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Meta-analysis

The effect of adjuvant chemotherapy in resectable cholangiocarcinoma: A meta-analysis and systematic review

Ming-Liang Wang[a], Zhang-Yan Ke[b], Shuai Yin[a], Chen-Hai Liu[a], Qiang Huang[a,*]

[a] Department of General Surgery, Affiliated Provincial Hospital of Anhui Medical University, Hefei 230001, China
[b] Department of Internal Medicine, The First Affiliated Hospital of Anhui Medical University, Hefei 230032, China

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ABSTRACT

Background: The benefit of adjuvant chemotherapy for resectable cholangiocarcinoma remains unclear due to the lack of randomized control studies. This study aimed to investigate the possible benefit of postoperative adjuvant chemotherapy for resectable cholangiocarcinoma.

Data sources: Relevant research articles published before 1st March 2018 in PubMed, Embase and the Cochrane library databases were retrieved. Published data were extracted and analyzed by RevMan 5.3, and the results were presented as hazard ratios (HRs) [95% confidence intervals (CI)] and forest plots.

Results: One prospective and eighteen retrospective studies were included, with a total number of 11,458 patients, 4696 of whom received postoperative chemotherapy. There was a significant improvement of the overall survival (OS) for patients who underwent operation + adjuvant chemotherapy compared to those who underwent operation alone (HR = 0.61; $P < 0.001$). Subgroup analyses show that the postoperative chemotherapy group compared with operation alone group are indicated as follows: hilar cholangiocarcinoma group (HR = 0.60; $P < 0.001$), intrahepatic cholangiocarcinoma group (HR = 0.60; $P < 0.001$), R1 resection group (HR = 0.71; $P = 0.04$), LN-positive diagnosis group (HR = 0.58; $P < 0.001$), gemcitabine-based chemotherapy group (HR = 0.42; $P < 0.001$), distal cholangiocarcinoma group (HR = 0.48; $P = 0.17$), R0 resection group (HR = 0.69; $P = 0.43$), and 5-flurouracil-based chemotherapy group (HR = 0.90; $P = 0.66$), respectively.

Conclusions: Postoperative adjuvant chemotherapy can improve the OS in intrahepatic and hilar cholangiocarcinoma patients. However, distal cholangiocarcinoma patients gain no benefit from postoperative adjuvant chemotherapy. Prospective randomized trials are warranted in order to define the standard chemotherapy regimen.

Introduction

Cholangiocarcinoma (CC) is a malignant tumor of the biliary system which can be defined as three different types based on the location: intrahepatic cholangiocarcinoma (ICC), hilar cholangiocarcinoma (HCCA) and distal cholangiocarcinoma (DCC). According to recent retrospective studies, the one-year and three-year postoperation survival rates of CC are 52.6%–66.8% and 30.0%–35.4%, respectively [1–4]. Some studies showed that postoperative adjuvant chemotherapy could improve the overall survival (OS) of CC patients [1,5]. Fluorouracil- or gemcitabine-based chemotherapy have been recommended and frequently used for treating high-risk patients like lymph nodes-positive and R1 resection [6]. However, a consensus has not yet been reached about whether postoperative adjuvant chemotherapy should be recommended as the routine treatment for resectable CC. Previous studies indicate the efficacy of adjuvant chemotherapy in biliary tract cancers after curative resection [7,8]. But the latest study show that different types of biliary tract cancers respond differently to chemotherapy. Differences in the molecular profiles between CC and gallbladder adenocarcinoma result in their differences of sensitivities to chemotherapy [9]. Thus, in this study, we investigated the possible benefit of postoperative adjuvant chemotherapy for resectable CC, and analyzed whether lymph node infiltration, the site of CC, populations and chemotherapy regimens affect the outcome of adjuvant chemotherapy.

* Corresponding author.
E-mail address: slyyhuangqiang@163.com (Q. Huang).

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Methods

Search strategy

PubMed, Embase and the Cochrane Library databases were searched for relevant articles published before March 2018. Searches were limited to human studies and English-language publications. The main keywords used for the PubMed search were ("cholangiocarcinoma" [MeSH Terms] OR "cholangiocarcinoma" [Title/Abstract]) AND ("chemotherapy" [Title/Abstract] OR "chemotherapy" [MeSH Terms]). The main keywords used for the Embase search were ('bile duct carcinoma'/exp OR 'cholangiocarcinoma') AND ('chemotherapy'/exp OR 'chemotherapy'). Citation lists of included literature were manually screened to ensure sensitivity of the search strategy.

Selection criteria

The inclusion criteria were as follows: (1) studies associated with the postoperative adjuvant chemotherapy in resectable CC patients; (2) studies with a total sample size greater than 40 patients; (3) studies that provided survival data or curves of postoperative chemotherapy; and (4) if the literature comes from the same center, the one with the larger sample was chosen. The exclusion criteria were as follows: (1) studies that included gallbladder cancer and did not analyze CC independently; (2) studies with only one of postoperative radiotherapy, chemoradiotherapy or other adjuvant therapy performed; and (3) studies without survival data.

Data extraction

Two authors independently extracted information using predefined selection criteria; the third researcher evaluated the literature if there was a dispute. The quality of the publications was expressed using Jadad scores for randomized studies [10] and the Newcastle–Ottawa Scale (NOS) for retrospective studies [11]. The following details were extracted from each study: author; study period, institution and country; sample size; tumour site; margin; lymph node infiltration; chemotherapy regimen; median overall survival (MOS); five-year survival rate; and the HR and 95% CI of postoperative adjuvant chemotherapy in a multivariate analysis. If HR and 95% CI were not reported, it was then calculated by two different reviewers independently using Engauge Digitizer 4.1 (free software downloaded from http://sourceforge.net) and Tierney et al. [12] provided Excel form from survival curves.

Statistical analysis

Data were extracted from the primary publications and combined into the meta-analysis using RevMan 5.3 analysis software (Cochrane Collaboration, Copenhagen, Denmark). The significance level was set as $P < 0.05$. Pooled estimates of HRs were computed using the random-effect model [13]. Because of inter-study heterogeneity, studies were weighted using a generic inverse variance approach [14]. The survival benefit between adjuvant chemotherapy and no adjuvant chemotherapy patients was presented as a forest plot, HR and its 95% CI. Data analysis included the OS with or without postoperative chemotherapy for CC. Subgroup analyses were conducted in the ICC group, HCCA group, DCC group, LN-positive group, R0/R1 resection group and the recurrence-free survival (RFS) group.

Results

A total of 19 studies [15–33] were eligible for inclusion in the pooled analysis from the 5275 literatures that were retrieved.

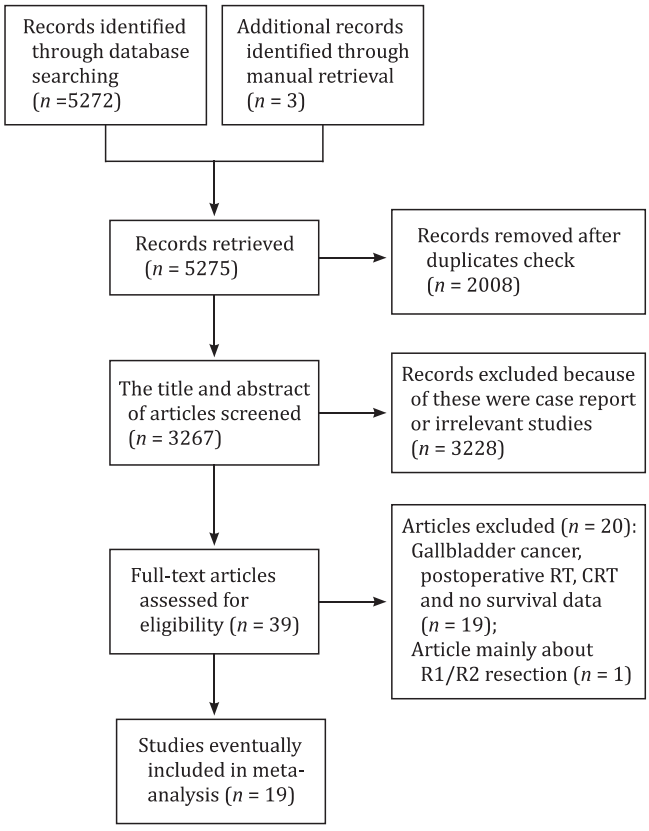

Fig. 1. The PRIMA flow chart. RT: radiotherapy; CRT: chemoradiotherapy.

These studies incorporated 11,458 patients; 6762 were treated with operation alone, and 4696 received adjuvant chemotherapy. Among these 19 studies, there were one randomized controlled trial (RCT) [33] and 18 retrospective studies [15–32]. Seven studies included ICC patients [15,20,21,25,29,31,32], six studies included HCCA patients [15,16,18,19,24,30], and three studies included DCC patients [15,22,30]. Two studies reported R1 resection [15,31], while three reported R0 resection [15,22,26] and four included LN-positive patients [15,16,31,32]. The literature screening process is shown in Fig. 1. Extracted data are summarized in Tables 1 and 2.

Cholangiocarcinoma

Heterogeneity analyses indicate that $I^2 = 79\%$, and $P < 0.05$, we therefore apply the random-effect model for the calculation (Fig. 2). Pooled data showed a significant improvement in survival for cholangiocarcinoma patients with adjuvant chemotherapy (HR = 0.61, 95% CI: 0.51–0.73, $P < 0.001$). Subgroup analyses in terms of different tumor locations were then carried out. A significant benefit from adjuvant chemotherapy was also observed when ICC and HCCA patients were analyzed independently (ICC: HR = 0.60, 95% CI: 0.46–0.77, $P < 0.001$; HCCA: HR = 0.60, 95% CI: 0.47–0.77, $P < 0.001$) (Fig. 3). The benefit of chemotherapy was not significant in the DCC patients (HR = 0.48, 95% CI: 0.17–1.36; $P = 0.17$) (Fig. 3).

Regions

This study included different populations from different countries, such as United States [29–32], China [20,21,24], Korea [17,22,23,26], and Japan [16,18,19,27,28,33]. In order to investigate the different populations in response to chemotherapy, we next perform the subgroup analysis. Pooled data confirmed a

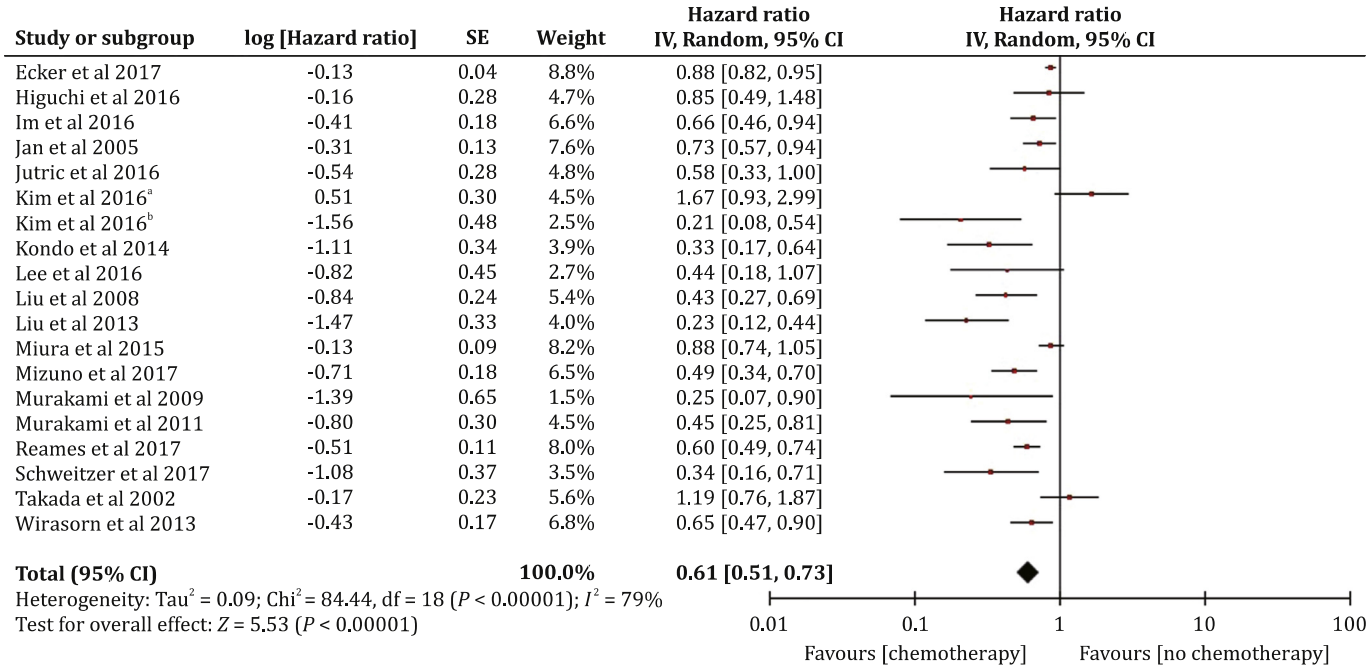

Fig. 2. Forest plot on overall survival in cholangiocarcinoma patients. a: reference 26; b: reference 22.

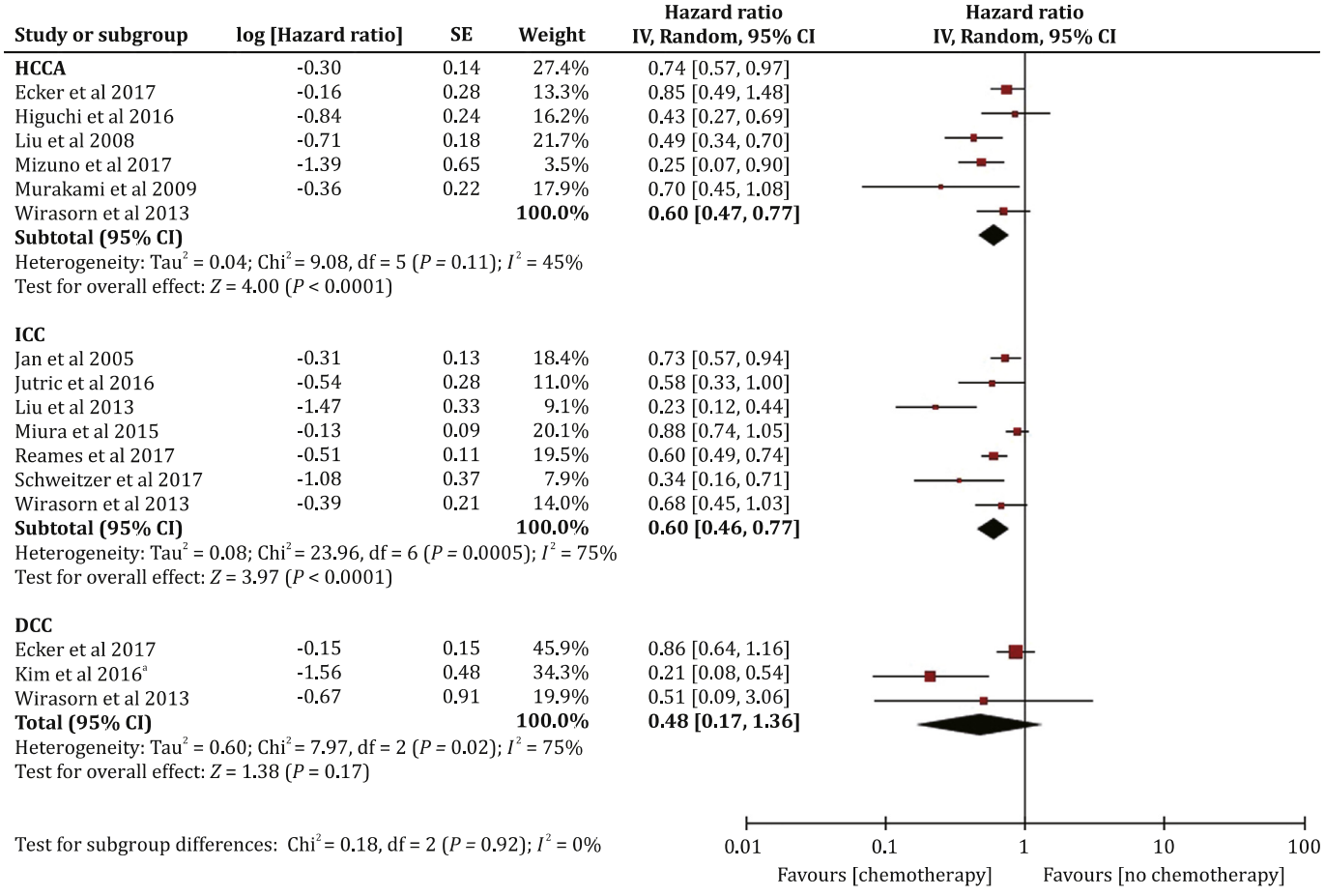

Fig. 3. Subgroup analysis: different types of cholangiocarcinoma. a: reference 22.

Table 1
Characteristics of included studies.

Studies	Study period	Country	Intrahepatic/ perihilar/distal	R0/R1	T stage (1–2/3–4)	LN (+/−)
Takada et al. 2002 [33]	1986–1992	Japan	NR	72/46	NR	102/16
Jan et al. 2005 [21]	1997–2001	China	312/0/0	NR	75/237	NR
Liu et al. 2008 [24]	1990–2004	China	0/115/0	95/20	NR	NR
Murakami et al. 2009 [18]	1990–2007	Japan	0/42/0	31/11	16/26	19/23
Murakami et al. 2011 [28]	1990–2009	Japan	21/50/56	95/32	NR	53/74
Wirasorn et al. 2013 [15]	2009–2012	Thailand	166/91/6	96/167	142/120	96/167
Liu et al. 2013 [20]	2005–2011	China	81/0/0	NR	NR	50/31
Kondo et al. 2014 [27]	2002–2012	Japan	25/48/33	78/28	65/41	45/61
Miura et al. 2015 [29]	1998–2011	USA	2751/0/0	1729/371	1363/834	1346/1405
Lee et al. 2016 [17]	2005–2011	Korea	0/5/92	70/27	41/56	34/63
Higuchi et al. 2016 [19]	1974–2014	Japan	0/182/0	153/86	96/87	103/77
Kim et al. 2016 [22]	2001–2013	Korea	0/0/158	158/0	103/55	47/111
Im et al. 2016 [23]	2001–2010	Korea	109/227	251/85	150/186	127/209
Kim et al. 2016 [26]	2001–2013	Korea	80/57/0	137/0	109/28	35/102
Jutric et al. 2016 [32]	1998–2011	USA	160/0/0	98/49	72/66	160/0
Mizuno et al. 2017 [16]	2001–2011	Japan	0/180/0	141/39	44/136	180/0
Schweitzer et al. 2017 [25]	2000–2012	Germany	210/0/0	165/43	139/66	62/119
Ecker et al. 2017 [30]	2004–2014	USA	NR	3382/1287	1094/2575	1204/1215
Reames et al. 2017 [31]	1990–2015	USA	1154/0/0	992/146	921/233	200/315

NR: detail not reported. LN: lymph node.

Table 2
Survival rate of patients with and without postoperative adjuvant chemotherapy.

Studies	Chemotherapy regimens	NOS scale	Adjuvant chemotherapy (Yes/No)		
			n	MOS (mon)	5-yr OS (%)
Takada et al. 2002 [33]	Gemcitabine-based or platinum-based or 5-FU-based	3	58/60	NR	26.7/24.1
Jan et al. 2005 [21]	5-FU, cisplatin, gemcitabine, doxorubicine and oxaliplatin	7	118/194	11.4/4.6	11.9/3.6
Liu et al. 2008 [24]	5-FU with cisplatin-based or gemcitabine-based	7	48/67	41/36	NR
Murakami et al. 2009 [18]	Tegafur/uracil, gemcitabine, cisplatin and FU	7	18/24	NR	5.5/20.8
Murakami et al. 2011 [28]	Gemcitabine	8	49/78	NR	8.2/32.0
Wirasorn et al. 2013 [15]	Gemcitabine, capecitabine, 5-FU + or mitomycin C	6	137/125	21.6/13.4	NR
Liu et al. 2013 [20]	Titanium silicate-1 or gemcitabine	6	18/63	22/8	NR
Kondo et al. 2014 [27]	5-FU-basedl, S-1, gemcitabine/cisplatin and mytomycin/irinotecan	6	75/31	NR	NR
Miura et al. 2015 [29]	Gemcitabine-based	6	985/1766	23/24.8	NR
Lee et al. 2016 [17]	Gemcitabine	7	31/66	40.3/39.5	34.0/55.0
Higuchi, 2016 [19]	Gemcitabine-based	7	42/197	NR	NR
Kim et al. 2016 [22]	5-FU-based	7	27/131	NR	NR
Im et al. 2016 [23]	5-FU, doxifluridine, tegafur/uracil and gemcitabine-based	6	90/246	NR	43.2/37.9
Kim, 2016 [26]	Gemcitabine alone or with cisplatin combination with oxaliplatin	7	48/89	NR	NR
Jutric et al. 2016 [32]	Mitomycin C and 5-FU	8	42/118	NR	NR
Mizuno et al. 2017 [16]	NR	8	67/113	37/20	NR
Schweitzer et al. 2017 [25]	Epirubicin, mitomycin, FU, and hydroxycamptothecin	8	39/171	32.9/26.9	7.9/15.5
Ecker et al. 2017 [30]	NR	6	2456/2416	NR	NR
Reames et al. 2017 [31]	NR	8	347/807	NR	NR

MOS: median overall survival; NOS: Newcastle–Ottawa Scale; NR: detail not reported; OS: overall survival.

significant benefit for patients with adjuvant chemotherapy from the United States (HR = 0.79, 95% CI: 0.64–0.97; $P = 0.03$) and China (HR = 0.44, 95% CI: 0.23–0.83; $P = 0.01$). However, the difference was not statistically significant in Korea (HR = 0.61, 95% CI: 0.29–1.27; $P = 0.19$) and Japan (HR = 0.58, 95% CI: 0.33–1.01; $P = 0.05$) (data not shown).

High-risk factors

Lymph node metastasis [15,17,22,23,25–30] and resection margin positivity [15,16,19,21,28–30] were widely considered to be independent prognostic factors for CC. Four studies that evaluated the effect of chemotherapy on node-positive CC were analyzed [15,16,31,32], and the difference was statistically significant, suggesting a benefit of chemotherapy for node-positive patients (HR = 0.58, 95% CI: 0.49–0.68; $P < 0.001$) (data not shown). There were only two [15,31] and three studies [15,22,26] that included R1 and R0 resection, respectively (Fig. 4). It suggested that postoperative adjuvant chemotherapy could improve the OS of R1 resection (HR = 0.71, 95% CI: 0.51–0.98; $P = 0.04$); however, the difference was not significant when R0 resection patients were analyzed (HR = 0.69, 95% CI: 0.28–1.71, $P = 0.43$). An unplanned exploratory subgroup analysis confirmed that adjuvant chemotherapy did not improve the RFS of CC when relevant studies [16,22,26] were analyzed (HR = 0.72, 95% CI: 0.40–1.28; $P = 0.26$) (Fig. 5).

Chemotherapy regimen

The chemotherapy regimens of postoperative patients with cholangiocarcinoma are various. Among the 19 studies, gemcitabine-based chemotherapy was the most frequently used regimen [16,18,25,27,28], followed by 5-flurouracil-based regimen [21,33]. Other studies involved more than two types of different chemotherapy regimens, thus the survival data cannot be extracted for specific regimen. Pooled data confirmed a significant benefit for patients who received gemcitabine-based chemotherapy (HR = 0.42, 95% CI: 0.33–0.55; $P < 0.001$). In contrast, the difference was not statistically significant among 5-flurouracil-based studies (HR = 0.90, 95% CI: 0.56–1.44; $P = 0.66$) (Fig. 6).

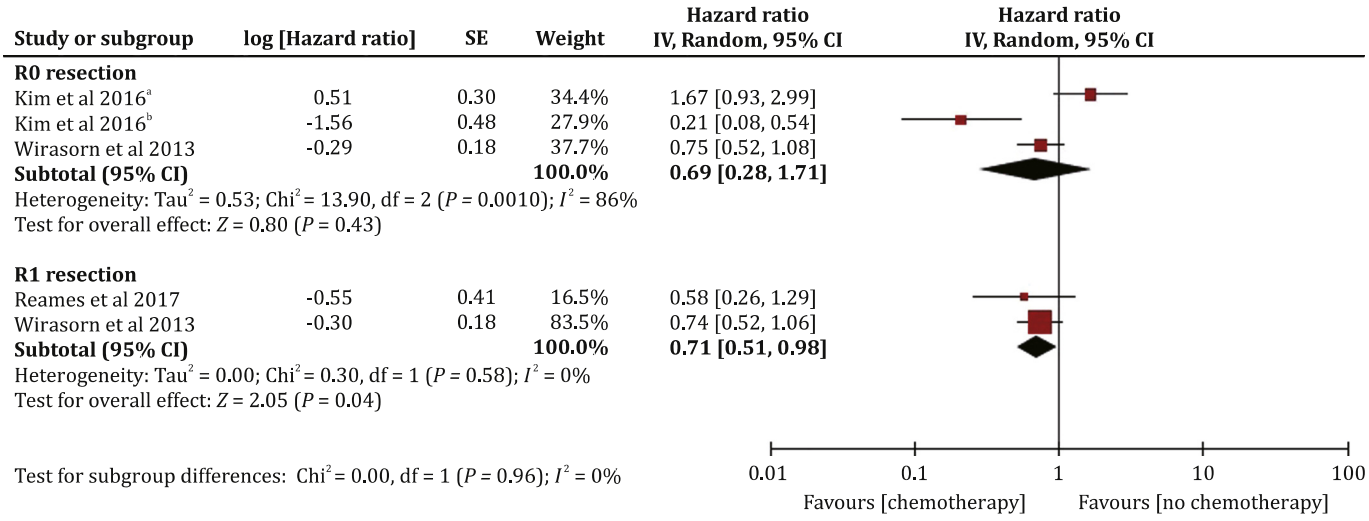

Fig. 4. Subgroup analysis: different margin status. a: reference 26; b: reference 22.

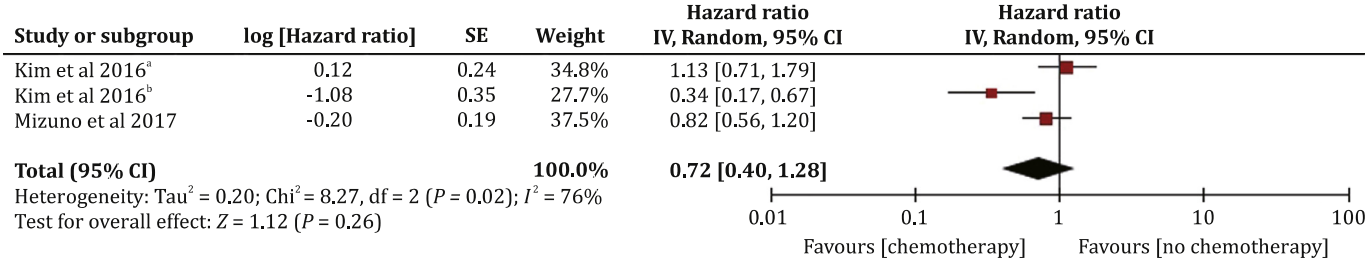

Fig. 5. Forest plot on the recurrence-free survival in cholangiocarcinoma. a: reference 26; b: reference 22.

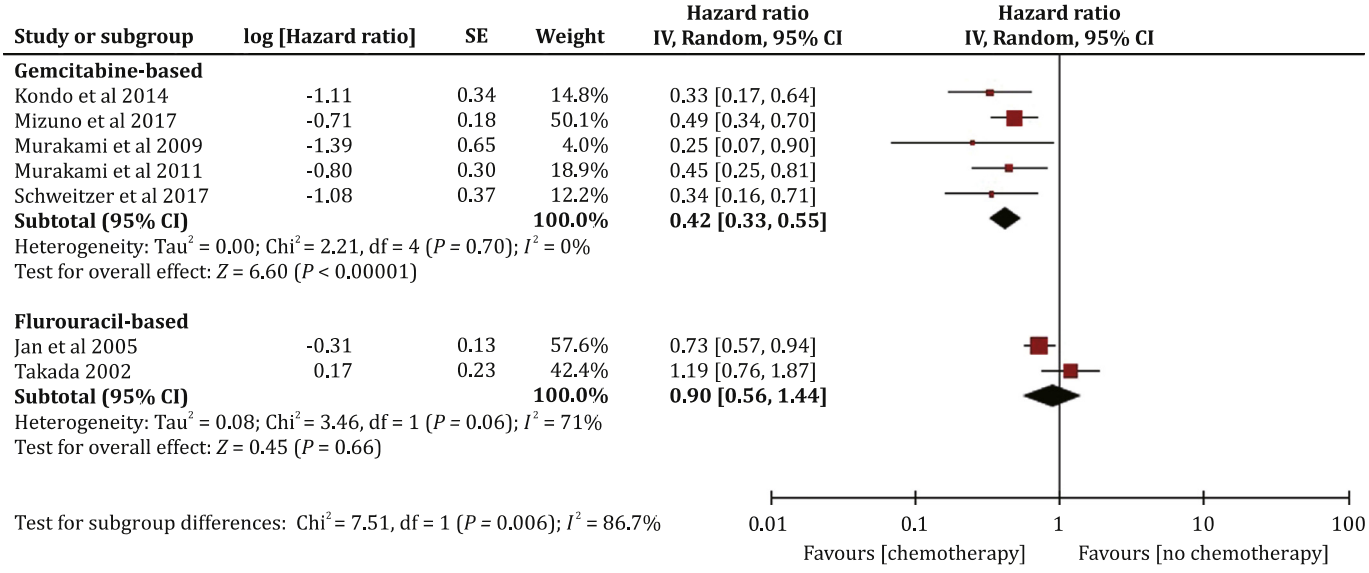

Fig. 6. Forest plot on overall survival in different chemotherapy regimens.

Discussion

The role of postoperative chemotherapy for resectable cholangiocarcinoma is still unclear. Only one RCT research suggested that postoperative adjuvant chemotherapy can improve the five-year survival rate of gallbladder cancer (26% vs 14%; $P=0.0367$), but there were no significant differences between the chemotherapy and control arms in patients with CC (five-year survival, 27% vs 24%) [33]. A number of RCTs are ongoing, and a consensus has not yet been reached [34,35]. In 2012, the meta-analysis of total 6712 patients by Horgan et al. [7] did not confirm a significant OS benefit of adjuvant therapy for biliary cancer patients (pooled OR = 0.74, $P=0.06$). Another meta-analysis by Ghidini et al. [8] analyzed 22,499 patients diagnosed with biliary cancer, of which 18,532 were treated with surgery alone and 3967 received adjuvant therapy. The conclusion is that adjuvant chemotherapy administration gives OS benefits in resected biliary cancer patients (HR = 0.59, $P<0.01$). However, the study bias matters due

to the inclusion of a large number of patients with gallbladder cancer and postoperative radiotherapy.

The present analysis included 19 studies (involving 11,458 patients), and evaluated the outcomes of chemotherapy to treat CC patients. The pooled analysis indicated a significant benefit of adjuvant chemotherapy for unselected patients; similar benefits were also observed in patients with HCCA, ICC, LN-positive metastasis and R1 resection. However, in subgroups defined by geographical regions, a comparable benefit was observed when Korean and Japanese studies were analyzed independently. We found that these studies included many DCC patients. When the DCC subgroup analysis was conducted, the difference was not significant. Therefore, we suggest that adjuvant chemotherapy can be routinely used after operation for ICC and HCCA patients but more trails should be conducted to verify the usefulness of adjuvant chemotherapy for DCC.

Most of the literature included in the present study reported multivariate analyses for prognosis risk factors of CC. Our study suggested that adjuvant chemotherapy should be considered for both LN-positive and R1 resection patients. Besides LN metastasis and positive margin, some researchers also indicated that the tumour T stage [15,16,21,22,25,28–30,32] and high levels of CA19-9 [15,17,23,26,27] were independent predictors for poor OS. For these patients, we suggest that postoperative chemotherapy should be used; however, further research is needed to confirm this suggestion.

In recent years, more researchers support that postoperative chemotherapy combined with radiotherapy can improve the survival rate of cholangiocarcinoma patients. Several retrospective studies show that postoperative radiotherapy can prolong the median survival time (from 8 to 24 months) and the five-year survival rate (from 13.5% to 33.9%) [36–38]. In 2012, Kim et al. [39] found that chemoradiotherapy after curative resection can significantly prolong the survival time of CC patients. In 2018, Nassour et al. [40] conducted a retrospective analysis of 1846 CC patients and concluded that postoperative chemoradiotherapy significantly improved the OS rate compared to adjuvant chemotherapy alone (HR = 0.8, $P = 0.04$). Although most studies supported the combined use of postoperative chemoradiotherapy, no RCTs have been conducted to date.

Some chemotherapy drugs have demonstrated considerable benefit for unresectable CC, such as gemcitabine [41], capecitabine [42], oxaliplatin [43], and S-1 [44]. With regard to resectable CC, although the NCCN guidelines recommend gemcitabine or fluorouracil as the basic chemotherapy drugs [6], the evidence level was low. Based on preliminary results of the phase III BILCAP study [35], adjuvant capecitabine is associated with a 25% lower risk of death compared to control arm for patients with biliary tract cancer. However, the choice of chemotherapy regimen has not been studied. We performed a subgroup analysis for chemotherapy protocols, and the results showed that gemcitabine chemotherapy had a significant improvement in survival, but the difference was not significant between adjuvant fluorouracil-based chemotherapy and operation alone. The results need further confirmed because there were fewer studies on fluorouracil chemotherapy. Previous literatures verified that gemcitabine-based combination chemotherapy yielded more benefits in OS in bile duct cancer patients than other regimens [45,46]. The present analysis also recommends the conventional use of gemcitabine-based chemotherapy after surgery.

This analysis has some limitations. First, eighteen of the studies were retrospective. It is true that there is inherent bias in retrospective studies, with high-risk patients more likely to have been offered adjuvant chemotherapy. Second, these studies included different types of CC, and patients underwent different operations and surgical methods, which may affect the prognosis.

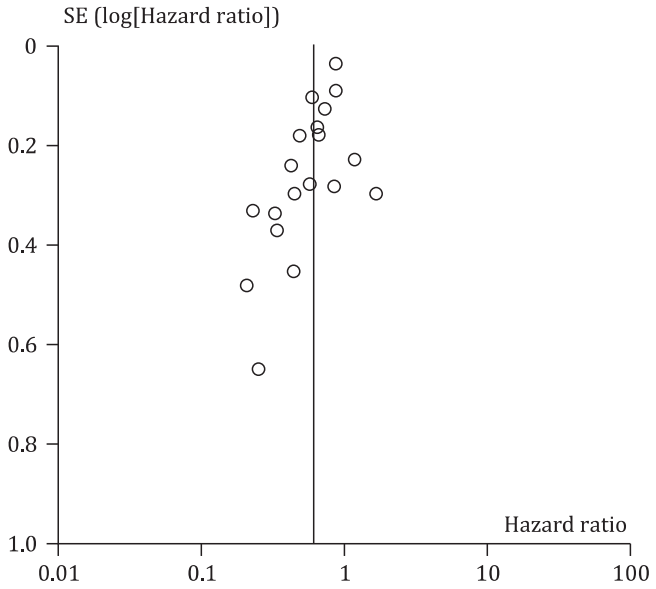

Fig. 7. Funnel plot of overall survival in cholangiocarcinoma patients.

Third, the heterogeneity of this paper was obvious; in order to find the source, we conducted subgroup analyses and simple sensitivity analyses, but neither could explain it. Therefore, we think that the use of random-effects modeling adequately addresses this heterogeneity. Fourth, for the literatures that did not provide HRs, we used Engauge Digitizer 4.1 and the tables provided by Tierney et al. [12] to calculate an HR from the survival curves, which may result in some differences with the original data. Furthermore, significant publication bias emerged from a funnel plot (Fig. 7), and different study designs could have substantially contributed to heterogeneity among publications.

The present study was the first meta-analysis to investigate the value of systemic chemotherapy in patients with resected CC. We also raised some questions—for example, what is the effect of adjuvant chemotherapy on distal CC and R0 resection patients—that may contribute to the design rationale of posterior prospective studies.

In conclusion, this strict meta-analysis indicated that postoperative adjuvant chemotherapy can improve the OS in CC patients. Subgroup analysis suggested that ICC and HCCA patients can benefit from adjuvant chemotherapy after operation. However, adjuvant chemotherapy is not recommended in DCC patients with R0 resection. Prospective randomized trials are needed to define the standard chemotherapy regimen.

Contributors

WML conceived the study. WML and KZY participated in the study design. WML, KZY and LCH searched the literature. WML and KZY collected the data. WML analyzed the data. All authors contributed to the interpretation of the study and to further drafts. WML and KZY contributed equally to the article. HQ is the guarantor.

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Ethical approval

Not needed.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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