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Meta-Analysis

Diagnostic performance of contrast-enhanced ultrasound and magnetic resonance imaging for detecting colorectal liver metastases: A systematic review and meta-analysis

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ABSTRACT

Objectives: To determine the diagnostic performance of contrast-enhanced ultrasound, diffusion-weighted magnetic resonance imaging and contrast-enhanced magnetic resonance imaging for detecting colorectal liver metastases.

Methods: We performed comprehensive searches of the MEDLINE, EMBASE, and Cochrane Library databases to identify studies reporting the per-lesion diagnostic accuracy of contrast-enhanced ultrasound, diffusion-weighted magnetic resonance imaging, and contrast-enhanced magnetic resonance imaging for detecting colorectal liver metastases. Studies published between January 2003 and December 2018 with reference standards, including histopathology and intraoperative observation, and/or follow-up, were included. Sources of bias were assessed using the QUADAS-2 tool. A linear mixed-effects regression model was used to determine sensitivity estimates.

Results: Overall, 47 articles were included. The sensitivity estimates for contrast-enhanced ultrasound, diffusion-weighted magnetic resonance imaging, and contrast-enhanced magnetic resonance imaging for detecting colorectal liver metastases were 85.3%, 83.0%, and 90.1%, respectively. For lesions ≥10 mm in diameter, the sensitivities were 93.1%, 92.9%, and 94.5%, respectively. In 21 articles using histopathology as the only reference standard, the sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio for contrast-enhanced ultrasound/contrast-enhanced magnetic resonance imaging were 86%/91%, 91%/95%, 9.2/16.6, 0.15/0.10, and 61/170, respectively.

Conclusions: CEUS showed a diagnostic ability comparable to that of DWI and CEMRI, particularly for lesions ≥10 mm in diameter.

1. Introduction

Colorectal cancer is a leading cause of cancer-related mortality worldwide. Liver metastases is the main prognostic factor for survival and is found in up to 50% of patients at initial presentation [1]. Surgical resection of liver metastases offers the best overall survival of all treatments. After surgical resection, the median survival was reported to be 34–45 months, with 3-, 5-, and 10-year survival rates of 45%–55%, 28%–50%, and 10%–20%, respectively, but disease recurred in about 90% patients at a median of 8–12 months after resection [2–4].

Early detection of colorectal liver metastases (CRLMs) is crucial for achieving cancer control in patients. Magnetic resonance imaging (MRI) is currently considered as the reference preoperative imaging modality for the detection of secondary liver lesions [5,6]. Vilgrain et al. recently performed a meta-analysis of 39 articles and reported that the sensitivities of diffusion-weighted MRI (DWI) and gadoxetic acid-enhanced MRI for detecting liver metastases on a per-lesion basis were 87.1% and 90.6%, respectively [7]. In recent years, contrast-enhanced ultrasound (CEUS) has gained traction for detecting liver metastases. Although most studies have shown that MRI is superior to traditional ultrasound (US), the introduction of contrast media has significantly improved the accuracy of US for detecting liver metastases, with an estimated sensitivity of 71%–93% [8–10].

Correct preoperative evaluation of the liver and identification of localized lesions are prerequisites for surgical resection of liver metastases. The low running cost and no radiation exposure of CEUS support its routine use for initial radiological diagnosis. To date, however, no meta-analyses have evaluated the diagnostic abilities

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of CEUS and MRI for detecting CRLMs. Therefore, we performed a systematic review of the literature with the objective of assessing the diagnostic performance of CEUS, DWI, and contrast-enhanced MRI (CEMRI) for detecting CRLMs on a per-lesion basis. We also planned subgroup analyses focusing on small liver metastases, contrast agents, gold standards, and study design.

2. Materials and methods

2.1. Literature search

A comprehensive literature search was performed to identify articles reporting the diagnostic performance of CEUS, DWI, and CEMRI for detecting CRLMs in humans. The search strategy involved the following keywords: "ultrasound" or "sonography" or "ultrasonography" or "ultrasonic" or "US" AND "diffusion-weighted" or "DWI" AND "magnetic resonance" or "MR" AND "contrast enhanced" or "CE" AND "colorectal liver metastases" or "CRLM" or "liver disease" AND "colorectal cancer". Review articles, letters, comments, case reports, unpublished articles, and articles that did not include raw data were not included.

2.2. Study selection

All search hits were evaluated for eligibility by two reviewers (Luni Zhang and Li Zhang), who screened the relevant titles and abstracts. An article was considered to be eligible if CEUS, DWI, or CEMRI was evaluated in adult patients (≥18 years) who underwent an imaging study for the diagnosis of CRLMs. The full text was reviewed to identify all potentially eligible studies.

Studies were included if they satisfied all of the following inclusion criteria: (1) CEUS, DWI, and/or CEMRI used in patients with CRLMs; (2) only per-lesion statistics with sufficient data to calculate sensitivity and/or specificity of imaging technique; (3) clear definition of the reference standard (histopathological analysis, intraoperative observation, or follow-up imaging, or a combination of these reference standards); and (4) the article is in English. Any disagreements between the two reviewers were resolved through discussion with a third reviewer (Libo Chen).

2.3. Quality assessment

The methodological quality of the included studies was assessed independently by the two reviewers (Luni Zhang and Li Zhang) in duplicate using QUADAS-2, a quality assessment tool developed for systematic review of diagnostic accuracy studies [11]. To manage disagreement between reviewers, a third reviewer (Libo Chen) assessed any discrepancies and the majority opinion was used for analysis. We used a graphical display proposed for QUADAS-2 results. The QUADAS-2 assessment was performed using Revman, version 5.3.5 (The Nordic Cochrane Centre, Copenhagen).

2.4. Data extraction

Both reviewers (Luni Zhang and Li Zhang) independently extracted relevant data regarding the study designs and examination results using a standardized form. Any disagreements were resolved by consensus through discussion with the third reviewer (Libo Chen).

2.4.1. Study characteristics

We extracted the following information from each article: (1) first author, country, and year of publication; (2) number of observers; (3) sample size; (4) description of the study population; (5) diameter of the CRLMs; (6) imaging features, namely contrast agent, dose, image analysis of CEUS and CEMRI, magnetic field strength for MRI, and *b* factor for DWI; (7) description of the reference standard; and (8) retrospective or prospective design.

2.4.2. Examination results

The number of true positives and false negatives for the detection of CRLMs were extracted on a per-lesion basis. One or several datasets were prepared for each article. Separate datasets were considered for studies that contributed two or more sensitivity values. The numbers of true negative and false positive results were also extracted if available.

2.5. Statistical analysis

2.5.1. Calculation of sensitivity and specificity

The paired sensitivity was calculated for all eligible studies. Overall, 60% (29/47) of articles using a composite gold standard did not calculate specificity. Therefore, the analysis of specificity was limited to studies in which histopathological examination alone was used as the reference standard. We also calculated the positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio (DOR). We used the bivariate model to estimate sensitivity and specificity with 95% confidence intervals (CIs). Because it is possible that several datasets were derived from the same study, we also considered that the datasets were nested within their own study in the random effects model.

To assess heterogeneity, we applied the Cochran Q test and the Higgins I2 heterogeneity index for each technique separately. Heterogeneity was classified as low (I^2 = 0%–30%), moderate (I^2 = 30%–50%), or substantial (I^2 > 50%). Statistical analyses were performed using STATA version 15.0 (STATA Corp., College Station, TX, USA).

2.5.2. Subgroup analyses

Factors that could affect diagnostic accuracy and cause heterogeneity were evaluated in subgroup analyses and meta-regression analyses. Heterogeneity was quantified using the Q test and $P < 0.05$ was taken to indicate significant heterogeneity [12–14].

If at least five datasets were available, subgroup analyses were performed for the following variables: (1) diameter of the CRLMs (cutoff value of 10 mm); (2) histopathology used as only reference standard or not used; (3) use of different contrast agents (Sonovue or Sonazoid for CEUS, only liver-specific contrast agents used for CEMRI, or not used); (4) patient selection and imaging evaluation performed retrospectively or prospectively. We considered factors to be explanatory of the observed heterogeneity in diagnostic accuracy if the corresponding regression coefficients were significant.

2.5.3. Publication bias

To assess the possibility of publication bias, we constructed funnel plots for each imaging modality with the inverse square root of the sample size (1/root(ESS)) as the *y*-axis and DOR as the *x*-axis. Publication bias was estimated using Deek's test in STATA version 15.0, and $P < 0.05$ was set as the threshold for statistical significance.

3. Results

3.1. Literature search and study selection

A total of 4486 articles were found in the initial search, of which 131 were retained after screening according to the eligibility criteria. After reading the full text, 47 articles (18 on CEUS, six on DWI, 16 on CEMRI, five on both CEUS and CEMRI, and two on both DWI and CEMRI) were included in the review and subjected to data extraction. A flowchart of study selection is shown in Fig. 1.

Table 1
Characteristics of included studies.

Author	Country	Year	Observers	Number of patients with metastases (number of CRLMs)	Number of metastases (number of CRLMs)	Gender (M/F)	Age	CEUS		CEMR imaging				Reference standard	Study design
								Contrast agent	Dose (ml)	Field strength (T)	*b* factor	Contrast agent	Dose (mmol/L)		
Isozaki et al. [15]	Japan	2003	2	183 (11)	183 (42)	121/62	Men 65, women 64	34	Levovist	NA	/	/	/	/	a
Oldenburg et al. [16]	Germany	2005	3	40 (15)	128 (128)	16/24	61	32	SonoVue	2.4	/	/	/	/	c
Quaia et al. [17]	NA	2006	3	196 (–)	551 (–)	138/115	57	NA	NA	NA	/	/	/	/	a
Numata et al. [18]	Japan	2006	2	283 (9)	283 (33)	195/88	Men 67, women 68	33	Levovist	3.6	/	/	/	/	a;c
Bleuzen et al. [19]	France	2006	2	138 (41)	381 (174)	76/62	Women 52, men 63	NA	SonoVue	1.2; 2.4	/	/	/	/	a;c
Janica et al. [20]	Poland	2007	NA	41(23)	134 (134)	NA	57	79 mets<10; 33 between 10–20; 22 > 20	SonoVue	2.4	/	/	/	/	a
Yarmenitis et al. [21]	Greece	2007	2	32 (22)	54 (54)	23/9	58	NA	SonoVue	2.4	/	/	/	/	c
Vilgrain et al. [7]	Italy	2007	3	109 (92)	132 (132)	64/45	66	NA	SonoVue	2.4(<70 kg); 4.8(>70 kg)	/	/	/	/	
Piscaglia et al. [8]	Germany	2008	3	40 (40)	61 (61)	NA	NA	26(4–89)	SonoVue	1.2;2.4	/	/	/	/	a
Kuehl et al. [22]	Germany	2008	2	16 (16)	33 (33)	13/3	62	20 (10–43)	/	/	1.5	/	Gd-DOTA	0.2	a;c
Koh et al. [23]	UK	2008	2	33 (33)	83 (83)	23/10	57	20 (5–95)	/	/	1.5	0, 150, 500	MnDPDP	NA	a;c
Strobel et al. [9]	Germany	2009	NA	364 (–)	383 (383)	677/672	60	NA	SonoVue	NA	/	/	/	/	a;c
Larsen et al. [24]	Denmark	2009	3	NA	365 (365)	NA	NA	NA	NA	NA	/	/	/	/	a;b;c
Hekimoglu et al. [25]	Turkey	2009	2	16 (16)	78 (78)	11/5	63	28 (5–55)	/	/	1.5	/	Gd-EOB-DTPA	NA	a;c
Rafaelsen and Jakobsen [10]	Denmark	2010	4	NA	271 (271)	146/125	68	NA	SonoVue	2.4	/	/	/	/	a;b;c
Cantisani et al. [26]	Italy	2010	2	110 (110)	430 (430)	65/45	62	24 (5–50)	SonoVue	2.4	/	/	/	/	a;b;c
Donati et al. [27]	Switzerland	2010	2	37 (37)	85 (55)	23/14	60	23 (10–80)	/	/	1.5	/	Gd-EOB-DTPA	0.025	a;c
Mainenti et al. [28]	Italy	2010	NA	34 (34)	57 (16)	20/14	63	NA	SonoVue	5	1.5	/	SPIO;Gd-EOB-DTPA	0.1	a
Hardie et al. [29]	USA	2010	2	51 (11)	98 (NA)	24/27	Men 63, women64	13 (3–111)	/	/	1.5	0, 50, 500	Gadopentetate dimeglumine	20 ml	NA
Correas et al. [30]	NA	2011	3	157 (81)	239 (165)	94/69	64	21	Sonazoid	0.008, 0.080.12, 0.36 μL/kg	/	/	/	/	c
Hohmann et al. [31]	Germany	2011	1	25 (4)	137 (137)	16/9	66	29	SonoVue	0.25; 1; 4	/	/	/	/	a
Seo et al. [32]	Korea	2011	2	68 (68)	165 (135)	NA	68	NA	/	/	3.0	/	Gd-EOB-DTPA	0.025	a;c
Kulemann et al. [33]	Austria	2011	NA	20 (20)	59 (59)	12/8	64	NA	/	/	1.5; 3.0	/	Gd-EOB-DTPA;Gd-DOTA	0.025	a
Sofue et al. [34]	Japan	2011	1	48 (48)	88 (88)	26/22	64	NA	/	/	3	/	Gd-EOB-DTPA	0.025	a
Chung et al. [35]	Korea	2011	1	47 (47)	78 (78)	31/16	60	24 (3–90)	/	/	3	/	Gd-EOB-DTPA	0.025	a
Motosugi et al. [36]	Japan	2011	2	45 (45)	105 (47)	26/19	60	16 (5–48)	/	/	1.5	/	Gd-EOB-DTPA	0.025	a;c
Kartalis et al. [37]	Sweden	2011	NA	15 (15)	31 (31)	8/7	64	16	SonoVue	NA	1.5	/	MnDPDP	0.1	NA
Muhi et al. [38]	Japan	2011	3	46 (46)	112 (112)	84/27	64	16 (3–67)	Sonazoid	2	1.5	/	SPIO;Gd-EOB-DTPA	0.025	c
Berger-Kulemann et al. [39]	Austria	2012	2	23 (23)	68 (68)	13/10	62	NA	/	/	3	/	Gd-EOB-DTPA	NA	a;b;c
Tajima et al. [40]	Japan	2012	2	29 (29)	85 (85)	20/8	61	20 (2–120)	/	/	1.5	0, 800	Gd-EOB-DTPA	0.025	a
Kim et al. [41]	Korea.	2012	2	67 (33)	110 (–)	38/29	56	13 (3–25)	/	/	1.5	/	Gd-EOB-DTPA	0.025	a;b
Kim et al. [42]	Korea.	2012	2	86 (72)	179 (NA)	51/35	57	NA	/	/	3	0, 100, 800	gadoxetic acid	0.025	a;c
Eiber et al. [43]	Germany	2012	2	68 (68)	268 (268)	49/19	NA	17 (5–92)	/	/	1.5	50, 300, 600	/	/	a;b;c
Ding et al. [44]	China	2013	2	30 (30)	81 (81)	20/10	Men 45, women43	25 (3–45)	/	/	1.5	/	Gd-EOB-DTPA	0.025	a
Scharitzer et al. [45]	Austria	2013	3	45 (32)	96 (96)	35/10	65	23 (2–75)	/	/	3	/	Gd-EOB-DTPA	0.025	a
Kim et al. [46]	Korea	2014	2	51 (51)	104 (104)	39/12	62	19	/	/	1.5	/	Gd-EOB-DTPA	NA	a;c
Vialle et al. [47]	France	2015	2	48 (48)	158 (158)	29/19	62	23 (3–58)	SonoVue	2.4	/	/	/	/	a;b
Yu et al. [48]	Korea	2015	2	77 (77)	140 (140)	51/26	61	24	/	/	1.5; 3.0	/	Gd-EOB-DTPA	0.025	a
Arita et al. [49]	Japan	2015	2	100 (100)	242 (242)	74/26	65	5 (2–13)	Sonazoid	0.5	1.5	/	Gd-EOB-DTPA	0.025	a
Achiam et al. [50]	Denmark	2016	2	20 (NA)	9 (9)	16/4	64	NA	/	/	1.5	0, 10, 150, 300, 450	/	/	b
Sivesgaard et al. [51]	Denmark	2017	2	80 (80)	260 (260)	47/33	68	13.6 (1–112)	/	/	1.5	0, 50, 800	/	/	a;b;c
Qin et al. [52]	China	2017	2	85 (85)	143 (143)	49/36	55	7 (3–10)	SonoVue	2	/	/	/	/	c
Kobayashi et al. [53]	Japan	2017	2	98 (51)	121 (126)	62/36	66	20 (5–109)	Sonazoid	NA	/	/	/	/	a
Shiozawa et al. [54]	Japan	2017	NA	69 (69)	133 (133)	46/23	66	21.3	Sonazoid	0.5	1.5	/	Gd-EOB-DTPA	0.025	a;c
Stein et al. [55]	Israel	2018	3	24 (13)	39 (20)	11/13	56	NA	/	/	3	50, 400, 800	/	/	a;c

a:histopathology;b:intraoperative observation;c:follow-up imaging; NA = not available; P:prospective; R: respective.

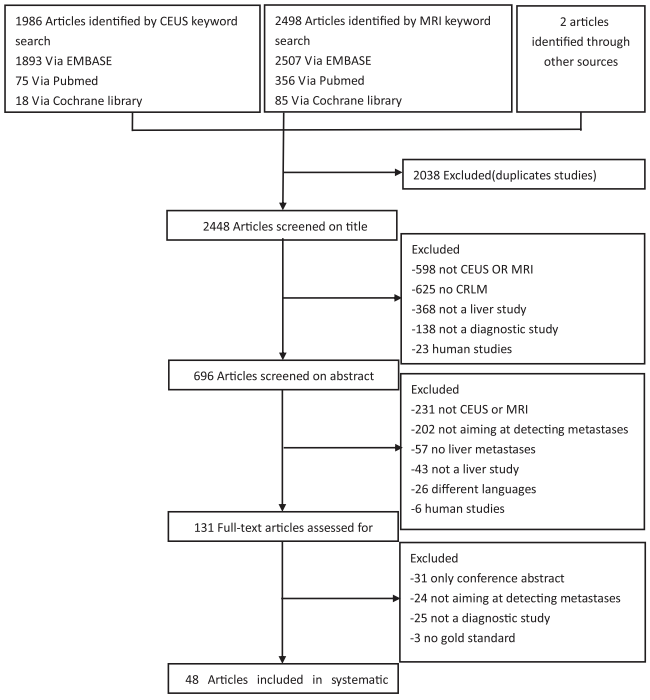


Fig. 1. Flow-chart for articles identified and analyzed in this meta-analysis for the detection of CRLMs.

3.2. Study design and patient characteristics

All of the included studies were performed at single centres or multiple centres, and were published between 2003 and 2018 for studies of CEUS, and between 2008 and 2018 for studies of DWI and CEMRI. Twenty-six studies (57%) were prospectively designed. A total of 3142 patients were included in the studies, comprising 1915 patients with 3361 lesions who underwent CEUS, 278 patients with 736 lesions who underwent DWI, 623 patients with 1172 lesions who underwent CEMRI, 264 patients with 534 lesions who underwent both CEUS and CEMRI, and 62 patients with 168 lesions who underwent both DWI and CEMRI. The median number of patients was 69, the mean age of patients was 61.5 years, and the male-to-female ratio was 1.5 (1901 males, 1241 females). There were 5871 CRLMs and the mean diameter was 20.5 mm. Further study and patient characteristics are summarized in Table 1.

The results of QUADAS-2 are presented in Fig. 2A. Although the quality of the included studies was high, QUADAS-2 identified several methodological shortcomings that might contribute to bias, especially regarding patient selection and the index test domains. The risk of bias regarding patient flow and timing mainly arose from the fact that more than half of the included studies used a combination of histopathological analysis, intraoperative observation, or follow-up imaging as reference standards, which may introduce verification bias.

3.3. Sensitivity estimates

Overall, 30, 15, and 38 datasets were retrieved for the CEUS, DWI, and CEMRI analyses, respectively, on a per-lesion basis. The overall sensitivity of CEMRI (91%; 95% CI: 89%, 93%) was slightly greater than that of CEUS (85%; 95% CI: 82%, 89%) and DWI (83%; 95% CI: 77%, 87%) when the sensitivity data were pooled from all of the included studies. The individual and summary estimates for the sensitivities of CEUS, DWI, and CEMRI are shown with forest plots in Fig. 3.

3.4. Sensitivity and specificity estimates

Although the sensitivity estimates were calculated for all studies, we decided to base the specificity estimates on studies in which the histopathological examination was the only reference standard because true negative and false positive results were not reported in most articles using a composite gold standard.

Because there were only two eligible datasets with DWI, we were unable to calculate sensitivity and specificity estimates for DWI.

Combined sensitivity and specificity analysis was performed in 27 datasets from eight articles about CEUS and CEMRI. For CEUS, the mean sensitivity and specificity were 86% (95% CI: 82%, 90%) and 91% (95% CI: 83%, 95%), respectively. For CEMRI, the mean sensitivity and specificity were 91% (95% CI: 86%, 94%) and 95% (95% CI: 88%, 97%), respectively. The pooled positive likelihood ratios for CEUS and CEMRI were 9.2 (95% CI: 4.9, 17.2) and 16.6 (95% CI: 7.8, 35.4), respectively. The pooled negative likelihood ratios for CEUS

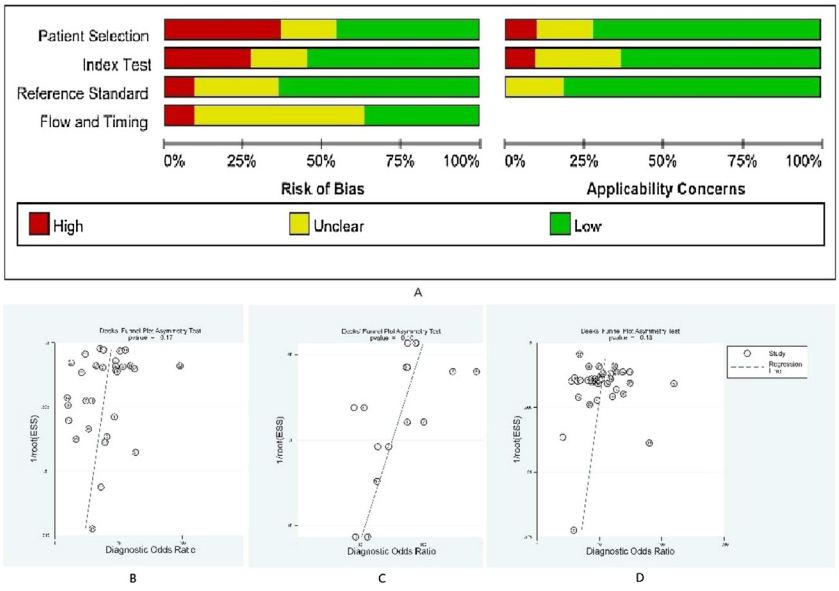


Fig. 2. A Risk of bias and applicability concerns. B, C, D Funnel plot for publication bias of CEUS, DWI, CEMRI.

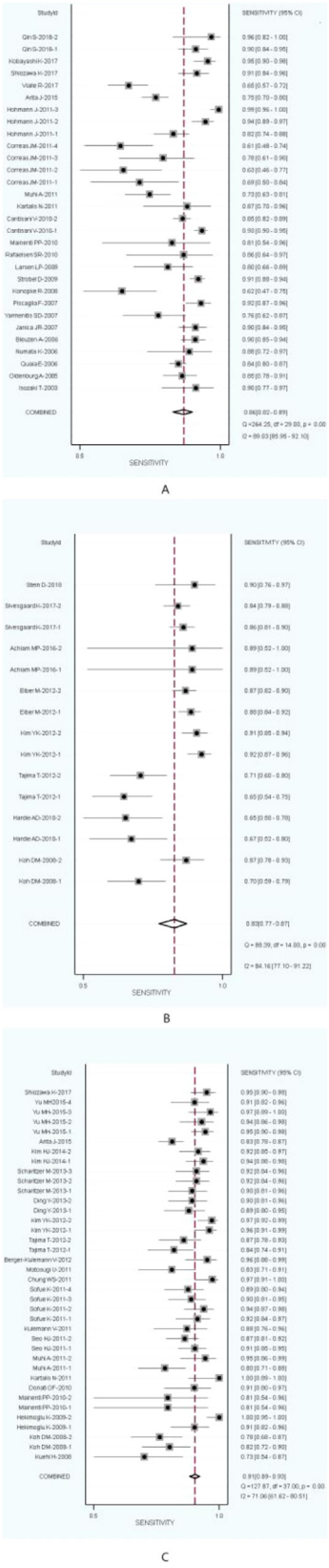


Fig. 3. A, B, C Overall sensitivity of CEUS, DWI and CEMRI.

and CEMRI were 0.15 (95% CI: 0.11, 0.20) and 0.10 (95% CI: 0.06, 0.15), respectively. The diagnostic odds ratio for CEUS and CEMRI were 61 (95% CI: 28, 133) and 170 (95% CI: 72, 398), respectively. The individual and summary estimates of sensitivity and specificity for CEUS and CEMRI are shown with forest plots in Fig. 4.

3.5. Subgroup analysis

The per-lesion sensitivity estimates for the individual subgroups are presented in Table 2. In datasets including only metastases <10 mm, the sensitivity of CEMRI (82%; 95% CI: 79%, 84%) was greater than those of CEUS (61%; 95% CI: 57%, 65%) and DWI (63%; 95% CI: 58%, 68%). In datasets including only metastases ≥10 mm, there were no significant differences in mean sensitivities between CEUS (93%; 95% CI: 91%, 95%), DWI (93%; 95% CI: 88%, 97%), and CEMRI (94%; 95% CI: 93%, 95%). The sensitivities of CEUS, DWI, and CEMRI were lower in prospective studies than in retrospective studies. We found some differences in sensitivities between the use of different contrast agents. In particular, the use of SonoVue in CEUS was associated with a greater per-lesion sensitivity than the use of Sonazoid (SonoVue: 88%; 95% CI: 86%, 89%; Sonazoid: 76%; 95% CI: 74%, 79%). The use of liver-specific contrast agents in CEMRI yielded a better per-lesion sensitivity than the use of other agents, with an estimate of 92% (95% CI: 90.7%, 93.0%). Interestingly, when histopathology was the only reference standard, the sensitivity of CEMRI was unchanged (91%; 95% CI: 89%, 92%) relative to the use of a composite standard (89%; 95% CI: 87%, 91%), whereas the sensitivity of CEUS was reduced (81%; 95% CI: 77%, 84% vs 86%; 95% CI: 85%, 87%).

3.6. Publication bias

Visual inspection of the three funnel plots for CEUS, DWI, and CEMRI suggests the data show a symmetrical distribution, indicating the absence of publication bias (Fig. 2B–D).

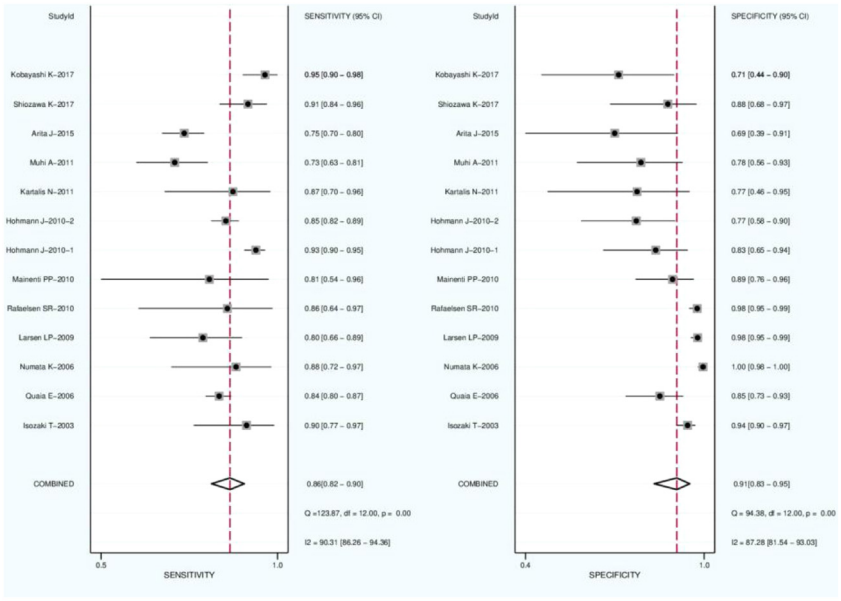
4. Discussion

In current clinical practice, patients with colorectal cancer undergo preoperative staging and follow-up evaluations via US because it is widely available and it does not use ionising radiation. The introduction of US contrast agents has increased the accuracy of US for detecting liver metastases substantially [44,46]. Second-generation contrast agents like SonoVue and Sonazoid have become mainstream contrast agents for use in the US because the microbubbles are less susceptible to destruction than earlier agents, providing adequate harmonic signals. SonoVue differs from the first-generation agents that comprise a low-solubility gaseous core of sulfur hexafluorane, which is covered by a phospholipid shell. SonoVue uses perfluoropropane or perfluorobutane as the gas core and a liposome or phosphatidyl serine as the outer membrane. Sonazoid behaves like SonoVue but has a longer half-life of >5 min after intravenous bolus injection. US contrast agents do not disperse into the extracellular space and can be used in patients with renal failure and patients allergic to contrast agents used in CT or MRI [56,57].

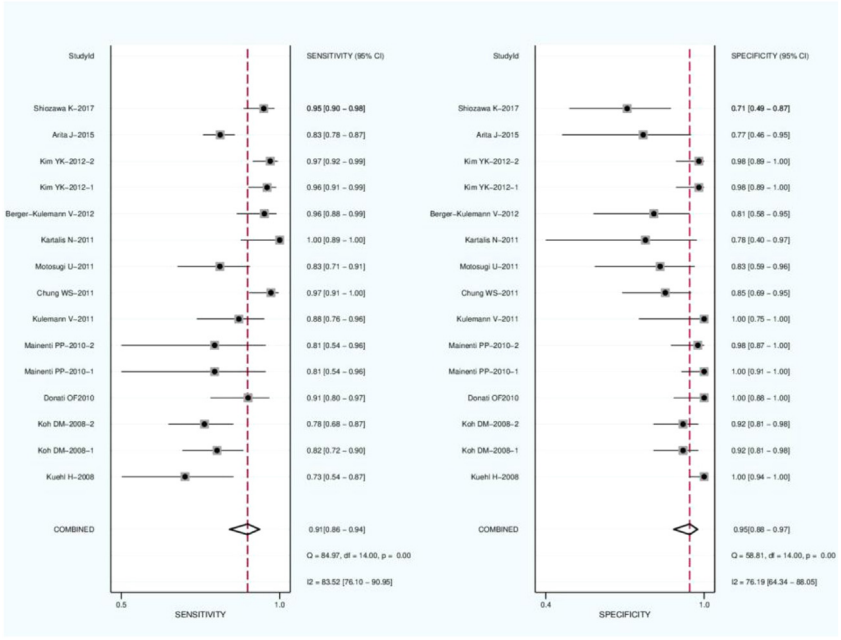
This meta-analysis, which is based on 47 articles with a large cohort of 3142 patients with nearly 6000 CRLMs, revealed that CEUS offered diagnostic ability comparable to that of DWI and CEMRI, particularly for lesions ≥10 mm.

Some regions of the liver may be blind spots for US, including the lateral segment of the left hepatic lobe near the stomach and segment S8 near the diaphragm. By contrast, the entire liver can be objectively observed by MRI, which may account for the higher sensitivity and specificity of the technique.

Regarding the effect of tumour size on the diagnosis of CRLMs, a confident diagnosis of CRLMs in subcentimeter hepatic nodules



A



B

Fig. 4. A, B Sensitivity and specificity of CEUS and CEMRI.

is considered unfeasible. This is consistent with our results, which showed that the sensitivity estimates were much lower for subcentimeter CRLMs than for larger lesions in CEUS (93% vs 61%), DWI (93% vs 63%), and CEMRI (94% vs 82%). For lesions ≥10 mm, the sensitivity estimates were comparable among CEUS (93%), DWI (93%), and CEMRI (94%), which suggests that CEUS may be the preferred imaging modality for the diagnosis of CRLMs. However, the maximum and minimum sensitivity of CEUS for detecting CRLMs of <10 mm were 83% and 32%, which indicates that the accuracy of CEUS is highly dependent on the examiner's expertise.

Most of the studies included in our meta-analysis used a composite reference standard. Interestingly, the subgroup analyses of the CEUS and CEMRI groups that only used histopathology as the gold standard provided similar results. Moreover, the accuracy was greater with Sonovue in CEUS (88% vs 76%) and with liver-specific contrast agents in CEMRI (92% vs 83%) compared with other agents. The study design also affected the diagnosis of CRLMs because the sensitivity estimates were lower in prospective studies than in retrospective studies for all three imaging modalities.

We assessed the quality of the selected studies using the QUADAS-2 tool. The low level of bias demonstrated using this tool suggests that our results can be extrapolated to most patients with liver metastases. The highest risk of bias was related to patient

Table 2
Subgroup analysis of CEUS, DWI and CEMRI.

Subgroup	Number of articles (number of data sets)	Sensitivity of CEUS	Sensitivity of CEMR	Sensitivity of DWI
All lesions	48 (83)	85.3% (95%CI, 84.2–86.4%)	90.1% (95%CI: 89.1–91.1%)	83.0% (95%CI: 77%, 87%)
Lesion size				
<10 mm	23 (42)	61.3% (95%CI, 57.4%, 65.1%)	81.8% (95%CI, 79.5%, 84.0%)	63.1% (95%CI, 58.2%, 68.3%)
>10 mm	22 (40)	93.1% (95%CI, 91.3%, 94.6%)	94.5% (95%CI, 93.2%, 95.6%)	92.9% (95%CI, 88.6%, 97.2%)
Gold standard(only with histopathological results)				
Yes	8 (11)	80.9% (95%CI, 77.3%, 84.1%)	90.9% (95%CI, 89.2%, 92.3%)	/
No	14 (25)	85.9% (95%CI, 84.7%, 87.1%)	89.1% (95%CI, 87.6%, 90.5%)	/
Contrast agent				
CEUS with SonoVue	16 (20)	87.8% (95%CI, 86.5%, 89.0%)	/	/
CEUS with Sonazoid	4 (10)	76.4% (95%CI, 73.8%, 78.8%)	/	/
CEMR with hepatospecific contrast agents				
Yes	12 (29)	/	91.9% (95%CI, 90.7%, 93.0%)	/
No	6 (9)	/	83.0% (95%CI, 80.0%, 85.7%)	/
Study design				
Retrospective studies	15 (29)	91.1% (95%CI, 87.7%, 93.9%)	92.1% (95%CI, 91.3%, 93.9%)	84.3% (95%CI, 76.1%, 90.7%)
Prospective studies	15 (32)	82.4% (95%CI, 81.0%, 83.7%)	87.2% (95%CI, 85.4%, 88.9%)	80.8% (95%CI, 74.4%, 85.3%)

flow and timing because the interval between imaging and surgical resection was not reported in most of the studies.

Finally, we observed considerable heterogeneity for CEUS, DWI, and CEMRI that was driven by the variability in study design characteristics, patient characteristics (e.g., disease severity and lesion size), technical aspects (e.g., use of contrast agent and different diagnostic thresholds), and the reference standard used. To overcome this heterogeneity, we used the random effects model. Because the 95% CIs were not relatively narrow, we believe that these results are clinically relevant. However, the heterogeneity in this type of diagnostic study remains a concern.

To our knowledge, this is the first comprehensive meta-analysis evaluating the diagnostic abilities of CEUS, DWI, and CEMRI for detecting CRLMs. However, this analysis has two limitations. First, combined CEUS and MRI (including unenhanced MRI and CEMRI), which evaluates the complementary role of both modalities, was not included in our study. Second, because the number of included studies was small and there was incomplete stratification of included samples, the sources of heterogeneity in the analysis were limited.

5. Conclusion

CEUS had a diagnostic ability comparable to that of DWI and CEMRI, particularly for lesions ≥10 mm in diameter. More rigorous and well-designed studies are needed to confirm these findings.

Conflict of interest statement

None declared.

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