Benefit of Adjuvant Radiotherapy for Gallbladder Cancer: A Comparability-Based Metaanalysis

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Benefit of adjuvant radiotherapy for gallbladder cancer: A comparability-based meta-analysis

Short title: Adjuvant radiotherapy for gallbladder cancer

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Abstract

Background & purpose: The benefits of adjuvant radiotherapy (ART) in gallbladder cancer (GBC) treatment remain inconclusive owing to the rarity of GBC and lack of randomized studies.

Methods: PubMed, Medline, Embase, and Cochrane Library were systematically searched until March 2021. The primary endpoint was overall survival (OS). Comparative clinical studies that reported survival outcomes in GBC patients treated with or without ART were included. The comparability of each study was assessed by considering all possible clinical indicators (group 2: ART arm with poor clinical profile; group 1: ART arm with statistically similar profile or no evidence of having inferior clinical factors compared to non-ART arm).

Results: Twenty-one studies involving 6876 GBC patients were reviewed. In pooled analyses of OS, the odds ratio (OR) was 1.26 (p=0.111). In subgroup analyses considering comparability, the OR significantly favored the ART arm (1.92, p=0.008) among comparability group 1 studies, whereas it was 1.03 (p=0.865) in comparability group 2 studies. The pooled rate of 5-yr OS in the ART vs. non-ART arms was 44.9% vs. 20.9% in group 1 and 34.1% vs. 40.0% in group 2. With ART, significant reduction in locoregional recurrence (OR: 0.21, p=0.001) but not in distant metastasis (OR: 1.32, p=0.332) was noted.

Conclusion: ART not only showed benefits in patients with a similar clinical profile to those treated without ART but also yielded comparable survival in patients with an inferior clinical profile. Our results strongly support the more active application of ART in GBC treatment.

Protocol registration: This study is registered in PROSPERO (CRD4202124062, available at: https://www.crd.york.ac.uk/).

Keywords: gallbladder neoplasm; radiotherapy; adjuvant; survival

Introduction

Gallbladder cancer (GBC) is an extremely aggressive malignancy of the biliary tract, and surgical resection remains the only potentially curative approach. However, only 10-30% of patients present with resectable disease, and high recurrence rates are reported even after curative resection [1-4]. Unfortunately, evidence supporting the role of adjuvant therapies in GBC is scarce, and adjuvant treatment is not yet considered standard practice. After one prospective randomized study showed survival benefits with adjuvant chemotherapy in 2002, [5] several phase II and retrospective studies have explored adjuvant strategies after resection of GBC. Owing to concerns about considerable locoregional recurrence, some researchers have attempted to investigate the benefits of adjuvant radiotherapy (ART). However, because of selection bias and heterogeneity in studies, the role of ART remains unclear.

Two meta-analyses evaluating the clinical benefits of ART for GBC have been published [6,7]. Both studies provided supporting evidence for the survival benefits of ART, especially in the subgroup of patients with positive nodes or margins. However, these meta-analyses did not consider bias due to comparability issues but assumed that the ART arm had an inferior clinical profile, which may not always be true (e.g., ART could be omitted in patients with a short life expectancy). Furthermore, clinical prognosticators other than node positivity and positive margins were not considered, and subgroup analyses for these factors included only two to five studies.

Presently, established data from randomized studies are unavailable, and clinical decisions are made on the basis of findings from observational studies. Furthermore, with developments in radiotherapy techniques, which further reduced the obstacles to ART application, evidence

supporting the application of ART for GBC in real clinical situations is needed.

Therefore, this meta-analysis aimed to evaluate whether ART for GBC yields oncologic benefits. We attempted to enhance the study's reliability by comprehensively considering the comparability between arms on an individual study basis.

Methods

Study searching and inclusion

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [8] for conducting this meta-analysis and referenced the Cochrane Handbook (version 6.2) for methodology [9]. The population, intervention, comparison, and outcome (PICO) question of the hypothesis was as follows: "Does ART confer a survival benefit in treating GBC?" The following inclusion criteria were used for recruiting studies: 1) comparative clinical studies involving GBC patient cohorts treated with and without ART, 2) studies with at least five GBC patients in each arm, and 3) studies that provided any measurement of overall survival (OS). We searched four databases (PubMed, Embase, Medline, and Cochrane Library), as recommended by the Cochrane Handbook [10], until March 2, 2021. The search terms and strategies according to the databases are described in Supplementary Data 1. No language restriction was applied. Chinese articles were translated by a professional Chinese-English translator, and Japanese and Korean articles were translated and interpreted by one of the authors (CH Rim). Conference abstracts were included if they fulfilled the inclusion criteria. To reduce the risk of missed articles, the reference lists of the included articles and previous meta-analyses were reviewed. Studies from the same institution, with possible duplication, were filtered using the following criteria in order: 1) study providing

target information and relevant clinical information, 2) study with a larger number of patients, and 3) more recent publication (when the number of patients was similar). Studies based on the National Cancer Database (NCDB) were also filtered using the same criteria when the possibility of duplication existed. All processes of study searching and inclusion were performed by two independent researchers; any disagreement was resolved through discussion and repeated searching.

Data collection processes and items

The primary endpoint was OS. Locoregional recurrence, distant metastases, grade ≥3 complications, and disease-free survival (DFS) were assessed as secondary endpoints. We used a standardized form to collect clinical and general information, including endpoints, as follows: 1) general information including author name, patient recruitment period, publication, institution where the study was performed, and conflicts of interest (commercial, academic, or none), and 2) clinical information including dose and modality of ART, application of concurrent chemotherapy, median OS, 3- and 5-yr OS, 3- and 5-yr DFS, grade ≥3 complications, and locoregional and distant recurrence rate. Data collection was performed by two independent researchers; any disagreement was resolved through a discussion based on a literature re-review.

Study quality and bias assessment

As most related studies were nonrandomized, possible confounders were carefully discussed, as recommended by the Cochrane Handbook. Considering the rarity of GBC, similarity of

treatment modalities (surgery and/or ART), and reliability of the primary endpoint (OS), a meta-analysis might be feasible. However, according to our preliminary literature analysis, the most significant potential confounder was comparability. Most studies were not prospectively controlled; they retrospectively assessed the treatment outcomes. Previous meta-analyses assumed that ART was performed in patients with inferior clinical profiles. However, ART may have been omitted in patients with a short life expectancy. Additionally, some studies suggested that clinical indicators were similar between groups treated with and without ART, based on statistical analyses. Some meta-analyses attempted to resolve bias in comparability through subgroup analyses, according to clinical indicators such as lymph node (LN) metastases and resection margin (RM). Although these are known clinical indicators, few studies provided comparative data to allow such analyses, and clinical decisions and patient prognoses were also affected by other clinical factors (e.g., T stage, performance status, age, and surgical extent).

The clinical indicators provided by studies significantly varied in terms of details and types of indicators. Therefore, we assessed the comparability of candidate studies via discussion between two independent clinical oncologists. Studies in which the ART arm had clearly unfavorable clinical factors were categorized into comparability group 2. In group 2 studies, one or more of the following factors had significantly higher rate in ART arms: rates of non-radical surgery, advanced stage, LN+, and positive RM (defined as having either a statistically significant or >20% difference). Studies with patient distribution in a direction unfavorable to ART arms with clinical discretion (e.g. patients with status of positive RM or LN+ underwent ART in a certain institution) were also categorized into group 2. On the other hands, studies with no evidence that the clinical profiles of the ART arms were inferior to non-ART arms into group 1. Considering that most related studies were nonrandomized, we used the Newcastle-Ottawa scale [11]. We investigated the studies recruited to be included in three categories; score

of 8 to 9 was regarded as high quality, 5 to 7 as medium quality, and less than 5 as low quality. Low quality studies were discussed among authors to be excluded in pooled analyses, according to the advice of the Cochrane handbook that only observational studies with moderate to low risk of bias should be pooled analyzed [12]. The above comparability and quality assessments were performed by two independent researchers; any disagreement was resolved through discussion.

Statistics

A random-effects model was used for pooled analyses, considering possible heterogeneity in clinical profiles, treatment details among institutions, and the Cochrane Handbook [13] recommendation that a random-effects model should be used as the default choice for nonrandomized studies. Pooled odds ratios (ORs) were calculated for OS, DFS, and locoregional and distant recurrence. Moreover, 3- and 5-yr OS percentiles were also pooled. Grade ≥3 complications were subjectively assessed. For studies with more than three arms (e.g., surgery only, surgery and chemotherapy, and surgery and chemoradiotherapy), two arms (the ART arm and the other arm most comparable to the ART arm) were chosen for analyses. Heterogeneity assessment was performed using I^2 statistics [14] and the Cochran Q test, [15] in which $p<0.1$ and $I^2>50\%$ were considered to indicate significant heterogeneity. Subgroup analyses were performed for OS (the primary endpoint) using the above comparability categories. Publication bias assessments including >10 studies were performed using visual funnel plots and quantitative Egger's test [16]. Possible publication bias was deemed to be present if the funnel plots showed asymmetry and the Egger's test p value was <0.1. Duval and Tweedie's trim-and-fill method [17] was performed for analyses with possible publication bias.

All statistical analyses were performed using Comprehensive Meta-Analysis (version 3; Biostat Inc., Englewood, NJ, USA).

Results

In total, 2491 studies were initially obtained from the search. Studies with irrelevant formats and duplicated records among the databases were filtered using automated processes. Subsequently, the abstracts of 683 studies were reviewed. After excluding studies with irrelevant formats, irrelevant subjects, or missing target information, 39 studies were investigated in full-text analysis. Finally, 21 studies [18-38] involving 6876 patients that fulfilled all inclusion criteria were included. The study inclusion process is shown in Fig. 1 and detailed in Supplementary Data 1.

Among the 21 studies, 18 were full-text articles and three were conference abstracts. Of the 18 studies, 16 were from individual affiliations and two were based on the NCDB of the United States. Seven studies were from the United States; four from Korea, three from Japan, three from India, two from China, and one each from Mexico and Sweden. The earliest study recruited patients from 1976 to 1998, whereas the latest study recruited patients from 2007 to 2017. None of the studies reported any commercial conflict of interest. Conventionally fractionated external beam radiotherapy at a dose ranging from 45 to 50.4 Gy was used in most studies. The rates of extended surgery or simple cholecystectomy varied across studies. Table 1 shows the general information of the included studies (full version in Supplement Table 1).

Quality and bias assessments

Study quality was assessed using the Newcastle-Ottawa scale. Considering the low incidence of GBC, specificity of treatment modality, reliability of treatment records, and lack of the possibility of the outcome of interest being present at study initiation, most studies received full points for the selection criteria. Regarding outcome criteria, since all studies involved outcome data obtained from hospital records or national databases, they received points according to follow-up period and quality. Regarding comparability, two points were given if there was comparable data on two or more clinical factors, one point was given to studies that had information on a single clinical factor or institution's treatment policy. Studies without relevant information had zero point on comparability. Since all studies analyzed were to have medium or high qualities, all recruited studies were pooled analyzed for endpoints of interest. The details and results of quality assessment are shown in Supplement Table 2.

Synthesis of clinical endpoints

The median survival of all cohorts was 23 months (range, 7-58 months). In the ART arm, the median survival was 25 months (range, 13-58 months), whereas it was 15 months (range, 7-50 months) in the non-ART arm. The median 5-yr OS percentile was 39% (range, 0-81%) in the ART arm and 23% (range, 0-73%) in the non-ART arm.

In pooled analyses of the primary endpoint (i.e., OS), the OR was 1.26 (95% CI: 0.95-1.67, p=0.111), which was not significant. In subgroup analyses considering comparability, the OR significantly favored the ART arm (OR: 1.92, 95% CI: 1.18-3.12, p=0.008) among comparability group 1 studies. (e.g., excluding comparability group 2: studies of which ART arm has inferior clinical profile). For comparability group 2 studies (in which the ART arm had an inferior clinical profile), the OR was 1.03 (95% CI: 0.74-1.44, p=0.865), but the difference

was not significant. In pooled analyses of the secondary endpoints, the effect size favored the ART arm with respect to DFS, with borderline significance (OR: 1.96, 95% CI: 0.92-4.18, p=0.083). Regarding locoregional recurrence, the effect size strongly suggested that the ART arm was correlated with a lower recurrence rate (OR: 0.21, 95% CI: 0.13-0.36, p=0.001). Regarding distant metastases, the effect size was not significant (OR: 1.32, 95% CI: 0.75-2.31, p=0.332). The synthesis results for the endpoints of interest are summarized in Table 2. The pooled rate of 5-yr OS in comparability group 1 was 44.9% vs. 20.9% in the ART vs. non-ART arms. In comparability group 2, it was 34.1% vs. 40.0% in the ART vs. non-ART arms. The pooled locoregional recurrence rate was 19% vs. 51.7% and the pooled distant metastasis rate was 27.6% vs. 23.6% in the ART vs. non-ART arms. The pooled numerical percentiles of the clinical endpoints are shown in detail in Table 3. Forest plots of each clinical endpoint (OS, DFS, locoregional recurrence, and distant metastasis) are shown in Figure 2. The detail of comparability assessment categorizing the comparability group is described in Supplement Table 3.

Heterogeneity analyses and publication bias assessment

Significant heterogeneity was found in pooled analyses of OS among all included cohorts and cohorts in comparability group 2, as well as in pooled analyses of DFS among the available studies. These heterogeneities may be influenced by differences in patient characteristics, differences in surgical extent, and simple subgrouping (e.g., owing to the limited number of studies, especially in comparability group 1, subgroup analyses were performed with two groups). Publication bias was assessed in pooled analyses including >10 studies, and no possible publication bias was detected.

Complications

Most studies did not report numerous or specific ART-related complications. Yang et al. [38] reported an overall incidence of nine cases (21%) of grade 3 complications in which the symptoms were reversible. Gu et al. [23] reported that although grade 1 or 2 hematologic and gastrointestinal toxicities were common in the ART arm, no grade ≥3 complications occurred. Mondragón-Sánchez et al. [33] reported three cases of chronic abdominal pain that were difficult to control. Okamoto et al. [35] reported one case of postoperative mortality in the non-ART arm and two cases of mortality due to subphrenic abscess in the ART arm, of which one case was related to intraoperative radiotherapy-related stump injury.

Discussion

Most of the studies on adjuvant treatment for GBC to date are retrospective case series. As the field of radiation oncology is relatively small with less established research capacity, fewer related studies exist than that in medical and surgical oncology. To our knowledge, no randomized studies have verified the benefits of ART for GBC [39] Therefore, in the current clinical situation, therapeutic decisions are made by interpreting information obtained from existing retrospective studies.

Several researchers have attempted to synthesize findings through meta-analyses to aid clinical decisions. Ma et al. [6] studied the benefit of adjuvant treatment (chemotherapy and/or radiotherapy) for GBC and reported that the benefit of chemoradiotherapy (hazard ratio [HR]: 0.65, 95% CI: 0.36-1.16) or radiotherapy (HR: 0.64, 95% CI: 0.26-1.59) was not significant

compared with that of surgery alone. However, only three and four studies were included in the analyses of the chemoradiotherapy and radiotherapy groups, respectively. Kim et al. [7] performed a meta-analysis of studies specifically related to ART for GBC; more relevant studies (pooled analysis of OS: 13 studies) than those in Ma et al.'s analysis were analyzed, and the OS benefit of ART was significant in the pooled analysis (HR 0.54, $p<0.001$). Both of these studies performed subgroup analyses for the LN+ and RM+ groups and suggested that adjuvant treatment would be effective, especially in these subgroups. However, these studies might be insufficiently persuasive because of some limitations. They assumed that the adjuvant arm would have a poor clinical profile; however, although adjuvant treatment is commonly used in patients vulnerable to recurrence, it may be omitted in patients with a short life expectancy or poor general condition. Furthermore, the number of studies providing comparative information necessary for subgroup analyses was limited (only two to five studies). LN status and RM status are only two of several clinical factors, and various other factors such as T stage, tumor grade, and age can be considered in evaluating actual clinical comparability. Owing to the scarcity of convincing literature, ART has not been fully applied in clinical practice, and its indications have not been established. In the National Cancer Comprehensive Network guidelines, as an adjuvant option for GBC, systemic treatment or clinical trial participation is preferred even for RM+ or LN+ patients, and chemoradiotherapy is suggested as the next option [40].

We attempted to increase the reliability of the meta-analysis by individually analyzing the comparability of the studies. In the overall pooled analysis, ART did not show a significant OS benefit (OR: 1.26, $p=0.111$); however, ART showed a significant benefit in the subgroup analysis (group 1) that excluded studies with an ART arm having an inferior clinical profile (OR: 1.92, $p=0.008$). Additionally, in the group of studies with an ART arm having an inferior

clinical profile (group 2), the OR was 1.03 (p=0.865), and the 5-yr OS rate was 34.1% vs. 40% (ART vs. non-ART). These results suggest that ART might yield comparable oncologic outcomes even in patients with an inferior clinical profile. As the reduction in locoregional recurrence with ART (OR: 0.21, locoregional recurrence rate: 19% vs. 51.7%) but not in distant metastasis (OR: 1.32, p=0.332) was significant, the OS benefit in group 1 and the comparable results in group 2 seemed to be affected by the reduction in locoregional recurrence.

Only few studies have reported ART-related complications, partly because most included studies were conducted by surgeons or medical oncologists. We investigated the included studies to identify complications, especially grade ≥3 gastrointestinal toxicities, but none of the studies clearly reported such complications. Okamoto et al. [35] reported a fatal case after intraoperative radiotherapy; however, intraoperative radiotherapy is not a common modality in current clinical practice. From the perspective of radiotherapy techniques, as conventionally fractionated schemes of 45-50 Gy (below the tolerance dose of the small bowel) [41] were mostly used and only a small portion of the normal liver was irradiated, the possibility of serious complications might be insignificant. Additionally, although three- or two-dimensional multibeam treatment was used in studies included in the present meta-analysis, intensity-modulated radiotherapy has been increasingly used in clinical practice in the recent decade [42]. Sun et al. [43] reported that the application of intensity-modulated radiotherapy significantly reduced the irradiated volume of the normal liver and kidney. Among the 20 patients treated, no grade ≥3 complications occurred; grade 2 nausea and diarrhea were the most common complications. Bittner et al. [44] also reported that the application of intensity-modulated radiotherapy significantly reduced the incidence of grade ≥3 diarrhea (2% vs. 11.6%, p<0.001) and late gastrointestinal toxicity (5% vs. 10.6%, p=0.017) compared with the application of conventional three-dimensional radiotherapy in treating pancreatic cancer, which has a similar

radiotherapy target to GBC.

Thus, the results of this meta-analysis support more active ART application in GBC treatment. Particularly, ART should not be limited to LN+ or RM+ patients, but clinical decisions should be made after a comprehensive consideration of various clinical factors and situations.

Our study had some limitations. Meta-analyses of observational studies have been controversial because the pooled effect can be affected by heterogeneity among studies and uncontrolled confounders [13]. However, narrow subjects, such as adjuvant treatment of rare cancers such as GBC, may inevitably be supported by observational studies [45,46]. In this situation, a meta-analysis is one of the few methods available to aid clinical decisions. Notably, to enhance the reliability of the meta-analysis, we performed statistical complements, including heterogeneity and publication bias assessments and subgroup analyses, as well as comparability assessment on an individual study basis. Another limitation is that this study had no specific indication for ART, compared with previous studies and meta-analyses. However, this study aimed to support the more active application of ART by interpreting the literature, while providing reliable synthesized information. Similarly, our study is expected to stimulate future studies investigating more specific and personalized indications that are not limited to the LN+ or RM+ status.

Conclusion

This study comprehensively considered comparability between arms on an individual study basis and confirmed that ART has relevant oncologic benefits. Our results support the clinical application of ART in practice, and provide a basis for future research toward the creation of

personalized indications for ART.

Declarations

Author contributions: Seo Hee Choi, writing (original draft), data curation; **In-Soo Shin,** formal analysis, data curation, methodology; **Jinsil Seong,** writing (editing), supervision; **Woong Sub Koom, Won-Sup Yoon**, supervision; **Chai Hong Rim,** conceptualization, writing (original draft, review, and editing), formal analysis, data curation.

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Informed Consent Statement: Not applicable

Ethical statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Reporting Checklist: The authors have completed the PRISMA reporting checklist.

Protocol registration: This study is registered in PROSPERO (CRD4202124062, available at: https://www.crd.york.ac.uk/).

Data sharing statement: Data available within the article or its supplementary materials.

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Competing interest: None of the authors have any conflicts of interest to disclose.

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Figure legends

Fig. 1. Study inclusion process

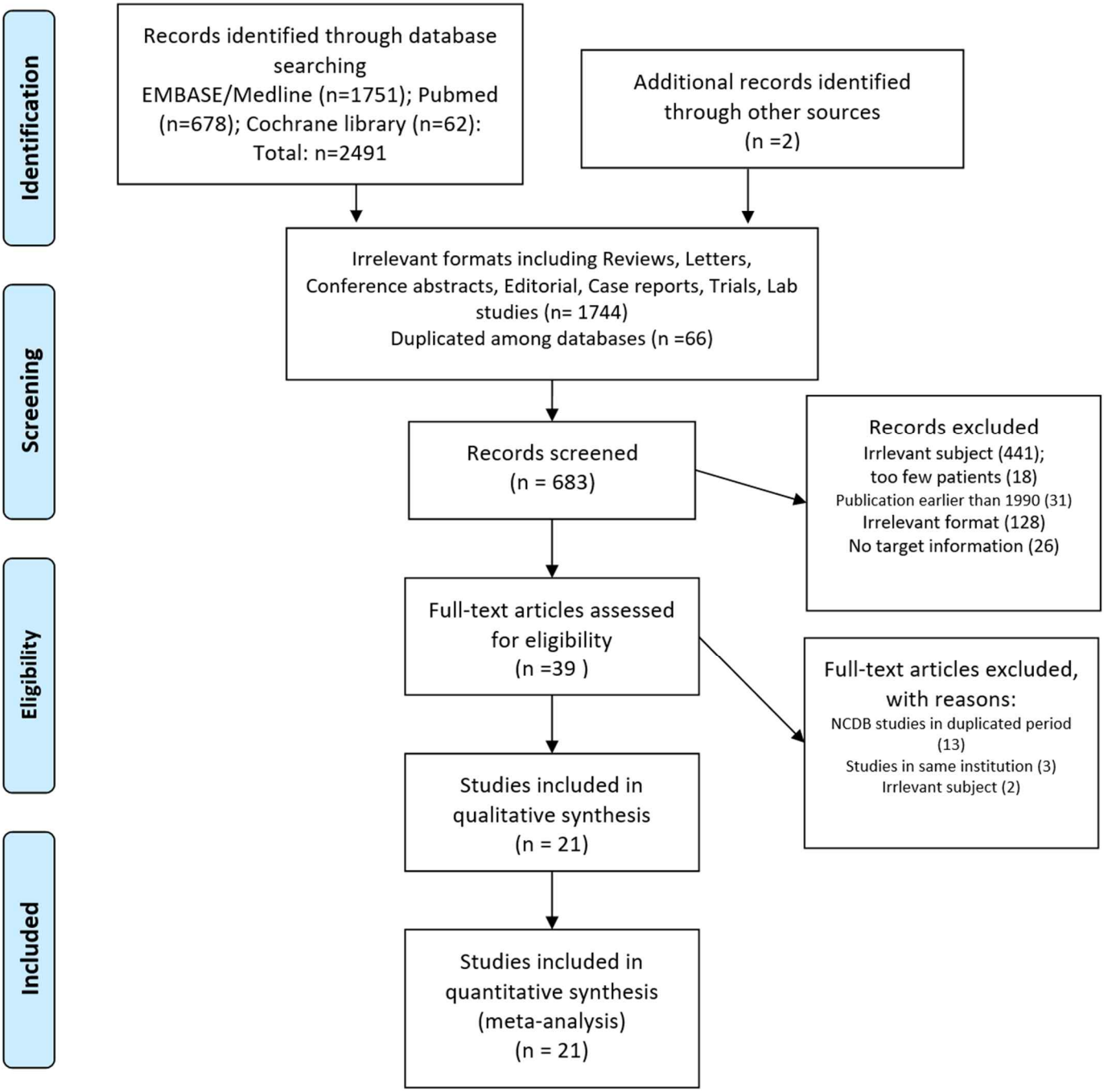
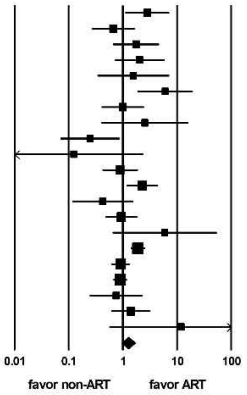


Fig. 2. Forest plots. (A) Overall survival in all studies: odds ratio (OR) 1.26 (95% confidence interval [CI]: 0.95-1.67, p=0.111; (B) overall survival in all studies with subgroup analyses (group 2 included studies in which the adjuvant radiotherapy [ART] arm had a significantly inferior clinical profile than the non-ART arm; group 1 denote the rest of the studies): OR 1.03 (95% CI: 0.74-1.44, p=0.865) in comparability group 2 studies and 1.92 (95% CI: 1.18-3.12, p=0.008) in comparability group 1 studies; (C) disease-free survival: OR 1.96 (95% CI: 0.92-4.18, p=0.083); (D) locoregional recurrence: OR 0.21 (95% CI: 0.13-0.36, p=0.001); and (E) distant metastases: OR 1.32 (95% CI: 0.75-2.31, p=0.332)

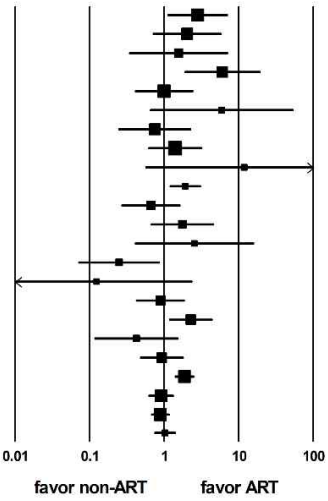
(A)

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Balachandran	2.827	1.106	7.226	2.170	0.030
Go	0.666	0.266	1.667	-0.868	0.386
Gold	1.756	0.657	4.694	1.122	0.262
Gu	2.041	0.704	5.917	1.314	0.189
KimTH_N0	1.563	0.337	7.246	0.571	0.568
KimTH_N+	6.054	1.863	19.669	2.995	0.003
KimWS	1.000	0.403	2.481	0.000	1.000
Todoroki	2.550	0.403	16.142	0.994	0.320
Mondragon	0.249	0.070	0.880	-2.157	0.031
Okamoto	0.125	0.006	2.407	-1.378	0.168
Wang	0.894	0.418	1.910	-0.289	0.772
Yang (meanOS)	2.286	1.165	4.487	2.403	0.016
Itoh(3yrOS)	0.426	0.115	1.574	-1.280	0.201
Lee	0.934	0.473	1.843	-0.198	0.843
Lindell	5.935	0.643	54.769	1.571	0.116
Mitin_C	1.883	1.385	2.561	4.037	0.000
Mitin_nC	0.910	0.613	1.352	-0.465	0.642
Mojica	0.893	0.666	1.197	-0.757	0.449
Bekhor	0.750	0.243	2.317	-0.499	0.618
Kothari	1.405	0.609	3.241	0.797	0.425
Nandagopal	11.892	0.561	252.184	1.589	0.112
	1.260	0.949	1.674	1.596	0.111



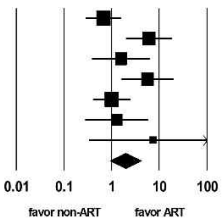
(B)

Group by comparability_simp	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
0or1	Balachandran	2.827	1.106	7.226	2.170	0.030
0or1	Gu	2.041	0.704	5.917	1.314	0.189
0or1	KimTH_N0	1.563	0.337	7.246	0.571	0.568
0or1	KimTH_N+	6.054	1.863	19.669	2.995	0.003
0or1	KimWS	1.000	0.403	2.481	0.000	1.000
0or1	Lindell	5.935	0.643	54.769	1.571	0.116
0or1	Bekhor	0.750	0.243	2.317	-0.499	0.618
0or1	Kothari	1.405	0.609	3.241	0.797	0.425
0or1	Nandagopal	11.892	0.561	252.184	1.589	0.112
0or1		1.922	1.183	3.124	2.638	0.008
2.00	Go	0.666	0.266	1.667	-0.868	0.386
2.00	Gold	1.756	0.657	4.694	1.122	0.262
2.00	Todoroki	2.550	0.403	16.142	0.994	0.320
2.00	Mondragon	0.249	0.070	0.880	-2.157	0.031
2.00	Okamoto	0.125	0.006	2.407	-1.378	0.168
2.00	Wang	0.894	0.418	1.910	-0.289	0.772
2.00	Yang (meanOS)	2.286	1.165	4.487	2.403	0.016
2.00	Itoh(3yrOS)	0.426	0.115	1.574	-1.280	0.201
2.00	Lee	0.934	0.473	1.843	-0.198	0.843
2.00	Mitin_C	1.883	1.385	2.561	4.037	0.000
2.00	Mitin_nC	0.910	0.613	1.352	-0.465	0.642
2.00	Mojica	0.893	0.666	1.197	-0.757	0.449
2.00		1.030	0.736	1.440	0.170	0.865



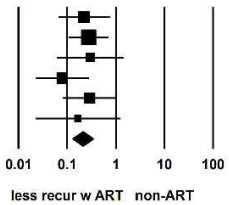
(C)

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Go	0.677	0.286	1.604	-0.886	0.376
Gu(3yr)	6.083	2.000	18.504	3.181	0.001
KimTH_N0	1.580	0.386	6.470	0.636	0.525
KimTH_N+	5.693	1.612	20.102	2.702	0.007
KimWS	1.000	0.403	2.481	0.000	1.000
Kapoor(3yr)	1.274	0.278	5.843	0.312	0.755
Nandagopal	7.378	0.334	163.115	1.265	0.206
	1.956	0.916	4.177	1.733	0.083



(D)

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Gold	0.224	0.067	0.750	-2.425	0.015
Gu	0.277	0.109	0.705	-2.692	0.007
KimTH_N0	0.297	0.062	1.432	-1.512	0.130
KimTH_N+	0.080	0.023	0.279	-3.963	0.000
Wang	0.291	0.082	1.027	-1.918	0.055
Lindell	0.167	0.023	1.232	-1.756	0.079
	0.212	0.126	0.355	-5.894	0.000



(E)

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Gold	1.272	0.443	3.653	0.448	0.654
Gu	1.451	0.544	3.866	0.744	0.457
Wang	1.439	0.557	3.717	0.751	0.453
Lindell	0.444	0.034	5.880	-0.615	0.538
	1.319	0.754	2.307	0.971	0.332

Tables

Table 1. Information of the included studies (full version in Supplementary Table 1)

Author	Comparability category*	RT profile	Surgery extent	Simple cholecystectomy	Group	n	Concurrent CTx	Median OS (mo)	3-yr OS	5-yr OS	MDFS	3-yr DFS	5-yr DFS	LRR and DM
Balachandran, 2006	1	NA	Extended surgery: 32%	68%	S+CR	73	NA	24	50.7% (2-yr)	35%	NA			
			Simple cholecystectomy: 68%		S	44		11	18.9% (2-yr)	16%				
Choudhary, 2015	1	M45 Gy	Open radical cholecystectomy: 88%	12%	S+CR	12	100%	13.3	16.6%	16.6%	13.3%	16.5%	NA	
			Laparoscopic simple cholecystectomy: 12%		S+C	16	0%	8	NA	NA	8	NA	NA	
Go, 2016	2	NA	All underwent "curative R0 resection"	0%	S+CR	45	100%		72.4%	62.0%	NA	47.3%	47.3%	
					S+C	39	0%		87.7%	71.0%		70.3%	57.0%	
Gold, 2009	2	M50.4 Gy (multibeam 100%)	Cholecystectomy and hepatic wedge resection: 76.7%	23.3%	S+CR	25	100%	4.8 (yr)	70.6%	48.6%	NA			LRR: 16%, DM: 32%
			Cholecystectomy: 23.3%		S	48	0%	4.2 (yr)	54.5%	35.0%				LRR: 46%, DM: 27%
Gu, 2018	1	M50 Gy (multibeam 100%)	Open extended cholecystectomy: 100%	0%	S+CR	39	100%	27	56.4%	30.8%	23	48.7%	NA	LRR: 35.7%, DM: 33.3%
					S	39	0%	13	56.4%	17.9%	7	13.5%		LRR: 66.7%, DM: 25.6%
Kim TH, 2019 (N0 cohort)	1	M50.4 Gy (3D CRT 100%)	NA		S+CR	24	100%		81.1%	81.1%	NA	82.4%	75.0%	5-yr LRFS: 86.2%
					S+C	15	0%		79.3%	73.3%		73.4%	65.5%	5-yr LRFS: 65.0%

Kim TH, 2019 (N+ cohort)		44-45 Gy			S+CR	35			73.5%	64.0%		52.9%	53.3%	5-yr LRFS: 82.1%
					S+C	24			31.4%	22.7%		21.0%	16.7%	5-yr LRFS: 26.8%
Kim WS, 2010	1	44-45 Gy	Extended surgery: 80.1%	19.9%	S+R	22	0%				NA	45.9%	45.9%	
			Simple cholecystectomy: 19.9%		S	126	0%					45.9%	45.9%	
Todoroki, 1999	2	m38.9 Gy	Radical resection: 91.1%	8.9%	S+R	25	NA	13.2		14%	NA			
			Simple cholecystectomy: 8.9%		S	32		6.5		6%				
Mondragón-Sánchez, 2003	2	40-50 Gy	Radical resection: 44.4%, Simple cholecystectomy: 55.6%	S+R: 100%, S: 0%	S+R	25	NA	23	37.7%	39.0%	NA			
					S	20		48	74.2%	72.0%				
Okamoto, 1996	2	IORT±EBRT: EBRT m44 Gy, IORT 18-20 Gy	S+R: 100% combined resection+RT (all tumors spread to the hepatoduodenal ligament)	0%	S+R	12	0%		0%	0%	NA			
			S: 100% combined resection alone		S	26	0%		32%	23%				
Wang, 2015	2	M50.4 Gy	100% radical resection	0%	S+R	68	56.3%		53.1%	49.7%	NA			LR: 6%, DM: 24%
					S	44	0%		58.3%	52.5%				LR: 18%, DM: 18%
Yang, 2013	2	M50 Gy (3D CRT 100%)	S+R: 2% simple, 98% extended	S+R: 2% S: 5%	S+R	43	0%	m13.3 (11.6-65.7)			NA			
			S: 5% simple, 95% extended		S	84	0%	m9.7 (5.4-13.2)						
Itoh, 2005	1		S+R: 100% extended	0%	S+R	5	0%	13	40%	NA	NA			

		m45.2 Gy (3D CRT 100%)	S: 54% cholecystectomy alone (+lymphadenectomy), 46% extended		S	13		34	61%	61%						
Lee, 2012	2	NA	Laparoscopic cholecystectomy: 29%, conversion to open cholecystectomy: 13%, radical second resection: 2%, primary open cholecystectomy: 51%, hemihepatectomy: 5%	29%	S+CR	62	100%	46	53.3%	44.4%	NA					
					S+C	73		NA	61.8%	46.1%						
Kapoor, 2013	1	M45 Gy (3D CRT 100%)	Extended surgery: 75%, simple: 25%	25%	S+CR	13	100%				NA	39.1%	NA			
					S+C	16						33.5%	NA			
Lindell, 2003	1	IORT: 20 Gy or EBRT: 40 Gy (3D CRT 100%)	Extended surgery: 100%	0%	S+CR	10	100%	28.8	58%	47%	NA			LRR: 10%	40%,	DM:
					S	10		20.2	40%	13%				LRR: 20%	80%,	DM:
Mitin (NCDB), 2017	2	NA	Local tumor excision: 4.4%		S+CR	484	100%		43.0%		NA					
			Simple/partial/total removal of the gallbladder: 84%		S+C	303	0%		28.6%							
			Partial/total removal of the gallbladder: 11.6%		S+R	111	0%		36.5%							

					S	2231			38.7%			
Mojica (NCDB), 2007	2	NA	Extended surgery: 16%, simple cholecystectomy: 77%	77%	S+R	424	NA	14	25.0%	15.0%	NA	
			Others: 7%		S	1901		8	21.5%	16.5%		
Bekhor (abst), 2019	1	NA	S+CR: 100% radical cholecystectomy	S+CR: 0% S+C: 5%	S+CR	21	100%	m25			m18	
			S+C: 95% radical cholecystectomy		S+C	19	0%	m26			m18	
Kothari (abst), 2015	1	NA	S+R: 100% radical cholecystectomy	36%	S+R	34	NA	47			NA	
			S: 100% simple cholecystectomy		S	39		26.5				
Nandagopal (abst), 2017	1	NA	NA		S+CR	12	100%	54.2		35%	45.7	24%
					S+C	10	0%	14.9		0%	13.4	0%

Abbreviations: S, surgery; CR, chemoradiotherapy; R, radiotherapy; RT, radiotherapy; CTx, chemotherapy; OS, overall survival; DFS, disease-free survival; MDFS, median disease-free survival; LRR, locoregional recurrence; DM, distant metastasis; LRFS, locoregional recurrence-free survival; LR, local recurrence; NA, not available; EBRT, external beam radiotherapy; IORT, intraoperative radiotherapy; 3D CRT, three-dimensional conformal radiotherapy; abst, abstract

Capital M headings denote median values, and small m headings denote mean values.

*Comparability group 2: studies in which the adjuvant radiotherapy (ART) arm had an inferior clinical profile than the non-ART arm; group 1: studies in which ART arm had statistically similar profile or no evidence of having inferior clinical factors compared to non-ART arm.

Table 2. Pooled analyses of endpoints of interest

Subjects	Cohort (n)	Patients (n)	Heterogeneity p, I^2 (%)	Effect size (95% CI, p)	Subgroup p	Egger's p
Overall survival (all studies)	21	6768	<0.001, 58.9%	OR: 1.26 (0.95-1.67, 0.111)		0.71
Overall survival (group 1*)	9	596	0.157, 32.6%	OR: 1.92 (1.18-3.12, 0.008)	0.038	NA
Overall survival (group 2*)	12	6172	0.001, 62.3%	OR: 1.03 (0.74-1.44, 0.865)		0.307
Disease-free survival	7	459	0.018, 60.7%	OR: 1.96 (0.92-4.18, 0.083)		NA
Locoregional recurrence	6	381	0.678, ~0.0%	OR: 0.21 (0.13-0.36, 0.001)		NA
Distant metastases	4	283	0.860, ~0.0%	OR: 1.32 (0.75-2.31, 0.332)		NA

Abbreviations: OR, odds ratio; NA, not available.

*Comparability group 2: studies in which the adjuvant radiotherapy (ART) arm had an inferior clinical profile than the non-ART arm; group 1: studies in which ART arm had statistically similar profile or no evidence of having inferior clinical factors compared to non-ART arm.

Table 3. Pooled analyses of percentile rates

Subjects	Cohort (n)	Patients (n)	ART vs. non-ART (%, 95% CI)
5-yr OS (all studies)	15	3309	39% (27.4-52.1) vs. 32.3% (20.2-47.4)
5-yr OS (group 1*)	7	382	44.9% (29.6-61.2) vs. 20.9% (8.9-41.7)
5-yr OS (group 2*)	9	2927	34.1% (19.3-52.8) vs. 40.0% (22.3-60.8)
3-yr OS (All studies)	15	6212	50.1% (40.3-59.9) vs. 50.8% (40.9-60.8)
3-yr OS (group 1*)	5	208	60.4% (41.1-77.0) vs. 51.5% (32.1-70.5)
3-yr OS (group 2*)	10	6004	45.6% (35.2-56.5) vs. 50.6% (39.3-61.9)
Locoregional recurrence	6	381	19% (10.4-32.3) vs. 51.7% (32.1-70.7)
Distant metastases	4	282	27.6% (20.8-35.7) vs. 23.6% (17.2-31.3)
3-yr disease-free survival	7	449	49.5% (37.9-61.3) vs. 41.4% (24.2-61.0)
5-yr disease-free survival	5	352	50.9% (37.7-63.9) vs. 41.9% (25.7-60.0)

Abbreviations: ART, adjuvant radiotherapy; OS, overall survival

*Comparability group 2: studies in which the adjuvant radiotherapy (ART) arm had an inferior clinical profile than the non-ART arm; group 1: studies in which ART arm had statistically similar profile or no evidence of having inferior clinical factors compared to non-ART arm.