Original Article

Improved sensitivity and positive predictive value of contrast-enhanced intraoperative ultrasound in colorectal cancer liver metastasis: a systematic review and meta-analysis

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Background: Surgery is an effective treatment for improving the survival rate of patients with colorectal cancer liver metastases (CRLM). However, accurately determining the resection margin of liver lesions during surgery remains challenging. Therefore, this study aimed to evaluate the sensitivity and predictive value of intraoperative contrast-enhanced ultrasound (CE-IOUS) in CRLM patients undergoing surgery.

Methods: We performed a literature search of the PubMed, Cochrane Central Register of Controlled Trials, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), Wanfang, and Weipu databases using the following search terms: metastatic liver cancer, colorectal cancer, sensitivity, contrast-enhanced intraoperative ultrasound, CE-IOUS, colorectal liver metastases, and CRLM. The search period was set from the date of establishment of the database to September 2021. Quality assessment of diagnostic accuracy studies 2 (QUADAS-2) recommended by the Cochrane Collaboration was used to assess the methodological quality of the included studies, and network meta-analysis was performed using Stata 15.0 software.

Results: A total of 10 articles met the inclusion criteria. The meta-analysis results showed that the overall sensitivity and specificity of CE-IOUS were 0.96 [95% confidence interval (CI), 0.95–0.97] and 0.75 (95% CI, 0.70–0.80), respectively. The overall sensitivity and specificity of IOUS were 0.84 (95% CI, 0.82–0.86) and 0.82 (95% CI, 0.77–0.87), respectively. The area under the summary receiving operating characteristic (SROC) curves (AUCs) of CE-IOUS and IOUS were 0.9753 and 0.8590, respectively. The odds ratio (OR) and 95% CI of CE-IOUS changed the surgical margin were 0.205 and 0.071–0.465, P=0.000, the difference was statistically significant.

Discussion: Based on the results of this meta-analysis, CE-IOUS improved the sensitivity and predictive value of CRLM detection compared with IOUS, and is more suitable for intraoperative planning of surgical margins. At present, it is the most sensitive imaging method available, and is recommended for use during liver resection to provide doctors with more reliable information during surgery.

Keywords: Contrast-enhanced intraoperative ultrasound; contrast-enhanced intraoperative ultrasound (CE-IOUS); colorectal liver metastases; colorectal cancer liver metastasis (CRLM); meta-analysis

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Introduction

Colorectal cancer (CRC) has become one of the deadliest tumors and has a poor prognosis. Hepatectomy is the only possible cure for patients with colorectal cancer liver metastasis (CRLM), and the postoperative recurrence rate is as high as 70% (1-3). The benefits of surgical resection for patients with liver metastases from CRC have been fully confirmed (4). Hepatectomy combined with interventional imaging ablation is the only treatment that can provide these patients with long-term survival (1,5-9).

The surgical treatment of liver metastasis is guided by imaging to determine the characteristics of the liver lesions. Therefore, intraoperative imaging methods must provide high sensitivity and specificity for the detection and characterization of liver lesions. Clinicians are unanimously committed to exploring suitable intraoperative imaging monitoring methods. In the case of CRLM, computed tomography (CT), magnetic resonance imaging (MRI) using extracellular contrast agents, and fluorodeoxyglucose positron emission tomography have been shown to have sensitivity (74.4%, 80.3%, and 81.4% respectively) (10). Recently, it has been reported that the use of liver-specific gadolinium (Gd-EOB-DTPA) alone or in combination with diffusion-weighted imaging (DWI) can provide good diagnostic performance and high sensitivity (90%), which can be used to detect CRLM (11,12). The incidence of liver metastasis of colorectal cancer is as high as 20–35% (8,9,13,14), and it is very necessary to find a more sensitive auxiliary examination method.

Contrast-enhanced intraoperative ultrasound (CE-IOUS) is a new imaging tool that can assess liver parenchyma in real time during surgery, allowing surgeons to make better adjustments intraoperatively (7). During CE-IOUS, a microbubble-based ultrasound contrast agent is administered to the patient to enable angiography of small-diameter blood vessels (7). Therefore, CE-IOUS can provide surgeons with dynamic real-time imaging information of CRLM with abnormal blood vessels. In addition, isoechoic liver lesions, which account for approximately 35% of CRLM (8), are easily missed on IOUS, but can be detected using contrast agents. As the number of studies evaluating the feasibility of CE-IOUS increases, it is necessary to investigate whether the results are at least equal to or better than other imaging methods. This meta-analysis aims to evaluate the possible benefit of CE-IOUS in the differential diagnosis of metastatic liver disease with adequate sensitivity and specificity. We present the following article in accordance with the PRISMA reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-881/rc).

Methods

Search strategy

We performed a literature search of English biomedical databases including PubMed, Cochrane Central Register of Controlled Trials, Embase, Web of Science, and major Chinese biomedical databases including CNKI, Wanfang, and Weipu. Other search methods include website, organization and citation searching. The following search terms were used: metastatic liver cancer, colorectal cancer, sensitivity, contrast-enhanced intraoperative ultrasound, CE-IOUS, colorectal liver metastases, and CRLM. The retrieval time was from the date of establishment of the database to September 2021.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (I) patients diagnosed with CRLM; (II) patients who underwent CE-IOUS, intraoperative ultrasound (IOUS), MRI, or preoperative imaging included in CT or MRI for the detection of liver metastasis, as well as histopathology (surgery, biopsy) or intraoperative ultrasound evaluation tool for examination/manual palpation; (III) The research has sufficient data to calculate the sensitivity and specificity of the imaging technique; (IV) studies with sample sizes of at least 10 patients; (V) studies is published in English or Chinese; and (VI) studies involving a comparison between CE-IOUS and other imaging studies. We excluded studies that only investigated the sensitivity and specificity of MRI and/or CT instead of CE-IOUS or IOUS.

Paper screening and data extraction

According to the pre-established inclusion criteria, two review authors independently reviewed the titles and abstracts of all retrieved articles. When the review opinions were inconsistent, a third reviewer joined the review. The two review authors independently extracted data from the articles obtained after screening, including the first author, country, year of publication, ultrasound machine, contrast agent, as well as the true-positive, true-negative, false-positive, and false-negative forms. Disagreements in the data extraction process were resolved through discussion until a consensus was reached. If the required data was

unclear or the full text was not provided, and the relevant data could not be obtained by contacting the author, the article was excluded. The included studies evaluated the value of CE-IOUS compared with MRI, and performed a patient-by-patient analysis to evaluate the value of CE-IOUS on surgical methods compared with preoperative MRI for CRLM.

Quality assessment

The included articles use the Quality assessment of diagnostic accuracy studies 2 (QUADAS-2) research quality assessment scale recommended by the Cochrane Collaborative Organization to evaluate the methodological quality of the research. The evaluation scope included patient selection, index testing, reference standards, as well as flow and time evaluation. Each indicator was evaluated based on the risk of bias, and the first three indicators were evaluated based on applicability issues. The methodological quality of each study was rated as "low risk", "high risk", or "unclear".

Statistical analysis

All analyses were based on each lesion data. We used bivariate meta-analytical methods to aggregate weighted estimates of sensitivity and specificity, which were the main outcome indicators, and the summary receiver operating characteristics (SROC) models with 95% confidence intervals (CI) was used to establish prediction zone. A fixed-effects model based on the degree of heterogeneity was used to aggregate the data from each study. The Chi-square test and Higgins I^2 test were used to assess the heterogeneity of the included studies; $P<0.05$ or $I^2=50\%$ was considered to indicate significant heterogeneity. And a sensitivity analysis was carried out according to the Cochrane systematic review method. All analyses were performed using Stata 15.0 software (StataCorp LLC, College Station, TX, USA), and $P<0.05$ was considered statistically significant.

Results

Search results and study characteristics

The database search initially retrieved 739 records, and 32 unavailable records were eliminated. After screening, 336 articles remained, including 294 English articles and 42 Chinese articles. After excluding low quality studies, articles with unsatisfactory requirements, those with incomplete data, as well as reviews and case reports, 10 articles were included for analysis. And the website, organization, and citation search did not get articles that met the requirements. The specific literature retrieval process is shown in *Figure 1*. Among the 10 included articles, the publication period as from 2006 to 2019. The basic data of the included studies, such as the first author, country, publication year, journal, ultrasound machine, and contrast agent, were extracted. The basic characteristics of the included articles are shown in *Table 1*.

Risk of bias and applicability judgments

All articles had a low risk of patient selection and index test bias. As for the reference standard bias risk, one article had an unclear risk, and five articles had a low risk. Two articles had a low risk of flow and time bias, while four articles had an unclear risk. As for applicability bias, one article had a high risk of patient selection bias, and five articles had a low risk of patient selection bias. The index test bias risk and reference standard bias risk of all articles are low. The risk of bias is shown in *Figure 2*.

Meta analysis results

Overall analyses of CE-IOUS

Meta regression analysis showed that the pooled sensitivity of CE-IOUS sensitivity and predictive value in CRLM surgery was 0.96 (95% CI: 0.95–0.97) (*Figure 3*), and the pooled specificity was 0.75 (95% CI: 0.70–0.80) (*Figure 4*). In addition, the sensitivity and specificity I^2 were 78.7% and 85.9%, respectively, and thus, the random effects model was used. The SROC showed a higher accuracy (AUC =0.9753) (*Figure 5*); the closer the AUC is to 1.0, the higher the sensitivity and predictive value of CE-IOUS in CRLM surgery, and the more beneficial it is for monitoring the liver.

Overall analyses of IOUS

Meta regression analysis showed that the pooled sensitivity of IOUS sensitivity and predictive value for CRLM was 0.84 (95% CI: 0.82–0.86) (*Figure 6*), and the pooled specificity was 0.82 (95% CI: 0.77–0.87) (*Figure 7*). In addition, the sensitivity and specificity I^2 were 96.1% and 92.6%, respectively, so the random effects model was used. SROC showed higher accuracy (AUC =0.8590) (*Figure 8*); the closer the AUC is to 1.0, the higher the sensitivity and predictive value of IOUS in CRLM surgery, and the more favorable it is for surgeons to perform surgery.

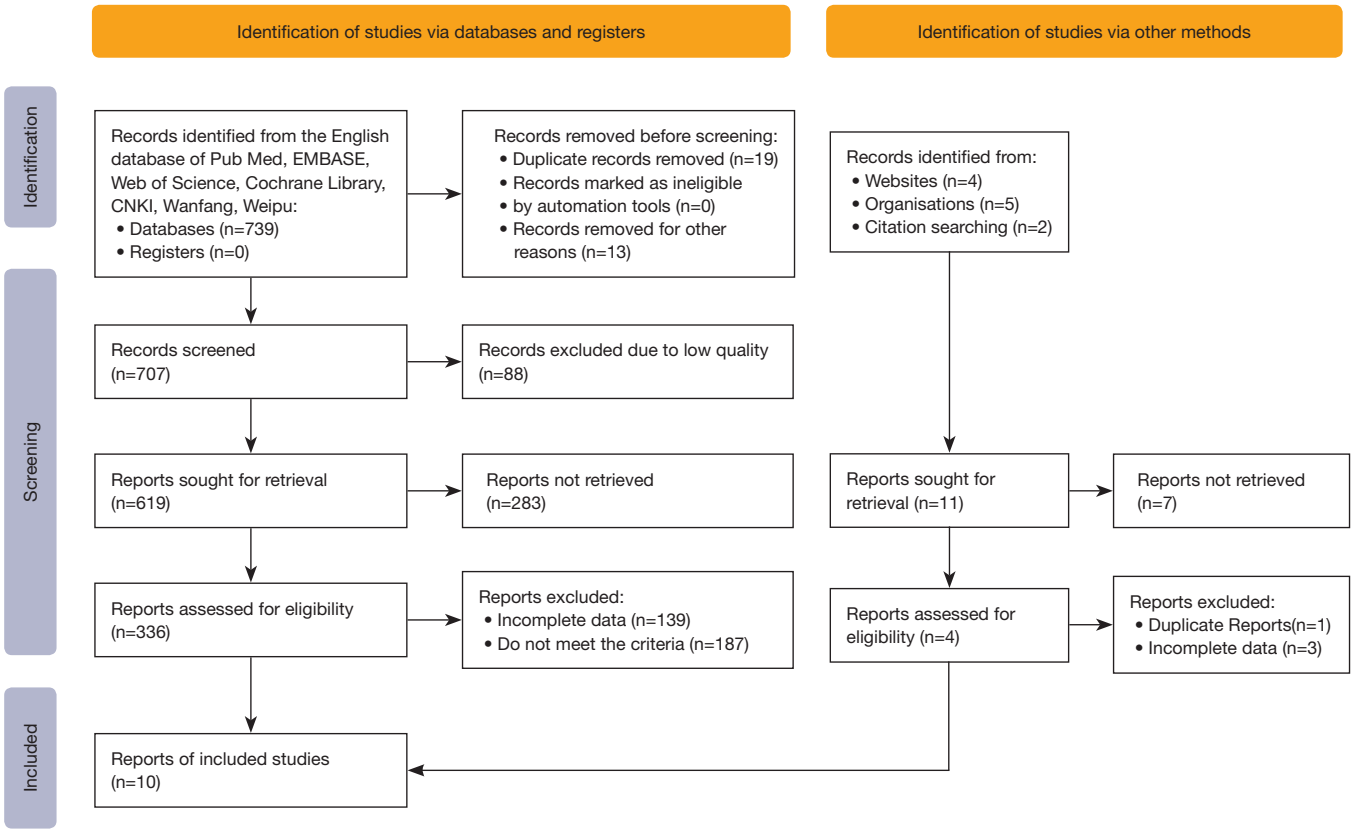

Figure 1 Flow diagram of the search, screening, and inclusion process.

Table 1 Basic characteristics of the study articles.

Author	Country	Year	Journal	Contrast agent	Ultrasound machine
Arita *et al.* (15)	Japan	2015	*Ann Surg*	Sonazoid	Toshiba, Aplio MX
Desolneux *et al.* (16)	France	2019	*Eur J Surg Oncol*	SonoVue	BK Medical, Profocus 2202
Hoareau *et al.* (17)	France	2016	*World J Surg*	SonoVue	Toshiba, Aplio MX
Leen *et al.* (18)	Germany	2006	*Ann Surg*	SonoVue	Philips, HDI 5000
Oba *et al.* (19)	Japan	2018	*HPB (Oxford)*	Sonazoid	Toshiba, Aplio MX
Ruzzenente *et al.* (20)	Italy	2013	*J Gastrointest Surg*	SonoVue	Aloka, ProSound a10
Takahashi *et al.* (21)	Australia	2012	*Br J Surg*	Sonazoid	Aloka, ProSound a10
Torzilli *et al.* (22)	Italy	2014	*HPB (Oxford)*	SonoVue	Aloka a10/Esaote MyLab Twice
Schulz *et al.* (23)	Norway	2012	*Acta Radiol*	SonoVue	Acuson Sequoia TM 512
Uchiyama *et al.* (24)	Japan	2010	*World J Surg*	SonoVue	ProSound a10

CE-IOUS surgical resection margin changes

From the above results, it can be seen that CE-IOUS has improved the sensitivity and predictive value of CRLM compared with IOUS. Therefore, we further analyzed the CE-IOUS surgical plan changes, and four articles were included in the analysis. The analysis results showed that I^2=46.7%, suggesting that this indicator is homogeneous, so the fixed effects model was used for combined analysis.

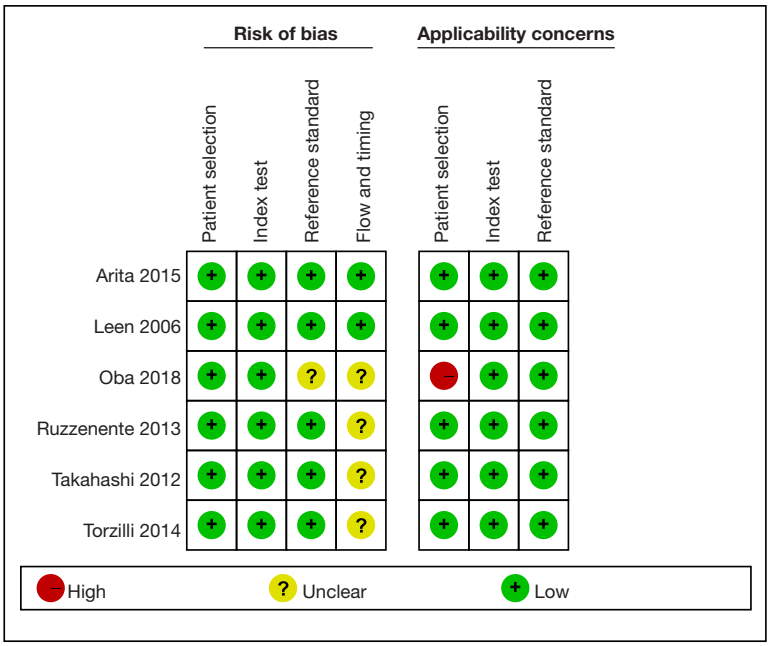

Figure 2 Literature quality evaluation details.

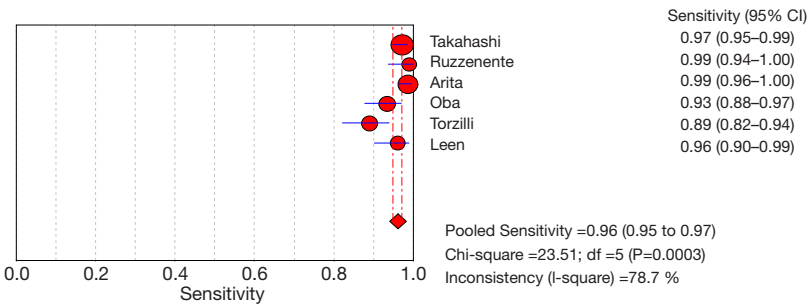

Figure 3 Sensitivity of studies: forest plot of sensitivities of six studies. Statistical method: inverse variance of the random effects model. CI, confidence interval.

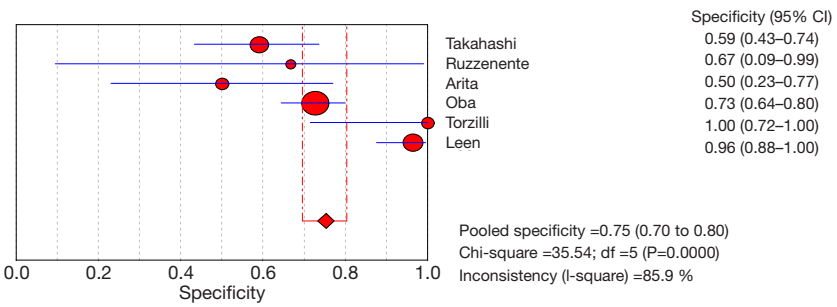

Figure 4 Specificity of studies: forest plot of specificities of six studies. Statistical method: inverse variance of the random effects model. CI, confidence interval.

AUC. Therefore, CE-IOUS will achieve a higher detection rate than preoperative imaging and conventional IOUS, and further surgical margin changes. This analysis results

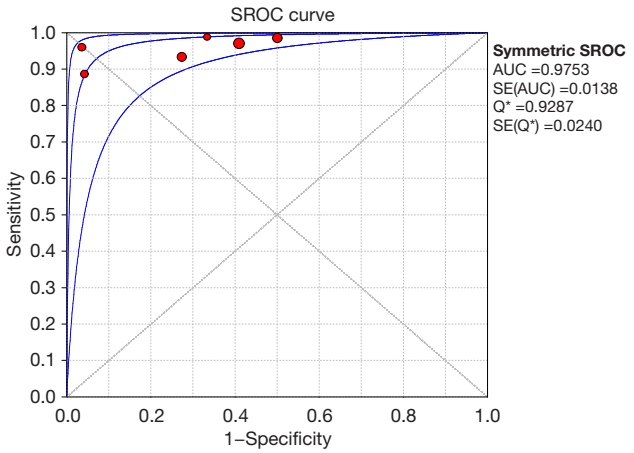

Figure 5 Summary receiving operation characteristic (SROC) curve for individual studies on CE-IOUS improve the sensitivity and predictive value in colorectal cancer liver metastasis. AUC, area under the curve; SE, standard error.

As shown in *Figure 9*, the combined effect size odds ratio (OR) was 0.205 (95% CI: 0.071–0.465). The result of the comprehensive effect size test was P=0.000, which indicated that CE-IOUS will change the surgical plan, and the difference was statistically significant.

Risk of bias

The quality assessment found that all of the included articles had a low risk of patient selection and research index test bias. One article had an unclear risk of reference standard bias (19), and five articles had a low risk (15,18,20-22). Also, two studies had a low risk of flow and time bias (15,18), and four articles had an unclear risk (19-22). Regarding the risk of applicability bias, except for one article with a high risk of patient selection bias (19), while the remaining 5 articles had a low risk of patient selection bias (15,18,20-22). The index test bias and reference standard bias of all articles were low risk, as shown in *Figure 10*.

Discussion

Surgical removal of the tumor is currently the best choice

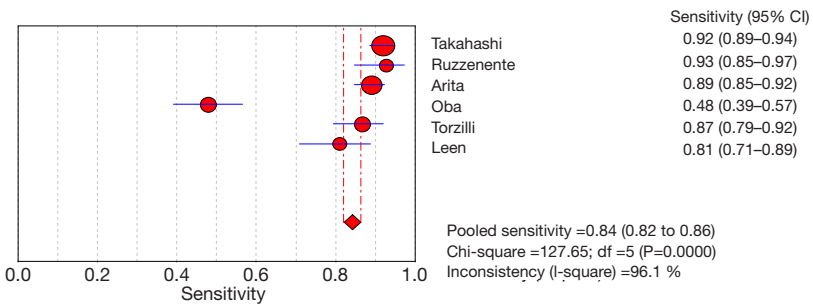

Figure 6 Sensitivity of studies: forest plot of sensitivities of six studies. Statistical method: inverse variance of the random effects model. CI, confidence interval.

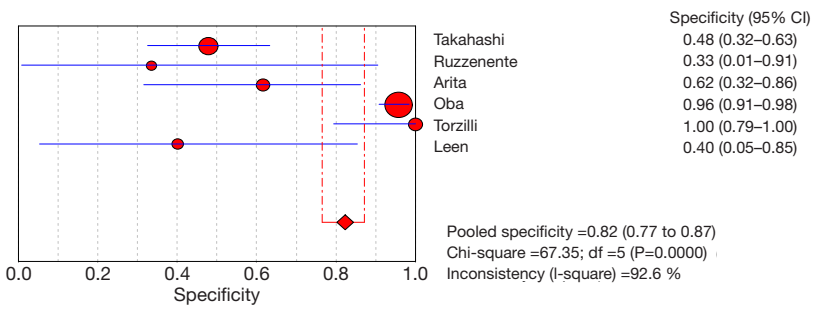

Figure 7 Specificity of studies: forest plot of specificities of six studies. Statistical method: inverse variance of the random effects model. CI, confidence interval.

for the long-term survival of CRLM patients; thus, an optimal surgical plan must be developed before the operation (25). The success of the procedure depends on the preoperative detection of CRLM and the intraoperative localization of all intrahepatic and extrahepatic tumor deposits. Although there are now multimodal preoperative diagnostic methods, CRLM imaging remains challenging.

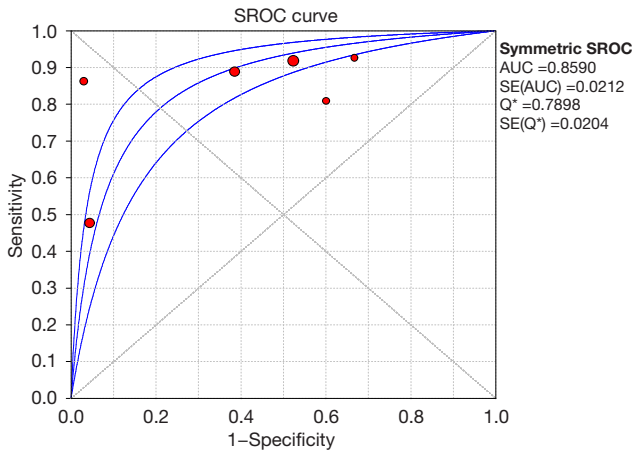

Figure 8 Summary receiving operation characteristic (SROC) curve for individual studies on IOUS improve the sensitivity and predictive value in colorectal cancer liver metastasis. AUC, area under the curve; SE, standard error.

Owing to its high resolution, IOUS plays an important role as the last diagnostic method before liver resection. It has the highest sensitivity (94–100%) and specificity (95–100%) in terms of the number and location of liver lesions, as well as their relationship with major blood vessels and biliary structures (26-29). Increasing this will have an impact on the resection margin, intraoperative blood loss, and surgical outcome (30).

Compared with most imaging methods including IOUS, CE-IOUS uses perfluorobutane microbubbles for intraoperative examination, and is more sensitive to the diagnosis of CRLM. Improving the contrast between the tumor and surrounding parenchyma is a very important advantage (31,32). The policy of removing multiple liver metastases with the smallest margin has been widely accepted by surgeons (33). The analysis results in this study showed that CE-IOUS does change the pre-planned resection line, mainly because visualization can monitor whether there is vascular invasion. If vascular invasion is found, the resection line of the surgical plan is changed. This feature is crucial for multiple non-anatomical limited liver resections, where most of the main intrahepatic blood vessels are preserved. The more CRLMs present, the more tumors can be detected by CE-IOUS alone (32,34).

Our analysis results showed that CE-IOUS has better sensitivity and specificity than IOUS, as well as a higher

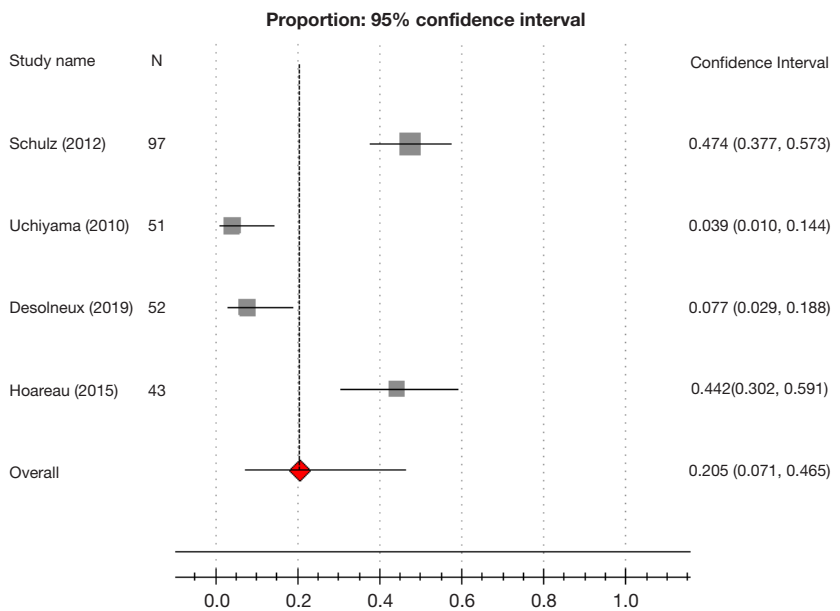

Figure 9 Forest plot of surgical plan changes. We compared and analyzed whether CE-IOUS has an impact on surgical planning. Statistical method: Der-Simonian Laird of the fixed effects model (OR and 95% CI). CE-IOUS, contrast-enhanced intraoperative ultrasound.

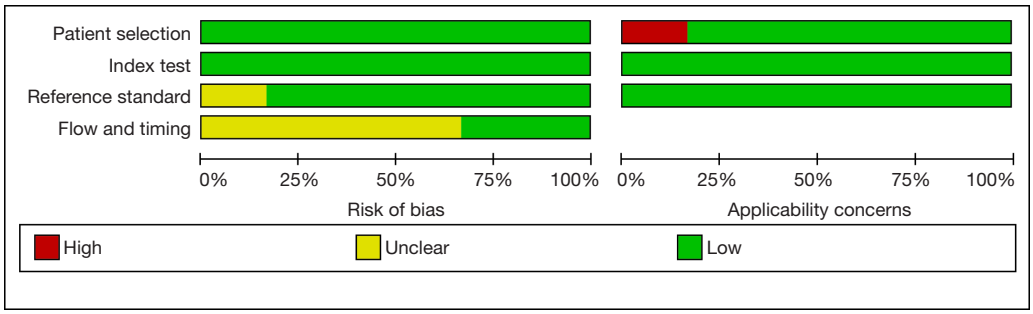

Figure 10 The intensity and distribution of the quality risk of the articles included in the study.

have also been confirmed by other scholars (32). In theory, a true comparison of diagnostic accuracy can only be made by keeping researchers ignorant of previous imaging results. However, in actual clinical work, surgeons will often have a clear understanding of imaging before and during surgery, and because of this, doctors will obtain more clinical data through pre- and post-operative contrast imaging.

The current meta-analysis has some inherent limitations, including selection bias, research heterogeneity, and population differences. Firstly, due to differences between eligible studies, an important bias is the inclusion of patients suspected of having CRLM and those with confirmed CRLM. Another limitation is that the number of studies eligible for this review was very small, especially in the subgroup analysis. It is necessary to conduct multi-center and large-sample studies to confirm the uniform diagnosis of CRLM patients, in order to further verify the sensitivity and predictive value of CE-IOUS in CRLM.

Conclusions

Based on the results of this meta-analysis, CE-IOUS has improved the sensitivity and predictive value of CRLM detection compared with IOUS, and is more suitable for the intraoperative planning of surgical margins. At present, it is the most sensitive imaging method, and it is recommended for use during liver resection to provide doctors with more reliable information during surgery. However, further multi-center, large-sample controlled studies should be conducted in the future to provide more reliable data for the clinical application of CE-IOUS.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-881/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-21-881/coif). The authors have no conflicts of interest to declare.

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

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