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REVIEW ARTICLE – HEPATOBILIARY TUMORS

Is Precision Surgery Applicable to Colorectal Liver Metastases? A Systematic Review and Meta-analysis of Studies that Investigate the Association of Surgical Technique with Outcomes in the Context of Distinct Tumor Biology

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ABSTRACT

Background. Although some data suggest that patients with mut*RAS* colorectal liver metastases (CRLM) may benefit from anatomic hepatectomy, this topic remains controversial. We performed a systematic review and meta-analysis to determine whether *RAS* mutation status was associated with prognosis relative to surgical technique [anatomic resection (AR) vs. nonanatomic resection (NAR)] among patients with CRLM.

Patients and Methods. A systematic review and meta-analysis of studies were performed to investigate the association of AR versus NAR with overall and liver-specific disease-free survival (DFS and liver-specific DFS, respectively) in the context of *RAS* mutation status.

Results. Overall, 2018 patients (831 mut*RAS* vs. 1187 wt*RAS*) were included from five eligible studies. AR was associated with a 40% improvement in liver-specific DFS [hazard ratio (HR) = 0.6, 95% confidence interval (CI) 0.44–0.81, $p = 0.01$] and a 28% improvement in overall DFS (HR = 0.72, 95% CI 0.54–0.95, $p = 0.02$) among patients with mut*RAS* tumors; in contrast, AR was not associated with any improvement in liver-specific DFS or overall DFS among wt*RAS* patients. These differences may have been mediated by the 40% decreased incidence in R1 resection among patients with mut*RAS* tumors who underwent AR versus NAR [relative risk (RR): 0.6, 95% CI 0.40–0.91, $p = 0.02$]. In contrast, the probability of an R1 resection was not decreased among wt*RAS* patients who underwent AR versus NAR (RR: 0.93, 95% CI 0.69–1.25, $p = 0.62$).

Conclusions. The data suggest that precision surgery may be relevant to CRLM. Specifically, rather than a parenchymal sparing dogma for all patients, AR may have a role in individuals with mut*RAS* tumors.

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One of the few variables that can be controlled by the surgeon and may influence prognosis in surgically treated colorectal liver metastases (CRLM) is the choice of surgical technique (anatomic vs. nonanatomic hepatectomy).[1] Several studies have attempted to identify the optimal surgical technique to treat CRLM, but the results have varied.[2–4] One possible explanation for the varied results may be the effect of anatomic versus nonanatomic hepatectomy relative to patient characteristics. For example, Margonis et al. reported that tumor biology, defined by specific biomarkers such as *RAS* mutation status, may impact outcomes following surgery relative to surgical technique.[5] Specifically, patients with *RAS*-mutated CRLM benefited the most from an anatomic hepatectomy, which was contrary to the dogma of pursuing more limited resection for all CRLM tumors. In a separate study based on data from the University of Texas M.D. Anderson Cancer Center, no association between anatomic resections (AR) and survival was noted among patients with *RAS*-mutated or wild-type CRLM; in contrast, a multi-institutional study from Japan reported an association between AR and survival only among patients with *RAS* wild-type CRLM.[6,7]

A common limitation of previous studies that may explain the disparate findings is the limited sample size and statistical power. Therefore, a meta-analysis may help overcome this limitation by synthesizing the results of each study and increasing the statistical power. The aim of the current study is to perform a systematic review and meta-analysis of observational, cohort studies to determine whether tumor biology (i.e., *RAS* mutation status) can be used to select the surgical technique for patients with CRLM. In turn, such information may help shift the landscape from "one size fits all" to a more precise surgery based on tumor biology. Furthermore, we investigated whether a lower utilization of R1 resections may be the mechanism through which surgical technique benefits patients with a specific tumor biology.

METHODS

Literature Search

A systematic literature search of the Medline, Embase, CENTRAL, CINAHL, Web of Science, and ClinicalTrials.gov databases was undertaken using the search terms "colorectal neoplasms," "liver," "hepatic," "metastases," "metastatic," "resection," "surgery," "hepatectomy," "*kras*," and "*nras*," combined with the Boolean operators AND/OR as appropriate for each database. Inclusion criteria were: (1) studies reporting on patients with known *RAS* status, (2) studies reporting on the type of resection performed (anatomic or nonanatomic), and (3) studies reporting on resection margin status.

After removing duplicate studies, the generated title and abstract list were independently screened by two authors with training in clinical investigation (D.P. and N.P.). The predetermined exclusion criteria were: (1) case reports and nonclinical studies, (2) studies not reporting patients' *RAS* status, (3) studies published in a non-English language, (4) studies with overlapping patient populations, (5) clinical studies not reporting patients' long-term survival outcomes, and (6) studies with patients managed primarily with modalities other than liver resection. Potentially eligible studies were identified and reviewed in full text, with a third author (D.D.) acting as a referee in cases of disagreement. Reference lists were also manually checked for other potentially relevant studies.

The present systematic review and meta-analysis were conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines (Supplementary file "MOOSE checklist") and were registered in the "International Prospective Register of Systematic Reviews" (PROSPERO ID: CRD42022375583).[8,9]

Data Extraction and Outcomes of Interest

Data extraction was performed by two authors (D.P. and A.P.) to ensure data accuracy and completeness. The primary outcomes of interest were the reported hazard ratios regarding overall disease-free survival (DFS) and liver-specific disease-free survival (liver-specific DFS), stratified according to patient *RAS* status, type of liver resection, and resection margin status. Disease-free survival and liver-specific disease-free survival were chosen as the primary outcomes of interest because overall survival alone can obscure a causal relationship between a specific surgical technique and the prevention of recurrence. For example, even if a specific surgical technique prevents liver recurrence in patients with a distinct biology, overall survival of these patients may be similar to patients who undergo surgery without that specific technique and, consequently, have recurrence but benefit from a second hepatectomy. Furthermore, liver-specific relapse-free survival (RFS) was the primary endpoint in the "Anatomical Resection of Liver Metastases in Patients with *RAS*-Mutated Colorectal Cancer (ARMANI)" randomized trial (https://www.clinicaltrials.gov/study/NCT04678583). The ARMANI trial is the first of its kind, testing the hypothesis that anatomical resections exclusively benefit patients with *RAS*-mutated colorectal liver metastases. Overall survival (OS) was chosen as a secondary variable of interest.

Other data of interest were patient demographics, tumor-related characteristics (size of the largest tumor, number of tumors, distribution, and timing of disease), year of publication, and country of origin. Extracted data were entered into

standardized Excel spreadsheets (Microsoft, Redmond, WA) for further tabulation.

Definitions

Patients with *RAS* mutations (mut*RAS*), irrespective of the type of mutation, were evaluated separately from their wild-type counterparts (wt*RAS*). Anatomic resections were defined as removal of at least one Couinaud segment containing the tumor, along with its respective portal triad. Nonanatomic resections were defined as parenchymal resections with no regard to segmental or sectional anatomy. Margin status was defined as R0 resection in cases with ≥ 1 mm distance between the tumor and specimen margin and as R1 resection in cases of < 1 mm margin.

Risk of Bias Assessment

The risk of bias was evaluated independently by two authors (D.P. and G.M.) using the ROBINS-I tool, which assesses studies across seven domains: bias due to confounding, bias due to selection of participants, bias in classification of interventions, bias due to deviations of intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported results. For each domain, the risk of bias can be low, moderate, or serious.

Statistical Analyses

Statistical analyses were performed using Stata v. 17 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC). Hazard ratios (HR) and the corresponding 95% confidence intervals (CI) were calculated for all survival-related outcomes (DFS, liver-specific DFS, and OS), while risk ratios (RR) were utilized to compute the risk for margin positivity. Hazard ratios were extracted from the published Kaplan–Meier (KM) survival curves using the "WebPlotDigitizer" software (https://automeris.io/WebPlotDigitizer) and the method described by Guyot et al.[10] A random effects model (DerSimonianLaird) was selected due to anticipated high clinical heterogeneity in terms of patient and tumor baseline parameters. Statistical heterogeneity was quantified with the Higgin's I^2 statistic; values below 30% represent low heterogeneity, values between 30 and 60% represent moderate heterogeneity, and values above 60% represent substantial heterogeneity. For all statistical analyses, a p value less than 0.05 was considered statistically significant. Testing for publication bias could not be performed due to the small number of included studies.

RESULTS

A total of 630 unique studies were screened during the study selection process. After applying the exclusion criteria, a total of ten studies (five studies assessing AR vs. NAR and five studies assessing R1 vs. R0) published between 2016 and 2023 were deemed eligible for inclusion in the quantitative analysis (Fig. 1).[5–7,11–17] The study and patient characteristics are reported in Tables 1 and 2, respectively.

Outcomes of Anatomic versus Nonanatomic Resections in Patients with Known RAS Mutation Status

The association of AR versus nonanatomic resections (NAR) with DFS and liver-specific DFS in patients with known *RAS* status was evaluated in five studies with a total of 2018 patients (831 mut*RAS* and 1187 wt*RAS*).[5–7,11,17] AR was associated with improved liver-specific DFS (HR = 0.60, 95% CI 0.44–0.81, $p = 0.01$; Fig. 2A) and overall DFS (HR = 0.72, 95% CI 0.54–0.95, $p = 0.02$; Fig. 3A) in mut*RAS* patients but not in wt*RAS* patients (Figs. 2B, 3B). Statistical heterogeneity was moderate to substantial across evaluated outcomes ($I^2 = 48.2–82.1\%$).

R1 Resection Rates in Patients with Known RAS Mutation Status Who Underwent Anatomic versus Nonanatomic Resections

Among four studies incorporating 1289 patients (488 mut*RAS* and 801 wt*RAS*), AR was associated with a decreased incidence in R1 resection among mut*RAS* patients (HR = 0.6, 95% CI 0.4–0.91, $p = 0.02$; Fig. 4A) but not in wt*RAS* patients (HR = 0.93, 95% CI 0.69–1.25, $p = 0.62$; Fig. 4B). No statistical heterogeneity was detected.

Association of R1 Margins with OS and Liver-Specific DFS

Five studies including 2580 patients (969 mut*RAS* and 1611 wt*RAS*) reported the association of R1 resection margin with OS for mut*RAS* and wt*RAS* patients.[12–16] The R1 resection margin was significantly associated with poor OS in both groups (mut*RAS*: HR = 1.34, 95% CI 1.07–1.66, $p = 0.01$; wt*RAS*: HR = 1.8, 95% CI 1.44–2.25, $p < 0.001$), with low statistical heterogeneity (Fig. 5).

Liver-specific DFS was evaluated in only two studies, for a total of 804 patients (318 mut*RAS* and 486 wt*RAS* patients).[14,15] R1 resection margin was associated with worse outcomes among both mut*RAS* (HR = 1.46, 95% CI 1.04–2.05, $p = 0.03$) and wt*RAS* (HR = 2.64, 95% CI

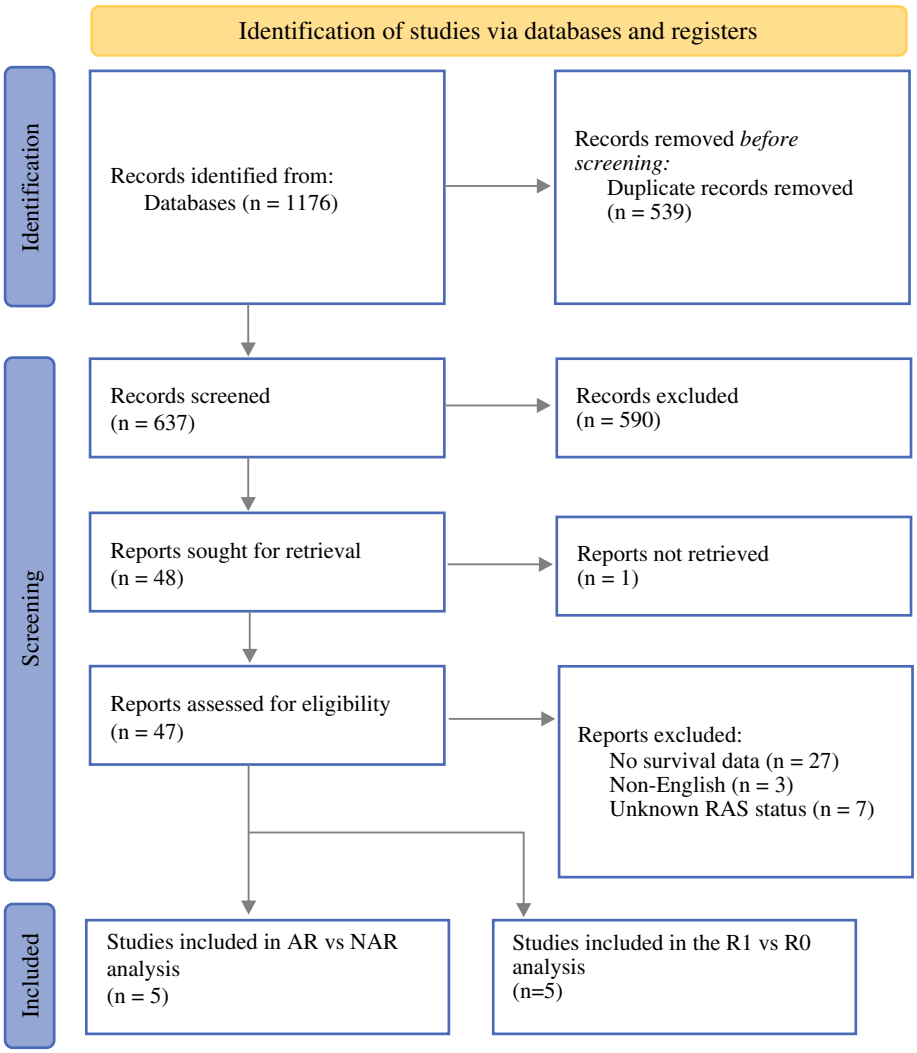

FIG. 1 Prisma flowchart of study selection

1.99–3.5, $p < 0.001$) patients, with no statistical heterogeneity present (Supplementary Fig. 1).

Critical Appraisal and Risk of Bias Assessment

The ROBINS-I tool was used to assess risk of bias given the retrospective nature of the included studies. Across evaluated domains, bias due to confounding, deviation from intended interventions, and missing data were encountered. No studies were at serious risk of confounding bias, but moderate risk was noted in eight studies that did not utilize propensity score matching. A deviation from intended interventions was present in three studies in the AR versus NAR comparison, as tumors in the former group were larger, suggesting a predilection toward more aggressive surgery in such patients. In turn, it is likely that the true effects of AR may be even more favorable, as patients with mut*RAS* tumors who underwent AR had unfavorable tumor characteristics compared with their counterparts who underwent NAR. Moderate risk of bias due to missing data was encountered in a single study in which patients lost to follow-up were excluded from the final analysis. Overall, the risk of bias was judged to be moderate in eight studies, and low in one (Supplementary Table 1).

DISCUSSION

Five studies have previously examined the association of AR vs NAR with overall and liver-specific DFS among patients with known *RAS* mutation status. A significant association between AR and superior overall and liver-specific DFS in mut*RAS* tumors was noted only in the largest two studies.[5–7,11,17] Notably, the other three studies also reported an association of AR with improved overall and liver-specific DFS in mut*RAS* tumors but failed to reach statistical significance. Interpreting the lack of statistical significance as conflicting with the largest two studies may be misleading, since the estimated treatment benefit of AR was similar (Fig. 2A).[18] As Goodman noted, "A nonsignificant difference does not make the null effect the most

TABLE 1 Study and patient characteristics for patients undergoing anatomic versus non-anatomic resections

Author	Year	Country of origin	Number of patients	Sex (M/F)	Number of tumors	Bilateral disease	Tumor size (cm)	Synchronous disease	R1 resections
Mutated RAS (anatomic vs. non-anatomic resections), n (%)									
Chang	2023	China	96 (28) versus 247 (72)	59 (61.5)/37 (38.5) versus 167 (67.6)/80 (32.4)	n/a	9 (9.4) versus 63 (25.5)	n/a	69 (71.9) versus 171 (69.2)	n/a
Choi	2022	South Korea	28 (29.2) versus 66 (70.8)	21 (75)/7 (25) versus 40 (60.6)/26 (39.4)	2.6 ± 1.8 versus 2.2 ± 2.1	5 (17.8) versus 17 (25.8)	3.4 ± 1.9 versus 1.6 ± 0.9	n/a	0 versus 3 (4.5)
Kawai	2022	Japan	44 (42.3) versus 60 (57.7)	25 (57)/19 (43) versus 37 (62)/23 (38)	1.0 ± 1.4 versus 1.0 ± 1.6	n/a	3.5 ± 3.4 versus 2.0 ± 1.7	20 (45) versus 37 (62)	6 (14) versus 7 (12)
Joechle	2019	USA	75 (50) versus 75 (50)	35 (47)/40 (53) versus 41 (55)/34 (45)	1 (1–9) versus 1 (1–7)*	16 (21) versus 18 (24)	2 (0.5–6.5) versus 2 (0.1–9.5)*	49 (65) versus 48 (64)	14 (9) versus 22 (18)
Margonis	2017	USA	83 (59.3) versus 57 (40.7)	41 (49.4)/42 versus 35 (61.4)/22 (48.6)	2 (1–3) versus 2 (1–3)*	24 (28.9) versus 29 (50.9)	3 (2.1–4.5) versus 1.9 (1.2–2.6)*	40 (48.2) versus 39 (68.5)	13 (15.7) versus 16 (28.1)
Wild-type RAS (anatomic vs. non-anatomic resections), n (%)									
Chang	2023	China	139 (38.6) versus 247 (61.4)	101 (72.7)/38 (27.3) versus 178 (72.1)/69 (27.9)	n/a	22 (15.8) versus 67 (27.1)	n/a	104 (74.8) versus 179 (72.5)	n/a
Choi	2022	South Korea	51 (32.7) versus 105 (67.3)	34 (66.6)/17 (33.4) versus 75 (71.4)/30 (28.6)	2.94 ± 2.49 versus 3.26 ± 3.81	11 (21. 6) versus 43 (41)	3.5 ± 2.5 versus 1.9 ± 1.2	n/a	2 (3.9) versus 2 (1.9)
Kawai	2022	Japan	77 (41.8) versus 109 (58.2)	49 (64)/28 (36) versus 65 (60)/44 (40)	2.0 ± 1.8 versus 2.0 ± 1.8	n/a	3.0 ± 3.2 versus 2.0 ± 1.2	48 (62) versus 62 (57)	9 (12) versus 18 (17)
Joechle	2019	USA	105 (50) versus 105 (50)	71 (68)/34 (32) versus 69 (66)/36 (34)	1 (1–9) versus 1 (1–8)*	31 (30 versus 33 (31)	2 (0.16–5.3) versus 1.8 (0.1–5.8)*	75 (71) versus 81 (77)	34 (32) versus 26 (24.8)
Margonis	2017	USA	141 (56.6) versus 108 (43.4)	82 (58.2)/59 (41.8) versus 73 (67.6)/35 (32.4)	2 (1–3) versus 2 (1–3)*	43 (30.5) versus 47 (43.5)	3 (2–5) versus 2 (1.3–3)*	79 (56) versus 65 (60.2)	30 (21.3) versus 28 (25.9)

*Values are expressed as medians and ranges. *n/a* not available

likely. The effect best supported by the data from a given experiment is always the observed effect, regardless of its significance."[18] Indeed, in examining the KM curves from the MD Anderson publication, AR was associated with better liver-specific DFS in both unselected (see Fig. 3C of that publication) and matched mut*RAS* cases (Fig. 3F) versus NAR.[6] In contrast, there was no difference in the outcomes of AR versus NAR in both unselected (Fig. 3B) and matched wt*RAS* cases (Fig. 3E). A meta-analysis is an ideal methodological tool to use in situations such as this, in which smaller studies noted a trend toward efficacy as pooling individual studies allows for an increase in overall sample size, enhances the statistical power of the analysis, and reduces the confidence interval for the point estimate

TABLE 2 Study characteristics and baseline patient demographics for patients undergoing R1 versus R0 resections

Author	Year	Country of origin	Number of patients	Sex (M/F)	Number of tumors	Bilateral disease	Tumor size (cm)	Anatomical resections	R1 resections
mutRAS versus wtRAS, n (%)									
Hatta	2021	UK	152 (30.4) versus 348 (69.6)	90/62 versus 222/126	2 (1–3) versus 2 (1–3)*	n/a	3 (2–5) versus 3 (2–4)*	n/a	42 (27.6) versus 84 (24.1)
Procopio	2020	Italy	155 (45) versus 185 (55)	n/a	n/a	n/a	n/a	n/a	59 (38) versus 82 (44.3)
Xu	2019	China	100 (46.7) versus 114 (53.3)	n/a	n/a	n/a	n/a	n/a	41 (41) versus 26 (22.8)
Margonis	2016	USA	312 (36.4) versus 544 (63.6)	n/a	n/a	n/a	n/a	n/a	35 (11.2) versus 70 (12.8)
Brudvik	2016	USA	229 versus 404	n/a	n/a	n/a	n/a	n/a	26 (11.4) versus 22 (5.4)

*Values represent medians (ranges). *CLM* colorectal liver metastases, *n/a* not available

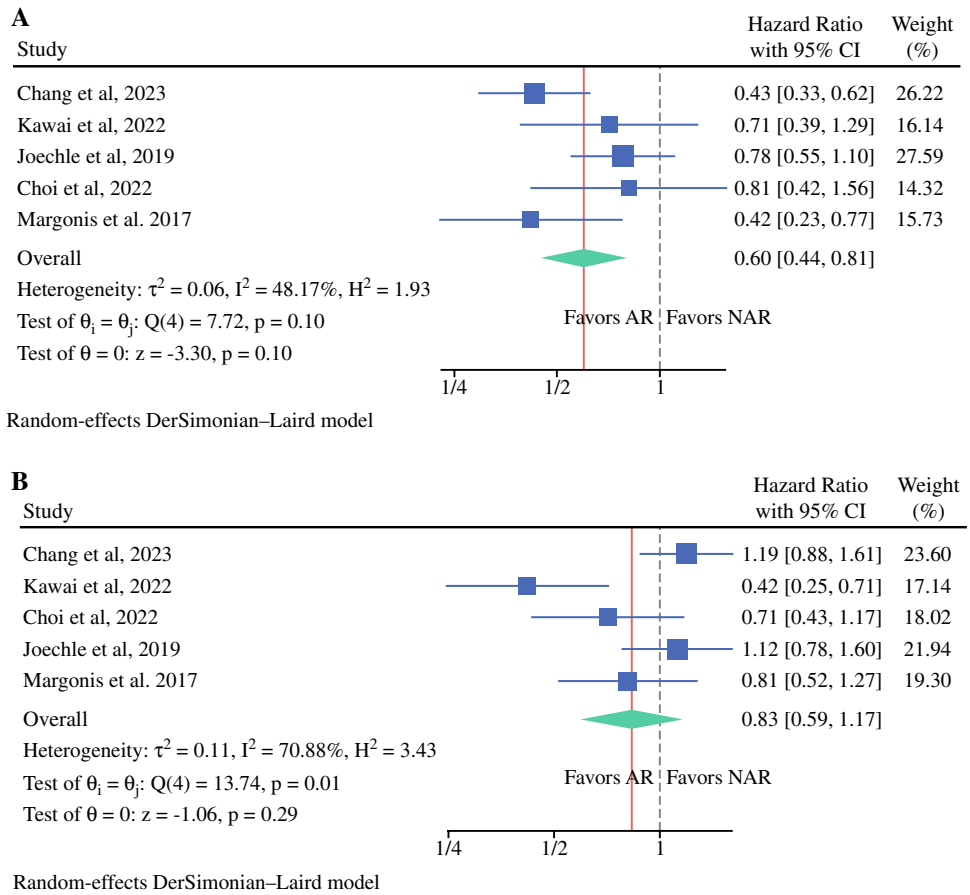

FIG. 2 Forest plots of liver-specific disease-free survival in **A** mut*RAS* and **B** wt*RAS* patients

of the effect.[19] This approach may unveil a true and significant benefit of therapy that would have been otherwise missed.[20] In the current meta-analysis, AR was significantly associated with a 40% and a 28% improvement in liver-specific and overall DFS, respectively, versus NAR in patients with mut*RAS* tumors.

The benefit of AR in patients with mut*RAS* tumors may be related to more favorable characteristics of patients who

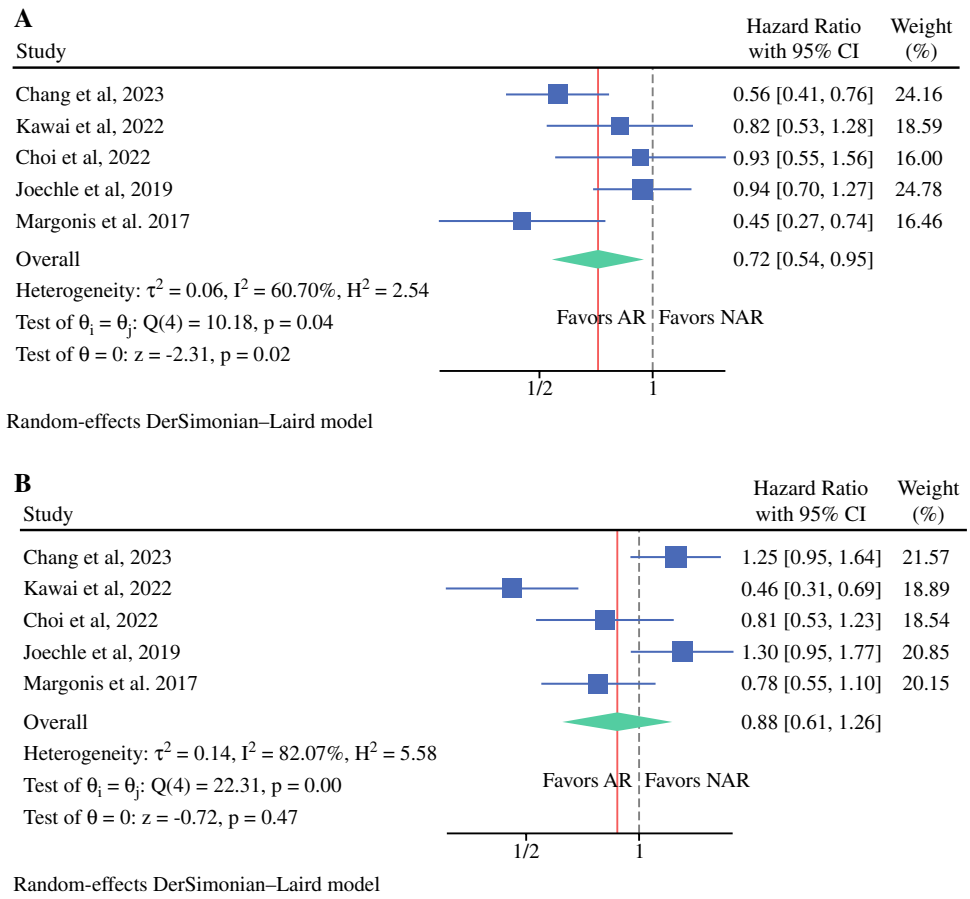

FIG. 3 Forest plots of overall disease-free survival in **A** mut*RAS* and **B** wt*RAS* patients

underwent AR. However, this was not the case in any of the five studies, as AR was associated with unfavorable and not favorable characteristics. For example, in the study from M.D. Anderson, the only relevant differences in patient characteristics were in favor of NAR.[6] Specifically, patients with mut*RAS* tumors who underwent AR were more likely to have larger and more CRLMs than their counterparts who underwent NAR. Unsurprisingly, when patients were matched for these differences, the benefit of AR over NAR became even more visually apparent (see Fig. 3F, C of that publication). Similarly, the median size of the largest CRLM was greater in patients with mut*RAS* tumors who underwent AR compared with NAR in the study from Johns Hopkins and the study from Fudan University.[5,6,17] In addition, in the study from Fudan University, patients who underwent AR were more likely to have high (over 200 ng/mL) carbohydrate antigen (CA) 19-9 levels.[17] Two additional significant differences include a lower rate of bilateral disease and less use of radiofrequency ablation (RFA) (only in the Johns Hopkins study) among individuals with mut*RAS* disease who underwent AR. Importantly, when all factors were adjusted in a multivariable analysis, the AR-associated improvement in overall and liver-specific DFS persisted in both studies [HR for overall DFS: 0.45 ($p = 0.002$) and 0.5 ($p < 0.001$) in the Johns Hopkins and Fudan University studies, respectively; HR for liver-specific DFS: 0.42 ($p = 0.006$) and 0.43 ($p < 0.001$) in the Johns Hopkins and Fudan University studies, respectively]. The remaining two studies identified a greater tumor size among patients who underwent AR as the only significant difference between patients with mut*RAS* tumors who underwent AR versus NAR.[7,11] Thus, it is unlikely that the favorable effects of AR were confounded by other factors, as patients with mut*RAS* tumors who underwent AR had unfavorable tumor characteristics.

We also investigated the mechanism through which AR confers an oncologic benefit in patients with mut*RAS* but not wt*RAS* tumors. One possibility was the lower rate of R1 resections among patients with mut*RAS* who undergo AR, as a more extensive tumor growth pattern of mut*RAS* tumors can only be eradicated by AR. In contrast, a NAR may be sufficient to eliminate tumor cells of wt*RAS* tumors, and thus AR would not decrease the rate of R1 resections in this patient group. Indeed, among patients who underwent AR, only patients with mut*RAS* CRLM had a markedly lower rate of R1 resections. This novel finding again highlights the ability of meta-analyses to maximize statistical power and uncover relationships that are masked by small sample sizes of individual studies. For example,

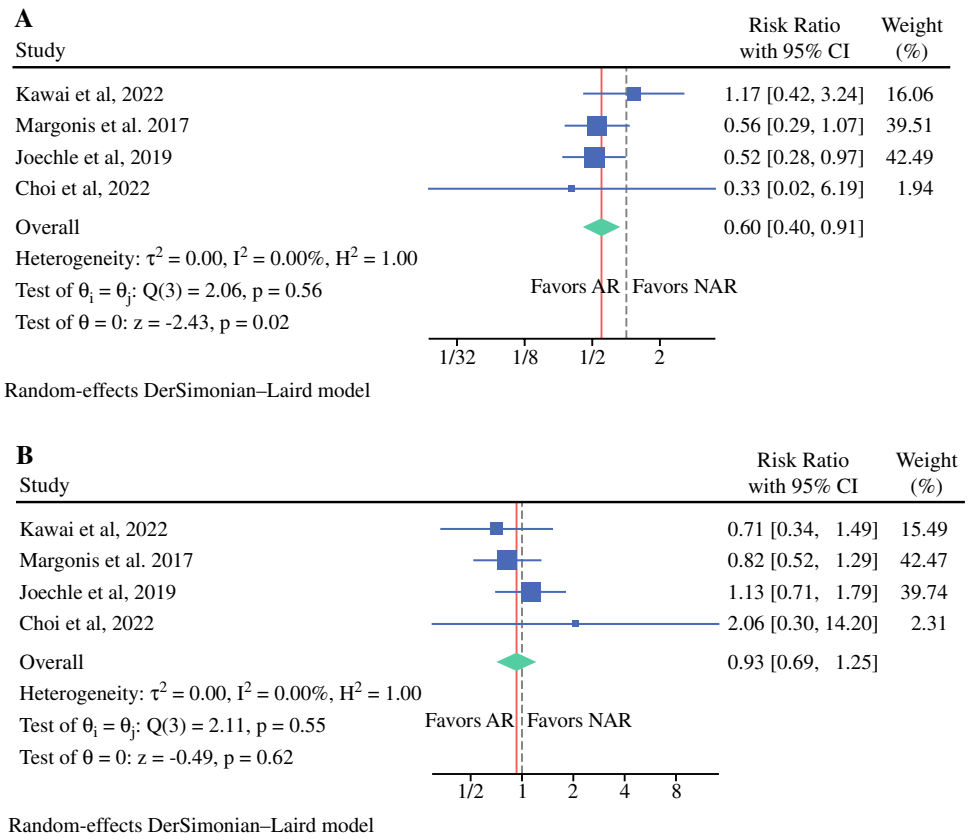

FIG. 4 Forest plots of risk for R1 resection after anatomic versus nonanatomic resections in **A** mut*RAS* and **B** wt*RAS* patients

although not statistically significant, a trend toward lower rates of R1 resection after AR for mut*RAS* CRLM was reported in the study by Choi et al. Specifically, R1 resection was 0% versus 4.5% among patients with mut*RAS* tumors who underwent AR versus NAR, respectively ($p=0.550$), and 3.9% versus 1.9% in those with wt*RAS* tumors who underwent AR versus NAR, respectively.[11] In the study by Margonis et al., although AR was associated with lower rates of R1 in both mut*RAS* and wt*RAS* groups, the absolute reduction in R1 resection with AR was more pronounced in the mut*RAS* group at 12.4% versus 4.6%.[5] In addition, the study by Joechle et al. reported a rate of R1 resection that was significantly lower in the mut*RAS* group who underwent AR versus NAR; similar to the previous studies, there was no difference in the wt*RAS* group.[6]

Subsequently, we evaluated whether R1 resection was associated with worse oncologic outcomes in patients with mut*RAS* tumors, which is important as the association between R1 and outcomes has generally been controversial.[21,22] Of note, R1 resection was associated with worse liver-specific DFS in patients with mut*RAS* tumors. Given that only two studies were included in this analysis, we performed another analysis to examine the association of R1 with OS in patients with mut*RAS* CRLM, as this yielded more eligible studies. Similarly, we noted that R1 resection was also associated with worse OS in those with mut*RAS* tumors.

While the results presented in this analysis carry significant implications, it is important to acknowledge several limitations. The included studies, although generally sound in their overall methodology, predominantly utilized retrospective designs and often failed to adequately account for potential confounding factors. Notably, this was particularly evident in studies that compared anatomical resections and nonanatomical resections, as a tendency toward AR in larger tumors was observed in some studies. In turn, there was the potential for selection bias. Substantial statistical heterogeneity among the included studies was observed for many of the evaluated outcomes. While we employed a random-effects analysis model to mitigate some of the impact of this heterogeneity on the overall robustness of the analysis, a more comprehensive exploration of the causes of this heterogeneity through meta-regression analysis was not feasible due to the limited number of included studies. It is worth noting that meta-regression is generally not advisable when there are fewer than ten studies published on the topic.[23] Lastly, we did not report on the association of surgical technique (AR vs. NAR) and OS, as only two studies reported relevant data, and therefore a meta-analysis was not possible.

Although the results obtained offer valuable insights into the impact of *RAS* status on the choice of the optimal surgical procedure and subsequent expected survival, it is important to highlight that a direct causal relationship

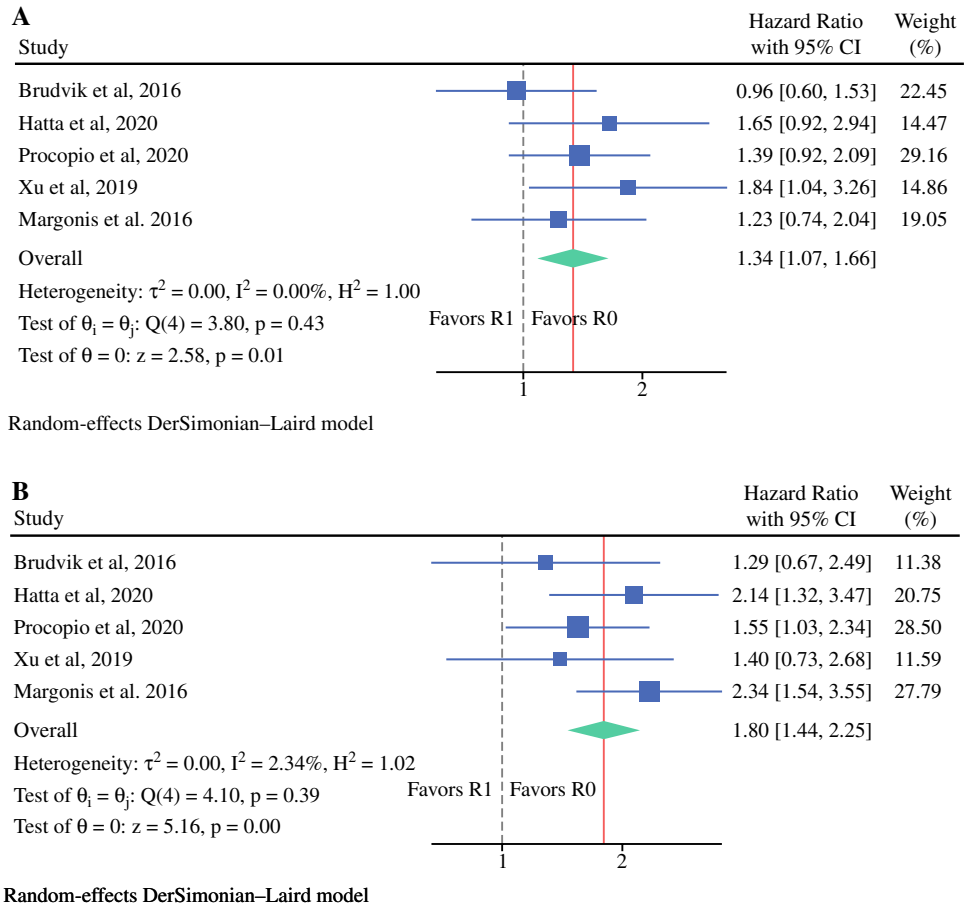

FIG. 5 Forest plots of overall survival based on resection margin status in **A** mut*RAS* and **B** wt*RAS* patients

between AR and DFS cannot be definitively established using observational data. For example, it is possible that wider margins accompanying AR, not AR itself, might be the reason for the observed association with improved DFS. If this was the case, one would anticipate that extended margins (e.g., > 1 cm) and AR would exhibit a similar impact on outcomes in CRLM. However, according to the most recent meta-analysis on margin width (> 1 cm vs. < 1 cm) and all meta-analyses comparing AR versus NAR for CRLM, this conclusion is not supported by the data.[24–27] Specifically, the evidence suggests that while a margin width greater than 1 cm is associated with improvements in OS and DFS compared with a margin width less than 1 cm, AR has not been associated with improvements in OS or DFS compared with NAR. Future studies that independently evaluate margin width (as opposed to R0 vs. R1 status) and surgical technique (AR vs. NAR) among patients with *RAS*-mutated and wild-type tumors will be essential. Currently, only one study has provided data on both these factors, underscoring the need for additional research in this area.

In conclusion, the current systematic review and meta-analysis of surgical technique (AR vs. NAR) relative to tumor biology revealed a 40% decrease in the risk of liver recurrence and a 28% decrease in the risk of any recurrence for AR compared with NAR. The effect of AR versus NAR was only noted, however, among patients with mut*RAS* tumors. This finding serves to reopen the discussion on AR in *RAS*-mutated CRLM, which conflicts with existing dogma of pursuing more limited resections for all tumors. The current meta-analysis may be the best source of evidence until 2025 when the ongoing "Anatomical Resection of Liver Metastases in Patients with *RAS*-mutated Colorectal Cancer" (ARMANI) randomized trial will report prospective data on this topic.

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