Diagnostic accuracy of MRI for detecting cervical invasion in patients with endometrial carcinoma: A meta-analysis

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Research

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Abstract

Background: Clinical management and the prognosis of endometrial cancer is closely related to cervical invasion. The diagnostic performance of MRI for detecting cervical invasion has not been comprehensively assessed. We aim to evaluate the diagnostic accuracy of magnetic resonance imaging (MRI) in the preoperative assessment of cervical invasion and to analyze the influence of different imaging protocols in patients with endometrial carcinoma.

Methods: An extensive search of articles about MRI in assessing cervical invasion in patients with endometrial carcinoma was performed in PubMed, Embase, Web of Science, Cochrane Library, and Clinical Trials from January 2000 to July 2019. Two reviewers independently evaluated the methodological quality of each study by using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2). Diagnostic accuracy results and additional useful information were extracted. Pooled estimation data was obtained by statistical analysis.

Results: A total of 42 eligible studies were included in the meta-analysis. Significant evidence of heterogeneity was found for detecting cervical invasion ($I^2 = 74.1\%$, $P = 0.00$ for sensitivity and $I^2 = 56.2\%$, $P = 0.00$ for specificity). And the pooled sensitivity and specificity of MRI were 0.58 and 0.95 respectively. The use of higher field strength (3.0 T) demonstrated higher pooled sensitivity (0.74). Using diffusion-weighted imaging (DWI) alone presented higher pooled sensitivity (0.86) than using other sequences. Studies that used dynamic contrast-enhanced MRI (DCE-MRI) alone showed higher sensitivity (0.80) and specificity (0.96) than that used T2-weighted image (T2WI) alone.

Conclusions: MRI shows high specificity for detecting cervical infiltration in endometrial carcinoma. Using DWI or a 3.0-T device may improve the pooled sensitivity. The use of DCE-MRI demonstrate higher pooled sensitivity and specificity than T2WI.

Background

Endometrial carcinoma is one of the most common gynecological malignancies [1]. Cervical invasion is one of the important prognostic factors, and is associated with higher risk of lymph node metastases [2, 3]. Hysterectomy and bilateral salpingo-oophorectomy are the primary treatment of endometrial carcinoma [4]. However, in patients with cervical infiltration, radical hysterectomy or preoperative radiotherapy with bilateral salpingo-oophorectomy and bilateral pelvic-para-aortic lymphadenectomy may be necessary [4]. Consequently, it is important to evaluate cervical involvement preoperatively in planning treatment.

Magnetic resonance imaging (MRI) is widely used to detect cervical invasion in endometrial carcinoma and is also more accurate than hysteroscopy [5] and endocervical curettage [6]. Compared with computed tomography [7] and transvaginal sonography [8], MRI has no radiation and has high soft-tissue resolution for uterus and cervix. Therefore, MRI is considered to be optimal imaging modality for a preoperative assessment of cervical invasion [9]. With the development of functional imaging of MRI, diffusion weighted imaging (DWI) and dynamic contrast-enhanced MRI (DCE-MRI) are increasingly applied to detecting cervical infiltration in endometrial carcinoma [10–14]. A mass of studies have investigated the accuracy of MRI in detecting cervical invasion [6, 12–31]. These studies are different in MR pulse sequences, magnetic field strength, and number of patients, so that research results are diverse. Which leading to the ongoing dispute about the availability of MRI and the best imaging protocol for evaluating cervical involvement of endometrial carcinoma.

The purpose of the present study was to evaluate the diagnostic accuracy of MRI in detecting cervical invasion and to analyze the influence of different imaging protocols in patients with endometrial carcinoma.

Methods

Literature search

According to the Preferred Reporting Items for Systematic Reviews-Diagnostic Test Accuracy (PRISMA-DTA) guidelines [32], we performed this meta-analysis. A comprehensive literature search of articles about the accuracy of cervical invasion using MRI in endometrial carcinoma was performed by using the following keywords (including subject word and random word): "endometrial neoplasms", "magnetic resonance imaging", and "cervical". Two authors (GB, a radiologist with 20 years of experience and QB, a radiologist with 5 years of experience) independently conducted the searches on the PubMed, Embase, Web of Science, Cochrane Library, and Clinical trials from January 2000 to December 2019 for English language articles on human subjects. To identify possible missing citation, the reference lists of relevant articles were manually searched.

Study selection

The same two authors who performed a literature search independently reviewed all the titles, abstracts, and full texts to identify potentially eligible articles. Studies meeting the following criteria were included if: (a) Accuracy was evaluated for cervical invasion by using MRI as the index test in endometrial carcinoma; (b) Histopathological results after surgery resection was used as the reference standard; (c) Sufficient information were presented to reconstruct the 2 × 2 tables. When data or patient cohort overlapped in included studies, we choose the article with the largest number of patients.

Data extraction and processing

Data on diagnostic accuracy results and additional useful information in original studies were collected by two researchers (QB and JW) who had experience in data extraction for diagnostic studies independently for 5 years. In case of discrepancies, consensus was made after discussion with each other. For each study, the following items were extracted: author name, year of publication, nation, patient age, sample size, number of observers, study design, patient recruitment, blinded to reference, magnetic field, manufacturer, sequences of observing cervical infiltration, depth of cervical invasion,
interval between MRI and pathology, and the true-positive, true-negative, false-positive, and false-negative values of MRI in detecting cervical invasion in patients with endometrial carcinoma. When two or more observers existed, the most experienced observer was selected, if the experience was not reported, the first observer was prioritized. The most contemporary MRI scan was preferred when different MR pulse sequences were reported at the same time (eg, DWI before DCE-MRI). When the accuracy of any cervical invasion and stromal invasion was reported separately, the latter was preferred.

**Assessment of data quality**

Quality assessment was conducted by the Quality Assessment of Diagnostic Accuracy Studies-2 [33] (QUADAS-2) by two investigators (GB and JZ, a radiologist with 15 years of experience in pelvic imaging) independently. Any disagreements were resolved by discussion with each other. The QUADAS-2 form is composed of four domains: patient selection (assessing methods of patient selection), index test (assessing the index test and how it was conducted and interpreted), reference standard (assessing the reference standard and how it was conducted and interpreted), and flow and timing (assessing any patients who did not receive the index test and/or reference standard or who were excluded from the 2×2 table).

**Statistical analysis**

Analyses were performed by using Review Manager 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark), MetaDisc 1.4 (Ramón y Cajal Hospital, Madrid, Spain), and Stata 15.1 (StataCorp, Texas, USA). The threshold effect was assessed by the spearman correlation coefficient between the logit of sensitivity and the logit of (1-specificity) [34]. P values < 0.05 indicated the threshold effect existed [34]. Heterogeneity for sensitivity and specificity was explored by using the inconsistency index (I² value) in forest plots [35]. I² values ≥ 50.0% are considered to indicate substantial heterogeneity [35]. A fixed-effects model was used to summarize the overall pooled diagnostic results if homogeneity existed. A random-effects model was utilized if heterogeneity existed. Summary receiver-operating characteristics (sROC) curves and the area under the curve were used to elucidate the relationship between sensitivity and specificity. If heterogeneity existed, meta-regression was performed to assess covariates. Several relevant covariates were as follows: patient age (≥ 60 year or < 60 year), magnetic field (1.5 T or 3.0 T), MR pulse sequences, design (prospective or retrospective), blind to reference (yes or unknown), depth of cervical infiltration (stromal invasion or any cervical invasion), and appropriate interval between MRI and pathology (yes or unknown). Sensitivity analyses were performed on the basis of those potential influencing factors of heterogeneity. Publication bias was assessed by using Deeks' funnel plot with P values < 0.05 [36].

**Results**

**Literature search and data extraction**

The detailed flowchart summarizing literature search and selection is given in Fig. 1. A total of 1111 records from January 2000 to December 2019 for English language articles on human subjects were provided. Two additional records identified, after manual reference checking. After duplicates, 678 unique citations remained. Based on screening of titles and abstracts, 599 studies were excluded. The full text of 79 studies was reviewed, then a total of 42 eligible studies comprising 4196 patients were included in this meta-analysis. The details of principal characteristics of every included studies are summarized in Table 1.
| Study     | Year | Country   | Age (y) | Sample size | Design | Patient recruitment | Blind to reference | Magnetic field | Manufacturer | Sequences | Depth of cervical invasion |
|-----------|------|-----------|---------|-------------|--------|---------------------|-------------------|----------------|-------------|-----------|--------------------------|
| Morimura  | 2000 | Japan     | 47      | U           | R      | U                   | U                 | U             | U           | U         | T2          | Any cervix               |
| Seki      | 2000 | Japan     | 39      | P           | U      | Yes                 | 1.5T Siemens      | DCE           |            |            | Any cervix               |
| Cunha     | 2001 | Portugal  | 40      | P           | U      | Yes                 | 1.0T Philips       | T2 + DCE       |            |            | Any cervix               |
| Manfredi  | 2004 | Italy     | 37      | P           | C      | Yes                 | 1.5T GE           | T2            |            |            | Any cervix               |
| Akaeda    | 2005 | Japan     | 21      | P           | U      | Yes                 | 1.5T Siemens      | CO2-VIBE       |            |            | Any cervix               |
| Haider    | 2006 | Canada    | 38      | R           | U      | Yes                 | 1.5T GE           | T2            |            |            | Any cervix               |
| Nagar     | 2006 | UK        | 135     | R           | C      | Yes                 | 1.5T Siemens      | T2            |            |            | Stroma                  |
| Rockall   | 2007 | UK        | 84      | R           | U      | Yes                 | 1.5T GE           | DCE           |            |            | Stroma                  |
| Vasconcelos | 2007 | Portugal  | 101     | P           | U      | Yes                 | 1.0T Philips       | T2 + DCE       |            |            | Any cervix               |
| Cabrita   | 2008 | Portugal  | 162     | U           | U      | U                   | 1.5T U            | U             |            |            | Any cervix               |
| Cicinelli | 2008 | Italy     | 100     | U           | C      | Yes                 | 1.5T Philips       | T2            |            |            | Any cervix               |
| Sanjuan   | 2008 | Spain     | 72      | R           | C      | U                   | 1.0T Siemens      | T2 + DCE       |            |            | Any cervix               |
| Savelli   | 2008 | Italy     | 74      | P           | C      | Yes                 | 1.5T U            | T2            |            |            | Any cervix               |
| Hori      | 2009 | Japan     | 30      | P           | C      | Yes                 | 3.0T GE           | T2            |            |            | Any cervix               |
| Undurraga | 2009 | Switzerland | 108   | R           | C      | Yes                 | 1.5T U            | T2 + CE        |            |            | Stroma                  |
| Celik     | 2010 | Turkey    | 64      | P           | C      | Yes                 | 1.5T Siemens      | U             |            |            | Any cervix               |
| Emlik     | 2010 | Turkey    | 53      | P           | C      | Yes                 | 1.5T Siemens      | DCE           |            |            | Any cervix               |
| Duncan    | 2012 | UK        | 748     | U           | U      | U                   | U                 | U             | U           | U         | Stroma                  |
| Haldorsen | 2012 | Norway    | 146     | P           | U      | Yes                 | 1.5T Siemens      | U             |            |            | Stroma                  |
| Tong      | 2012 | China     | 168     | R           | C      | U                   | 1.5T GE           | T2 + DCE       |            |            | Stroma                  |
| Zamani    | 2012 | Iran      | 54      | U           | U      | Yes                 | 1.5T U            | U             |            |            | Stroma                  |
| Aly       | 2013 | Egypt     | 40      | U           | U      | Yes                 | 1.5T GE           | DCE           |            |            | Stroma                  |
| Antonsen  | 2013 | Denmark   | 226     | P           | C      | Yes                 | 1.5T Philips       | U             |            |            | Any cervix               |
| Foti      | 2013 | Italy     | 20      | P           | C      | Yes                 | 1.5T GE           | T2            |            |            | Any cervix               |
| Hahn      | 2013 | Korea     | 131     | R           | U      | Yes                 | 1.5T Philips       | U             |            |            | Stroma                  |
| Hori      | 2013 | Japan     | 71      | P           | C      | Yes                 | 3.0T Philips       | T2 + DWI       |            |            | Stroma                  |
| Kitajima  | 2013 | Japan     | 30      | R           | U      | Yes                 | 1.5T GE           | U             |            |            | Stroma                  |

U, unknown; P, prospective; R, retrospective; C, consecutive; CE, contrast-enhanced MRI; DCE, dynamic contrast-enhanced MRI; DWI, diffusion weighted imaging; CO2-VIBE, CO2-volumetric interpolated breathhold examination.
Quality assessment and publication bias

Figure 2 is the methodological quality graph of the evaluation of the risk of bias and applicability concerns of the selected studies, according to QUADAS-2. Regarding risk of bias and the domain patient selection, 14 studies explicitly reported that the patients were consecutives [10, 12, 13, 16, 21, 23, 25–28, 31, 37–39], the remaining 28 studies only reported the start and end times of collecting patients [5, 6, 8, 11, 14, 15, 17–20, 22, 24, 29, 30, 40–53]. Concerning the domain index test, 6 studies did not interpret that histopathology was blinded from MRI [5, 22, 23, 27, 40, 45]. Eleven studies did not present the threshold defining cervical invasion [5, 8, 15, 17, 22, 27, 38, 45, 48, 51, 52]. As for the domain reference standard, only 7 studies explicitly stated that pathology results were blinded to MRI findings [18, 20, 24, 26, 31, 38, 41], the rest 35 studies were short of reporting. In relation to the domain flow and timing, twenty four studies reported an appropriate interval between MRI and pathological examination [5, 6, 8, 10, 12–16, 18–21, 23, 24, 26, 30, 31, 38, 39, 41, 44, 45, 50], the remaining 18 studies did not report it. All studies applied pathological evaluation of the removed uterus except for one study wasn't reported [22].

The slope coefficients for the Deeks'funnel plot for MRI in assessing cervical invasion in endometrial carcinoma are presented in Fig. 3. Publication bias was detected in the diagnosis of cervical invasion in the funnel plots ($P=0.01$).

Diagnostic accuracy

The threshold effect did not exist for detecting cervical invasion (spearman correlation coefficient = -0.282, $P=0.070$). Figure 4 was the forest plots of sensitivity and specificity of MRI for detecting cervical invasion, which showed significant evidence of heterogeneity ($\hat{I}^2 = 74.1\%, P=0.000$ for sensitivity and $\hat{I}^2 = 56.2\%, P=0.000$ for specificity). The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratios for diagnostic accuracy of MRI in detecting cervical invasion were 0.58 (95% confidence interval [CI] 0.55–0.62), 0.95 (95% CI 0.94–0.95), 9.37 (95% CI 7.78–11.28), 0.43 (95% CI 0.36–0.51), and 29.68 (95% CI 21.16–41.63), respectively. On the basis of sROC (Fig. 5), the area under the curve were 0.94. Fagan

| Study   | Year | Country | Age (y) | Sample size | Design | Patient recruitment | Blind to reference | Magnetic field | Manufacturer | Sequences | Depth of cervical invasion |
|---------|------|---------|---------|-------------|--------|---------------------|-------------------|---------------|--------------|-----------|--------------------------|
| Gitte   | 2013 | Denmark | U       | 143         | P      | U                   | Yes               | 1.5T          | GE           | U         | Any                      |
| Koplay  | 2014 | Turkey  | 58      | 58          | P      | C                   | Yes               | 1.5T          | Siemens      | DWI       | Any                      |
| Teng    | 2015 | China   | 57.9    | 167         | R      | U                   | Yes               | 1.5T          | GE           | T2 + DCE   | Any                      |
| Yin     | 2015 | China   | 54.6    | 98          | R      | U                   | Yes               | 3.0T          | U            | T2 + DCE   | Any                      |
| Zamani  | 2015 | Iran    | U       | 68          | P      | U                   | Yes               | U             | U            | U         | Stroma                   |
| Angioli | 2016 | Italy   | 53      | 41          | P      | U                   | Yes               | 1.5T          | GE           | DWI       | Any                      |
| Chan    | 2016 | China   | 55.2    | 90          | R      | U                   | Yes               | 1.5T          | Siemens      | T2 + DCE   | Stroma                   |
| Shrivastava | 2016 | India  | 52.8    | 36          | R      | U                   | Yes               | 1.5T          | Philips      | U         | Stroma                   |
| Lin     | 2017 | China   | 56      | 83          | U      | C                   | Yes               | 3.0T          | Siemens      | DWI       | Stroma                   |
| Rahmani | 2018 | Iran    | U       | 27          | P      | U                   | Yes               | 3.0T          | Siemens      | U         | Any                      |
| Xu      | 2018 | China   | 51.89   | 88          | R      | U                   | U                 | U             | U            | U         | Any                      |
| Yildirim| 2018 | Turkey  | 61.1    | 40          | P      | U                   | Yes               | 1.5T          | Philips      | U         | Any                      |
| Ytre-Hauge | 2018 | Norway | 67      | 178         | P      | C                   | Yes               | 1.5T          | Siemens      | U         | Stroma                   |
| Goel    | 2019 | India   | 60.2    | 58          | P      | U                   | Yes               | 1.5T          | GE           | T2 + DCE   | Any                      |
| Yang    | 2019 | China   | 54.1    | 182         | R      | U                   | Yes               | 3.0T          | GE           | T2        | Any                      |

U, unknown; P, prospective; R, retrospective; C, consecutive; CE, contrast-enhanced MRI; DCE, dynamic contrast-enhanced MRI; DWI, diffusion weighted imaging; CO₂-VIBE, CO₂-volumetric interpolated breathhold examination.
nomograms showed that the pre-test probability of cervical invasion was 50%, the corresponding positive post-test probability and negative post-test probability were 93% and 27% respectively (Fig. 6).

Meta-regression and sensitivity analyses

Meta-regression showed that patient age, magnetic field, MR pulse sequences, design, blind method, depth of cervical infiltration, and interval between MRI and pathology did not explain heterogeneity observed for sensitivity and specificity (Table 2).

| Variable                      | Coefficient | Standard error | P value | Diagnostic odd ratio | 95% CI      |
|-------------------------------|-------------|----------------|---------|----------------------|-------------|
| Age                           | 0.402       | 0.2274         | 0.0850  | 1.49                 | (0.94–2.37) |
| Design                        | -0.082      | 0.2363         | 0.7296  | 0.92                 | (0.57–1.49) |
| Blind to reference            | 0.444       | 0.4159         | 0.2926  | 1.56                 | (0.67–3.61) |
| Magnetic field                | 0.383       | 0.2181         | 0.0865  | 1.47                 | (0.94–2.28) |
| Sequences                     | 0.109       | 0.0660         | 0.1080  | 1.11                 | (0.98–1.27) |
| Depth of cervical invasion    | -0.043      | 0.3423         | 0.8996  | 0.96                 | (0.48–1.91) |
| Interval between MRI and pathology | -0.309     | 0.3274         | 0.3518  | 0.73                 | (0.38–1.42) |

Table 3 presents the results of sensitivity analyses performed for different subgroups. Overall, several differences were observed for sensitivity and specificity estimates in sensitivity analyses, and the forest plots of sensitivity and specificity are presented in Fig. 7–8. Studies with higher field strength (3.0 T) had higher pooled sensitivity (0.74; 95% CI: 0.60–0.84) than studies with a 1.5-T device (0.60; 95% CI: 0.56–0.65) or 1.0-T device (0.51; 95% CI: 0.37–0.65). And the higher the field strength, the higher the pooled sensitivity. But the pooled specificity was lower by using a 3.0-T device (0.96; 95% CI: 0.93–0.97) than 1.0-T device (0.99; 95% CI: 0.96-1.00). In regard to the MR pulse sequences of observing cervical invasion, three studies [10, 16, 17] that used DWI alone had higher sensitivity (0.86; 95% CI: 0.71–0.95) compared with studies that used DCE-MRI (0.80; 95% CI: 0.65–0.91) or T2-weighted image (T2WI) (0.73; 95% CI: 0.64–0.80) alone. Four studies [11, 13, 14, 43] that used DCE-MRI alone presented higher sensitivity (0.80; 95% CI: 0.65–0.91) and specificity (0.96; 95% CI: 0.92–0.98) than that used T2WI alone. T2WI combined with DCE-MRI could not improve diagnostic performance in comparison with DCE-MRI alone. As for the depth of cervical invasion, the pooled sensitivity and specificity of MRI were 0.55 (95% CI 0.50–0.61) and 0.95 (95% CI 0.94–0.96) respectively for assessing stromal invasion in endometrial carcinoma.
diagnostic accuracy for detecting cervical infiltration in endometrial carcinoma. As a consequence, the pooled specificity was not the highest by using a 3.0 T imaging particularly for the pelvis, such as larger susceptibility effect, larger chemical shift, and so on \[28x83\].

demonstrate higher pooled sensitivity (0.74) for detecting cervical invasion in endometrial carcinoma. At the same time, there are some problems associated with 3.0 T imaging particularly for the pelvis, such as larger susceptibility effect, larger chemical shift, and so on \[25\]. These factors may affect diagnostic accuracy for detecting cervical infiltration in endometrial carcinoma. As a consequence, the pooled specificity was not the highest by using a 3.0-T device (0.96).

| Analysis                                      | Number of studies | Sensitivity | Specificity | PLR          | NLR          | DOR          |
|-----------------------------------------------|-------------------|-------------|-------------|--------------|--------------|--------------|
| Overall                                       | 42                | 0.58 (0.55–0.62) | 0.95 (0.94–0.95) | 9.37 (7.78–11.28) | 0.43 (0.36–0.51) | 29.68 (21.16–41.63) |
| Age (y)                                        |                   |             |             |              |              |              |
| ≥ 60                                          | 15                | 0.51 (0.45–0.56) | 0.93 (0.92–0.95) | 6.73 (5.18–8.74) | 0.54 (0.44–0.67) | 15.54 (9.49–25.45) |
| < 60                                          | 19                | 0.72 (0.66–0.78) | 0.94 (0.93–0.96) | 10.95 (8.61–13.94) | 0.27 (0.18–0.42) | 58.71 (37.51–91.89) |
| Design                                        |                   |             |             |              |              |              |
| Prospective                                   | 21                | 0.58 (0.52–0.64) | 0.94 (0.92–0.95) | 7.96 (5.93–10.68) | 0.43 (0.33–0.56) | 26.78 (15.43–46.50) |
| Retrospective                                 | 15                | 0.64 (0.58–0.70) | 0.94 (0.93–0.96) | 9.62 (7.53–12.30) | 0.38 (0.26–0.54) | 35.25 (23.09–53.81) |
| Blind to reference                            |                   |             |             |              |              |              |
| Yes                                           | 36                | 0.61 (0.57–0.65) | 0.94 (0.93–0.96) | 9.81 (7.82–12.30) | 0.39 (0.32–0.49) | 34.44 (23.00–51.57) |
| Unknown                                       | 6                 | 0.51 (0.44–0.59) | 0.95 (0.93–0.96) | 8.76 (6.21–12.35) | 0.53 (0.39–0.72) | 19.45 (11.01–34.34) |
| Magnetic field                                |                   |             |             |              |              |              |
| 3.0T                                          | 6                 | 0.74 (0.60–0.84) | 0.96 (0.93–0.97) | 16.22 (8.69–30.25) | 0.33 (0.19–0.58) | 68.56 (28.18–166.78) |
| 1.5T                                          | 28                | 0.60 (0.56–0.65) | 0.93 (0.92–0.94) | 8.15 (6.61–10.04) | 0.40 (0.31–0.51) | 27.08 (17.60–41.66) |
| 1.0T                                          | 3                 | 0.51 (0.37–0.65) | 0.99 (0.96–1.00) | 19.99 (6.73–69.76) | 0.54 (0.39–0.76) | 39.81 (9.15–173.19) |
| MR pulse sequences                            |                   |             |             |              |              |              |
| DWI                                           | 3                 | 0.86 (0.71–0.95) | 0.92 (0.87–0.96) | 10.18 (4.97–20.86) | 0.16 (0.07–0.37) | 61.42 (19.65–191.93) |
| DCE                                           | 4                 | 0.80 (0.65–0.91) | 0.96 (0.92–0.98) | 17.65 (8.10–38.48) | 0.21 (0.07–0.61) | 78.46 (24.60–250.18) |
| T2                                             | 9                 | 0.73 (0.64–0.80) | 0.92 (0.89–0.94) | 8.34 (6.14–11.33) | 0.33 (0.21–0.51) | 34.57 (19.48–61.35) |
| T2 + DCE                                       | 9                 | 0.60 (0.52–0.67) | 0.96 (0.94–0.97) | 14.35 (7.78–28.46) | 0.45 (0.30–0.67) | 42.38 (20.56–87.35) |
| Depth of cervical invasion                    |                   |             |             |              |              |              |
| Stromal invasion                              | 16                | 0.55 (0.50–0.61) | 0.95 (0.94–0.96) | 9.29 (7.01–12.30) | 0.46 (0.36–0.59) | 25.98 (16.52–40.85) |
| Any cervical invasion                         | 26                | 0.61 (0.56–0.66) | 0.94 (0.93–0.95) | 9.53 (7.38–12.32) | 0.39 (0.30–0.50) | 33.69 (20.43–55.56) |
| Interval between MRI and pathology            |                   |             |             |              |              |              |
| Appropriate                                    | 24                | 0.59 (0.54–0.63) | 0.94 (0.93–0.95) | 9.10 (7.00–11.83) | 0.42 (0.32–0.54) | 30.02 (17.73–50.80) |
| Unknown                                       | 18                | 0.58 (0.53–0.64) | 0.95 (0.94–0.96) | 9.86 (7.68–12.65) | 0.43 (0.34–0.54) | 28.66 (20.11–40.86) |

PLR, positive likelihood ratio; NLR, negative likelihood ratio; DOR, diagnostic odds ratios; DWI, diffusion weighted imaging; DCE, dynamic contrast-enhanced MRI.

Data in parentheses are 95% confidence interval.

Bold fonts, indicating I² values < 50.0%.

Discussion
This meta-analysis demonstrated high pooled specificity of MRI for detecting any cervical infiltration and stromal invasion in patients with endometrial carcinoma. Sensitivity analyses revealed that magnetic field and MR pulse sequences were helpful to explain heterogeneity observed for sensitivity and specificity of MRI for detecting cervical invasion.

Clinical management and the prognosis of endometrial carcinoma are closely related to cervical invasion \[4\]. Using a preoperative technique to detect cervical invasion of endometrial carcinoma may be helpful to reduce the scope of operation, minimize costs, and offer fertility-preserving treatment options for young women without cervical invasion \[54\]. MRI is considered as the best non-invasive method for preoperative staging of endometrial carcinoma \[9\]. In this meta-analysis, MRI shows low sensitivity (0.58) and high specificity (0.95) for detecting cervical invasion. It is similar to a previous meta-analysis \[55\]. More than that, further sensitivity analyses of magnetic field strength were performed in our meta-analysis. We found that studies with higher field strength (3.0 T) had higher sensitivity (0.74) than studies with a 1.5-T device (0.60) or 1.0-T device (0.51). Hori et al \[25\] discovered that 3.0-T imaging improved tumor signal-to-noise ratio by around 12% compared with 1.5 T imaging. The main reason is the signal-to-noise ratio is influenced by magnetic field strength, with higher fields having a better signal-to-noise ratio. Hence, using a 3.0-T device can provide a better quality of MRI and demonstrate higher pooled sensitivity (0.74) for detecting cervical invasion in endometrial carcinoma. At the same time, there are some problems associated with 3.0 T imaging particularly for the pelvis, such as larger susceptibility effect, larger chemical shift, and so on \[25\]. These factors may affect diagnostic accuracy for detecting cervical infiltration in endometrial carcinoma. As a consequence, the pooled specificity was not the highest by using a 3.0-T device (0.96).
T2WI is a conventional MR pulse sequence and one of the best MRI protocols for staging in patients with endometrial carcinoma according to the Updated Guidelines of the European Society of Urogenital Radiology [56]. On T2WI, cervical invasion was defined as a mass within the endocervical canal and/or disruption of the normal cervical stroma [25]. The normal cervical stroma appears hypointense on T2WI on account of containing rich fibrous tissue, and endometrial carcinoma appears hyperintense, leading to high contrast resolution [31]. In consequence, MRI shows high specificity for detecting cervical invasion. However, microscopic cervical infiltration may not be observed by using MRI, only macroscopic cervical invasion could be found, result in low sensitivity for detecting cervical invasion in patients with endometrial carcinoma [55].

According to a recent meta-analysis, DCE-MRI can help improve sensitivity and specificity for detecting myometrial invasion [55]. Because DCE-MRI provides the observer with obvious contrast resolution between the markedly enhanced normal myometrium and the moderately enhanced tumor. On DCE-MRI, cervical invasion was defined as interruption of the enhancement of the normal cervical epithelium [16]. Moreover, delayed DCE-MRI (4–5 min after the injection) are optimal for the detection of cervical invasion [56]. Previous research reported that DCE-MRI improved the detection of cervical infiltration by endometrial carcinoma [11]. Our meta-analysis also found that using DCE-MRI could improve sensitivity (0.80) and specificity (0.96) than using T2WI. DCE-MRI is accepted as the state-of-the-art standard for tumour delineation and is accepted as one of the best approach for local staging of endometrial carcinoma [56]. However, it is commonly difficult to assess cervical invasion when endometrial carcinoma enter the endocervical canal and give rise to obliterating the interface between the tumor and the cervix [57]. Other MRI functional imaging techniques are needed for accurate preoperative evaluation of cervical infiltration.

DWI is a functional technique of MRI to reflect the diffusivity of water molecules in tumors. DWI offers potential advantages over DCE-MRI owing to it does not need to use a contrast administration and entails a shorter imaging time. Recent evidence suggests that DWI improves the evaluation of myometrial invasion of endometrial carcinoma on account of DWI is able to determine malignant lesions as a hyperintense area with excellent tissue contrast [10]. To avoid the influence of T2 shine-through effect, cervical invasion was defined as the appearance of higher signal intensity on high-b-value DWI and low signal intensity on apparent diffusion coefficient (ADC) maps, compared with the surrounding normal cervical parenchyma [16, 56]. This meta-analysis found studies that used DWI alone had higher sensitivity (0.86) compared with studies that used DCE-MRI (0.80) or T2WI (0.73) alone. Significant improvement in sensitivity was also found in DWI compared with DCE-MRI and T2WI for detecting cervical invasion in a previous original study [16]. False positive rate may increase when cervical mucus presents, because it shows a high signal on DWI and low signal on ADC maps. Which will lead to a decrease in specificity. Furthermore, DWI also has other disadvantages, such as limited spatial resolution and image distortions because of susceptibility artefacts. Thus referring to other MR pulse sequences for an anatomical landmark is warranted. As a result, DWI is now routinely used as an adjunct to T2WI and DCE-MRI [56].

There are some limitations in this meta-analysis. Firstly, due to the lack of support of enough literature, sensitivity analyses of other techniques such as CO2-volumetric interpolated breathhold examination was not performed. Secondly, some studies did not afford sequences of observing cervical infiltration. In addition, the number of included studies is limited. It remains to be determined whether combined DWI and T2WI is superior to DCE-MRI, whether a 3.0-T device combined with DWI or DCE-MRI had the higher sensitivity and specificity, and so on. Thirdly, publication bias was existed. One possible reason was that we excluded relevant studies published in other languages. Another possible reason was that the sensitivity for detecting cervical invasion was low. Perhaps some articles of negative results were not published.

In conclusion, this meta-analysis shows low pooled sensitivity and high specificity of MRI for detecting any cervical infiltration and stromal invasion in endometrial carcinoma. Studies with 3.0-T device demonstrate the higher pooled sensitivity than any other study. And the higher the field strength, the higher the pooled sensitivity. Using DWI alone demonstrated higher pooled sensitivity compared with using DCE-MRI or T2WI only. Studies that used DCE-MRI alone showed higher sensitivity and specificity than that used T2WI alone.

**Abbreviations**

MRI: magnetic resonance imaging; DWI: diffusion-weighted imaging; DCE-MRI: dynamic contrast-enhanced MRI; T2WI: T2-weighted image; ADC: apparent diffusion coefficient; sROC: summary receiver-operating characteristics; CI: confidence interval; PRISMA-DTA: Preferred Reporting Items for Systematic Reviews-Diagnostic Test Accuracy; QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies-2

**Declarations**

**Ethics approval and consent to participate:** Not applicable.

**Consent for publication:** Not applicable.

**Availability of data and materials:** All data generated or analysed during this study are included in this published article.

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Figures

Figure 1
Flowchart of the study selection process.

Figure 3
Histogram plot of the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) scores of methodological study quality.
Figure 6
Deeks’ funnel plot for evaluating cervical invasion in endometrial carcinoma. A value of P<0.05 was considered to indicate significant publication bias. Numbers in circles represent study number. ESS, effective sample size.

Figure 7
Forest plots show the pooled sensitivity and specificity of MRI for detecting cervical invasion in endometrial carcinoma. I² values ≥ 50.0% are considered to indicate substantial heterogeneity in each study. CI, confidence interval.

Figure 9

Summary receiver-operating characteristics (sROC) curves of MRI for detecting cervical invasion in endometrial carcinoma. AUC, area under the curve.
Fagan nomogram shows pre-test probability, positive post-test probability, and negative post-test probability of MRI for assessing cervical involvement in endometrial carcinoma. LR, likelihood ratio; Prob, probability.
Figure 13

Forest plots of pooled sensitivity and specificity of using a 3.0-T device, 1.5-T device, and 1.0-T device for assessing cervical involvement in endometrial carcinoma. CI, confidence interval.
Figure 15

Forest plots of pooled sensitivity and specificity of diffusion weighted imaging (DWI), dynamic contrast-enhanced MRI (DCE-MRI), and T2-weighted image (T2WI) for assessing cervical involvement in endometrial carcinoma. CI, confidence interval.