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Transvaginal ultrasound for preoperative assessment of myometrial invasion in patients with endometrial cancer: a systematic review and meta-analysis

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KEYWORDS: endometrial cancer; meta-analysis; myometrial invasion; systematic review; transvaginal ultrasound

ABSTRACT

Objective *To review the diagnostic accuracy of transvaginal ultrasound (TVS) in the preoperative detection of deep myometrial infiltration in patients with endometrial cancer, comparing subjective and objective methods.*

Methods *An extensive search was performed in MEDLINE (PubMed) and EMBASE for studies published between January 1989 and December 2014. The eligibility criterion was use of TVS for preoperative assessment of myometrial infiltration by subjective evaluation and/or objective measurements. Objective measurements included, specifically, the approaches of Gordon (ratio of the distance between endometrium–myometrium interface and maximum tumor depth to the total myometrial thickness) and Karlsson (endometrial tumor thickness/anteroposterior uterine diameter ratio), in women with endometrial cancer, using the surgical pathological data as a reference standard. Study quality was assessed using the QUADAS-2 tool.*

Results *Our extended search identified a total of 184 citations, among which we examined the full text of 24 articles. Overall pooled sensitivity, specificity, positive likelihood ratio (LR+) and negative likelihood ratio (LR–) of TVS for detecting deep myometrial infiltration were 82% (95% CI, 76–87%), 81% (95% CI, 76–85%), 4.3 (95% CI, 3.6–5.3) and 0.22 (95% CI, 0.16–0.30), respectively. We did not observe differences among the three methods in terms of diagnostic performance. Significant heterogeneity was found for sensitivity and specificity of all three methods (I^2 range, 60.6–95.0). The main limitation was that very few studies compared different approaches in the same set of patients.*

Conclusion *Diagnostic performance of TVS for detecting deep myometrial infiltration in women with endometrial cancer is moderate. Copyright © 2015 ISUOG. Published by John Wiley & Sons Ltd.*

INTRODUCTION

Cancer of the corpus uteri, mainly endometrial cancer (EC), is the sixth most frequent form of cancer in women worldwide, with approximately 320 000 new cases and 76 200 deaths in 2012, with the highest incidence rates estimated in North America ($19.1/10^5$) and Northern and Western Europe ($12.9/10^5$–$15.6/10^5$) with 54 700 and 53 400 new cases each year, respectively[1]. The most important prognostic features for EC are FIGO stage (International Federation of Gynecology and Obstetrics), myometrial infiltration (MI), histological type and differentiation grade, most of which are independent of each other[2]. Among these, MI $\geq 50\%$ is associated with both pelvic lymph-node involvement and extension into the parametrium[3,4]. Thus, selecting low-risk cases preoperatively, based on MI assessment, may contribute to surgical planning and may avoid unnecessary lymph-node dissections[5]. To assess the depth of MI, a number of imaging procedures have been applied, including transvaginal ultrasound (TVS), computed tomography (CT) and magnetic resonance imaging (MRI)[6–8]. Since the first paper published by Cacciatore *et al.* in 1989[9], TVS has been used extensively to assess MI in EC. Several approaches have been proposed, including both the examiner's subjective assessment and objective measurements such as those proposed by Gordon *et al.*[10] and Karlsson *et al.*[11].

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However, there is currently no clear evidence concerning overall diagnostic performance and whether one approach is superior to the others.

The purpose of this systematic review was to evaluate the diagnostic accuracy of TVS, comparing subjective and objective approaches, in the preoperative detection of deep MI in patients with EC, using surgical pathological data as a reference standard.

METHODS

Protocol and registration

We performed this systematic review and meta-analysis according to the PRISMA Statement (http://www.prisma-statement.org/). All methods for inclusion/exclusion criteria, data extraction and quality assessment were specified in advance. The protocol was not registered.

Data sources and searches

Studies published between 1989 and December 2014 were screened by one of the authors (J.L.A.) using two electronic databases, EMBASE and PubMed/MEDLINE, to identify potentially eligible studies. We did not use methodological filters in database searches to avoid possible omission of relevant studies, according to the recommendations of Leeflang *et al.*[12]. The search terms included and captured the concepts of 'endometrial cancer', 'transvaginal ultrasound' and 'myometrial invasion'. There were no language restrictions in the search.

Study selection and data collection

One author (J.L.A.) screened the titles and abstracts identified by the searches to exclude obviously irrelevant articles, i.e. those not strictly related to the topic under review. Full-text articles were obtained to identify potentially eligible studies, and three authors (R.O., T.M.-A.C. and L.J.) independently applied the following inclusion criteria: 1) prospective cohort study with ≥ 50 patients; 2) adult participants with biopsy-proven primary adenocarcinoma of the endometrium, at any stage of the disease, undergoing preoperative staging prior to surgery; 3) presurgical detection of deep MI in primary endometrial adenocarcinoma by TVS as the target condition; 4) TVS as the index test, using both subjective impression and objective methods, the latter consisting of Gordon's approach, i.e. ratio of distance between maximum tumor depth and total myometrial thickness[10] (Figure 1) and/or Karlsson's approach, i.e. ratio between maximum anteroposterior diameter of the endometrial lesion and the uterine anteroposterior diameter, both measured in the sagittal plane[11] (Figure 2); 5) pathological assessment of the presence of deep MI in the uterus removed at surgery as reference standard; 6) presence of results sufficient to construct the 2×2 table of diagnostic performance as minimum data requirement.

The PICOS (Patients, Intervention, Comparator, Outcomes, Study design) criteria used for inclusion and exclusion of studies are shown in Table 1. Diagnostic accuracy results and additional useful information on patients and procedures were retrieved from selected primary studies independently by the same authors (J.L.A., R.O., T.M.-A.C. and L.J.). Disagreements arising during the process of study selection and data collection were resolved by consensus among three of the authors (J.L.A., R.O. and T.M.-A.C.).

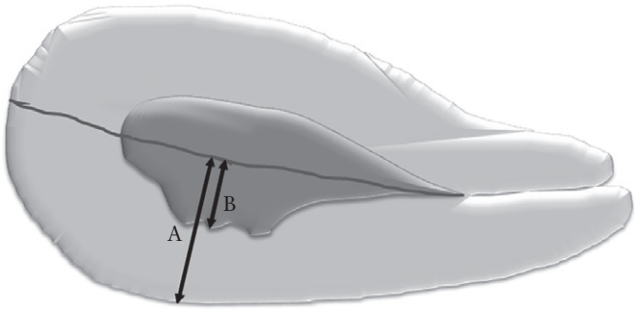

Figure 1 Schematic illustration of the uterus in the sagittal plane, showing Gordon's approach. Depth of infiltration was measured as the ratio of the distance between the maximum tumor depth (B) and the total myometrial thickness (A), with B/A >50% indicating deep myometrial infiltration.

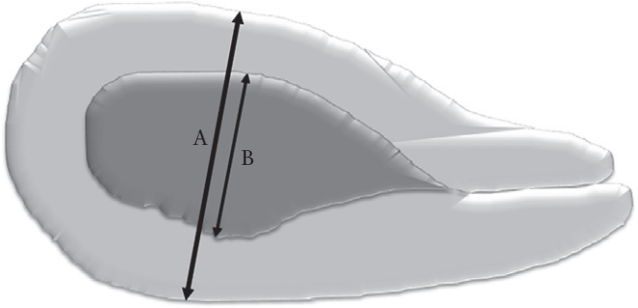

Figure 2 Schematic illustration of the uterus in the sagittal plane, showing Karlsson's approach. Depth of infiltration was measured as the ratio between the maximum anteroposterior (AP) diameter of the endometrial lesion (B) and the uterine AP diameter (A), with B/A >50% indicating deep myometrial infiltration.

Risk of bias in individual studies

Quality assessment was conducted, adapting to this particular review the tool provided by QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2)[13]. The QUADAS-2 format includes four domains: 1) patient selection, 2) index test, 3) reference standard, 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 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. Signaling questions are shown in Appendix S1. Three authors (J.L.A., R.O. and T.M.-A.C.) independently evaluated the methodological quality, using a standard form with quality assessment criteria and a flow diagram; they resolved disagreements by discussion among three of the authors (J.L.A., R.O. and T.M.-A.C.).

Table 1 Characteristics of studies included according to PICOS (Patients, Intervention, Comparator, Outcomes, Study design) criteria

Reference	*Setting*	*Consecutive recruitment*	n	*Method*	*Observers*	*Cases with MI ≥ 50% (n)*
Artner (1994)[38]	Single center	Yes	69	Gordon	Single	28
Prömpeller (1994)[44]	Single center	Unclear	96	Karlsson	NA	44
Weber (1995)[45]	Single center	Unclear	80	Karlsson	NA	27
Osmers (1995)[53]	Single center	Unclear	76	Subjective	NA	33
Gabrielli (1996)[46]	Single center	Unclear	67	Karlsson	Multiple	26
Valsecchi (1997)[47]	Single center	Yes	77	Karlsson	Two	34
Olaya (1998)[48]	Single center	Yes	50	Karlsson	Single	17
Alcázar (1999)[49]	Single center	Yes	50	Karlsson	Single	15
Arko (2000)[39]	Single center	Unclear	120	Gordon	Single	48
Van Doorn (2002)[54]	Multicenter	Unclear	93	Subjective	Multiple	33
Sawicki (2003)[50]	Single center	Unclear	90	Karlsson	NA	36
De Smet (2006)[55]	Single center	Yes	97	Subjective	Single	59
Takač (2007)[40]	Single center	Unclear	53	Gordon	Single	28
Yahata (2007)[41]	Single center	Unclear	177	Gordon	NA	58
Savelli (2008)[56]	Multicenter	Yes	74	Subjective	Two	32
Alcázar (2009)[58]	Multicenter	Yes	96	Subjective	Two	27
Ozdemir (2009)[57]	Single center	Unclear	64	Subjective	Single	20
Savelli (2012)[59]	Multicenter	Unclear	155	Subjective	Multiple	76
Ørtoft (2013)[42]	Single center	Yes	156	Gordon	Multiple	66
Mascilini (2013)[51]	Multicenter	Yes	144	Karlsson/subjective	Multiple	60
Antonsen (2013)[8]	Multicenter	Yes	318	Subjective	Multiple	82
Miklos (2004)[43]	Single center	Unclear	150	Gordon	Single	39
Van Holsbeke (2014)[52]	Multicenter	Unclear	211	Karlsson/subjective	Multiple	77
Fischerova (2014)[60]	Single center	Yes	210	Subjective	Multiple	87

All studies were prospective and included women with diagnosis of endometrial carcinoma after dilatation and curettage, pipelle or hysteroscopic biopsy. In all studies, the index test was transvaginal ultrasound and the reference standard was uterine pathological findings after hysterectomy. Only the first author of each study is given. MI, myometrial infiltration; NA, not available.

Statistical analysis

We extracted or derived information on diagnostic performance of TVS. All studies had as the reference standard patients presenting with at least 50% MI according to surgical pathological data. Primary outcome was pooled sensitivity, specificity, positive likelihood ratio (LR+) and negative likelihood ratio (LR−), and analyses were pooled separately for both objective approaches and for the subjective approach. We used a random-effects model. Positive and negative likelihood ratios (LRs) were used to characterize the clinical utility of a test and to estimate the post-test probability of disease. An LR of 0.2–5.0 provides weak evidence for either ruling out or confirming the disease. An LR of 5.0–10.0 or 0.1–0.2 provides moderate evidence to either confirm or rule out the disease. An LR > 10 or < 0.1 provides strong evidence to either confirm or rule out the disease[14]. Using the mean prevalence of MI ≥ 50% (pretest probability) in each subset, depending upon the method and LRs, post-test probabilities were calculated and plotted on Fagan nomograms.

We explored graphically heterogeneity of all studies, drawing forest plots of sensitivity and specificity. We then formally assessed the presence of heterogeneity for sensitivity and specificity using Cochran's Q test and the I^2 index for all three approaches[15]. A test for heterogeneity examines the null hypothesis that all studies are evaluating the same effect[15]. Cochran's Q statistic is computed by summing the squared deviations of each study's estimate from the overall meta-analytic estimate, weighting each study's contribution in the same manner as in the meta-analysis. A P-value < 0.1 indicates heterogeneity. The I^2 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[15].

Summary receiver–operating characteristics (sROC) curves for each approach were plotted to illustrate the relationship between sensitivity and specificity. Comparison of diagnostic performance among the three approaches for estimating MI was done using the bivariate method[14]. All analyses were performed using MIDAS (Meta-analytical Integration of Diagnostic Accuracy Studies) command in 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 232 citations but after removal of 68 duplicate records, 164 citations remained. Of these, 114 were excluded because it was clear from the title or abstract that they were not relevant to the review. We examined the full text of the remaining 50 articles. Finally, 26 studies[7,9–11,16–37] were discarded because they did not meet inclusion criteria and the

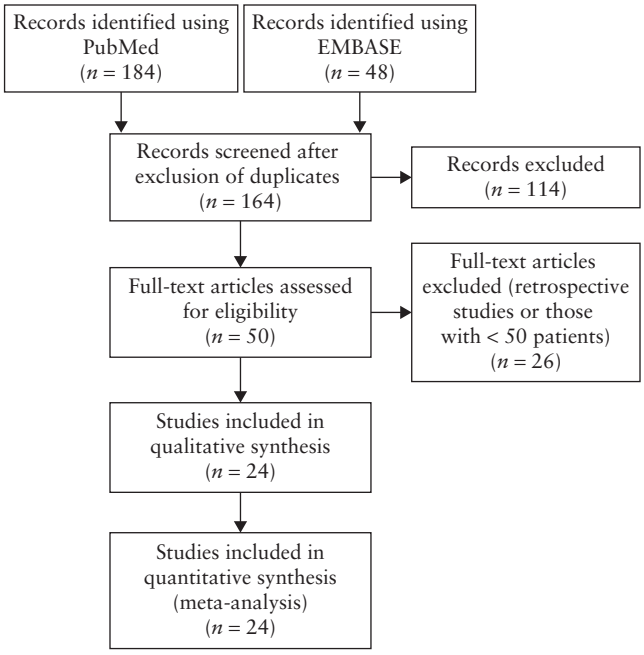

Figure 3 Flowchart showing literature identification and selection.

remaining 24 studies were included in the review and meta-analysis[8,38–60]. No additional relevant studies were found from references cited in the papers included in the review. A flowchart summarizing literature identification and selection is given in Figure 3.

Characteristics of included studies

A total of 24 studies[8,38–60] reporting on 2773 patients between 1994 and 2014 were included in the final analyses. In two studies a total of 355 women underwent TVS to assess two different approaches[51,52]. Among the 2773, 1052 (38%) women had MI ≥ 50%. This was considered as prevalence and, therefore, pretest probability.

In 15 studies, objective measurement approaches were used to assess MI; six studies used Gordon's approach[38–43] and nine used Karlsson's approach[44–52]. In 11 studies MI assessment was based on the examiner's subjective impression[8,51–60]. The main patient characteristics in these studies are not available. Most studies included low- and high-risk tumors of all histological types. No patient underwent oncological therapy between TVS and surgery.

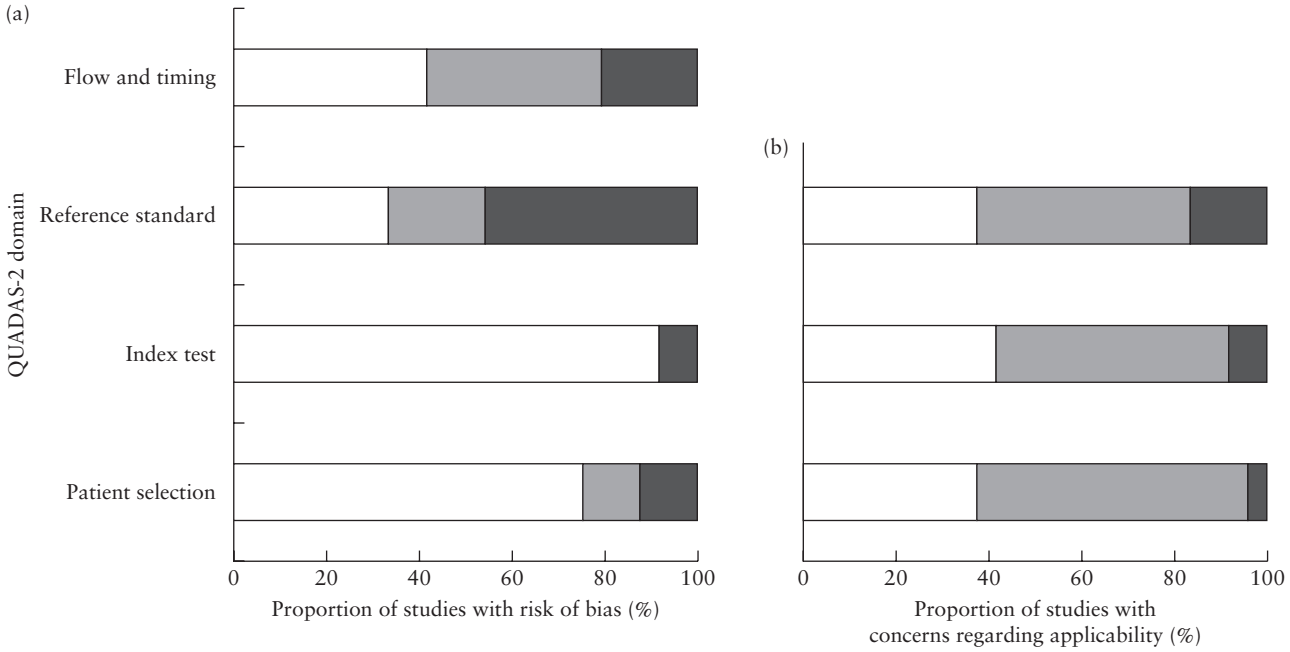

Figure 4 Quality evaluation of all studies included in the meta-analysis, according to QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) criteria[13], with respect to risk of bias (a) and concerns regarding applicability (b). □, low; ▒, high; ■, unclear.

Table 2 Pooled diagnostic performance of each approach for detection of deep myometrial infiltration using transvaginal ultrasound

Parameter	*Subjective*	*Karlsson's*	*Gordon's*
Sensitivity (%)*	78 (72–83)	84 (76–90)	85 (60–95)
Specificity (%)*	81 (71–87)	82 (76–86)	80 (65–90)
LR+	4.0 (2.6–6.3)	4.6 (3.3–6.3)	4.3 (2.3–7.9)
LR–	0.27 (0.20–0.38)	0.19 (0.12–0.30)	0.19 (0.06–0.56)

*$P > 0.05$ for all paired comparisons. LR+, positive likelihood ratio, LR–, negative likelihood ratio.

Methodological quality of included studies

A graphical display of the evaluation of the risk of bias and concerns regarding applicability of the selected studies, according to predefined criteria, is shown in Figure 4. Regarding risk of bias and the domain patient selection, six studies did not report explicitly or were not clear regarding patient inclusion criteria[39,43,48,50,54,56]. Concerning the domain index test, all but two studies described clearly the index test as well as how it was performed and interpreted. All studies adopted the same prespecified threshold to define deep MI (≥ 50% of myometrial thickness). Concerning the domain reference standard, all studies stated that permanent frozen sections were analyzed after uterus removal, but most of them did not describe in detail how this was done. Concerning the flow and timing domain, 14 studies did not report the interval between TVS and surgery or this information was unclear[8,38–40,43,45–57].

Regarding applicability, the 11 studies using examiner's subjective impression[8,51–60] posed problems with the index test, as such methods were not generally applicable. However, it should be taken into consideration that 'objective approaches' are actually based on 'subjective measurements' by an individual examiner.

As mentioned before, all studies included pathological evaluation of the removed uterus; thus, there were no concerns about reference standard applicability. However, 15 studies did not allow for confirmation or did not state explicitly if pathological evaluation of MI was blinded to TVS results and we consider these studies to be highly inapplicable or unclearly so [8,38–40,43,44,46–48,51,52,54–57].

Regarding patient selection, in 13 studies it was not clear whether the sample was consecutive or random and in some studies inappropriate exclusions may have been made. We did not exclude any studies from the meta-analysis because of methodological flaws.

Diagnostic performance of TVS for detection of deep myometrial invasion

We analyzed the overall sensitivity and specificity of TVS in all studies and for each of the three approaches (subjective assessment, Karlsson's approach and Gordon's approach). Overall, pooled sensitivity, specificity, LR+ and LR– of TVS in detecting deep MI were 82% (95% CI, 76–87%), 81% (95% CI, 76–85%), 4.3 (95% CI, 3.6–5.3) and 0.22 (95% CI, 0.16–0.30), respectively. Pooled diagnostic performance of all three approaches is shown in Table 2. We did not find statistical differences among the results using all approaches. sROC curves are shown in Figure 5. Areas under the curve were similar for the three approaches.

Heterogeneity was significant for sensitivity (I^2, 69.5% (95% CI, 50.6–88.5%) using subjective assessment, 76.6% (95% CI, 61.4–91.8%) using Karlsson's approach and 95.0% (95% CI, 92.3–97.6%) using Gordon's approach), and for specificity (I^2, 85.5%

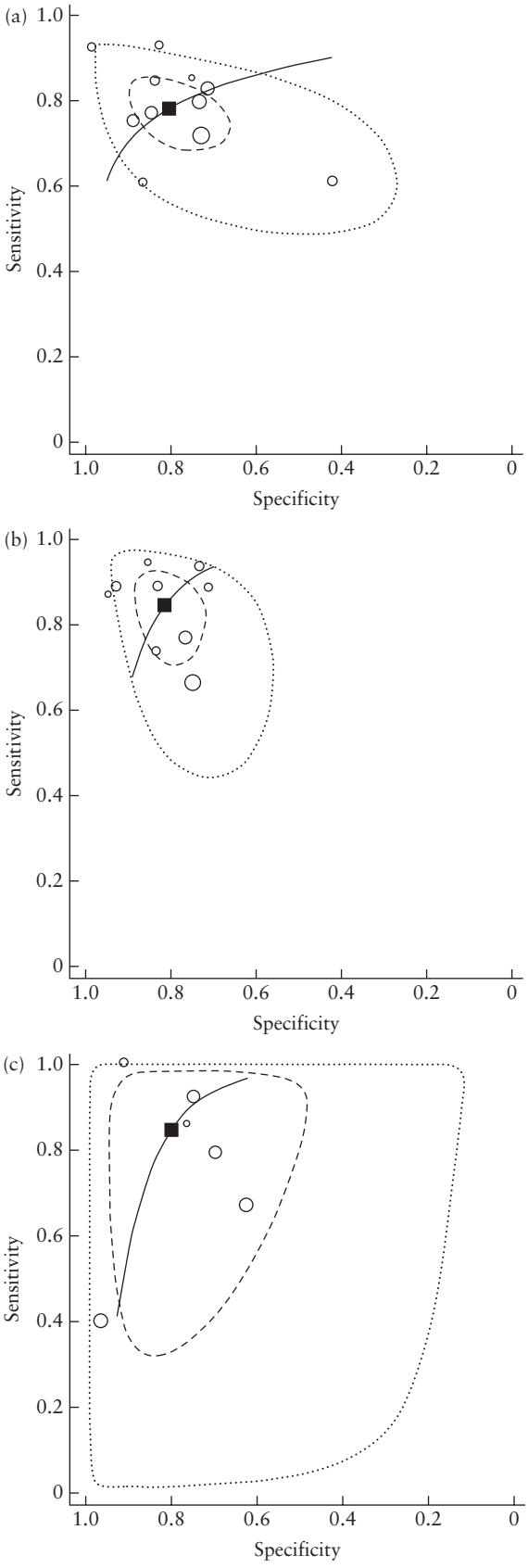

Figure 5 Summary receiver–operating characteristics (sROC) curves for each approach to detection of deep myometrial infiltration using transvaginal ultrasound: (a) subjective impression, (b) Karlsson's approach and (c) Gordon's approach. ○, study estimate; ■, summary point; ——, sROC curve; – – –, 95% confidence region; ..... , 95% prediction region.

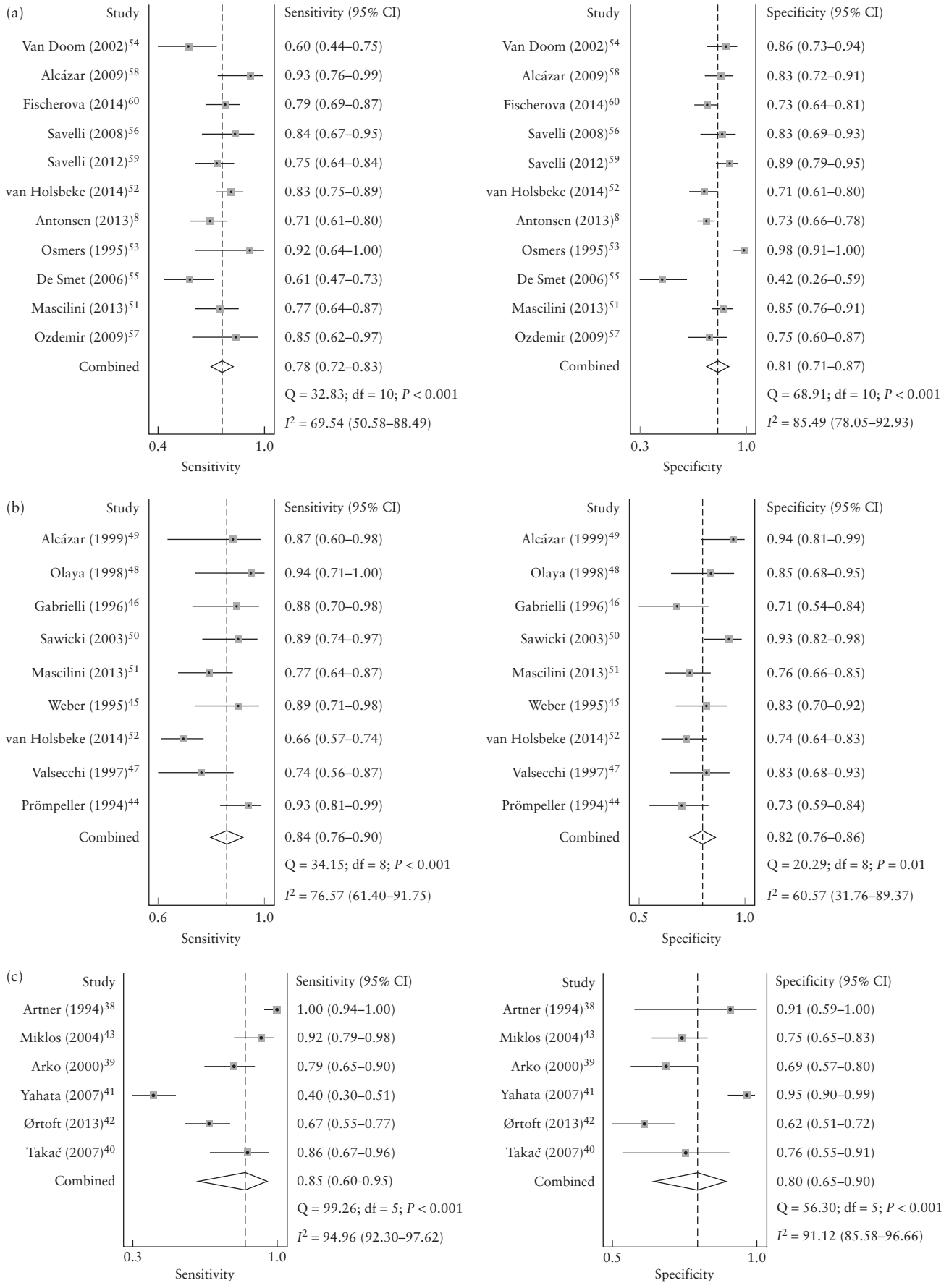

Figure 6 Forest plots of studies evaluated for the three approaches to assessment of myometrial infiltration using transvaginal ultrasound. (a) Subjective impression. (b) Karlsson's approach. (c) Gordon's approach. Summary sensitivity and specificity as well as heterogeneity statistics (Cochran's Q and I^2) are shown.

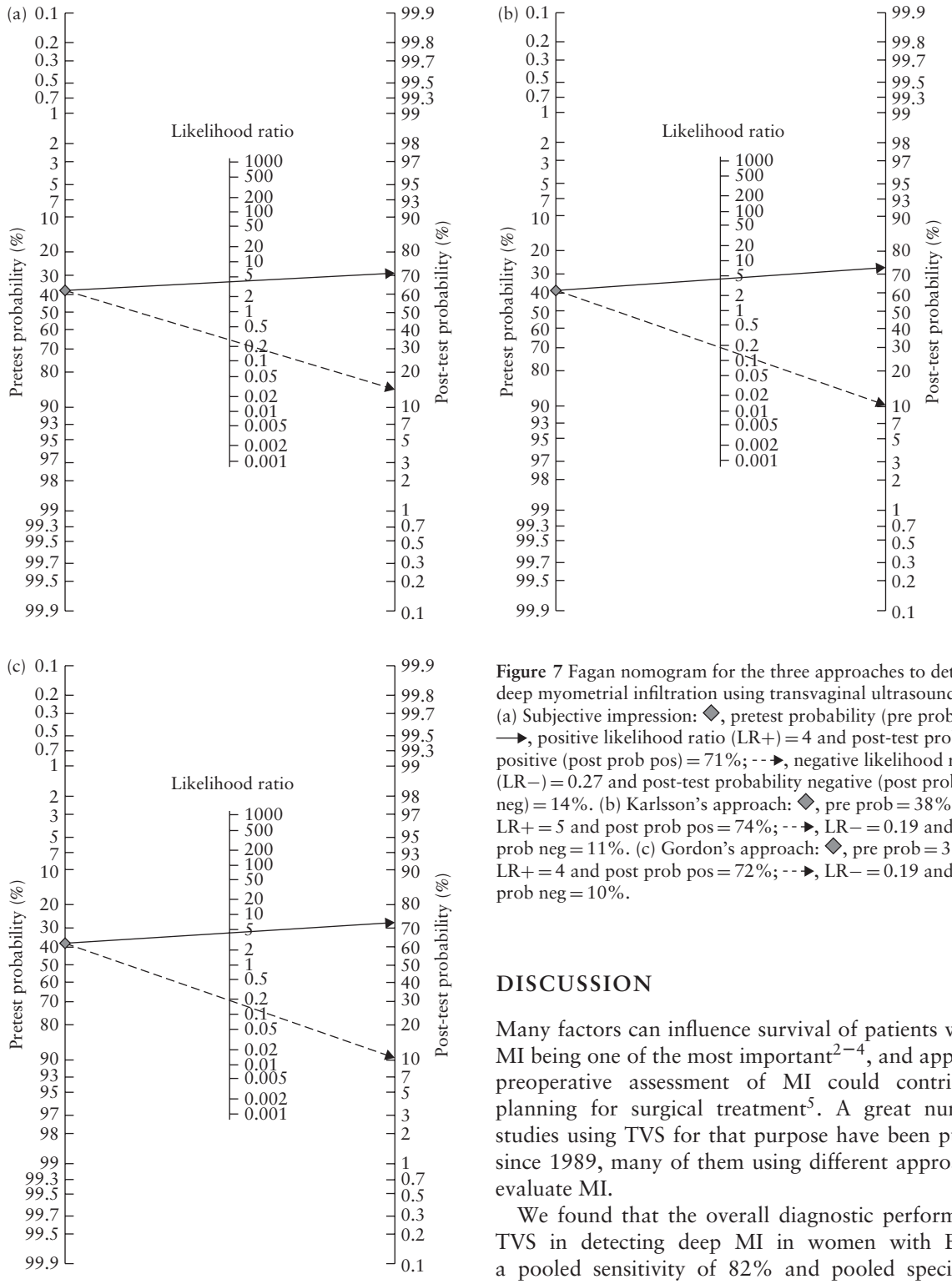

Figure 7 Fagan nomogram for the three approaches to detection of deep myometrial infiltration using transvaginal ultrasound. (a) Subjective impression: ◇, pretest probability (pre prob) = 38%; ⟶, positive likelihood ratio (LR+) = 4 and post-test probability positive (post prob pos) = 71%; - - →, negative likelihood ratio (LR−) = 0.27 and post-test probability negative (post prob neg) = 14%. (b) Karlsson's approach: ◇, pre prob = 38%; ⟶, LR+ = 5 and post prob pos = 74%; - - →, LR− = 0.19 and post prob neg = 11%. (c) Gordon's approach: ◇, pre prob = 38%; ⟶, LR+ = 4 and post prob pos = 72%; - - →, LR− = 0.19 and post prob neg = 10%.

(95% CI, 78.0–92.9%) using subjective assessment, 60.6% (95% CI, 31.8–89.4%) using Karlsson's approach and 91.1% (95% CI, 85.6–96.7%) using Gordon's approach), as shown in Figure 6. Fagan nomograms show that for all three approaches a positive test significantly increased the pretest probability of MI ≥ 50%, while a negative test significantly decreased the pretest probability of MI ≥ 50% (Figure 7).

DISCUSSION

Many factors can influence survival of patients with EC, MI being one of the most important[2–4], and appropriate preoperative assessment of MI could contribute to planning for surgical treatment[5]. A great number of studies using TVS for that purpose have been published since 1989, many of them using different approaches to evaluate MI.

We found that the overall diagnostic performance of TVS in detecting deep MI in women with EC gave a pooled sensitivity of 82% and pooled specificity of 81%. Comparing subjective impression with objective measurement techniques, we observed that all methods were similar, without statistical differences, in terms of diagnostic performance. However, it should be taken into account that the number of studies concerning each approach was small.

We observed a significant heterogeneity across studies in terms of sensitivity and specificity, whatever the approach used. In test accuracy studies, one of the primary causes of heterogeneity is the threshold effect. This arises when different cut-offs or thresholds are used in

different studies. It could be argued that a threshold effect should not exist in this meta-analysis since, based on subjective impression, there is no quantitative threshold or cut-off and all studies using objective measurements used the same threshold. However, looking at the sROC curves a clear 'shoulder arm' pattern was observed, suggesting a threshold effect. In fact, we were somewhat surprised to observe heterogeneity in studies using Karlsson's approach; we expected low heterogeneity using this approach since it is a very clear and easy way to estimate MI. On the contrary, we expected high heterogeneity using Gordon's approach and subjective assessment since these approaches may be more difficult to reproduce.

A possible explanation for this high heterogeneity is the potentially low reproducibility of the methods. However, Eriksson *et al.* recently estimated the reproducibility of subjective impression in assessing MI in 53 cases of EC using offline videoclips. A total of 18 examiners participated in the study and interobserver reproducibility ranged from fair to very good, being moderate or good in most pair comparisons[61].

This review provides an idea of the methodological quality of studies using TVS for assessment of deep MI. It is clear that quality could be improved in most studies, especially concerning patient selection, reference standard and flow and timing.

Regarding the clinical use of TVS for predicting deep MI in women with EC we found that LR+ (4.0, 4.6 and 4.3 using subjective impression, Karlsson's and Gordon's approaches, respectively) and LR– (0.27, 0.19 and 0.19 using subjective impression, Karlsson's and Gordon's approaches, respectively) were essentially within the range of poor estimates for confirming the disease and within the range of moderate estimates for ruling out the disease.

MRI has been advocated also as a non-invasive technique for predicting deep MI in EC. Recent meta-analyses concerning this technique have shown pooled sensitivities ranging from 81% to 90% and pooled specificities ranging from 82% to 89%[6,62,63]. No differences were found between contrast-enhanced MRI and diffusion-weighted MRI. These figures are slightly better than those reported in our meta-analysis for TVS. However, when considering the 95% CI reported in these studies for sensitivity and specificity we observed an overlap with our results. Therefore, it is unlikely that any significant difference exists between the methods. For this reason, and taking into account the cost of MRI, we believe that TVS may have a role as the first imaging technique for assessing MI in women with EC. Notwithstanding, no single meta-analysis has formally compared the diagnostic performance of MRI with that of TVS in predicting deep MI and there is obviously a need for this.

We also observed that, in all but one study[52], those included were both high- and low-risk patients. This may affect the clinical applicability of TVS because, from the point of view of gynecological oncologists, preoperative assessment is appropriate in women with preoperative histological data indicating potential low risk, i.e. women with well or moderately differentiated endometrioid cancer. Therefore, we cannot rule out that the diagnostic performance could be overestimated because of inclusion of high-risk cases, in whom the probability of deep MI is higher. This applies to TVS and MRI studies and could also explain the heterogeneity observed among studies.

The main strength of our study is that, to the best of our knowledge, no previous meta-analysis on the same topic has been reported previously. As in other meta-analyses, there are some limitations in our study. Ideally, for comparing the diagnostic performance of different approaches to assess MI, studies should apply all approaches in the same set of patients. This has been done in only three studies[51,52,55]. Analyzing data reported in these three studies, we observed that objective measurement techniques were not superior to subjective assessment. Considering all studies, the same finding was observed.

Some studies did not mention the time interval between TVS and surgery. We assumed that this period was probably not long enough to modify the disease progression; otherwise, those cases would have been excluded for obvious reasons. However, this may not be true and possible bias may exist. Some unanswered questions remain. One concerns the reproducibility of these different approaches in real-time ultrasound examinations.

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SUPPORTING INFORMATION ON THE INTERNET

Appendix S1 may be found in the online version of this article.

