

Assessing Myometrial Infiltration by Endometrial Cancer: Uterine Virtual Navigation with Three-dimensional US¹

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Purpose:

To describe and analyze the diagnostic performance of uterine virtual navigation with three-dimensional (3D) ultrasonography (US) for the assessment of the depth of myometrial infiltration by endometrial cancer.

Materials and Methods:

Institutional review board approval was obtained; patients gave oral informed consent. Women with endometrial cancer were evaluated by using 3D US prior to surgical staging. A 3D volume of the whole uterus was obtained and analyzed by using software. Virtual navigation through three orthogonal planes was performed to identify the shortest myometrial tumor-free distance to serosa (TDS) by analyzing the lateral, anterior, posterior, and fundal portions of the myometrium. Myometrial infiltration was also assessed by subjective impression of an examiner. Histologic findings of myometrial infiltration and TDS measured by a pathologist were used as the reference standard. A receiver operating characteristic curve was plotted to identify the best cutoff for TDS for identifying myometrial infiltration of 50% or more.

Results:

Ninety-six women (mean age, 61.8 years; range, 31–86 years) with endometrial cancer were included in the study. At histologic analysis, myometrial invasion was found to be less than 50% in 69 (72%) cases and 50% or more in 27 (28%) cases. TDS measured with US was positively correlated with histologically measured TDS ($r = 0.649$; 95% confidence interval: 0.52, 0.76). The best cutoff for US-measured TDS was 9.0 mm (sensitivity, 100%; specificity, 61%; negative predictive value, 100%; positive predictive value, 50%). Subjective impression had a sensitivity of 92.6%, a specificity of 82.3%, a negative predictive value of 96.6%, and a positive predictive value of 67.7%.

Conclusion:

Uterine virtual navigation with 3D US is a reliable method for the assessment of myometrial infiltration in patients with endometrial cancer.

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Endometrial carcinoma is the most frequent gynecologic malignancy (1). Since 1988, the International Federation of Gynecology and Obstetrics has recommended surgical staging as the initial treatment in these patients to determine the extent of disease. This implies total abdominal hysterectomy with bilateral salpingo-oophorectomy, peritoneal cytologic samplings, and pelvic and paraaortic lymphadenectomy (2). However, complete routine staging has come under criticism in cases of low risk of lymph node involvement (3–5). Low-risk patients are mainly defined with three histologic factors—tumor type, tumor histologic grade, and myometrial infiltration (3). For this reason, many authors advocate intraoperative gross or frozen section evaluation of myometrial invasion and tumor grade in clinical stage I endometrial carcinoma to aid in the decision of whether lymphadenectomy should be performed or could be obviated (6,7). Frozen section analysis has been shown to be highly accurate (94%) for determining myometrial invasion (8). However, frozen section analysis may be time consuming, and it is not performed in all hospitals. On the other hand, gross evaluation has been shown to be much less accurate (9–13) than frozen section analysis. Therefore, a method that could reliably assess myometrial invasion preoperatively would be helpful to provide individual tailoring of the surgical approach.

Several imaging techniques performed prior to surgery are currently used for the assessment of the depth of myometrial infiltration by endometrial cancer. Contrast material-enhanced magnetic resonance (MR) imaging is considered the most reliable method and has an accuracy ranging from 62% to 95% (14–20). However, MR imaging is costly, has limited availability, and cannot be performed in all patients.

Advance in Knowledge

- With uterine virtual navigation and three-dimensional US, we were able to predict deep myometrial infiltration in all cases.

Some groups (13,21–26) have assessed the role of transvaginal two-dimensional (2D) ultrasonography (US) for the assessment of myometrial invasion with considerable variation in methods and results. This could be explained by the fact that this technique is highly operator dependent because it is mainly based on the subjective impression of the examiner.

Recently, three-dimensional (3D) US has been introduced in clinical practice. This allows unique ways for assessing the uterus, such as virtual navigation through multiplanar display and tomographic US imaging (27). This technique has been demonstrated to be much less operator dependent than 2D US (28,29).

The purpose of our study was to describe and analyze the diagnostic performance of uterine virtual navigation with 3D US for the assessment of the depth of myometrial infiltration by endometrial cancer.

Materials and Methods

Patients

Institutional review board (Clínica Universitaria de Navarra) approval was obtained before starting the study, and all women gave verbal informed consent. From January 2003 to December 2007, 113 consecutive women with clinical stage I endometrial cancer (cancer confined to the uterine corpus according to results of physical examination, chest radiography, and abdominal and pelvic CT scanning) were recruited for this prospective observational study (Fig 1). Patients were from two centers—Clínica Universitaria de Navarra, Pamplona, Spain ($n = 78$, 69%), and Clinic Hospital, Barcelona, Spain ($n = 35$, 31%).

Implication for Patient Care

- Three-dimensional US with uterine virtual navigation offers a relatively simple, reliable, and reproducible way for preoperative assessment of myometrial infiltration in patients with endometrial cancer.

All patients had histologically proved endometrial cancer according to results of office microcurettage or hysteroscopic biopsy and were scheduled for surgical staging.

Exclusion criteria were as follows: surgery not performed ($n = 4$); surgery performed in hospital other than that of recruitment ($n = 5$); incomplete pathologic report ($n = 2$); and incomplete 3D volume with exclusion of uterine serosal margins, including one case that also did not have a reference standard ($n = 6$). Three premenopausal women with child-bearing desire with well-differentiated focal endometrioid carcinoma associated with endometrial hyperplasia with atypia and no signs of myometrial infiltration at MR imaging and who were considered to have stage IA G1 endometrioid carcinoma were offered fertility-sparing treatment. These patients did not undergo surgical staging. However, we did not exclude them in our analysis and considered them to have no myometrial infiltration for analytic purposes on the basis of MR imaging results, in spite of the absence of histologic data.

US Examination

All US examinations were performed within 1 week prior to surgery, with patients in the lithotomy position and with an empty bladder by using a scanner (Voluson 730 Expert; GE Healthcare, Milwaukee, Wis) equipped with a multifrequency endovaginal probe (3–9 MHz). Three operators (J.L.A., R.G.,

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Abbreviations:

TDS = tumor-free distance to serosa

3D = three-dimensional

2D = two-dimensional

Author contributions:

Guarantors of integrity of entire study, J.L.A., R.G., S.A.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, J.L.A.; clinical studies, all authors; statistical analysis, J.L.A.; and manuscript editing, J.L.A.

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and S.A., with 7, 3, and 1 year of experience in 3D US, respectively) performed all examinations according to a predetermined scanning protocol (29). A 2D US exploration of the uterus and adnexa was initially performed. Endometrial thickness was measured in the sagittal plane, including both layers, at the level of maximal thickness. Thereafter, the 3D volume box was activated and was manually adjusted to include the entire uterus. With a sweep angle of 90° and with the patient remaining as still as possible, a 3D volume was acquired. Acquisition time lasted from 6 to 10 seconds. Once the volume was acquired, it was stored and evaluated later with a personal computer.

Stored Volume Analysis

Two examiners (J.L.A. and S.A.) performed all volume examinations in consensus and were blinded to histologic results. Myometrial infiltration was assessed off-line in the stored volume by using software (4DView, version 5.0; GE Healthcare). By using the “selected planes” utility, we performed rotations until uterine transverse, sagittal, and coronal planes were placed on planes A, B, and C, respectively, on the computer screen (Fig 2). Virtual navigation through the uterus then was performed. By first going through plane B (sagittal) from the anterior to the posterior uterine serosa, we navigated through plane C (coronal). By using the image with the subjective thickest endometrial distance, we measured the myometrial TDS in the lateral wall and fundus (Fig 3).

We then navigated in plane C (coronal) from one uterine cornu to the other. By using the image with the subjective thickest endometrial distance in plane B (sagittal), we measured TDS in the anterior and posterior uterine walls (Fig 4).

To determine myometrial infiltration depth, we selected the subjective shortest TDS found in any area. Only one measurement per area was obtained.

Myometrial infiltration depth was also estimated subjectively by the examiners according to their impression of depth of invasion (>50% or <50%)

during virtual navigation. This was performed by looking at the point in which myometrial-endometrial interface was not clearly identified and then by looking at the supposedly tumor-free myometrial wall at this point. By using the

opposite myometrial wall as a comparison, if a marked asymmetry was found, deep (>50%) infiltration was stated; if myometrial thickness was similar in both myometrial walls, superficial (<50%) infiltration was stated.

Figure 1

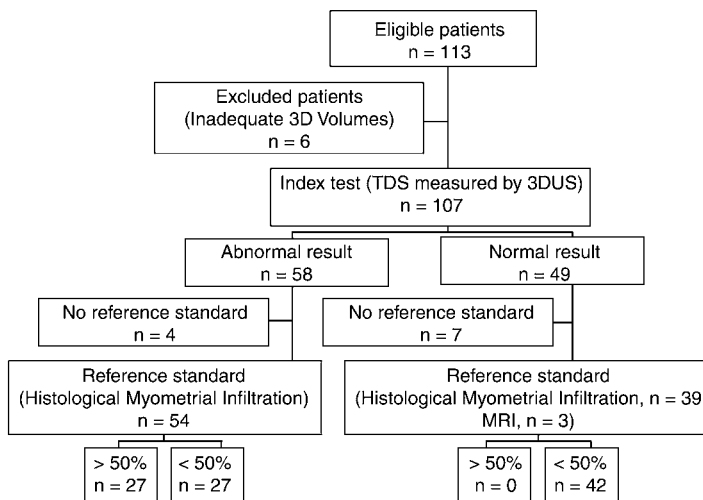


Figure 1: Flowchart shows patient eligibility, exclusions, and results of tests on the basis of tumor-free distance to serosa (TDS) measurement and reference standard.

Figure 2

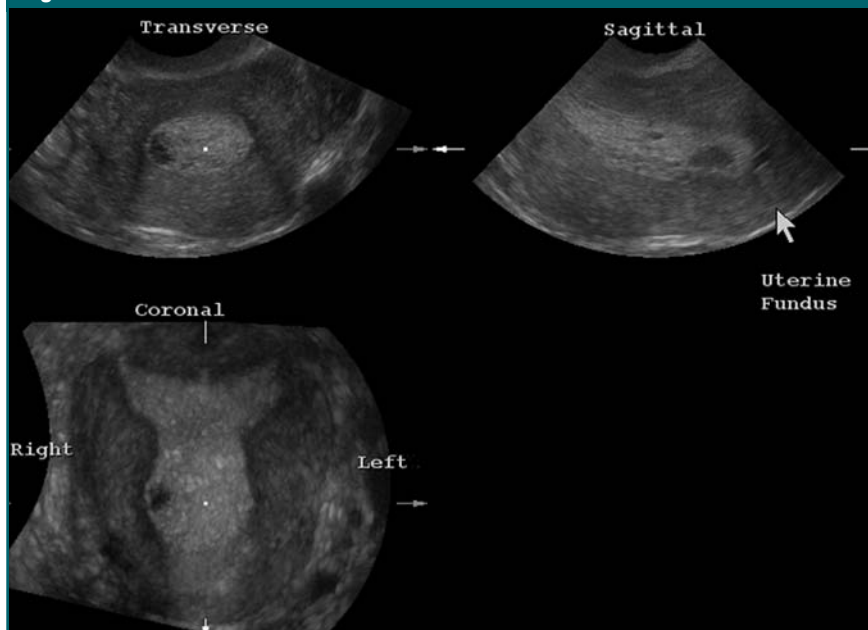


Figure 2: Three-dimensional US images in the uterus in a case of endometrial cancer.

Figure 3

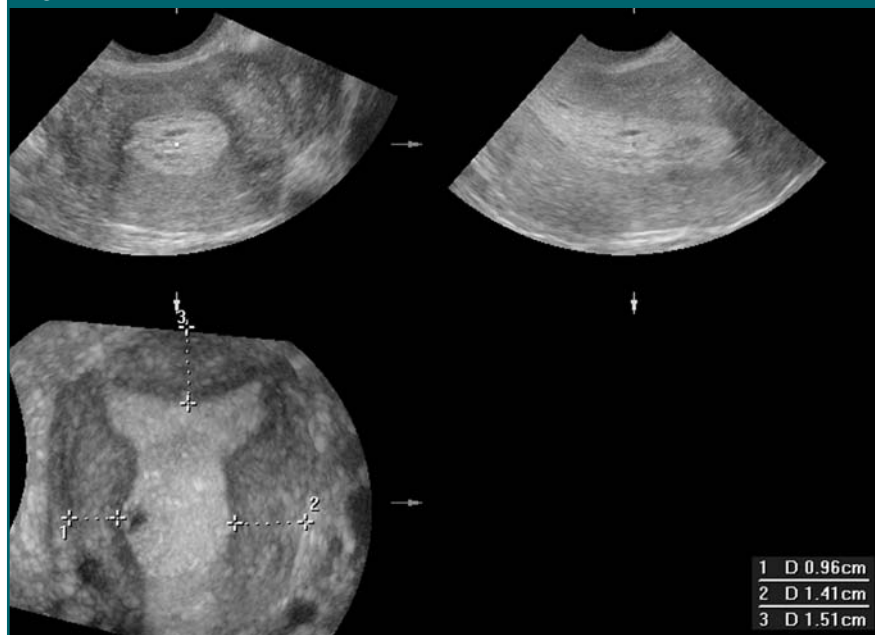


Figure 3: Three-dimensional US images (transverse, top left; sagittal, top right; coronal, bottom left) show measurement of TDS in coronal plane (9.6 mm in right uterine wall, 14.1 mm in left uterine wall, and 15.1 in fundus). *D* = distance.

Figure 4

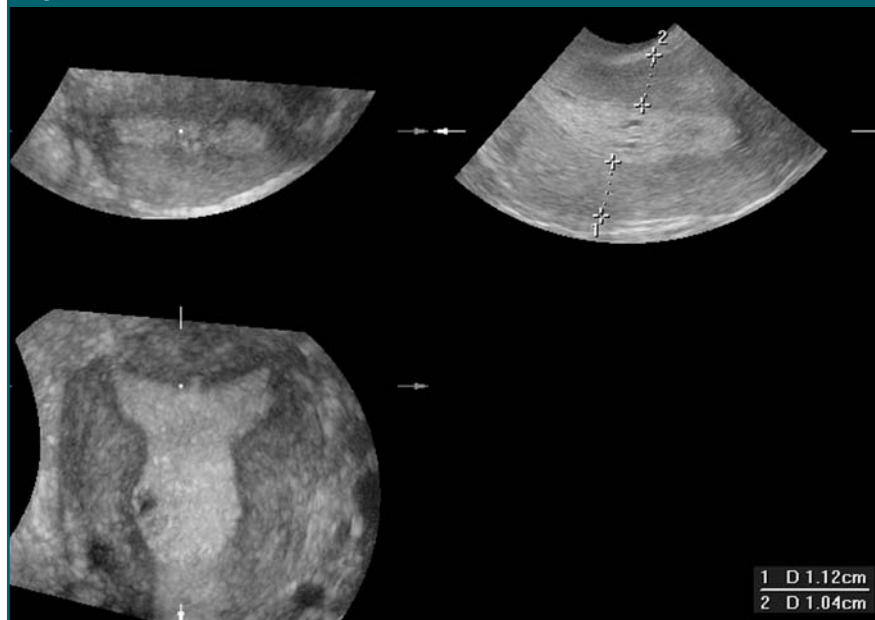


Figure 4: Three-dimensional US images (transverse, top left; sagittal, top right; coronal, bottom left) show measurement of TDS in sagittal plane (11.2 mm in anterior uterine wall and 10.4 mm in posterior uterine wall). *D* = distance.

Cervical involvement was stated to be present when there was subjective disruption of the cervical canal.

Uterine myomas were noted, and the subjective effect of myomas on myometrial measurements was assessed.

Control Subjects

To determine normal TDS in uteri without pathologic examination results, we used two control groups of asymptomatic women. One group included premenopausal women ($n = 20$), and the other group included postmenopausal women ($n = 20$). We defined menopause as 1 year of absence of menstruation in women older than 45 years.

None of these women had subjective uterine or endometrial pathologic conditions (leiomyomas, adenomyosis, congenital anomalies, endometrial polyps, hyperplasia, or endometrial thickness > 4 mm in postmenopausal women). None of these women were taking hormonal treatments, such as contraceptives, hormone replacement therapy, or tamoxifen citrate.

Reproducibility Studies

Reproducibility of TDS measurements was assessed in the first 15 volumes. One examiner (J.L.A.) analyzed the same volume twice, with the second analysis being performed at least 1 week after the first analysis. To determine interobserver reproducibility, a second examiner (R.G.) analyzed the same 15 volumes. Examiners were blinded to each other's reviews when performing analysis. These evaluations were performed with one examiner of the pair different than those who evaluated the volume by consensus.

Surgical Procedure and Tumor Staging

Surgery included total abdominal hysterectomy with bilateral salpingo-oophorectomy, peritoneal washings, omentectomy, and pelvic and paraaortic lymphadenectomy. After surgery, the pathologic report included histologic type, histologic grade and myometrial infiltration depth, lymphovascular space involvement, TDS, and lymph node metastases. These data were used as the reference standard. All surgeries were performed by gynecological on-

Table 1

Histologic Features of Endometrial Cancer

Parameter	No. of Patients
Histologic type	
Endometrioid	80 (83)
Adenosquamous	8 (8)
Serous papillary	6 (6)
Clear cell	2 (2)
Histologic grade	
G1	42 (44)
G2	31 (32)
G3	23 (24)
Myometrial infiltration	
None*	10 (10)
<50%	59 (61)
≥50%	27 (28)
Tumor stage	
IA	10 (10)
IB	48 (50)
IC	14 (15)
II	8 (8)
III	16 (17)

Note.—Data in parentheses are percentages. Percentages may not add up to 100% because of rounding.

* In three cases, no myometrial infiltration was considered on the basis of MR imaging results.

Table 2

Measurement of TDS in Control Groups according to Site of Measurement

Control Group	Anterior and Posterior Uterine Walls (mm)*	Lateral Uterine Wall (mm)†	Fundus (mm)‡
Premenopausal	17 (11–22)	15 (11–20.5)	13 (8–16)
Postmenopausal	15 (9–21)	13 (11–22)	11 (10–18)

Note.—Data are medians, with ranges in parentheses.

* $P = .224$, Mann-Whitney U test.

† $P = .195$, Mann-Whitney U test.

‡ $P = .026$, Mann-Whitney U test.

and TDS measured by using US in study group according to histologic depth of invasion.

The Wilcoxon signed rank test was used for comparing TDS measured by using US and TDS measured by a pathologist. Categorical variables were compared by using a χ^2 test. The Spearman correlation coefficient (r) was used to assess the correlation between TDS measured by using US and TDS measured by a pathologist. A receiver operating characteristic curve was plotted to determine the best cutoff value for TDS for identifying deep myometrial invasion. The best cutoff value was chosen according to the best sensitivity with the lowest false-positive rate. Positive and negative likelihood ratios were also calculated.

Sensitivity and specificity of TDS measured by using US and those measured by using subjective impression of infiltration depth were compared by using the McNemar test.

This was a convenience sample. Because no previous data were available for determining a significant difference in sensitivity or specificity for this technique, we were not able to estimate a sample size properly.

Reproducibility was assessed by using the intraclass and interclass correlation coefficients according to the Bland-Altman method (30).

A P value of .05 or less was considered to indicate a statistically significant difference. All analyses were performed by using software (SPSS, version 15.0; SPSS, Chicago, Ill).

Results

Patient mean age was 61.8 years, ranging from 31 to 86 years. Eighty-five (89%) women were postmenopausal,

Table 3

TDS Measured by Using US and by a Pathologist according to Myometrial Infiltration

Parameter	US-Measured TDS (mm)*	Histologically Measured TDS (mm)†
Myometrial infiltration		
<50%	10 (2–20)	15 (6–35)
≥50%	4 (1–8)	4 (0–16)
Control subjects		
	12 (8–22)	NA

Note.—Data are medians, with ranges in parentheses. NA = not applicable.

* $P < .001$ for comparison among all three groups (myometrial infiltration < 50%, myometrial infiltration ≥ 50%, and control subjects), according to the Mann-Whitney U test.

† $P < .001$ for myometrial infiltration of less than 50% versus that of 50% or more, according to the Mann-Whitney U test.

and 11 (11%) women were premenopausal.

Tumor histologic features are shown in Table 1.

Median endometrial thickness for the study group was 13.0 mm (interquartile range, 10.0; range, 1.0–49.0 mm). Median TDS at the level of fundus, anterior and posterior uterine walls, and lateral uterine wall in the control groups are shown in Table 2. TDS in all uterine walls was longer in premenopausal women than in postmenopausal women.

Median TDS measured by a pathologist and that measured by using US were significantly shorter in those tumors with 50% or more myometrial infiltration than in those with less than

gynecologists (M.J., G.L., J.L.A., J.P., and S.M., each with more than 10 years of experience in gynecological oncology surgery).

Tumor stage was determined according to International Federation of Gynecology and Obstetrics criteria (2). Tumor histologic grade was determined according to the following three-grade system: Grade 1 carcinoma showed solid growth pattern in less than 5% of the tumor. Grade 2 carcinoma showed solid growth pattern in 5%–50% of the tumor. Grade 3 carcinoma showed solid growth pattern in more than 50% of the tumor.

Statistical Analysis

The Kolmogorov-Smirnov test was used to assess normal distribution of continuous data. Continuous data were compared by using one-way analysis of variance when data were normally distributed or by using the Mann-Whitney U test when data were not normally distributed. These tests were used for comparing TDS measured by using US in the control group according to the site of measurement, TDS measured by using US in the control subject and study groups,

50% infiltration (Table 3). There was a positive correlation between pathologically measured and US-measured TDS ($r = 0.649$; 95% confidence interval: 0.52, 0.76). Median TDS measured by using US (7.0 mm; range, 1–20 mm) was significantly shorter than that measured by a pathologist (11.0 mm; range, 0–35 mm) ($P < .001$) (Fig 5).

Median TDS in control groups was significantly longer than in the study group for tumors infiltrating less than 50% and for those infiltrating more than 50% (Table 3).

The receiver operating characteris-

tic curve showed that shorter US-measured TDS was a predictor for deep myometrial infiltration (Fig 6). The best cutoff value for US-measured TDS was 9.0 mm, which allowed for identification of all cases of deep infiltration with no false-negative cases. However, by applying this cutoff, a 39% false-positive rate was obtained. Figure 7 shows a

case of deep myometrial infiltration as determined by using 3D US.

One case in the control group had a TDS of 8.0 mm.

Sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratio for TDS and subjective impression are shown in Tables 4 and 5. With subjective impression, the

Figure 5

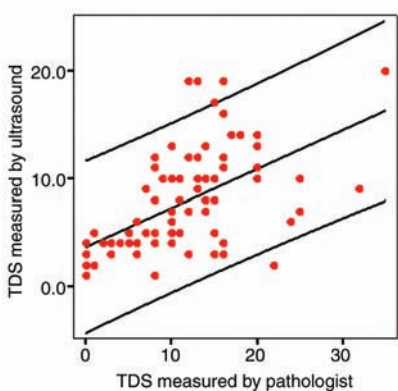


Figure 5: Scatterplot shows TDS measured by using US versus that measured by a pathologist.

Figure 6

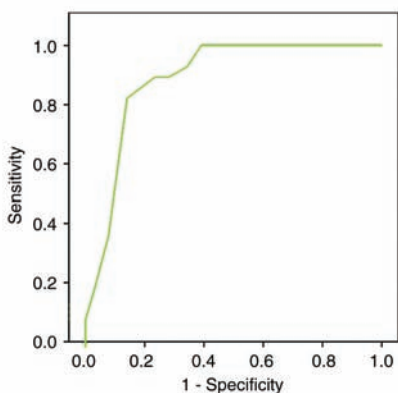


Figure 6: Receiver operating characteristic curve for TDS. Area under the curve for TDS was 0.89 (95% confidence interval: 0.82, 0.95). Best cutoff for TDS was 9.0 mm.

Figure 7

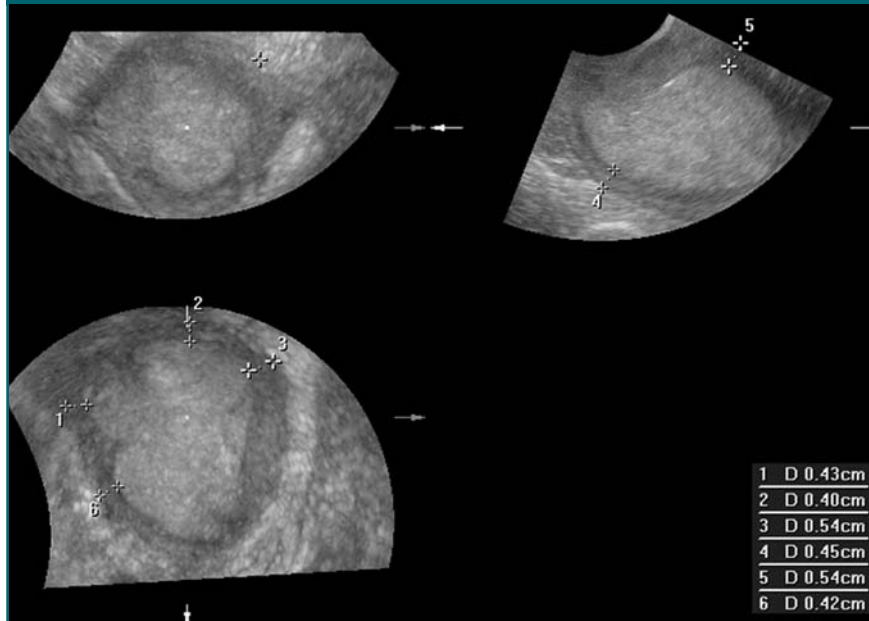


Figure 7: Three-dimensional US images show deep myometrial infiltration. The shortest TDS was 4.0 mm in the fundus. *D* = distance.

Table 4

Diagnostic Performance of Shortest TDS Measured by Using US

Parameter	Myometrial Infiltration		Total
	<50%	≥50%	
TDS			
>9.0 mm	42	0	42
≤9.0 mm	27	27	54
Total	69	27	96

Note.—Sensitivity was 100% (95% confidence interval: 87.5%, 100%). Specificity was 61% (95% confidence interval: 48%, 71.5%). Positive predictive value was 50%. Negative predictive value was 100%. Positive likelihood ratio was 2.56 (95% confidence interval: 1.90, 3.43).

Table 5

Diagnostic Performance of Subjective Impression of Examiner

Parameter	Myometrial Infiltration		Total
	<50%	≥50%	
Subjective impression			
<50%	57	2	59
≥50%	12	25	37
Total	69	27	96

Sensitivity was 92.6% (95% confidence interval: 76.6%, 97.9%). Specificity was 82.6% (95% confidence interval: 72.0%, 89.8%). Positive predictive value was 67.6%. Negative predictive value was 96.6%. Positive likelihood ratio was 5.32 (95% confidence interval: 3.15, 9.00). Negative likelihood ratio was 0.09 (95% confidence interval: 0.02, 0.34).

false-positive rate was 17.4%, which was much lower than that of TDS ($P < .001$). However, sensitivity was also lower at 92.6%.

Myomas were found in 26 (27%) patients. In most of the cases, the location was subserous. In five cases, the presence affected the measurement of TDS. In three of these cases, myometrial infiltration was overestimated because the examiner measured from the myometrial-endometrial interface to the inner border of the myoma, resulting in a TDS shorter than what it actually was.

Intraobserver and interobserver reproducibility for US TDS measurement were high, with intraclass correlation coefficients of 0.967 and 0.912, respectively.

Cervical involvement was correctly identified in seven of eight (88%) cases of stage II endometrial carcinoma.

Discussion

Myometrial infiltration is one of the most important factors associated with lymph node metastases (31) in endometrial carcinoma. In spite of International Federation of Gynecology and Obstetrics recommendations about surgical staging in endometrial cancer, the role of comprehensive lymphadenectomy in cases of endometrioid histologic type (32,33) remains controversial. The key question is whether systematic pelvic and para-aortic lymphadenectomy is beneficial in all patients or could be safely obviated in selected cases. Therefore, reliable estimation of myometrial infiltration is essential for deciding whether to perform lymph node dissection. Most gynecologic oncologists rely on intraoperative gross or frozen section pathologic analysis once the uterus has been removed. However, gross evaluation has a sensitivity of 67%–77%, which means a false-negative rate for detection of deep myometrial invasion of about 23%–33% (10–14).

MR imaging and transvaginal 2D US have been proposed for preoperative evaluation of myometrial infiltration by endometrial cancer. In many institu-

tions, MR imaging has become a standard method. Sensitivity reported for this technique ranges from 80% to 91% (16–21).

Three-dimensional US allows virtual navigation by using multiplanar display and tomographic US imaging, which renders images in planes similar to those seen at MR imaging (28). This technique has been demonstrated to be much less operator dependent than 2D US (29).

A study by Lindauer et al (34) demonstrated that TDS has a significant prognostic importance for predicting recurrence in endometrial cancer. On the basis of this study, we speculated that we could reliably measure this distance by using 3D US and performing a virtual navigation throughout the uterus to identify the shortest myometrial TDS. This should be performed in all orthogonal planes because tumors may infiltrate any region of the myometrium.

Assessment of the sagittal plane by using 2D US is the traditional image plane utilized, but the coronal plane is frequently impossible to visualize by using 2D US. However, 3D US allows the assessment of the uterine coronal plane in almost all circumstances.

We found a significant positive correlation between TDS measured by using US and that measured by a pathologist. The presence of myomas may affect the reliability of TDS measurement because they may be a source of false-positive cases. This could be considered a shortcoming of this technique. However, similar problems have been found when using MR imaging (35).

Our data show that a 9.0-mm cutoff for TDS can accurately identify all cases of deep infiltration with no false-negative cases. By applying this cutoff, a 39% false-positive rate was obtained. This relatively high false-positive rate is a shortcoming for this technique in clinical practice.

Another limitation for this measurement was that healthy women may have TDS less than 9.0 mm.

With subjective impression, the false-positive rate was 17.4%, which is much lower; however, sensitivity decreased to 92.6%. Therefore, it could

be argued that subjective impression has a better performance than 3D US. However, because it is important to perform surgery only once, false-positive cases are less relevant than false-negative cases from the point of view of the oncologist. Therefore, we believe that this technique could be helpful in those cases in which MR imaging is not available or cannot be performed.

In summary, we have shown that virtual navigation with 3D US is reproducible and helps identify all cases of deep myometrial infiltration. However, future larger prospective studies are needed to define its actual role in clinical practice.

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