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Preoperative assessment of myometrial and cervical invasion in endometrial carcinoma by transvaginal ultrasound

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ABSTRACT

Objective. To evaluate the diagnostic accuracy of transvaginal ultrasound (TVS) in preoperative assessment of the depth of myometrial infiltration and the presence of cervical invasion in endometrial carcinoma.

Methods. 298 consecutive patients with a diagnosis of endometrial cancer were evaluated by TVS within 3 days of surgical intervention. The depth of myometrial invasion was classified into two groups: no or <50% invasion and ≥50% invasion. Invasion of cervix was diagnosed when the neoplastic tissue distended the cervix and showed ill-defined borders with the cervical stroma.

Results. The sensitivity, specifity, positive predictive value (PPV), negative predictive value (NPV) and overall diagnostic accuracy of TVS in evaluation of the depth of myometrial infiltration were 68.4%, 82%, 65.1%, 84.1% and 77.5%, respectively. While the sensitivity and PPV were significantly higher among grade 3 tumors, the specifity, NPV and accuracy were significantly higher among grade 1 tumors.
The sensitivity, specifity, PPV, NPV, and overall diagnostic accuracy of TVS in assessment of the presence or absence of neoplastic tissue in cervix were 76.5%, 99.3%, 86.7%, 98.2% and 98%, respectively. While the sensitivity and PPV were significantly higher among grade 1 tumors, the NPV and accuracy were significantly lower among grade 3 tumors.

Conclusion. TVS can be considered as a feasible, economical and simple imaging modality with a high diagnostic accuracy for the prediction of cervical involvement. However, it is not a reliable method in estimating the depth of myometrial infiltration.

Introduction

Endometrial cancer is the most common malign neoplasm of the female genital tract [1,2]. As clinical staging carries an overall understaging rate of 13–22%, routine surgical staging has been recommended by the International Federation of Gynecology and Obstetrics (FIGO) since 1988 [3]. However, data in the literature suggest that some of the patients with a low risk for retroperitoneal lymph metastases do not probably benefit from routine pelvic and para-aortic lymphadenectomy [4]. Besides the histological grading, the depth of tumor invasion in the myometrium affect the selection of surgical procedure as the invasion greater than 50% is directly associated with the prevalance of pelvic and paraaortic nodal metastases [5]. Furthermore, tumor extension into the cervix requires irradiation as the first line treatment or a more radical surgical approach [6]. Thus, accurate preoperative staging of the disease is needed in order to avoid excessive or insufficient invasive procedures.

Although utrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) are known to be accurate in the assessment of the depth of myometrial invasion [7–10], a large-scale meta-analysis demonstrated that contrast-enhanced MR imaging had a higher diagnostic accuracy than US and CT [11]. However, sonographic technology has allowed the development of higher frequency transvaginal probes which improved the diagnostic accuracy of transvaginal ultrasound (TVS) [12]. For this reason, recent investigations have shown a higher performance of TVS that is comparable to MRI [4,12].

In this study we aimed to evaluate the diagnostic accuracy of transvaginal ultrasound in preoperative assesment of the depth of myometrial infiltration and the presence of cervical invasion in endometrial carcinoma.

Materials and methods

The data of 298 consecutive patients operated between January 2002–December 2010 with a diagnosis of endometrial cancer were evaluated retrospectively. The patients who underwent prior chemotherapy or pelvic radiation therapy, as well as the women with a

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diagnosis of uterine sarcomas were excluded. The disease was diagnosed by dilatation and curettage which was performed at least 15 days before the examination. Transvaginal ultrasound was carried out as a part of routine preoperative work-up within 3 days of surgical intervention in all cases. The sonographic examinations were performed together by three gynecologists (O.A., C.N., V.U.) who had a 10-year experience on sonography of gynecologic oncology patients. A Voluson 730 Expert scanner and a 5–9 MHz transvaginal probe (GE Helthcare, Milkwaukee, WI) was used to assess the intrauterine extension of the tumor.

The endometrium and myometrium were assessed on images obtained in the long and short axis of the endometrium. The depth of myometrial invasion was determined by measuring the tumor thickness with respect to the total thickness of the uterine wall in sagittal plane. The depth of myometrial invasion was classified into two groups: no or <50% invasion (completely intact endometrium-myometrium interface or the abnormal echo of the tumor extending into the inner half of the myometrium) and ≥50% invasion (the abnormal echo of the tumor extending into the outer half of the myometrium). Invasion of cervix was diagnosed when the neoplastic tissue distended the cervix and showed ill-defined borders with the cervical stroma.

All patients underwent hysterectomy with bilateral salpingo-oopherectomy and routine surgical staging. Sonographic findings were compared with the pathological findings. The pathologist was blind to transvaginal ultrasound results. Stage was determined according to FIGO guidelines revised in 1988 [13]. The carcinomas were classified using a three-grade system in which grade 1 carcinomas showed gland formation greater than 95% of the tumor, grade 2 showed a solid pattern in 5–50%, and grade 3 showed a solid pattern in more than 50% of the tumor.

Statistical analysis was carried out using Statistical Package for the Social Sciences (SPSS) software version 11.5. All continuous data were expressed as mean and SD. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated. Fisher exact was performed in the comparison of these parameters.

Results

298 patients (mean age 56.54 ± 9.69) with endometrial cancer who underwent preoperative TVS enrolled in the study. Body mass index of patients was 31.47 ± 6.20, and 223 (75%) patients were postmenopausal. The distribution of surgical FIGO stages was 32 (10.7%) Stage Ia, 134 (44.9%) Stage Ib, 56 (18.7%) Stage Ic, 7 (2.3%) Stage 2a, 2 (0.6%) Stage 2b, 30 (10%) Stage 3a, 2 (0.6%) Stage 3b, 30 (10%) Stage 3c, 2 (0.6%) Stage 4a, and 3 (1%) Stage 4b. The histological subtypes comprised 262 (87%) endometrioid adenocarcinoma, 21 (7%) serous papillary carcinoma, 8 (2%) adenosquamous carcinoma, and 7 (2%) clear cell carcinoma. Lymphovascular space invasion was detected in 71 (23%) cases. 31 of them had no or <50% myometrial invasion and 40 of them had ≥50% myometrial invasion. Pelvic lymph node metastasis was detected in 13 (4.3%), and paraaortic lymph node metastasis in 20 (6.7%). 15 had no or superficial myometrial invasion, while 18 had deep myometrial invasion. Patients with deep myometrial invasion had significantly higher proportion of lympho-vascular space and lymph node involvement compared with patients without no or superficial myometrial invasion ($p = 0.0001$ and $p = 0.005$, respectively).

The diagnostic performance of TVS in predicting deep myometrial invasion is summarized in Tables 1 and 2. The depth of myometrial infiltration was correctly assessed by TVS in 231 (78%) cases, overestimated in 36 (12%) and underestimated in 31 (10%). Among 102 patients with grade 1 endometrial carcinoma, the depth of myometrial invasion was correctly diagnosed in 89 (87%) women, overestimated in eight (8%), and underestimated in five (5%). Among 139 patients with grade 2 carcinoma, TVS correctly assessed myometrial infiltration in 96 (69%) cases, overestimated in 23 (17%), and underestimated in 20 (14%). Finally among 57 patients with grade 3 carcinoma, the depth of myometrial invasion was correctly diagnosed in 46 (80%) women, overestimated in five (9%), and underestimated in six (11%). When the diagnostic indices of grade 3 tumors were compared with grade 1 and 2, sensitivity and PPV were found to be significantly higher among grade 3 tumors ($p = 0.022$ and $p < 0.001$, respectively). There were no statistically significant differences between the other indices. Also, specificity, NPV, and accuracy were significantly higher among grade 1 tumors in comparison to grade 2 and 3 tumors ($p = 0.005$, $p < 0.001$, and $p = 0.009$, respectively). Sensitivity and PPV were not statistically different between grade 1 tumors and grade 2–3 tumors.

Tables 3 and 4 summarize the diagnostic performance of TVS in predicting the presence of cervical invasion. TVS correctly assessed the presence or absence of neoplastic tissue in cervix in 292 (98%) women, overestimated in two (0.5%), and underestimated in four (1.5%). Out of the 19 women with cervical involvement, 7 had endocervical glandular and 12 had stromal invasion. All of the cases

Table 1
Determination of myometrial invasion according to grades: transvaginal sonography (TVS) vs histopathology (TVS, transvaginal ultrasound; MI: myometrial invasion).

Transvaginal ultrasound		Histopathology		
		MI(−) or <50%	MI ≥50%	Total
Total	MI(−) or <50%	164	31	195
	MI ≥50%	36	67	103
	Total	200	98	298
Grade 1	MI(−) or <50%	79	5	84
	MI ≥50%	8	10	18
	Total	87	15	102
Grade 2	MI(−) or <50%	68	20	88
	MI ≥50%	23	28	139
	Total	91	48	51
Grade 3	MI(−) or <50%	17	6	23
	MI ≥50%	5	29	34
	Total	22	35	57

Table 2
Performance of TVS in predicting myometrial invasion in endometrial cancer. (PPV: positive predictive value; NPV: negative predictive value).

	Sensitivity (%)	Specifity (%)	PPV (%)	NPV (%)	Accuracy (%)
Total	68.4	82	65.1	84.1	77.5
Grade 1	66.7	90.8	55.6	94	87.3
Grade 2	58.3	74.7	54.9	77.3	72.2
Grade 3	82.9	77.3	85.3	73.9	80.7

Table 3
Determination of cervical invasion according to grades: transvaginal sonography (TVS) vs histopathology. (TVS, transvaginal ultrasound; CI: cervical invasion).

Transvaginal ultrasound		Histopathology		
		CI(−)	CI(+)	Total
Total	CI(−)	279	4	283
	CI(+)	2	13	15
	Total	281	17	298
Grade 1	CI(−)	101	0	101
	CI(+)	0	1	1
	Total	101	1	102
Grade 2	CI(−)	132	1	133
	CI(+)	1	5	6
	Total	133	6	139
Grade 3	CI(−)	46	3	49
	CI(+)	1	7	8
	Total	47	10	57

Table 4
Performance of TVS in predicting cervical invasion in endometrial cancer. (PPV: positive predictive value; NPV: negative predictive value).

	Sensitivity (%)	Specifity (%)	PPV (%)	NPV (%)	Accuracy (%)
Total	76.5	99.3	86.7	98.2	98
Grade 1	100	100	100	100	100
Grade 2	83.3	99.2	83.3	99.2	98.6
Grade 3	70	97.9	87.5	93.9	93

with grade 1 carcinoma were assessed correctly with TVS in means of cervical involvement. Among 139 patients with grade 2 carcinoma, TVS correctly diagnosed cervical invasion in 137 (98.6%) cases, overestimated in one (0.7%), and underestimated in one (0.7%). Among 57 patients with grade 3 carcinoma, cervical involvement was correctly assessed in 53 (93%) women, overestimated in one (2%), and underestimated in three (5%). When we compared the diagnostic indices of grade 1 tumors with grade 2 and 3, we found that sensitivity and PPV were significantly higher among grade 1 tumors ($p<0.001$ and $p=0.001$, respectively), but the other indices were not statistically different. When the diagnostic indices of grade 3 tumors were compared with that of grade 1 and 2, NPV and accuracy were significantly lower among grade 3 tumors ($p=0.023$, $p=0.024$, respectively). There was no statistically significant difference between the other indices.

Transvaginal ultrasound was superior in detecting the cervical spread in comparison to the depth of myometrial invasion (98% vs 77.5%, $p<0.001$).

Discussion

Treatment and prognosis of endometrial carcinoma is affected by tumor morphologic prognostic factors that include histologic and patient factors such as age and health, as well as tumor extent. The range of lymph node metastasis is mainly related to the depth of myometrial invasion and degree of differentiation, varying between 1% for well-differentiated tumor limited to the endometrium and 36% for poorly differetiated neoplasia in which invasion exceeds 50% of the myometrium [4]. As a result, aggressive surgery is unnecessary in selected patients because of the low risk of tumor spreading. In addition, lymphadenectomy can cause serious complications such as lymphocysts, bleeding and vascular damage, as well as gastrointestinal and urogenital complications [14]. Since the majority of patients are obese, aged and with general medical problems, it is important to avoid unnecessary procedures in order to decrease morbidity and mortality.

The most common factor that can be assessed preoperatively is the degree of differentiation [4]. While the incidence of pelvic and paraaortic lymph node metastasis are 3% and 2%, respectively for grade 1, they are 9% and 5% for grade 2, and 18% and 11% for grade 3 [5]. Therefore, lymphadenectomy might be avoided in patients with grade 1 endometrial cancers with only superficial myometrial invasion. However, preoperative grading can underestimate tumor grades, and concordance rates between biopsy and histologic examination results have been reported as 63% [4].

Other factors that can be assessed before surgery are the depth of myometrial infiltration and the presence of cervical invasion. In the cases with no myometrial invasion or infiltration less than half of the myometrial thickness, the incidence of regional nodal involvement is less than 3%, whereas in those with infiltration more than half of the myometrium, it is more than 40% and lymphadenectomy is required [2,15]. Although gross evaluation of myometrial invasion can be beneficial to some extent, it becomes less reliable with increasing tumor grade (gross inspection has 80% reliability vs 94% for frozen section analysis) [11]. Besides, frozen section is a time-consuming method which is not available all the time. Another disadvantage of these methods is that the extent of tumor is not detected until the surgery. However, if it is known before the operation, it can be decided whether to refer the patient to a gynecologic oncologist, or not. Another important point is that Pfannensteil incision can be applied to the obese patients with well-differentiated endometium carcinomas, if deep myometrial invasion is ruled out before the operation, since median incision has a higher rate of complications in these patients. In addition, the detection of cervical invasion is essential in order to determine the type of hysterectomy or perform irradiation rather than immediate surgery [16]. Endocervical curettage is one of the options to determine cervical invasion with a false-positive rate as high as 25% and false-negative rate up to 10% [17].

The diagnostic performance of MRI, CT and TVS, has been extensively evaluated in assessing the depth of myometrial invasion and cervical extension. MRI is more accurate than CT in evaluation of myometrial infiltration [18,19]. Also, investigators reported similar performances for MRI and TVS with a sensitivity of 76.9%–86.4% and a specifity of 65%–92.6% [20,21]. However, MRI with contrast-enhancement is reported to have the highest diagnostic accuracy (sensitivity 84%–100%, specifity 71%–100%) [11]. MRI is costly, time consuming, not always available and requires contrast agents that can cause allergic reaction. TVS, in contrast, is a simple, low-cost, and noninvasive technique for myometrial assessment. In addition, as the sonography technology has evolved, the diagnostic accuracy of TVS has become as high as MRI [22–24]. The detection of cervical involvement by TVS has been investigated, as well. Savelli et al., reported that the diagnostic accuracy of TVS was higher than that of MRI for the prediction of cervical involvement (92% vs 85%) [12]. Artner et al., reported only 3 false-negative and no false-positive results among 69 patients in the study group [25]. Also, Kose et al., reported that TVS in the assesment of cervical involvement had a sensitivity of 75%, a spesifity of 100%, and a PPV of 100% [6].

In this study, the overall sensitivity in predicting the depth of myometrial infiltration was 68.4% with an accuracy rate of 77.5%. Although we used a high-quality TVS, this is not as high as the rates reported in the other studies. The number of women enrolled in them are lower than our study, which might be the main reason for that. The results of this study show that the ultrasonographic assessment of the depth of myometrial infiltration is not as reliable as it has been suggested recently.

Our results in cervical involvement is consistent with the literature. There were only 2 false-positive and 4 false-negative results among 298 patients. The cases understaged by TVS had only endocervical involvement, and none of the cases with stromal invasion were understaged. For those who were understaged, management was not influenced negatively, since the patients with endocervical disease do well with limited surgery, whereas those with deep stromal invasion need more aggressive treatment [25]. We have found that the accuracy of TVS in the assessment of cervical involvement was superior to that achieved in myometrial assessment. This was also consistent with the findings in the study of Kose et al. [6].

We also investigated the diagnostic performance of TVS according to the grades. We found that the sensitivity and PPV in predicting the depth of myometrial invasion were higher among grade 3 tumors. Since grade 1 tumors are less aggressive than undifferentiated tumors, the infiltration of myometrium $\geq 50\%$ may be microscopic, which might have resulted in underestimation of the invasion depth during TVS examination. As with our study, Ruangvutilert et al., compared TVS performance between the grades and found a significant difference in PPV which was higher among grade 3 than grade 1 and 2 tumors [26].

To our knowledge this is the first study that compared the performance of TVS in the assessment of cervical involvement between the grades. We have found that preoperative TVS examination had a higher sensitivity and PPV in grade 1 tumors in comparison

to grade 2 and 3 tumors. It is known that the cervical invasion rate increases as the differentiation of tumor decreases [27], and in grade 1 tumors the number of patients with cervical invasion is very low. Therefore, the sensitivity of TVS in assessment of cervical invasion is much higher in well-differentiated tumors. In this study, only one out of 102 patients had cervical invasion, as a result, the sensitivity of TVS were 100%, whereas the sensitivity of TVS in grade 3 tumors was only 70%. When preoperative histologic examination reveals grade 3 endometrium carcinoma, if the presence of the cervical invasion is not excluded certainly because of the location of tumor in the ishmic area, the other diagnostic modalities such as MRI and/or endocervical curettage should be added to confirm this finding before the operation.

In conclusion, TVS performed by specialists who are experienced in ultrasonography, can be considered as a feasible, economical and simple imaging modality with a high diagnostic accuracy for the prediction of cervical involvement. However, this study shows that TVS is not a reliable method in estimating the depth of myometrial infiltration.

Conflict of interest statement
There is no conflict of interest.

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