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Comparison of Anatomical and Nonanatomical Hepatectomy for Colorectal Liver Metastasis: A Meta-Analysis of 5207 Patients

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It remains unclear whether hepatectomy for colorectal liver metastasis (CRLM) should be performed as anatomical resection (AR) or nonanatomical resection (NAR). The aim of this study is to compare the short- and long-term outcomes of AR and NAR for CRLM. PubMed, Web of Science, EMBASE and the Cochrane Library were systematically searched to identify eligible studies. Twenty one studies involving 5207 patients were analyzed: 3034 (58.3%) underwent AR procedure and 2173 (41.7%) underwent NAR procedure. The results showed that overall survival (OS, hazard ratio (HR) 1.06, 95% confidence interval (CI) 0.95–1.18) and disease free survival (DFS, HR 1.11, 95% CI 0.99–1.24) did not differ significantly between AR and NAR. Duration of operation, postoperative morbidity and mortality were higher in AR than in NAR. There were no significant differences in blood loss and prevalence rate of postoperative positive margins (OR 0.79, 95% CI 0.37–1.52). Our analysis shows that AR does not seem to bring more prognostic benefits than NAR for the treatment of CRLM, and does seem to be inferior to NAR in terms of duration of operation, incidence of postoperative morbidity and mortality.

Colorectal cancer (CRC) is one of the most common human malignancies. Worldwide, approximately 1.2 million new cases are diagnosed and over 600 thousand deaths are estimated to occur annually¹. About 40% patients with CRC develop liver metastasis at the time of presentation, with approximately 20% presenting as synchronous metastasis (within 6 months of resection of the primary tumor) and the remaining 20% as metachronous metastasis (after this period)^{2–4}. Liver resection has been shown to present the best chance of cure in the treatment of colorectal liver metastasis (CRLM), with a five-year survival rate exceeding 50% and nearly 20% postoperative patients surviving more than ten years^{5–8}.

Anatomical resection (AR)⁹ for hepatocellular carcinoma (HCC), through a systematic removal of the liver parenchyma of one or more Couinaud's segments fed by portal branches bearing the HCC, may reasonably reduce recurrence and return survival benefits compared to nonanatomical resection (NAR) or wedge resection. Through decades of practice, a widely accepted survival superiority of AR has been confirmed by several large cohort studies and meta-analyses^{10–17}. Similar to HCC, in CRLM tumor cells from colorectal primary lesions also travel and spread via the portal vein as an afferent and efferent vessel¹⁸. However, whether an analogical survival superiority can be achieved by AR for CRLM in comparison with NAR remains unclear. Several reports^{19–21} have documented long-term survival benefits of AR procedure for CRLM over NAR procedure, whereas other reports^{22–25} have failed to demonstrate such benefits, with results showing equivalent five-year overall survival (OS) rate between the two procedures.

Therefore, a meta-analysis of all available studies comparing the efficacy (short- and long-term outcomes) of AR procedure and NAR procedure for CRLM was conducted to get more reliable and up-to-date evidence.

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Methods

The meta-analysis was conducted in adherence with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines^{26,27}. All analyses were based on previously published studies, thus no ethical approval and patient consent are required. To ensure accuracy and minimize bias, all vital stages of the analysis were carried out separately by two reviewers; any disagreement was settled through consensus discussion.

Study Selection. A systematic literature search of PubMed, Web of Science, EMBASE and the Cochrane Library was performed to select articles comparing AR with NAR for CRLM. Searches were limited to studies published in English from the initiation of the databases to June, 2016. No additional restrictions were applied to the searches with regard to region or publication type. The following medical subject headings (MeSH) were used: “Colorectal Neoplasms,” “Neoplasm Metastasis,” “Liver Neoplasms” and “Hepatectomy”. Besides, the following keywords were used to complete the literature search: “Hepatectomy,” “liver resection,” “hepatic resection,” “anatomic/anatomical,” “nonanatomic/ nonanatomical,” “major,” “minor,” “limited,” “wedge,” “CRLM/CLM” and “colorectal liver metastasis.” Furthermore, the references given in the retrieved papers were manually checked for further relevant articles. In the case of repeated studies describing the same group of population, only the most recent or the highest in quality was included. The latest search was performed on July 3, 2016. To ensure the reliability and verifiability of our analysis, eligible studies were identified in according with the following inclusion and exclusion criteria. Inclusion criteria were: (1) studies on human; (2) patients with pathologically confirmed diagnoses of CRLM primarily undergoing potentially curative resections; (3) articles comparing AR with NAR; (4) articles reporting short- and (or) long-term outcomes of AR and NAR. A study had to meet all four inclusion criteria for inclusion. Exclusion criteria were: (1) review articles, letters, case reports, editorials or comments and conference abstracts. (2) articles with no clear definition or grouping of AR and NAR. (3) main outcomes of interest not stated or impossible to calculate. (4) articles including patients mainly undergoing repeated hepatectomy for CRLM or with unresectable extrahepatic metastases. A study meeting any of the four exclusion criteria was excluded.

Data Extraction and Definition. The following relevant parameters were extracted and summarized independently by two reviewers (Haowen Tang and Bingmin Li) for each study included in the meta-analysis: first author, study region, year of publication, total sample size, number of patients enrolled in each group (AR and NAR), population characteristics, primary tumor location, liver metastasis characteristics, short-term outcomes (operative and post-operative data) and long-term outcomes (OS and disease free survival (DFS)). At the same time, each screened article was graded by the Newcastle-Ottawa Scale (NOS) that was mainly concerned with three aspects (selection of patients, comparability of groups, and assessment of outcomes). Studies achieving more than seven points on the NOS were regarded to be of high quality.

Subgroups were generated if at least two studies were available; otherwise, subgroup analyses were not performed. A two-tailed P value < 0.05 was considered statistically significant.

Outcomes of Comparison and Statistical Analysis. Short-term outcomes included duration of operation (min), blood loss during operation (mL), incidence of blood transfusion, prevalence rate of postoperative positive margins, postoperative (30 day) morbidity and mortality. Long-term outcomes included OS and DFS.

For dichotomous variables, odds ratio (OR, calculated by the numbers of events and patients) with a 95% confidence interval (CI) was used for analysis. For continuous variables, weighted mean difference (WMD) with a 95% CI was used for analysis. For studies describing such variables as median and range, corresponding mean and variance were estimated by the methods proposed by Hozo²⁸. For comparison of OS and DFS, the hazard ratio (HR, describing a summary statistic for censored outcomes) with a 95% CI was used. An HR value (reference NAR group) less than one indicated a survival benefit favoring AR over NAR. If such survival-type data or additional key data were absent in the article, the corresponding author of each report was contacted by e-mail. In the absence of replies from the authors, the methods introduced by Tierney²⁹ were used to calculate HR and corresponding CI from other information such as the OS Kaplan-Meier curve. For comparison of categorical variables, the chi-squared (χ^2) test or Fisher’s exact test was utilized, as appropriate. A fixed effect model was used in the absence of significant heterogeneity ($I^2 < 50\%$); otherwise, a random effect model was used. Review Manager (version 5.3.5) software was utilized to conduct the meta-analysis. Further statistical analysis of time to event data (HR and 95% CI) were performed by STATA (version 12.0) statistical software. Between-study heterogeneity was assessed using Cochran’s Q and I^2 tests. Begg’s funnel plot and Egger’s tests were used to assess publication bias. Sensitivity analysis was performed using studies of high quality. Subgroup analysis was used to explore the between-study heterogeneity according to predefined parameters: cohorts without chemotherapy and sample size (size ≥ 200 and size < 200).

Results

Study Selection and Patients Characteristics. A PRISMA flowchart of the Study selection was shown in Fig. 1. The search returned a total of 1706 references. By meticulously screening titles and abstracts, 1432 references were eliminated. Among the remaining 274 potentially appropriate studies, 253 were excluded by full text analysis for matching one of the exclusion criteria. Ultimately, a total of 21 studies reporting on 5207 patients were eligible to be included in the present meta-analysis^{19–25,30–43}. All 21 studies were retrospective, nonrandomized studies published between 1987 and 2016 that were conducted in the United States of America (five studies), Italy (four studies), Japan (four studies), the United Kingdom (two studies), Germany (two studies), Netherland (one study), Turkey (one study) or Sweden (one study) or that were multicenter (one study). Among the 5207 patients enrolled, 3034 (58.3%) underwent AR procedure and 2173 (41.7%) underwent NAR procedure. The sample size

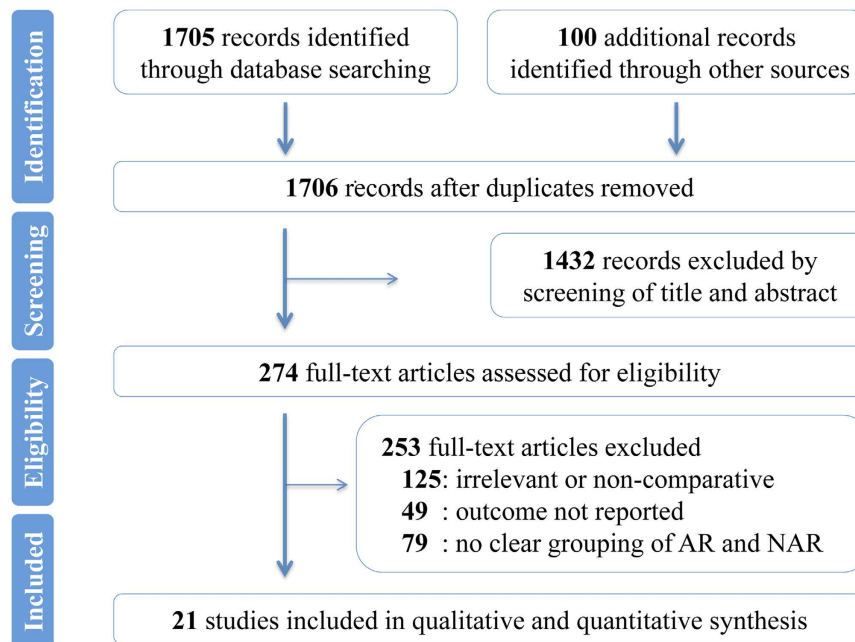


Figure 1. PRISMA flowchart of the study selection.

for these studies varied from 31 to 1001. The median follow-up length of the studies ranged from 20 to 94 months. For most of the studies, the mean or median age was in the 60 s or 70 s. The proportions of male patients were similar in both groups. Besides, based on the available data of some studies, the proportions of patients with carcinoembryonic antigen (CEA) level less than 200 ng/mL and amounts of tumors were comparable in both groups. The site of the primary tumor was reported for 1601 neoplasms, of which 1117 (69.8%) were located in colon and 484 (30.2%) in rectum, respectively. In AR group, 612 of the total 850 (72.0%) neoplasms were located in the colon; in NAR group, 505 of the total 751 (67.2%) neoplasms were in the colon. In addition, a commensurate rate of patients who received chemotherapy was observed between AR group and NAR group (χ^2 test, $P = 0.58$). The number of patients with bilobar metastases in the liver were comparable in the AR and NAR groups (22.95% versus 20.37%, $P = 0.15$). Similarly, no significant differences between the two groups were identified in terms of the presence of resectable extrahepatic metastases (2.29% in AR group versus 1.27% in NAR group, $P = 0.09$). Study characteristics, patient demographic information, and quality scoring were summarized in Table 1. Main outcomes were outlined in Table 2.

Short-term Outcome. Twelve of the 21 studies described the short-term outcomes (operative and postoperative)^{21,23–25,30–34,36,41,42}.

Ten studies were pooled to find a combined effect on the prevalence rate of postoperative positive margins. The results showed an OR of 0.79 in favor of AR group; however, the 95% CI crossed the no-effect line (95% CI 0.49–1.29, Fig. 2a).

The analysis of blood loss during operation revealed no significant differences. As to incidence of blood transfusion, the combined results favored NAR group (OR 2.94, 95% CI 1.87–4.62).

With regard to duration of operation, overall outcome from four studies indicated that NAR group was characterized by a reduced duration of operation in comparison with AR group (WMD 43.62, 95% CI 5.25–81.99).

Postoperative morbidity was reported in eight studies involving 2439 patients. The difference identified by the pooled analysis approached statistical significance in favor of NAR group (OR 1.68, 95% CI 1.13–2.50, Fig. 2b), with moderate between-study heterogeneity.

A similar advantage of mortality favoring NAR group was also presented among seven studies with slight between-study heterogeneity, indicating that NAR was associated with a lower mortality rate than AR (OR 3.74, 95% CI 1.60–8.75, Fig. 2c).

Long-term Outcome. Thirteen of the 21 studies described the long-term outcomes (OS and DFS). For OS, HR values extracted from 12 studies assessing 1803 patients were put into overall analysis^{21,23–25,31,32,35,36,40–42}. No clear evidence of a benefit of AR on time to survival was identified (HR 1.06, 95% CI 0.95–1.18, Fig. 3a). With regard to DFS, pooling the data from five studies showed no significant difference between the two groups (HR 1.11, 95% CI 0.99–1.24, Fig. 3b)^{23,31,39,41,42}.

Subgroup Analyses. In accordance with the predefined parameters, namely, the subgroup of cohorts entirely without chemotherapy, subgroup of sample size ≥ 200 and size < 200 , three subgroup analyses of OS were conducted. Uniformly, pooled analyses showed similar results in comparison with the overall finding (Fig. 4). For the limited studies for inclusion, subgroup analyses of DFS were not performed. All the above results are detailed in Table 2.

First author	Year	Country	No. of Patients			Gender (M/F)		Age		Primary tumor (Colon/Rectum)	
			Total	AR	NAR	AR	NAR	AR	NAR	AR	NAR
Ekberg H	1987	Sweden	68	55	13	—	—	—	—	—	—
Docì R	1991	Italy	95	46	49	—	—	—	—	—	—
Scheele J	1995	Germany	350	291	59	—	—	—	—	—	—
Wanebo HJ	1996	the US	74	51	23	—	—	—	—	—	—
Fong Y	1999	the US	1001	631	370	—	—	—	—	—	—
Yamamoto J	1999	Japan	96	23	73	—	—	—	—	—	—
DeMatteo RP	2000	the US	267	148	119	60/88	67/52	<70 (n = 110)	<70 (n = 83)	110/38	86/33
Kokudo N	2001	Japan	174	96	78	54/42	46/32	58.7 ± 1.0 [†]	60.3 ± 1.2 [†]	71/25	49/29
Belli G	2002	Italy	181	56	125	—	—	—	—	—	—
Nagakura S	2003	Japan	102	61	41	35/26	28/13	<60 (n = 27)	<60 (n = 11)	39/22	26/15
Zorzi D	2006	Multicenter	253	181	72	113/68	46/26	<65 (n = 120)	<65 (n = 44)	113/46	42/17
Finch RJ	2007	the UK	376	280	96	171/109	64/32	63 (26–84) [‡]	63 (24–79) [‡]	—	—
Guzzetti E	2008	Italy	208	102	106	58/44	63/43	<70 (n = 78)	<70 (n = 77)	55/21	60/31
Sarpel U	2009	the US	183	94	89	54/40	51/38	60.8 ± 10.4 [†]	62.3 ± 11.6 [†]	60/10	59/12
Lalmahomed ZS	2011	Netherlands	201	88	113	56/22	70/43	65 (30–82) [‡]	65 (36–86) [‡]	55/33	59/54
Kavlakoglu B	2011	Turkey	42	18	24	—	—	—	—	—	—
Inoue Y	2012	Japan	106	32	74	—	—	—	—	—	—
Heesen M	2012	Germany	108	47	61	—	—	—	—	—	—
Urbani L	2015	Italy	31	8	23	5/3	13/10	64 (33–83) [‡]	68 (41–77) [‡]	4/4	11/12
Pandanaboyana S	2016	the UK	991	582	409	—	—	<65 (n = 282)	<65 (n = 175)	—	—
Mise Y	2016	the US	300	144	156	80/64	94/62	58 (22–87) [‡]	60 (30–88) [‡]	105/39	113/43
First author	CEA Level (ng/mL)		Tumor Amount		Tumor Presentation Syn/ Meta		Follow-up (months)	NOS			
	AR	NAR	AR	NAR	AR	NAR					
Ekberg H	—	—	—	—	—	—	20 (3–167) [‡]	5			
Docì R	—	—	—	—	—	—	17 (1–97) [‡]	6			
Scheele J	—	—	—	—	—	—	—	6			
Wanebo HJ	—	—	—	—	—	—	—	6			
Fong Y	—	—	—	—	—	—	32 [‡]	7			
Yamamoto J	—	—	—	—	—	—	—	6			
DeMatteo RP	<200 (n = 101)	<200 (n = 84)	>1 (n = 30)	>1 (n = 23)	—	—	—	7			
Kokudo N	—	—	>1 (n = 42)	>1 (n = 36)	50/46	22/56	—	7			
Belli G	—	—	—	—	—	—	—	6			
Nagakura S	<100 (n = 41)	<100 (n = 34)	>3 (n = 7)	>3 (n = 2)	—	—	94 (4–234) [‡]	8			
Zorzi D	<200 (n = 160)	<200 (n = 63)	>1 (n = 82)	>1 (n = 27)	73/108	25/47	25 [‡]	8			
Finch RJ	18 (1–37140) [‡]	5 (1–12124) [‡]	2 (2–14) [‡]	1 (1–9) [‡]	117/163	36/60	33 (24–144) [‡]	8			
Guzzetti E	<200 (n = 52)	<200 (n = 51)	>1 (n = 43)	>1 (n = 39)	—	—	—	8			
Sarpel U	—	—	1.7 ± 1.2 [†]	1.4 ± 1.0 [†]	—	—	34 [‡]	7			
Lalmahomed ZS	<200 (n = 78)	<200 (n = 107)	2 (1–7) [‡]	1 (1–7) [‡]	35/53	43/70	35 (1–111) [‡]	8			
Kavlakoglu B	—	—	—	—	—	—	40.40 ± 12.87 [†]	6			
Inoue Y	—	—	1.8 ± 1.4 [†]	2.2 ± 2.2 [†]	—	—	—	6			
Heesen M	—	—	—	—	—	—	31.7 ± 1.6 [†]	6			
Urbani L	—	—	2 (1–10) [‡]	1 (1–12) [‡]	6/2	15/8	25.2 (0.3–62.7) [‡]	7			
Pandanaboyana S	—	—	2 ± 1.5 [†]	2 ± 1.5 [†]	294/288	228/181	32.2 (17.5–56.9) [‡]	7			
Mise Y	2.9 (0.4–250.3) [‡]	2.5 (0.4–430.9) [‡]	—	—	—	—	37 (2–208) [‡]	6			

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Table 1. Characteristics of included studies. AR: Anatomical resection; NAR: Nonanatomical resection; Syn: synchronous metastasis (within 6 months of resection of the primary tumor); Meta: metachronous metastasis (after 6 months of resection of the primary tumor); NOS: Newcastle-Ottawa Scale. [‡]Values are median with or without range. [†]Values are mean and standard deviation.

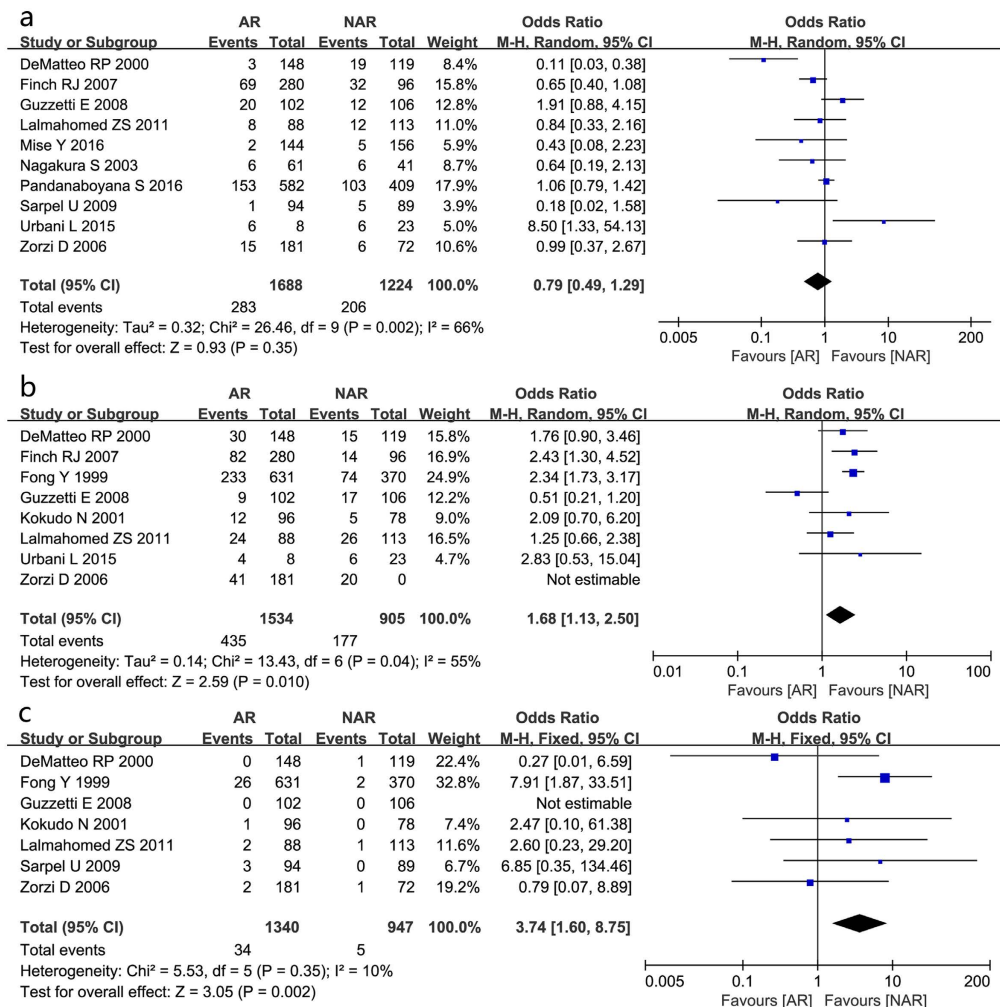


Figure 2. Results of the meta-analysis on short-term outcome. (postoperative positive margins (a), postoperative morbidity (b) and mortality (c)).

Outcome	Number of studies	Number of patients			HR/OR/WMD (95%) CI	P value	I ² (%)	Effect model	
		AR	NAR	Total					
Long-term									
OS	Overall	12	1803	1400	3203	1.06 (0.95–1.18) [†]	0.18	27.30	Fixed
	Without Chemotherapy	3	608	333	275	1.14 (0.86–1.51) [†]	0.76	0	Fixed
	Size ≥200	7	1525	1071	2596	0.98 (0.79–1.22) [†]	0.80	0	Fixed
	Size <200	5	278	329	607	1.10 (0.85–1.41) [†]	0.04	55.10	Random
DFS	5	1126	848	1974	1.11 (0.99–1.24) [†]	0.76	0	Random	
Short-term									
Postoperative margin	10	1688	1224	2912	0.79 (0.49–1.29) ⁺	0.35	66.00	Random	
Blood loss (mL)	4	490	459	949	243.52 (–78.29–565.33) [†]	0.14	99.00	Random	
Blood transfusion	3	190	225	415	2.94 (1.87–4.62) ⁺	<0.01	0	Fixed	
Duration of operation (min)	4	354	326	680	43.62 (5.25–81.99) [†]	0.03	99.00	Random	
30-day morbidity	8	1534	905	2439	1.68 (1.13–2.50) ⁺	0.01	55.00	Random	
30-day mortality	7	1340	947	2287	3.74 (1.60–8.75) ⁺	<0.01	10.00	Fixed	

Table 2. Results of meta-analysis comparing AR and NAR for CRLM. AR: Anatomical resection; NAR: Nonanatomical resection; HR: hazard ratio; OR: odds ratio; WMD: weighted mean difference; CI: confidence interval; OS: overall survival; DFS: disease free survival. [†]Values are HR with corresponding CI. ⁺Values are OR with corresponding CI. [†]Values are WMD with corresponding CI; Statistically significant results are shown in bold.

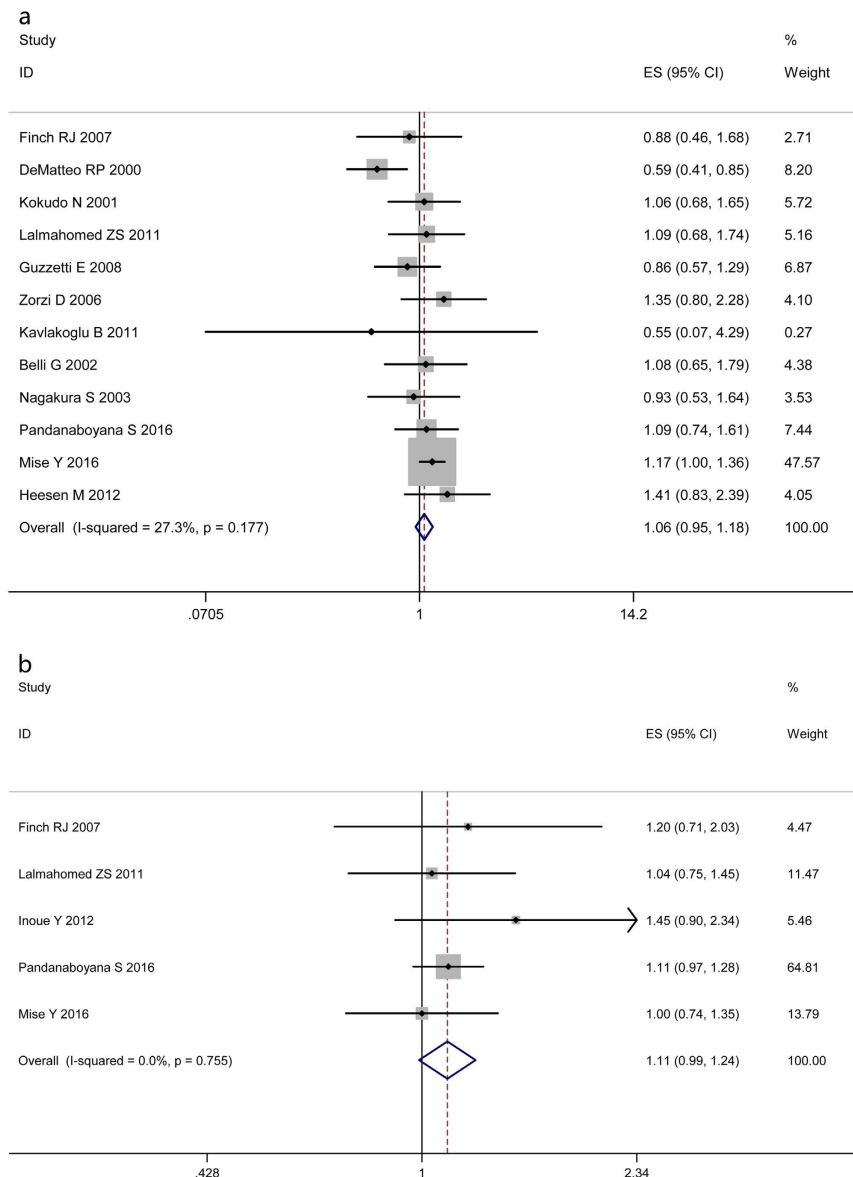


Figure 3. Results of the meta-analysis on OS (a) and DFS (b).

Analysis of Sensitivity and Test for Publication Bias. Basing on nine high-quality studies^{21,23–25,30–32,34–36,39,41}, a further sensitivity analysis was performed. No significant changes of the previous outcomes were produced in comparison with the overall analysis. As regards to OS, a commensurate result (HR 0.93, 95% CI 0.79–1.09, Fig. 5) was produced. And the between-study heterogeneities of the previous comparisons were slightly reduced. There was no evident publication bias based on Egger's test ($P = 0.32$), with symmetry in Begg's funnel plot (Fig. 6).

Discussion

This meta-analysis has broadly reviewed the differences of a variety of patient important outcomes between AR and NAR in performing hepatectomy for CRLM. The results suggest that AR is inferior to NAR in terms of duration of operation, as well as incidence of postoperative morbidity and mortality. Prevalence rate of postoperative positive margins and blood loss were comparable between AR and NAR. Regarding long-term outcomes, OS and DFS did not differ significantly between AR and NAR. These findings are commensurate with the sensitivity analysis of high-quality studies.

Hepatectomy for secondary liver malignancies remains to be a crucial and useful therapeutic option. Widely recognized advantages in OS and DFS were achieved by AR in surgical treatment of HCC compared to NAR^{10–13,15–17}. However, such benefits of AR for CRLM were not demonstrated in comparison with NAR in the present meta-analysis, with both groups showing equivalent results in terms of long-term survival outcomes (OS and DFS).

Such inconsistent results may be explained from the following two aspects: the influences of postoperative margins and the different disseminating modes of tumor cells. (1) Postoperative margin largely depending upon

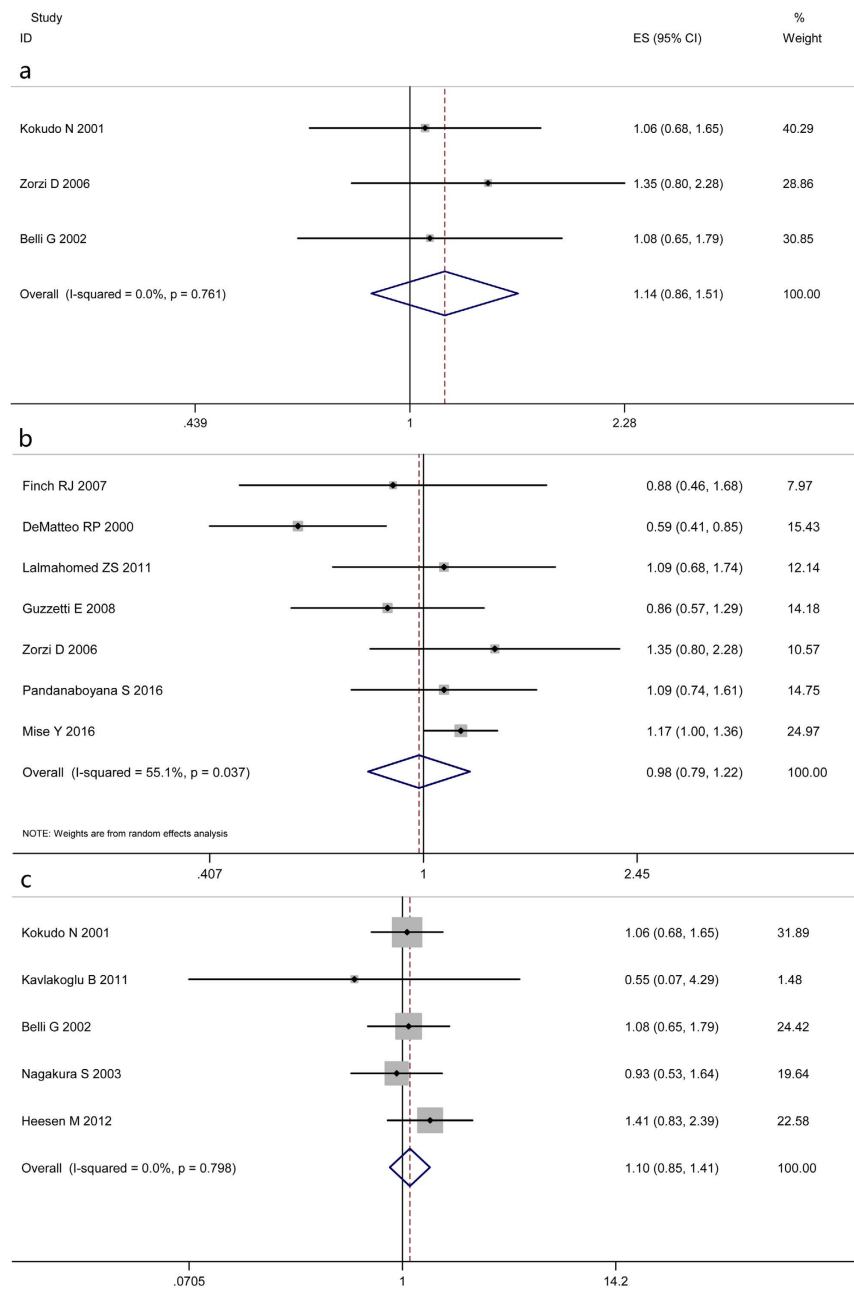


Figure 4. Results of three subgroup analyses of OS. (subgroup of cohorts entirely without chemotherapy (a), subgroup of sample size ≥ 200 (b) and size < 200 (c)).

the surgical technique has been extensively investigated and consistently considered to be strongly associated with OS and DFS in CRLM. Consensus has been widely accepted that a positive surgical margin is a powerful predictor of patient survival and recurrence^{7,34,44}. As has been reported, the rate for five-year survival ranges only from 17.1% to 20% for patients with positive margins compared with that ranging from 37% to 63.8% with negative margins^{7,34}. As to median survival, the median length was 23 months for patients with positive margins, less than 45 months with negative margins³⁴. Besides, overall recurrence rates were significantly different between patients with positive margins and with negative margins (51.1% and 38.6%, respectively)³⁴. Furthermore, both univariate and multivariate analysis revealed that a positive resection margin predicted an increased recurrence rate (relative risk (RR) 2.60, 95% CI 1.55–4.38 and RR 2.34, 95% CI 1.37–4.01, respectively)⁴⁴. In the present meta-analysis, there were no statistically significant differences in the prevalence rate of positive margins. The similarity in the prevalence of postoperative margin would consequently result in no significant difference of OS and DFS between AR and NAR. Therefore, our study confirms the correlation between margin status and its impact on OS and DFS. (2) As to tumor disseminating mode, secondary malignancies of liver may run some particular metastatic modes^{18,45–47} involving trans-arterial spread to the liver from various sources (pulmonary metastasis, the other metastasis, recurrent foci) and intrahepatic spread via changed portal venous circulation,

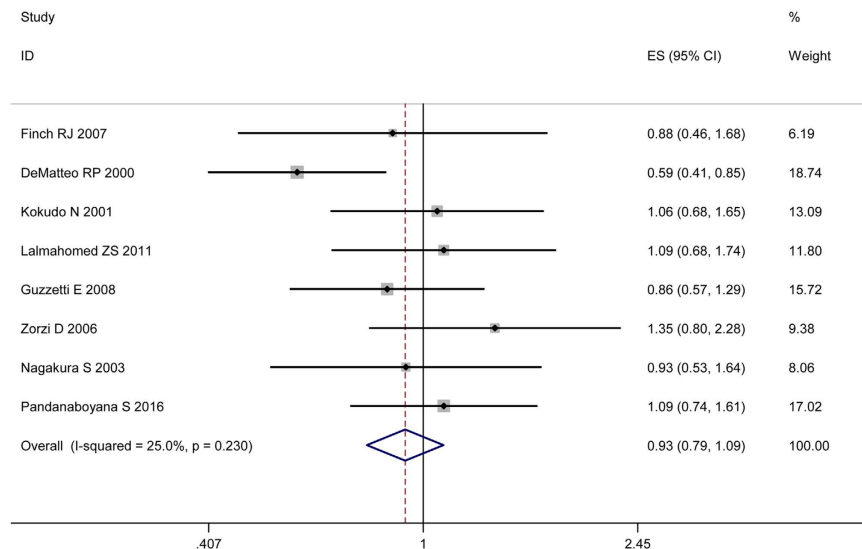


Figure 5. Results of the sensitivity analysis basing on nine high-quality studies.

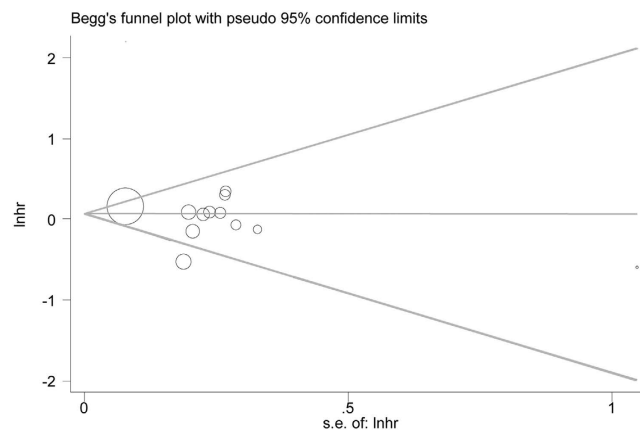


Figure 6. Begg's funnel plot to evaluate OS.

which differs greatly from that of primary liver malignances. In theory, HCC tumor cells originating from the liver itself are thought to spread through the intra-segmental portal vein in the same segment. By erasing the tumor-bearing intra-segmental portal vein together with the corresponding segment, AR may effectively remove the intra-segmental metastasis and thus achieving a favorable outcome for HCC patients. Tumor cells of CRLM derived from the colon or rectum lesions travel through the superior mesenteric vein (SMV) and proximal portal vein and then flow into the liver¹⁸. The blood-borne metastasis is likely to be delivered evenly to any part of the liver. Previous reports^{46,48,49} using autopsy showed that colorectal carcinoma metastases were distributed homogeneously in hepatic parenchyma. Shirai Y.¹⁸ described the distribution of a total of 67 liver metastases from the left colon, of which 28 were in the right lobe, 16 in the left lobe and 23 in both lobes. Besides, these findings, to some degree, corroborate the notion that the prevalence of extrahepatic metastasis for CRLM is more common than that for HCC. The above analysis may explain why AR did not provide a survival advantage over NAR for CRLM^{18,50}.

At the meantime, the pooled analysis demonstrated that AR had a higher risk of post-operative morbidity (OR 1.68, 95% CI 1.13–2.50) and mortality (OR 3.74, 95% CI 1.60–8.75) than NAR. An increased morbidity rate could be due to a heightened surgical stress caused by the AR itself. As previously reported^{31,51–53}, AR featuring higher level of surgical technique difficulty would often be associated with longer operation duration and more liver parenchyma loss. And this is consistent with the results from the studies included in this meta-analysis^{21,24,31,33}. Bile leakage, wound infection and intra-abdominal collections constituting the major types of complications all show evident preferences to AR group over NAR group. Taken together, AR might promote the incidence of postoperative morbidity. The main cause for the inferiority of AR to NAR in terms of mortality is thought to be its larger loss of liver parenchyma. With more extensive parenchymal resection, AR would consequently carry a more substantial risk. As reported by Lalmahomed ZS²³, postoperative hepatic failure resulting from insufficiency of liver remnant was the primary cause of mortality in AR group.

With regard to the longer operation duration of AR, it could be explained by the fact that standard AR is involved with some additional extensive surgical procedures, such as hepatic pedicle dissection or even segmental staining.

It was notable that the pooled result of blood loss during operation revealed no statistically significant differences. But a higher incidence of blood transfusion was found in AR (OR 2.94, 95% CI 1.87–4.62), which appeared not to agree well with earlier reports^{12,54,55} that concluded similar incidences of blood transfusion between AR and NAR. These inconsistent results could be caused by rather small sample sizes and selection bias as there are only three studies that assessed relevant data.

To our best knowledge, there is only one published meta-analysis concerning this topic⁵⁶, due to the imperfectness in literature search and the neglect of variability or between-study heterogeneities, and some of its results remain inconclusive.

Comparatively speaking, our present study has three main strengths. (1) A substantial size of the studies included was produced by a comprehensive and extensive searching strategy. (2) As to time to event data, the best option of using HR value to perform the pooled analysis of OS effect was conducted. (3) On subgroup and sensitivity analyses, similar results were produced and thus confirmed the overall findings. Hence, our results were reliable and robust.

In spite of the above-mentioned improvements, certain limitations of the present study should be taken into consideration. The main limitation was that no RCTs were available to get included, thus reducing the reliability of the results. Besides, the lack of relevant data did not permit comprehensive subgroup analysis according to additional parameters, such as tumor size, tumor amount, primary tumor location, the use of chemotherapy, extent of metastases in the liver (unilobar or bilobar distribution of metastases) and the presence of resectable extrahepatic metastases (despite the fact that most of the parameters remained comparable between studies, as shown in Table 1), to be conducted. In addition, several HR values were calculated by corresponding OS Kaplan-Meier curves, because of the unavailability of these values in the articles and absence of replies from the authors. Finally, some of the between-study heterogeneities were relatively obvious, which might have been caused by the differences in sample size or other factors among these studies, and by the limited studies for inclusion. Hence random effect models were implemented for those comparisons. Nevertheless, the present analysis undoubtedly represents one more step in obtaining a more reliable and up-to-date evidence to give a relatively persuasive argument for resection type in CRLM.

To conclude, AR seems to have no prognostic advantages over NAR for the treatment of CRLM. Besides, AR is inferior to NAR with respect to incidence of postoperative morbidity and mortality. In addition there has been concern that the policy of AR would relatively restrict later surgical treatment possibilities for recurrent lesions. Taken together, our current results might not give support to AR for CRLM patients. Surgeons ought to be cautious when they select the procedures in the surgical treatment of CRLM. Further multicenter and high-quality RCTs will be required to support this conclusion.

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Author Contributions

H.T. and B.L. carried out most of vital stages of the analysis including literature search, data extraction, statistical analysis, manuscript completion and submission. H.Z. contributed to statistical analysis and figure preparation. J.D. and W.L. designed the project and analyzed the results. All authors reviewed and approved the final manuscript.

Additional Information

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