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Role of adjuvant (chemo)radiotherapy for resected extrahepatic cholangiocarcinoma: a meta-analysis*#

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Abstract: Background: Adjuvant (chemo)radiotherapy (A(C)RT) may be an important supplement to surgery for extrahepatic cholangiocarcinoma (EHCC). However, whether all patients would achieve benefits from A(C)RT and which adjuvant regimen, adjuvant radiotherapy (ART) or adjuvant chemoradiotherapy (ACRT), would be preferred, are still undetermined. The low incidence of EHCC makes it difficult to carry out randomized controlled trials (RCTs); therefore, almost all clinical studies on radiotherapy are retrospective. We have conducted a meta-analysis of these retrospective studies. Methods: We conducted a meta-analysis of current retrospective studies using PubMed, Embase, and ClinicalTrials databases. All studies published in English that were related to A(C)RT and which analyzed overall survival (OS), disease-free survival (DFS), or locoregional recurrence-free survival (LRFS) were included. Estimated hazard ratios (HRs) were calculated for OS, DFS, and LRFS. Results: Data from eight studies including 685 patients were included. Our analysis showed that A(C)RT significantly improved OS (HR 0.69, 95% confidence interval (CI) 0.48–0.97, *P*=0.03), DFS (HR 0.60, 95% CI 0.47–0.76, *P*<0.0001), and LRFS (HR 0.27, 95% CI 0.17–0.41, *P*<0.00001) of EHCC overall. In subgroups, patients with microscopically positive resection margin (R1) could achieve a benefit from A(C)RT (HR 0.44, 95% CI 0.27–0.72, *P*=0.001). No statistically OS difference was observed in negative resection margin (R0) subgroup (HR 0.98, 95% CI 0.30–3.19, *P*=0.98).Significant OS benefit was found in patients who received concurrent ACRT (HR 0.40, 95% CI 0.26–0.62, *P*<0.0001), while the result of ART without chemotherapy showed no significant benefit (HR 1.14, 95% CI 0.29–4.50, *P*=0.85). In the distal cholangiocarcinoma subgroup, no significant difference was seen when ACRT and ART were included (HR 0.61, 95% CI 0.14–2.72, *P*=0.52), but a significant difference was seen when analyzing the concurrent ACRT only (HR 0.29, 95% CI 0.13–0.64, *P*=0.002). Conclusions: A(C)RT may improve OS, DFS, and LRFS in EHCC patients, especially in those with R1 resection margins. ACRT may be superior to ART especially in distal patients.

Key words: Adjuvant (chemo)radiotherapy; Extrahepatic cholangiocarcinoma; Meta-analysis; Disease-free survival; Overall survival

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1 Introduction

Cholangiocarcinoma is a rare malignancy with poor prognosis. The incidence of cholangiocarcinoma is between 0.35 to 2.00 per 100000 annually in the Western world, but in Asia the incidence could be up to 40 times the rate observed in Western countries (Bridgewater et al., 2016). Extrahepatic cholangiocarcinoma (EHCC) comprises approximately 75% of all cholangiocarcinomas (Doherty et al., 2017). The five-year overall survival (OS) rate of EHCC ranges

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from 2% to 30%, depending on stage (Chaiteerakij et al., 2014). EHCC is further subdivided into perihilar cholangiocarcinoma and distal cholangiocarcinoma based on anatomic location. Curative surgery provides the only chance for cure. However, it was reported that fewer than one-third of patients were deemed to have resectable disease at the time of diagnosis (Khan et al., 2012), and even after resection, the postoperative five-year OS rates for perihilar cholangiocarcinoma and distal cholangiocarcinoma were 24.2% and 39.8%, respectively (Ishihara et al., 2016).

Adjuvant therapy has been used to improve the outcome of EHCC and has received increasing attention in the past ten years. In the latest National Comprehensive Cancer Network (NCCN) guidelines, adjuvant treatment regimens for EHCC based on adjuvant chemoradiotherapy (ACRT) are recommended. However, whether all EHCC patients or certain subgroups could benefit from ACRT or adjuvant radiotherapy (ART) is still undetermined because of the limited clinical data (NCCN, 2019). To date, almost all clinical data available are from retrospective studies, because the low incidence of EHCC makes it difficult to recruit enough patients for randomized controlled trials (RCTs). Moreover, the inclusion criteria of patients and adjuvant (chemo)radiotherapy (A(C)RT) regimens were not uniform in those retrospective studies. Several studies also included gallbladder and other bile duct tumors.

Meta-analysis is a reasonable alternative when large randomized trials are not feasible. A previous meta-analysis (Bonet Beltrán et al., 2012) discussed the value of A(C)RT after curative resection of EHCC; however, the study included intraluminal brachytherapy mixed with external beam radiotherapy, as well as gallbladder cancer and other extrahepatic biliary tract tumors with EHCC. Consequently, the results of the study were of little value in present clinical practice. Therefore, we performed a meta-analysis to explore the benefits of A(C)RT vs. surgery alone in EHCC.

2 Methods

2.1 Search strategy

We searched for relevant studies in PubMed, Embase, and ClinicalTrials (https://clinicaltrials.gov) databases with no publication type or time restrictions (up to Oct. 10, 2019). The main search terms were as follows: extrahepatic/perihilar cholangiocarcinoma, biliary tract cancers, adjuvant (chemo)radiotherapy, postoperative (chemo)radiotherapy, radiotherapy/radiation therapy after surgery/resection and clinical trial. Meeting abstracts and presentations at the American Society of Clinical Oncology Annual Meetings and the European Society of Medical Oncology Congresses from 2009 to 2019 were searched manually. The reference lists of some key articles were also searched manually.

This meta-analysis was registered at the International Prospective Register of Systematic Reviews (No. CRD42020149802).

2.2 Inclusion and exclusion criteria

Inclusion criteria were: (1) studies involving patients with clearly diagnosed EHCC; (2) studies comparing treatments between ACRT or ART and surgery only, which meant that studies had to include patients who underwent surgery alone as a comparator group; (3) studies reporting hazard ratios (HRs) of OS and/or disease-free survival (DFS), or studies in which these data could be calculated; and (4) studies reported in English.

Exclusion criteria were: (1) relevant data that were not reported and could not be calculated; (2) studies that enrolled intraluminal brachytherapy in the A(C)RT group; (3) studies that enrolled adjuvant chemotherapy (ACT) without ART in the experimental group; and (4) studies that enrolled patients with gallbladder cancer or intrahepatic cholangiocarcinoma together with EHCC but specific data for EHCC were not provided.

The outcomes assessed were OS, DFS, and locoregional recurrence-free survival (LRFS) of patients in the two groups. OS was defined as time to death or to the end of follow-up. DFS was defined as time to any recurrence or death, whichever occurred first. LRFS was defined as the time from the date of surgery to the date of treatment failure in the postsurgical tumor bed (Kim YJ et al., 2017).

Two authors reviewed study titles and abstracts, and studies that satisfied the inclusion criteria were retrieved for full-text evaluation. Data of the trials selected for detailed analysis were extracted independently by two authors, and disagreements were resolved by discussion. We extracted the following data from the selected studies: study period, center, total number of patients, age, sex, pathology, primary site of tumor, tumor-node-metastasis (TNM) stage, lymphovascular invasion, perineural invasion, resection margin status, lymph node (LN) status, total and

fraction dose of ART, with concurrent chemotherapy or not, chemotherapy regimen, follow-up time, and HRs of OS, DFS, and LRFS of the two groups (Tables 1 and S1). Also, we paid attention to radiation-induced toxicity.

2.3 Assessment of study quality

Because the included studies were all retrospective, we used the Newcastle-Ottawa Scale (NOS) (Wells et al., 2019) for assessing study quality. Studies that received 7–9 stars were considered to be high-quality, those that received 4–6 stars were defined as moderate-quality, and those that received 0–3 stars were regarded as low-quality (Table S2).

2.4 Statistical analysis

The primary outcome evaluated was OS, and the secondary outcomes were DFS and LRFS. Estimated HRs were calculated for OS, DFS, and LRFS. If the HR and its 95% confidence interval (CI) were not provided in the original article, they were calculated from available reported data as described previously (Tierney et al., 2007). We calculated I^2 and Q to evaluate the heterogeneity of the included studies. If P was <0.1 and I^2 was ≥50%, the heterogeneity was considered significant (Lau et al., 1997; Higgins and Thompson, 2002). When significant heterogeneity between studies was observed, the random-effects model was used; otherwise, the fixed-effects model was used (DerSimonian and Laird, 1986). Publication bias was assessed using the Egger's test by the funnel plot method (Egger et al., 1997). Publication bias was considered to be present if the 2-tailed P value with Egger's test was <0.05. We also sub-grouped patients by resection margin status, LN metastasis, adjuvant therapy regimen (ACRT or ART), and the site of the tumor (perihilar or distal). Statistical analyses were done using Review Manager Version 5.3 software (Cochrane collaboration, Oxford, UK) and publication bars were derived with the STATA 11.0 package (Stata Corp., College Station, TX, USA).

3 Results

3.1 Baseline characteristics of included studies

Our initial search identified 433 studies. We excluded 406 studies by title and abstract. We read the full-text of the remaining 27 articles and excluded 19; among which, seven were based on the National Cancer Database (NCDB)/Surveillance, Epidemiology, and End Results (SEER) database; one included patients undergoing intraoperative radiotherapy (IORT); two included patients undergoing intraluminal brachytherapy; three included patients who received ACT without ART in the adjuvant therapy group; five studies included intrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer, while the data for EHCC were not provided; one study received only three stars in the NOS scale and was regarded as low-quality. Ultimately, we identified eight articles (Itoh et al., 2005; Hughes et al., 2007; Gwak et al., 2010; Matsuda et al., 2013; Im et al., 2016; Kim MY et al., 2016; Kim YS et al., 2016; Kim YJ et al., 2017) that met our inclusion criteria. The inclusion process is described in Fig. 1. In these eight articles, patients of the A(C)RT group received external beam radiotherapy, the mean dose ranging from 50.4 to 52.3 Gy. The concurrent chemotherapy agents used in the A(C)RT group included 5-fluorouracil (5-FU), capecitabine, and gemcitabine (Table 1). All eight studies were retrospectively designed; seven received 4–6 stars and the other one received 7 stars according to the NOS, and were evaluated as moderate- and high-quality studies, respectively (Table S2).

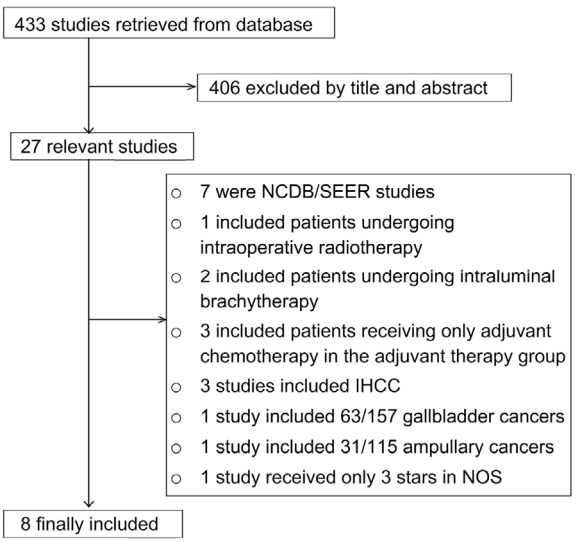

Fig. 1 Flow diagram showing the selection process for the included studies

NCDB: National Cancer Database; SEER: Surveillance, Epidemiology, and End Results; IHCC: intrahepatic cholangiocarcinoma; NOS: Newcastle-Ottawa Scale

Table 1 Characteristics of the included studies

Study	Study period	Center	Patient number (A(C)RT vs. control)	Primary site	TNM stage
Gwak et al., 2010	1997 to 2005	Korea	31 vs. 47	Perihilar/distal	I–III
Hughes et al., 2007	1994 to 2003 1970 to 1992	USA	34 vs. 30	Distal	II–III
Im et al., 2016[#]	Jan. 2001 to Dec. 2010	Korea	49 vs. 168	Perihilar/distal	I–III
Im et al., 2016[#]	Jan. 2001 to Dec. 2010	Korea	29 vs. 168	Perihilar/distal	I–III
Itoh et al., 2005	Apr. 1994 to Mar. 2004	Japan	11 vs. 8	Perihilar/distal	I–III
Kim MY et al., 2016	Jan. 2000 to Dec. 2013	Korea	19 vs. 33	Perihilar/distal	I–III
Kim YJ et al., 2017	1997 to 2015	Korea	23 vs. 36	Perihilar/distal	
Kim YS et al., 2016[#]	Jan. 2001 to Dec. 2013	Korea	20 vs. 102	Distal	I–III
Kim YS et al., 2016[#]	Jan. 2001 to Dec. 2013	Korea	9 vs. 102	Distal	I–III
Matsuda et al., 2013	Jan. 2000 to Mar. 2010	Japan	11 vs. 25	Perihilar/distal	I–IVB

Study	Radiation therapy dose (Gy)[*]	Concurrent chemotherapy used in A(C)RT group	CRT patients number in A(C)RT group	Resection margin status	LN status
Gwak et al., 2010	50.4 (45.0–54.0)	5-FU based	16/31	R0/R1	N(+)/N(−)
Hughes et al., 2007	50.4 (40.0–54.0)	5-FU based	34/34	R0/R1/R2	N(+)/N(−)
Im et al., 2016[#]	50.4 (41.4–54.0)	5-FU/gemcitabine based	49/49	R0/R1/R2	N(+)/N(−)
Im et al., 2016[#]	50.4 (41.4–54.0)	No	0/29	R0/R1/R2	N(+)/N(−)
Itoh et al., 2005	52.3 (37.8–79.8)	No	0/11	R0/R1/R2	N(+)/N(−)
Kim MY et al., 2016	50.4 (45.0–54.0)	5-FU/gemcitabine based	12/19	R0/R1	N(+)/N(−)
Kim YJ et al., 2017	50.4 (45.0–61.0)	5-FU/gemcitabine based	15/23	R0/R1/R2	N(+)/N(−)
Kim YS et al., 2016[#]		5-FU/capecitabine/ gemcitabine based	20/20	R0	N(+)/N(−)
Kim YS et al., 2016[#]		No	0/9	R0	N(+)/N(−)
Matsuda et al., 2013	46.0–60.0	Unknown	5/11	R0/R1	N(+)/N(−)

A(C)RT: adjuvant (chemo)radiotherapy; TNM: tumor-node-metastasis; 5-FU: 5-fluorouracil; CRT: concurrent chemoradiotherapy; R0: negative resection margin; R1: microscopic positive resection margin; R2: macroscopic positive resection margin; LN: lymph node. [#] Two articles contained three groups, comparing ACRT vs. surgery alone and ART vs. surgery alone; thus, they were calculated respectively (Im et al., 2016; Kim YS et al., 2016). [*] Data are expressed as median (range), except that from Matsuda et al. (2013)

Two articles contained three groups, comparing ACRT vs. surgery alone and ART vs. surgery alone; thus, they were calculated respectively (Im et al., 2016; Kim YS et al., 2016). OS data could be obtained from all included studies. As for DFS, Gwak et al. (2010) provided data of A(C)RT vs. surgery alone in the microscopic positive resection margin (R1) and negative resection margin (R0) subgroups, which were calculated respectively. Im et al. (2016) explored progression-free survival (PFS, defined as time from date of resection to first reported recurrence or death) instead of DFS. We included the PFS in DFS analysis since all the patients had undergone surgery. There were three articles reporting LRFS (Im et al., 2016; Kim MY et al., 2016; Kim YJ et al., 2017).

3.2 Efficacy of A(C)RT on OS

The meta-analysis of all relevant studies showed that the A(C)RT group had significantly better OS than the surgery alone group, although these trials showed significant heterogeneity (HR 0.69, 95% CI 0.48–0.97, P=0.03, I^2=53%, random-effects model; Fig. 2). To explore further which patients benefited from A(C)RT, we performed subgroup analysis firstly according to the resection margin status and LN metastasis status because these are important factors affecting prognosis of EHCC. Patients with R1 resection margin could achieve a benefit from A(C)RT with low heterogeneity (HR 0.44, 95% CI 0.27–0.72, P=0.001, I^2=0%, fixed-effects model; Fig. 3a). There was no statistical OS difference observed in the R0 subgroup comparing A(C)RT with surgery only (HR 0.98, 95% CI 0.30–3.19, P=0.98, I^2=78%, random-effects model; Fig. 3b). Only one article provided data for patients who had positive LN metastasis (LN(+)), thus an LN(+) subgroup could not be performed. Significant OS benefit was found in patients who received concurrent ACRT (HR 0.40, 95% CI 0.26–0.62, P<0.0001, I^2=0%, fixed-effects model; Fig. 3c) while the result of ART without chemotherapy showed no significant benefit (HR 1.14, 95% CI 0.29–4.50, P=0.85, I^2=86%, random-effects model; Fig. 3d). We

also did subgroup analysis according to the site of tumor. Because of limited data, we could not analyze a perihilar subgroup. In the distal cholangiocarcinoma subgroup, we did not get a significant difference when adjuvant chemoradiation and adjuvant radiation were analyzed (HR 0.61, 95% CI 0.14–2.72, P=0.52, I^2=85%, random-effects model; Fig. 3e). However, it is worth noting that in the three studies included, two studies were concurrent chemoradiotherapy vs. surgery while one study was ART alone vs. surgery. So we performed an ACRT for distal cholangiocarcinoma subgroup, and as we expected, significant OS benefit was observed (HR 0.29, 95% CI 0.13–0.64, P=0.002, I^2=0%, fixed-effects model; Fig. 3f).

3.3 Efficacy of A(C)RT on DFS and LRFS

Significant differences in DFS were observed between patients who did and did not receive A(C)RT (HR 0.60, 95% CI 0.47–0.76, P<0.0001, I^2=26%, fixed-effects model; Fig. 4). In subgroup analysis, patients who underwent R1 resection achieved a significant benefit in DFS from A(C)RT (HR 0.38, 95% CI 0.18–0.78, P=0.008, I^2=63%, random-effects model; Fig. 5). There were inadequate data to perform further subgroup analyses.

Four studies provided information about LRFS. LRFS of EHCC also benefited from A(C)RT overall (HR 0.27, 95% CI 0.17–0.41, P<0.00001, I^2=0%, fixed-effects model; Fig. 6).

3.4 Treatment toxicity

Radiation-induced toxicities, as reported in the selected studies, are shown in Table S3. The grade of toxicity was scored according to the Common Terminology Criteria for Adverse Events v.3.0. Kim MY et al. (2016) reported that two patients experienced grade 3 duodenal ulcer at 14 and 36 months after ART. Kim YJ et al. (2017) showed two patients suffered grade 3 toxicity among 23 patients, one patient experiencing severe nausea and vomiting and the other patient having decreased platelet and white blood cell count. No other grade 3 or greater toxicity was observed.

3.5 Publication bias

Funnel plots of publication bias are shown in Fig. 7. There was no publication bias for OS (Begg's P=0.929, Egger's P=0.933), DFS (Begg's P=0.452, Egger's=0.257), or LRFS (Begg's P=0.308, Egger's= 0.301).

4 Discussion

Adjuvant therapy including ACT, ART, and ACRT as an important supplement to surgery has attracted the attention of many researchers in recent years, but the benefits remain unclear. A randomized, controlled, multi-center, phase III study compared capecitabine with observation following resection of biliary tract cancer; the OS primary endpoint in the intention-to-treat population did not reach statistical significance while the per-protocol OS and recurrence-free survival analyses showed benefit (Primrose et al., 2019). A meta-analysis indicated that ACT could improve OS in perihilar cholangiocarcinoma patients, but distal cholangiocarcinoma patients gained no benefit from ACT (Wang et al., 2019). A phase II trial Southwestern Oncology Group (SWOG) S0809 analyzed the effect of gemcitabine and capecitabine

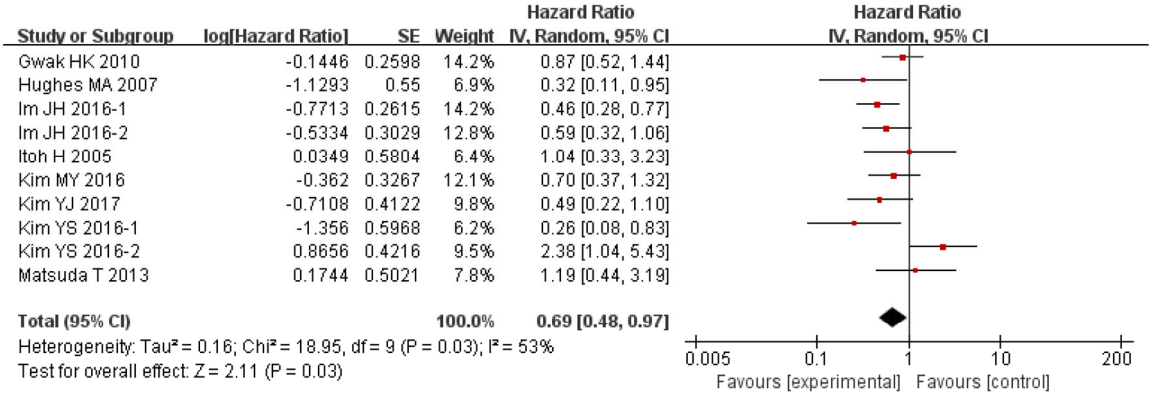

Fig. 2 Forest plot showing HR for OS between A(C)RT and surgery alone groups in all included studies

HR: hazard ratio; OS: overall survival; A(C)RT: adjuvant (chemo)radiotherapy; SE: standard error; CI: confidence interval

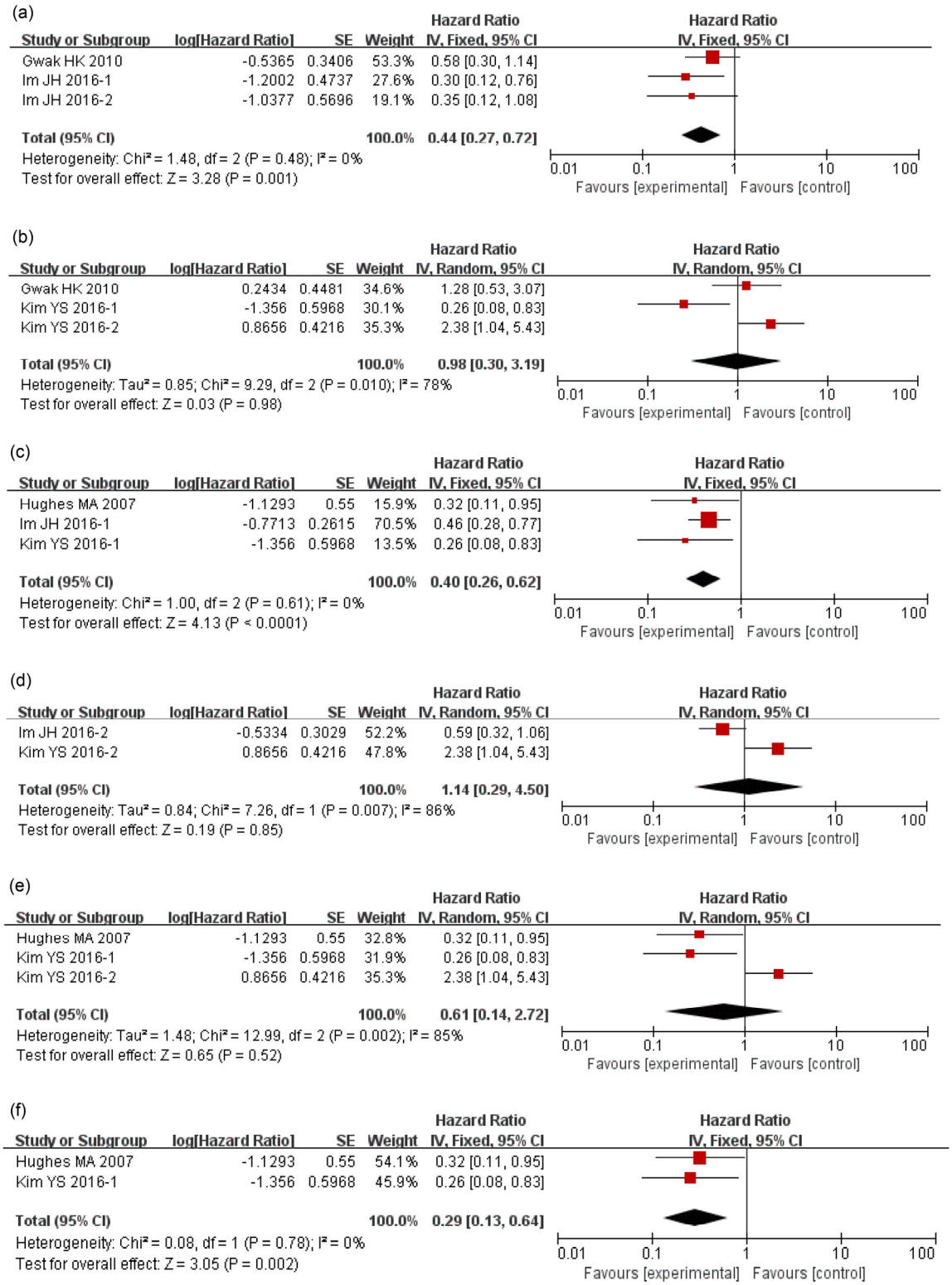

Fig. 3 Forest plot showing HR for OS between A(C)RT and surgery alone groups in subgroup analysis

(a) R1 subgroup; (b) R0 subgroup; (c) ACRT subgroup; (d) ART subgroup; (e) ACRT and ART in distal EHCC subgroup; (f) ACRT only in distal EHCC subgroup. HR: hazard ratio; OS: overall survival; A(C)RT: adjuvant (chemo)radiotherapy; R1: positive resection margin; R0: negative resection margin; ACRT: adjuvant chemoradiotherapy; ART: adjuvant radiotherapy; EHCC: extrahepatic cholangiocarcinoma; SE: standard error; CI: confidence interval

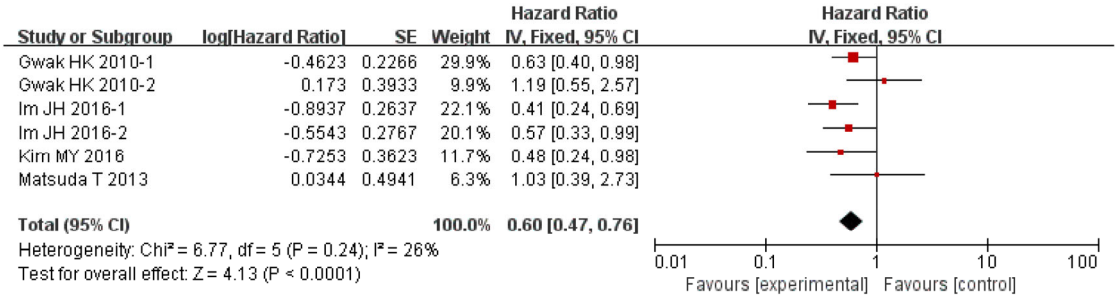

Fig. 4 Forest plot showing HR for DFS between A(C)RT and surgery alone groups in all studies included

HR: hazard ratio; DFS: disease-free survival; A(C)RT: adjuvant (chemo)radiotherapy; SE: standard error; CI: confidence interval

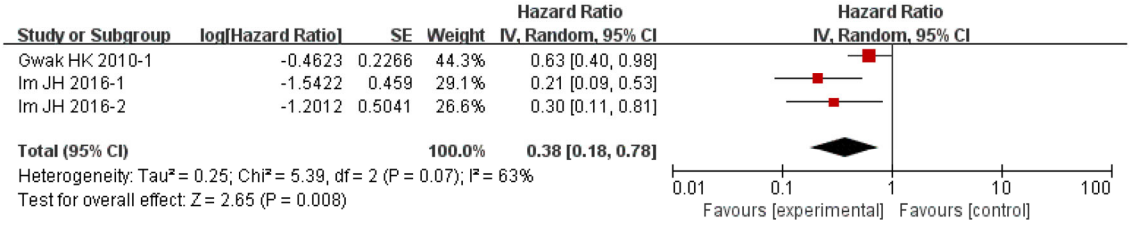

Fig. 5 Forest plot showing HR for DFS between A(C)RT and surgery alone groups in R1 subgroup

HR: hazard ratio; DFS: disease-free survival; A(C)RT: adjuvant (chemo)radiotherapy; SE: standard error; CI: confidence interval

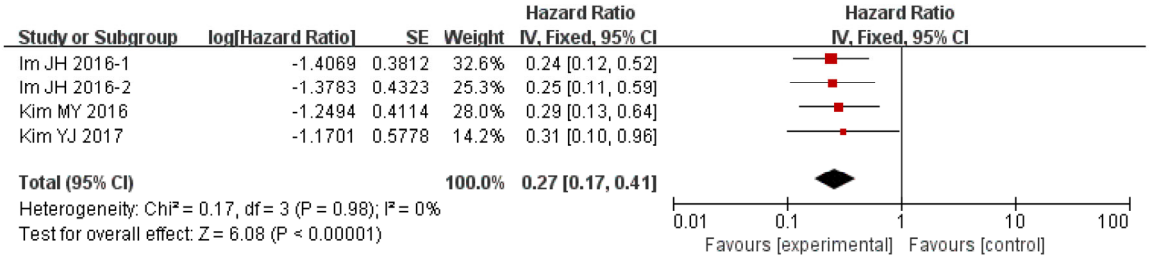

Fig. 6 Forest plot showing HR for LRFS between A(C)RT and surgery alone groups in all studies included

HR: hazard ratio; LRFS: locoregional recurrence-free survival; A(C)RT: adjuvant (chemo)radiotherapy; SE: standard error; CI: confidence interval

followed by concurrent capecitabine and radiotherapy in resected EHCC (68%) and gallbladder carcinoma (32%). The results of the trial implied that ACRT could be an effective and promising treatment method (Ben-Josef et al., 2015). Therefore we sought to elucidate the role and effective subgroups of A(C)RT. To date, there were no data from RCTs. We asked the following questions: how much benefit can A(C)RT bring to patients? Which subgroup of patients could benefit from A(C)RT? Which regimen is the better option? Therefore, we analyzed the existing retrospective data and performed a meta-analysis, hoping to answer these questions.

According to our analyses for all patients, A(C)RT significantly improved OS, DFS, and LRFS in EHCC. A study, based on NCDB, which included 8741 patients between 1998 and 2006, also argued that A(C)RT was associated with survival improvement in EHCC (Hoehn et al., 2015). This is consistent with our meta-analysis. There were some previous studies not supporting our results. Two studies based on SEER database showed that A(C)RT was not associated with improvement in long-term OS (Shinohara et al., 2009; Vern-Gross et al., 2011). However, one of them admitted that because of the lack of some key data, including margin status and use of combined chemotherapy,

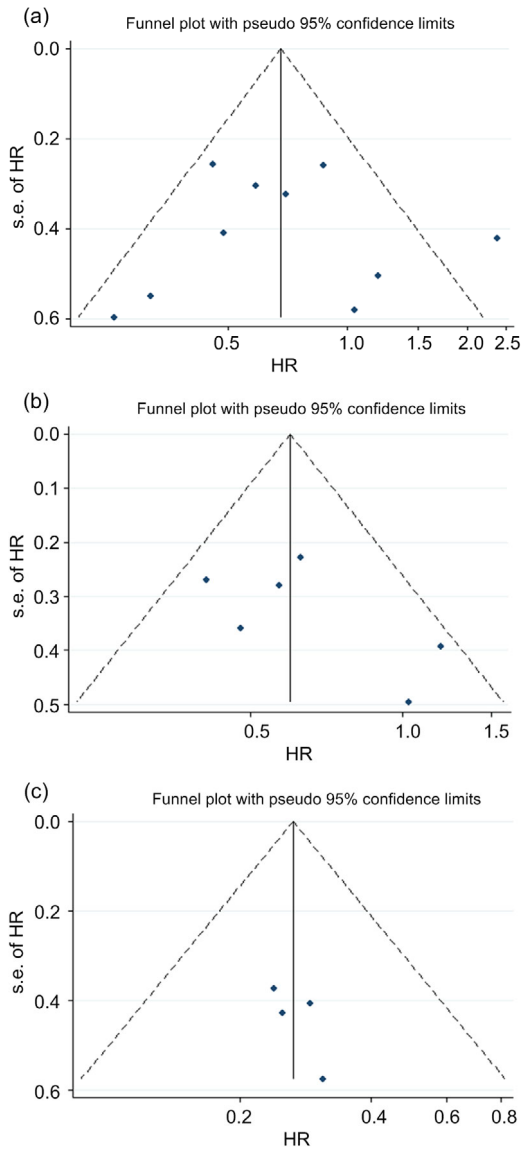

Fig. 7 Funnel plots showing publication bias of included studies

(a) OS; (b) DFS; (c) LRFS. OS: overall survival; DFS: disease-free survival; LRFS: locoregional recurrence-free survival; HR: hazard ratio; s.e.: standard error

in the SEER database, they failed to determine whether A(C)RT was beneficial for the local control in some subgroups (Vern-Gross et al., 2011). The other argued that, in carefully selected patients, such as those with positive margins, A(C)RT would be of benefit (Shinohara et al., 2009).

R0 resection is related with good prognosis but could be achieved in fewer than one-third of EHCC patients, and local clearance (R0 or R1 status) was independently associated with survival (Khan et al., 2012). Therefore, we did subgroup analysis, based on resection margins, to explore the value of A(C)RT in R1 and R0 subgroups and we found that A(C)RT was beneficial in the R1 but not the R0 subgroup. One study on distal cholangiocarcinoma also indicated that long-term survival may be achieved in patients with R0 resection (Chua et al., 2017). A study by Lee et al. (2018) compared patients who underwent R0 resection without any adjuvant treatment with those who underwent R1 resection but received A(C)RT; as a result, no significant survival difference was observed. This suggested that A(C)RT ameliorated the negative effect of microscopic positive resection margins, which is consistent with our meta-analysis.

Compared with ART, ACRT can increase radiation sensitivity of tumor cells, control microscopic residual tumor growth, and reduce distant recurrence from hematogenous spread, thus reducing the recurrence risk (Jarnagin et al., 2003; Im et al., 2016; Sahai and Kumar, 2017). At the same time, ACRT may be associated with more toxicity. ACRT rather than ART has become an indispensable treatment in other digestive tract tumors, such as rectal cancer (Yoon et al., 2019) and gastric cancer (Yu et al., 2019). In our analysis, the ACRT subgroup showed significant OS improvement in EHCC rather than ART. Similarly, the study of Kim YS et al. (2017) showed that ACRT significantly improved recurrence-free survival than in the "surgery only" group and suggested that ACRT appeared to be an appropriate treatment in perihilar cholangiocarcinoma after complete resection. Prospective RCTs are needed to confirm the superiority of ACRT over ART.

Prognosis of EHCC is influenced by location (Nakeeb et al., 1996). So we also explore the impact of A(C)RT on EHCC in different sites. In the distal cholangiocarcinoma subgroup, three studies were included. Among them, two studies compared ACRT with observation after resection, and one study compared ART (no chemotherapy performed) with observation after resection (Hughes et al., 2007; Kim YS et al., 2016). No significant benefit was seen in distal EHCC when including studies with ACRT and ART, but significant outcomes were seen when analyzing ACRT studies only, which was consistent with the proposition that ACRT rather than ART would benefit, as discussed above. Kim YS et al. (2016) pointed out that the small size of the ART group might influence

the evaluation of the efficacy of ART, and the adverse effect of radiotherapy might be obvious in the small group of people. Despite this, he argued that the survival benefit in the ACRT group was statistically significant. We need more studies to assess the effect of ART alone, but current studies show that distal cholangiocarcinoma patients could benefit from ACRT (Kim YS et al., 2016). So we argue that for patients with resected distal cholangiocarcinoma, ACRT should be recommended. We also tried to perform the perihilar subgroup, but we failed because of the limited data.

Only a few patients in these study experienced treatment-induced toxicity, which could not be analyzed statistically. No patient-reported outcomes could be analyzed. We have described the toxicity in results, hoping to provide a reference for further research.

The following limitations should be considered when interpreting our study. First, because of the lack of RCTs, all included studies were retrospectively designed, and thus randomized control could not be achieved and clinicopathologically detailed covariates were not adequately adjusted. The unequal radiation dose and chemotherapy drugs might also lead to heterogeneity. Second, because of the limited number of articles, we could not make more detailed subgroups such as perihilar or macroscopic residual (R2) resection. Third, no direct comparison to ACT could be made, so we could not answer the question of ACT vs. ACRT. Fourth, the analysis was done at the level of data available from the full text of the paper, so there might be biases and confounding factors that were unaccounted for. Also, the studies included were overwhelmingly from East Asian populations, so it was unclear how well these findings might be applied to other non-East Asian patient populations.

Funnel plots of OS, DFS, and LRFS were basically symmetrical, suggesting no publication bias. We also did Egger's regression test (Egger et al., 1997) and Begg's rank correlation test (Begg and Mazumdar, 1994) to evaluate publication bias; the *P* values were all greater than 0.1, which confirmed the outcome of funnel plots.

We look forward to RCTs being performed in the future. We also suggest that more retrospective data be summarized, from more different medical centers and in more detailed subgroups. For those who would undergo ACRT, we need to conduct clinical trials to find out the best regimen of concurrent chemotherapy and the best program of radiotherapy. For those who could not tolerate chemotherapy, we suggest ART be an option since current studies cannot rule out the potential benefit of ART.

5 Conclusions

A(C)RT may improve OS, DFS, and LFRS in EHCC patients, especially in those with R1 resection margins. ACRT may be superior to ART especially in distal patients.

Contributors

Ai-lin LI designed the study. Xin-qi SHI participated in the study design, performed the data collection and analyses, and wrote and edited the manuscript. Jing-yu ZHANG, Hua TIAN, and Ling-na TANG participated in literature screening and the drafting of the manuscript. All authors have read and approved the final manuscript and, therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Xin-qi SHI, Jing-yu ZHANG, Hua TIAN, Ling-na TANG, and Ai-lin LI declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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List of electronic supplementary materials

Table S1 Characteristics of the included studies

Table S2 Newcastle-Ottawa Scale (NOS) for quality assessment of non-randomized studies in the meta-analysis (cohort studies)

Table S3 Toxicities (CTCAE Version 3.0) reported in the selected studies

中文概要

题　目：辅助放(化)疗在肝外胆管细胞癌中的作用：荟萃分析

目　的：分析术后辅助放(化)疗在肝外胆管细胞癌中的作用，找到具体哪些临床亚组能从辅助放(化)疗中获益。

创新点：本研究报告了辅助放(化)疗可以改善肝外胆管细胞癌患者尤其是显微镜下切缘阳性患者的总生存期、无病生存期和无转移生存期，为这一无定论的临床问题提供循证证据。

方　法：我们检索了截至 2019 年 10 月，收录在 PubMed、Embase 和 ClinicalTrials 三个数据库中关于术后辅助放(化)疗在肝外胆管细胞癌中的作用的文献。经过筛选，最终有 8 篇文献符合纳入标准，并采用 RevMan 软件进行数据分析。

结　论：辅助放(化)疗可以改善肝外胆管细胞癌患者的总生存期、无病生存期和无转移生存期，尤其是在显微镜下阳性切缘的患者中。辅助同步放化疗可能优于单纯辅助放疗，尤其是在远端胆管癌患者中。

关键词：辅助放(化)疗；肝外胆管细胞癌；荟萃分析；无病生存期；总生存期