Preoperative Transvaginal Ultrasonography and Intraoperative Gross Examination for Assessing Myometrial Invasion by Endometrial Cancer

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Objective. Endometrial cancer is the most common gynecologic malignancy. The cornerstone of treatment remains surgery according to International Federation of Gynecology and Obstetrics staging. The aim of this study was to evaluate the concordance between myometrial infiltration detected by ultrasonography and gross examination with respect to definitive histologic examination and to select a population in which lymphadenectomy could be excluded. We also evaluated the concordance for the degree of tumor differentiation between diagnostic biopsy and final histologic results. ***Methods.*** Our study included 75 patients with International Federation of Gynecology and Obstetrics stage I endometrial cancer. We evaluated preoperative and definitive grading and myometrial infiltration detected by ultrasonography and gross examination. The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of the procedures under study were determined with the Bayes theorem. To determine the predictive value of preoperative transvaginal ultrasonography and intraoperative gross examination for myometrial invasion, we used a multiple logistic regression model with a statistical software package. ***Results.*** Our study showed 60% concordance between biopsy and histologic results. In 80% of the cases with discordant results, the tumor was undergraded. Ultrasonography had diagnostic accuracy of 73%, whereas gross examination correctly determined myometrial invasion in 82.6% of the patients, with sensitivity of 62% and specificity of 79%. ***Conclusions.*** Preoperative transvaginal ultrasonography and macroscopic gross examination appear to be simple, fast, and reliable methods to predict in myometrial invasion in patients with a low risk for lymph node metastasis, for which lymphadenectomy can reasonably be avoided. ***Key words:*** endometrial cancer; histologic grading; intraoperative gross examination; myometrial invasion; preoperative transvaginal ultrasonography.

Abbreviations
CT, computed tomography; D&C, dilation and curettage; FIGO, International Federation of Gynecology and Obstetrics; MRI, magnetic resonance imaging; NPV, negative predictive value; PPV, positive predictive value; TVUS, transvaginal ultrasonography

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Endometrial cancer is the most common gynecologic malignancy and accounts for 6% of all cancers in women.[1,2] The cornerstone of endometrial carcinoma treatment remains surgery according to International Federation of Gynecology and Obstetrics (FIGO) staging.

The rate of lymph node metastasis is mainly related to the degree of differentiation and the depth of invasion of the tumor into the myometrium, ranging between 1% for well-differentiated tumors limited to the endometrium to 36% for poorly differentiated neoplasia in which invasion exceeds 50% of the myometrium.

Even if complete surgical staging should be recommended routinely in all patients with endometrial cancer,[3,4] data in the literature suggest that at least in some patients, knowledge of tumor grading and the depth of myometrial invasion could help the surgeon in planning surgical treatment, limiting lymphadenectomy only to patients at high risk for node metastasis.[5]

Imaging techniques such as ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) have all been used with different degrees of reliability to evaluate the depth of myometrial invasion.[6] A recent review of the literature showed that MRI is currently seen as the best method for myometrial assessment.[7] However, MRI is costly, is not always widely available, and can induce contrast agent allergies, whereas ultrasonography is a simple, low-cost, noninvasive, and reproducible technique with diagnostic accuracy that varies between 85% and 95%.

The aim of this study was to retrospectively evaluate how the grade of myometrial infiltration detected by transvaginal ultrasonography (TVUS) and intraoperative gross examination could be confirmed by definitive histologic examination to assess how these methods can be used in clinical practice. We also evaluated the concordance for the degree of tumor differentiation between diagnostic biopsy and final histologic results. For both preoperative TVUS and intraoperative gross examination, we calculated the accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) using standard statistical formulas.

Materials and Methods

We retrospectively selected and analyzed a series of patients with a histologic diagnosis of FIGO stage I endometrial adenocarcinoma treated at the Department of Obstetrics and Gynecology of the University of Parma between January 2001 and December 2005. We excluded patients who underwent prior chemotherapy or pelvic radiation therapy and those with tumors of an unfavorable histologic type (serous-papillary carcinoma, clear cells, or undifferentiated). The study was approved by the University of Parma Ethics Committee, and all patients agreed to publication of this article.

Preoperative grading on endometrial biopsies and the histologic diagnosis were reevaluated by a pathologist with experience in gynecologic oncology. We recorded preoperative grading, the depth of myometrial invasion on preoperative TVUS, the depth of myometrial invasion on intraoperative gross examination, and grading and myometrial invasion on the final histologic examination. Grading was in accordance with FIGO guidelines: grade G1, when at least 95% of the tumor forms glands; grade G2, when 6% to 50% of the tumor shows solid growth; and grade G3, when more than 50% of the tumor has a solid growth pattern.

Before surgery, all patients with histologically proven endometrial cancer underwent clinical gynecologic examinations, abdominal/pelvic CT, chest radiography, cancer antigen 125 screening, and TVUS. Transvaginal ultrasonography was performed after endometrial biopsy with a high-resolution 6.5-MHz ultrasound machine (AU5 Harmonic; Esaote SpA, Genoa, Italy). The ultrasonographic examinations were performed by a gynecologist with specific experience in ultrasonography. Tumor invasion into the myometrium was determined by measuring the tumor thickness with respect to the total thickness of the uterine wall (from the endometrium/myometrium interface down to the deepest point of infiltration) in a sagittal plane. The endometrial thickness was measured to the nearest 0.1 mm at its thickest part. In addition, the following ultrasonographic features were recorded: a regular or irregular endometrium, the endometrial aspect according to the phase of the menstrual cycle, and the presence or absence echogenic spots in the endometrium/myometrium. According to the FIGO staging system, the depth of myometrial invasion was rated as superficial (M1, <50%; Figure 1) or deep (M2, >50%; Figure 2).

During surgery, as soon as they were surgically removed, the uterus and adnexa were immediately sent to the pathologist for intraoperative gross examination to determine the depth of myometrial invasion. The examination was performed by making 2 lateral incisions in the uterus, from the cervix to the cornua, along the uterine vessels. The uterine cavity was folded open and inspected. Multiple incisions were

Figure 1. M1 myometrial invasion with a 6-mm endometrial thickness (middle segment of dotted line marked by calipers) and a 24.5-mm anteroposterior diameter (entire length of dotted line).

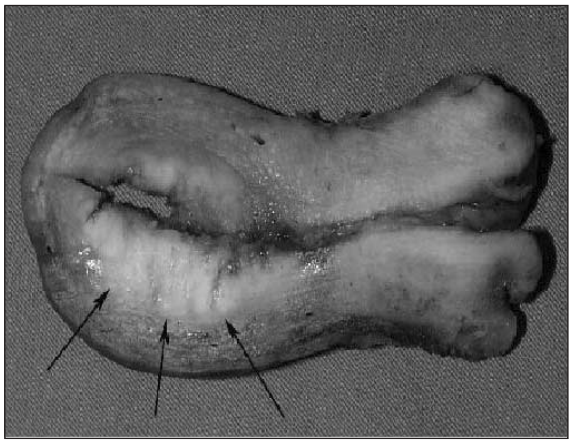

Figure 3. M2 myometrial infiltration: macroscopic evaluation. Arrows indicate the myometrium/cancer interface.

made in the whole myometrial thickness affected by the tumor. The depth of invasion was measured as the deepest point reached by the tumor inside the myometrial thickness and was rated as less than 50% (M1) or more than 50% (M2) of the uterine wall (Figures 3 and 4).

The accuracy, sensitivity, specificity, PPV, and NPV of the procedures under study were determined using the Bayes theorem. We used the Cohen κ test to value the agreement of preoperative data versus final grading. To determine the predictive value of preoperative TVUS and intraoperative gross examination for myometrial invasion, we used a multiple logistic regression model with the SPSS version 11.0 software package (SPSS Inc, Chicago, IL). With a block method, we considered microscopic infiltration as an independent variable and the TVUS findings and myometrial invasion detected by gross examination as dependent variables.

Results

The study group included 75 patients with FIGO stage I endometrial carcinoma. Their main cancer features are reported in Table 1. A histologic diagnosis was made by in-office biopsy with Vabra aspiration in 30 patients (40%) and by dilation and curettage (D&C) in 45 (60%). Data regarding endometrial biopsy grading and final histologic findings for the 75 patients are shown in Table 2 .

Figure 2. M2 myometrial invasion with a 30.3-mm endometrial thickness (D1), a 6.3-mm remaining anterior myometrial thickness (D2), and a 44.6-mm remaining posterior myometrial thickness (D3).

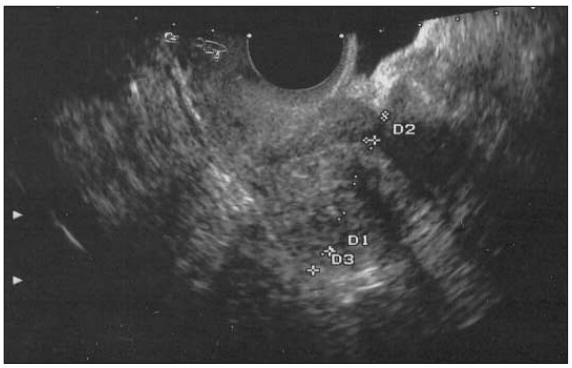

Figure 4. M2 myometrial invasion by endometrial cancer: invasion of the external third of the myometrium.

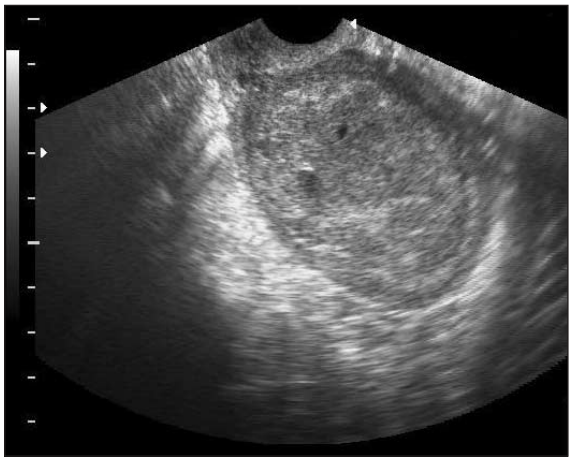

Table 1. Patient Cancer Characteristics (N = 75)

Characteristic	Value
Age, y, median (range)	63 (47–80)
Menopause, n (%)	71 (95)
Nonmenopause, n (%)	4 (5)
Surgical stage, n (%)	
Ia	4 (5)
Ib	44 (59)
Ic	27 (36)
Tumor histologic type, n (%)	
Endometrioid	73 (97)
Adenosquamous	2 (3)
Tumor grade (final), n (%)	
G1	17 (23)
G2	44 (59)
G3	14 (18)
Microscopic myometrial invasion, n (%)	
>50%	27 (36)
<50%	48 (64)

Preoperative grading resulted in grade G1 in 33 patients, G2 in 34, and G3 in 8. There was concordance of results in 47 (63%) of 75 cases, including 15 G1 (46%), 26 G2 (76%), and 6 G3 (75%). The highest correspondence between preoperative grading and final grading was found in the G2 group (76%). In the 28 cases with discordant results (37%), the grading was underestimated in 24 patients, including 16 with final grading of G2 and 8 with final grading of G3. On the other hand, the grading was overestimated in 4 patients, including 2 with final grading of G2 and 2 with final grading of G1. From a comparison of the two biopsy techniques used, it appears that in-office biopsy undergraded cancer lesions in 41% of the patients, and D&C undergraded in 36%.

The κ value was 0.4; the variable κ value was 0.04; and the z value was 2, with $P < .05$ (significant); therefore, the hypothesis that data were influenced by the case was not significant (Table 2).

Table 2. Preoperative Versus Final Grading (N = 75)

Preoperative Grade	Final G1, n (%)	Final G2, n (%)	Final G3, n (%)
G1: 33	15 (46)	16 (48)	2 (6)
G2: 34	2 (6)	26 (76)	6 (18)
G3: 8	0	2 (25)	6 (75)

$\kappa = 0.4$; variable $\kappa = 0.04$; and $z = 2$. The value of probability that corresponded to $z = 2$ was $P < .05$; therefore, events were not dependent on the case.

The depth of myometrial invasion on preoperative TVUS versus final histologic examination is shown in Table 3. There was concordance of results in 55 patients (73%), including 42 M1 (76%) and 13 M2 (24%). In the remaining 20 patients (26%), ultrasonography underestimated the myometrial invasion in 9 cases (12%) and overestimated it in 11 (15%). The sensitivity of TVUS in evaluating M2 invasion was 62%, with specificity of 79%, a PPV of 54%, and an NPV of 82%. The diagnostic accuracy of this procedure was 73%. Evaluation of myometrial invasion by ultrasonography was predictive of microscopic myometrial invasion ($P = .001$).

Table 4 summarizes data related to intraoperative gross examination versus final histologic examination. Intraoperative gross examination correctly graded the depth of myometrial invasion in 62 (82.6%) of 75 cases, including 44 M1 (71%) and 18 M2 (29%). In the remaining 13 cases, lesions were underestimated in 9 (69%) and overestimated in 4 (30%). The sensitivity and specificity of the procedure in evaluating the depth of tumor invasion were 67% and 92%, respectively, with a PPV of 82% and an NPV of 83%. Diagnostic accuracy was 83% (Table 4). On the basis of the logistic regression model for myometrial invasion, the predictive value of intraoperative gross examination turned out to be statistically significant ($P = .001$). Combining preoperative TVUS with intraoperative gross examination did not significantly increase the efficacy of either procedure ($P < .1$).

Discussion

The surgical staging adopted by FIGO in 1988 for endometrial cancer recommends abdominal hysterectomy with bilateral salpingo-oophorectomy, peritoneal cytologic examination, 1- to 2-cm colpectomy, and systematic pelvic and selective paraaortic lymphadenectomy. In practice, no more than 50% of cases are surgically staged for a variety of reasons: patients are often obese and of advanced age, with general medical problems. A further consideration is the awareness that in selected patients, aggressive surgery might be unnecessary because of the low risk of tumor spreading. In addition, lymphadenectomy is not entirely risk free and may lead to severe complica-

tions, such as lymphocysts, bleeding, and ureteral and vascular damage.[8] Lagasse et al[9] reported gastrointestinal and urogenital complication rates of 1.6% intraoperatively and 2.9% postoperatively with lumboaortic lymphadenectomy.

A preoperative distinction between patients with stage Ia-Ib carcinoma and patients with stage Ic carcinoma would allow identification of high-risk patients who might benefit from pelvic lymphadenectomy. On this basis, several preoperative and intraoperative diagnostic procedures were evaluated to assess how they could eventually be of help to surgeons in planning adequate surgical treatment for patients with endometrial cancer.

The degree of differentiation of the tumor is the most common factor that can be assessed preoperatively. Because the incidence rates of pelvic and aortic lymph node metastases are 4% and 2%, respectively, for G1 and 30% and 17% for G3,[3,4,9] patients with G2 and G3 endometrial cancer should undergo extensive surgery, whereas in patients with superficially invasive G1 endometrial cancer, lymphadenectomy might be avoided. The problem is that the degree of tumor differentiation found on diagnostic biopsy does not always correspond to that observed on the final histologic examination. In our study, the concordance rate between biopsy and histologic examination results was 63% (47/75 cases). Concordance rates reported in the literature vary between 56% and 85%.[9–11] Oakley and Nabbas[12] reported 28% discordance in grading between preoperative curettage and the final histologic examination. In our study, the tumor was underestimated in 24 (86%) of the 28 cases with discordant results. In-office biopsy undergraded lesions in 41% of cases, and D&C biopsy undergraded in 36%. The results of our study confirm other literature reports[10,12] indicating that, irrespective of the procedure used, preoperative grading is not reliable in predicting final grading because it frequently underestimates tumor grades. Nevertheless, in our series of patients, we observed that tumors graded G3 on preoperative diagnosis had the same degree of differentiation confirmed on histologic examination in 75% of cases.

Imaging techniques such as ultrasonography, CT, and MRI have all been used with different degrees of reliability to evaluate the depth of myometrial invasion.[6] A recent review of the literature showed that MRI is currently seen as the most reliable method for myometrial assessment.[7] However, MRI is costly, is not always widely available, and is not appropriate for all patients (eg, those with claustrophobia, obesity, and contrast agent allergies); therefore, it is difficult to use MRI as a routine procedure in clinical practice. However, Yahata et al[13] recently reported that the accuracy rates of MRI, TVUS, and gross examination were similar; MRI showed the highest sensitivity, whereas TVUS showed the highest specificity for detection of M2 invasion.

In our study, TVUS had diagnostic accuracy of 73%, failing to detect deep tumor infiltration in 20 (27%) of 75 cases. Although some studies have shown comparable results,[14,15] others[16,17] indicated diagnostic accuracy rates of 84% to 88%. A possible explanation is that fixity of the uterus, myomas, or adenomyosis made the ultrasonographic depiction of myometrial invasion less accurate.

The ultrasonographic examination was performed after endometrial sampling, which can affect some features of the endometrium; in fact, all cutoff values for endometrial thickness were originally validated in patients before biopsy. In this study ultrasonography was performed at least 2 or 3 weeks after biopsy. Van den Bosch et al[18] showed that endometrial thickness measure-

Table 3. Myometrial Invasion: Preoperative TVUS Versus Final Histologic Results (N = 75)

	Ultrasonographic Evaluation	
Histologic Result	**<50% (n = 53)**	**>50% (n = 22)**
<50%, n (%)	42 (56)	9 (12)
>50%, n (%)	11 (15)	13 (17)

Sensitivity, 62%; specificity, 79%; false-negative rate, 12%; false-positive rate, 15%; accuracy, 73%; PPV, 54%; and NPV, 82%.

Table 4. Myometrial Invasion: Intraoperative Gross Examination Versus Final Histologic Results (N = 75)

	Gross Evaluation	
Histologic Result	**<50% (n = 53)**	**>50% (n = 22)**
<50%, n (%)	44 (83)	4 (18)
>50%, n (%)	9 (17)	18 (82)

Sensitivity, 67%; specificity, 92%; false-negative rate, 33%; false-positive rate, 8%; accuracy, 83%; PPV, 82%; and NPV, 83%.

ment was altered by Pipelle sampling when TVUS was performed immediately after biopsy. For this reason, we performed TVUS 3 weeks after Pipelle sampling to enable regeneration of the endometrium.

Some authors[19,20] showed that the use of spectral Doppler analysis did not contribute to the prediction of the degree of myometrial invasion in endometrial cancer, and blood flow indices did not contribute to the prediction of the stage; this is the reason why Doppler analysis was not performed in our study. In our experience, TVUS is an accurate and highly significant technique (P = .001) for measuring the depth of myometrial invasion, being noninvasive, inexpensive, and readily available and enabling preoperative evaluation.

Several studies have been published in the literature on the value of intraoperative gross examination, with mixed results. Some authors[10,21] indicated poor concordance for myometrial invasion between gross examination and final histologic examination, whereas others[12,22,23] reported a high degree of accuracy for the intraoperative procedure (>86%). In our study, intraoperative gross examination performed by the pathologist was able to accurately evaluate the depth of tumor invasion in 62 (83%) of 75 patients, with accuracy of 83%, sensitivity of 67%, specificity of 92%, and PPV and NPV values of 82% and 83%, respectively. In 9 cases (12%), gross examination underestimated myometrial invasion; in all of these patients, the distance between the deepest point of tumor invasion in the myometrium and the tunica serosa was 4 mm. A possible explanation is that in the early stages of tumor invasion into the myometrium, the desmoplastic reaction may be minimal or absent, resulting in the virtual impossibility of grossly detecting the tumor. The possibility of false-negative results should be considered during intraoperative gross examination, but in these circumstances, even a frozen section may also prove inadequate.[21] In other words, gross examination of myometrial invasion substantially provides results comparable with those of frozen-section sampling.[10]

Moreover, this technique is highly feasible and reliable, and a further consideration is that when no pathologist is available during surgery or when time is a limiting factor, gross examination can be performed accurately by the same experienced gynecologic cancer surgeon. Our data on myometrial invasion confirm that gross examination is a simple, fast, and, above all, reliable procedure.

In conclusion, we think that patients with endometrial cancer graded G3 preoperatively and with no contraindications to surgery should be treated surgically by laparotomy and lymph node dissection.[24] The same procedure should be used when patients have gross myometrial invasion exceeding 50% and also when intraoperative gross examination is not possible, unless frozen-section sampling suggests superficial tumor infiltration. In patients with G1 and G2 grading at diagnosis and with gross myometrial invasion of less than 50%, we think that lymphadenectomy could reasonably be avoided, minimizing surgical time and intraoperative and postoperative complications while ensuring appropriate clinical treatment of patients.

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