Systematic Review and Meta-Analysis

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Diagnostic value of diffusion-weighted imaging/magnetic resonance imaging for peritoneal metastasis from malignant tumor

A systematic review and meta-analysis

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Abstract

Background: Previous meta-analyses examined either multiple tools for the diagnosis of peritoneal metastases (PMs), but not diffusion-weighted imaging (DWI), or included only 1 tumor type. This study aimed to determine the summary diagnostic value of DWI/magnetic resonance imaging in determining PMs originating from various tumors.

Methods: PubMed, Embase, and Cochrane library were searched for available papers up to 2019/12. Pooled estimates for sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and accuracy were calculated using random-effects models.

Results: Ten studies were included and could be used to calculate the pooled sensitivity and specificity. The pooled sensitivity of DWI for PMs was 89% (95% confidence interval [CI]: 83%–93%). The pooled specificity was 86% (95% CI: 79%–91%). When considering only the retrospective studies, the pooled sensitivity of DWI for PMs was 85% (95% CI: 81%–89%). The pooled specificity was 84% (95% CI: 72%–92%). When considering only the studies about gastrointestinal tumors, the pooled sensitivity of DWI for PMs was 97% (95% CI: 68%–100%). The pooled specificity was 86% (95% CI: 69%–95%). No publication bias was observed (P=dd.27).

Conclusion: DWI magnetic resonance imaging is highly sensitive and specific for the detection of PMs from various abdominal cancers.

Abbreviations: CI = confidence interval, CT = computed tomography, DWI = diffusion-weighted imaging, MRI = magnetic resonance imaging, PET = positron emission tomography, PMs = peritoneal metastases.

Keywords: diffusion magnetic resonance imaging, meta-analysis, peritoneal neoplasms, peritoneal neoplasms/secondary, sensitivity, specificity

1. Introduction

Peritoneal metastases (PMs) are a major clinical issue in patients with abdominal cancers. Indeed, PMs are found in 10% and 25% of patients with primary and recurrent colorectal cancer, respectively.[1] About 60% to 80% of patients with ovarian cancers are diagnosed at an advanced stage and display PM and/or distant metastases.[2] In all cases, the presence of PMs is associated with poor survival[2–4] and may change the treatment strategy drastically.[5–7]

A major problem in treating PMs originating from the various intra-abdominal tumors (eg, gastric, colorectal, and ovarian) is how to identify these malignant implants as early as possible in order to stage the patients accurately and to select those patients who are eligible to cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy. The classical and imaging diagnostic tools include laparoscopy, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)-CT. Laparoscopy is highly invasive and can easily miss gross lesions that are hidden by other anatomical structures.[8] CT is easily accessible, has a fast image acquisition time, and allows reformation at multiple planes, but sensitivity is highly variable (at 25%–100%), while specificity is relatively high (78%–100%).[9] PET-CT has 78% to 97% sensitivity and 55% to 90% specificity, but the risk of false-negatives is high for small lesions, and the risk of false-positive is high in the presence of inflammatory noncancerous lesions.[9]

Conventional MRI is equivalent to CT for the detection of peritoneal lesions >1 cm, but the use of fat-suppression and delayed gadolinium enhancement improved the sensitivity of MRI to lesions of 5 mm.[9] Diffusion-weighted imaging (DWI) is a type of MRI based on the generation of signal contrast based on

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LD and KL contributed equally to this work.

No additional data are available.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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the differences of Brownian movements of water molecules. This method revolutionized MRI by allowing the observation of very small anatomical structures.[10] DWI allows diffusion tensor imaging, a new paradigm that allows the imaging of highly-structured fibrous structures.[10] The most common use of DWI is in the diagnosis of stroke,[11] but it is also used in oncology. DWI allows imaging with striking contrast of highly-cellular structures such as tumors, metastases, and positive lymph nodes.[10] In addition, DWI can show responses of lesions to chemotherapy before the lesion actually starts to shrink.[10] The high cellular content of tumors due to high division rates will restrict the diffusion of water, and those lesions will appear with a high DWI signal.[12] Previous meta-analyses examined either multiple tools for the diagnosis of PMs but not DWI or included only 1 tumor type.[13–15]

Therefore, the present meta-analysis was designed to determine the summary diagnostic value of DWI/MRI in determining PMs originating from various tumors. The results could provide some evidence for the use of this imaging modality for the detection of PMs.

2. Method

All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

2.1. Literature search

This meta-analysis was strictly carried out according to the preferred reporting items for systematic reviews and meta-analyses guidelines. The relevant articles were searched using the Population, intervention, comparison, and outcome principle,[16] followed by screening on the basis of inclusion and exclusion criteria. The extracted data, including basic characteristics and end-point data, were reviewed by 2 different investigators according to a pre-specified protocol.

PubMed, Embase, and Cochrane library were searched for available papers up to 2019/12 using the MeSH terms "Peritoneal Neoplasms," "Peritoneal Neoplasms/secondary," and "Diffusion Magnetic Resonance Imaging," as well as using relevant keywords.

To be eligible to this meta-analysis, a study had to include patients with peritoneal metastasis originating from abdominal tumors, in whom DWI was used for the evaluation of peritoneal lesions compared with the gold standard of surgical pathological examination; in addition, the study could be either a cohort study or a randomized control trial. The language was restricted to English.

2.2. Data extraction and quality assessment

The selection and inclusion of studies were performed in 2 stages by 2 independent reviewers (Li Dong and Kuo Li). This included the analysis of the titles and abstracts, followed by the full texts. Disagreements were resolved by discussion with a third reviewer (Taisong Peng).

The study characteristics were extracted from each included study: year of publication, study design, country, inclusion criteria, the time between imaging and reference standard (histopathological examination), abnormal regions/sites, and the number of true positives, true negatives, false positives, and false negatives. The extracted patient characteristics included the number of patients, age, sex, and information about the primary tumor.

If a study included 2 independent investigators, the results of both investigators were extracted and analyzed. The values of the best set of the 2 were used for the primary analysis, while the worse results of the 2 investigators were presented as Supplemental Digital Content, http://links.lww.com/MD/F571, http://links.lww.com/MD/F572, http://links.lww.com/MD/F573, http://links.lww.com/MD/F574.

The QUADAS 2 tool (Quality Assessment of Diagnostic Accuracy Studies) was used to assess the methodological quality of the included primary studies and to detect potential bias.

2.3. Summary measures

The primary endpoint was to assess the per-patient diagnostic accuracy of DWI/MRI in detecting PM.

2.4. Statistical analysis

The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and accuracy were calculated to assess the diagnostic value of MRI for PM. Sensitivity and specificity were estimated as the weighted average according to the sample size of each study. For the meta-analysis, the effect size (reported as the Z value) and the heterogeneity among studies using the Higgins I^2 test and the Cochran Q test. I^2 of <25%, 25% to 50%, and >50% were considered as low, moderate, and high heterogeneity, respectively. The I^2 indicates the variability (in %) of the effect estimated being explained by heterogeneity rather than by chance. If P was <.10 for the Cochran test or I^2 >50%, a random-effects model was applied; otherwise, a fixed-effect model was used. The sensitivity and specificity of each included study were used to plot the summary receiver operating characteristics SROC curves and calculate the area under the SROC curve, with 95% confidence interval (CI). Because publication bias is a concern for meta-analyses, the Deeks' funnel plot asymmetry test was used, with $P<.10$ indicating statistical significance. The statistical analyses were carried out using STATA SE 14.0 (StataCorp, College Station, TX).

3. Results

3.1. Literature search and study selection

Figure 1 summarizes the search process. A total of 309 papers were identified from PubMed, Embase, and Cochrane library. Forty-five duplicates were excluded, and 264 papers were screened; 222 were excluded because of the study type or others; 42 full-text papers were reviewed, and 32 were excluded for study characteristics. Finally, 10 studies were included in the present meta-analysis[7,17–25] (Table 1). The meta-analysis included 353 patients (range, 19–60/study). There were 6 retrospective studies. There were 4 studies on gastrointestinal cancers.

Table 2 presents the QUADAS 2 analysis. One study showed an item at a high risk of bias,[20] and 1 study showed 1 item at a high risk of bias and another with an unclear risk.[23] All other studies were at low risk of bias.

3.2. Quantitative synthesis of diagnostic accuracy

All 10 studies[7,17–25] could be used to calculate the pooled sensitivity and specificity (Fig. 2 and Supplemental Digital Content 1, http://links.lww.com/MD/F571). The pooled sensitivity of DWI for PMs was 89% (95%CI: 83%–93%). Heterogeneity was observed ($P<.01$, $I^2=72.8\%$). The pooled specificity was 86% (95% CI: 79%–91%). Heterogeneity was observed

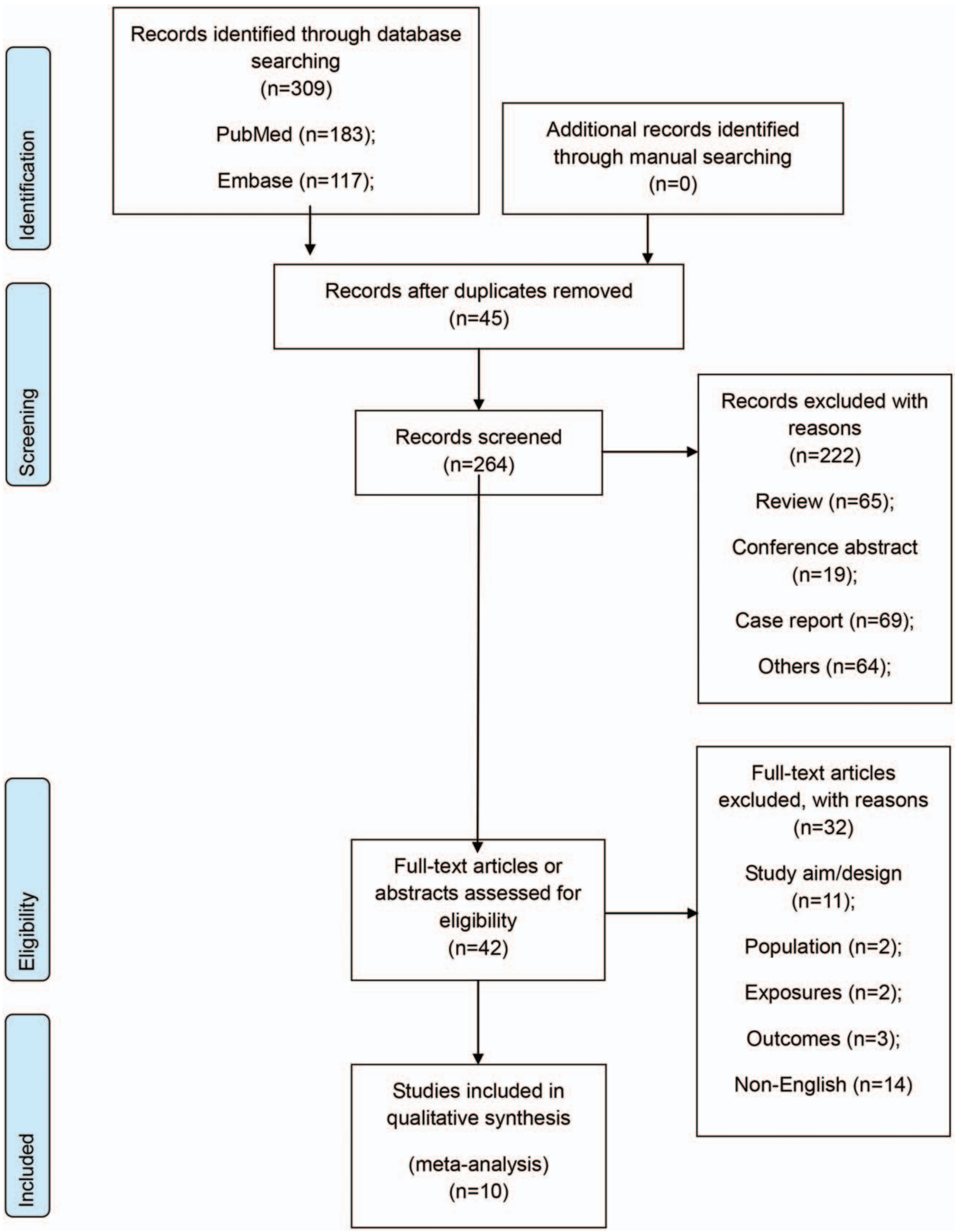

Figure 1. Flowchart of the search process.

($P<.01$, $I^2=83.0\%$). Figure 3 (and Supplemental Digital Content 2, http://links.lww.com/MD/F572) presents the SROC analysis. The pooled positive likelihood ratio of 6.53 (95% CI: 4.24–10.07). Heterogeneity was observed ($P<.01$, $I^2=75.4\%$). The pooled negative likelihood ratio of 0.13 (95% CI: 0.09–0.19). Heterogeneity was observed ($P<0.01$, $I^2=70.7\%$) (Fig. 4

Table 1

Characteristics of the studies included in this meta-analysis.

Study	Design	Sample size	Sex Female, n (%)	Age Years, mean or median	Country	Inclusion criteria	Time gap	Abnormal regions/ sites	Standard of reference
van't Sant, 2019[17]	Prospective	49	26 (53%)	62±10	Netherlands	Proven colorectal cancer and suspected or confirmed PM	16.4 (1–42) d	13	Laparoscopy or exploratory laparotomy
Garcia Prado, 2019[18]	Prospective	50		56±13	Spain	Suspected diagnosis of a primary or recurrent ovarian carcinoma	12 (37) d	13	Pathologically-proven surgical standard of reference
Engbersen, 2019[19]	Prospective	25		62±9	Netherlands	Advanced stage ovarian cancer (FIGO stage IIb and above)		13	Exploratory laparoscopy or diagnostic laparotomy
Dresen, 2019[7]	Retrospective	60	24 (40%)	56 (25–81)	Belgium	Primary or recurrent colorectal cancer with a clinical suspicion of PM		13	Exploration during laparotomy/ laparoscopy with histopathology; image-guided biopsy; imaging follow-up
Cianci, 2019[20]	Retrospective	24 (216 sites)	15 (63%)	57.4 (45–68)	Italy	For peritonectomy HIPEC	16.8 (5–30) d	9	Histopathology
Zhang, 2018[21]	Retrospective	27 (351 regions)	13 (48%)	51 (26–67)	China	With colorectal malignancy, in whom PM were known or suspected		13	Surgical and histopathological records
Michielsen, 2014[22]	Prospective	32	32 (100%)	61.9 (20–83)	Belgium				DOL and/or surgery with histopathology; histopathology after surgery; PET/CT biopsy
Low, 2012[23]	Retrospective	33	24 (73%)	50	USA	Primary tumors of the appendix, ovary, colon and mesothelioma		13	PCI score tabulated at the surgery
Bozkurt, 2011[25]	Retrospective	19	7 (37%)	64±6	Turkey	With known malignancy	within 1 mo	10	Surgical exploration and histopathological evaluation
Low, 2009[24]	Retrospective	34	23 (68%)	58.5	USA	Oncology patients	within 6 wk	16	Histopathology combined with results of surgery

DOL = diagnostic open, HIPEC = hyperthermic intraperitoneal chemotherapy, PET-CT = positron emission tomography-computed tomography, PM = peritoneal metastasis.

and Supplemental Digital Content 3, http://links.lww.com/MD/F573).

3.3. Subgroup analysis

When considering only the retrospective studies,[7,20,21,23–25] the pooled sensitivity of DWI for PMs was 85% (95% CI: 81%–89%). Heterogeneity was observed (P=.03, I^2=60.3%). The pooled specificity was 84% (95% CI: 72%–92%). Heterogeneity was observed (P<.01, I^2=78.1%) (Fig. 5). Figure 6 presents the SROC analysis.

When considering only the studies about gastrointestinal tumors,[7,17,21,24] the pooled sensitivity of DWI for PMs was 97% (95%CI: 68%-100%). Heterogeneity was observed (P<.01, I^2=91.5%). The pooled specificity was 86% (95% CI: 69%–95%). Heterogeneity was observed (P<.01, I^2=84.7%) (Fig. 7). Figure 8 presents the SROC analysis.

3.4. Publication bias

The publication bias of the studies was assessed using the Deeks' funnel plot asymmetry test (Fig. 9 and Supplemental Digital Content 4, http://links.lww.com/MD/F574). It suggests the absence of publication bias (P=.27).

4. Discussion

Previous meta-analyses examined either multiple tools for the diagnosis of PMs, but not DWI, or included only 1 tumor type.

Table 2

QUADAS 2 results.

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
van't Sant, 2019[17]	Low	Low	Low	Low	Low	Low	Low
Garcia Prado, 2019[18]	Low	Low	Low	Low	Low	Low	Low
Engbersen, 2019[19]	Low	Low	Low	Low	Low	Low	Low
Dresen, 2019[7]	Low	Low	Low	Low	Low	Low	Low
Cianci, 2019[20]	Low	High	Low	Low	Low	Low	Low
Zhang, 2018[21]	Low	Low	Low	Low	Low	Low	Low
Michielsen, 2014[22]	Low	Low	Low	Low	Low	Low	Low
Low, 2012[23]	High	Unclear	Low	Low	Low	Low	Low
Bozkurt, 2011[25]	Low	Low	Low	Low	Low	Low	Low
Low, 2009[24]	Low	Low	Low	Low	Low	Low	Low

Therefore, this study aimed to determine the summary diagnostic value of DWI/MRI in determining PMs originating from various tumors. This meta-analysis suggests that DWI MRI is highly sensitive and specific for the detection of PMs from various abdominal cancers.

The presence of PMs is associated with poor survival in all types of abdominal cancer.[2–4] In addition, their detection is essential to the correct staging of the patients and treatment strategy.[5–7] This is especially important for small lesions that are difficult to detect by CT, conventional MRI, and PET-CT.[9] Patients detected with PMs might benefit from cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.[26,27] The present meta-analysis revealed that DWI had 89% pooled sensitivity (95% CI: 83%–93%) and 86% pooled specificity (95% CI: 79%–91%) for the diagnosis of PMs from various abdominal cancers.

Imaging studies are often performed retrospectively using a set of images previously collected. Although they allow for obtaining a large set of patients rapidly, they can suffer from biases due to techniques and original interpretation.[28] The present meta-analysis showed that the pooled sensitivity and specificity of the

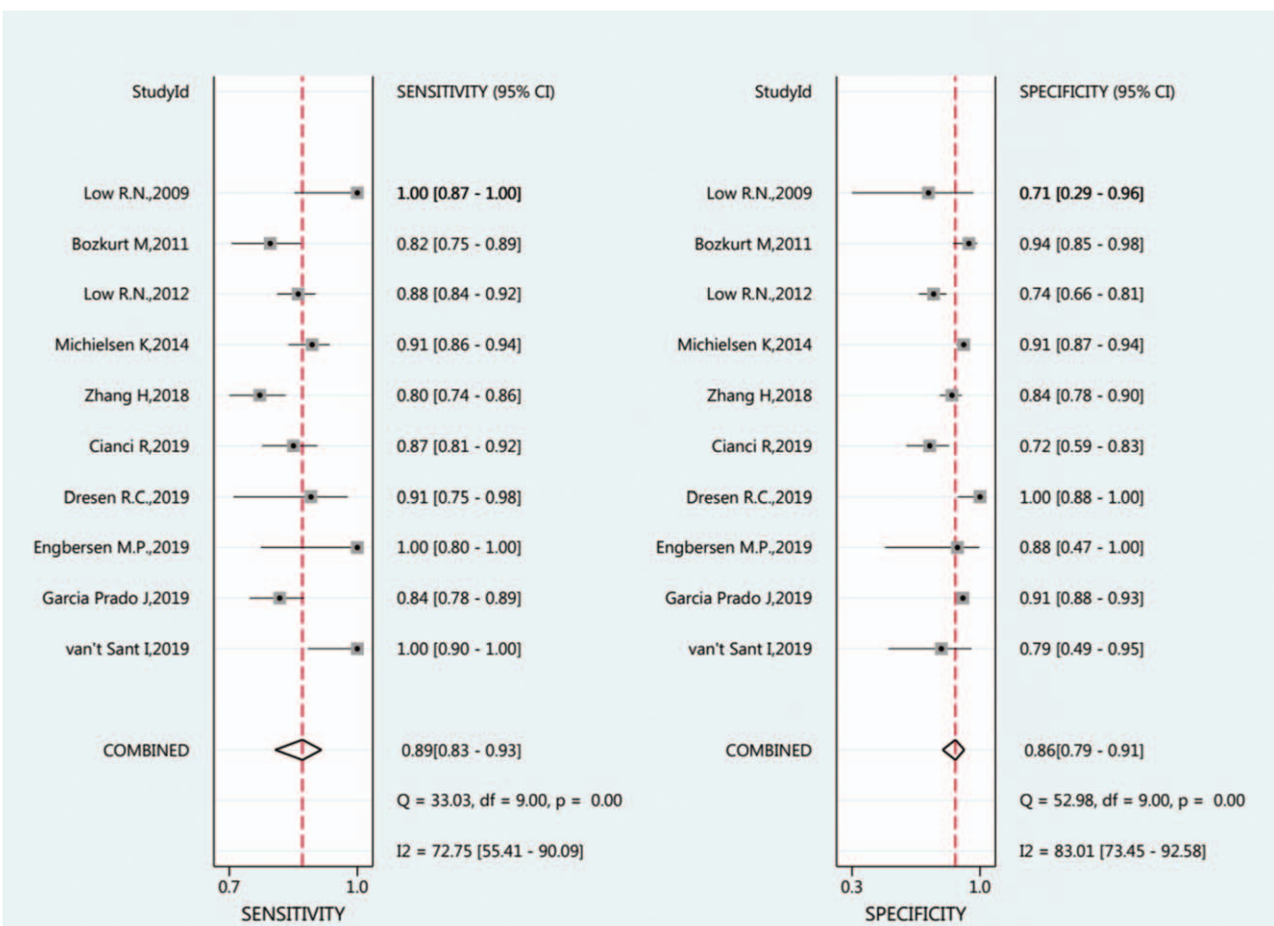

Figure 2. Forest plots of the pooled sensitivity and specificity analysis.

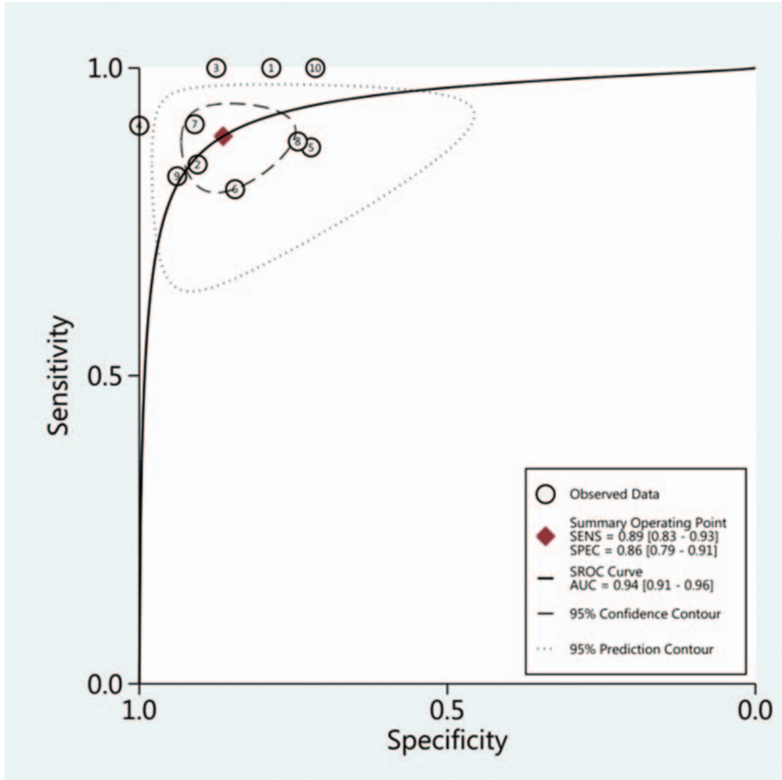

Figure 3. Summary ROC (SROC) curve of MRI for PM. MRI = magnetic resonance imaging, PM = peritoneal metastases.

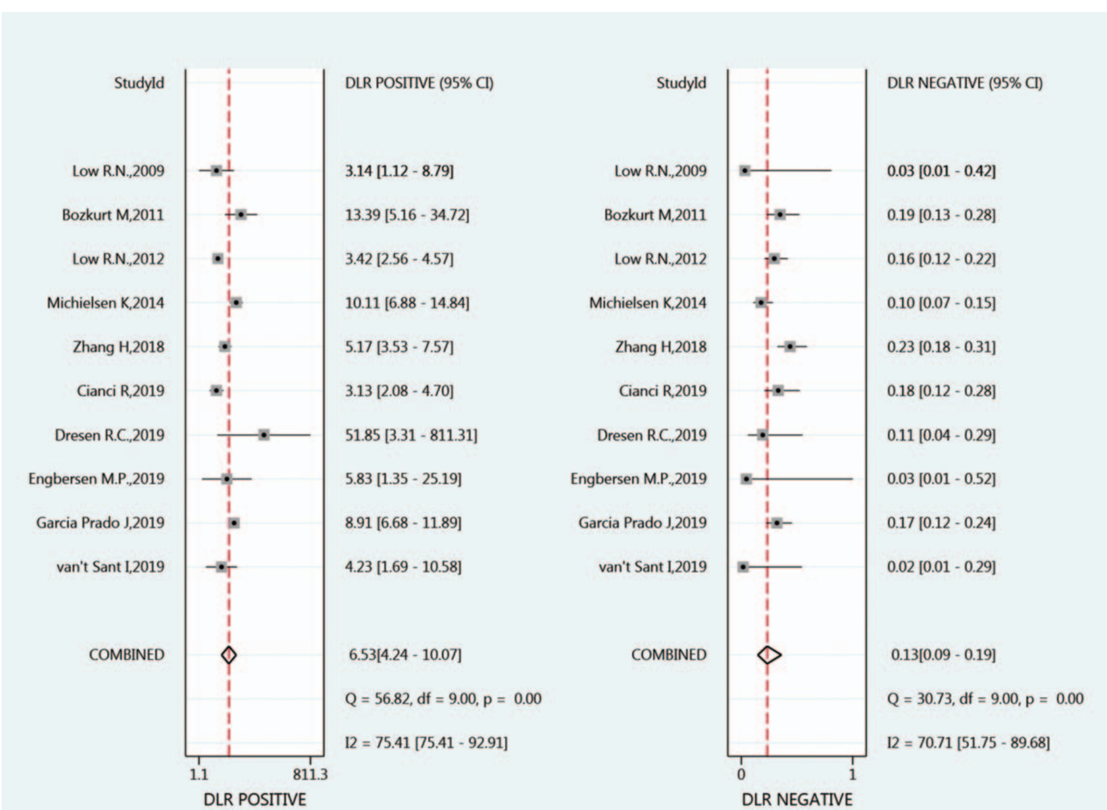

Figure 4. Forest plots of the pooled positive likelihood ratio and negative likelihood ratio analysis.

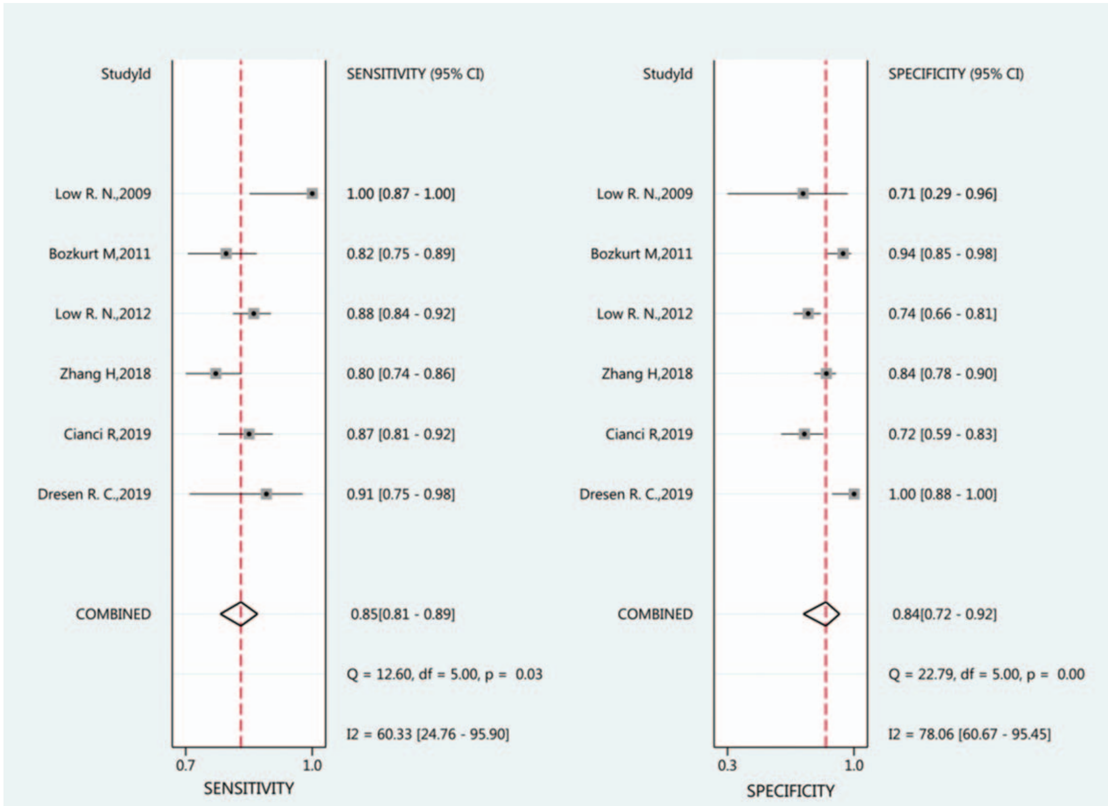

Figure 5. Forest plots of the pooled sensitivity and specificity analysis of prospective studies.

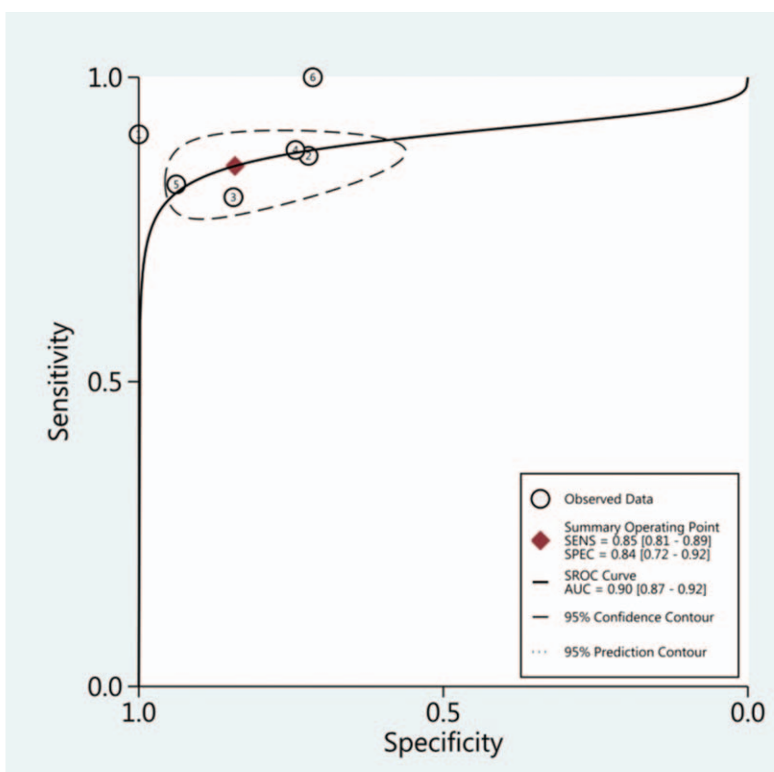

Figure 6. Summary ROC (SROC) curve of prospective studies.

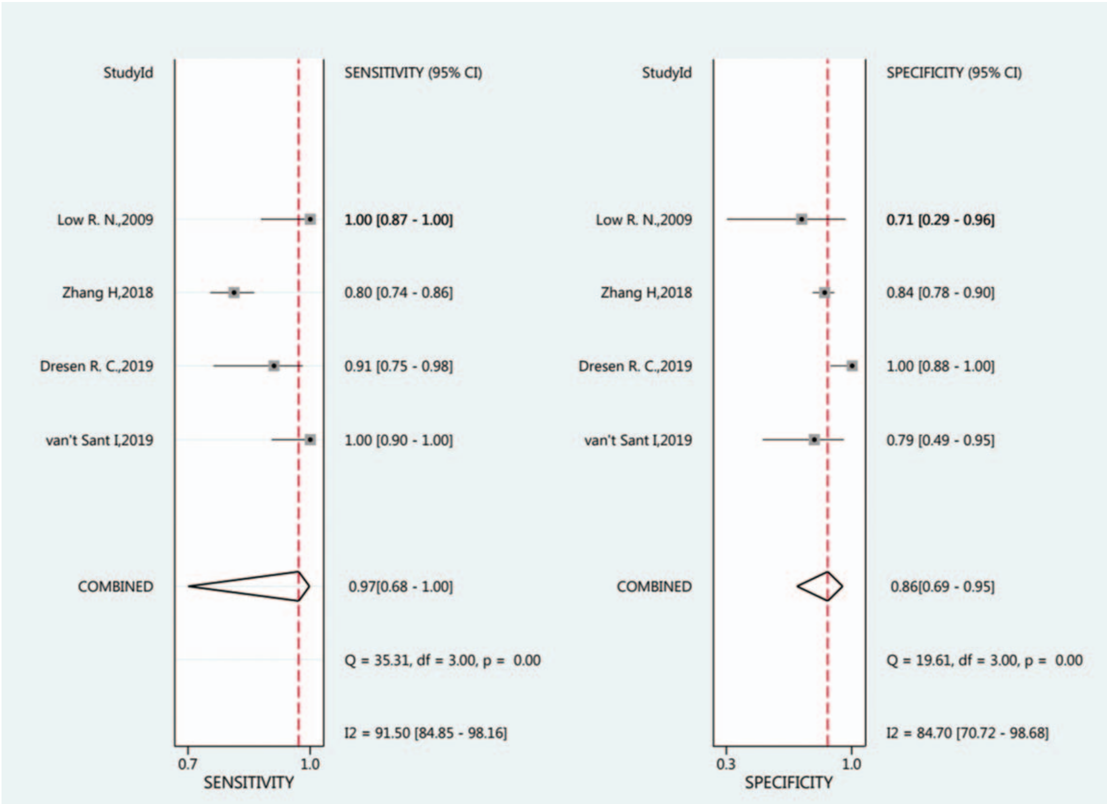

Figure 7. Forest plots of the pooled sensitivity and specificity analysis of gastrointestinal tumors.

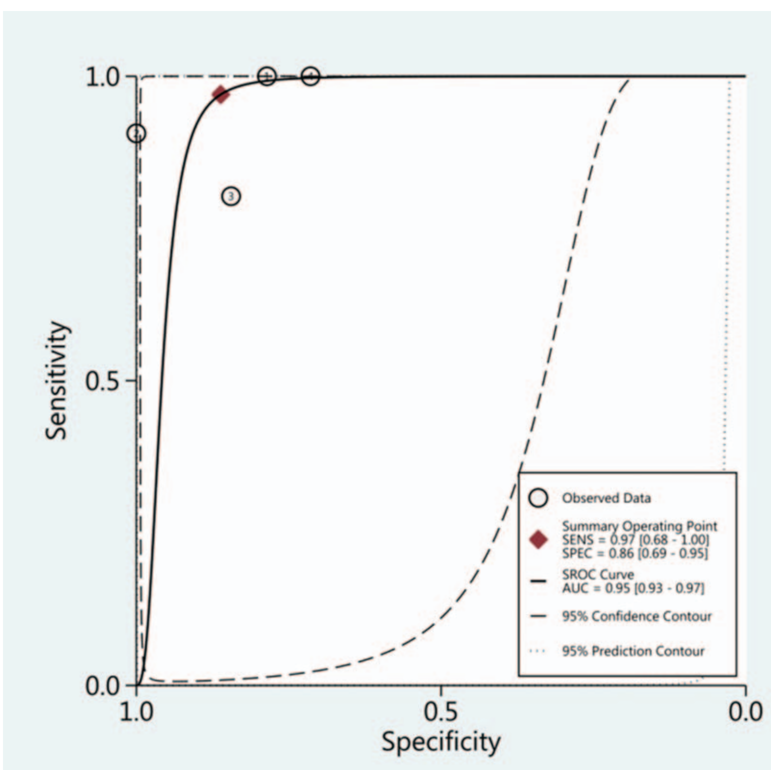

Figure 8. Summary ROC (SROC) curve of gastrointestinal tumors.

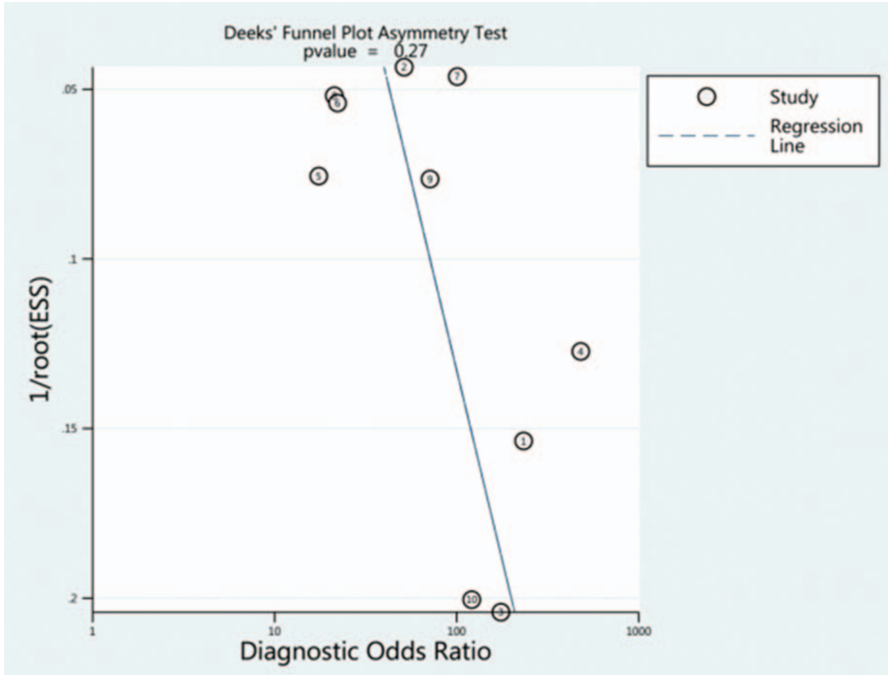

Figure 9. Deeks' funnel plot with a regression line.

were similar to that of the whole meta-analysis. This suggests that biases due to the retrospective analysis of images did not influence the results.

The other subgroup analysis showed that better sensitivity was achieved when considering only the gastrointestinal tumors, suggesting that DWI could perform better for PMs from gastrointestinal tumors than from ovarian tumors. This is supported by a previous meta-analysis that revealed 86% sensitivity and 81% specificity for PMs from ovarian cancer,[29] which are lower than in the present meta-analysis. A meta-analysis of patients with cervical cancer showed that PET-CT was better than DWI for the detection of positive lymph nodes.[30] Such differences between different primary cancers might be related, at least in part, to the different modes of metastatic spread.[31] Future studies should specifically examine this point. In addition, the results showed that the retrospective studies had relatively similar sensitivity and specificity than all the studies considered together, suggesting that the type of study does not influence the outcomes.

This study has limitations. Only 10 studies encompassing a relatively small number of patients were included. In addition, the outcomes of interest may be biased by the studies that were selected since they were conducted at various institutions. The baseline characteristics of the patients were different among studies, and the physicians who perform the examinations and surgeries can bias the result too. Nevertheless, those limitations are inherent to all meta-analyses, but no publication bias was detected in the present meta-analysis, and 70% of the included papers scored high on the QUADOS 2 scale. Finally, because many studies reported the performance of 2 different investigators, the primary analyses were performed with the best dataset, and the analyses with the worst datasets were presented as Supplemental Digital Content, http://links.lww.com/MD/F571, http://links.lww.com/MD/F572, http://links.lww.com/MD/F573, http://links.lww.com/MD/F574.

5. Conclusions

In conclusion, DWI MRI is highly sensitive and specific for the detection of PMs from various abdominal cancers. The subgroup analysis showed that the sensitivity and specificity were even higher for gastrointestinal cancers. This meta-analysis indicates that DWI MRI is an appropriate imaging method for PMs, even for small lesions. The early detection of lesions could provide a better opportunity for early treatments.

Author contributions

Conceptualization: Li Dong, Kuo Li, Taisong Peng.
Data curation: Li Dong, Kuo Li.
Formal analysis: Li Dong, Kuo Li, Taisong Peng.
Investigation: Li Dong, Kuo Li.
Project administration: Taisong Peng.
Writing – original draft: Li Dong, Kuo Li.
Writing – review and editing: Taisong Peng.

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