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

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



中國醫科大學
CHINA MEDICAL UNIVERSITY

# 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).

●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).

●We performed a meta analysis to explore the benefits of A(C)RT vs. surgery alone in EHCC.

# Methods

●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.

●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.

# Methods

●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; (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.

●Because the included studies were all retrospective, we used the Newcastle-Ottawa Scale (NOS) (Peterson et al., 2018) for assessing study quality.

# Methods

●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. We calculated I2 and Q to evaluate the heterogeneity of the included studies. If P was <0.1 and I2 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).

# Results

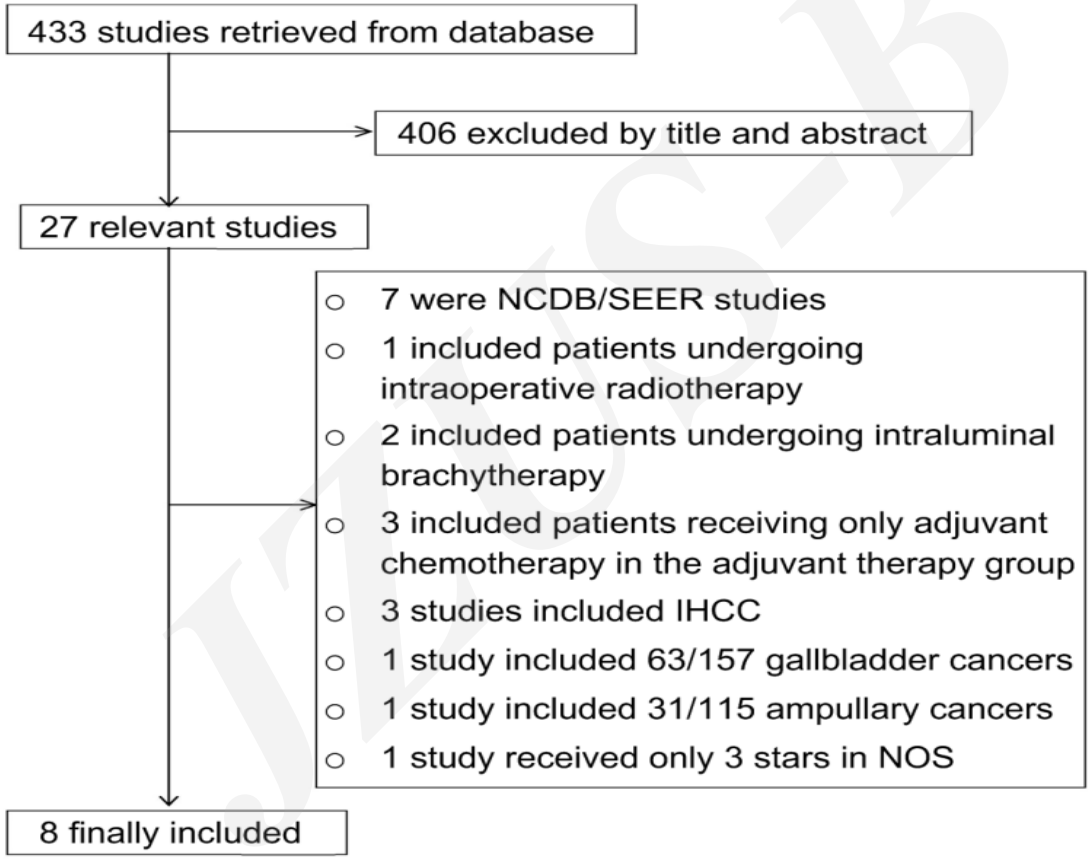
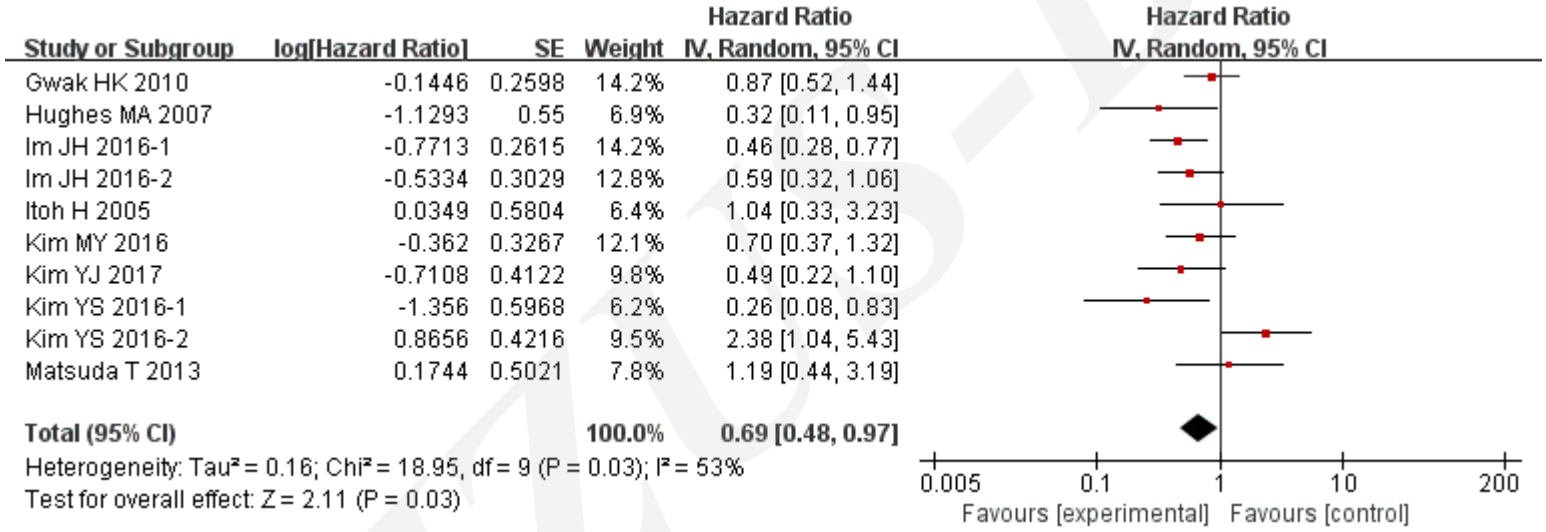



Fig. 1 Flow diagram showing the selection process for the included studies

# Results



| Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Gwak HK 2010 | -0.1446 | 0.2598 | 14.2% | 0.87 [0.52, 1.44] |
| Hughes MA 2007 | -1.1293 | 0.55 | 6.9% | 0.32 [0.11, 0.95] |
| Im JH 2016-1 | -0.7713 | 0.2615 | 14.2% | 0.46 [0.28, 0.77] |
| Im JH 2016-2 | -0.5334 | 0.3029 | 12.8% | 0.59 [0.32, 1.06] |
| Itoh H 2005 | 0.0349 | 0.5804 | 6.4% | 1.04 [0.33, 3.23] |
| Kim MY 2016 | -0.362 | 0.3267 | 12.1% | 0.70 [0.37, 1.32] |
| Kim YJ 2017 | -0.7108 | 0.4122 | 9.8% | 0.49 [0.22, 1.10] |
| Kim YS 2016-1 | -1.356 | 0.5968 | 6.2% | 0.26 [0.08, 0.83] |
| Kim YS 2016-2 | 0.8656 | 0.4216 | 9.5% | 2.38 [1.04, 5.43] |
| Matsuda T 2013 | 0.1744 | 0.5021 | 7.8% | 1.19 [0.44, 3.19] |
| **Total (95% CI)** | | | **100.0%** | **0.69 [0.48, 0.97]** |

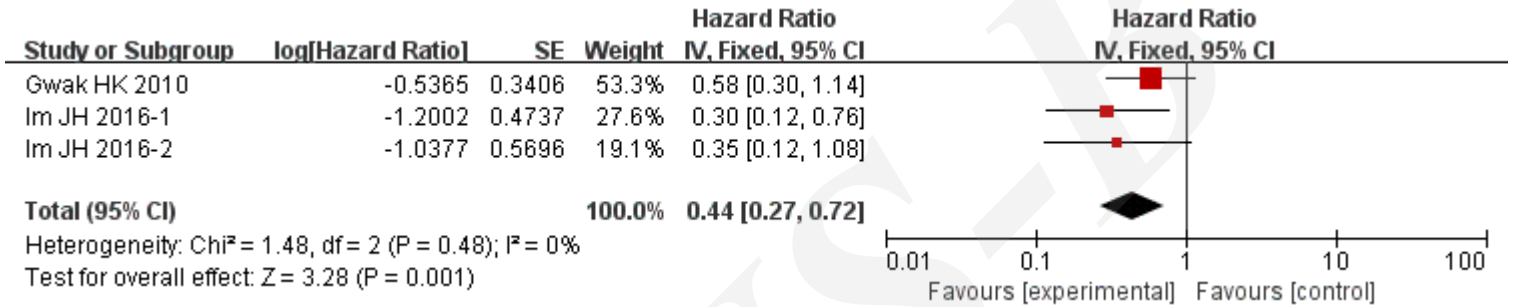
Heterogeneity: Tau² = 0.16; Chi² = 18.95, df = 9 (P = 0.03); I² = 53%

Test for overall effect: Z = 2.11 (P = 0.03)

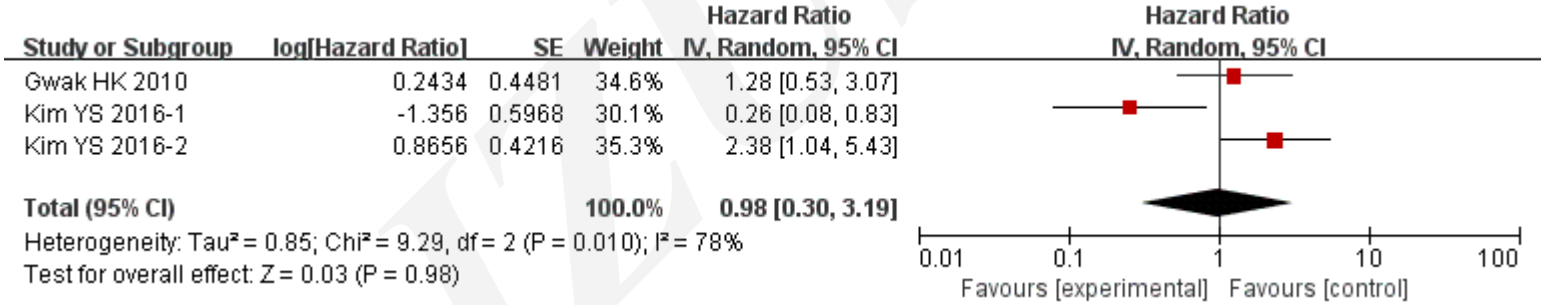


Fig. 2 Forest plot showing HR for OS between A(C)RT and surgery alone groups in all included studies

# Results



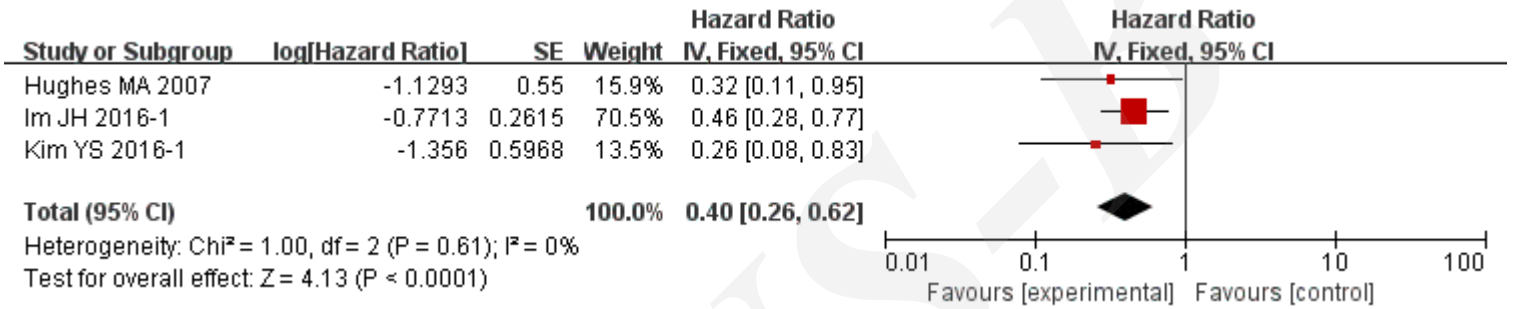

(a) R1 subgroup



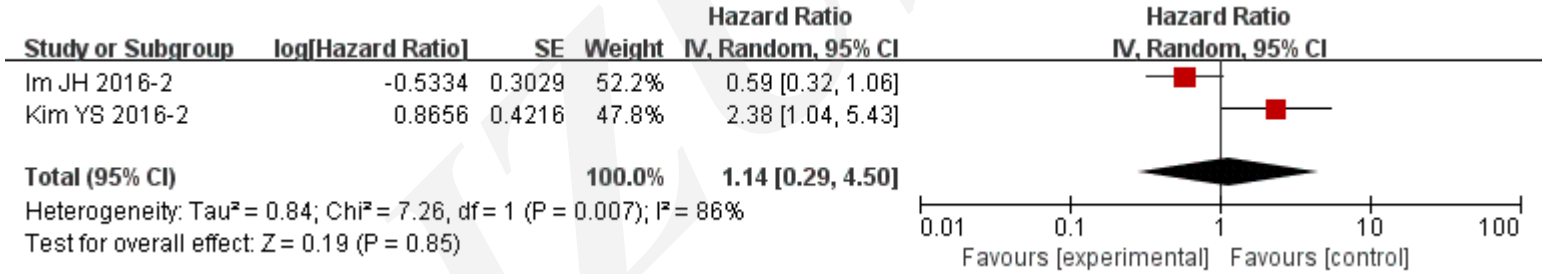

(b) R0 subgroup

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

# Results



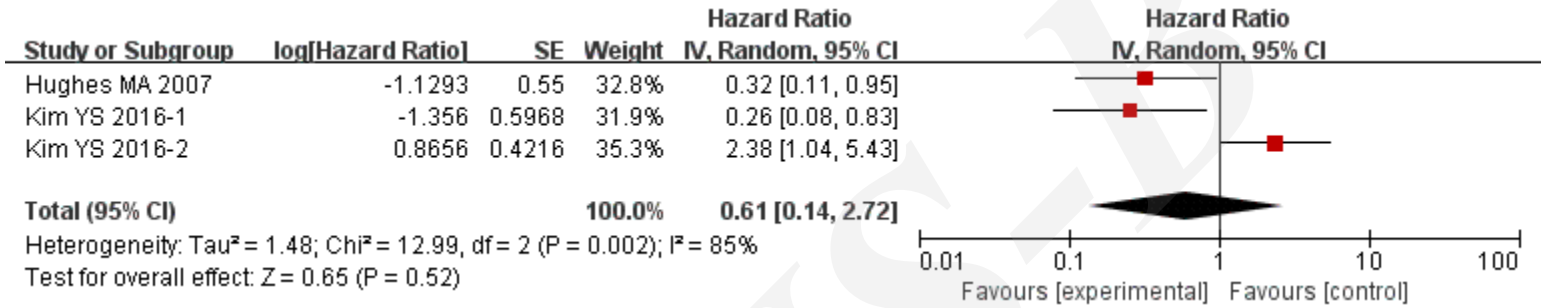

(c) ACRT subgroup



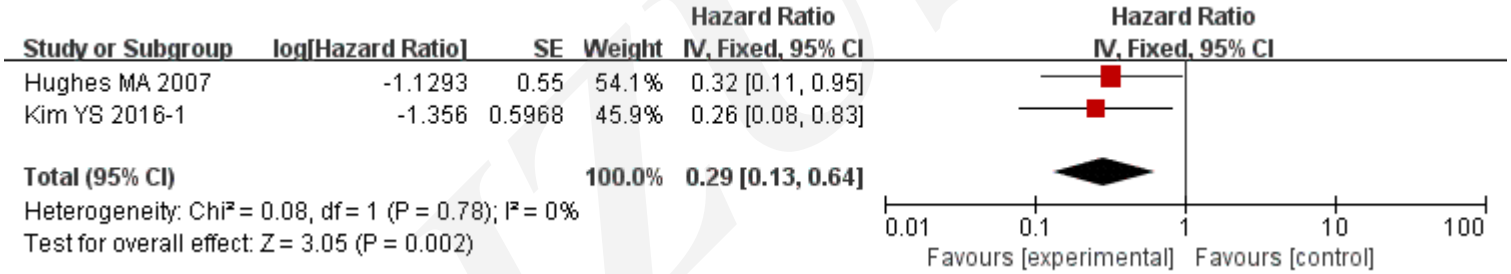

(d) ART subgroup

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

# Results



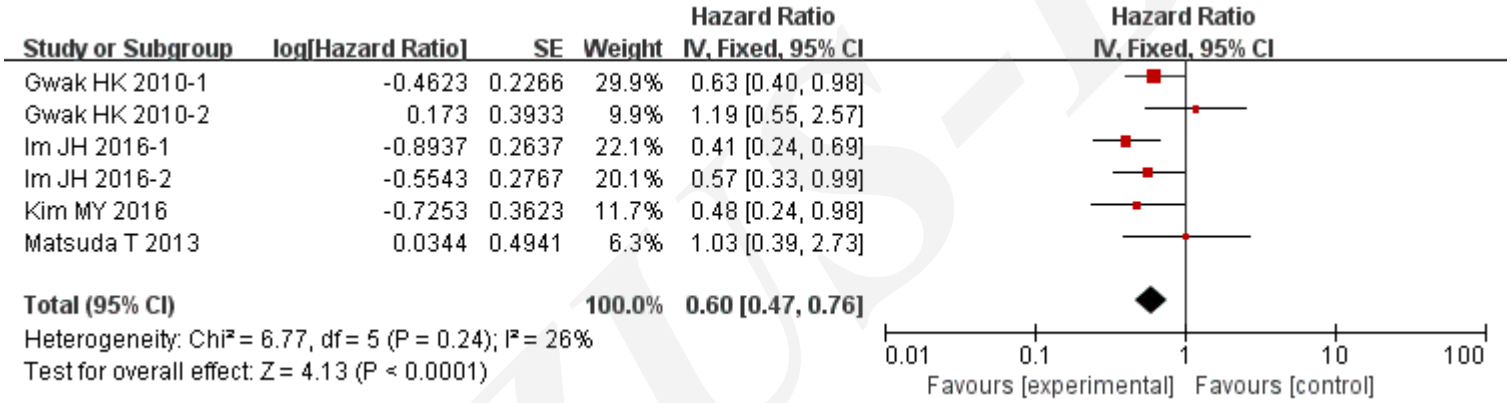

(e) ACRT and ART in distal EHCC subgroup




(f) ACRT only in distal EHCC subgroup

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

# Results



| Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|
| Gwak HK 2010-1 | -0.4623 | 0.2266 | 29.9% | 0.63 [0.40, 0.98] |
| Gwak HK 2010-2 | 0.173 | 0.3933 | 9.9% | 1.19 [0.55, 2.57] |
| Im JH 2016-1 | -0.8937 | 0.2637 | 22.1% | 0.41 [0.24, 0.69] |
| Im JH 2016-2 | -0.5543 | 0.2767 | 20.1% | 0.57 [0.33, 0.99] |
| Kim MY 2016 | -0.7253 | 0.3623 | 11.7% | 0.48 [0.24, 0.98] |
| Matsuda T 2013 | 0.0344 | 0.4941 | 6.3% | 1.03 [0.39, 2.73] |
| **Total (95% CI)** | | | **100.0%** | **0.60 [0.47, 0.76]** |

Heterogeneity: Chi² = 6.77, df = 5 (P = 0.24); I² = 26%

Test for overall effect: Z = 4.13 (P < 0.0001)



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

# Results

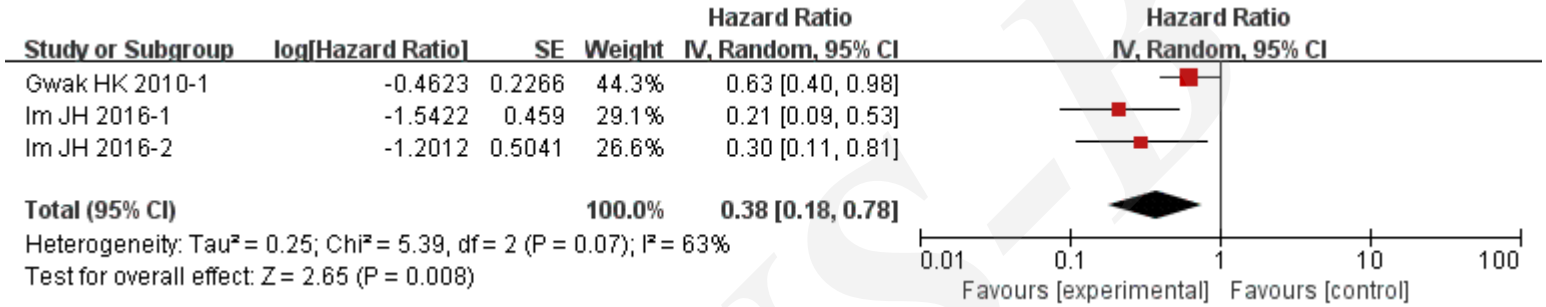



Fig. 5 Forest plot showing HR for DFS between A(C)RT and surgery alone groups in R1 subgroup

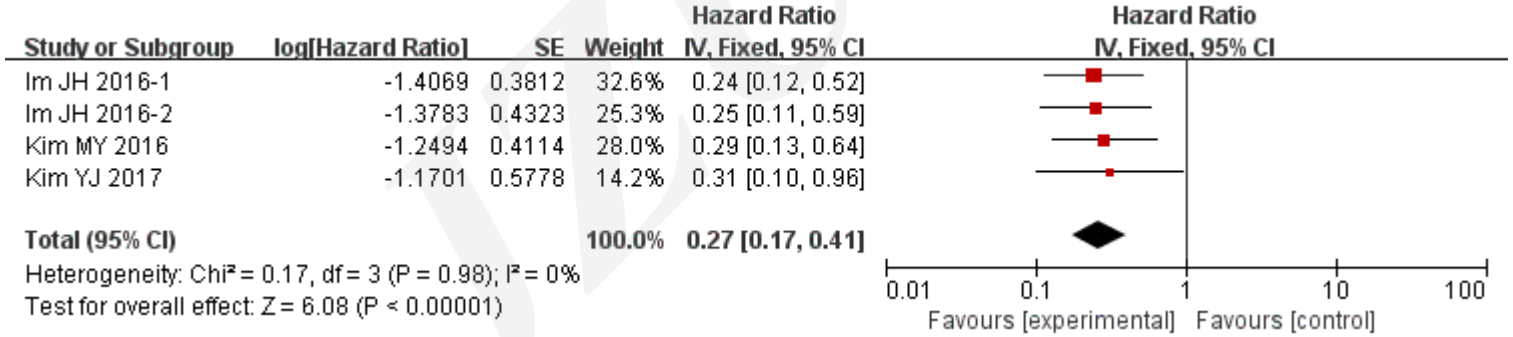



Fig. 6 Forest plot showing HR for LRFS between A(C)RT and surgery alone groups in all studies included

# Results

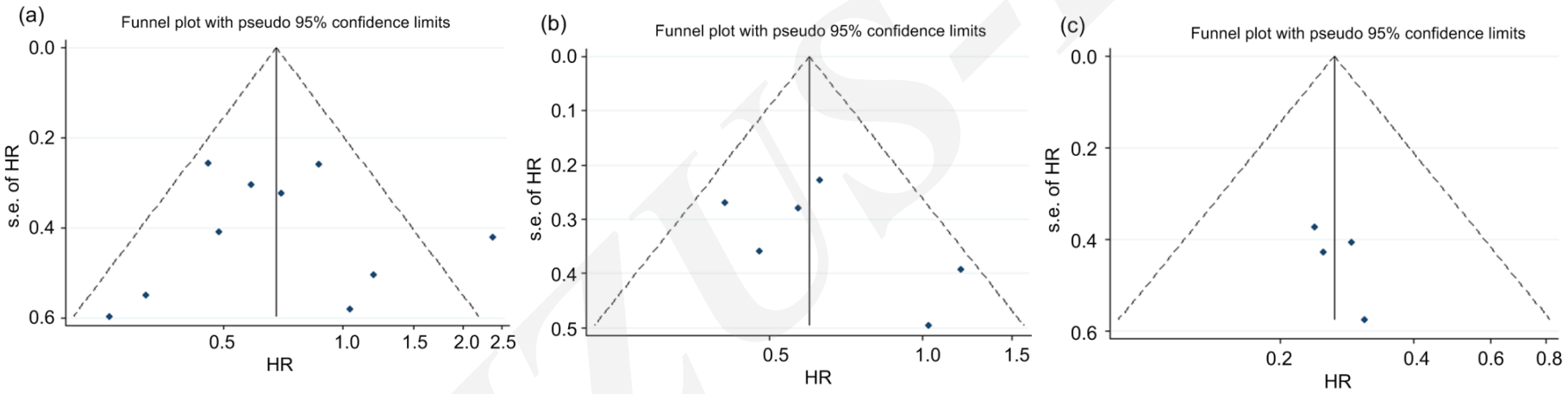



Fig. 7 Funnel plots showing publication bias of included studies (a) OS; (b) DFS; (c) LRFS.

# 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.