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Original Articles

Evaluation of three-dimensional ultrasound measurement techniques used to assesses myometrial invasion in endometrial cancer

J.W. Christensen[1,2], G. Ørtoft[3], E.S. Hansen[4], M. Dueholm[1]

[1]*Department of Gynecology and Obstetrics, Aarhus University Hospital, Aarhus*
[2]*Department of Clinical Physiology and Nuclear Medicine, Herlev and Gentofte Hospital, Herlev*
[3]*Department of Gynecology and Obstetrics, Rigshospitalet, Copenhagen*
[4]*Department of Histopathology, Aarhus University Hospital, Aarhus (Denmark)*

Summary

Purpose: To assess interobserver variation and efficiency of various measurements on 3-dimensional transvaginal ultrasound (3D-TVS) and saline infusion sonography (3D-SIS) for preoperative measurement of deep myometrial invasion (DMI) in endometrial cancer. *Materials and Methods:* One hundred ten women with atypical endometrial hyperplasia or endometrial adenocarcinoma had preoperative 3D-TVS and 3D-SIS. Endometrial thickness (ET), ET in percent of uterine diameter (PAP) and various volumes were measured. AUC, sensitivity, and specificity of most optimal cut-points, and kappa statistics for observer variation were calculated. *Results:* PAP identified two-thirds of women with DMI. ET and 3D volume measurements had substantial observer agreement compared to moderate agreement of subjective evaluation of DMI. AUC for measurements ranged 0.63–0.73 for identification of DMI. Subjective evaluation of DMI had highest AUC only marginally improved by adding PAP. *Conclusion:* Preoperative staging of endometrial cancer is not improved by adding 3D volume measurements to subjective evaluation, but PAP could be used to select women with a high risk of DMI for further MRI.

Key words: Endometrial neoplasms; Imaging; 3-dimensional; Ultrasonography; Tumor burden; Preoperative procedures.

Introduction

Surgical treatment of women with endometrial cancer is determined by tumor stage and grade; therefore, correct preoperative staging is essential. All women are offered total abdominal hysterectomy and bilateral salpingo-oophorectomy. Routine lymphadenectomy does not seem to increase survival in Stage 1 disease, but does induce increased morbidity [1]. In Denmark, women with endometrial cancer are therefore offered lymph node resection according to risk assessment. Women with deep myometrial invasion (DMI) (≥ 50%, apparent FIGO Stage IB), and/or tumor grade 3, or high risk tumors are also offered lymphadenectomy [2].

DMI can be evaluated either preoperatively [using magnetic resonance imaging (MRI), two-dimensional transvaginal ultrasonography (2D-TVS) and/or three-dimensional transvaginal ultrasonography (3D-TVS)], or perioperatively (using frozen section or gross inspection during surgery) [3–12].

Preoperative evaluation of DMI with imaging has an accuracy almost identical to perioperative evaluation, but in contrast to the perioperative techniques, imaging has the advantage of providing individual preoperative planning of the extent of surgery and thus a reduced operating time. However, evaluation of DMI with imaging is subverted by prior hysteroscopic resection of the endomyometrium and must be performed before hysteroscopy.

The authors have previously compared the value of 3D-TVS to 2D-TVS and MRI for preoperative assessment of DMI in endometrial cancer. 3D-TVS was significantly inferior to MRI, although when scans deemed of subjectively inadequate quality were excluded, similar accuracies could be obtained [13]. MRI has a high accuracy and seems to be slightly better than 2D-TVS [14–17], although the two techniques have comparable sensitivities. Preoperative addition of MRI or PET/CT is often preferred in women with DMI to evaluate node status and involvement of parametrium or other organs. However, TVS is a much simpler and less expensive technique used at the first step investigation, and it could provide information for selection of more advanced imaging.

A fast-track schedule has been introduced in several countries to minimize the time between first complaint of bleeding and treatment of cancer. Most endometrial cancers may be identified on structured evaluation of en-

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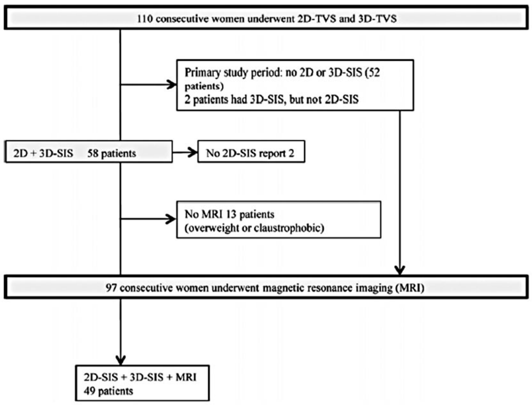

Figure 1. — Patient inclusion. Detailed description of patient inclusion is provided in previous publications [13, 14].

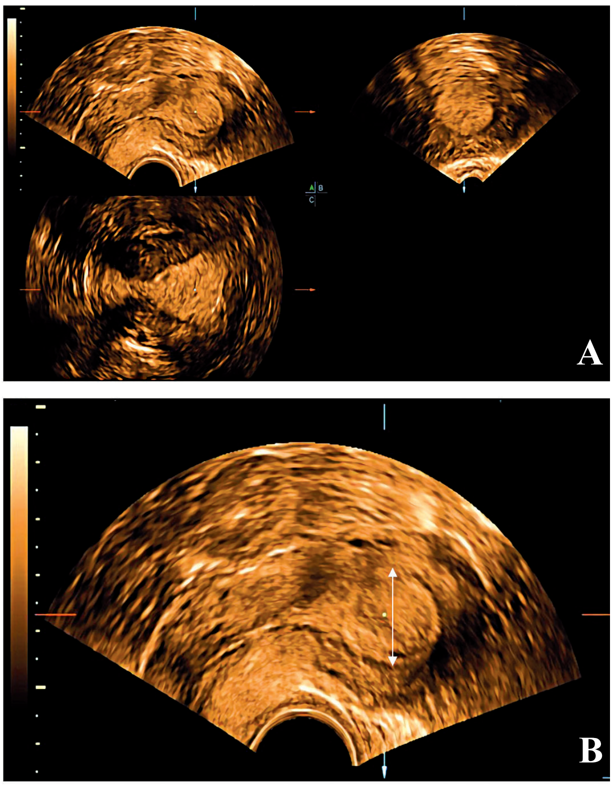

Figure 2. — 2A) 3D-TVS image of a uterus with endometrial cancer. Image is adjusted to a standardized multiplanar view (35): (A) sagittal view, (B) transverse view, and (C) coronal view. The volume contrast imaging function is used in order to visualize the endometrial myometrial junction zone.
2B) Measurement of endometrial thickness is done in the sagittal plane using "Dist. 2 Point" in the "Sect. Planes" view of 4D View software. The authors measured the thickest endometrium, ensuring not to measure near the ostia, which would give a falsely large measurement. Figure 2B shows the sagittal plane with an arrow marking the thickest endometrium.

dometrial morphology with TVS and Doppler [18]. Ideally, experienced sonographers trained in the evaluation of DMI should examine the TVS before hysteroscopy. However, as these sonographers are not always at hand at first investigation, women are often sent for secondary time-consuming evaluation at oncology centers, often after hysteroscopy. Simple measurements of 3D-TSV volumes can easily be obtained by most sonographers at initial investigation in order to identify women with low/high risk of DMI. This 3D-volume can be used for immediate measurement and be sent to an oncology center. When needed, appropriate additional imaging techniques could be offered immediately to reduce time.

Several attempts have been made to identify an optimal cutoff value regarding endometrial thickness (ET) that could differentiate between carcinoma with superficial or deep invasion [19–21]. Furthermore, an ET of 2 cm has been suggested for use in estimating the risk of lymph node metastasis [22]. However, subjective evaluation of DMI (subj-DMI) with TVS seems to be the most optimal strategy [23,24].

The aim of the present study was to evaluate whether one or two simple preoperative measurements using stored 3D volumes of the uterus could be used to identify patients with a high or low risk of DMI. Moreover, the authors sought to assess whether subj-DMI on 3D-TVS in endometrial cancer could be improved by the addition of simple measurements. Interobserver variation was assessed and taken into consideration in the evaluation.

Materials and Methods

Women with histologically proven endometrial cancer ($n = 61$) or hyperplasia with atypia ($n = 49$) were included from Aarhus University Hospital, Denmark 2008–2011. Characteristics of the 110 women included in the present study have been published in a previous article [13] (Figure 1).

According to Danish guidelines [25], women with an initial diagnosis of atypia must be guideline evaluated exactly like women diagnosed with endometrial cancer, as 59% of this patient group has been shown to have endometrial cancer on final histology [15].

All women were scanned using 2D- and 3D-TVS on an ultrasound machine equipped with a multifrequency (5–13 MHz) endovaginal probe. Scans were performed at inclusion and later analyzed using "4D View" according to a defined scanning protocol, as previously described [13].

Ultrasound analysis was performed by two senior physicians with ultrasound experience (A and B) and a junior research assistant (C). A's findings were used for most of the following calculations; while the findings of B and C were used for interobserver evaluations only.

Initially, each 3D volume was optimized in the "Sect. Planes" view to display the perfect sagittal, transverse, and coronal planes and by changing the "Image Settings" if necessary. The uterine volume was adjusted to a standardized multi-planar view. (Figure 2A)

Following the initial analysis of each 3D-TVS image, ET and the volumes of the endometrium, total uterus, fluid, cervix, and

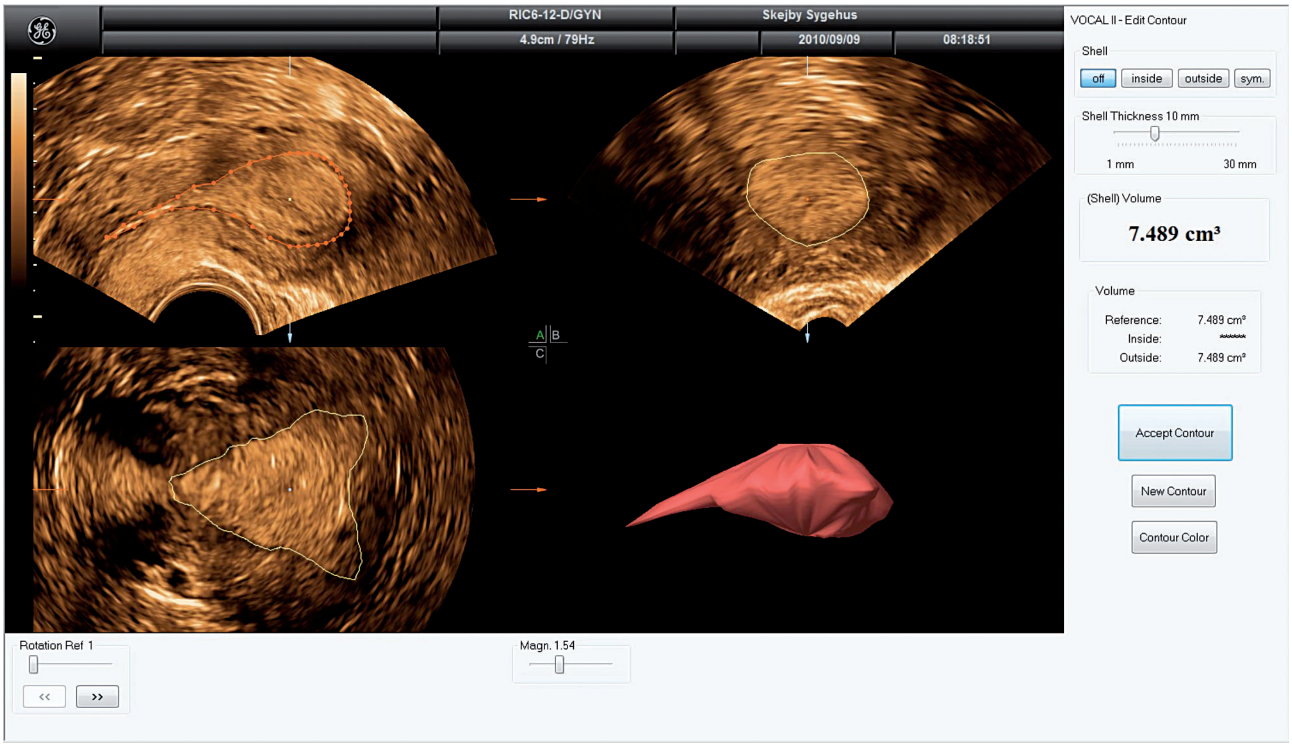

Figure 3. — Measurement of endometrial volume is done using VOCAL and a rotation step of 9° in 4D View software. The sagittal view is used as the reference plane. (A) Sagittal view, the traced line is visible and each marker can be adjusted for optimal volume. (B) and (C) transverse and coronal views, respectively, in each case the traced line is automatically calculated from the trace manually entered in the sagittal plane. Adjustments can only be made in the reference plane (A). In the bottom left corner a 3D image of the traced object is generated and the volume is calculated automatically, in this case 7.489 cm^3.

any fibroids were measured according to the following: 1) Measurements of endometrial thickness and uterine dimensions: thickness measurements were made in the "Sect. Planes" view using "Measure" and "Dist. 2 Point". The volume contrast imaging function was applied to obtain clearer contours. A standard slice thickness of 1–3 mm was used, but individual adjustment to achieve the optimal image possible was allowed. (Figure 2B). The endometrium was measured in three perpendicular planes (anterior posterior (AP), longitudinal (L), and transverse (T). The uterine corpus was also measured in these three planes. 2) Endometrial thickness in proportion of uterine anterior posterior thickness (PAP): PAP has previously been investigated by Karlsson *et al.* in 2D-TVS, describing this method as maximal ET in relation to the anterior posterior thickness of the uterus [26]. Measurement of PAP was performed in the transverse AP plane after the uterus had been perfectly aligned in a standardized multiplanar view [27]. 3) Endometrial and uterine volume measurements: Endometrial volume was calculated by the ellipse formula [0.523×AP×L×T] and by 3D volume measurements.

The "Volume Analysis" function was used for 3D volume measurements. Options were set to "VOCAL", "Manual" and "Rotation step: 9°". The sagittal plane was used as the reference plane, and the image rotated around a vertical axis at 9° steps. In each frame the object in question was traced, after which the trace was adjusted and optimized taking all three dimensions into consideration. The "4D view" software then estimated the final volume (Figure 3). This was repeated for endometrium, total uterus, cervix, as well as fluid and fibroids when relevant.

After completion of all measurements, endometrial percentage of the uterine corpus was calculated as endometrium (A) in percentage of the volume of the total uterus (B) excluding the volume of cervix, any fibroids, and any instilled saline (X). Calculated as (A/(B-X))*100. 4) Subjective impression: Subj-DMI was performed as previously described [13] and also performed by others [24]. At the point of impression of maximum myometrial involvement, the distance from tumor to serosal surface was measured (A). Myometrial thickness was also measured at the point of no invasion or of least invasion (B). Myometrial involvement in percentage was defined as [(B–A)/B]*100 and categorized as ≥ or <50%, i.e. deep or superficial invasion. All measurements described were repeated in 3D-SIS images.

All women underwent surgery within 21 days of ultrasound. The histopathological findings were used as a reference standard. Pathology examination was performed by one of two pathologists specialized in gynecological oncology blinded to imaging results.

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the performance of endometrial measurements to diagnose DMI.

The authors calculated the area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratios (LR+ and LR-) for most optimal cutoff points. Optimal cut-points were estimated by the ROCMIC stata module. ROCMIC estimates minimally important change (MIC) thresholds using three different methods. The first (a) is the cut-point corresponding to a 45 degree tangent line intersection; this is mathematically equiv-

Table 1. — *Diagnostic performance of image parameters on 3-dimensional transvaginal sonography (3D-TVS) and 3D-saline infusion sonography (3D-SIS) for prediction of deep myometrial invasion over 50% (DMI) in patients with endometrial cancer or atypia.*

Parameter	Calculation of optimal ROC cutoff[1]	AUC (95% CI)	Cut off point ≥	Sens (%)	Spec (%)	Correctly classified (%)	LR+	LR–
3D-TVS (n = 110)								
Endometrial thickness	(a, c)	0.64	23.8	53.2	61.9	58.2	1.40	0.76
(ET)	(b)	(0.53–0.74)	28.7	36.2	87.3	65.5	2.85	0.73
Max endometrial	(a)	0.63	34.1	56.5	62.3	59.8	1.50	0.67
diameter	(b)	(0.52–0.74)	39.2	37.0	83.6	63.6	2.25	0.75
Endometrial volume	(a)	0.66	12.9	57.5	60.3	59.1	1.45	0.71
(3D rotation) (EVR)	(b)	(0.55–0.76)	15.9	51.1	71.4	62.7	1.79	0.69
Endometrial volume	(a)	0.63	8190	63.0	61.7	62.3	1.65	0.60
(ellipse calculation) (EVE)	(b)	(0.52–0.74)	1500	45.7	85.0	67.9	3.04	0.64
Endometrial volume in	(a,c)	0.67	22.2	59.6	65.1	62.7	1.71	0.62
% of uterus volume	(b)	(0.57–0.78)	32.5	40.4	85.7	66.4	2.83	0.70
(3D rotation) (PEVR)								
Endometrial thickness in %	(a)	0.73	59.6	66.0	66.7	66.4	1.98	0.51
of uterus AP diameter (PAP)	(b)	(0.63–0.83)	68.0	53.2	85.7	71.8	3.72	0.55
3D-SIS (n = 58)								
Endometrial thickness	(a)	0.66	17.5	59.1	63.9	62.1	1.64	0.64
(ET)	(b)	(0.50–.081)	22.7	45.5	94.4	75.9	8.18	0.58
	(c)	19.1	50.0	75.0	65.5	2.00	0.67	
Endometrial volume	(b)	0.64	4.52	90.0	38.7	58.8	1.47	0.26
(3D rotation) (EVR)	(c)	(0.48–0.79)	7.35	75.0	51.6	60.8	1.55	0.48
Endometrial volume	(a)	0.70	8700	61.9	57.1	58.9	1.44	0.67
(ellipse calculation) (EVE)	(b)	(0.55–0.84)	16000	47.6	82.9	69.6	2.78	0.63
Endometrial volume in	(b)	0.70	9.3	80.0	45.2	58.8	1.46	0.44
% of uterus volume	(c)	(0.55–0.84)	12.4	75.0	58.1	64.7	1.79	0.43
(3D rotation) (PEVR)								
Endometrial thickness in %	(a, c)	0.65	32.0	72.7	50.0	58.6	1.46	0.55
of uterus AP diameter (PAP)	(b)	(0.50–0.80)	42.5	63.6	63.9	63.8	1.76	0.57

AUC: area under the receiver–operating characteristics curve (ROC curve); LR+: positive likelihood ratio; LR–: negative likelihood ratio; Sens.: sensitivity; Spec.: specificity; 95% CI: 95% confidence interval. [1)] Optimal cut off point of ROC curve calculated by the 45-degree tangent line intersection (a); smallest sum of 1-sensitivity and 1-specificity (b); smallest sum of squares of 1-sensitivity and 1-specificity (c).

alent to the point at which the sensitivity and specificity are closest together. The second (b) is the cut-point corresponding to the smallest sum of 1-sensitivity and 1-specificity. The third (c) is the cut-point corresponding to the smallest sum of squares of 1-sensitivity and 1-specificity in accordance with Pythagorean theorem and always chooses the cut-point closest to the top-left corner of ROC space, regardless of the shape of the ROC curve [28].

Interobserver variation of volume and size measurements was estimated by kappa analysis and stated with 95% confidence intervals. The strength of agreement for the kappa coefficient was interpreted as follows: ≤0 = poor, 0.01–0.20 = slight, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = substantial and 0.81–1 = almost perfect. Data was analyzed using Stata.

Results

In all, 110 women were included, 47 with deep and 63 with superficial myometrial invasion. Age and BMI were similar in the two groups (age 32–85 and 42–83, respectively; BMI 16.8–41.8 and 19.2–57.2, respectively). In both groups, tumor grade 1 represented about half of the patients (55.3% and 49.2%, respectively), while grade 3 tumors were more heavily represented in the deep invasion group (29.8% *vs.* 6.3%). In both the deep and superficial invasion groups, tumor Stage 1 represented approximately 60% (61.7% and 58.7%). In the deep invasion group, the remaining tumors were divided between Stages II (21.8%), III (21.3%), and IV (4.3%), while in the superficial invasion group, the remaining tumors were mainly atypia and "no residual tumor" (28.6% total), while only 12.7% were Stage II or higher.

Table 1 displays ROC curve analyses of the diagnostic performance of ET and volume measurements using 3D-TVS and 3D-SIS for prediction of DMI. All parameters were related to deep invasion and had AUCs of 0.63 to 0.73. Volume measurements by 3D rotation presented no advantage compared to simple measurements based on the ellipse formula. No parameters had cut-points with both a

Table 2. — *The efficiency of measurement of endometrial thickness in percentage of the uterine anterior posterior (AP) diameter alone and combined with subjective evaluation of deep myometrial invasion (subj DMI) by 3D-TVS for identification of DMI.*

Parameter	AUC (95% CI)	Sens %	Spec %	PPV	NPV	LR+	LR–
Endometrial thickness in percentage of uterine AP diameter (PAP) with cutoff of 70%	0.649 (0.57–0.73)	42.6 (28–58)	87.3 (77–94)	71.4 (51–87)	67.1 (56–77)	3.4 (1.6–6.9)	0.66 (0.50 –.86)
Endometrial thickness in percentage of uterine AP diameter (PAP) with cutoff of 65%	0.687 (0.60–0.78)	59.6 (44–74)	77.8 (66–87)	66.7 (51–80)	72.1 (60–82)	2.7 (1.6–4.5)	0.52 (0.36–0.75)
Subjective evaluation of deep invasion alone (subj DMI)	0.711 (0.63–0.80)	72.3 (57–84)	69.8 (57–81)	64.2 (50–77)	77.2 (64–87)	2.4 (1.6–3.6)	0.40 (0.24–0.66)
Endometrial thickness in percentage of uterine AP diameter (PAP) with cutoff of 65% *AND* subj DMI	0.684 (0.60–0.77)	51.1 (36–66)	85.7 (75–93)	72.7 (55–87)	70.1 (59–80)	3.6 (1.8–7.0)	0.57 (0.42–0.78)
Endometrial thickness in percentage of uterine AP diameter (PAP) with cutoff of 50% *NO* subj DMI	0.656 (0.58–0.73)	91.5 (80–98)	39.7 (28–53)	53.1 (42–64)	86.2 (68–96)	1.5 (1.2–1.9)	0.21 (0.08–0.58)
Endometrial thickness in percentage of uterine AP diameter (PAP) with cutoff of 65% *NO* subj DMI	0.714 (0.63–0.80)	80.9 (67–91)	61.9 (49–74)	61.3 (48–73)	81.3 (67–91)	2.12 (1.5–3.0)	0.31 (0.17–0.57)

DMI: deep myometrial invasion; 3D-TVS: three-dimensional transvaginal ultrasonography; AP: anterior posterior diameter; AUC: area under the receiver–operating characteristics curve (ROC curve); Sens.: sensitivity; Spec.: specificity; PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR–: negative likelihood ratio. 95% CI: 95% confidence interval.

Table 3. — *Interobserver variation of image parameters on 3-dimensional transvaginal sonography (3D-TVS) and 3D-saline infusion sonography (3D-SIS) for prediction of deep myometrial invasion over 50% in patients with endometrial cancer or atypia. Comparison of three observers.*

Parameter	Cut off point ≥	Percentage agreement (%)	Kappa	(95% CI)
3D-TVS (n = 110)				
Two trained observers (A *vs.* B)				
Endometrial thickness	25 mm	87.3	0.649	(0.48–0.82)
Endometrial volume (ellipse)	8,000 mm^3	80.2	0.605	(0.46–0.75)
Subjective evaluation of deep invasion		76.4	0.525	(0.37–0.68)
Trained *vs.* not trained (B *vs.* C)				
Endometrial thickness	25 mm	81.8	0.521	(0.34–0.70)
Endometrial volume (ellipse)	8,000 mm^3	75.5	0.509	(0.35–0.67)
Endometrial volume 3D-rotation	14.000 mm^3	79.1	0.567	(0.41–0.72)
Endometrial volume ratio 3D-rotation	22%	70.0	0.389	(0.22–0.56)
Subjective evaluation of deep invasion		67.3	0.359	(0.19–0.53)
3D-SIS (n = 58)				
Two trained observers (A *vs.* B)				
Endometrial thickness	20 mm	80.7	0.575	(0.36–0.79)
Endometrial volume (ellipse)	9,000 mm^3	75.9	0.510	(0.30–0.72)
Subjective evaluation of deep invasion		73.7	0.430	(0.19–0.67)
Trained *vs.* not trained (B *vs.* C)				
Endometrial thickness	20 mm	76.8	0.501	(0.27–0.74)
Endometrial volume (ellipse)	9,000 mm^3	74.6	0.488	(0.27–0.71)
Endometrial volume 3D-rotation	8,000 mm^3	86.0	0.717	(0.52–0.91)
Endometrial volume ratio 3D-rotation	12%	86.0	0.706	(0.51–0.90)
Subjective evaluation of deep invasion		71.4	0.435	(0.22–0.65)

Observer A: Senior physician, trained in 3D-TVS and 3D-SIS acquisition and analysis. Observer B: Senior physician, trained in 3D-TVS and 3D-SIS acquisition and analysis. Observer C: Junior research assistant, not trained in 3D-TVS and 3D-SIS acquisition and analysis. 95% CI: 95% confidence interval.

sensitivity and a specificity above 70% (signifying a good diagnostic test).

In the present study, using a tumor size of 2 cm to distinguish between deep and superficial myometrial invasion resulted in sensitivity and specificity of only 55.2% and 66.7%, respectively.

Measurement of PAP in the standardized multi-planar view showed the highest AUC. Sensitivity was moderate,

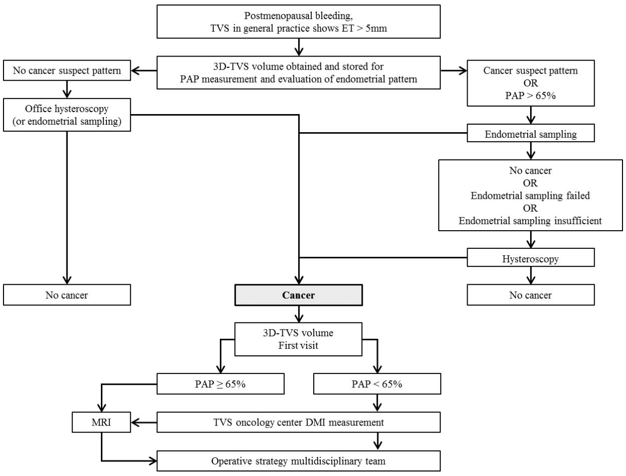

Figure 4. — A proposed set-up for diagnosis of women with increased endometrial thickness and postmenopausal bleeding based on pattern evaluation of endometrium and PAP measurement for immediate referral to MRI [36].

but specificity was high, indicating that most women with a ratio above the cut-point would have deep invasion. Using a PAP cutoff of 65% for additional MRI, only 13% of the patients would undergo MRI without DMI. Saline infusion was performed in 58 women and did not increase the AUC markedly.

Logistic regression of subj-DMI with addition of the parameter PAP had an AUC of 0.77 and displayed a *P* value of 0.06, indicating only marginal benefit of adding this parameter to a subjective evaluation. Adding other parameters did not improve the AUC of subjective evaluation (0.71). In Table 2, the diagnostic performances of different selected cut-points for PAP are displayed along with the efficiency of the combined parameters: 38% of all women had PAP ≥ 65% and 60% of all women with DMI were present in the group with PAP ≥ 65%. Moreover, 67% of women with PAP ≥ 65% had DMI.

In the group of women with both PAP ≥ 65% and subj-DMI, PPV was only marginally higher. However, in the group of women with PAP < 65%, there was a marked increase in NPV after addition of subjective evaluation of DMI.

Interobserver agreement between two trained observers was substantial for ET and volume measurements (ellipse) (Table 3). There was only a moderate agreement between trained and untrained investigators, indicating difficulties in identification of the outline of the endometrium. However, after saline injection the agreement was substantial between a 3D-TVS-trained and a 3D-TVS-untrained observer. Observer agreement was lower for subj-DMI, especially when a trained and an untrained observer were compared.

Discussion

In this study, simple measurements of tumor dimensions by 3D-TVS or 3D-SIS had lower AUC than subj-DMI. There was marginal benefit of additional PAP, but not of other tumor dimension or volume measurements. MRI may be the most efficient technique in women with DMI, and PAP may be used for initial selection of additional MRI.

Subj-DMI with 3D-TVS had the highest efficiency (AUC 0.71), but had lower efficiency than MRI (AUC 0.83) [13]. In concordance, other studies have shown a higher efficiency of subjective evaluation compared to simple 2D- and 3D-volume measurements [23, 24].

One-third of all investigated women and approximately two-thirds of women with DMI had PAP ≥ 65%. Using a PAP cutoff of 65% for additional MRI, only 13% of patients would undergo MRI without having DMI. Only 17% of women had both PAP < 65% and DMI. Direct selection of lymphadenectomy for type 3 tumors would leave only 11% of patients with undiagnosed DMI (Stage 1b). These women could be diagnosed based on experienced evaluation with TVS in an oncology center with only a few additional MRIs. The observer variation for ET measurements was lower than for subj-DMI, indicating that less expertise is needed for this simple measurement compared to subjective evaluation of invasion, which seems to call for experience.

Gynecologists in general practice (with little ultrasound expertise) may be able to measure PAP on 3D-TVS to determine risk of DMI as early as possible, and women with PAP ≥65% could be sent directly to image centers in a fast-track set-up for MRI.

MRI may identify extrauterine disease and is increasingly used for preoperative determination of disease dissemination and myometrial invasion and is often preferred in patients with non-endometroid cancers or suspected DMI. However, MRI is more expensive and is not as generally available as is 3D-TVS, which is increasingly being introduced into general practice. Selection of MRI for all women is expensive and time consuming, as is the addition of MRI based on an additional TVS by an experienced investigator at an oncology center. Thus, simple alternatives like a PAP measurement in general practice for fast-track selection of women for MRI at the first ultrasound in general practice may save time and money.

When hysteroscopy is planned for women with postmenopausal bleeding, it is especially important to obtain 3D volumes of the uterus beforehand, as image evaluation of DMI is hampered by hysteroscopic removal of endomyometrial tissue. Moreover, endometrial sampling should be preferred to hysteroscopy when there is malignancy suspect pattern on TVS or when DMI is suspected (PAP ≥ 65%). Thereby the risk of perforation of a fragile uterus with DMI during hysteroscopy may be avoided. Women with PAP < 65% may, however, have some benefit of a subjective evaluation of their 3D volumes by experienced sonographers. A proposed set-up for fast-track diagnosis of women with increased ET and postmenopausal bleeding based on endometrial morphology and 3D-volume evaluation is shown in Figure 4. More validation studies of its efficiency in general practice are required before this set-up should be introduced.

None of the tumor dimension measurements are sufficient diagnostic tools but may be an aid in association with other tests in detecting DMI. Endometrial volume in percentage of the uterine corpus (PEVR) was not a better indicator of DMI than endometrial volume (EVR) alone, although it is a far more time-consuming method.

ET is based on a single measurement and far easier to reproduce than volume measurements. EVR is dependent on many volume measurements in repeated rotational steps, each measurement being subject to inaccuracy due to subjective evaluation of volume borders. Saline infusion decreased observer variation in 3D volume measurements by displaying a clear tumor border.

In a previous 2D-TVS study, ET and volume measurements had slightly higher AUCs, while a 3D-TVS study had AUCs similar to the present [23]. The accuracy of PAP was concordant with the present findings in these studies [19, 23], while other studies had higher AUCs [29–32]. Different selection criteria could explain disconcordant results. In a 3D volume, perfect alignment of the image is possible, allowing for a more precise measurement than 2D-TVS. However, efficiency of PAP measurements must be evaluated in future studies.

The present findings are in accordance with publications that do not propose a possible cutoff value of tumor size for distinction between deep and superficial myometrial invasion groups [20, 33] and thus do not support the recommended cutoff value of 2 cm in tumor size as sole measurement for estimating high-risk patients [22].

The optimal 3D-TVS results found by subjective evaluation of myometrial invasion demonstrated in the authors' previous publication can be marginally improved by adding PAP [13].

This paper has several strengths. The number of high-risk patients was high, giving a valid population for evaluation of preoperative staging of endometrial cancer in patients sent to oncology centers for evaluation of DMI. Women with atypia belong to the study group of interest, because 59% of women with atypia in endometrial samples have endometrial cancer on final histology and therefore, according to Danish guidelines, these women are referred to oncology centers to ensure proper diagnosis and treatment [15, 25]. Moreover, inclusion of women with cancer and women with atypia prevents the observer from being biased to the results. The present authors used mathematical calculations for the optimal cutoff of the ROC curves to avoid subjectivity in selection of cutoff values [28]. They used a rotation angle of 9° as recommended by Raine-Fenning *et al.* [27] and the sagittal plane as supported by Merce *et al.* [34].

A limitation is that scan settings were not standardized but optimized for each individual woman. This was chosen in order to create the best possible image for each patient. The present authors' experience with 3D evaluation was limited, and a learning curve may have influenced the results, although for all statistical analyses except interobserver analysis, the findings of the most experienced physician were used.

Conclusion

The present findings demonstrate that subj-DMI using 3D-TVS is superior to all 3D-TVS measurements of endometrial dimensions. However, PAP is the superior endometrial measurement: it is simple, simple to obtain, and has the lowest interobserver variation. MRI is optimal in diagnosing tumor dissemination to lymph nodes and other organs, but offering all patients MRI is expensive and time consuming. Therefore, a simple method, resistant to interobserver variation, to evaluate DMI at first TVS in general practice (i.e. PAP) could be ideal; a high risk group (PAP ≥ 65%) may be selected and sent directly to MRI. 3D-TVS with PAP < 65% may be stored and further evaluated by ultrasound specialists at oncology centers.

Use of this strategy (PAP ≥ 65% and no DMI) would prevent unnecessary MRIs; only 13% of women in this study would have received an unnecessary MRI, although more research is needed before this can be introduced into general practice.

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Corresponding Author:
GITTE ØRTOFT, M.D.
Department of Gynecology and Obstetrics
Rigshospitalet
DK-2100 Copenhagen (Denmark)
e-mail: Ortoft@dadlnet.dk