BMJ Open

Clinical efficacy of adjuvant treatments for patients with resected biliary tract cancer: a systematic review and network meta-analysis

Ye Chen,[1] Baoxia Zhang ,[2] Chang Liu,[2] Ye Cao,[3] Cheng Lyu,[2] Meng Qiu[1]

To cite: Chen Y, Zhang B, Liu C, *et al*. Clinical efficacy of adjuvant treatments for patients with resected biliary tract cancer: a systematic review and network meta-analysis. *BMJ Open* 2022;**12**:e051421. doi:10.1136/bmjopen-2021-051421

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-051421).

Received 19 March 2021
Accepted 13 March 2022

[1]Department of Medical Oncology, Cancer Center, Sichuan University West China Hospital, Chengdu, Sichuan, China
[2]Department of Medicine, CSPC ZhongQi Pharmaceutical Technology (Shijiazhuang) Co., Ltd, Shijiazhuang, China
[3]Department of Medicine, Ascentage Pharma (Suzhou) Co. Ltd, Suzhou, China

Correspondence to
Dr Meng Qiu;
qiumeng33@hotmail.com

ABSTRACT

Objective This study aimed to determine the benefits of adjuvant therapy in patients with resected biliary tract cancer (BTC) and identify the optimal adjuvant treatment scheme.

Design Systematic review and network meta-analysis.

Data sources Studies comparing different adjuvant therapies in patients with BTC were searched in PubMed, Embase, CINAHL, Cochrane Central Register of Controlled Trials and ClinicalTrials.gov databases from inception to December 2021. Additionally, the references were manually searched for the related literature.

Materials and methods Eligible studies were identified, and data were extracted independently by two authors. A random-effects network meta-analysis was performed using R software. The pooled outcomes of overall survival (OS) and disease-free survival (DFS) were measured using the combined HRs with 95% CIs.

Results Nineteen eligible studies reporting three types of adjuvant therapies were included in our network meta-analysis. Adjuvant radiotherapy (ART, HR 0.62; 95% CI 0.42 to 0.93), adjuvant chemoradiotherapy (ACRT; HR 0.71; 95% CI 0.54 to 0.83) and adjuvant chemotherapy (ACT; HR 0.84; 95% CI 0.68 to 0.98) were more effective in prolonging OS than that of observation, with no significant difference between the three adjuvant therapies. Moreover, the improvement in DFS was also found in ACRT and ACT compared with that of observation (HR 0.60; 95% CI 0.45 to 0.75; HR 0.82; 95% CI 0.68 to 0.97, respectively). Furthermore, ACRT obtained a slightly better DFS benefit compared with that of ACT (HR 0.73; 95% CI 0.53 to 0.95).

Conclusions Our primary results demonstrated that, compared with that of observation, ACRT and ACT after radical resection could provide better OS and DFS benefits in patients with BTC. However, ART only showed improvement in OS, but not in DFS. Due to the lack of head-to-head studies of ACT, ACRT and ART, the above results need to be further verified by prospective randomised controlled trials.

Strengths and limitations of this study

- ► This network meta-analysis compared the efficacy of three major types of adjuvant treatments for patients with biliary tract cancer (BTC) after radical resection.
- ► This review was conducted with a strict selection criterion to lower the risk of bias and increase the homogeneity, including only patients with negative resection margins (R0) or microscopic positive resection margins (R1), but not macroscopic involvement resections (R2), and excluding studies with unbalanced or unclear baseline profiles in age, sex, disease severity or residual tumour status.
- ► A comprehensive analysis was performed, including the transitivity assumption, local inconsistency of the model, global and local heterogeneity, sensitivity analysis, subgroup analysis, rank probability and publication bias.
- ► All studies regarding adjuvant radiotherapy (ART) and adjuvant chemoradiotherapy (ACRT) were retrospective studies, which were inherent to selection bias.
- ► Because of the small sample sizes of ART, the claim of optimal treatment for patients with BTC should be interpreted with caution. The optimal regimens and dosing schedules for adjuvant chemotherapy and ACRT need to be further explored.

INTRODUCTION

Biliary tract cancer (BTC) is classified into gallbladder cancer (GBC), intrahepatic cholangiocarcinoma (iCCA) and extrahepatic cholangiocarcinoma (eCCA), and eCCA is further subdivided into perihilar cholangiocarcinoma (pCCA or Klatskin tumour) and distal cholangiocarcinoma (dCCA).[1] BTC accounts for approximately 3% of digestive system cancers and 10%–15% of primary liver cancers.[2] The incidence of BTC is higher in Asian countries and lower in European countries, the USA and Australia; however, its incidence is increasing globally.[2 3] The vast majority (>90%) of BTC cases were adenocarcinoma. Moreover, most cases are usually in the advanced or metastatic stage at the initial diagnosis. Only approximately 20% of BTC cases are considered resectable.[4]

Surgical resection remains the primary curative treatment in patients with resected

BTC. However, the high recurrence rates (including locoregional or distant recurrence) and low survival rates (5-year survival rates of patients ranging from 5% to 15%) are prominent problems, even with complete (R0) resection.[4–8] Previously published studies have shown that histologic margin status, lymph node (LN) involvement and intrahepatic metastasis are the main prognostic factors.[9–11] Adjuvant chemotherapy (ACT), adjuvant radiotherapy (ART) and adjuvant chemoradiotherapy (ACRT) are the main options following resection for adjuvant therapy.

A variety of guidelines have suggested that postoperative adjuvant therapy could be considered an option for BTC patients.[12–15] The use of ACT and ACRT for patients with GBC and eCCA was supported by the National Comprehensive Cancer Network (NCCN) guidelines. Adjuvant capecitabine is recommended by the American Society of Clinical Oncology (ASCO) guidelines for patients with resected BTC for 6 months, based on the results of the BILCAP study, which showed a protocol-specified adjusted overall survival (OS) HR of 0.71 (95% 0.55 to 0.92).[16] However, some experts still hold reservations regarding the BILCAP study due to the underpowered statistical design and concerns over data maturity.[17] The discrepancy between the BILCAP study and the PRODIGE-12/ACCORD-18 studies also results in more discussions on the optimal scheme of adjuvant therapy.[18] Despite the tremendous effort, universal agreement on the optimal scheme of adjuvant therapy has not been established due to the lack of high-quality evidence.[19]

Moreover, conflicting results were also observed in the meta-analyses on this topic. A previous study by Rangarajan *et al* showed a significant improvement in OS with adjuvant therapy after resection compared with that of resection only.[20] In contrast, Horgan *et al* reported a non-significant improvement in OS with adjuvant therapy compared with that of observation in the overall population. However, a more significant benefit from adjuvant therapy was found in patients with positive LN involvement and R1 resection.[21] Three network meta-analyses of adjuvant therapies in patients with resected BTC have been published previously. One made comparisons among ACT, ACRT and resection only and did not consider ART.[22] One only summarised three randomised clinical trials (RCTs) covering three different ACT regimens, and the robustness of their results was limited due to the very small sample sizes.[23] A recent study indicated that ACRT could provide a survival benefit in patients with positive margins or nodal involvement, but the inclusion of patients with R2 margins is still debatable.[24]

Therefore, it is essential to perform a new network meta-analysis to elucidate the efficacy of adjuvant therapy and identify the optimal scheme of adjuvant therapy for patients with resected BTC.

METHODS

The study design was built in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyse extension statement for network meta-analysis for healthcare (online supplemental table 1).[25]

Search strategy

PubMed, Embase, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials. gov databases were searched from inception to December 2021 to find relevant literature using the main keywords “biliary tract cancer” and “adjuvant therapy.” In addition, references in the relevant literature were manually checked for potentially relevant papers. The detailed search strategy is presented in online supplemental table 2.

Selection criteria

Studies that met the following criteria were included: (1) those including patients with histologically or cytologically confirmed resected BTC and treated with adjuvant therapy or observation after curative-intent resection (defined as negative resection margins (RM, R0) or microscopic positive resection margins (R1), but not macroscopic involvement resections (R2)); (2) studies reporting at least one of the following clinical outcomes, OS or disease-free survival (DFS) and (3) studies with treatment and control arms.

Studies that involved the following were excluded: (1) studies including patients with ampullary carcinomas or other primary cancers or neoadjuvant therapy, palliative therapy or therapy after postoperative recurrence; (2) studies comparing the same type of adjuvant therapies; (3) those with unbalanced baseline profiles in age, sex, disease severity (American Joint Committee on Cancer staging) or residual tumour status; (4) reviews, conference abstracts, posters or case reports and (5) studies not written in English or without a full text, or with a small sample size (<10 in any group).

All study titles and abstracts were screened, and then the full texts of potentially eligible articles were sequentially assessed for final inclusion.

Data extraction and quality assessment

The following details were extracted from each study: author, study period, country, study type, sample size, tumour site (BTC type), disease severity, age, female sex (%), RM status, LN status, OS and DFS. OS was defined as the period from the date of surgery (or randomisation in RCTs) to the date of death (or last follow-up). DFS was defined as the time from the surgery date (or randomisation in RCTs) to recurrence of tumours (locoregional or distant). Moreover, the authors were contacted when there was confusion or missing data in any article. Data were excluded or not considered if no response was received.

The quality of the studies was assessed using the Newcastle-Ottawa Scale for observational studies, based

on the following domains: selection, comparability and outcome.[26] The detailed information can be found in online supplemental table 3. A study that scored 8–9 points, of which 2 points for comparability, is considered high quality; a score of 4–7 points indicates moderate quality and 0–3 means low quality. The Cochrane Risk of Bias Tool was used to grade the RCT quality.[27]

Two investigators (YCh and BZ) independently conducted the study selection and data extraction, and four authors (YCh, BZ, CLi and YCa) assessed the risk of bias of each eligible study. Discrepancies were resolved by consensus and arbitration by other investigators (CLu and MQ).

Data synthesis and statistical analysis

The primary outcomes were OS and DFS and measured using the HR with a 95% CI. When HRs and 95% CIs for OS and DFS were not reported in the original article, they were extracted from survival curves using Engauge Digitizer V.10.9 (2014 Mark Mitchell) and estimated by the method suggested by Tierney.[28]

A Bayesian network meta-analysis was performed using the R software (V.4.1.2, https://www.r-project.org/). Network plots were generated for different outcomes to clarify which treatments were compared directly or indirectly. A random-effects model (including subgroup analyses based on the RM status, tumour sites, regions and patients without distal metastasis) was used to compare all direct and indirect evidence using 'Rjags' and 'gemtc' packages in the R software. To fit the non-informative uniform and normal prior distributions, the parameters were set with four chains, 50 000 sample iterations (n.inter), and 20 000 burn-ins (n.adapt) with a thinning interval of 1. The convergence of the chains was assessed using the Gelman–Rubin statistics and inspection of the trace plots (online supplemental figure 1).[29 30] The deviance information criterion (DIC) was used to test the goodness of fit of consistent and inconsistent models.[31]

The transitivity assumption was evaluated by comparing the distribution of clinical variables (age, percentage of females, sample size, publication year, RM status, LN status), which could be effect modifiers. The local inconsistency of the model was evaluated using the node-splitting approach.[32 33] The global and local heterogeneity was assessed via between-study variance τ^2 and I^2 inconsistency statistic.[34–36] Heterogeneity was considered low, moderate, and high for estimated τ^2 or I^2 values <25%, between 25% and 50%, and larger than 50%, respectively. Within the Bayesian framework, the network meta-analysis provided a ranking probability of each treatment and estimated the overall rankings by calculating the surface under the cumulative ranking (SUCRA).[37 38] To assess the reliability of results, sensitivity analyses for OS and DFS were performed by excluding RCT studies, only including high-quality studies, and only including the studies for which HRs were reported in the original articles. The 'netmeta' package in the R software was used to generate the comparison-adjusted funnel plots to visualise publication bias. Egger's test was used to assess funnel plot asymmetry.[39 40] Values of p<0.05 were considered statistically significant. All statistical tests were two sided.

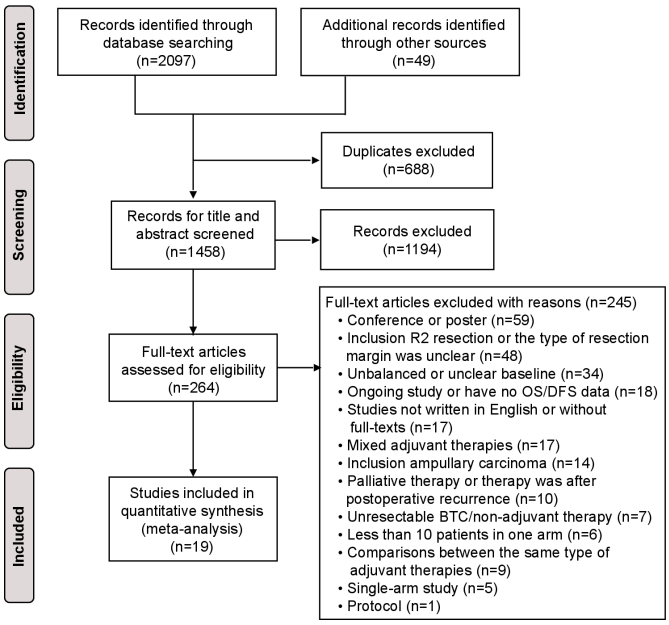

Figure 1 A PRISMA flow diagram of the study selection. BTC, biliary tract cancer; OS, overall survival; DFS, disease-free survival; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Patient and public involvement

Patients or the public were not involved in our research design, conduct, reporting or dissemination plans.

RESULTS

Characteristics of the included studies

A total of 2146 records were identified, including 49 records that were manually searched by reviewing the references of relevant publications. After reviewing the abstracts, 264 full-text articles were retrieved and reviewed after excluding 688 duplicates and 1194 ineligible records (figure 1). Nineteen studies comprising a total of 5595 patients who received one of the following four different treatments after radical resection—ACT, ART, ACRT and surgical resection alone (observation group)—were included in our analysis. It is worth noting that 34 studies[11 41–73] were excluded because of unbalanced or unclear baselines. Of the included patients, 2774 patients received adjuvant treatments following curative-intent resection, and 2821 patients underwent curative-intent resection without adjuvant treatments.

The main characteristics of the studies included in the network meta-analysis are presented in table 1. These 19 studies consisted of 3 RCTs[16 74 75] and 16 retrospective studies.[76–91] The patients of 6 studies[16 75 79 83 84 91] were Westerners (Americans, French and British) and 13 studies[74 76–78 80–82 85–90] were Asian (Japanese, Korean, Indian and Chinese). Four studies[80 87 88 91] assessed patients

Table 1 Characteristics of included studies

Studies	Country	Study period	BTC type	Disease severity	Therapy	Regimen of CT/ type of RT	Sample size	Margin status (R0/R1)	Nodal status (negative/ positive)	Female no (%)	Age, mean (SD/range), years	5-year OS (%); MOST (months)	5-year DFS (%); MDFST (months)
Characteristics of included observational studies													
ACT vs observation													
Kobayashi 2012[78]	Japan	1989–2010	CCA	I–IV	ACT	GEM/S–1	51	39/12	N0:26; N+: 25	28 (55)	–*	46.0; –	–
					Observation	–	54	37/17	N0:31; N+:23	14 (26)		23.0; –	
Morine 2017[81]	Japan	1995–2012	CCA/GBC	II–IVb (T1–T4)	ACT	GEM +5–FU+Cis	28	18/10	9/19	16 (57)	70.9 (±6.8)	44.2; –	–
					Observation	–	34	27/7	9/25	11 (32)	66.9 (±9.0)	5.9; –	
Akahoshi 2018[82]	Japan	2004–2015	CCA	0–IVa (T1–T4)	ACT	GEM	26	15/11	15/11	9 (35)	–*	–	25.6;–
					ACT	S–1	36	23/13	23/13	6 (17)			34.0;–
					Observation	–	36	23/13	25/11	13 (36)			26.8;–
Bergeat 2018[83]	France	2000–2015	dCCA	Ia–III	ACT	GEM	49	12/37	7/42	18 (37)	62.0 (36–77)†	–; 26.3	–; 15.5
					Observation	–	49	6/43	14/35	20 (41)	65.0 (35–82)†	–; 43.3	–; 14.7
Miyata 2021[90]	Japan	2007–2018	GBC/ pCCA/ dCCA	I–IV	ACT	S–1	38	29/9	N0: 21; N1: 17	13 (34)	72 (52–82)†	71.0; –	51.6; 61.2
					Observation	–	38	28/10	N0: 22; N1: 16	16 (42)	74 (42–85)†	42.9; 28.2	35.9; 13.1
ART vs observation													
Todorokia 2000[76]	Japan	1976–1999	pCCA (HDC)	IVa	ART	EBRT	17	All R1	N0:11; N1:2; N2:4	7 (41)	59.4 (34–76)	33.9‡; 32.0	–
					Observation	–	19		N0:7; N1:4; N2:8	5 (26)	60.6 (19–82)	13.5 ‡; 10.0	
Jiang 2010[86]	China	1998–2008	iCCA	–	ART	EBRT	24	–	N1: 8; Nx: 16	7 (29)	–*	11.9; 19.1	–
					Observation	–	66		N1: 23; Nx: 43	31 (47)		9.5; 1.5	
Zheng 2018[85]	China	2007–2016	iCCA	I–IVa	ART	IMRT	26	14/12	22/4	10 (38)	57.2 (45–76)	55.0 ‡§; 19.1 ‡	44.0 §;–
					Observation	–	23	9/14	17/6	8 (35)	55.6 (36–72)	20.0‡§; 9.5 ‡	10.0 §;–
ACRT vs observation													
Kim 2011[77]	Korea	2001–2009	eCCA	Ib, IIa, IIb	ACRT	5–FU/Leu/ Cap+EBRT	75	58/17	N0: 39; N+: 36	17 (23)	60.6 (37–74)	41.1 §;–	37.4 §;–
					Observation	–	34	28/6	N0: 26; N+: 8	30 (9)	65.0 (44–85)	35.3 §;–	29.8 §;–
Dover 2016[79]	USA	2000–2013	CCA	I–IV	ACRT	GEM/5–FU+EBRT	23	11/12	N0: 13; N+: 10	10 (43)	62.0 (38–80)	–; 30.2	–; 21.6
					Observation	–	72	56/16	N0: 51; N+: 21	28 (39)	65.0 (39–86)	–; 26.3	–; 17.3

Continued

Table 1 Continued

Studies	Country	Study period	BTC type	Disease severity	Therapy	Regimen of CT/ type of RT	Sample size	Margin status (R0/R1)	Nodal status (negative/ positive)	Female no (%)	Age, mean (SD/range), years	5-year OS (%); MOST (months)	5-year DFS (%); MDFST (months)
ACRT vs ACT													
Gu 2017[87]	China	2003–2013	GBC	II–IVa	ACRT	Cap/S–1/Ox +5–FU/Cap/GEM +EBRT	39	All R0	–	29 (74)	61 (35–77)	42.4; 27	48.7; 23
					Observation	–	39			26 (67)	63 (45–85)	17.9; 13	13.5; 7
Hester 2018[84]	USA	2004–2013	dCCA	I–IV	ACRT	–	348	258/76	N0:126; N+:211	135 (39)	64.3 (±10.0)	31.3 §; 32.1	–
					ACT		348	256/78	N0:118; N+:206	136 (39)	64.4 (±10.8)	29.4 §; 29.5	
Choudhary 2019[88]	Indian	2008–2017	GBC	II– III	ACRT	GEM+Cis +EBRT/3DCRT/ IMRT	23	17/2 (Rx:4)	–	20 (87)	55 (24–73)*†	–	–
					ACT	GEM+Cis	20	16/2 (Rx:2)		17 (85)			
Multiple comparison													
Kim 2016[80]	Korea	2000–2015	GBC	I–IV	ACT	GEM/Cis/OTHs	61	54/7	N0:21; N1/ Nx:36/4	42 (69)	64.5 (56–73)	Total: 33.0 §; 28.3	Total: –; 19.8
					ACRT	–	44	36/8	N0:15; N1/ Nx:24/5	28 (64)	63.9 (55–70)		
					Observation	–	186	159/25	N0:105; N1/ Nx:50/31	122 (66)	67.7 (56–74)		
Im 2021[89]	Korea	2001–2017	pCCA	II–IVa	ACT	5–FU/GEM based	45	31/14	–	22 (33)	65 (32–82)*†	38.9; –	24.6; –
					ART	EBRT/IMRT	16	2/14		10 (63)		8.2; –	5.6; –
					ACRT	5–FU/GEM based +EBRT/IMRT	16	5/11		4 (19)		49.4; –	40.4; –
					Observation	–	37	25/12		35 (38.9)		27.0; –	24.5; –
Wan 2021[91]	USA (SEER database)	1973–2015	GBC	II–IV	ACT	–	444	–	N0: 162; Nx: 282	311 (70)	–*	38.9/15.0; –	–
					ACRT		542		N0: 156; Nx: 386	374 (69)		41.5/21.1; –	
					Observation		1703		N0: 961; Nx: 742	1192 (70)		32.8/11.3; –	
Characteristics of included RCT studies													
Ebata 2018[74]	Japan	2007–2011	pCCA/ dCCA	I–III (T1–T4)	ACT	GEM	117	106/11	N0: 75; N1: 42	40 (34)	–*	51.7; 62.3	45.0; 36.0
					Observation	–	108	94/14	N0: 72; N1: 36	26 (24)		51.6; 63.8	44.0; 39.9
Edeline 2019[75]	France	2009–2014	CCA/GBC	I–IV (T1–T4)	ACT	GEMOX	95	82/13	N0:49; N+:35; Nx:11	38 (40)	63.0 (33–83)†	60.0 ‡; 75.8	–; 30.4
					Observation	–	99	87/12	N0:48; N+:36; Nx:15	49 (50)	63.0 (40–80)†	65.0 ‡; 50.8	–; 18.5

Continued

Table 1 Continued

Studies	Country	Study period	BTC type	Disease severity	Therapy	Regimen of CT/ type of RT	Sample size	Margin status (R0/R1)	Nodal status (negative/ positive)	Female no (%)	Age, mean (SD/range), years	5-year OS (%); MOST (months)	5-year DFS (%); MDFST (months)
Primrose 2019[16]	UK	2006–2014	BTC	I–IV	ACT	Cap	223	139/84	N0: 121; N1: 102	112 (50)	62.0 (55–68)	25.1¶; 51.1	–; 24.4
					Observation	–	224	140/84	N0: 115; N1:108	112 (50)	64.0 (55–69)	20.5¶; 36.4	–; 17.5

–Indicates that the data was not given originally.
*Indicates that studies were presented as younger or older than a specific age.
†Indicates that median age was given instead of mean age.
‡Indicates a 3-year OS or DFS.
§Indicates that the method of the value calculated is unclear.
¶Indicates overall survival rates but not survival probability.
ACRT, adjuvant chemoradiation therapy; ACT, adjuvant chemotherapy; ART, adjuvant radiotherapy; BTC, biliary tract cancer; Cap, capecitabine; CCA, cholangiocarcinoma; Cis, cisplatin; CT, chemotherapy; dCCA, distal cholangiocarcinoma; 3DCRT, three-dimensional conformal radiotherapy; EBRT, external beam radiotherapy; eCCA, extrahepatic cholangiocarcinoma; 5-FU, 5-fluorouracil; GBC, gallbladder cancer; GEM, Gemcitabine; GEMOX, gemcitabine and oxaliplatin; iCCA, Intrahepatic cholangiocarcinoma; IMRT, intensity-modulated radiotherapy; Leu, Leucovorin; MDFST, median DFS time; MOST, median OS time; N+, positive lymph node; Nx, unclear; OTHs, others; Ox, oxaliplatin; pCCA, Perihilar cholangiocarcinoma (or hepatic duct carcinoma=HDC); R0, negative resection margin; R1, microscopic positive resection margin; RCT, randomised clinical trial; RT, radiotherapy; Rx, unknown; S-1, tegafur gimeracil oteracil potassium; Total, means the value of all patients in the study; 5-year DFS (%), 5-year disease-free survival probability; 5-year OS (%), 5-year overall survival probability.

with GBC, and 11 studies[74 76–79 82–86 89] assessed patients with CCA. Of the 11 studies, 2 studies[85 86] particularly examined the outcomes of iCCA, and 6 studies[74 76 77 83 84 89] examined the outcomes of eCCA, including pCCA[76 89] and dCCA.[83 84] In the remaining four studies,[16 75 81 90] the BTC subtypes involved were varied.

The quality assessment of 16 retrospective studies is listed in online supplemental table 4), which shows that 12 studies[76–78 81–85 87 89–91] were judged to be of high quality, and 4 studies[79 80 86 88] were judged to be of moderate quality. Of these studies, four were assigned only one star in 'comparability' due to the unreported RM[79 86] or LN status.[80 88] Ten studies obtained 0 star in item 8 in relation to 'outcome' due to the inadequacy of follow-up.[77 79–84 86–88 90] Online supplemental figure 1) summarises the risk of bias assessments of three RCTs. All three RCTs were conducted in an open-label fashion, one[75] did not reveal the details of allocation concealment, and all were at low risk of bias in the domains of 'random sequence generation,' 'incomplete outcome data' and 'other bias'.

Transitivity, heterogeneity and inconsistency assessment

The transitivity assumption was assessed across treatments in our network. Patient characteristics that are known modifiers of treatment efficacy, such as age, percentage of female participants, sample size, publication year, RM status and LN status, were evaluated and visualised using box plots (online supplemental figure 2). No difference in these characteristics was observed between the different therapies (online supplemental table 5). Therefore, the transitivity assumption was ensured in this network.

Heterogeneity was also evaluated between eligible studies. Low global heterogeneity was detected in the OS, with I^2=0.0% for a pairwise effect and I^2=19.4% for a consistency effect and τ^2=0.022 for the between-study variance (online supplemental table 6). Minimal global heterogeneity was seen in the DFS, with I^2=0.0% for a pairwise pooled effect and a consistency effect (online supplemental table 6). High local heterogeneities were detected in the OS for the direct comparison of ART vs observation and the DFS for the direct comparison of ACRT vs observation, with I^2=81.9% and 82.2%, respectively, for the pooled network effect.

The local inconsistency was evaluated by comparing the corresponding pooled HRs of OS and DFS after comparing the results from pairwise and network meta-analyses. Statistical inconsistency between the direct and indirect evidence after node-splitting was not found, except for the comparison of ACRT vs ART ($p<0.001$) and ACT vs ART (p=0.001) in OS and ACRT vs ART (p=0.009) in DFS, owing to the fact that only one study contained OS and DFS data comparing ACRT vs ART and ACT vs ART (online supplemental table 7).

To further check the consistency at the treatment level, the goodness of fit of the inconsistency model (unrelated mean effects model, UME) was compared with that of the consistency model. The DICs of the consistency model

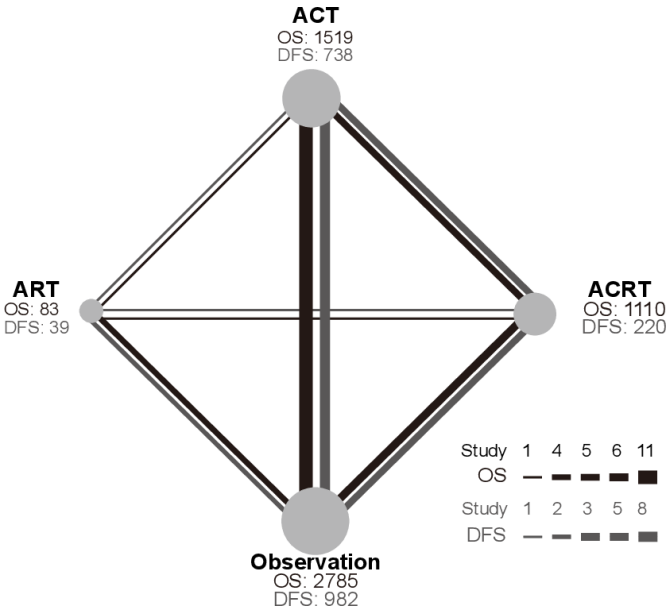

Figure 2 Network plot of comparisons on overall survival (OS) and disease-free survival (DFS) of treatments in patients with biliary tract cancer. Each circular node represents a type of treatment. The node size corresponds to the total number of participants assigned to each treatment. Each line represents a type of direct comparison, and its width corresponds to the number of studies evaluating the connected treatments. ACT, adjuvant chemotherapy; ACRT, adjuvant chemoradiation therapy; ART, adjuvant radiotherapy.

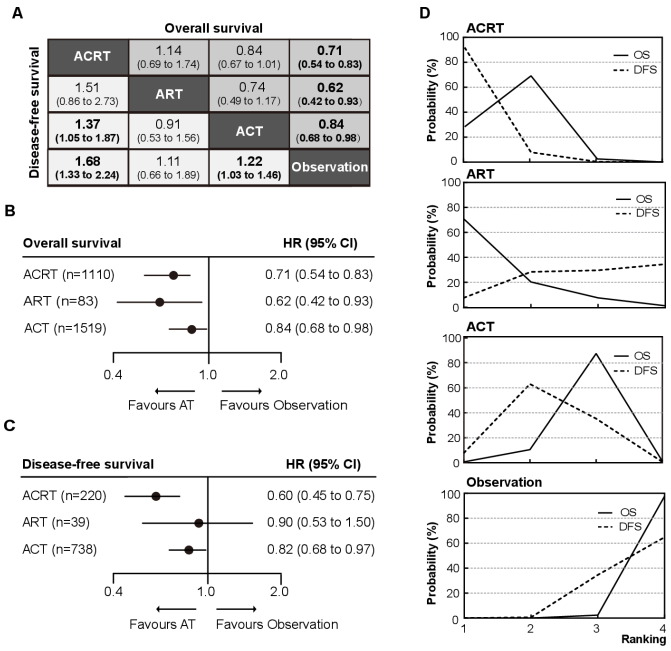

Figure 3 Network meta-analysis results for efficacy outcomes. (A) League table of the network meta-analysis. Pooled HRs and 95% CIs for the overall survival (OS) and disease-free survival (DFS) are listed in the upper and lower triangle, respectively. The estimate in each cell compares the row-defining treatment versus column-defining treatment. In the left lower half (DFS results), HR >1 favours the column-defining treatment, and in the upper right half (OS results), HR <1 favours the row-defining treatment. significant results are in bold. (B) Forest plot of the network meta-analysis for OS. (C) Forest plot of the network meta-analysis for DFS. HRs and 95% CIs are provided and visually represented by the squares and error bars. (D) Bayesian ranking curves of comparable treatments on efficacy for patients with biliary tract cancer. Ranking curves indicate the probability of each treatment ranked first to last on OS (solid lines) and DFS (dotted lines). Data of the curves are presented in online supplemental table 9. ACT, adjuvant chemotherapy; ACRT, adjuvant chemoradiation therapy; ART, adjuvant radiotherapy.

were 46.17 for OS and 29.93 for DFS, which were similar to the DICs of the inconsistency model (46.05 and 31.15, respectively), suggesting no evidence of inconsistency in the network. The more parsimonious model, the consistency model, was used for our analyses (online supplemental table 8).

Network meta-analysis of treatments in BTC

A network meta-analysis was conducted to assess the efficacy (OS and DFS) of the following treatments in a Bayesian framework: observation alone after surgery, surgery with ACT, surgery with ART, and surgery with ACRT.

A network plot is shown in figure 2. OS data were available from 18 studies that included 5497 patients, of whom 2785 (50.7%) were in the observation group, 1519 (27.6%) received ACT, 83 (1.5%) received ART and 1110 (20.2%) received ACRT. The pooled OS data indicated that ART (HR 0.62; 95% CI 0.42 to 0.93), ACRT (HR 0.71; 95% CI 0.54 to 0.83) and ACT (HR 0.84; 95% CI 0.68 to 0.98) were more beneficial in patients with BTC compared with that of observation (figure 3A–B). No significant benefits in OS were observed in the comparisons between the different adjuvant therapies (figure 3A).

In terms of DFS, 14 studies with 1979 patients were included in the network meta-analysis (figure 2). The pooled DFS data demonstrated a significant improvement for ACRT and ACT compared with that of observation (HR 0.60; 95% CI 0.45 to 0.75, and HR 0.82; 95% CI 0.68 to 0.97, respectively). Furthermore, a slightly better efficacy for ACRT was obtained compared with that of ACT (HR 0.73; 95% CI 0.53 to 0.95). Significant differences in DFS were not observed between the other pairwise comparisons (figure 3A,C).

The ranking analysis was performed using SUCRA. Based on the pooled OS and DFS data, the ranking order of OS and DFS was inconsistent. The best therapy for OS was ranked as follows: ART, ACRT, ACT and observation (figure 3D). The best SUCRA value of ART was 87.0%, which was close to that of ACRT with a SUCRA value of 75.3% (online supplemental table 9). As for DFS, the best therapy was ranked as ACRT, ACT, ART, and observation (figure 3D). The SUCRA value of ACRT was approximately 97.1%, which was far higher than that of the others (online supplemental table 9).

Subgroup analyses for OS in patients with different residual tumour status, tumour sites, regions and absence of distant metastasis were performed. Seven studies

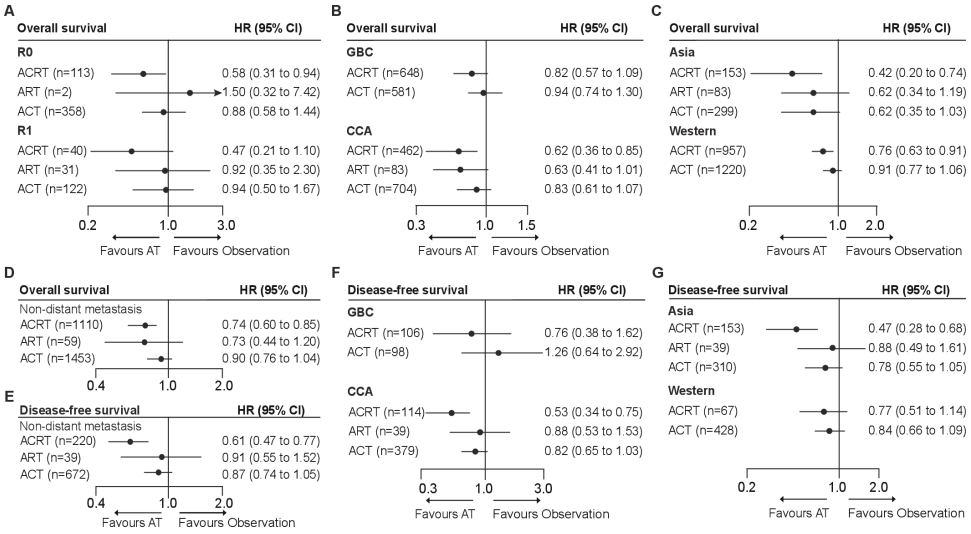

Figure 4 Forest plots of the network meta-analysis for overall survival (OS) and disease-free survival (DFS) in the subgroup analyses. (A) Forest plots of os in patients stratified into the R0 and R1 groups. (B, E) Forest plots of OS and DFS in patients stratified into the gallbladder cancer (GBC) and cholangiocarcinoma (CCA) groups. (C, F) Forest plots of os and DFS in patients stratified into the Asian and Western groups. (D) forest plots of OS and DFS in patients with non-distant metastasis. Effect sizes are presented as HRs with 95% CIs. ACT, adjuvant chemotherapy; ACRT, adjuvant chemoradiotherapy; ART, adjuvant radiotherapy.

reported the outcomes of patients after R0 resection, and seven studies reported the outcomes of patients after R1 resection (online supplemental figure 3A). In the R0 group, only ACRT had a survival advantage compared with that of surgery alone. In the R1 group, no survival advantage was observed in patients who underwent adjuvant therapies than in those with surgery alone (figure 4A, online supplemental figure 4A). In the subgroup analysis by primary tumour sites, 6 studies enrolled patients with GBC, and 11 studies recruited patients with CCA (online supplemental figure 3B). The OS benefit of ACRT was clear compared with that of observation in the CCA group (HR 0.62; 95% CI 0.36 to 0.85). The benefit of ART is unclear due to the lack of eligible ART studies. Among the comparable treatments in the GBC group, no significant differences in OS were found between ACT, ACRT and observation (figure 4B, online supplemental figure 4B). When studies were grouped according to region, 12 studies included patients in Asian countries and 7 from Western countries (online supplemental figure 3C). In both the Asian and Western groups, the pooled OS results favoured ACRT (HR 0.42; 95% CI 0.20 to 0.74 in Asia; HR 0.76; 95% CI 0.63 to 0.91 in Western countries) (figure 4C, online supplemental figure 4C). Subgroup analysis was also conducted for 15 studies investigating OS in patients with non-distant metastasis (online supplemental figure 3D). The pooled results showed superior efficacy of ACRT compared with that of observation (HR 0.74; 95% CI 0.60 to 0.85). Moreover, ACRT tended to be more effective compared with that of ACT (HR 0.82; 95% CI 0.67 to 0.96) (figure 4D, online supplemental figure 4D).

Subgroup analyses were also performed for DFS in patients with different tumour sites and regions and the absence of distant metastasis (online supplemental figure 5). Due to the small number of studies, subgroup analyses for DFS by different residual tumour statuses cannot be conducted. In patients without distant metastasis, the results from this subgroup were similar to that of the primary analysis; ACRT demonstrated statistically significant improvement with an HR of 0.61 (figure 4E, online supplemental figure 4D). When studies were split by primary tumour sites, only ACRT showed an apparent advantage in patients with CCA (figure 4F, online supplemental figure 4E). Furthermore, the stratified meta-analysis by region indicated that the favourable treatment was ACRT in Asia (HR 0.47; 95% CI 0.28 to 0.68) (figure 4G, online supplemental figure 4F).

To assess the robustness of the primary results, sensitivity analyses were performed for OS and DFS by excluding RCT studies, removing moderate-quality observational studies, and only including the studies for which HRs were reported in the original articles. The first sensitivity analysis included 15 retrospective studies of OS and 11 retrospective studies of DFS. The pooled results (online supplemental figure 6) and the ranking profiles of comparable treatments from retrospective studies confirmed the reliability of the primary OS results (figure 5A, online supplemental table 10). In terms of DFS, ACRT was still ranked as the best treatment option (figure 5B). Furthermore, the second and third sensitivity analyses were performed by removing moderate-quality observational studies (14 studies for OS and 11 studies for DFS) and by combining HRs reported in the original articles (11 studies for OS and 8 studies for DFS). The results did not suggest a material change in the efficacy estimation for ACRT, but ART no longer showed advantages over observation in both OS and DFS; the improvement

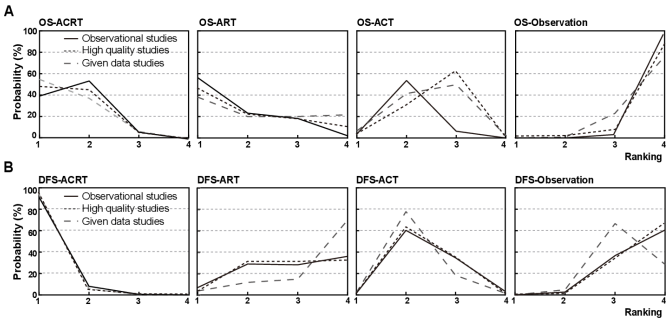

Figure 5 Bayesian ranking plots of comparable treatments on efficacy in patients with biliary tract cancer in the sensitivity analyses. Ranking curves indicate the probability of each comparable treatment being ranked from first to last on overall survival (OS) (solid lines) and disease-free survival (DFS) (dotted lines). Data of the curves are presented in online supplemental table 10). ACT, adjuvant chemotherapy; ACRT, adjuvant chemoradiation therapy; ART, adjuvant radiotherapy.

in OS and DFS between ACT and observation was insignificant except for the pooled DFS in high-quality studies (online supplemental figure 6).

The visual examination of the comparison-adjusted funnel plots did not suggest a publication bias for OS presented in our network meta-analysis (online supplemental figure 7A). The result of Egger's test (p=0.251) also rejected the presence of small-study effects. However, both the visual examination of the comparison-adjusted funnel plots and the results of Egger's test (p=0.018) suggested a publication bias for DFS in our network meta-analysis (online supplemental figure 7B).

DISCUSSION

BTCs are an uncommon and heterogeneous type of cancer with a higher prevalence in Asian countries.[92] In general, BTCs include cancers raised from the intrahepatic, hilar, and distal bile ducts, as well as the gallbladder.[7] Surgical resection provides the only chance for cure in patients with BTC at an early stage, but the survival outcomes are poor. The 5-year survival rate was as low as 10%.[93] The most recent NCCN and ASCO guidelines recommend the use of adjuvant therapy for BTC patients after resection.[12 15] However, experts mentioned that the use of adjuvant therapy is based on a very limited number of studies, and the benefit of adjuvant therapy remains unclear in many pivotal BTC trials.[16 74 75 94 95] Therefore, it is necessary to compile up-to-date studies to validate the efficacy of adjuvant therapy in BTC patients.

In this network meta-analysis, 19 studies were included to evaluate the comparative benefits (involving 5497 patients for OS and 1979 patients for DFS) between adjuvant therapy (ACT, ART and ACRT) following surgical resection and curative-intent resection (observation group). Our primary results demonstrated that adjuvant therapy was more effective than that of observation in OS. However, no statistically significant difference was detected between ACT, ACRT and ART. Moreover, the pooled DFS results suggested a statistically significant benefit for ACRT and ACT over observation. Although ART was ranked first in OS, its DFS result was inconsistent with OS, and caution should be exercised regarding the bias that arises from the small sample size effect of ART evidence (only 83 patients). In addition, a previously published meta-analysis of adjuvant therapy in the treatment of BTC suggested that ART did not provide a significant advantage over observation.[21] We hold reservations on the conclusion of the efficacy of ART, and further evidence is needed to elucidate this matter.

Combining the results of OS with DFS, ACRT, and ACT after radical resection could provide a survival benefit in patients with BTC. This was in line with another meta-analysis that showed that both ACT (HR 0.61; 95% CI 0.47 to 0.79) and ACRT (HR 0.35; 95% CI 0.14 to 0.83) could significantly improve the clinical survival of patients with resected BTC compared with that of surgery alone.[96] As known, the BILCAP study is a unique positive randomised trial of ACT in patients with BTC. Despite the concerns regarding the findings of the BILCAP trial, this study established adjuvant capecitabine as the new standard of care for resected BTC. However, no randomised trials of ACRT vs ACT are available. Although in our study, the ACRT ranked high in terms of OS and DFS (second place for OS, first place for DFS), whether it is genuinely superior to ACT needs further confirmation in prospective RCTs.

The types of patients who are more likely to benefit from adjuvant therapy are also the focus. A previous phase II study indicated that the risk factors were GBC, eCCA, pathological stage T2–4, positive LN or positive RM.[97] In our study, we were only able to conduct subgroup analyses on the effects of the RM, primary tumour site, regions and absence of distant metastasis, but not LN and tumour size, on adjuvant therapy due to the availability of data. We observed that ACRT showed a modest improvement in DFS than that of ACT in CCA and Asian patients and ranked first in each subgroup (online supplemental table 11). We noticed that approximately 95% (for OS analysis) and 80% (for DFS analysis) of CCA patients treated with ACRT had eCCA. The benefit of ACRT observed in CCA patients may be mainly derived from eCCA patients. Inconsistent with most studies, ACRT has an OS benefit in the R0 group, but not in the R1 group. This was possibly due to the more stringent selection of studies and the effects of small sample sizes. Subgroup analyses for DFS by R0 or R1 were not conducted because of limited data. Therefore, the subgroups of patients who could benefit more from postoperative adjuvant therapy need to be further elucidated. We look forward to seeing more randomised controlled studies in this field, especially head-to-head trials and trials designed for more specific subgroups. Using the primary tumour site, tumour size, disease severity, LN metastases and RM as stratification factors in future studies would reduce selection bias due to the heterogeneity of the population.

This study had several limitations. First, RCT data were only available to compare ACT and observations. Unfortunately, there are neither RCTs for ART and ACRT nor head-to-head RCTs between different adjuvant treatments. The notable differences in the study design level may introduce confounding factors in our data analysis, although data transitivity and consistency could be assumed statistically. Second, the included studies spanned over a 45-year period during which operative techniques and methods have changed and improved over time. These changes in treatment methods could potentially bias our results, but the impact on the outcome was unclear and difficult to interpret. Third, most comparisons were indirect, and direct evidence was obtained from two or three studies. The comparisons between the different treatment modalities and treatment regimens may substantially contribute to heterogeneity among included studies. Patients in ACT, ART or ACRT groups were treated with different modalities. Even within the same treatment modality, different regimens offered various efficacy results. Such as, the adjuvant capecitabine monotherapy (BILCAP study) appeared more effective compared with observation, whereas adjuvant gemcitabine (BCAT study) or gemcitabine plus oxaliplatin (PRODIGE 12 study) did not.[98] Furthermore, we noticed that the number of patients treated with ART was small. These may result in a considerable risk of bias. Fourth, the definitions of OS and DFS in RCTs and retrospective studies were calculated differently. In RCTs, it started from the date of randomisation to the date of surgery in retrospective studies. The span was relatively short compared with the expected survival duration, but the slight variation in data collection should still be considered. Finally, we failed to compare the safety outcomes due to a lack of sufficient data on adverse events. Taking all these into account, our estimates should be interpreted with caution.

CONCLUSIONS

Our primary results demonstrated that, compared with that of observation, ACRT and ACT after radical resection could provide better OS and DFS benefits in patients with BTC. However, ART only showed improvement in OS. ACRT had a modest DFS advantage compared with that of ACT. Due to the absence of direct evidence from head-to-head prospective studies, thorough and high-quality RCTs are warranted to consolidate our results further. Optimal regimens and dosing schedules still need to be explored.

Acknowledgements We thank the study authors Zhaochong Zeng (Jiang, 2010), Tae Hyun Kim (Kim, 2011), Wei-Hu Wang (Zheng, 2018) and Xiaojian. Ni (Wan, 2021) responded to our request for additional data and questions. We thank Lei Wang for the help in the manuscript proofreading.

Contributors As the guarantor, MQ designed, coordinated and supervised this study. YCh, BZ and CLi screened the articles, YCh and BZ extracted the data and assessed the quality. YCa and CLi contacted study authors for additional information. YCh, BZ and YCa analysed and prepared the material. YCh, BZ, CLi and CLu interpreted the data and wrote the draft of the report. All authors had reviewed and approved the final submitted version of the report. MQ was responsible for the integrity and accuracy of the data.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information. All data relevant to the study are included in the article or uploaded as supplemental information. All the data extracted, and analysed, and reported in this paper were from published literature.

ORCID iD

Baoxia Zhang http://orcid.org/0000-0003-2445-3031

REFERENCES

1 Nakeeb A, Pitt HA, Sohn TA, *et al*. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. *Ann Surg* 1996;224:463–73. discussion 73-5.
2 Benavides M, Antón A, Gallego J, *et al*. Biliary tract cancers: SEOM clinical guidelines. *Clin Transl Oncol* 2015;17:982–7.
3 Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. *Hepatology* 2001;33:1353–7.
4 Valle JW, Lamarca A, Goyal L, *et al*. New horizons for precision medicine in biliary tract cancers. *Cancer Discov* 2017;7:943–62.
5 Anderson CD, Pinson CW, Berlin J, *et al*. Diagnosis and treatment of cholangiocarcinoma. *Oncologist* 2004;9:43–57.
6 DeOliveira ML, Cunningham SC, Cameron JL, *et al*. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg* 2007;245:755–62.
7 Bridgewater JA, Goodman KA, Kalyan A, *et al*. Biliary tract cancer: epidemiology, radiotherapy, and molecular profiling. *Am Soc Clin Oncol Educ Book* 2016;35:e194–203.
8 Doherty MK, Knox JJ. Adjuvant therapy for resected biliary tract cancer: a review. *Chin Clin Oncol* 2016;5:64.
9 Mavros MN, Economopoulos KP, Alexiou VG, *et al*. Treatment and prognosis for patients with intrahepatic cholangiocarcinoma: systematic review and meta-analysis. *JAMA Surg* 2014;149:565–74.
10 Murakami Y, Uemura K, Sudo T, *et al*. Prognostic factors after surgical resection for intrahepatic, hilar, and distal cholangiocarcinoma. *Ann Surg Oncol* 2011;18:651–8.
11 Wirasorn K, Ngamprasertchai T, Khuntikeo N, *et al*. Adjuvant chemotherapy in resectable cholangiocarcinoma patients. *J Gastroenterol Hepatol* 2013;28:1885–91.
12 National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. hepatobiliary cancers, version 5, 2021. Available: https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf [Accessed 20 Jan 2022].
13 Valle JW, Borbath I, Khan SA, *et al*. Biliary cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016;27:v28–37.

14 HJ L, SK Q, S F. Biliary tract caner: CSCO consensus for diagnosis and treatment. *Chin Clin Oncol* 2019;24:828–38.
15 Shroff RT, Kennedy EB, Bachini M, *et al*. Adjuvant therapy for resected biliary tract cancer: ASCO clinical practice guideline. *J Clin Oncol* 2019;37:1015–27.
16 Primrose JN, Fox RP, Palmer DH, *et al*. Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study. *Lancet Oncol* 2019;20:663–73. -.
17 Rizzo A, Brandi G. BILCAP trial and adjuvant capecitabine in resectable biliary tract cancer: reflections on a standard of care. *Expert Rev Gastroenterol Hepatol* 2021;15:483–5.
18 Rizzo A, Brandi G. Pitfalls, challenges, and updates in adjuvant systemic treatment for resected biliary tract cancer. *Expert Rev Gastroenterol Hepatol* 2021;15:547–54.
19 Lamarca A, Edeline J, McNamara MG, *et al*. Current standards and future perspectives in adjuvant treatment for biliary tract cancers. *Cancer Treat Rev* 2020;84:101936.
20 Rangarajan K, Simmons G, Manas D, *et al*. Systemic adjuvant chemotherapy for cholangiocarcinoma surgery: a systematic review and meta-analysis. *Eur J Surg Oncol* 2020;46:684–93.
21 Horgan AM, Amir E, Walter T, *et al*. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. *J Clin Oncol* 2012;30:1934–40.
22 Zhu G-Q, Shi K-Q, You J, *et al*. Systematic review with network meta-analysis: adjuvant therapy for resected biliary tract cancer. *Aliment Pharmacol Ther* 2014;40:759–70.
23 Kish M, Chan K, Perry K, *et al*. A systematic review and network meta-analysis of adjuvant therapy for curatively resected biliary tract cancers. *Curr Oncol* 2020;27:e20–6.
24 Chen X, Meng F, Xiong H, *et al*. Adjuvant therapy for resectable biliary tract cancer: a Bayesian network analysis. *Front Oncol* 2021;11:600027.
25 Hutton B, Salanti G, Caldwell DM, *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777–84.
26 Ottawa Hospital Research Institute. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, 2014. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Accessed 29 Jun. 2020].
27 Higgins J, Altman D, Sterne J. Assessing risk of bias in included studies. In: Higgins J, Green S, eds. *Cochrane Handbook of systematic reviews of interventions. assessing risk of bias in included studies*. 5.1.0 ed. England: The Cochrane Collaboration, Wiley, 2011. : 187–235p..
28 Tierney JF, Stewart LA, Ghersi D, *et al*. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;8:16.
29 Gelman A, Rubin DB. Inference from iterative simulation using multiple sequences. *Stat Sci* 1992;7:457–511.
30 Lynch SM. *Introduction to applied Bayesian statistics and estimation for social scientists*. 1st edition. New York, NY: Springer-Verlag, 2007.
31 Higgins JPT, Jackson D, Barrett JK, *et al*. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* 2012;3:98–110.
32 Dias S, Welton NJ, Caldwell DM, *et al*. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med* 2010;29:932–44.
33 van Valkenhoef G, Dias S, Ades AE, *et al*. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. *Res Synth Methods* 2016;7:80–93.
34 Higgins JPT, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–60.
35 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
36 Debray TP, Damen JA, Riley RD, *et al*. A framework for meta-analysis of prediction model studies with binary and time-to-event outcomes. *Stat Methods Med Res* 2019;28:2768–86.
37 Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64:163–71.
38 Veroniki AA, Vasiliadis HS, Higgins JPT, *et al*. Evaluation of inconsistency in networks of interventions. *Int J Epidemiol* 2013;42:332–45.
39 Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
40 Begg CB, Mazumdar M. Operating characteristics of a RANK correlation test for publication bias. *Biometrics* 1994;50:1088–101.
41 Sagawa N, Kondo S, Morikawa T, *et al*. Effectiveness of radiation therapy after surgery for hilar cholangiocarcinoma. *Surg Today* 2005;35:548–52.
42 Borghero Y, Crane CH, Szklaruk J, *et al*. Extrahepatic bile duct adenocarcinoma: patients at high-risk for local recurrence treated with surgery and adjuvant chemoradiation have an equivalent overall survival to patients with standard-risk treated with surgery alone. *Ann Surg Oncol* 2008;15:3147–56.
43 Gold DG, Miller RC, Haddock MG, *et al*. Adjuvant therapy for gallbladder carcinoma: the Mayo clinic experience. *Int J Radiat Oncol Biol Phys* 2009;75:150–5.
44 Ercolani G, Vetrone G, Grazi GL, *et al*. Intrahepatic cholangiocarcinoma: primary liver resection and aggressive multimodal treatment of recurrence significantly prolong survival. *Ann Surg* 2010;252:107–14.
45 Kim K, Chie EK, Jang J-Y, *et al*. Postoperative chemoradiotherapy for gallbladder cancer. *Strahlenther Onkol* 2012;188:388–92.
46 Kondo N, Murakami Y, Uemura K, *et al*. Elevated perioperative serum Ca 19-9 levels are independent predictors of poor survival in patients with resectable cholangiocarcinoma. *J Surg Oncol* 2014;110:422–9.
47 Bektas H, Yeyrek C, Kleine M, *et al*. Surgical treatment for intrahepatic cholangiocarcinoma in Europe: a single center experience. *J Hepatobiliary Pancreat Sci* 2015;22:131–7.
48 Hoehn RS, Wima K, Ertel AE, *et al*. Adjuvant chemotherapy and radiation therapy is associated with improved survival for patients with extrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2015;22:1133–9.
49 Sur MD, In H, Sharpe SM, *et al*. Defining the benefit of adjuvant therapy following resection for intrahepatic cholangiocarcinoma. *Ann Surg Oncol* 2015;22:2209–17.
50 Im JH, Seong J, Lee IJ, *et al*. Surgery alone versus surgery followed by chemotherapy and radiotherapy in resected extrahepatic bile duct cancer: treatment outcome analysis of 336 patients. *Cancer Res Treat* 2016;48:583–95.
51 Kim YS, Hwang IG, Park S-E, *et al*. Role of adjuvant therapy after R0 resection for patients with distal cholangiocarcinoma. *Cancer Chemother Pharmacol* 2016;77:979–85.
52 Kim TG. Patterns of initial failure after resection for gallbladder cancer: implications for adjuvant radiotherapy. *Radiat Oncol J* 2017;35:359–67.
53 Kim YS, Oh SY, Go S-I, *et al*. The role of adjuvant therapy after R0 resection for patients with intrahepatic and perihilar cholangiocarcinomas. *Cancer Chemother Pharmacol* 2017;79:99–106.
54 Kim YS, Jeong C-Y, Song H-N, *et al*. The efficacy of fluoropyrimidine-based adjuvant chemotherapy on biliary tract cancer after R0 resection. *Chin J Cancer* 2017;36:9.
55 Lee J, Kang SH, Noh OK, *et al*. Adjuvant concurrent chemoradiation therapy in patients with microscopic residual tumor after curative resection for extrahepatic cholangiocarcinoma. *Clin Transl Oncol* 2018;20:1011–7.
56 Mitin T, Enestvedt CK, Jemal A, *et al*. Limited use of adjuvant therapy in patients with resected gallbladder cancer despite a strong association with survival. *J Natl Cancer Inst* 2017;109:djw324.
57 Tran Cao HS, Zhang Q, Sada YH, *et al*. The role of surgery and adjuvant therapy in lymph node-positive cancers of the gallbladder and intrahepatic bile ducts. *Cancer* 2018;124:74–83.
58 Lin Y-K, Hsieh M-C, Wang W-W, *et al*. Outcomes of adjuvant treatments for resectable intrahepatic cholangiocarcinoma: chemotherapy alone, sequential chemoradiotherapy, or concurrent chemoradiotherapy. *Radiother Oncol* 2018;128:575–83.
59 Geng Z-M, Cai Z-Q, Zhang Z, *et al*. Estimating survival benefit of adjuvant therapy based on a Bayesian network prediction model in curatively resected advanced gallbladder adenocarcinoma. *World J Gastroenterol* 2019;25:5655–66.
60 Kattepur AK, Patkar S, Goel M, *et al*. Role of adjuvant chemotherapy in resected T2N0 gall bladder cancer. *J Gastrointest Surg* 2019;23:2232–8.
61 Navarro J, Kang I, Hwang HK, *et al*. Glucose to lymphocyte ratio as a prognostic marker in patients with resected PT2 gallbladder cancer. *J Surg Res* 2019;240:17–29.
62 Kim TH, Woo SM, Lee WJ, *et al*. Benefit of adjuvant chemoradiotherapy in resected gallbladder carcinoma. *Sci Rep* 2019;9:N.PAG-N.PAG.
63 Kizy S, Altman AM, Marmor S, *et al*. Surgical resection of lymph node positive intrahepatic cholangiocarcinoma may not improve survival. *HPB* 2019;21:235–41.
64 Lu J, Li B, Li F-Y, *et al*. Prognostic significance of mucinous component in hilar cholangiocarcinoma after curative-intent resection. *J Surg Oncol* 2019;120:1341–9.

65 Han D, Yang J, Xu F, *et al*. Prognostic factors in patients with gallbladder adenocarcinoma identified using competing-risks analysis: a study of cases in the seer database. *Medicine* 2020;99:e21322.
66 Kim H, Heo MH, Kim JY. Comparison of the effects of adjuvant concurrent chemoradiotherapy and chemotherapy for resected biliary tract cancer. *BMC Gastroenterol* 2020;20:20.
67 Mao W, Deng F, Wang D, *et al*. Treatment of advanced gallbladder cancer: a SEER-based study. *Cancer Med* 2020;9:141–50.
68 Zhou W, Qian L, Rong Y, *et al*. Prognostic factors and patterns of recurrence after curative resection for patients with distal cholangiocarcinoma. *Radiother Oncol* 2020;147:111–7.
69 Zhu WH, Xie WY, Zhang ZD, *et al*. Postoperative complications and survival analysis of surgical resection for hilar cholangiocarcinoma: a retrospective study of Fifty-Nine consecutive patients. *Chin Med Sci J* 2020;35:157–69.
70 Benzing C, Krenzien F, Mieg A, *et al*. A tailored approach in lymph node-positive perihilar cholangiocarcinoma. *Langenbecks Arch Surg* 2021;406:1499–509.
71 Chang WI, Kim BH, Kang H-C, *et al*. The role of adjuvant chemoradiotherapy in Nonhilar extrahepatic bile duct cancer: a long-term single-institution analysis. *Int J Radiat Oncol Biol Phys* 2021;111:395–404.
72 Kosaka H, Kaibori M, Matsui K, *et al*. Investigation of a tumor location-specific therapeutic strategy for intrahepatic cholangiocarcinoma. *Asian Pac J Cancer Prev* 2021;22:1485–93.
73 Sumiyoshi T, Uemura K, Kondo N, *et al*. The prognostic impact of peritoneal washing cytology for otherwise resectable extrahepatic cholangiocarcinoma patients. *Surg Today* 2021;51:1227–31.
74 Ebata T, Hirano S, Konishi M, *et al*. Randomized clinical trial of adjuvant gemcitabine chemotherapy versus observation in resected bile duct cancer. *Br J Surg* 2018;105:192–202.
75 Edeline J, Benabdelghani M, Bertaut A, *et al*. Gemcitabine and oxaliplatin chemotherapy or surveillance in resected biliary tract cancer (Prodige 12-accord 18-Unicancer Gi): a randomized phase III study. *J Clin Oncol* 2019;37:658–67.
76 Todoroki T, Ohara K, Kawamoto T, *et al*. Benefits of adjuvant radiotherapy after radical resection of locally advanced main hepatic duct carcinoma. *Int J Radiat Oncol Biol Phys* 2000;46:581–7.
77 Kim TH, Han S-S, Park S-J, *et al*. Role of adjuvant chemoradiotherapy for resected extrahepatic biliary tract cancer. *Int J Radiat Oncol Biol Phys* 2011;81:e853–9.
78 Kobayashi H, Murakami Y, Uemura K, *et al*. Human equilibrative nucleoside transporter 1 expression predicts survival of advanced cholangiocarcinoma patients treated with gemcitabine-based adjuvant chemotherapy after surgical resection. *Ann Surg* 2012;256:288–96.
79 Dover LL, Oster RA, McDonald AM, *et al*. Impact of adjuvant chemoradiation on survival in patients with resectable cholangiocarcinoma. *HPB* 2016;18:843–50.
80 Kim Y, Amini N, Wilson A, *et al*. Impact of chemotherapy and external-beam radiation therapy on outcomes among patients with resected gallbladder cancer: a multi-institutional analysis. *Ann Surg Oncol* 2016;23:2998–3008.
81 Morine Y, Shimada M, Ikemoto T, *et al*. Effect of adjuvant gemcitabine combined with low-dose 5-fluorouracil and cisplatin chemotherapy for advanced biliary carcinoma. *Anticancer Res* 2017;37:6421–8.
82 Akahoshi K, Ban D, Kuboki R, *et al*. Orotate phosphoribosyltransferase as a predictor of benefit from S-1 adjuvant chemotherapy for cholangiocarcinoma patients. *J Gastroenterol Hepatol* 2019;34:1108–15.
83 Bergeat D, Turrini O, Courtin-Tanguy L, *et al*. Impact of adjuvant chemotherapy after pancreaticoduodenectomy for distal cholangiocarcinoma: a propensity score analysis from a French multicentric cohort. *Langenbecks Arch Surg* 2018;403:701–9.
84 Hester C, Nassour I, Adams-Huet B, *et al*. Improved survival in surgically resected distal cholangiocarcinoma treated with adjuvant therapy: a propensity score matched analysis. *J Gastrointest Surg* 2018;22:2080–7.
85 Zheng X, Chen B, Wu J-X, *et al*. Benefit of adjuvant radiotherapy following narrow-margin hepatectomy in patients with intrahepatic cholangiocarcinoma that adhere to major vessels. *Cancer Manag Res* 2018;10:3973–81.
86 Jiang W, Zeng Z-C, Tang Z-Y, *et al*. Benefit of radiotherapy for 90 patients with resected intrahepatic cholangiocarcinoma and concurrent lymph node metastases. *J Cancer Res Clin Oncol* 2010;136:1323–31.
87 Gu B, Qian L, Yu H, *et al*. Concurrent chemoradiotherapy in curatively resected gallbladder carcinoma: a propensity score-matched analysis. *Int J Radiat Oncol Biol Phys* 2018;100:138–45.
88 Choudhary S, Gupta N, Verma CP, *et al*. Influence of adjuvant therapy on pattern of failure and survival in curatively resected gallbladder carcinoma. *J Cancer Res Ther* 2021;17:1064–8.
89 Im JH, Choi GH, Lee WJ, *et al*. Adjuvant radiotherapy and chemotherapy offer a recurrence and survival benefit in patients with resected perihilar cholangiocarcinoma. *J Cancer Res Clin Oncol* 2021;147:2435–45.
90 Miyata Y, Kogure R, Nakazawa A, *et al*. The efficacy of S-1 as adjuvant chemotherapy for resected biliary tract carcinoma: a propensity score-matching analysis. *J Clin Med* 2021;10:1–10.
91 Wan W, Zheng B, Sun W, *et al*. Adjuvant therapy in resected nonmetastatic stage II-IV gallbladder cancer: a generalized propensity score analysis. *Oncol Res Treat* 2021;44:390–9.
92 Tariq N-U-A, McNamara MG, Valle JW. Biliary tract cancers: current knowledge, clinical candidates and future challenges. *Cancer Manag Res* 2019;11:2623–42.
93 Khan SA, Davidson BR, Goldin RD, *et al*. Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. *Gut* 2012;61:1657–69.
94 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.
95 Neoptolemos JP, Moore MJ, Cox TF, *et al*. 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.
96 Song S, Yang W, Tian H, *et al*. The efficacy and safety of 5-fluorouracil based adjuvant therapy in resected biliary tract cancer: a systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol* 2022;46:101788.
97 Ben-Josef E, Guthrie KA, El-Khoueiry AB, *et al*. Swog S0809: a phase II intergroup trial of adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine in extrahepatic cholangiocarcinoma and gallbladder carcinoma. *J Clin Oncol* 2015;33:2617–22.
98 Edeline J, Hirano S, Bertaut A, *et al*. Individual patient data meta-analysis of adjuvant gemcitabine-based chemotherapy for biliary tract cancer: combined analysis of the BCAT and PRODIGE-12 studies. *Eur J Cancer* 2022;164:80–7.