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# Optimizing radiotherapy in unresectable or metastatic intrahepatic cholangiocarcinoma: systematic review and meta-analysis of the literature

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## Abstract

**Background** This systematic review and meta-analysis assessed the role of radiotherapy (RTx) in patients with unresectable or metastatic intrahepatic cholangiocarcinoma (ICC).

**Methods** A systematic search of the MEDLINE, EMBASE, and Cochrane databases was conducted to identify relevant studies published before November 2024. Meta-analyses were performed to assess the median overall survival (OS), 1- and 2-year OS rates, and local control (LC) rates in patients with unresectable or metastatic ICC treated with RTx. For studies reporting hazard ratios (HR), OS was compared between patients receiving chemotherapy (CTx) with RTx versus CTx alone and between dose-escalated and conventional-dose RTx. The toxicity outcomes of the included studies were systematically reviewed.

**Results** Nine articles ($n = 1,792$) were included in the analysis. Pooled analysis revealed a median OS of 15.59 months, with 1-year and 2-year OS rates of 69% and 38%, respectively. The one- and 2-year LC rates were 79% and 55%, respectively. Four studies comparing CTx with RTx versus CTx alone revealed that the combination group had significantly improved OS (HR, 0.67). Additionally, dose-escalated RTx was associated with better OS than conventional-dose RTx (HR, 0.53). Grade ≥ 3 gastrointestinal toxicity occurred in 3.7% of patients, and grade 5 toxicity was rare (0.3%).

**Conclusions** RTx, particularly with dose escalation or in combination with CTx, may provide survival benefits with acceptable toxicity, supporting further prospective evaluations of unresectable or metastatic ICC.

**Keywords** Intrahepatic cholangiocarcinoma, Radiation therapy, Chemotherapy, Meta-analysis

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## Background

Although complete surgical resection is generally considered the only potentially curative treatment for intrahepatic cholangiocarcinoma (ICC), most patients are diagnosed at an advanced stage. Systemic chemotherapy (CTx) is generally considered the standard of care for patients with unresectable or metastatic ICC. Based on evidence from recent prospective randomized phase 3 studies, a combination of gemcitabine, cisplatin, and durvalumab or gemcitabine, cisplatin, and pembrolizumab is recommended for patients with unresectable and metastatic biliary tract cancer [1, 2]. However, the prognosis of this disease remains poor, with a median overall survival (OS) of less than 13 months.

External beam radiotherapy (RTx) for ICC is considered advantageous based on the hypothesis that it can help achieve effective local tumor control and consequently prolong OS [3], with several studies reporting durable local control and improved OS in patients with unresectable ICC treated with RTx [4–6]. The American Society for Radiation Oncology (ASTRO) guidelines recommend RTx for unresectable ICC [7]. Despite the lack of consensus, studies have demonstrated that CTx combined with RTx improves survival compared to CTx alone in metastatic ICC [8, 9]. Nevertheless, optimal treatment strategies for unresectable and metastatic ICC remain poorly established.

Regarding the level of evidence, previous studies have indicated that the average outcomes of observational studies tend to yield estimates comparable to those of randomized controlled trials [10, 11]. Although high-level studies in this field are warranted, a meta-analysis may serve as an alternative approach to estimate comparative results, and a review of the available evidence can provide valuable insights into the design of prospective trials, temporarily bridging the knowledge gap. Several systematic reviews have examined the role of RTx in biliary tract cancer [12, 13]; however, reviews specifically focusing on unresectable and metastatic ICC are lacking. The present systematic review and meta-analysis aimed to evaluate the role of RTx in local control (LC) and OS and assess its feasibility and survival benefits for unresectable and metastatic ICC.

## Methods

### Literature search strategy

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14]. The study protocol was registered in the International Prospective Register of Systematic Reviews (Registration No.: CRD42024613220). A comprehensive search was conducted across the MEDLINE, EMBASE, and Cochrane databases to identify all relevant studies published up to November 12, 2024. Our search strategy included synonyms and related terminology for both "intrahepatic cholangiocarcinoma" and "radiotherapy" (Supplementary Text 1 in Additional file 1).

### Selection criteria

Two investigators (JH and JI) independently reviewed the titles and abstracts of the initial search results and selected studies for full-text review. The inclusion criteria were as follows: (a) patients diagnosed with primary unresectable or metastatic ICC, (b) patients who received RTx, and (c) studies that contained adequate data on outcomes such as OS. The exclusion criteria were as follows: (a) duplicate articles; (b) case reports, abstracts, letters, editorials, reviews, or guidelines; (c) non-English full-text articles; (d) studies that included resectable ICC; (e) studies that included patients with extrahepatic cholangiocarcinoma or gallbladder cancer; and (f) studies that included recurrent cholangiocarcinoma.

## Data extraction

Any disagreements between the investigators were resolved through discussion. When the data were insufficient to estimate outcomes (OS rate and hazard ratios (HR)), individual survival data were extracted from Kaplan–Meier graphs using Digitizelt software (version 2.5.9; I. Bormann, Braunschweig, Germany), followed by reconstruction using the Guyot method [15].

Two investigators independently extracted and verified the descriptive data from the included studies. The following study characteristics were extracted: age, sex, disease stage, treatment method, follow-up duration, LC, and OS.

### Quality assessment

The methodological quality of the included studies was evaluated using the Quality in Prognostic Studies tool (QUIPS) (Supplementary Text 2 in Additional file 1) [16]. Two investigators independently conducted the assessments and resolved any disagreements through discussion.

### Statistical analysis

A random-effects model with DerSimonian–Laird estimation was used to analyze the median OS. Effect sizes were calculated as the natural logarithm of survival time, and standard errors were derived from log-transformed confidence intervals. Analyses were performed using the inverse-variance weighting method, and heterogeneity across studies was assessed using the $I^2$ statistic [17]. Funnel plots and Egger's tests were used to assess publication bias [18].

A meta-analysis of the proportions was performed to analyze the 1-year and 2-year OS and LC rates. The

number of events (surviving patients) and total sample size were extracted from each study. A random-effects model was applied using the inverse-variance method. Effect sizes were calculated as logit-transformed proportions, and study weights were assigned using the inverse-variance weighting method.

A meta-analysis was performed if the study provided survival data, comparing patients who received CTx with RTx with those who received CTx alone. Similarly, studies comparing a dose-escalated RTx group with a conventional-dose RTx group were analyzed. A random-effects meta-analysis was conducted for the HR analysis. Effect sizes were calculated as natural logarithms of the reported HR with standard errors derived from log-transformed confidence intervals. Analysis was performed using the inverse-variance weighting method.

All statistical analyses were performed using the R 4.4.1 software (R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Characteristics of included studies

A total of 2,020 articles were identified through the database search. After duplicate removal, 1,761 unique records remained. Screening titles and abstracts reduced the number of to 44 articles for full-text evaluation. Ultimately, 9 studies [4–6, 8, 19–23] met the inclusion criteria and were included in the review and meta-analysis (Fig. 1). The characteristics of the included studies are summarized in Tables 1 and 2 [4–6, 8, 19–23]. All nine studies had a retrospective design.

### Quality assessment and publication bias

The results of the quality assessment are summarized in Supplementary Fig. 1 (Additional file 1). One study [20] was assessed as having a moderate risk of bias due to insufficient reporting on the consecutive enrollment of patients. All studies exhibited a moderate risk of attrition bias due to inadequate descriptions of loss to follow-up. Additionally, one study [20] did not analyze multivariable prognostic factors, leading to a high-risk rating in the confounding section of the study. Two studies [19, 21] lacked data regarding survival outcomes or HR, resulting in a moderate risk rating for statistical analysis and reporting. Publication bias was assessed using funnel plots (Supplementary Fig. 2 in Additional file 1) and Egger's test. The funnel plot revealed no significant asymmetry, indicating publication bias. Egger's test for funnel plot asymmetry yielded a p-value of 0.7919 (z = 0.2638), indicating no significant publication bias.

### Pooled estimates

The meta-analysis of OS from all nine studies reported a median OS of 15.59 months (95% confidence interval (CI): 11.44–21.24, Fig. 2). One-year and two-year OS rates were 69% (95% CI, 50–82%) and 38% (95% CI, 24–54%), respectively (Fig. 2).

An additional meta-analysis restricted to the four studies that exclusively enrolled M0 patients was performed. In this subgroup analysis, the pooled median OS was 14.02 months (95% CI, 8.3–23.67) (Fig. 3). The one-year and two-year OS rates were 56% (95% CI, 38–72%) and 29% (95% CI, 13–53%), respectively (Fig. 3).

Four studies [4, 6, 8, 21] reported LC rates. One-year and two-year LC rates were 79% (95% CI, 73–84%) and 55% (95% CI, 47–64%), respectively (Fig. 4).

### RTx toxicity

Six articles reported grade 3 or higher gastrointestinal toxicity [4, 6, 20–23]. Yamazaki et al. [22] included patients with both intrahepatic and extrahepatic cholangiocarcinoma; therefore, a grade 3–4 gastrointestinal toxicity analysis was conducted based on five articles. Im et al., Shimizu et al., and Zhang et al. [6, 21, 23] observed grade 3–4 gastrointestinal toxicity in three patients, with incidence rates of 2.6%, 8.1%, and 7%, respectively. In a study by Tao et al. [4], two patients (2.5%) experienced grade 3–4 gastrointestinal toxicity, which was suspected to be related to RTx. An analysis of the five studies revealed that grade 3–4 gastrointestinal toxicity occurred in 11 of 300 patients (3.7%). An analysis of six studies further suggested that grade 5 toxicity occurred in one out of 368 patients.

### Comparison of OS between CTx with RTx group and CTx alone group

Four studies compared OS between the CTx with RTx and CTx alone groups [5, 8, 19, 20]. In the present study, the concurrent chemoradiotherapy and sequential CTx and RTx groups from the study by Chang et al. [19] were combined and defined as the CTx with RTx group. The combination of CTx with conventional or ablative RTx reported by De et al. [5] were grouped and defined as the CTx with RTx group. The meta-analysis showed that the CTx with RTx group had a HR of 0.67 (95% CI: 0.51–0.89) compared to the CTx alone group (Fig. 5).

### Comparison of OS between dose-escalated RTx group and conventional-dose RTx group

Three studies [4–6] investigated the impact of RTx dose on OS. Two studies [4, 5] classified patients into two groups based on a biologically equivalent dose (BED) of 80.5 Gy, while one study [6] used an equivalent RTx dose in 2 Gy fractions of 60 Gy (corresponding to a BED of 72 Gy) as the cutoff. In the present study, patients in the higher radiation dose groups from the three studies were classified into the dose-escalated RTx group, whereas those in the lower dose groups were classified into the

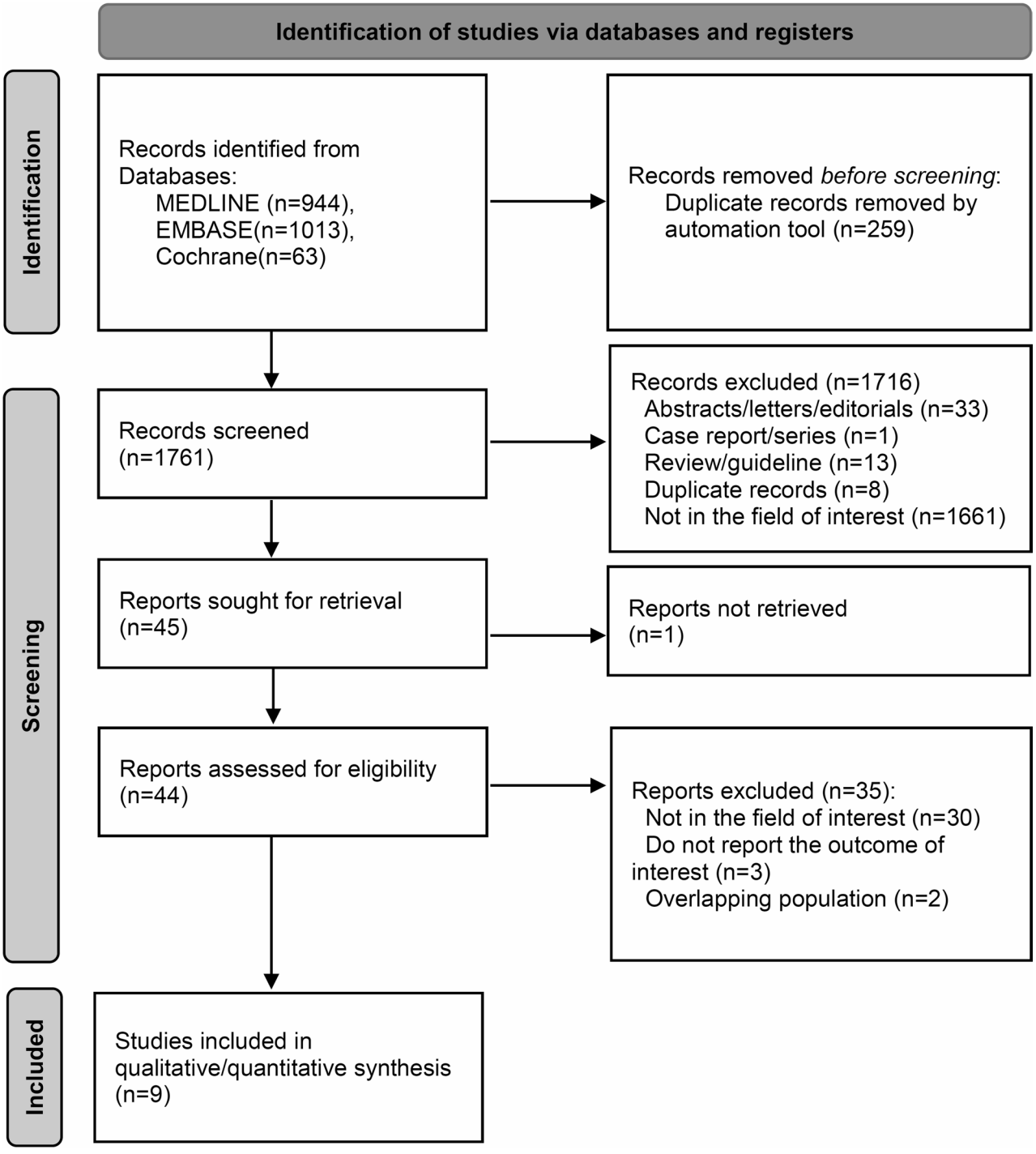


**Fig. 1** Flowchart illustrating the study selection process

conventional-dose RTx group. The meta-analysis showed that the dose-escalated RTx group had a HR of 0.53 (95% CI: 0.39–0.73) compared to the conventional-dose RTx group (Fig. 6).

## Discussion

Although previous prospective studies have included ICC, perihilar bile duct cancer, distal bile duct cancer, and gallbladder cancer [1, 2, 24–26], the distinct biological and clinical behaviors observed among these biliary tract cancers highlight the need for separate evaluation and tailored treatment approaches [27–29]. Notably,

**Table 1** Characteristics of the included studies

| Author, year | Institution (country) | Study period | Number of patients | M stage, Number of patients |
|---|---|---|---|---|
| Kim et al., 2013 | National Cancer Center (South Korea) | 2001–2012 | 92 | M0: 43<br>M1: 49 |
| Tao et al., 2016 | MD Anderson Cancer Center (USA) | 2002–2014 | 79 | M0: 63<br>M1: 16 |
| Chang et al., 2018 | Taiwan Cancer Registry (Taiwan) | 2006–2015 | 844 | M0: 844<br>M1: 0 |
| Shimizu et al., 2019 | University of Tsukuba (Japan) | 2001–2017 | 37 | M0: 27<br>M1: 10 |
| De et al., 2022 | NCDB (USA) | 2004–2018 | *11,541 | Not reported separately |
| Yamazaki et al., 2022 | 6 Multicenter (Japan) | 2009–2019 | 68 | M0: 68<br>M1: 0 |
| De et al., 2023 | MD Anderson Cancer Center (USA) | 2010–2021 | 281 | M0: 0<br>M1: 281 |
| Zhang et al., 2023 | Naval Military Medical University (China) | 2016–2018 | 43 | M0: 43<br>M1: 0 |
| Im et al., 2024 | 6 Multicenter (South Korea) | 2001–2021 | 116 | M0: 116<br>M1: 0 |

NCDB, National Cancer Database

* Data presented are sourced from the population-level National Cancer Database registry, and not a single-center study

**Table 2** Characteristics of included studies related to treatment details

| Author, year | Treatment group, Number of patients | RTx total dose, Median or mean (range) | RTx fractions, Median (range) | RTx modality, Number of patients |
|---|---|---|---|---|
| Kim et al., 2013 | CTx + RTx: 25<br>CTx: 67 | 44.7 Gy (25–60 Gy) | Not reported | Not reported separately |
| Tao et al., 2016 | CTx + RTx: 79 | 58.05 Gy (35–100 Gy) | (3–30) | 3DCRT or IMRT: 54<br>Particle therapy: 25 |
| Chang et al., 2018 | CTx + RTx: 422<br>CTx: 211 | 60 Gy | 30 | Not reported |
| Shimizu et al., 2019 | RTx ± CTx: 37 | 72.6 Gy (46.4–74 Gy) | 22 (10–37) | Particle therapy: 37 |
| De et al., 2022 | CTx + RTx: 941<br>CTx: *10,600 | Not reported | Not reported | Not reported |
| Yamazaki et al., 2022 | RTx ± CTx: 68 | 72.6 Gy (60–77 Gy) | 22 (10–38) | Particle therapy: 68 |
| De et al., 2023 | CTx + RTx: 61<br>CTx: 220 | 62.5 Gy | Not reported | Not reported |
| Zhang et al., 2023 | RTx: 43 | 40 Gy (24–50 Gy) | (3–6) | 3DCRT or IMRT: 43 |
| Im et al., 2024 | RTx ± CTx: 116 | 50 Gy (30–75 Gy) | 25 (4–30) | 3DCRT or IMRT: 110<br>Particle therapy: 6 |

CTx, Chemotherapy; RTx, Radiotherapy; 3DCRT, Three-dimensional conformal radiotherapy; IMRT, Intensity-modulated radiotherapy;

* Data presented are sourced from the population-level National Cancer Database registry, and not a single-center study

although dose-escalated RTx has been shown to be beneficial in terms of LC and OS in patients with ICC, whether similar benefits exist in patients with extrahepatic cholangiocarcinoma remains unclear [30]. Therefore, we conducted a meta-analysis exclusively on ICC, excluding extrahepatic cholangiocarcinoma and gallbladder cancer. Nine retrospective studies investigating RTx in patients with unresectable or metastatic ICC were included. The pooled median OS was 15.59 months (95% CI: 11.44–21.24), with 1-year and 2-year OS rates of 69% and 38%, respectively. Four studies reporting LC outcomes demonstrated favorable 1-year and 2-year LC rates of 79% and 55%, respectively. Grade 3–4 gastrointestinal toxicity occurred in 3.7% of the patients in the five studies included, and one case (0.3%) of grade 5 toxicity was reported in six studies.

Systemic CTx alone remains the standard treatment for patients with unresectable metastatic ICCs. Given the historically high rate of distant metastases in unresectable and metastatic intrahepatic ICC [4, 6, 22, 31–33], the added benefit of adding RTx to CTx has remained controversial. Although many patients with unresectable and metastatic ICC eventually develop distant metastases, inadequate local tumor control often leads to significant morbidity. Local tumor progression often leads to obstruction of the biliary system, infiltration into the

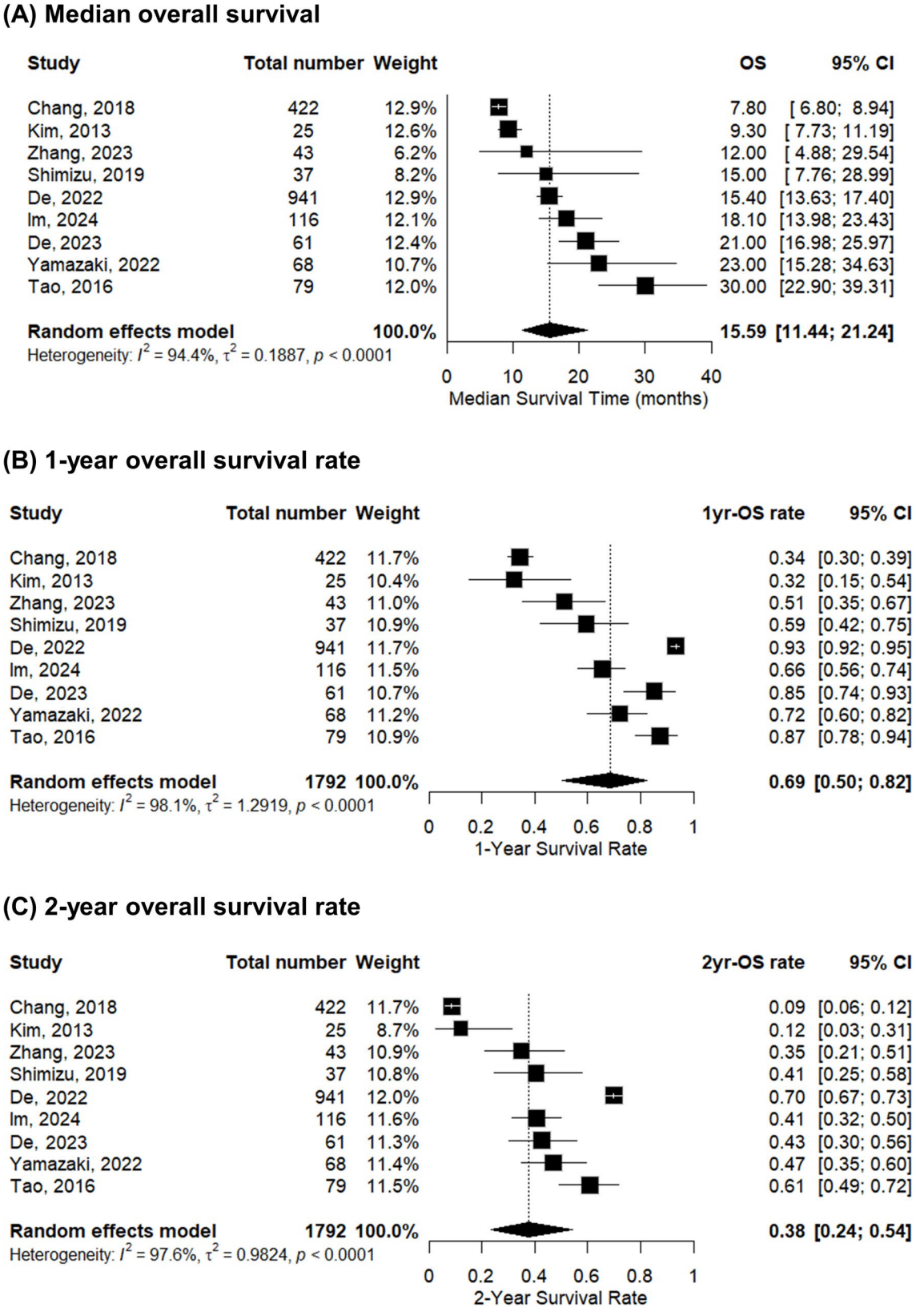


**Fig. 2** Forest plots display the overall survival outcomes across analyzed studies. Presented as (**A**) median, (**B**) 1-year, and (**C**) 2-year overall survival in the analyzed studies

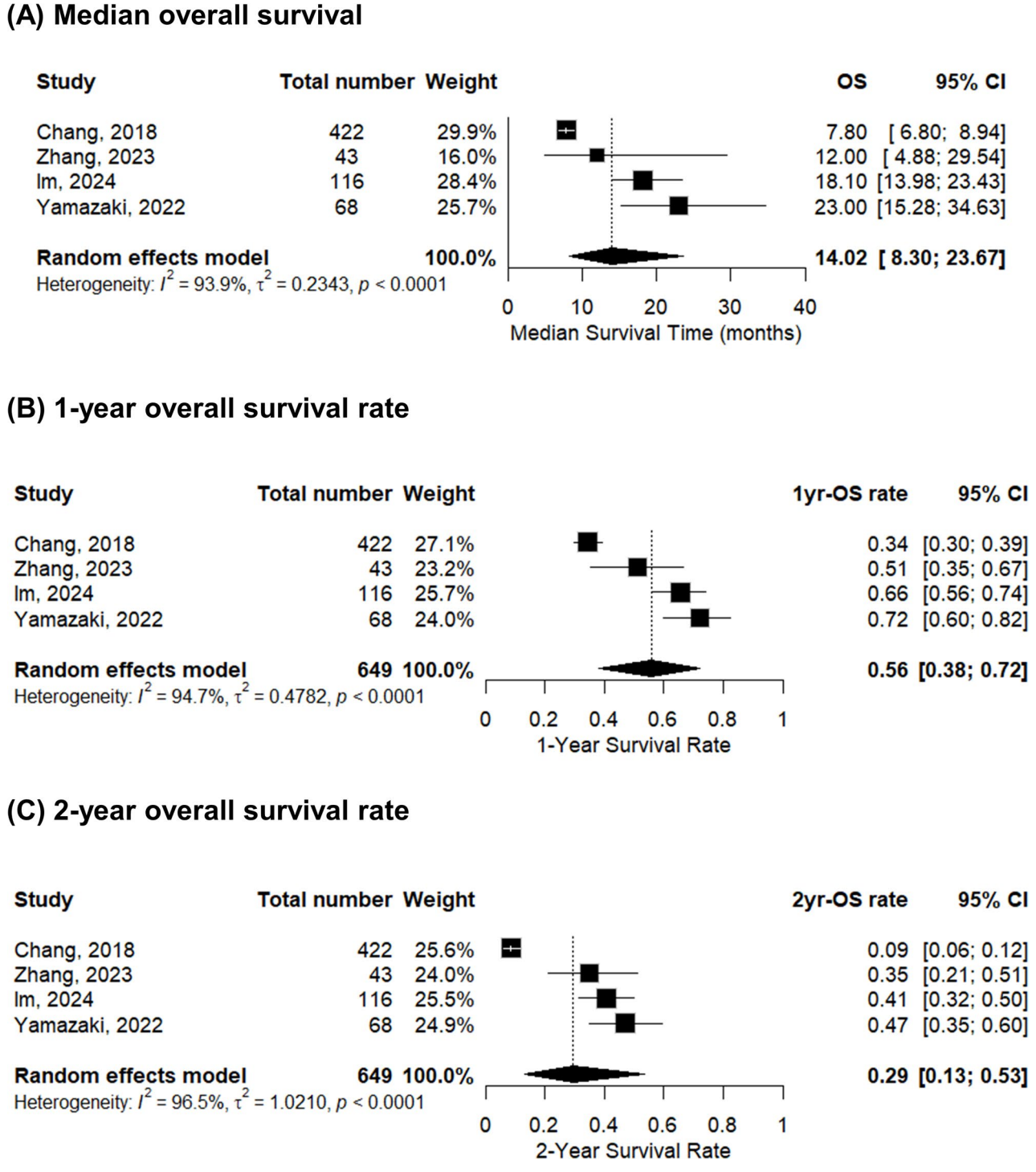


**Fig. 3** Forest plots display the overall survival outcomes in studies exclusively enrolling M0 patients. Presented as (**A**) median, (**B**) 1-year, and (**C**) 2-year overall survival

adjacent vasculature, and ultimately, liver failure. Therefore, in the absence of category 1 evidence, the need for local treatment has been increasingly advocated in patients with unresectable and metastatic ICC. Previous studies have suggested that both RTx and surgical resection can mitigate the risk of liver failure and potentially enhance OS [3, 9]. Several retrospective studies have demonstrated that the combination of CTx and RTx is associated with improved OS compared to CTx alone, suggesting a potential synergistic effect of local and systemic therapies in the management of unresectable and metastatic ICC [8, 19, 20, 34, 35]. The results of this

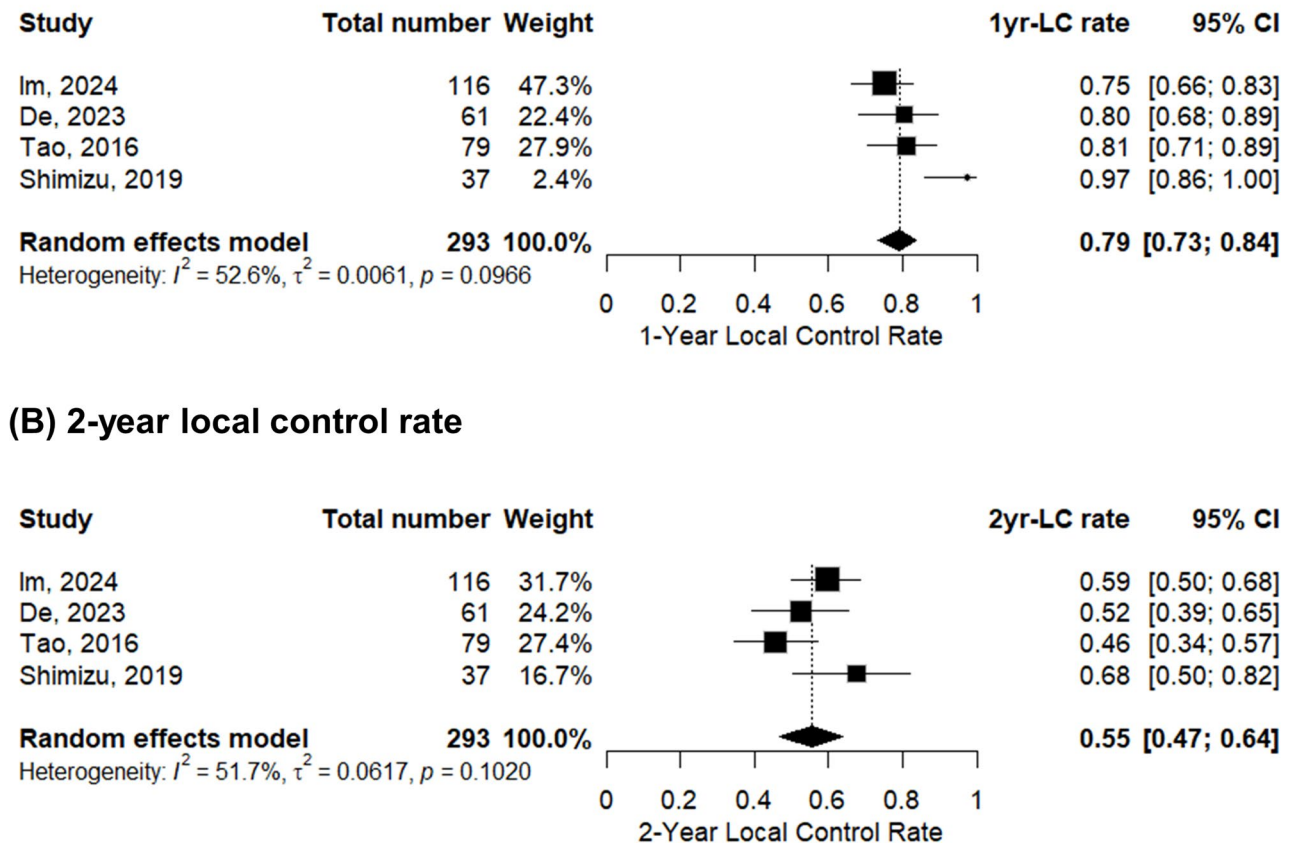


**Fig. 4** Forest plot illustrating the local control rates across the analyzed studies. (**A**) 1-year and (**B**) 2-year local control

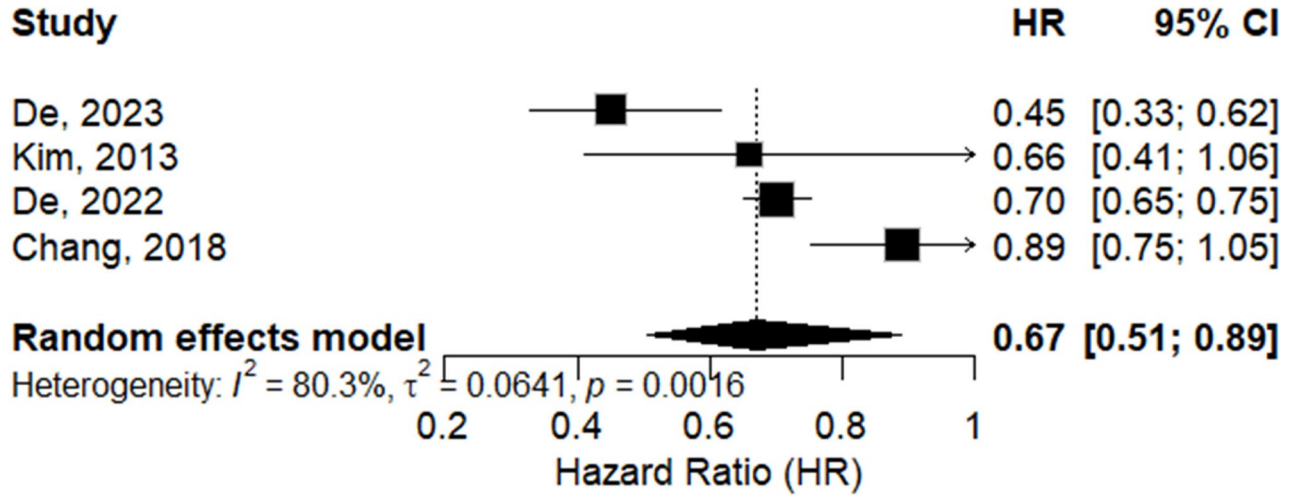


**Fig. 5** Forest plot comparing the overall survival between patients treated with chemotherapy plus radiotherapy group versus chemotherapy alone

meta-analysis also confirmed that combining CTx with RTx significantly improved OS compared to CTx alone (HR 0.67, 95% CI: 0.51–0.89). These findings further indicate that the integration of systemic CTx and RTx may lead to better outcomes in patients with advanced ICC.

Recent advancements in RTx techniques, such as intensity-modulated RTx, respiratory motion management, adaptive RTx, and image-guided RTx, have enabled the safe delivery of high-dose, potentially ablative radiation to inoperable liver tumors, including large lesions [7, 36].

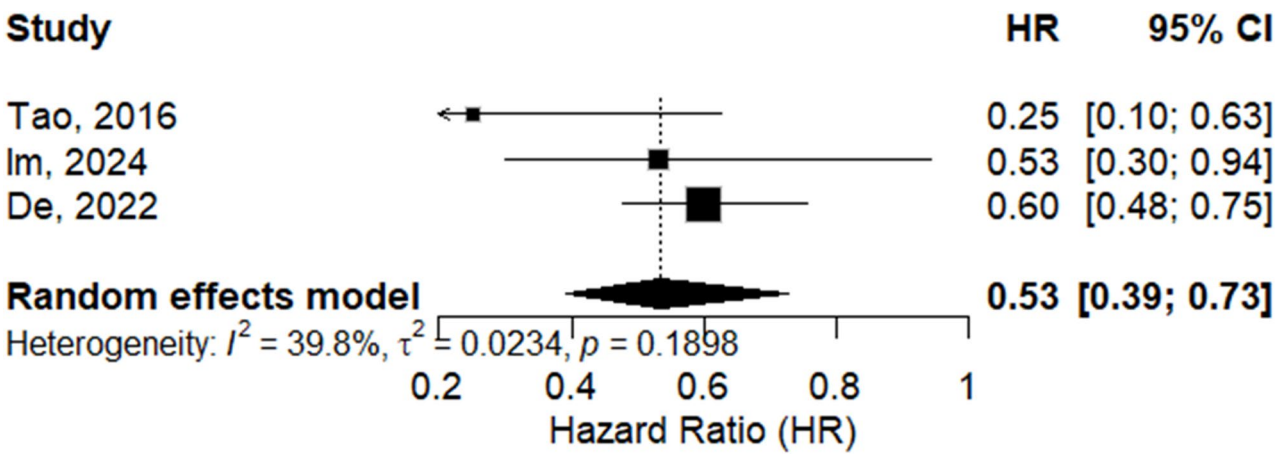


**Fig. 6** Forest plot comparing the overall survival between the dose-escalated group and conventional-dose group

Previous studies have reported that dose-escalated RTx can help achieve high LC rates in patients with unresectable or recurrent ICC, with 2-year LC rates ranging from 93% to 94% [33, 37]. Three studies reported that patients with unresectable and metastatic ICC who received dose-escalated RTx exhibited more durable LC and OS than those treated with lower doses, and multivariate analysis also revealed a significant association between dose-escalated RTx and improved OS [4–6]. Based on the meta-analysis of these three studies, dose-escalated RTx was associated with improved OS compared with conventional-dose RTx (HR 0.53, 95% CI: 0.39–0.73). These findings highlight the pivotal role of LC in ICC and support the need to investigate aggressive RTx strategies across all disease stages.

Gastrointestinal toxicity remains a significant concern in patients with ICC receiving RTx. Only one death (0.3%) attributed to RTx was reported in six studies. The patient developed duodenal perforation and subsequent liver failure more than three years after receiving dose-escalated RTx [22]. This meta-analysis of five studies found a 3.7% incidence of grade 3–4 gastrointestinal toxicity, indicating that RTx-related acute and late gastrointestinal toxicities were within an acceptable range. In a study by Tao et al., biliary stenosis occurred in seven patients, with six cases attributed to tumor progression [4]. One case each of biliary stenosis and one case of gastric bleeding were considered potentially related to RTx. Three other studies reported adverse events, including one case each of gastrointestinal bleeding, gastrointestinal obstruction, and biliary stenosis, as well as three cases of biliary tract infections and three cases of elevated liver enzyme levels [6, 21, 23]. In clinical practice, radiation oncologists must endeavor to deliver dose-escalated RTx within the tolerance limits of critical normal organs using advanced techniques to minimize treatment-related toxicity.

Given the globally increasing mortality due to ICC [38], clinicians are increasingly encountering elderly patients or those with poor medical status who may not be suitable candidates for curative surgical resection or cytotoxic CTx in real-world clinical settings. RTx alone is often considered a feasible treatment option for elderly patients or those with compromised health status. However, evidence regarding the clinical outcomes of RTx alone in patients with ICC is currently limited. One study reported that among patients aged ≥ 75 years with ICC of all stages, those who received RTx with or without other treatment modalities had a median OS of 14 months [39]. Among the nine studies included in this meta-analysis, three reported the outcomes of RTx alone [5, 7, 23]. The meta-analysis of RTx alone in patients with unresectable and metastatic ICC demonstrated a median OS of 12.36 months (95% CI, 10.64–14.35), with 1- and 2-year OS rates of 50% (95% CI, 45–55) and 33% (95% CI, 28–37), respectively. In patients with advanced biliary tract cancer, the median OS was 12.8 months with durvalumab (TOPAZ-1) and 12.7 months with pembrolizumab (KEYNOTE-966), both in combination with gemcitabine and cisplatin [1, 2]. Although a direct comparison between the TOPAZ-1 and KEYNOTE-966 trials is not feasible, the outcomes of RTx alone may be comparable. The ASTRO guidelines suggest that RTx alone should be considered in patients who are not suitable candidates for CTx [7]. RTx should be considered a primary treatment option for patients with advanced ICC, including elderly patients for whom curative surgical resection or cytotoxic CTx is not feasible.

Although RT offers effective LC and potential survival benefits in unresectable and metastatic ICC, distant failure outside the irradiated field remains a major clinical concern. In patients with advanced biliary tract cancer, the addition of immunotherapy to gemcitabine and cisplatin CTx has demonstrated superior efficacy compared to gemcitabine and cisplatin alone [1, 2]. Recent advances in molecular profiling have revealed the genetic heterogeneity of ICC, leading to the identification of several

actionable mutations. Key molecular targets, such as fibroblast growth factor receptor 2 fusions and isocitrate dehydrogenase-1 mutations, have been identified and are currently targetable with approved therapies [40, 41]. The combination of dose-escalated RTx with gemcitabine and cisplatin and immunotherapy or targeted therapy may be a promising treatment strategy for improving clinical outcomes; however, to the best of our knowledge, no studies have investigated this approach. Further research is required to determine the optimal combination of novel systemic therapies and RTx for the treatment of unresectable and metastatic ICC.

This meta-analysis had several inherent limitations, primarily stemming from the retrospective nature and heterogeneity of the included studies. All studies were retrospective, which introduces the risk of selection bias and confounding factors that cannot be fully controlled. Furthermore, there was significant variability across studies in terms of tumor characteristics, treatment intent, RTx dose and fractionation schedules, CTx regimens, and sequencing of CTx and RTx. The lack of standardized definitions for unresectable ICC [42, 43] and inconsistent indications for RTx may have further affected the comparability of the results. In addition, due to the inclusion of patients who received diverse multimodal treatments, it was not possible to determine the specific impact of RTx or CTx on survival outcomes. Moreover, in the comparison between CTx with RTx and CTx alone, a potential selection bias related to disease burden cannot be excluded. Meaningful subgroup analyses or meta-regression based on metastatic extent were not feasible because the included studies did not report or define whether M1 patients were oligometastatic versus widely metastatic. Moreover, the small number of eligible studies made any such analyses statistically underpowered and likely to yield unreliable results. These limitations underscore the need for prospective, well-designed randomized controlled trials with more homogeneous patient populations and standardized reporting to validate the findings of this study and clarify the true impact of disease burden on the comparative effectiveness of RTx combined with CTx.

## Conclusion

Our findings from this meta-analysis suggest that combining dose-escalated RTx with CTx may be beneficial for select patients with unresectable and metastatic ICC. However, large-scale randomized controlled trials are required to validate these findings.

### Abbreviations

| | |
|---|---|
| ICC | Intrahepatic cholangiocarcinoma |
| CTx | Chemotherapy |
| OS | Overall survival |
| RTx | Radiotherapy |
| ASTRO | American Society for Radiation Oncology |
| LC | Local control |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| HR | Hazard ratio |
| QUIPS | Quality in Prognostic Studies |
| BED | Biologically equivalent dose |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13014-025-02777-7.

Supplementary Material 1

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### Author contributions

Conception/design: J.H.I; Data acquisition and Data analysis: J.H.I and J.I.B; Statistical analysis: J.I.B; Manuscript writing: J.H.I, J.I.B, I.J.L; All authors reviewed and approved the final manuscript.

### Data availability

No datasets were generated or analysed during the current study.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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### References

1. Oh DY, Ruth He A, Qin S, Chen LT, Okusaka T, Vogel A, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. NEJM Evid. 2022;1(8):EVIDoa2200015.
2. Kelley RK, Ueno M, Yoo C, Finn RS, Furuse J, Ren Z, et al. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2023;401(10391):1853–65.
3. Yamashita S, Koay EJ, Passot G, Shroff R, Raghav KP, Conrad C, et al. Local therapy reduces the risk of liver failure and improves survival in patients with intrahepatic cholangiocarcinoma: A comprehensive analysis of 362 consecutive patients. Cancer. 2017;123(8):1354–62.
4. Tao R, Krishnan S, Bhosale PR, Javle MM, Aloia TA, Shroff RT, et al. Ablative radiotherapy doses lead to a substantial prolongation of survival in patients with inoperable intrahepatic cholangiocarcinoma: A retrospective dose response analysis. J Clin Oncol. 2016;34(3):219–26.
5. De B, Tran Cao HS, Vauthey JN, Manzar GS, Corrigan KL, Raghav KPS, et al. Ablative liver radiotherapy for unresected intrahepatic cholangiocarcinoma: patterns of care and survival in the united States. Cancer. 2022;128(13):2529–39.
6. Im JH, Yu JI, Kim TH, Kim TG, Kim JW, Seong J. Combined High-Dose radiotherapy with sequential Gemcitabine-Cisplatin based chemotherapy increase the resectability and survival in locally advanced unresectable

intrahepatic cholangiocarcinoma: A Multi-institutional cohort study. Cancer Res Treat. 2024;56(3):838–46.
7. Apisarnthanarax S, Barry A, Cao M, Czito B, DeMatteo R, Drinane M, et al. External beam radiation therapy for primary liver cancers: an ASTRO clinical practice guideline. Pract Radiat Oncol. 2022;12(1):28–51.
8. De B, Upadhyay R, Liao K, Kumala T, Shi C, Dodoo G, et al. Definitive liver radiotherapy for intrahepatic cholangiocarcinoma with extrahepatic metastases. Liver Cancer. 2023;12(3):198–208.
9. Sebastian NT, Tan Y, Miller ED, Williams TM, Noonan AM, Hays JL, et al. Association of Liver-Directed local therapy with overall survival in adults with metastatic intrahepatic cholangiocarcinoma. JAMA Netw Open. 2019;2(9):e1911154.
10. Shrier I, Boivin JF, Steele RJ, Platt RW, Furlan A, Kakuma R, et al. Should meta-analyses of interventions include observational studies in addition to randomized controlled trials? A critical examination of underlying principles. Am J Epidemiol. 2007;166(10):1203–9.
11. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med. 2000;342(25):1887–92.
12. Frakulli R, Buwenge M, Macchia G, Cammelli S, Deodato F, Cilla S, et al. Stereotactic body radiation therapy in cholangiocarcinoma: a systematic review. Br J Radiol. 2019;92(1097):20180688.
13. Lee J, Yoon WS, Koom WS, Rim CH. Efficacy of stereotactic body radiotherapy for unresectable or recurrent cholangiocarcinoma: a meta-analysis and systematic review. Strahlenther Onkol. 2019;195(2):93–102.
14. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
15. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012;12:9.
16. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013;158(4):280–6.
17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60.
18. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629–34.
19. Chang WW, Hsiao PK, Qin L, Chang CL, Chow JM, Wu SY. Treatment outcomes for unresectable intrahepatic cholangiocarcinoma: Nationwide, population-based, cohort study based on propensity score matching with the Mahalanobis metric. Radiother Oncol. 2018;129(2):284–92.
20. Kim YI, Park JW, Kim BH, Woo SM, Kim TH, Koh YH, et al. Outcomes of concurrent chemoradiotherapy versus chemotherapy alone for advanced-stage unresectable intrahepatic cholangiocarcinoma. Radiat Oncol. 2013;8:292.
21. Shimizu S, Okumura T, Oshiro Y, Fukumitsu N, Fukuda K, Ishige K, et al. Clinical outcomes of previously untreated patients with unresectable intrahepatic cholangiocarcinoma following proton beam therapy. Radiat Oncol. 2019;14(1):241.
22. Yamazaki H, Kimoto T, Suzuki M, Murakami M, Suzuki O, Takagi M, et al. Particle beam therapy for intrahepatic and extrahepatic biliary duct carcinoma: a multi-institutional retrospective data analysis. Cancers (Basel). 2022;14(23).
23. Zhang XX, Ma HB, Li TH, Huang B, Jia NY, Meng Y. Actual over 3-year survival after stereotactic body radiation therapy in patients with unresectable intrahepatic cholangiocarcinoma. Clin Transl Oncol. 2023;25(3):731–8.
24. Shroff RT, King G, Colby S, Scott AJ, Borad MJ, Goff L, et al. SWOG S1815: A phase III randomized trial of gemcitabine, cisplatin, and Nab-Paclitaxel versus gemcitabine and cisplatin in newly Diagnosed, advanced biliary tract cancers. J Clin Oncol. 2025;43(5):536–44.
25. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362(14):1273–81.
26. Okusaka T, Nakachi K, Fukutomi A, Mizuno N, Ohkawa S, Funakoshi A, et al. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. Br J Cancer. 2010;103(4):469–74.
27. Nakamura H, Arai Y, Totoki Y, Shirota T, Elzawahry A, Kato M, et al. Genomic spectra of biliary tract cancer. Nat Genet. 2015;47(9):1003–10.
28. Bridgewater JA, Goodman KA, Kalyan A, Mulcahy MF. Biliary tract cancer: Epidemiology, Radiotherapy, and molecular profiling. Am Soc Clin Oncol Educ Book. 2016;35:e194–203.
29. McNamara MG, Lopes A, Wasan H, Malka D, Goldstein D, Shannon J, et al. Landmark survival analysis and impact of anatomic site of origin in prospective clinical trials of biliary tract cancer. J Hepatol. 2020;73(5):1109–17.
30. Avila S, Smani DA, Koay EJ. Radiation dose escalation for locally advanced unresectable intrahepatic and extrahepatic cholangiocarcinoma. Chin Clin Oncol. 2020;9(1):10.
31. Chen YX, Zeng ZC, Tang ZY, Fan J, Zhou J, Jiang W, et al. Determining the role of external beam radiotherapy in unresectable intrahepatic cholangiocarcinoma: a retrospective analysis of 84 patients. BMC Cancer. 2010;10:492.
32. Gkika E, Hallauer L, Kirste S, Adebahr S, Bartl N, Neeff HP, et al. Stereotactic body radiotherapy (SBRT) for locally advanced intrahepatic and extrahepatic cholangiocarcinoma. BMC Cancer. 2017;17(1):781.
33. Hong TS, Wo JY, Yeap BY, Ben-Josef E, McDonnell EI, Blaszkowsky LS, et al. Multi-Institutional phase II study of High-Dose hypofractionated proton beam therapy in patients with Localized, unresectable hepatocellular carcinoma and intrahepatic cholangiocarcinoma. J Clin Oncol. 2016;34(5):460–8.
34. Jackson MW, Amini A, Jones BL, Rusthoven CG, Schefter TE, Goodman KA. Treatment selection and survival outcomes with and without radiation for Unresectable, localized intrahepatic cholangiocarcinoma. Cancer J. 2016;22(4):237–42.
35. Verma V, Kusi Appiah A, Lautenschlaeger T, Adeberg S, Simone CB 2nd, Lin C. Chemoradiotherapy versus chemotherapy alone for unresected intrahepatic cholangiocarcinoma: practice patterns and outcomes from the National cancer data base. J Gastrointest Oncol. 2018;9(3):527–35.
36. Dudzinski SO, Newman NB, McIntyre J, Engineer R, Sanford NN, Wo JY, et al. Emerging evidence-based role for external-beam radiation therapy in hepatocellular carcinoma. Lancet Gastroenterol Hepatol. 2025;10(4):387–98.
37. Smart AC, Goyal L, Horick N, Petkovska N, Zhu AX, Ferrone CR, et al. Hypofractionated radiation therapy for Unresectable/Locally recurrent intrahepatic cholangiocarcinoma. Ann Surg Oncol. 2020;27(4):1122–9.
38. Bertuccio P, Malvezzi M, Carioli G, Hashim D, Boffetta P, El-Serag HB, et al. Global trends in mortality from intrahepatic and extrahepatic cholangiocarcinoma. J Hepatol. 2019;71(1):104–14.
39. Zhu H, Ji K, Wu W, Zhao S, Zhou J, Zhang C, et al. Describing treatment patterns for elderly patients with intrahepatic cholangiocarcinoma and predicting prognosis by a validated model: A Population-Based study. J Cancer. 2021;12(11):3114–25.
40. Kelley RK, Bridgewater J, Gores GJ, Zhu AX. Systemic therapies for intrahepatic cholangiocarcinoma. J Hepatol. 2020;72(2):353–63.
41. Moris D, Palta M, Kim C, Allen PJ, Morse MA, Lidsky ME. Advances in the treatment of intrahepatic cholangiocarcinoma: an overview of the current and future therapeutic landscape for clinicians. CA Cancer J Clin. 2023;73(2):198–222.
42. Bridgewater J, Galle PR, Khan SA, Llovet JM, Park JW, Patel T, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. J Hepatol. 2014;60(6):1268–89.
43. Guro H, Kim JW, Choi Y, Cho JY, Yoon YS, Han HS. Multidisciplinary management of intrahepatic cholangiocarcinoma: current approaches. Surg Oncol. 2017;26(2):146–52.

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