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Adjuvant Radiotherapy for Extrahepatic Cholangiocarcinoma: A Quality Assessment-Based Meta-Analysis

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Keywords
Cholangiocarcinoma · Extrahepatic cholangiocarcinoma · Radiotherapy · External beam radiation therapy · Adjuvant radiotherapy

Abstract
Introduction: The benefits of adjuvant radiotherapy (ART) for extrahepatic cholangiocarcinoma are uncertain largely because existing publications lack clear comparisons between ART and non-ART arms. ***Methods:*** PubMed, Medline, Embase, and the Cochrane library were systematically searched until December 2020. The primary endpoint was overall survival (OS). Sensitivity analysis was performed for studies with reliable comparability (i.e., no favorable prognosticators in the ART arm that could skew the data). ***Results:*** Twenty-three studies involving 1,731 patients with extrahepatic cholangiocarcinoma were reviewed. The overall median of all median prescribed doses was 50.4 Gy; brachytherapy or an intraoperative boost of 10–21 Gy was applied in 5 studies. The pooled 1-, 3-, and 5-year OS rates in the non-ART and ART arms were 69.2% versus 81.0%, $p = 0.035$; 34.3% versus 44.7%, $p = 0.025$; 25.6% versus 31.7%, $p = 0.115$, respectively. The corresponding pooled locoregional recurrence rates were 52.1% versus 34.9% ($p = 0.014$). The pooled rate of grade ≥3 gastrointestinal complications was 9.8%. Sensitivity analysis performed on 14 eligible studies showed that the ART arms had a lower pooled R0 rate (36.8% vs. 63.2%, $p = 0.02$) and a higher rate of positive lymph nodes (47.4% vs. 34.9%, $p = 0.08$). The pooled 1-, 3-, and 5-year OS rates in the non-ART versus ART arms of the selected studies were 78.2% versus 84.9%, $p = 0.143$; 38.5% versus 49.2%, $p = 0.026$; and 27.8% versus 34.5%, $p = 0.11$, respectively. ***Conclusions:*** ART was shown to improve OS in all studies and in those selected for their reliable comparability.

Introduction

Biliary tract cancers are rare but have a poor prognosis; the 5-year survival rate is generally <20% [1, 2]. Surgical resection is the only potentially curative treatment; however, high rates of recurrence and poor survival necessi-

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tate adjuvant therapy. The BILCAP phase 3 study comparing capecitabine with observation following biliary tract cancer resection demonstrated a survival benefit. However, a standard strategy has yet to be established regarding adjuvant radiotherapy (ART) as all relevant studies are nonrandomized case series.

Several meta-analyses have been performed to suggest a clinical strategy for ART [3–6]. Despite the sound methodologies used, these studies have room for improvement with respect to their inclusion of types of malignancies with different clinical behaviors (e.g., cholangiocarcinoma and gallbladder cancer) [7, 8]. The aforementioned meta-analyses assumed that patients in the ART arms may have an inferior clinical profile compared to non-ART arms; However, ART may not be applied to patients with a short life expectancy or poor performance status. Some researchers performed subgroup analyses on patients with lymphatic metastasis or positive resection margin, but the included studies were based on limited information from 2 to 5 studies [4–6]. Although all these meta-analyses concluded that ART could be beneficial, their findings were less persuasive owing to such limitations, and ART has yet to be fully utilized in clinical practice. In recent NCCN guidelines, systemic treatment, clinical trial, and chemoradiotherapy are proposed as adjuvant options after surgery for extrahepatic cholangiocarcinoma without preference, regardless of status of resection margin or lymphatic metastases [9].

Physicians in practice should inevitably refer to a diverse body of literature before making clinical decisions. Therefore, we designed a quality assessment-based meta-analysis, focused on whether ART for extrahepatic cholangiocarcinoma yields oncological benefits considering the clinical comparability between groups on an individual study basis.

Materials and Methods

Study Design and Eligibility Criteria

Using the PICO method, the hypothetical question was "Does the administration of ART after surgical resection of extrahepatic cholangiocarcinoma confer a survival benefit to patients compared with those who did not undergo ART"? Furthermore, we reviewed 3 previous related meta-analyses, 2 of which were highly referenced [3, 4], while the third was published most recently [5]. Previously published studies had room for improvement in the following areas (with consideration provided for possible intervention complexity [10]) that our study was designed to address: (1) diseases with different types of treatment or recurrence patterns were included; (2) comparability between the study arms was less rigorously considered; and (3) outcome-based results, which might have been useful, were not provided.

Studies eligible for inclusion were those that met the following criteria: (1) clinical studies of extrahepatic cholangiocarcinoma (i.e., not pancreatic cancer, gallbladder cancer, or intrahepatic cholangiocarcinoma); (2) overall survival (OS) data were provided; (3) inclusion of at least 10 patients who underwent ART; and (4) each comparative arms (ART and non-ART) had >5 patients. There was no language restriction. Conference abstracts were excluded. We did not restrict the publication period. Studies based on the cancer registries in which data potentially overlapped with those from individual studies were also excluded to sustain the assumption of independence [11].

Protocol Registration

This study is registered in PROSPERO (Registration number: CRD42021235051).

Information Sources and Searching Strategy

We systematically searched the PubMed, Medline, Embase, and Cochrane Library until 16 December 2020. Search terms and a detailed search strategy are given in the online suppl. materials; for all online suppl. material, see www.karger.com/doi/10.1159/000518298. Regarding multiple studies from the same institution, those with the greater number of eligible patients were included. Multiple studies were all included if the recruiting periods did not overlap. We also cross-referenced 3 related systematic reviews [3–5] to identify studies that may have been missed. Searching for published studies was performed by 2 independent reviewers, and any disagreement on final inclusion was resolved by mutual discussion.

Data Items and Collection Process

We used a pre-standardized data sheet that included the following: general information such as the author names, affiliation, country of origin, patient recruiting period, number of patients, and conflict of interest status; clinical information regarding external beam radiotherapy dose and modality; concurrent chemotherapy; rates of lymphatic metastasis (LN+); poor differentiation; pathologic lymphovascular invasion (LVI); ≥ pT3; R0 status; clinical outcomes including the median and 1-, 3-, and 5-year OS rates; pattern of failure (locoregional or distant); grade ≥3 gastrointestinal (GI) complications; and clinical factors affecting OS on multivariate analysis. Survival data were acquired from descriptive graphs in the absence of a numerical report. Data collection was performed by 2 independent researchers, both of whom checked all information and resolved any disagreements by discussing and re-evaluating the literature.

Risk of Bias and Quality Assessment

Since most of the candidate studies were nonrandomized, possible confounders were carefully assessed as advised by the Cochrane group [12]. The most significant confounder was the unknown distribution of patients. Previous meta-analyses suggested that patients who underwent ART showed better OS than did those without, despite the assumption of their having an inferior clinical status. However, it is potentially not advisable to arrive at practical decisions based on these data because certain clinical covariates were not rigorously considered. Moreover, previous assumptions may not have been true (e.g., patients with better clinical or physical conditions may have decided to undergo ART, while those with poorer clinical indicators might not have been expected to achieve additional benefits from it).

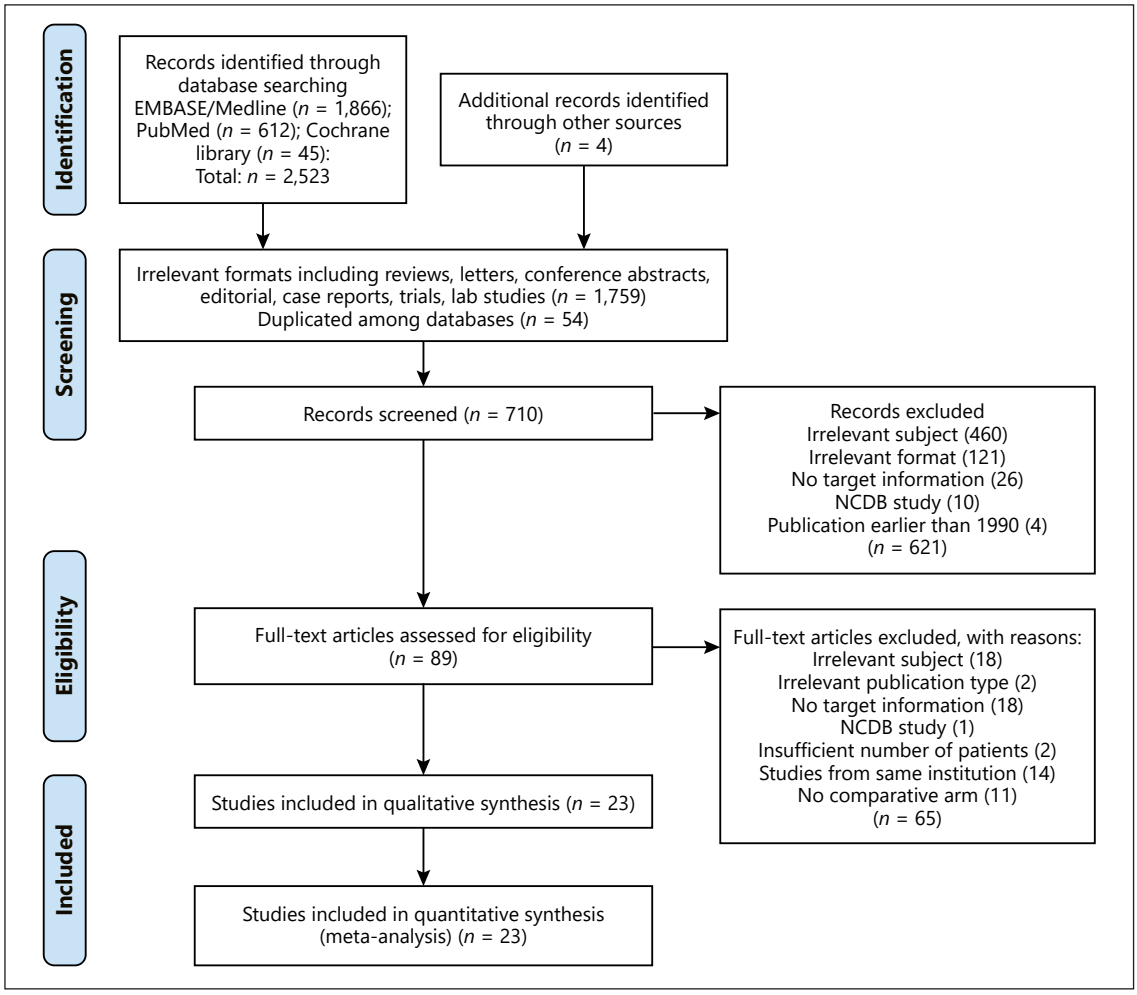


Fig. 1. Study inclusion process. NCDB, National Cancer Database.

Since the majority of studies published to date were observational, we used the Newcastle-Ottawa Scale for our analysis [13]. This showed that the quality differences between the studies were mostly due to cohort comparability as the majority of candidate studies had similar scores in other compartments. To avoid subjectivity, we categorized the comparability of the included studies based on discussions between clinical oncologists and a biostatistician. Reliable comparability was defined as (1) the provision of at least 2 of 5 clinical prognosticators (rates of LN+, poor differentiation, LVI, ≥ pT3, and R0 status), with none of these indicators having a clinically favorable slant toward the ART arm (defined as having either a statistically significant [e.g., p value of <0.05 in a comparative statistical test such as the χ^2 test or as stated in the article that there is a statistically significant difference between groups] or >20% difference) and (2) the patients' distributions between the arms were according to participant selection or a temporal difference and not owing to clinical considerations. Such studies were assigned 2 (full) points for comparability scoring; as such, they were considered to have reliable comparability and underwent further sensitivity analysis. Studies that did not fulfill the aforementioned criteria were assigned 1 point.

Statistics

The principal summary measures are the pooled outcome rates (shown as percentiles). The random-effects analysis model was used considering the clinical heterogeneity among studies and their designs and referencing the Cochrane handbook that states that the random-effects model should be the default choice when analyzing nonrandomized studies [12]. The primary endpoint was the OS rate, while rates of recurrence and grade ≥3 GI complications were analyzed as secondary endpoints. Complication data were also qualitatively analyzed. Sensitivity analysis was performed for those regarded as having reliable comparability as defined before. For subgroup comparisons between the ART and non-ART arms, mixed-effects analysis was performed, and a p value of <0.1 indicated a significant difference [14]. For studies with ≥3 arms (e.g., a non-ART arm and 2 arms with different radiotherapy modalities), either the ART arm that was most comparable to the non-ART arm or that had a larger number of patients was selected.

Heterogeneity among studies was assessed using the Cochran Q test [15] and I^2 statistics [16]. Significant heterogeneity was defined as a p value of <0.1 and I^2 of ≥50%. Publication bias was evaluated using visual assessment of funnel plots and Egger's test

Table 1. General information of included studies

Author	Institution	Country	Recruiting period	RT profile	F/U period, months	Patients without/with ART, *n*
Sagawa et al. [36]	Hokkaido University	Japan	1980–1998	EBRT and/or IORT	M32	30/39
Gwak et al. [23]	Inha University	Republic of Korea	1997–2005	EBRT, M50.4 Gy	M19.5	47/31
Kobayashi et al. [30]	Osaka University	Japan	2007	EBRT, M50 Gy	M16.7	23/21
Hughes et al. [24]	Johns Hopkins	USA	1994–2003 (S: 1970–1992)	EBRT, M50.4 Gy	M41	30/34
Lee et al. [31]	Korea, Haundae Paik, Ajou, Konyang	Republic of Korea	1994–2013	EBRT, 50 or 50.4 Gy	M26	52/19
Kim et al. [29]	Keimyung University, Daegu	Republic of Korea	2000–2013	EBRT, M50.4 Gy	M24	33/19
Cheng et al. [20]	Eastern Hepatobiliary Surgery Hospital	China	1997–2002	EBRT, m50 Gy	M21	52/23
Sugiura et al. [39]	Shizuoka Cancer Center	Japan	2002–2014	EBRT, M50.4 Gy		22/22
Schoenthaler et al. [37]	UCSF and Lawrence Berkeley Laboratory	USA	1977–1987	EBRT, M46.3 Gy	Minimum 5 years	62/45
Tollenaar et al. [41]	Leiden University	The Netherlands	1968–1983	EBRT, 40–60 Gy	M4	39/16
Borghero et al. [19]	MDACC	USA	1984–2005	EBRT, M45 Gy + boost 10 or 20 Gy (brachy)	M31	23/42
Serafini et al. [38]	South Florida University	USA	1988–1999	EBRT, 39–54 Gy	Unknown	57/34
Pitt et al. [35]	Johns Hopkins (old cohort)	USA	1988–1993	EBRT, m46 Gy + boost IR-192 implant m13 Gy	Unknown	27/23
Kamiya et al. [27]	Yokohama University (old cohort)	Japan	1992–1997	EBRT, 45 or 54 Gy in 30F	m20.6	19/10
Li et al. [32]	Hunan Provincian Hospital	China	2010–2013		Unknown	109/72
Gerhards et al. [21]	Amsterdam University	The Netherlands	1983–1998	EBRT, m42.3 Gy± Brachy m10.4 Gy	m28.8	20/71
Grove et al. [22]	Cleveland Clinic Foundation	USA	1977–1985	EBRT, m37.7 Gy	Unknown	9/19
Im et al. [25]	Yonsei University	Republic of Korea	2001–2010	EBRT, M50.4 Gy	M63	168/29 90/49 (with CTx)
Mcmaster et al. [33]	Louisville University	USA	1983–1996		M12	11/20
Itoh et al. [26]	Kanazawa Medical Center	Japan	1994–2004	EBRT, m52.3 Gy	m32	8/11
Todoroki et al. [40]	Tsukuba University	Japan	1976–1999	EBRT, m43.6 Gy± IORT m21.0 Gy	Unknown	19/17
Kim et al. [29]	Ewha University	Republic of Korea	1997–2015	EBRT, M50.4 Gy	M19	36/23
Meng et al. [34]	Shanghai Eastern Hepatobiliary Hospital	China	1992–1997	EBRT, M52 Gy	M30	19/28

Capital M headings denote median and small m heading mean values. RT, radiotherapy; ART, adjuvant radiotherapy; EBRT, external beam radiation therapy; IORT, intraoperative radiotherapy; CTx, chemotherapy.

[17]; a test of publication bias was performed for analyses that included >10 studies. Duval and Tweedie's [18] trim-and-fill method was performed if significant publication bias was likely (i.e., a 2-tailed p value <0.1 in Egger's test). All statistical analyses were conducted using Comprehensive Meta-Analysis version 3 (Biostat Inc., Englewood, NJ, USA).

Results

Study Selection and Characteristics

Among 2,523 studies initially searched, 710 underwent abstract review after machine screening to exclude those with irrelevant formats or duplicates. Full-text reviewing was performed for 89 studies that were filtered after abstract review, 23 of which [19–41] fulfilled all inclusion criteria and were ultimately analyzed. These studies involved a total of 1,731 patients with extrahepatic cholangiocarcinoma who underwent surgical resection, including 717 who underwent ART. The selection process is shown in detail in Figure 1.

Seven studies were from the USA, 6 from Japan, 5 from Korea, 3 from China, and 2 from the Netherlands. All studies were reported in English, except for one by Kamiya et al. [27] that was in Japanese and another by Meng et al. [34] that was in Chinese. The earliest study recruited patients from 1968 to 1983 [41], whereas the latest did so from 1997 to 2015 [29]. The median follow-

Table 2. Clinical outcome of included studies

Author	Comparability†	Modality	Concurrent CTx, %	S; SR, *n*	LN+	Poor differentiation	LVI	pT3 or 4	R0 status	1-year OS	3-year OS	5-year OS	LRR and distant failure, %
Sagawa et al. [36]	Yes	S S+R *p*	0 0	30 39				46.7% 51.3% NS	43.3% 51.3% NS	79.6% 77.1% 0.554	33.3% 40.9%	31.4% 26.1%	
Gwak et al. [23]	Yes	S±C S+R±C *p*	17 51.6	47 31	44.7% 45.2% NS	10.6% 3.2% NS	38.3% 35.5% NS	21.3% 16.1% NS	57.4% 64.5% NS	61.7% 80.8% NS	36.2% 26.9%	11.6% 21.0%	61.7/36.2 35.6/51.6
Kobayashi et al. [30]	No	S S+R *p*	0 0	23 21	52% 29% 0.08		30.4% 28.6% 0.892	47.8% 61.9% 0.727	39.1% 42.9% 0.82	47.8% 85.7% 0.039	23.0% 47.6%	17.4% 23.8%	47.6/28.6
Hughes et al. [24]	Yes	S S+CR *p*	0 100	30 34	37% 82%	42% 44%			93.0% 74.0%	70.0% 79.4%	30.0% 52.9%	26.7% 35.3%	17.6/83.3
Lee et al. [31]	Yes	S S+CR *p*	0 100	52 19	13.5% 68.4% <0.001	9.6% 13.6% 0.377		42.3% 31.6% 0.610	100.0% 0.0% NA	76.9% 68.4% 0.148 (S vs. SCR) 0.017 (S vs. SR)	48.1% 36.8%	36.5% 26.3%	23.1/38.5 42.1/52.6
Kim et al. [28]	Yes	S S+R±C *p*	0 63.2	33 19	27.3% 42.1% 0.272	18.2% 26.3% 0.747	57.6% 52.6% 0.765	10.0% 5.0% 0.427	69.7% 26.3% 0.004	93.9% 89.5% 0.274	37.4% 55.7%	15.2% 21.1%	78.8/15.6 21.1/52.7
Cheng et al. [20]	Yes	S±C S+R *p*	34 0	52 23						77.1% 100.0% <0.001	42.7% 62.8%	21.9% 25.3%	
Sugiura et al. [39]	Yes	S S+CR *p*	0 100	22 22	45% 41% 0.779	55% 41% 0.209		50% 82% 0.081	0% 0% NA	89.6% 100.0%	63.6% 68.2%	31.5% 44.1%	55/46 50/45
Schoenthaler et al. [37]	No	S±C S+R±C *p*	3 56	62 45	29% 13%	18% 13%		74% 37%	40.0% 0.0%	37.8% 48.8%	8.3% 8.7%	3.7% 4.3%	
Tollenaar et al. [41]	No	S S+R *p*		39 16						23.3% 75.3%	NA 7.6%	NA NA	
Borghero et al. [19]	Yes	S S+CR *p*	0 100	23 42	13% 45%	30% 40%		52% 52%	100.0% 36.0%	95.8% 91.9%	50.0% 43.6%	43.0% 36.3%	30/24 24/9
Serafini et al. [38]	Yes	S±C S+CR *p*	5 100	57 34				76.7%§ 88.2%§	73.7% 76.5%	79.7% 78.9%	47.7% 53.8%	22.3% 34.8%	

Table 2 (continued)

Author	Comparability†	Modality	Concurrent CTx, %	S; SR, *n*	LN+	Poor differentiation	LVI	pT3 or 4	R0 status	1-year OS	3-year OS	5-year OS	LRR and distant failure, %
Pitt et al. [35]	Yes	S±C S+R±C		27 23 *p*	29% 13%		33% 52%		22% 13%	74.5% 65.5%	26.3% 22.0%	NA NA	
Kamiya et al. [27]	Yes	S S+R		19 10 *p*	31.6% 60.0% 0.14			47.4%§ 70.0%§ 0.403	5.30% 10.0% 0.771	64.8% 100.0% 0.036 (Cox)	25.9% 67.7%	0.0% 50.8%	
Li et al. [32]	No	S S+R		109 72 *p*								33.0% 45.7% 0.825	
Gerhards et al. [21]	No	S S+R		20 71 *p*					10% 15%	69.5% 84.1%	17.0% 40.1%	17.0% 23.7% 0.62	27/67 37/48
Grove et al. [22]	No	S±C S+R±C		9 19 *p*						11.0% 57.0%	NA NA	NA NA	
Im et al. [25]	Yes	S S+R S+C S+CR	0 0 0 100	168 29 90 49 *p*	23.8% 41.4% 60.1% 42.9% <0.001	15.5% 17.2% 16.7% 12.2% 0.906	19.6% 20.7% 36.7% 16.3% 0.009	54.8% 51.7% 62.2% 46.9% 0.348	86.3% 34.5% 85.6% 38.8% <0.001	77.5% 100.0% 92.7% 96.0%	30.6% 63.9% 40.8% 64.8%	43.2% 42.9% 37.9% 47.6%	44.6/46.4 31/58.6 53.3/52.2 34.7/40.8
Mcmaster et al. [33]	No	S S+R	0 100	11 20 *p*					54% 54% <0.001	100% 100%	26.0% 42.0%	26.0% 22.0%	
Itoh et al. [26]	No	S S+R	0 0	8 11 *p*						50.0% 73.0%	50.0% 21.0%	50.0% 21.0%	LRR 57 LRR 0
Todoroki et al. [40]	No	S S+R		19 17 *p*	63.2% 35.3% NS	21.1% 11.8% NS		100.0% 100.0% NS	0.0% 0.0% NS	44.9% 70.8% 0.0108	19.8% 45.7%	13.5% 33.9%	
Kim et al. [29]	Yes	S S+R	0 65	36 23 *p*	41.7% 34.8%	30.6% 13.0%		47.2% 39.1%	69.4% 52.2%	55.3% 69.7%	28.5% 33.1%	29.0% 27.0%	80/33 50/83
Meng et al. [34]	Yes	S S+R		19 28 *p*	63.1% 53.6% 0.762	21.1% 17.9% 0.948			0% 0%			14.0% 34.0%	

S, surgery; R, radiotherapy; C, chemotherapy; CTx, chemotherapy; LN+, rate of patients with positive lymph node; LVI, lymphovascular invasion; OS, overall survival; LRR, locoregional recurrence; NS, not significant; NA, not applicable; AJCC, American Joint Committee on Cancer. † Definition of reliable comparability is described in method section of the manuscript. § Classified as stage III or IV according to the AJCC staging system.

Table 3. Pooled results of endpoint outcomes

	Cohorts, *n*	Patients, *n*	Heterogeneity (p, I^2)	Pooled rates (95% CI)	Subgroup comparison	Eggers' *p*	Trimmed value
1-year OS							
All studies							
Without ART	21	852	<0.001, 84.0%	69.2% (59.1–77.8)	0.035	0.713	
With ART	21	619	<0.001, 64.6%	81.0% (74.1–86.4)		<0.001	76.2% (67.8–83.0)
Selected studies							
Without ART	13	659	<0.001, 68.3%	78.2% (71.1–83.9)	0.143	0.183	
With ART	13	374	0.023, 49.2%	84.9% (77.8–90.0)		<0.001	80.7% (71.1–87.7)
3-year OS							
All studies							
Without ART	20	831	<0.001, 58.7%	34.3% (28.9–40.1)	0.025	0.285	
With ART	20	607	<0.001, 64.3%	44.7% (37.6–52.0)		0.356	
Selected studies							
Without ART	14	686	0.067, 39.0%	38.5% (33.6–43.6)	0.026	0.695	
With ART	14	397	0.004, 57.4%	49.2% (41.3–57.2)		0.705	
5-year OS							
All studies							
Without ART	21	932	<0.001, 65.8%	25.6% (20.5–31.4)	0.115	<0.001	30.1% (24.2–36.8)
With ART	21	684	0.019, 43.1%	31.7% (26.9–36.9)		0.007	36.9% (31.2–42.9)
Selected studies							
Without ART	14	678	0.001, 64.3%	27.8% (21.9–34.6)	0.11	<0.001	32.5% (25.8–40.1)
With ART	14	402	0.399, 4.8%	34.5% (29.8–39.5)		0.11	
LRR							
Without ART	10	495	<0.001, 79.7%	52.1% (40.6–63.3)	0.014	0.647	
With ART	10	275	0.167, 30.3%	34.9% (28.0–42.4)		0.188	
Distant recurrence							
Without ART	9	479	0.010, 60.3%	39.3% (31.7–47.6)	0.265	NA	
With ART	9	258	<0.001, 72.4%	48.0% (35.4–60.8)		NA	

OS, overall survival; ART, adjuvant radiotherapy; CI, confidence interval; NA, not applicable; LRR, locoregional recurrence.

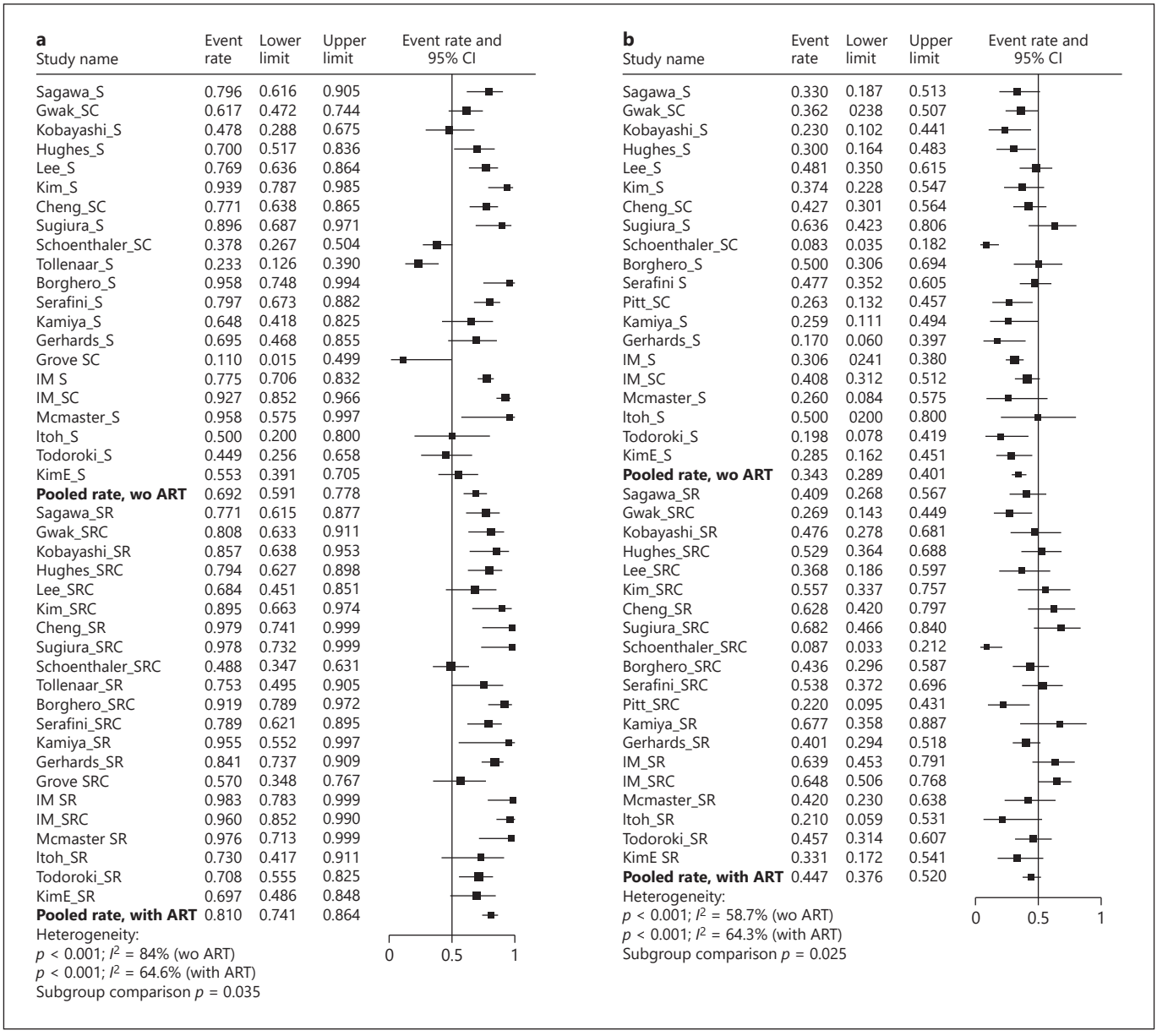
up periods were provided in 17 studies, with the pooled median value being 26 (range: 4–63) months. Regarding the ART modality used, advanced techniques such as intensity-modulated radiotherapy were not applied, but conventional 3-dimensional or 2-dimensional, multi-directional portal-based radiotherapy was used. The overall median of all median prescribed doses was 50.4 (range: 37.7–52.3) Gy, and brachytherapy or an intraoperative boost of 10–21 Gy was performed in 5 studies. Concurrent chemotherapy was administered in 12 studies. None of the studies reported significant conflicts of interest. General information from the included studies is given in Table 1.

Among the clinical covariates, the median R0 rates were 54.0% (range: 0–100%) and 34.5% (range: 0–76.5%) in the non-ART and ART arms, respectively; the median LN + rates were 37% (range: 13–63.2%) and 42.1% (range: 13–82%), respectively. The overall median of all reported median survival times was 19.5 (range: 2.2–43) months in the non-ART arms and 27.5 (range: 11–49) months in the ART arms. The detailed clinical information of patients in the included studies is given in Table 2.

Quality Assessment and Study Selection

All studies shared fundamentally similar clinical designs and had similar scores in their selection and outcome categories (except the adequacy of follow-up). Comparability was evaluated as described in the Materials and Methods. Studies with a follow-up period of ≥2 years were regarded as having an adequate follow-up period, whereas those with shorter or unknown follow-up durations were not. Scoring results are provided in online suppl. Table 1.

Following the confirmation of reliable comparability, we performed sensitivity analysis on the eligible studies in a manner where they were less affected by possible bias (unknown patient distribution). Studies that did not provide data regarding at least 2 of the 5 clinical indicators



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[21, 22, 26, 32, 33, 41] or those with control arms exhibiting inferior clinical profiles (e.g., >20% higher value in LN + or pT3/4 rates) [30, 37, 40] were not subjected to further sensitivity analysis. In 14 selected studies, the ART arms had a lower pooled R0 rate (36.8% vs. 63.2%, $p = 0.02$) and a higher rate of LN+ (47.4% vs. 34.9%, $p = 0.08$), whereas rates of pT3 or pT4, poor differentiation, and LVI were not significantly different between ART and non-ART arms (online suppl. Fig. 1).

Pooled Results of Endpoints and Sensitivity Analyses

The pooled 1-, 3-, and 5-year OS rates in the non-ART and ART arms were 69.2% (95% confidence interval [CI]: 59.1–77.8%) versus 81.0% (74.1–86.4%), $p = 0.035$; 34.3% (28.9–40.1%) versus 44.7% (37.6–52.0%), $p = 0.025$; and 25.6% (20.5–31.4%) versus 31.7% (26.9–36.9%), $p = 0.115$, respectively. The pooled locoregional recurrence (LRR) rates in the non-ART and ART arms were 52.1% (40.6–63.3) versus 34.9% (28.0–42.4%), $p = 0.014$, whereas the distant recurrence rates were 39.3% (31.7–47.6%) versus 48.0% (35.4–60.8%), $p = 0.265$. Significant heterogeneity

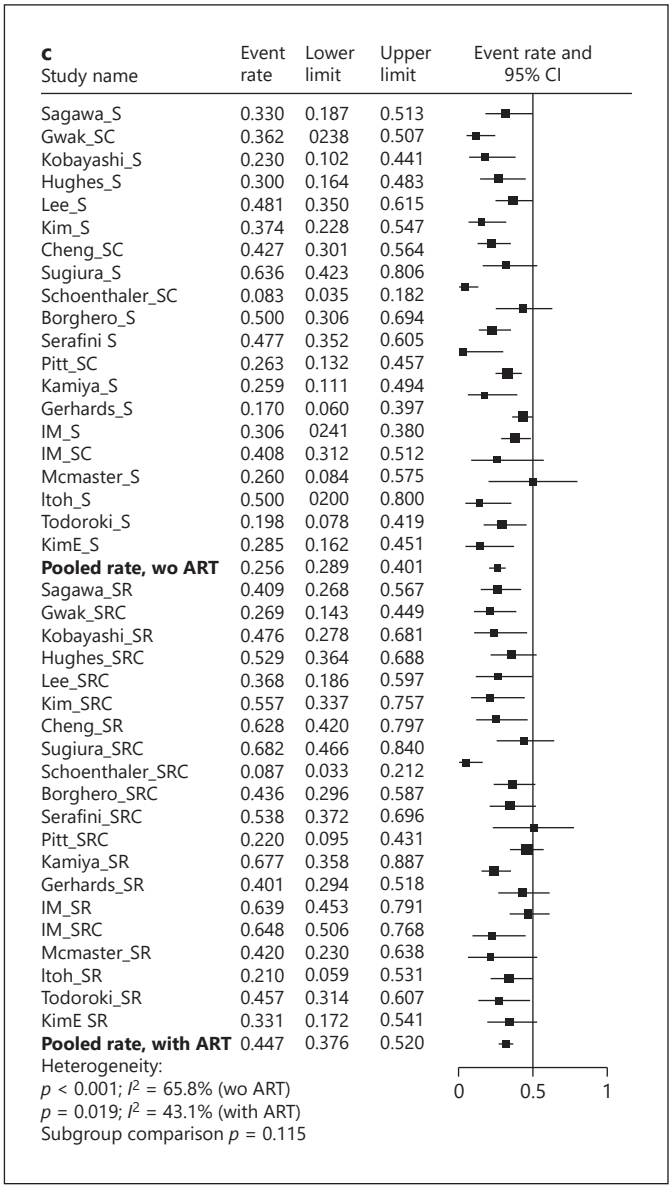


Fig. 2. Forest plot of pooled analyses of all included studies regarding (**a**) 1-year, (**b**) 3-year, and (**c**) 5-year OS rates. ART, adjuvant radiotherapy; CI, confidence interval; S, surgery; R, radiotherapy; C, concurrent chemotherapy; OS, overall survival.

was found in all analyses, except for those of the 5-year OS and LRR rates in the ART arms.

On sensitivity analysis of the selected studies, the pooled 1-, 3-, and 5-year OS rates in the non-ART and ART arms were 78.2% (95% CI: 71.1–83.9%) versus 84.9% (77.8–90.0%), $p = 0.143$; 38.5% (33.6–43.6%) versus 49.2% (41.3–57.2%), $p = 0.026$; and 27.8% (21.9–34.6%) versus 34.5% (29.8–39.5%), $p = 0.11$, respectively. Significant heterogeneity was found upon pooled analyses of the 1-year and 5-year OS rates of patients in the non-ART arms and in the 3-year OS rates among patients in the ART arms. These results are given in Table 3 in detail and are also depicted in Figure 2 (all studies) and Figure 3 (selected studies). Forest plots of locoregional and distant recurrences are shown in online suppl. Figure 2.

Publication Bias

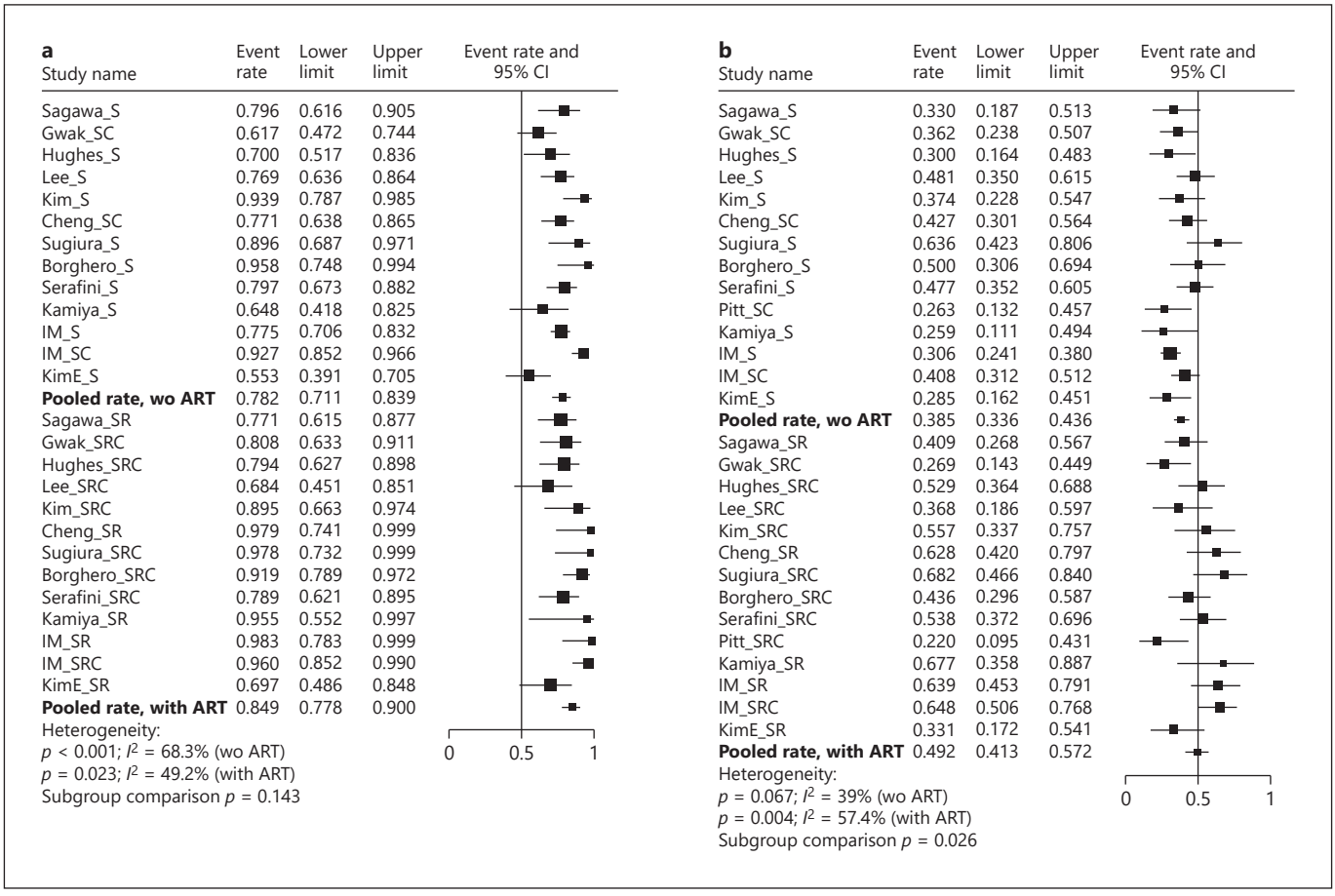
Possible publication bias was noted in the pooled analysis of the 1-year OS in the ART arms of all studies; the trimmed value (76.2%) was lower than the original (81.0%). A similar finding was observed when analyzing the 1-year OS in the ART arms of only the 14 selected studies, in which the trimmed value (80.7%) was also lower than the original (84.9%). The difference between arms might be reduced when considering these trimmed values. Regarding pooled analyses of the 5-year OS rates in all studies, possible publication bias was noted, and the trimmed values increased from their originals in both arms. Possible bias was noted in the pooled analysis of the 5-year OS rate in the non-ART arms of the selected studies. The trimmed value (32.5%) was higher than the original (27.8%), which may reduce the difference between arms. The detailed results are given in Table 3.

GI Complications

Qualitative and quantitative data regarding complications were available for 10 studies. We evaluated grade ≥3 GI complications but not grade ≥3 hematologic complications that did not cause mortality. Duodenal ulcers and bile duct damage were the most common types of serious GI complications. Two studies did not report any serious complications, but 1 reported that 21.4% of patients had GI bleeding or jaundice. One study reported 4 patients among 45 (8.9%) who experienced grade 5 fatal events owing to duodenal ulcer and cholangitis [37]. The pooled rate of grade ≥3 GI complications was 9.8% (95% CI: 6.2–15.0, $I^2 = 16.2\%$, $p_{\text{heterogeneity}}$: 0.294). The qualitative data are summarized in Table 4, while the pooled result is depicted in online suppl. Figure 3.

OS Comparison in R+ Patients

Five studies were suitable for the comparative OS analysis of R+ patients. The 5-year OS rate, which was the most frequently reported, was used for pooled analysis. The pooled 5-year OS rates in the ART and non-ART arms were 32.1% (95% CI: 20.1–47.1%) and 16.5% (8.3–30.2%), respectively, $p = 0.089$. No significant heterogeneity was observed in the analyses of both arms; a forest plot is shown in online suppl. Figure 4.



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(Figure continued on next page.)

Table 4. Grade ≥3 GI complication reported

Author	RT arm, *n*	Grade ≥3 GI complication, %
Sagawa et al. [36]	39	2.6 (biliary fistula)
Gwak et al. [23]	31	0.0
Kobayashi et al. [30]	21	4.7 (op leakage)
Kim et al. [28]	19	10.5 (duodenal ulcer)
Sugiura et al. [39]	22	9.1 (nausea and neutropenia)
Schoenthaler et al. [37]	45	8.9 (G5, cholangitis, and duodenal ulcer)
Tollenaar et al. [41]	16	0.0
Borghero et al. [19]	42	14.3 (acute GI 3, late 2 ulcers, and 1 bile duct stricture)
Kim et al. [29]	23	4.3 (1 case N/V)
Meng et al. [34]	28	21.4 (5 late bleeding and 1 obstructive jaundice)

RT, radiotherapy; GI, gastrointestinal; N/V, nausea and vomiting.

Discussion

Currently, no clinical practice guidelines support preferential use or strong recommendation of ART as an adjuvant modality for extrahepatic cholangiocarcinoma because there are no sufficiently convincing studies or meta-analysis [9, 42, 43]. In this situation, the most prominent finding when compared with the previous literature was the observance of an OS benefit on the sensitivity analysis of the selected group. Since our study primarily considers

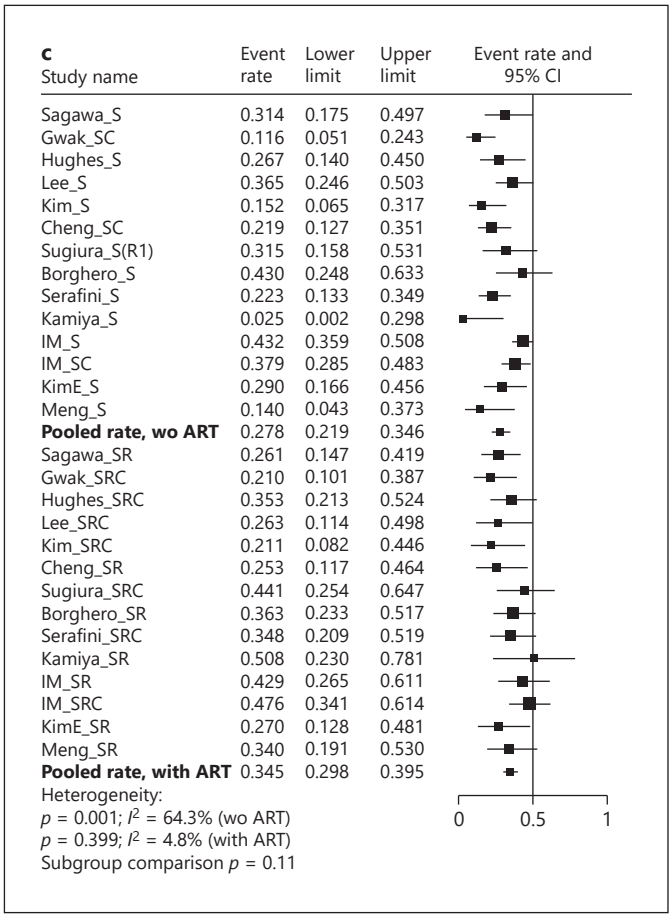

Fig. 3. Forest plot of pooled analyses of selected studies according to reliable comparability, regarding the (**a**) 1-year (**b**) 3-year, and (**c**) 5-year OS rates. ART, adjuvant radiotherapy; CI, confidence interval; S, surgery; R, radiotherapy; C, concurrent chemotherapy; OS, overall survival.

comparability and provides data comprehensible in clinical practice, it might support efficient use of ART and facilitate future researchto identify proper and specific indications.

Although the pooled 3-year OS rate was significantly higher in the ART arms, the pooled 1- and 5-year OS rates were also higher, with *p* values mildly exceeding the threshold of subgroup comparison. Considering that the non-ART groups among the selected studies had a significantly lower pooled R0 rate (36.8% vs. 63.2%, $p = 0.02$) and higher LN + status (47.9% vs. 34.9%, $p = 0.08$), the benefit of ART in terms of OS may be more convincing. Since the pooled LRR rate was significantly lower (34.9% vs. 52.1, $p = 0.014$), the OS benefit might therefore also extend to reducing such recurrences. This result is consistent with those of previous studies that found that approximately half of the recurrences observed after extrahepatic cholangiocarcinoma resections were locoregional and that most could be encompassed by the external beam radiotherapy target area [44–46]. However, it should be also noted that distant recurrences were not diminished with ART; some researchers claimed that such recurrences were even more frequent after ART [19, 29].

We found several meta-analyses in the literature that were of a similar topic as ours [3–6]. Previous meta-analyses used sound methodology; however, there is some room for improvement in terms of clinical decision-making. First, several meta-analyses included patients with cancers other than extrahepatic cholangiocarcinoma (e.g., gallbladder cancer). Although they might share some similarity in terms of their surgical treatment approaches, their patterns of recurrence and potential to benefit from adjuvant therapy can differ [47]. Another confounder is the unknown distribution of patients between arms. Previous researchers assumed that patients who underwent ART would have generally inferior clinical profiles and be more vulnerable to recurrence. However, such an assumption might not always be true; for instance, patients who are in better clinical condition may decide to undergo ART, whereas those whose expected prognoses are too poor may decide to forgo it. In Kobayashi et al.'s [30] study, the LN + rates were 52% and 29% in the non-ART and ART arms, respectively, and in Schoenthaler et al.'s [37] study, the pT3 or pT4 rates were 74% and 37% in the non-ART and ART groups, respectively; these studies were excluded from the sensitivity analysis. Additionally, from a technical perspective, nonrandomized studies could be difficult to unearth owing to poor indexing or inconsistent terminology [12]. The number of studies investigating extrahepatic cholangiocarcinoma included in previous meta-analyses ranged from 8 to 14, whereas our analysis included 23 studies. The present study was designed to overcome the aforementioned limitation and produced outcome-based results that can be more applicable to clinical practice.

Concerns regarding the application of ART are also described in the literature. Shinohara et al. [48] performed a Surveillance, Epidemiology, and End Results (SEER) database study of extrahepatic cholangiocarcinoma and found that although ART produced a survival benefit, it was not sustained after controlling for confounders. Vern-Gross et al. [49] also conducted a SEER database study and found that the addition of ART was only beneficial in the short term but was hazardous in the long

term. However, in both studies, it should be noted that the only clinical covariate included when controlling for confounders was disease stage, whereas all the remaining variables were social (such as age, race, sex, and year of diagnosis). Although both these studies have merit in terms of producing data from a large number of patients, the results after statistical balancing should be carefully interpreted.

The pooled grade ≥3 complication rate was 9.8% in our study; 4 patients with grade 5 (mortality) were reported, although they were from a relatively older study [37]. Although the rate of complications might not be high enough to outweigh the locoregional benefit of ART, efforts are necessary to reduce such toxicities. All studies included in the present meta-analysis reported outcomes of patients who underwent conventional 3- or 2-dimensional ART. Bittner et al. [50] reported that intensity-modulated radiotherapy significantly reduced grade ≥3 nausea and vomiting (7.8% vs. 13.4% vs., $p < 0.001$), diarrhea (2.0% vs. 11.6%, $p < 0.001$), and late GI toxicities (5.0% vs. 10.6%, $p = 0.017$) among patients treated for pancreatic cancer compared with 3-dimentional radiotherapy. Although the literature pertaining to cholangiocarcinoma is scarce, such results encourage the use advanced modalities because the radiotherapy targets for cholangiocarcinoma and pancreatic cancer have close similarity.

Our study had certain limitations. Meta-analyses of nonrandomized studies are controversial due to influences from heterogeneity and uncontrolled confounders [12]. However, the field of oncology is not always dependent on randomized studies; applying radiotherapy for rare cancers is inevitably supported by observational studies [51]. Several researchers reported that well-designed observational studies have results similar to those of randomized studies [52]; in the same vein, we performed all the statistical calculations and sensitivity analyses to enhance confidence in our result. Furthermore, one might argue that the present study did not provide specific clinical indication as compared to the previous literature. However, although lymphatic metastases or positive resection margins are known prognostic factors, actual clinical decision should be performed in consideration of other clinical factors, such as T stage, age, tumor grade, and treatment policy of institutions. The role of this study is to encourage the use of ART, which is not widely used compared to the actual role, and to support the production of more personalized indications in the future studies (e.g., nomograms). Finally, we could not comprehensively assess the effect of systemic chemotherapy partly because the rate of its application varied and the relevant information was scarce. On the other hand, in the recent BILCAP study, the effect of capecitabine was comprehensibly addressed, although the rate and effectiveness of ART administration were not reported [53]. We hope that future researchers investigate the roles of such treatments in their fields as well as in parallel disciplines.

Conclusion

The present study, confined to a single disease entity and primarily considering comparability, will support efficient use of ART and conduction of future studies to identify proper indications. Although a reduction of LRR was shown, further technical efforts to minimize complications are necessary.

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Statement of Ethics

Ethical approval was not required because this study retrieved and synthesized data from previously published studies.

Conflict of Interest Statement

Dr. Jinsil Seong is an editorial board member of *Liver Cancer*. Otherwise, the authors have no conflicts of interest to declare.

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Author Contributions

Seo Hee Choi contributed to writing the original draft and data curation; In-Soo Shin contributed to formal analysis, data curation, and methodology; Jinsil Seong contributed to writing-editing

and supervision; Woong Sub Koom and Won-Sup Yoon contributed to supervision; Chai Hong Rim contributed to conceptualization, writing (original draft, review, and editing), formal analysis, and data curation.

Data Availability Statement

All data generated or analyzed during this study are included in this article and/or its online suppl. files. Further inquiries can be directed to the corresponding author.

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