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Added Value of Liver MRI in Patients Eligible for Surgical Resection or Ablation of Colorectal Liver Metastases Based on CT

A Systematic Review and Meta-Analysis

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Background: Abdominal computed tomography (CT) is the standard imaging modality for detection and staging in patients with colorectal liver metastases (CRLM). Although liver magnetic resonance imaging (MRI) is superior to CT in detecting small lesions, guidelines are ambiguous regarding the added value of an additional liver MRI in the surgical workup of patients with CRLM. Therefore, this systematic review and meta-analysis aimed to evaluate the clinical added value of liver MRI in patients eligible for resection or ablation of CRLM based on CT.

Methods: A systematic search was performed in the PubMed, Embase, and Cochrane Library databases through June 23, 2023. Studies investigating the impact of additional MRI on local treatment plan following CT in patients with CRLM were included. Risk of bias was assessed using the QUADAS-2 tool. The pooled weighted proportions for the primary outcome were calculated using random effect meta-analysis.

Results: Overall, 11 studies with 1440 patients were included, of whom 468 patients (32.5%) were assessed for change in local treatment plan. Contrast-enhanced liver MRI was used in 10 studies, including gadoxetic acid in 9 studies. Liver MRI with diffusion-weighted imaging was used in 8 studies. Pooling of data found a 24.12% (95% confidence interval, 15.58%–32.65%) change in the local treatment plan based on the added findings of liver MRI following CT. Sensitivity analysis including 5 studies (268 patients) focusing on monophasic portal venous CT followed by gadoxetic acid-enhanced liver MRI with diffusion-weighted imaging showed a change of local treatment plan of 17.88% (95% confidence interval, 5.14%–30.62%).

Conclusions: This systematic review and meta-analysis found that liver MRI changed the preinterventional local treatment plan in approximately one-fifth of patients eligible for surgical resection or ablation of CRLM based on CT. These findings suggest a clinically relevant added value of routine liver MRI in the preinterventional workup of CRLM, which should be confirmed by large prospective studies.

Keywords: ablation, colorectal cancer, computed tomography, magnetic resonance imaging, resection

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INTRODUCTION

Colorectal cancer is the third most common cancer worldwide and the second leading cause of cancer-related death.[1,2] Approximately 50% of all patients with colorectal cancer are diagnosed with liver metastases at presentation (synchronous) or will develop them during follow-up (metachronous).[3–6] Local treatment, which may involve both surgical resection and local ablation, remains the cornerstone of curative intent therapy for colorectal liver metastases (CRLM), increasing the 5-year survival rate to more than 40%.[5–8] In the past few years, the role of local ablation for the curative treatment of CRLM increased, being a promising alternative for surgery for smaller size lesions.[9] Planning of surgical resection and local ablation relies on an adequate staging of the number and size of the lesions, their exact anatomical location, and relation to vascular or biliary structures.[10] Therefore, optimal preinterventional imaging of CRLM is of paramount importance.

Currently, contrast-enhanced abdominal computed tomography (CT) is the standard imaging modality in the preinterventional workup of patients with primary or recurrent CRLM.[11,12] CT has a sensitivity and specificity of 68% and 94% for CRLM, respectively, and provides whole-body staging. However, CT is not so accurate in the characterization of small liver lesions.[13–17] In recent years, liver magnetic resonance imaging (MRI) has been used increasingly in addition to CT in the preinterventional workup of CRLM.[18] Liver MRI has been shown to have a better diagnostic accuracy as compared to CT in detecting CRLM, especially for lesions smaller than 10 mm.[13,14,19,20] With the use of diffusion-weighted imaging (DWI) and liver-specific contrast agents, the sensitivity of liver MRI for the detection of CRLM has improved further.[20] Nonspecific gadoterate meglumine-enhanced liver MRI (Dotarem, Guerbet, Aulnay-sous-Bois, France) has a sensitivity of nearly 80%,[12] while the reported sensitivity of liver-specific contrast agent gadoxetic acid-enhanced liver MRI (gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid; Primovist, Bayer Schering Pharma, Berlin, Germany) ranges from 87% to 100%.[21,22]

Although several studies and systematic reviews showed the superiority of liver MRI in detecting CRLM as compared to CT, there is limited data regarding the actual clinical impact of an additional liver MRI on the local therapeutic management of patients with CRLM. The American College of Radiology Appropriateness Criteria for the pretreatment staging of colorectal cancer indicates that staging of CRLM can be accomplished with CT and liver MRI, but emphasizes that it is difficult to determine the best imaging modality for CRLM since very few studies are available.[23] Moreover, the 2023 European Society for Medical Oncology consensus guidelines for the management of patients with metastatic colorectal cancer recommends liver MRI in the preinterventional workup of CRLM, but does so based on a meta-analysis published in 2010, which did not specifically investigate the actual impact of liver MRI over CT on the preinterventional local treatment plan.[12,24] Therefore, this systematic review and meta-analysis aimed to determine the added value of liver MRI over CT on the preinterventional local treatment plan in patients with CRLM eligible for local treatment (ie, surgery or ablation).

METHODS

The current study has been conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[25] A protocol was developed a priori and published in the International Prospective Register of Systematic Reviews (PROSPERO): CRD42021220090.

Search Strategy and Eligibility

Three biomedical databases (PubMed, Embase, and Cochrane Library) were systematically searched until June 23, 2023. A comprehensive search strategy using relevant keywords, Medical Subject Headings, and Emtree terms was designed. In order to provide a sensitive literature search and not to miss relevant articles, search limits and filters other than the English language were not employed. In addition, reference lists of included studies were manually searched to identify relevant studies not identified by the formal literature search. The detailed search strategy is included in Supplemental Text 1, see http://links.lww.com/AOSO/A307.

Eligible studies were those including: (1) patients with CRLM amenable to local treatment including curative intent surgery and/or local ablation based on CT; (2) liver MRI in addition to CT in the preinterventional workup; (3) outcome measures including change in local treatment plan (surgical resection and/or local ablation) based on liver MRI findings in addition to CT findings; and (4) study design including observational studies (retrospective and prospective) as well as clinical trials. Excluded were: (1) case reports, review articles, editorials, letters, comments, and conference abstracts/proceedings and (2) studies outside the field of interest of this study such as studies that did not report clearly on change in local treatment based on liver MRI findings in addition to CT findings.

The primary outcome of this meta-analysis was defined as the proportion of patients in which MRI findings would lead to a change of local treatment plan initially based on CT findings. Change in local treatment was defined as any alteration in surgery or thermal ablation, including more extensive or less extensive surgical resection, adjustments in the number of ablation zones, transition from surgery to ablation or ablation to surgery, addition of ablation to surgery, and cancelation of local therapy.

Selection of relevant articles was performed in stages. Two independent reviewers (B.G. and I.M.V.) first screened all articles according to their titles and abstracts. After selecting potentially eligible abstracts, the full-text articles were reviewed by assessing if the inclusion criteria and outcome measures were met. The 2 reviewers eliminated only those articles that were clearly ineligible. In case of disagreement, consensus was reached between the 2 reviewers following discussion.

Data Extraction

Both reviewers extracted relevant data independently using a predefined data form. Any disagreements were resolved by consensus through discussion. Data were only reported if stated in the text, tables, graphs, or figures of the article, or if they could be accurately extrapolated from the data presented. The following information from each article was extracted: (1) study characteristics including first author, country and year of publication, study design, single-center or multicenter setting, number of patients, number of patients relevant for determining change in local treatment plan, and study period; (2) patient characteristics including age, gender, previous abdominal surgery, previous liver surgery, synchronous or metachronous disease, and neoadjuvant chemotherapy status; (3) number of readers, time interval between CT and MRI, and time interval between MRI and actual treatment; (4) imaging parameters of CT and MRI: for CT, these include type of scanner, oral contrast agent, intravenous contrast agent, dose intravenous contrast agent, and CT phases. For MRI, these parameters include magnetic field strength, type of contrast agent, and sequences including DWI, type of coil, and *b* values for DWI; (5) subsequent change in surgical or ablative local treatment plan.

Quality Assessment

Quality assessment of the selected studies was performed by the 2 reviewers separately and blindly using the QUADAS-2 tool.[26] Discrepancies were resolved in a consensus meeting. The QUADAS-2 tool assesses risk of bias for the following domains: patient selection, index test, reference test, and patient flow (Supplemental Table 2, see http://links.lww.com/AOSO/A307). Each domain consists of signaling questions that were answered with yes, no, or unclear. The risk of bias was "low" if the answers to all questions were "yes." If any of the questions were answered with "no," a potential risk of bias was determined, and the respective domain was rated as "high." The "unclear" option was chosen if insufficient data were reported to decide. The concerns regarding applicability were assessed for the domains patient selection, index test, and reference test. Results from the risk of bias assessments for all included studies are displayed in the figures.

Statistical Analysis

All studies were qualitatively summarized and quantitatively analyzed. Results of all included studies were pooled in meta-analyses by using R for Mac OS X version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). The degree of heterogeneity was investigated with the I^2 test. Considering the noncomparative nature of the included studies with respect to the current primary outcome, it was not feasible to report relative measures of association, hence only proportions are reported. The total number of patients with a change in local treatment plan based on liver MRI as numerator and the total number of patients who had undergone CT followed by liver MRI in the study as denominator were extracted for calculation of proportion, and these proportions were summarized by using random-effects meta-analysis. The presence of publication bias was not evaluated due to the small number of included studies. Several sensitivity analyses were performed: studies including suspected or known CRLM lesions on CT of all sizes, studies including monophasic portal venous CT followed by gadoterate meglumine- or gadoxetic acid-enhanced liver MRI with or without DWI, studies including monophasic portal venous CT followed by gadoxetic acid-enhanced liver MRI with DWI, studies including monophasic or multiphasic CT followed by gadoxetic acid liver MRI with or without DWI, and studies including monophasic or multiphasic CT followed by gadoxetic acid liver MRI with DWI. Post hoc sensitivity analyses explored the impact of liver MRI on the local treatment plan when excluding noncontrast-enhanced MRI scans and when interpreted without knowledge of the results of the CT.

RESULTS

Study Selection

The results of the literature search are presented in the PRISMA flow diagram (Fig. 1). The initial search revealed 2965 studies. After the exclusion of duplicates, a total of 2293 studies were screened for eligibility of which 91 were screened in full text, which resulted in the inclusion of 11 studies. All 11 studies were included in the qualitative analysis and meta-analysis.[17,27–36]

Risk of Bias Assessment

All eligible studies were evaluated using the QUADAS-2 tool. Five studies[28–30,34,36] were appraised as having a high risk of bias in the domain index test because the results of the index test (ie, liver MRI) were not interpreted without knowledge of the results of the reference standard (ie, CT). Furthermore, there was a high risk of bias in 2 studies[27,29] with regard to patient flow and timing because not all patients were included in the relevant analyses. Four studies[17,31,33,35] were considered to have a low risk of bias. Risk of bias assessment for each study is shown in Figure 2.

Study and Patient Characteristics

Study characteristics are listed in Table 1. The 11 eligible studies included 2 randomized controlled trials, 1 retrospective

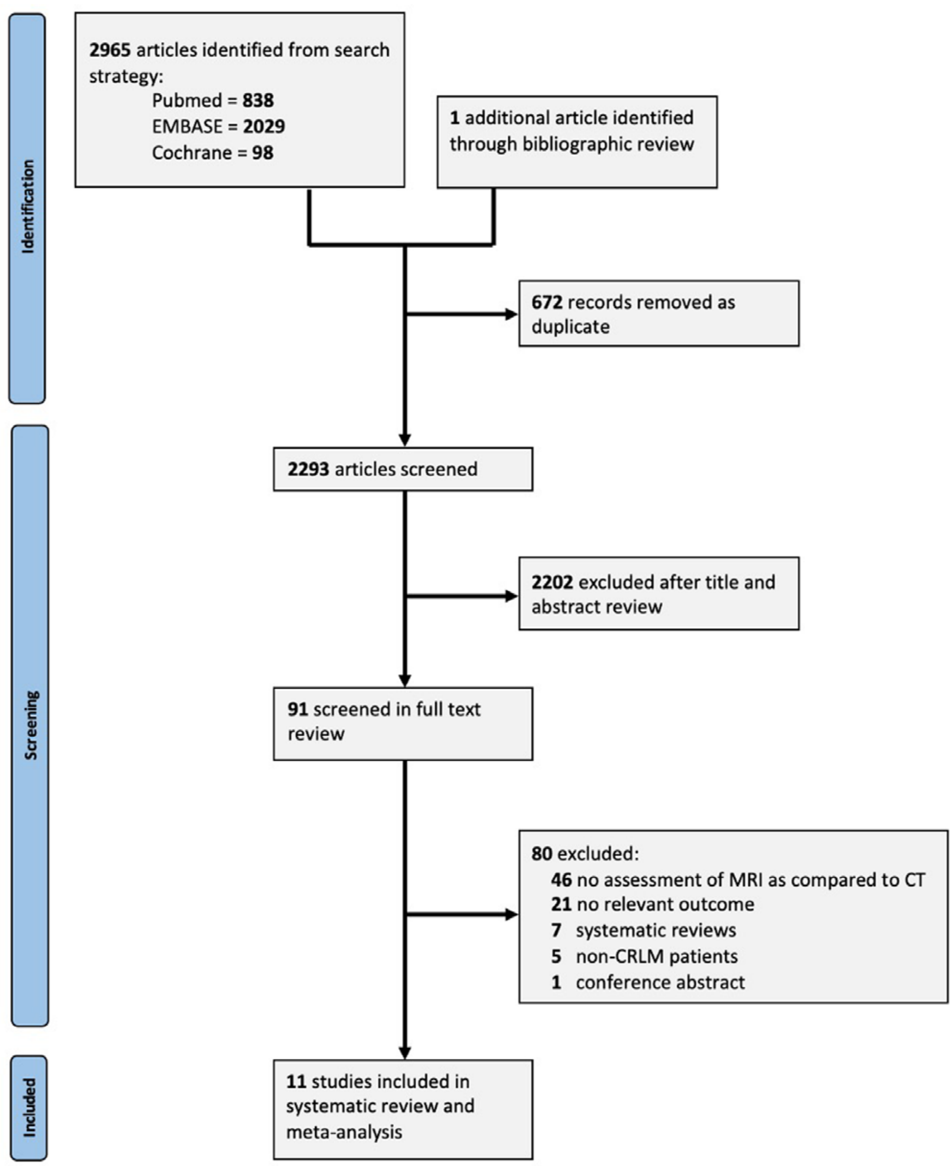

FIGURE 1. PRISMA flow chart of search results.

Study	RISK OF BIAS: PATIENT SELECTION	RISK OF BIAS: INDEX TEST	RISK OF BIAS: REFERENCE STANDARD	RISK OF BIAS: FLOW AND TIMING	APPLICABILITY CONCERNS: PATIENT SELECTION	APPLICABILITY CONCERNS: INDEX TEST	APPLICABILITY CONCERNS: REFERENCE STANDARD
Zech 2014	☺	☺	☺	☹	☺	☺	☺
Sofue 2014	☺	☹	☺	☹	☺	☹	☺
Patel 2014	☺	☹	?	☺	☺	☹	?
Kim 2015	☺	☺	☺	☺	☺	☺	☺
Cho 2015	☺	?	?	☺	☺	?	?
Achiam 2016	☺	☺	☺	☺	☺	☺	☺
Kang 2017	☺	☹	☺	☺	☺	☹	☺
Jhaveri 2017	☺	☺	☺	☺	☺	☺	☺
Koh 2017	☺	☺	☺	☺	☺	☺	☺
Sibinga Mulder 2018	☺	☹	?	☺	☺	☹	?
Moretto 2022	☺	☹	☺	☺	☺	☹	☺

☺ Low Risk ☹ High Risk ? Unclear Risk

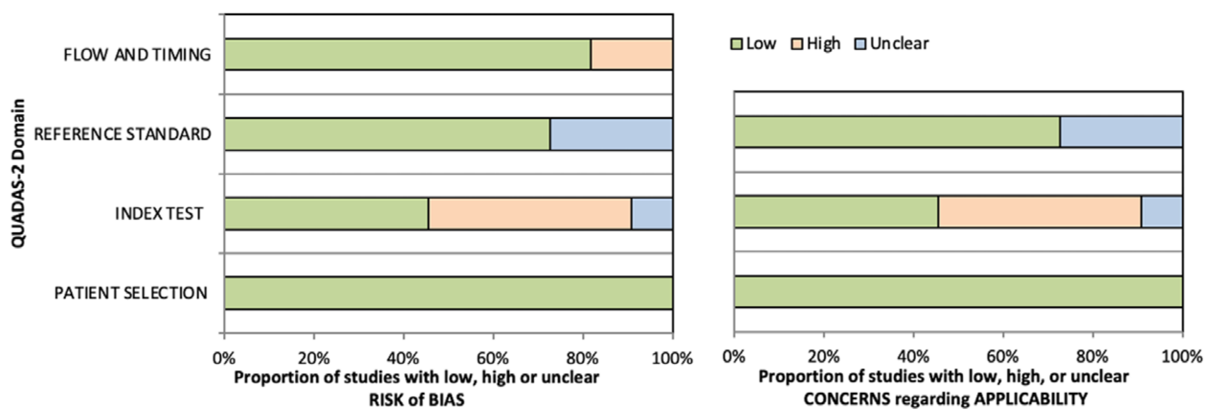

FIGURE 2. Risk of bias assessment of the included studies using the QUADAS-2 tool.

diagnostic accuracy study, 5 prospective, and 3 retrospective cohort studies from 9 countries (Switzerland, Japan, Korea, Denmark, The Netherlands, the United States, Canada, Singapore, and Italy) and were published between 2014 and 2022. One study was in a multicenter setting,[27] while 10 studies were single center.[17,28–36] One study[32] only focused on colorectal cancer patients with equivocal liver lesions smaller than 10 mm in size on preoperative staging CT who underwent an additional liver MRI, while the remaining 10 studies included patients with suspected or known CRLM of all sizes on staging CT who subsequently underwent a liver MRI. The total number of patients in the included studies was 1440, but only 468 patients (32.5%) were assessed with respect to a change in local treatment plan. The largest cohort relevant for this systematic review included 83 patients[36] and the smallest cohort included 13 patients.[27] Two studies[28,36] reported the proportion of synchronous and metachronous CRLM (53% vs 47% and 41% vs 59%, respectively). Seven studies reported on neoadjuvant chemotherapy[17,28,29,31,32,35,36] with 17.9% (n = 84) of patients receiving neoadjuvant chemotherapy, including 5 patients for their primary rectal cancer.[17]

Characteristics of CT and MRI

Seven[29,30,32–35,37] of the 11 studies had at least 2 readers of CT and MRI. Two of the 7 studies[29,35] performed an inter-observer analysis for CT and liver MRI. One study[35] included 2 readers and concluded that MRI had a higher reader concordance than CT for CRLM equal or smaller than 1 cm (72% vs 51%, P = 0.041). The other study[29] included 3 radiologists and showed a K value of 0.62 for CT and 0.70 for the combination of CT and gadoxetic acid-enhanced MRI. The time interval between CT and MRI was reported by 7 studies[29–32,35,36] and ranged between 4 days and 6 weeks (Supplemental Table 3, see http://links.lww.com/AOSO/A307). In all studies, a multidetector CT with intravenous iodinated contrast agent was used. The range of intravenous iodine dose was 30 to 52 g, reported in 7 studies.[27,29,31,32,34–36] In 6 studies,[17,31–35] a monophasic portal venous CT scan was performed and a multiphasic CT scan in 4 studies.[29,30,36] Ten of the 11 studies[27,29–36] used intravenous contrast-enhanced liver MRI, with the majority (n = 9) of studies[27,29–32,34,35] administering gadoxetic acid. Liver MRI with DWI was used in 9 studies.[17,27,31–36] In a multicenter study,[27] local imaging protocols were used and some scan parameters were not reported.

Change in Local Treatment Plan

All 11 studies reported on the change in preinterventional local treatment plan for patients with known or suspected CRLM according to CT that was followed by an additional MRI (n = 468). In 4 of the 11 studies,[27,28,34,36] a multidisciplinary team meeting before and after MRI was done to decide on the local treatment plan and whether any change in local treatment was indicated based on MRI. It is not specified whether predefined rules were used during the multidisciplinary team meeting. In 7 of the 11 studies,[17,29–33,35] the procedure for deciding on the local treatment plan and any change in local treatment based on MRI was not reported. Two studies investigated a change in preinterventional local treatment plan as a primary endpoint,[28,36] while 9 studies assessed a change in preinterventional local treatment

TABLE 1.

Study Characteristics of the Included Studies

Study (Year)	Country	Study Design	Single Center or Multicenter	Total No. Patients	No. Patients Relevant for Systematic Review	Study Period	Age, Years; Mean ± SD/ Median (IQR)	Gender, (Male/ Female)	Previous Abdominal Surgery (%)	Previous Liver Surgery (%)	Synchronous CRLM (%)	Neoadjuvant Chemotherapy (%)
Zech et al[27] (2014)	Switzerland	RCT*	Multicenter	342	13	October 2008–September 2010	63 (32–88)	74/38	NR	1/112	NR	NR
Sofue et al[29] (2014)	Japan	Prospective	Single center	39	39	NR	65 (45–79)	27/12	39 (100)	NR	NR	0
Patel et al[30] (2014)	USA	Retrospective	Single center	30	30	2011–2013	62 ± 10	15/15	NR	NR	NR	NR
Kim et al[31] (2015)	Korea	Prospective	Single center	51	47	March 2008–March 2009	62 (41–85)	39/12	21 (41.2)	NR	NR	5 (9.8)
Cho et al[32] (2015)	Korea	Retrospective diagnostic accuracy study	Single center	65	65	January 2009–December 2009	66.6 ± 11.2	35/30	NR	NR	NR	8 (12.3)
Achiam et al[33] (2016)	Denmark	RCT†	Single center	32	17	October 2010–February 2013	64 (17)	16/1	NR	NR	NR	NR
Kang et al[34] (2017)	Korea	Retrospective	Single center	690	75	April 2008–October 2014	64 (20–85)	413/277	NR	NR	NR	NR
Jhaveri et al[35] (2017)	Canada	Prospective	Single center	51	51	October 2010–June 2013	61 (40–83)	37/14	NR	NR	NR	51 (100)
Koh et al[17] (2018)	Singapore	Prospective	Single center	30	30	January 2011–August 2012	59.5 (47–81)	20/10	NR	NR	NR	5 (16.7)‡
Sibinga Mulder et al[36] (2018)	The Netherlands	Retrospective	Single center	83	83	July 2014–August 2017	64.8 ± 10.7	56/27	NR	18 (22)	44 (53)	15 (18)
Moretto et al[28] (2022)	Italy	Prospective	Single center	27	18	March 2018–May 2021	61 (54–67)	17/10	NR	NR	11 (41)	0

*The primary objective of this randomized trial was to compare the impact of gadoxetic acid-enhanced liver MRI, MRI with extracellular contrast medium and contrast-enhanced CT as a first-line imaging method in patients with suspected CRLM.
†The primary objective of this randomized trial was to evaluate the feasibility of diffusion-weighted MRI of the liver as part of a combined MR evaluation of patients with rectal cancers and compare it with the standard preoperative evaluation of the liver with CT.
‡All patients received chemoradiotherapy.
IQR indicates interquartile range; NR, not reported; RCT, randomized controlled trial; SD, standard deviation.

plan as a secondary endpoint.[17,27,29–35] Pooling of the results of all studies showed that 24.12% [95% confidence interval (CI), 15.58%–32.65%) of the patients had a change in local treatment plan based on the liver MRI findings (Fig. 3). The change in local treatment plan most often included resection of (an) additional liver segment(s) (n = 52; 11.1%). In 8 patients (1.7%), a reduction of segmental resections was reported. Twelve patients (2.6%), who were planned for local treatment based on CT findings, were deemed unresectable due to extensive metastatic disease on liver MRI. In 9 patients (1.9%), local therapy of lesions was withheld since the initial suspected malignant lesions on CT were assessed as benign lesions on liver MRI. Follow-up for these benign lesions on liver MRI was reported in 2 of the 4 studies,[29,34] including 4 of the 9 patients. Follow-up ranged from 11 to 21 months and showed that 1 of the 4 patients needed local therapy due to a single new CRLM on follow-up imaging. In 9 of the 11 studies,[17,27,29–33,35] the actual local treatment only included surgical resection and was performed in 263 of 280 patients. In one study,[34] 35 patients underwent surgical resection, and 4 patients underwent surgical resection combined with intraoperative local ablation. In another study,[36] actual local treatment was defined as surgical resection and/or ablation and further details were not provided (n = 50). In addition, 2 studies[27,36] reported on the accuracy of the local treatment plan based on liver MRI by comparing it to the actual surgical treatment based on intraoperative findings. One study[36] reported that in 77 patients (93%) the actual treatment was similar to the local treatment plan based on liver MRI, whereas the other study[27] reported that the final treatment was similar in 1 patient where the liver MRI changed the local treatment plan. Table 2 summarizes the findings of the included studies.

Sensitivity Analyses

Pooling of the results of the 10 studies (n = 438), focusing on suspected or known CRLM of all sizes on CT and excluding the study[32] that focused only on equivocal liver lesions smaller than 10 mm, showed a similar change of local treatment plan [23.03% (95% CI, 14.07%–31.99%)] as compared to the meta-analysis of all 11 studies (Fig. 4A). In the 6 studies (n = 285) where a monophasic portal venous CT was followed by a liver MRI (gadolinium or gadoxetic acid, and DWI or no DWI), a change in local treatment occurred in 16.89% of the patients (95% CI, 6.24%–27.54%) (Fig. 4B). Pooling of the results of the 5 studies (n = 268) using monophasic portal venous CT and gadoxetic acid-enhanced liver MRI with DWI showed similar results [17.88% (95% CI, 5.14–30.62)] (Fig. 4C). Sensitivity analysis of the 9 studies (n = 421), performing CT regardless of the number of CT phases followed by gadoxetic acid-enhanced liver MRI with or without DWI, showed a change in local treatment of 27.21% (95% CI, 17.65–36.77) (Fig. 4D). Excluding the 2 studies without DWI (n = 352) showed similar results (Fig. 4E). In the post hoc sensitivity analysis of studies wherein MRI scans were interpreted without knowledge of the results of the CT (n = 158), MRI led to a change in the local treatment plan in 21% of the patients in this sensitivity analysis (95% CI, 6–37) (Fig. 4F). The post hoc analysis wherein the study using noncontrast-enhanced MRI scans was excluded (n = 438) yielded results that were largely in line with the primary analysis, with a change in the local treatment in 26% of the patients (95% CI, 17–35) (Fig. 4G).

DISCUSSION

This systematic review and meta-analysis, including 468 patients from 11 studies, found a pooled 24.12% change in local treatment plan based on liver MRI findings in patients amenable to local treatment of CRLM according to CT findings. Sensitivity analysis of 5 studies focusing on monophasic portal venous CT followed by gadoxetic acid-enhanced liver MRI with DWI demonstrated a 17.9% change in the local treatment plan. These findings suggest a clinically relevant added value for routine liver MRI in the staging of CRLM, which should be confirmed by large prospective studies.

The results of our study are important because the most recent American College of Radiology Appropriateness Criteria and the latest European Society for Medical Oncology consensus guidelines lack specific recommendations concerning the use of liver MRI in the staging of CRLM.[23,24] One previous systematic review investigated the clinical impact of gadoxetic acid-enhanced liver MRI in addition to CT in patients with resectable CRLM.[21] However, that review included published studies until February 2015, inclusion was not limited to CRLM, included only 155 patients from 4 studies, and did not perform a formal meta-analysis. That review found a 16.8% change in surgical strategy based on additional liver MRI findings. Notably, none of the included studies investigated the change in local treatment plans based on liver MRI as a primary endpoint. Furthermore, 1 of the 4 studies focused on patients with equivocal liver lesions <10 mm, identified on CT instead

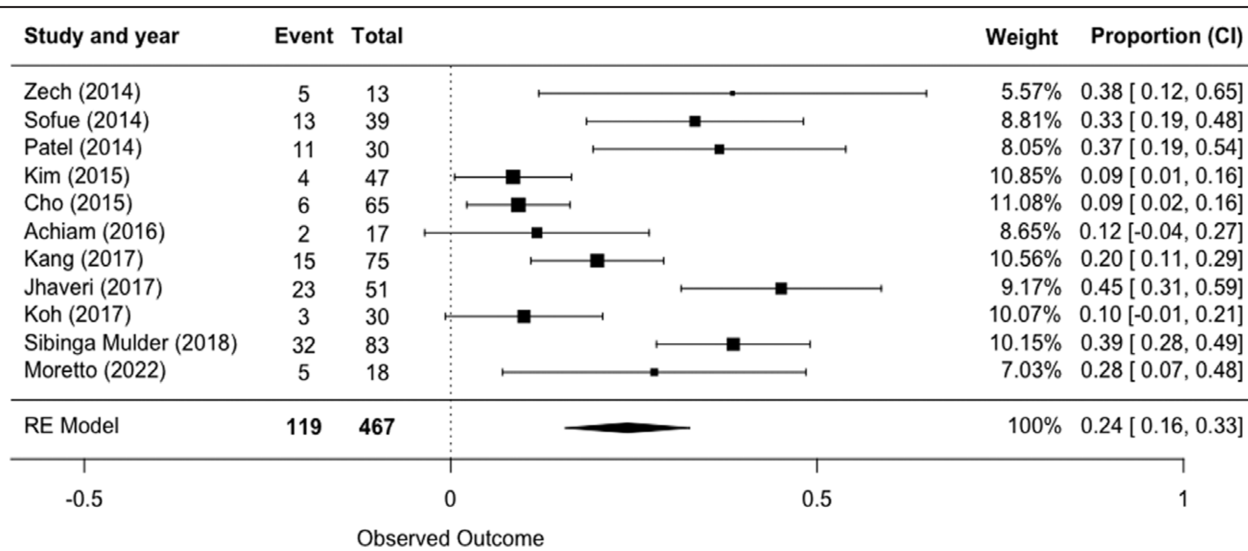

FIGURE 3. Pooled results of change in local treatment plan after MRI liver in patients amenable to local treatment of colorectal liver metastases according to CT scan.

TABLE 2.

Results of Change in Local Treatment Plan in the Included Studies

Study (Year)	Change in Local Treatment Plan Based on Liver MRI (%)	Additional Segments Resected	Reduced Segments Resected	Resection Could Not Be Performed (Resectable to Unresectable)	Benign Tumor on MRI (Resection to No Resection)	Accuracy of Local Treatment Plan Based on Liver MRI as Compared to Intraoperative Findings and the Actual Treatment (%)
Zech et al[27] (2014)	5 of 13 (38.4%)	1	0	0	4	100%
Sofue et al[29] (2014)	13 of 39 (33.3%)	8	1	2	2	NR
Patel et al[30] (2014)	11 of 30 (36.7%)	11	0	0	0	NR
Kim et al[31] (2015)	4 of 47 (8.5%)	3	0	1	0	NR
Cho et al[32] (2015)	6 of 65 (9.2%)	6	0	0	0	NR
Achiam et al[33] (2016)	2 of 17 (11.7%)	0	0	2	0	NR
Kang et al[34] (2017)	15 of 75 (20%)	10	1	2	2	NR
Jhaveri et al[35] (2017)	Reader 1: 25 of 51 (49.0%) Reader 2: 21 of 51 (41.2%) Overall: 45%	NR	NR	NR	NR	NR
Koh et al[17] (2018)	3 of 30 (10.0%)	2	0	0	1	NR
Sibinga Mulder et al[36] (2018)	32 of 83 (38%)	11	6	NR	NR	93%
Moretto et al[28] (2022)	5 of 18 (27.8%)	0	0	5	0	NR

NR indicates not reported.

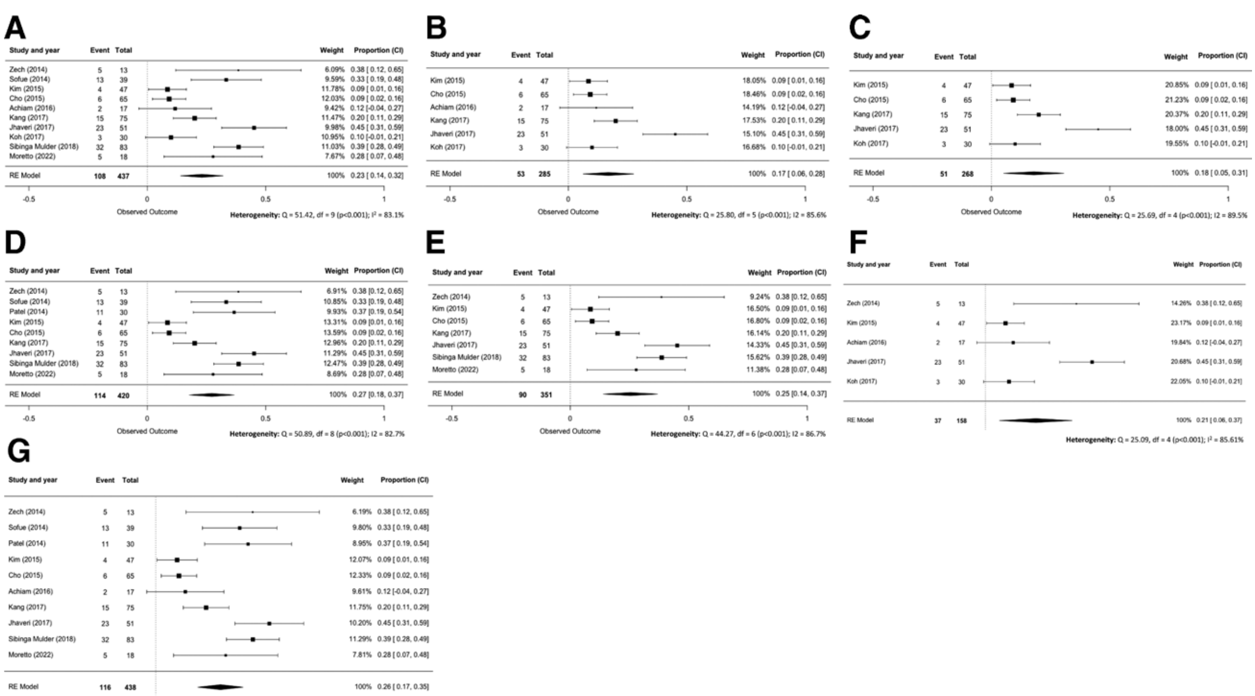

FIGURE 4. Sensitivity analyses with (A) pooled results of change in local treatment plan of studies including suspected or known CRLM lesions on CT of all sizes. B, Pooled results of change in local treatment plan of studies including monophasic portal venous CT followed by liver MRI (gadoterate meglumine or gadoxetic acid, and DWI or no DWI). C, Pooled results of change in local treatment plan of studies including monophasic portal venous CT followed by gadoxetic acid-enhanced liver MRI with DWI. D, Pooled results of change in local treatment plan of studies including CT (monophasic or multiphasic) followed by gadoxetic acid liver MRI (DWI or no DWI). E, Pooled results of change in local treatment plan of studies including CT (monophasic or multiphasic) followed by gadoxetic acid liver MRI with DWI. F, Pooled results of change in local treatment of studies with 2 independent readers of CT and MRI. G, Pooled results of change in local treatment of studies including contrast-enhanced liver MRI.

of patients with suspected or known CRLM of all sizes, which might skew the overall percentage of change in the management and the generalizability of these results. The remaining 3 studies included one randomized trial in which only 13 patients were assessed with regard to change in clinical management.

Most of the included studies (9 of 11 studies) in the current meta-analyses used gadoxetic acid-enhanced MRI combined with DWI. This is in line with a previous comprehensive meta-analysis consisting of 39 studies with a total of 1989 patients, which showed that the combination of gadoxetic acid-enhanced MRI and DWI has the highest sensitivity for detecting CRLM and should be performed in that combination in the staging of CRLM.[38] A recent meta-analysis focusing on the accuracy of imaging in case of disappearing liver metastases also demonstrated a high negative predictive value of liver MRI as compared to CT in this setting.[39]

It is important to emphasize that intraoperative ultrasound is still considered the reference standard for the detection of CRLM.[40] Several studies have shown that intraoperative ultrasound might change the intraoperative surgical strategy in 12.0% to 23.7% of patients as compared to the preinterventional local treatment plan based on liver MRI.[40–42] Nevertheless, a reliable preinterventional local treatment strategy is crucial to ensure optimal treatment of all lesions, which may require specific patient positioning and planned availability of a specific, dedicated ablation or surgical team, especially in the current era of minimally invasive (ie, robotic and laparoscopic) surgery. Deviation from the preoperative surgical plan due to additional intraoperative findings is undesirable, especially when preoperative findings of the actual extent of the disease would have resulted in a different multimodal treatment or patient positioning. Therefore, the use of liver MRI in the diagnostic workup of patients with CRLM may be beneficial. In fact, unneeded invasive procedures can be avoided with a better distinction between malignant and benign lesions on liver MRI. Previous studies have also demonstrated that liver MRI is cost-effective when compared with other imaging modalities.[43,44] Despite the potential benefits of liver MRI, it is important to emphasize that liver MRI as a first-line imaging without CT is currently not recommended since a thoracoabdominal CT is still needed for adequate staging of extrahepatic disease.

It would be highly valuable to identify subgroups that would benefit the most from a liver MRI in the diagnostic workup of patients with CRLM. Unfortunately, none of the included studies in the current meta-analysis focused on such subgroups. Previously, the PROMETEO-01 study demonstrated that MRI was more sensitive than CT in patients who received neoadjuvant chemotherapy (90% vs 77%).[3] Another study compared MRI with multidetector CT in 20 patients after neoadjuvant chemotherapy and consecutive diffuse steatosis and noted that MRI had a higher detection rate of CRLM as compared to CT, particularly for the detection of small lesions.[45] Of note, both studies were small and did not investigate change in local treatment plan as an outcome. Future studies assessing the added value of liver MRI with regard to the local treatment plan in specific subgroups (eg, patients with steatosis, metabolic associated liver disease, obesity or after chemotherapy) are warranted.

A previous multicenter retrospective study that performed a root cause analysis of mortality after liver resection has found that a more invasive procedure than preoperatively planned was associated with severe complications and mortality.[46] Liver MRI may lead to more accurate staging prior to neoadjuvant chemotherapy, thereby reducing intrahepatic recurrence and avoiding repeated thermal ablation or resection.[47] In addition, a change in surgical plans based on intraoperative findings may cause logistical issues and generate unexpected costs.[48] Of note, although only 2 of the 10 included studies investigated the accuracy of the local treatment plan based on liver MRI as compared to the actual treatment, an accuracy of at least 93% was shown.[27,36] This accuracy rate does not only emphasize the positive impact of liver MRI on the preoperative local treatment strategy but also on the actual treatment performed.

The current study has several limitations. First, a large heterogeneity between the included studies was noted with regard to the clinical impact of liver MRI and MRI scan protocols. This heterogeneity affects the generalizability of our results. Nevertheless, differences between studies were systematically explored and sensitivity analyses with random-effects model were performed to limit this effect. Second, 6 included studies were judged to have a risk of bias, especially in the domain index test since the results of the index test (ie, liver MRI) were not interpreted without knowledge of the results of the reference standard (ie, CT). However, this effect is minor since the aim of the current study was to investigate the added value of liver MRI to CT. Third, the included studies contained a small number of patients with only 2 randomized controlled trials. Although 2 studies including one randomized controlled trial had a large patient cohort, a change in clinical management based on liver MRI was a secondary endpoint in both studies and was assessed in a relatively small subgroup. However, the current study is the first meta-analysis performed so far containing all studies focusing on the clinical added value of liver MRI in the staging of CRLM. Fourth, only one study investigated a change in preinterventional local treatment plan as a primary endpoint, while the remaining 9 studies assessed change in preinterventional local treatment plan as a secondary endpoint. Fifth, all included studies collected limited information with regard to baseline patient characteristics. Subsequently, studies are lacking that analyzed (predictive) factors associated with clinically significant lesions on liver MRI and as such identifying subgroups that might benefit the most from additional liver MRI. Sixth, 7 of the 11 studies[17,28,29,31,32,35,36] provided information on the use of neoadjuvant chemotherapy, and none detailed the specific type or number of cycles administered. This introduces a significant bias since neoadjuvant chemotherapy may impact the surrounding liver parenchyma. Such influence may compromise the quality of liver imaging and subsequently affect the interpretation of our findings. Future studies in this field focusing on the impact of different chemotherapy regimens may be valuable. Seventh, a notable disparity existed in the time intervals between CT and liver MRI across the studies included. This discrepancy could potentially skew the primary endpoint. A sensitivity analysis to assess the effect of a short and long time interval on the local treatment plan was not feasible since individual data on time intervals were not available in the included studies. Nonetheless, the observed time intervals ranged from 4 days to 6 weeks, a range deemed sufficient to minimize any disease progression attributable solely to the passage of time.

In conclusion, this systematic review and meta-analysis suggests that liver MRI alters local treatment plan in more than one-fifth of the patients amenable to local treatment of CRLM, as compared to CT. At least one-sixth of the patients in studies focusing on monophasic portal venous CT and gadoxetic acid-enhanced liver MRI with DWI had their local treatment plan changed based on liver MRI. These results imply a significant clinical added value for liver MRI in the diagnostic workup of patients with CRLM. However, most studies were small in a single-center setting, had widely varying outcomes including only one retrospective study investigating a change in local treatment plan as a primary endpoint, and did not assess subgroups that might benefit the most from additional liver MRI. Therefore, further large international multicenter prospective studies are warranted, such as the international multicenter CAMINO study.[49]

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