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Combined use of preoperative transvaginal ultrasonography and intraoperative gross examination in the assessment of myometrial invasion in endometrial carcinoma

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ABSTRACT

Objective: To evaluate the diagnostic performance of gross examination and transvaginal ultrasonography in the assessment of the depth of myometrial infiltration when they are used alone or together as a combined test.

Study design: The data of 219 consecutive patients with a diagnosis of endometrial cancer were evaluated retrospectively. Transvaginal ultrasound was carried out as a part of the routine preoperative work-up within three days of surgical intervention in all cases. All patients underwent hysterectomy with bilateral salpingo-oophorectomy and routine surgical staging and all uterine specimens were examined immediately after hysterectomy. The depth of myometrial invasion was classified into two groups: no or $<$50% invasion and $\geq$50% invasion. The findings of ultrasound and intraoperative gross examination were compared with the final histopathological results. The data of these two methods were integrated to evaluate the diagnostic performance of the combined test. If the results of myometrial invasion evaluation were different for the same patient, the deeper one (the depth of invasion $\geq$50%) was accepted.

Results: Sensitivity, specificity, PPV, NPV and accuracy of preoperative ultrasonography in predicting myometrial infiltration $\geq$50% were 62%, 81%, 60%, 82%, and 75% respectively. The corresponding rates for intraoperative gross examination were 61%, 88%, 70%, 83% and 79%, respectively. For the combined test they were 78%, 76%, 60%, 88% and 70% respectively. There was no statistically significant difference in sensitivity and specificity between ultrasound and gross examination. The sensitivity of the combined test was significantly higher than that of ultrasound and gross examination ($p = 0.001$ and $p < 0.0001$, respectively). The specificity of the combined test was significantly lower than that of TVS and gross examination ($p = 0.008$ and $p < 0.0001$, respectively).

Conclusion: Combining ultrasonography and intraoperative gross examination may be a good option to assess the depth of myometrial invasion, as it has a higher sensitivity and negative predictive value in comparison to using these methods alone.

1. Introduction

Endometrial carcinoma is the most common malignancy of the female genital tract. In 70–75% of cases it is confined to the corpus uteri and surgery is mostly curative [1]. Although total abdominal hysterectomy and bilateral salpingo-oophorectomy successfully treat some patients with early endometrial cancer, extensive surgery including pelvic and paraaortic lymphadenectomy is indicated for surgical staging and planning the appropriate adjuvant therapy. The range of lymph node metastasis is mainly related to the depth of myometrial invasion and degree of differentiation, varying between 1% for a well-differentiated tumor limited to the endometrium and 36% for poorly differentiated neoplasia in which invasion exceeds 50% of the myometrium [2]. As the depth of myometrial invasion is significantly associated with the lymph node metastasis, methods of preoperative assessment have been a topic of concern for the last two decades. Many studies have shown that transvaginal ultrasound (TVS), computerized tomography (CT) and magnetic resonance imaging

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(MRI) can be used for the estimation of myometrial invasion [3–6]. Although a large-scale meta-analysis demonstrated that contrast-enhanced MRI had a higher diagnostic accuracy than TVS and CT [7], recent investigations have shown a high performance of TVS that is comparable to MRI, as a result of improvement in sonography technology [2,8]. Intraoperative gross examination or frozen section analysis are also used to identify the depth of myometrial invasion [1,9,10], but the results of the studies which investigated the accuracy of gross examination are controversial. While some of them reported a poor correlation between gross and histologic examinations of myometrial infiltration [11,12], others concluded that gross evaluation is a highly accurate method [13,14].

The combined use of pre- and intra-operative methods may improve accuracy in the prediction of the depth of myometrial invasion. To the best of our knowledge, there is no study in which the diagnostic performance of the combined use of preoperative TVS and intraoperative gross examination has been investigated.

In the present study, we aimed to evaluate the diagnostic performance of gross examination and TVS in the assessment of the depth of myometrial infiltration when they are used alone or together as a combined test.

2. Materials and methods

The data of 219 consecutive patients operated on between January 2002 and December 2010 with a diagnosis of endometrial cancer were evaluated retrospectively. The disease was diagnosed by dilatation and curettage that was performed at least 15 days before the examination. Women with a diagnosis of uterine sarcoma and those who underwent prior chemotherapy or pelvic radiation therapy were excluded. All patients underwent hysterectomy with bilateral salpingo-oophorectomy and routine surgical staging. Pelvic lymphadenectomy was performed in all patients except those with endometrioid carcinoma with no myometrial invasion and some of the morbidly obese patients due to technical difficulty. Also, paraaortic lymphadencetomy was added to surgical staging in patients with non-endometrioid histology, grade 3 tumor and deep myometrial invasion.

Transvaginal ultrasound was carried out as a part of the routine preoperative work-up within three days of surgical intervention in all cases. Three gynecologic oncologists experienced in ultrasound performed sonographic examinations together. A Voluson 730 Expert scanner and a 5–9 MHz transvaginal probe (GE Healthcare, Milkwaukee, WI) were 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 measured by determining the tumor thickness with respect to the total thickness of the uterine wall in the 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) (Fig. 1) and ≥50% invasion (the abnormal echo of the tumor extending into the outer half of the myometrium) (Fig. 2).

As a part of our routine operating room procedure, all uterine specimens were examined immediately after hysterectomy. The anterior wall was incised and opened from the uterine fundus to the cervix and along both horns of the uterus using a scalpel, creating a Y-shaped endometrial cavity. The myometrium was sliced at regular intervals to determine the presence and absence of gross tumor and to estimate the depth of myometrial invasion. A visible tumor seen extending from the endometrial cavity to the myometrium was considered to be myometrial invasion. The depth was measured as the deepest point reached by the tumor inside myometrial thickness, and was rated as no or <50% and ≥50% of the uterine wall.

The pathologist was blind to TVS and gross examination results. Stage was determined according to FIGO guidelines revised in 1988 [15]. 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.

The findings of TVS and intraoperative gross examination were compared with the final histopathological results. The data of these two methods were integrated to evaluate the diagnostic performance of the combined test. If the results of myometrial invasion evaluation were different for the same patient, the deeper one (the depth of invasion ≥50%) was accepted.

Descriptive analysis was performed using SPSS 15.0 (SPSS, Chicago, IL, USA). Differences of the final pathologic findings in patients with no or <50% invasion and ≥50% invasion were assessed using chi-square and Mann Whitney *U* tests for categorized variables. The correlation of histological invasion with TVS and intraoperative gross examination was assessed by Spearman's correlation. A $p < 0.05$ was considered as statistically significant. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated for the diagnosis of myometrial invasion with TVS and intraoperative gross examination. McNemar x^2 test was used to compare the

Fig. 1. The inner half of the myometrium was invaded by tumor. The depth of myometrial invasion was measured as 0.59 cm and the total thickness of the uterine wall was measured as 1.68 cm in sagittal plane.

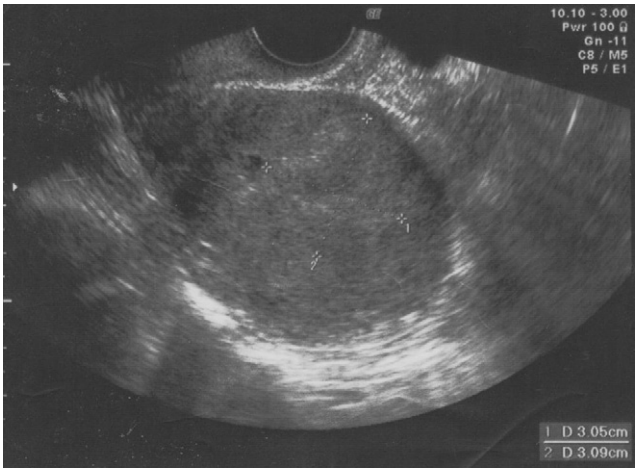

Fig. 2. The sagittal plane of the uterus shows deep myometrial invasion of the anterior wall by a tumor measuring 3.09 cm × 3.05 cm in diameter. The depth of invasion was 3 mm near the serosa.

sensitivity and specifity of TVS and gross examination both with each other and with the combined test.

3. Results

Two hundred and nineteen patients (mean age 56.7 ± 9.9) with endometrial cancer were enrolled in the study. Most of the patients were postmenopausal (n = 164; 74.9%). At the final diagnosis; 69.4% of the patients had stage 1 disease, 8.7% had stage 2 disease, and 19.6% and 2.3% had stage 3 and 4 disease, respectively. Almost half of the patients (44.3%) had FIGO grade 2 endometrioid tumor, and 34.4% and 21% had grade 1 and 3 tumors, respectively. The vast majority of the patients had endometrioid histology (n = 198; 90.4%) and lymph node involvement was detected in 10% of the patients. No or <50% myometrial invasion was detected in 68.5%, and ≥50% myometrial invasion was detected in 31.5% of the patients.

Table 1 summarizes the comparison of the depth of the myometrial invasion and final pathologic findings. Histologic grade, lympho-vascular space invasion (LVSI), lymph node involvement and stage of the disease were statistically significantly related with the depth of myometrial invasion ($p < 0.0001$, $p < 0.0001$, $p = 0.04$, and $p < 0.0001$, respectively). The histology of tumor, however, was not related with myometrial invasion ($p = 0.82$).

The diagnostic performance of TVS and gross examination in the prediction of deep myometrial invasion is summarized in Table 2. The depth of myometrial infiltration was correctly assessed by TVS in 165 (75.3%), overestimated in 28 (12.7%) and underestimated in 26 (12%) cases. Intraoperative gross examination correctly assessed the depth of myometrial infiltration in 174 (79.4%), overestimated it in 18 (8.2%), and underestimated it in 27 (12.3%) cases. The depth of myometrial invasion was correctly assessed in 168 (76.7%), overestimated in 36 (16.43%) and underestimated in 15 (6.8%) cases with the combined test. Myometrial invasion estimation with TVS, gross examination and the combined test were highly correlated with histopathologic results (r = 0.45, 0.53 and 0.51, p = 0.0001, 0.0001 and <0.0001, respectively).

Sensitivity, specificity, PPV, NPV and diagnostic accuracy of preoperative TVS in predicting the myometrial infiltration ≥50% were 62%, 81%, 60%, 82%, and 75% respectively. The corresponding rates for intraoperative gross examination were 61%, 88%, 70%, 83% and 79%, respectively, and for the combined test they were 78%, 76%, 60%, 88% and 70% respectively. There was no statistically significant difference in sensitivity and specificity between TVS and gross examination (p = 0.98 and 0.07, respectively). The sensitivity of the combined test was significantly higher than that of TVS and that of gross examination (p = 0.001 and $p < 0.0001$, respectively). The specificity of the combined test was significantly lower than that of TVS and that of gross examination (p = 0.008 and $p < 0.0001$, respectively).

The sensitivity of preoperative TVS, intraoperative gross examination and the combined test in the assessment of the depth of myometrial invasion was highest in grade 3 tumors, in which it was 79%, 76% and 96%, respectively, while the specificity was highest in grade 1 tumors, at 89%, 90% and 81%, respectively. The diagnostic indices of myometrial invasion prediction by final tumor grade are shown in Table 3.

Table 1
Comparison of the depth of the myometrial invasion and final pathologic findings of the patients.

	No or <50% MI n (%)	≥50% MI n (%)	p
Histologic grade			<0.0001
1	64 (43)	11 (15.9)	
2	68 (45.6)	29 (42)	
3	17 (11.4)	29 (42)	
LVSI			<0.0001
No	125 (83.3)	42 (60.9)	
Yes	25 (16.7)	27 (39.1)	
LN involvement			0.04
No	139 (92.7)	58 (84.1)	
Yes	11 (7.3)	11 (15.9)	
Stage			<0.0001
1	119 (79.3)	33 (47.8)	
2	5 (3.3)	14 (20.3)	
3	23 (15.3)	20 (29.0)	
4	3 (2.0)	2 (2.9)	
Histology			0.82
Endometrioid	138 (92)	60 (86.9)	
Clear cell	1 (0.06)	2 (2.9)	
Adenosquamous	2 (1.3)	1 (1.4)	
Serous	9 (6.1)	6 (8.6)	

MI: myometrial invasion; LN: lymph node; LVSI: lympho-vascular space invasion.

Table 2
Comparison of histopathological myometrial invasion with transvaginal ultrasound and intraoperative gross examination.

	Histopathologic MI			
	No or <50% MI	≥50% MI	r^*	p
TVS MI			0.45	0.0001
No or <50% MI	122	26		
≥50% MI	28	43		
Gross MI			0.53	0.0001
No or <50% MI	132	27		
≥50% MI	18	42		
Combined test			0.51	<0.0001
No or <50% MI	114	15		
≥50% MI	36	54		

MI: myometrial invasion; TVS: transvaginal ultrasound.
* r: Spearman's correlation coefficient.

4. Comment

Pre- and intra-operative assessment of prognostic factors is necessary for the tailoring of surgical staging in patients with endometrial cancer. The majority of patients with endometrial cancer are obese, elderly and with medical problems such as diabetes and hypertension. An unnecessarily extensive surgical approach increases morbidity and mortality for these patients, due to the increase in the duration of operation, as well as the risks of the procedure. Pelvic and paraaotic lympadenectomy have serious complications such as lymphocyst, bleeding, and vascular, gastrointestinal and genitourinary injury [16]. In the cases with no myometrial invasion or infiltration less than half of the

Table 3
Diagnostic indices of transvaginal ultrasound, intraoperative gross examination alone and together as a combined test in predicting myometrial invasion ≥50%.

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
TVS MI					
Overall	**62**	**81**	**60**	**82**	**75**
G1	54	89	46	91	84
G2	48	76	46	78	68
G3	79	70	82	66	76
Gross MI					
Overall	**61**	**88**	**70**	**83**	**79**
G1	37	90	40	89	82
G2	55	90	69	82	79
G3	76	70	81	63	74
Combined test					
Overall	**78**	**76**	**60**	**88**	**70**
G1	64	81	63	93	78
G2	66	75	53	84	72
G3	96	59	80	91	83

MI: myometrial invasion; TVS: transvaginal ultrasound; PPV: positive predictive value; NPV: negative predictive value; G1: Grade 1; G2: Grade 2; G3: Grade 3.

myometrial thickness, the incidence of regional lymph node involvement is less than 3%, whereas in those with infiltration of more than half of the myometrium, it is more than 40% and lymphadenectomy is required [17]. For this reason, pre- and intraoperative estimation of the depth of myometrial invasion is important to avoid unnecessary lymphadenectomy.

The diagnostic performance of MRI, CT and TVS has been extensively evaluated in the assessment of the depth of myometrial invasion. Although MRI with contrast enhancement is reported to have the highest diagnostic accuracy (sensitivity 84–100%, specificity 71–100%) [7], it is costly, time consuming and not always available, and includes the risk of allergic reaction. There are some reports that showed a poor accuracy of TVS when myometrial invasion was divided into three categories (none, superficial, and deep) [18], but the diagnostic performance of ultrasonography for myometrial invasion has risen to a level comparable to MRI due to the use of endovaginal probes with high resolution [8,19,20]. Although TVS is limited by being highly dependent on the operator, it is generally considered as a reliable, inexpensive and non-invasive method for diagnosing myometrial invasion.

Apart from the preoperative methods, the depth of myometrial invasion can be assessed intraoperatively either by frozen section or by visual gross examination. The accuracy of frozen section to predict the depth of myometrial invasion varies from 67% to 96.5% [10,21–23]. The main advantage of this method is that it can evaluate the grade of the tumor, since the tumor grade is often underestimated at dilatation and curettage or at office endometrial biopsy [24]. Frozen section, however, is a time-consuming method which is not available all the time.

The accuracy of visual gross examination of myometrial invasion in the uterine specimen has been evaluated in many studies. Noumoff et al. reported 67.7% correlation between gross and histological examination of myometrial infiltration [11]. Goff and Rice found a low prediction rate of gross examination in cases with grade 2 and grade 3, with unsuccessful prediction rates of 35.1% and 69.2%, respectively [12]. These studies were performed classifying the myometrial thickness in thirds, which was speculated to be the reason for these low rates [25]. Likewise, Teefey et al. reported that gross examination correctly diagnosed the depth of myometrial invasion in 53% and 80% of cases, when myometrial invasion was classified into three and two groups, respectively [3]. On the other hand, there are studies that showed an accuracy rate >85% [1,9,13,26,27]. It is mainly considered as a simple, cheap and quick way of assessment of the depth of myometrial invasion.

The main drawback of the intraoperative techniques is that the preoperative selection of low risk patients is not possible. If deep myometrial invasion is ruled out before the operation, a Pfannensteil incision can be used in obese patients with well-differentiated endometrium carcinomas, as a median incision has a higher rate of complications in these patients. Moreover, it enables the decision of referring high-risk patients to the gynecologic oncologist before the operation.

In this study we investigated whether the combined use of TVS and intraoperative gross examination increases the diagnostic performance of these methods. We found that sensitivity rose significantly up to 78% while it was only 62% and 61% with TVS and gross examination, respectively ($p = 0.001$ and $p < 0.0001$). As expected, the specificity was significantly lower with a rate of 76% with the combined test, while it was 81% with TVS and 88% with gross examination ($p = 0.008$ and $p < 0.0001$). This decrease in specificity can be disregarded, however, because insufficient surgery leads to much more serious problems than performing lymphadenectomy unnecessarily. Besides, in comparison to using TVS alone, only eight patients would undergo unnecessary surgery if we combined the methods, while deep myometrial invasion would be detected in 11 more patients. Likewise, when it was compared with gross examination alone, only 18 unnecessary lymphadenectomies would be performed to detect deep infiltration in 12 more patients. Therefore, the combined test seems to be a good method to avoid underestimation of the depth of infiltration with an insignificant increase in unnecessary lymphadenectomy.

In the majority of studies, the accuracy of gross prediction of myometrial was found to be higher in well-differentiated tumors (87.3–93.5%) and very low in grade 3 tumors (30.8–58.6%) [12,25]. On the other hand, Fishman et al. reported that the accuracy and sensitivity of TVS were superior among grade 2–3 cases in comparison to grade 1 cases [28]. Ruangvutilert et al. found that the PPV was significantly higher in grade 3 when compared with grade 1 and 2 tumors, while the other diagnostic indices were similar for each grade [29]. In our study, the specificity and NPV were higher, but the sensitivity and PPV were far lower in grade 1 tumors in comparison to grade 3 tumors. Although we do not exactly know the reason for this discrepancy, we can speculate that less aggressive tumors cause microscopic deep myometrial infiltration rather than macroscopic invasion, resulting in the underestimation of the invasion depth during both TVS and intraoperative gross examination. The low sensitivity rates of these methods limit their utility in tailoring the type of surgery, because our aim is to evaluate the necessity of lymphadenectomy in well-differentiated tumors rather than grade 3, in which lymphadenectomy is indicated regardless of the depth of invasion. Combining these two methods increases the sensitivity up to 64% and 66% in grade 1 and 2 tumors, respectively, making the pre- and intra-operative assessment more reliable for excluding the lymphadenectomy in low-risk patients.

In conclusion, combining TVS and intraoperative gross examination may be a good option to assess the depth of myometrial invasion, as it has a higher sensitivity and negative predictive value in comparison to using either method alone.

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