with observation alone[29].

Our study has some limitations. The indirect comparisons determined by network meta-analysis should be interpreted with caution. It should be noted that the BCAT trial contained only a subset of the types of patients included in the BILCAP and PRODIGE 12–ACCORD 18 trials because it did not include patients with gallbladder cancer or intrahepatic cholangiocarcinoma. Some clinical heterogeneity between the studies was found with respect to the survival outcomes in the control arms (supplementary Table 1). Median OS in the control group was highest in the BCAT trial. That observation could be explained by the location of the malignancy, because all patients the BCAT trial had either hilar or distal cholangiocarcinoma. Median OS was lower for patients in the BILCAP trial than for patients in the PRODIGE 12–ACCORD 18 trial, which could be explained by the higher proportion of patients with R1 resections and positive nodes in the BILCAP trial. Another limitation was the small number of studies included in the network analysis, which can be attributed to the lack of trials conducted in patients with resected BTC. Similarly, we were unable to compare toxicity of the therapies and their effects on QOL because of a lack of published data from the BILCAP and PRODIGE 12-ACCORD 18 trials.

CONCLUSIONS

We found no statistically significant improvements in OS or RFS for capecitabine compared with GEMOX or with gemcitabine alone. However, heterogeneity between the analyzed studies could have contributed to a lack of statistical significance. Given its clinically meaningful benefit in the BILCAP trial, adjuvant chemotherapy with capecitabine should be considered to be the current standard of care. Further prospective trials comparing adjuvant therapies with capecitabine in resected BTC are warranted and will help to elucidate a best standard of care. Because phase III trials are difficult to conduct because of the rarity of this disease, our results could—while results from prospective trials are awaited—be informative in terms of clinical decision-making.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

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REFERENCES

1. Anderson CD, Pinson CW, Berlin J, Chari RS. Diagnosis and treatment of cholangiocarcinoma. *Oncologist* 2004;9:43–57.
2. Prabhu RS, Hwang J. Adjuvant therapy in biliary tract and gall bladder carcinomas: a review. *J Gastrointest Oncol* 2017;8:302–13.
3. Ghouri Y, Mian I, Blechacz B. Cancer review: cholangiocarcinoma. *J Carcinog* 2015;14:1.
4. Howlader N, Noone AM, Krapcho M, *et al. SEER Cancer Statistics Review (CSR) 1975–2014*. Bethesda, MD: National Cancer Institute; 2018.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018;68:7–30.
6. Horgan AM, Amir E, Walter T, Knox JJ. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. *J Clin Oncol* 2012;30:1934–40.
7. Castro FA, Koshiol J, Hsing AW, Devesa SS. Biliary tract cancer incidence in the United States—demographic and temporal variations by anatomic site. *Int J Cancer* 2013;133:1664–71.
8. de Groen PC, Gores GJ, LaRusso NF, Gunderson LL, Nagorney DM. Biliary tract cancers. *N Engl J Med* 1999;341:1368–78.
9. Bridgewater JA, Stubbs C, Primrose JN on behalf of the National Cancer Research Institute Upper Gastrointestinal Studies Group. BILCAP: a randomized clinical trial evaluating adjuvant chemotherapy with capecitabine compared to expectant treatment alone following curative surgery for biliary tract cancer [abstract 4125]. *J Clin Oncol* 2011;29:. [Available online at: https://ascopubs.org/doi/abs/10.1200/jco.2011.29.15_suppl.4125; cited 6 January 2020]
10. Valle JW, Borbath I, Khan SA, Huguet F, Gruenberger T, Arnold D on behalf of the ESMO Guidelines Committee. Biliary cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016;27(suppl 5):v28–37.
11. Ghidini M, Tomasello G, Botticelli A, *et al.* Adjuvant chemotherapy for resected biliary tract cancers: a systematic review and meta-analysis. *HPB (Oxford)* 2017;19:741–8.
12. Edeline J, Bonnetain F, Phelip JM, *et al.* GEMOX versus surveillance following surgery of localized biliary tract cancer: results of the PRODIGE 12–ACCORD 18 (UNICANCER GI) phase III trial [abstract 225]. *J Clin Oncol* 2017;35:. [Available online at: https://ascopubs.org/doi/abs/10.1200/JCO.2017.35.4_suppl.225; cited 6 January 2020]
13. Primrose JN, Fox R, Palmer DH, *et al.* Adjuvant capecitabine for biliary tract cancer: the BILCAP randomized study [abstract 4006]. *J Clin Oncol* 2017;35:. [Available online at: https://ascopubs.org/doi/10.1200/JCO.2017.35.15_suppl.4006; cited 6 January 2020]
14. Ebata T, Hirano S, Konishi M, *et al.* on behalf of the Bile Duct Cancer Adjuvant Trial (BCAT) Study Group. Randomized clinical trial of adjuvant gemcitabine chemotherapy versus observation in resected bile duct cancer. *Br J Surg* 2018;105:192–202.
15. Moher D, Liberati A, Tetzlaff J, Altman DJ on behalf of the PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006–12.
16. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998;17:2815–34.
17. Salanti G, Higgins JP, Ades AE, Ionnidis JP. Evaluation of networks of randomized trials. *Stat Methods Med Res* 2018;17:279–301.
18. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ* 2005;331:897–900.
19. Neupane B, Richer D, Bonner AJ, Kibret T, Beyene J. Network meta-analysis using R: a review of currently available automated packages. *PLoS One* 2014;9:e115065. [Erratum in: *PLoS One* 2015;10:e0123364]
20. Rucker G, Schwarzer G. Automated drawing of network plots in network meta-analysis. *Res Synth Methods* 2016;7:94–107.
21. Hoaglin DC, Hawkins N, Jansen JP, *et al.* Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 2. *Value Health* 2011;14:429–37.
22. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Ver. 5.1.0 [updated March 2011]. Chichester, UK: The Cochrane Collaboration; 2011.
23. Takada T, Amano H, Yasuda H, *et al.* Is postoperative adjuvant chemotherapy useful for gallbladder carcinoma? A phase III multicenter prospective randomized controlled trial in patients with resected pancreaticobiliary carcinoma. *Cancer* 2002;95:1685–95.
24. Neoptolemos JP, Moore MJ, Cox TF, *et al.* on behalf of the European Study Group for Pancreatic Cancer. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. *JAMA* 2012;308:147–56.
25. National Comprehensive Cancer Network (NCCN). *NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancer*. Ver. 2.2018. Fort Washington, PA: NCCN; 2018. [Current version available online at: https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf (free registration required); cited 2 August 2018]
26. Horgan A, Knox J. Adjuvant therapy for biliary tract cancers. *J Oncol Pract* 2018;14:701–8.
27. Bridgewater JA, Fox R, Primrose JN. Exploratory analyses of the BILCAP study [abstract e16132]. *J Clin Oncol* 2018;36:. [Available online at: https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.e16132; cited 6 January 2020]
28. Stein A, Arnold D, Bridgewater J, *et al.* Adjuvant chemotherapy with gemcitabine and cisplatin compared to observation after curative intent resection of cholangiocarcinoma and muscle invasive gallbladder carcinoma (ACTICCA-1): a randomized, multidisciplinary, multinational phase III trial. *BMC Cancer* 2015;15:564.
29. Nakachi K, Konishi M, Ikeda M, *et al.* on behalf of the Hepatobiliary and Pancreatic Oncology Group of the Japan Clinical Oncology Group. A randomized phase III trial of adjuvant S-1 therapy vs. observation alone in resected biliary tract cancer: Japan Clinical Oncology Group Study (JCOG1202, ASCOT). *Jpn J Clin Oncol* 2018;48:392–5.