

Magnetic resonance imaging and ultrasound for assessing parametrial infiltration in cervical cancer. A systematic review and meta-analysis

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Abstract

Aims: To provide information on the current evidence regarding the diagnostic performance of ultrasound and MRI for assessing parametrial involvement in cervical cancer using the histological report as the reference standard. **Material and methods:** Meta-analysis. An extensive search of papers comparing ultrasound and MRI in assessing parametrial infiltration in cervical cancer using pathologic analysis as a reference standard was performed in Medline (Pubmed) and Web of Science from January 1990 to September 2019. Quality was assessed using the QUADAS-2 tool. **Results:** Our extended search identified 205 citations but after exclusions we finally included 9 articles in the meta-analysis. The risk of bias for most studies was low for four domains were assessed in QUADAS-2. Overall, for ultrasound pooled estimated sensitivity and specificity for diagnosing parametrial infiltration was 78% (95% confidence interval [CI]:48%–93%) and 96% (95% CI=89%–99%), respectively. For MRI these figures were 68% (95% CI=54%–80%) and 91% (95% CI=84%–95%), respectively. No statistical differences were found when comparing both methods ($p=0.548$). Heterogeneity was low/moderate for MRI and high for ultrasound. **Conclusion:** Ultrasound and MRI have similar diagnostic performance for detecting parametrial infiltration in women with cervical cancer. This might have relevance from the clinical point of view, since ultrasound is cheaper than MRI.

Keywords: uterine cervix; cancer; parametrium; ultrasound; magnetic resonance imaging

Introduction

Cervical cancer is the most frequent gynecological cancer worldwide [1]. Staging of cervical cancer is still

based on clinical findings [2]. However, it is well known that discrepancies between clinical examination and the actual extent of disease exist, especially for parametrial involvement [3]. For this reason, imaging methods, namely magnetic resonance (MRI) have been proposed for assessing parametrial infiltration [4].

Traditionally, the role of ultrasound for assessing cervical cancer has been considered very limited [5]. However, some studies have shown the ultrasound (US) might be a good imaging method for assessing the local extension of cervical cancer [6]. In fact, recently a FIGO report has indicated that ultrasound may be a good diagnostic tool for assessing parametrial invasion in cervical can-

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cer [2]. However, to the best of our knowledge no study comparing MRI and ultrasound for assessing parametrial infiltration in a large series, has been reported.

The aim of the present meta-analysis is to provide information on the current evidence regarding the diagnostic performance of ultrasound and MRI for assessing parametrial involvement in cervical cancer using the histological report as the reference standard.

Materials and methods

Protocol and registration

We performed this systematic review and meta-analysis according to PRISMA and Synthesizing Evidence from Diagnostic Accuracy TESts (SEDATE) guidelines [7,8]. All methods for inclusion/exclusion criteria, data extraction and quality assessment were specified in advance. The protocol did not require registration.

Data sources and searches

Studies published between 1990 and September 2019 were identified by three of the authors (JLA, MM, EG) using two electronic databases (PubMed/MEDLINE and Web of Science) to identify potentially eligible studies. The search terms included and captured the concepts of “cervix,” “cancer,” “carcinoma,” “ultrasound,” “sonography,” “parametrial,” and “magnetic resonance imaging.” Language restriction in the research was set to English.

Study selection and data collection

Three authors (JLA, MM, EG) screened the titles and abstracts identified to exclude irrelevant articles, i.e., those not strictly related to the topic under review. Full-text articles were obtained to identify potentially eligible studies, and reviewers applied independently the following inclusion criteria: 1) prospective or retrospective cohort study including patients who underwent both techniques, MRI and US (those including transvaginal (TVS), transrectal (TRS) or three-dimensional ultrasound), for evaluating parametrial infiltration in cervical carcinoma as index tests. We selected only those studies assessing both techniques in the same set of patients; 2) surgical assessment (radical hysterectomy) of the presence of parametrial infiltration according to the histopathological permanent frozen section as reference standard; 3) data reporting of results sufficient to construct the 2×2 table for diagnostic performance assessment, as a minimum data requirement.

We used the “snowball” strategy to identify potential interesting papers by reading the reference list of those papers selected for full text reading. We attempted to contact the authors in case of missing data.

The Patients, Intervention, Comparator, Outcomes, Study design (PICOS) criteria were used for describing the studies included.

Diagnostic accuracy results and additional useful information about patients and procedures were retrieved from selected primary studies independently by four of the authors (MM, EC, JE, RQ). Disagreements arising during the process of study selection and data collection were resolved by consensus among three of the authors (JLA, JE, RQ).

Risk of bias in individual studies

Quality assessment was conducted, adapting to this particular review the tool provided by the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) [9]. The QUADAS-2 format includes four domains: 1) patient selection, 2) index test, 3) reference standard, and 4) flow and timing. For each domain, the risk of bias and concerns about applicability (the latter not applying to the domain of flow and timing) were analyzed and rated as a low, high or unclear risk. The results of quality assessment were used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to investigate potential sources of heterogeneity. Three authors (JLA, JE, RQ) evaluated independently the methodological quality, using a standard form with quality assessment criteria and a flow diagram; they resolved disagreements by discussion between them to reach a consensus.

The methodology of quality criteria was based on the description of inclusion and exclusion criteria for the patient selection domain; a description about how the index test (US/MRI) was performed and interpreted for the index test domain; a description of the reference standard used and a description of the time elapsed from the index test assessment to the reference standard result.

Statistical analysis

We extracted or derived information on the diagnostic performance of US and MRI. A random-effects model was used to determine overall pooled sensitivity, specificity, positive likelihood ratio (LR+) and negative likelihood ratio (LR-). Positive and negative likelihood ratios (LRs) were used to characterize the clinical utility of the tests and to estimate the post-test probability of disease. A LR of 0.2–5.0 provides weak evidence for either ruling out or confirming the disease. A LR of 5.0–10.0 and 0.1–0.2 provides moderate evidence to either confirm or rule out the disease. A LR >10 or <0.1 provides strong evidence to either confirm or rule out the disease.

Using the mean prevalence of parametrial infiltration (pretest probability) in each subset, depending upon the technique assessed and LRs, post-test probabilities were calculated and plotted on Fagan nomograms.

We assessed the presence of heterogeneity for sensitivity and specificity using Cochran’s Q statistic and the I² index [10]. A p-value <0.1 indicates heterogeneity. The I² index describes the percentage of total variation across

studies that is due to heterogeneity rather than chance. According to Higgins et al. I^2 values of 25%, 50%, and 75% would be considered to indicate low, moderate and high heterogeneity, respectively [10]. Forest plots of sensitivity and specificity of all studies were plotted.

Summary receiver-operating characteristics (sROC) curves were plotted to illustrate the relationship between sensitivity and specificity. Comparison of diagnostic performance between US and MRI for detecting parametrial invasion was made using the bivariate method [11]. Meta-regression was used if high heterogeneity was found to assess covariates that could explain this heterogeneity. The covariates analyzed were sample size, prevalence, mean patient age and number of observers (single/multiple) and in the case of US, the technique used (TVS, TRS, 3D). Publication bias was assessed by a regression of diagnostic log odds ratio against $1/\sqrt{n}$ (effective sample size), weighted by effective sample size, with $p < 0.10$ for the slope coefficient indicating significant asymmetry [12].

All analyses were performed using the Meta-analytical Integration of Diagnostic Accuracy Studies (MIDAS) and METANDI commands in the STATA version 12.0 for Windows (Stata Corporation, College Station, TX, USA). A p-value < 0.05 was considered as statistically significant.

Results

Search results

The electronic search provided a total of 205 citations. After removal of 24 duplicate records, 181 citations remained. Of these, 169 were excluded because it was clear from the title or abstract that they were not relevant to this review (papers assessing US but not MRI [$n=2$], papers assessing MRI but not US [$n=38$], papers not related to the topic [$n=111$], reviews [$n=18$]). We examined the full text of the remaining 12 articles. Finally, six studies were discarded because they did not meet the inclusion criteria (two studies used MRI but not US, three studies

had no histopathological analysis as a reference standard and one study used the MRI/US fusion technique).

Thus, the remaining six studies were included in the review and meta-analysis. Three additional relevant studies were found from references cited in the papers included in the review. Thus, a total number of nine studies were included in this meta-analysis [13-21]. A flow-chart summarizing literature identification and selection is given in figure 1.

Characteristics of included studies

A total of nine studies published between September 1990 and May 2017 reporting on 561 patients were included in the final analyses [13-21]. Among these 561 women, 61 had parametrial invasion. Mean prevalence of parametrial invasion was 14%, ranging from 5% to 30%. All studies reported the clinical characteristics of the cohort to some extent. Mean patients' age was reported in all studies and ranged from 19 to 84 years. Table I shows PICOS features of the studies included.

Methodological quality of included studies

Study design was clearly stated as prospective in 7 out of 9 studies [13-18,20]. In two studies, the design was not clearly described [19,21]. A graphical display of the evaluation of the risk of bias and concerns regarding applicability of the selected studies is shown in figure. 2.

Regarding risk of bias and the domain patient selection, one study was not clear regarding the patient inclusion criteria [19] and another study was considered as a high risk for patient selection since it excluded patients with "large cervical cysts, calcifications and necrotic areas, factors which may confound diagnosis results" [21].

Concerning the domain index test, with regard to US, seven studies adequately described the method of the index test as well as how it was performed and interpreted. One study was unclear [14] and one study was considered as a high risk since no description about how US was interpreted was provided [19]. With regard to MRI, four studies adequately described the method of the index test as well as how it was performed and interpreted [13,15,20,21], four studies were unclear [14,16-18] and one study was considered as a high risk since no reporting for MRI evaluation was done [19].

Concerning the domain flow and timing, the time elapsed between the index test and reference standard was reported in all studies apart from one study [20].

For the domain reference standard, all studies were likely to correctly classify the target condition by the reference standard.

Regarding applicability, for the domain patient selection, all studies were deemed to include patients that matched the review question. For the domain index test, four studies were considered as having low concerns

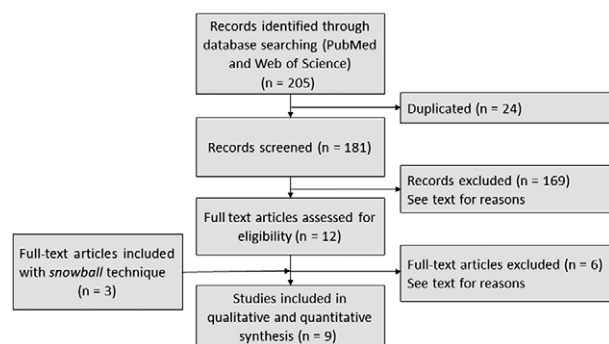


Fig 1. Flow chart showing the studies' selection process

Table I. Characteristics of included studies in this systematic review according to the PICO criteria

Author	Year	Study design	Multicenter	N patients	N surgery	N parametrial involvement	US technique	US criteria	US number of observers	MRI magnet strength	MRI criteria	Number of MRI observers	Reference standard
Cobby [13]	1990	Prospective	No	37	20	2	2D TVS/ TRS	Examiner's subjective impression	two	0.5 T	Reader's subjective impression	Two	Histology
Yang [14]	1996	Prospective	No	38	20	1	2D TRS	Examiner's subjective impression	one	1 T	Reader's subjective impression	Two	Histology
Fischerova [15]	2008	Prospective	No	95	95	6	2D TRS	Examiner's subjective impression	one	1.5 T	Reader's subjective impression	One	Histology
Testa [16]	2009	Prospective	No	75	68	5	2D TVS	Examiner's subjective impression	one	1.5 T	Reader's subjective impression	Two	Histology
Epstein [17]	2013	Prospective	Yes	182	182	13	2D TVS/ TRS	Examiner's subjective impression	More than two	1.5 T/ 3T	Reader's subjective impression	Multiple	Histology
Byun [18]	2013	Prospective	No	24	24	4	3D TVS	Examiner's subjective impression	one	NA	NA	NA	Histology
Han [19]	2015	NA	No	87	80	10	3D TVS	Examiner's subjective impression	one	NA	NA	NA	Histology
Moloney [20]	2015	Prospective	Yes	46	33	10	2D TVS	Examiner's subjective impression	two	1.5 T	Reader's subjective impression	NA	Histology
Ma [21]	2017	NA	No	52	39	11	2D TVS	Examiner's subjective impression	one	1.5 T	Reader's subjective impression	one	Histology

TVS: transvaginal ultrasound, TRS: transrectal ultrasound, NA: not available, T: tesla. MRI: magnetic resonance imaging, US: ultrasound, N: number

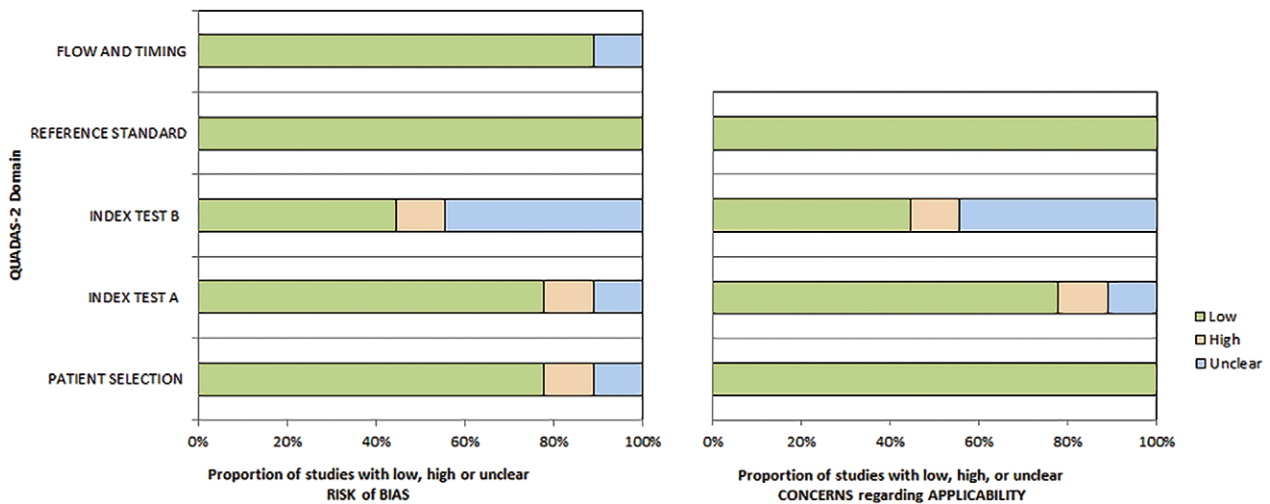


Fig 2. Histogram plot showing the quality assessment (risk of bias and concerns about applicability) for all studies included in the meta-analysis.

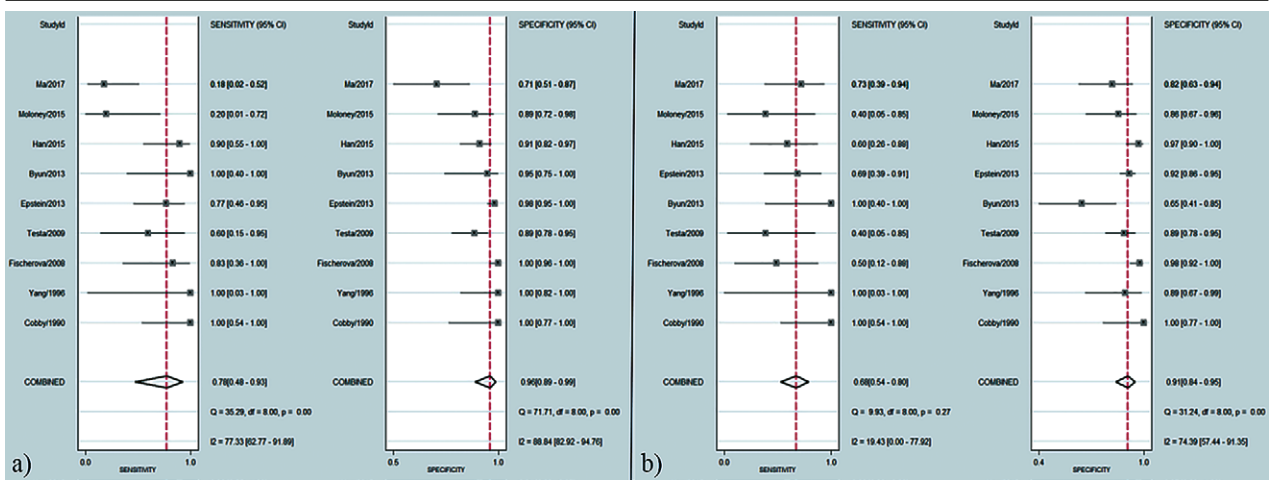


Fig 3. a) Forest plot for sensitivity and specificity for each study and pooled sensitivity and specificity for ultrasound; b) Forest plot for sensitivity and specificity for each study and pooled sensitivity and specificity for MRI

for applicability as the index tests were described well enough for study replication. However, four studies were unclear [16-19] and one was considered as a high risk [14]. All studies presented low concerns regarding the reference standard domain.

Diagnostic performance of TVS and MRI for detection of parametrial infiltration

Overall, pooled sensitivity, specificity, LR+ and LR- of US for detecting parametrial invasion were 78% (95% confidence interval [CI]=48%–93%), 96% (95% CI=89%–99%), 20 (95% CI=5.5–72) and 0.23 (95% CI=0.08–0.67), respectively. High heterogeneity was found for sensitivity (I²=77.3%; Cochran Q=35.29; p<0.01) and specificity (I²=88.84%; Cochran Q=71.71; p<0.01).

On the other hand, pooled sensitivity, specificity, LR+, and LR- of MRI for detecting parametrial invasion were 68% (95% CI=54%–80%), 91% (95% CI=84%–95%), 7.6 (95% CI=4.4–13.2), and 0.35 (95% CI=0.24–0.52), respectively. Low heterogeneity was found for sensitivity (I²=19.43%; Cochran Q=9.93; p=0.270) and moderate heterogeneity was found for specificity (I²=74.39%; Cochran Q=31.24; p<0.001).

No statistical differences were found when comparing both methods (p=0.548). Figure 3 shows forest plots for both methods. Meta-regression showed that study design, sample size, prevalence, number of observers (single/multiple) and type of US examination (2D ultrasound/3D ultrasound) did not explain the heterogeneity observed.

Summary ROC curves are shown in figure 4. Fagan nomograms show that a positive test for US and MRI increases significantly the pretest probability for parametrial infiltration, from 14% to 76% in the case of US and from 14% to 55% in the case of MRI. While a negative test significantly decreases the pretest probability, from

14% to 4% in the case of US and from 14% to 5% in the case of MRI (fig 5).

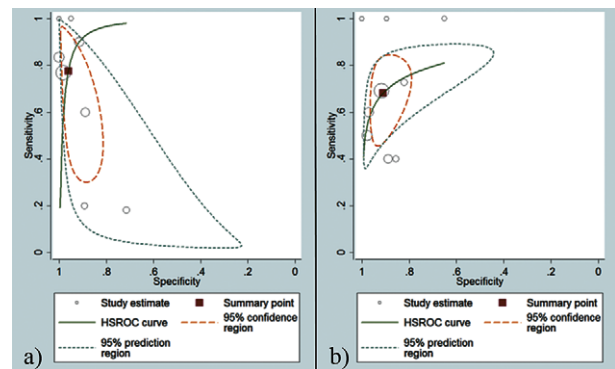


Fig 4. a) Summary ROC curve for ultrasound; b) Summary ROC curve for MRI

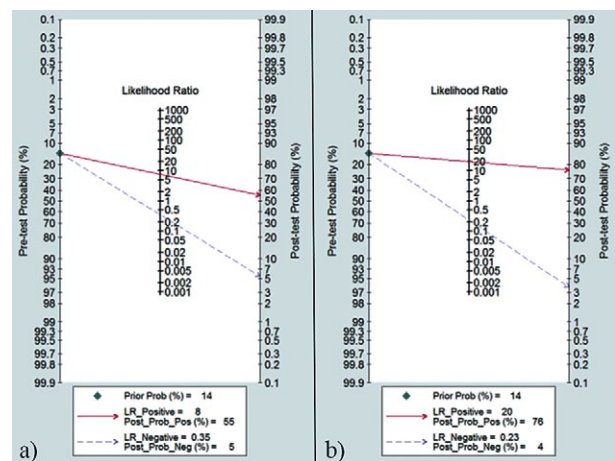


Fig 5. a) Fagan's nomogram for ultrasound; b) Fagan's nomogram for MRI

No publication bias was found, neither for US ($p=0.860$) nor for MRI ($p=0.760$).

Discussion

In the present meta-analysis, we have assessed and compared the diagnostic accuracy of ultrasound and MRI for detecting parametrial infiltration in cervical cancer, using pathological findings as a reference standard. We have found that both techniques have similar accuracy.

The main strength of this study is that, to the best of our knowledge, this is the first meta-analysis that address this issue, comparing both techniques. Another strength of our study is that we only included studies using both techniques in the same set of patients. This allow a direct comparison, reducing the risk of selection bias that could exist if we had compared studies using MRI but not ultrasound with studies using ultrasound but not MRI.

As stated above, there is no meta-analysis reported comparing ultrasound and MRI for assessing parametrial invasion in cervical cancer. However, there are some published meta-analysis assessing MRI accuracy. Bipat et al reported a meta-analysis in 2003 [22]. They included fifty-seven studies using MRI, reported between 1985 and 2002. The reference standard was the histopathology. Pooled sensitivity was 74% and specificity was about 85%. Heterogeneity among studies was found. Factors such as year of publication, sample size and magnet strength did not explain this heterogeneity. Thomeer et al included 40 studies reported between 1986 and 2011 using MRI in their meta-analysis [23]. However, they included patients with no pathological reference standard. They found that pooled sensitivity and specificity of MRI was 84% and 92%, respectively. Moderate heterogeneity among studies was observed. Meta-regression was not specifically stated as performed in this study. However, the authors reported that prevalence of parametrial invasion and magnet strength affected the pooled sensitivity and specificity. More recently, Woo et al reported a third meta-analysis using MRI, including 14 studies reported between 2012 and 2016 [24]. The pooled sensitivity and specificity reported were 73% and 93%, respectively. They also found moderate heterogeneity among studies. Meta-regression showed that magnet strength, use of Diffusion Weighted Imaging (DWI) and anti-spasmodic drugs explained this heterogeneity.

The results of all these three previous meta-analyses, in terms of pooled sensitivity and specificity, are similar to ours. We observed that pooled sensitivity and specificity was 68% and 91%, respectively. Probably, we observed a rather lower sensitivity because of our selection criteria for studies to be included in the meta-analysis,

excluding those studies not assessing ultrasound in the same study.

All three previous meta-analysis and ours, observed significant heterogeneity among studies using MRI. We also found heterogeneity among those studies using ultrasound. Apparently, one factor that could explain this heterogeneity for MRI studies could be magnet strength (observed in two meta-analyses). This heterogeneity among studies can be considered as a limitation for drawing meaningful conclusions regarding the use of MRI in these clinical setting and clearly shows that there is room for future research. We think the same is for ultrasound studies.

Another limitation of our study is the small number of patients included. Therefore, our findings must be interpreted with caution.

Our findings may have clinical relevance, especially when FIGO has stated recently that both techniques can be used for imaging staging of cervical cancer [7]. Ultrasound is much cheaper and more widely available than MRI. This is important, especially when considering that cervical cancer is much more prevalent in less developed countries [1]. Certainly, ultrasound examination should be performed by an experienced examiner. Therefore, training and experience is an important issue. However, there is no published information about the learning curve for ultrasound assessment of cervical cancer. MRI performance might also depend on the experience of the radiologist reading MRI images. Nevertheless, some technical factors may also be relevant, such as the magnet strength and use of DWI.

In **conclusion**, ultrasound and MRI have a similar diagnostic performance for assessing parametrial infiltration in cervical cancer. However, due to the heterogeneity found among the studies included in this meta-analysis and the relatively small sample size, these findings must be taken with caution. Further well-designed studies would be needed for comparing MRI and ultrasound in the assessment of parametrial invasion in cancer of the uterine cervix.

Conflict of interest: none

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