

The value of ultrasonography in preoperative assessment of selected prognostic factors in endometrial cancer

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Summary

Objective: To determine the efficiency of transabdominal and transvaginal ultrasonography (TAS and TVS) in the assessment of myometrial invasion, cervical involvement, pelvic lymph nodes, adnexal and omental metastases (preoperative staging) of endometrial cancer.

Methods: Transabdominal and transvaginal 2D, ultrasound were performed on 90 women to classify myometrial invasion, cervical involvement, pelvic lymph nodes and adnexal metastases in endometrial cancer. According to this 13 type E (invasion involving the endometrium), 41 type S (superficial, of less than 50% of myometrial infiltration), 36 type D (deep infiltration) and 22 cervical involvement were identified. There were 15 G₁, 60 G₂ and 15 G₃ cases. Adnexal, omental and lymph-node metastases were found in 11, two and 15 cases, respectively. Endometrial cancer was diagnosed on the basis of dilatation and curettage. The degree of invasion was evaluated preoperatively. Ultrasonographic findings were compared to surgical staging and histopathology of the surgical specimen.

Results: The median age of the 90 women was 63.3 ± 12.3 years (range 32 to 86 years). The median thickness of malignant endometrium was 19.5 ± 9.6 (range 7 to 54 mm). In type E the median thickness was 11.76 ± 4.2 , in type S 17.3 ± 7.6 , in type D 24.8 ± 9.8 and in cases with cervical involvement 23.2 ± 11 mm. Myometrial invasion evaluated by TVS was accurate in 76 of 90 cases (accuracy 84.4%). In type E sensitivity was 92.3%, specificity 87.0%, positive and negative predictive value, respectively, 63.1% and 98.6%. In type S these values were respectively: 78.0%, 93.9%, 91.4%, 80.0% and in type D - 88.9%, 92.6%, 88.9% and 100.0%. Tumor extension to the cervix was properly assessed in 19 of 22 women in which it was present (sensitivity 86.4%, specificity 85.3%, positive predictive value 85.5%, negative predictive value 95.1%). Adnexal metastasis was correctly diagnosed in 8 of 11 cases in which it was present (sensitivity 72.7%, specificity 97.5%, positive predictive value 80%, negative predictive value 96.3%), and lymph-node metastasis in only 5 of 15 cases (sensitivity 33.3%, specificity 100%, positive predictive value 100%, negative predictive value 88.2%).

Conclusion: These results suggest that 2D TAS and TVS evaluation of endometrial cancer are reliable methods for preoperative assessment of selected prognostic factors, e.g. myometrial invasion, cervical involvement and adnexal metastases. However in assessing lymph-node metastases, TVS with its low sensitivity, did not provide additional information. Preoperative ultrasound examination should be speculated as an important tool in the establishment of different surgical choices which can be made after a correct pretreatment prognosis.

Key words: Endometrial cancer; Prognostic factors; Transabdominal and transvaginal ultrasonography.

Introduction

Endometrial cancer is the fourth most frequently diagnosed malignancy in women. In 1989 surgico-pathological classification (SPS - surgico-pathological staging) was introduced in which intraoperative estimation permits the exact qualification of degree of the malignant process [1].

Factors correlated with disease recurrence include tumor stage and lymph node involvement. Therefore it is considered that in cases in which low mature cancer (G₂, G₃) infiltrates the uterine muscle, surgery should also include pelvic and para-aortic lymphadenectomy.

The high resolution images obtained with transvaginal sonography (TVS) enable the detection of endometrial abnormalities ranging from simple increased endometrial thickness measurements to sophisticated morphologic evaluation of complex endometrial architecture [2]. Cagnazzo *et al.* [3] stated that TVS is the established tool

in the presurgical evaluation of patients with carcinoma. TVS has high accuracy, a relatively low cost, is easily performed and repeatable. Therefore it has been suggested that assessment of the endometrium by TVS should be the primary method for excluding endometrial pathologic mechanisms in women with postmenopausal bleeding and that curettage should be performed exclusively in women with thicker than normal endometrium. Since 1984 special attention has been paid to risk factors connected with prognosis of endometrial cancer. These include: 1. histological maturity of the cancer (G₁, G₂, G₃); 2. depth of the uterine invasion; 3. infiltration of the cervical canal; 4. infiltration of the uterine serous membranes; 5. presence of cancer cells in the blood and lymphatic vessels; 6. metastases to pelvic and/or paraaortal lymphatic nodes; 7. adnexal and/or omental metastases; 10. distant metastases and, 11. positive peritoneal cytology [4]. Some of them, such as the depth of uterine muscle infiltration, involvement of the cervical canal and occupation of the great omentum, adnexal and some

distant metastases can be recognized preoperatively by ultrasound (transabdominal - TAS and transvaginal - TVS). These prognostic factors correlate with patient survival and the presence of lymph-node metastases.

The aim of our retrospective study was to evaluate the value of TAS and TVS in the diagnosis of selected prognostic factors in endometrial carcinoma before surgery.

Material and Methods

The material included 90 women with endometrial cancer established by histopatologic examination of the endometrial specimen acquired by D&C.

The women underwent transabdominal and transvaginal ultrasonographic examination within eight days preceding the curettage. The thickness of the endometrium was measured with calipers on the frozen ultrasonographic image, and measurements were taken from a longitudinal sonogram through the thickest area of the endometrium and from the outermost border of the endometrium on one side to that on the other. Thus measurements of endometrial thickness included both endometrial layers and any expansive process in the uterine cavity. Invasion of the endometrial carcinoma was assessed using Karlsson's coefficient of depth [5]. Accordingly, the type of infiltration was established: *type E* when cancer was concerned only to the endometrium, i.e., when the junctional zone is preserved or there is sharp tumor-myometrium interface with uniform thickening of the myometrium throughout the corpus, *type S* when infiltration was superficial – to the half of the uterine muscle, i.e., when there was disruption of the junctional zone, and a faded, irregular myometrial-endometrial interface, and *type D* with deep infiltration – over 50% of the uterine wall, i.e., when a heterogeneous area is visualized in the outer half of the myometrium. Additionally neoplastic cervical involvement, adnexal and omental, as well as pelvic lymph-node metastases were evaluated by TAS or TVS. In selected cases of adnexal tumors color Doppler assessment of vasculature was follow-up.

The equipment used was the Siemens Sonoline Versa Pro ultrasound system with a 6.5-7.5 MHz transvaginal and 3.5 MHz convex array abdominal transducers. Diagnosis was based on histologic examination of the hysterectomy specimen. Staging of malignant endometrial tumors was performed in accordance with the classification system recommended by the International Federation of Gynecology and Obstetrics [6].

The results of the ultrasonographic examinations were compared with the diagnosis on the basis of histologic examination. The statistical tests used were the chi-square (χ^2) test with continuity correction and Fisher's exact test. Two-tailed *p* values were given with 5% as the level of significance.

Results

The median age of the 90 women in the study was 63.3 ± 12.3 years (range 32 to 86 years). There were 14.4% (13/90) of cases when cancer concerned only the endometrium – *type E* – age 55.6 ± 13.4 , 45.6% (41/90) with superficial infiltration of the uterine muscle – *type S* – age 62.2 ± 12.5 , and 40% (36/90) with deep infiltration – *type D* – age 67.3 ± 10.7 . In 22 cases the cervical canal was also involved, age 64.9 ± 12.7 . Endosonographically correct neoplastic infiltration was diagnosed in 84.4% of

cases (accuracy), whereas in *type E* sensitivity was 92.3%, specificity 87.0%, positive and negative predictive value, respectively, 63.1% and 98.6%. In *type S* these values were respectively: 78.0%, 93.9%, 91.4%, 80.0% and in *type D* – 88.9%, 92.6%, 88.9% and 100.0%. These data are represented in Tables 1 and 2.

Table 1. — Endosonographic estimation of neoplastic myometrial infiltration vs histology.

TVS	Histology			Total
	E	S	D	
E	12	6	1	19
S	–	32	3	35
D	1	3	32	36
Total	13	41	36	90

Table 2. — Statistical parameters characterizing the ability of TVS to estimate neoplastic myometrial infiltration. Accuracy = 84.4%; ¹ and ² - *p* = 0.009; ¹ and ³ - *p* = 0.02.

Infiltration	Sensitivity	Specificity	PPV	NPV
E	92.3%	87.0%	63.1% ¹	98.6%
S	78.0%	93.9%	91.4% ²	80.0%
D	88.9%	92.6%	88.9% ³	100.0%

The histological maturity (grading) of cancer was as follows: G₁ – 16.7% (15/90), G₂ 66.7% (60/90) and G₃ 16.6% (15/90) of cases. In *type E* maturity of G₁ was found in 69.2% (9/13) and G₂ in 30.8% (4/13) of cases. In this group there were no G₃ cases. In *type S*, G₁ was found in 12.2% (5/41), G₂ in 70.8% (29/41) and G₃ in 17% (7/41). In *type D* histological maturity was respectively, 2.8% (1/36), 75% (27/36) and 22.2% (8/36). In cases with cervical involvement stage G₁ was found in 4.5% (1/22), G₂ in 68.2% (15/22) and G₃ in 27.3% (6/22) (Figure 1).

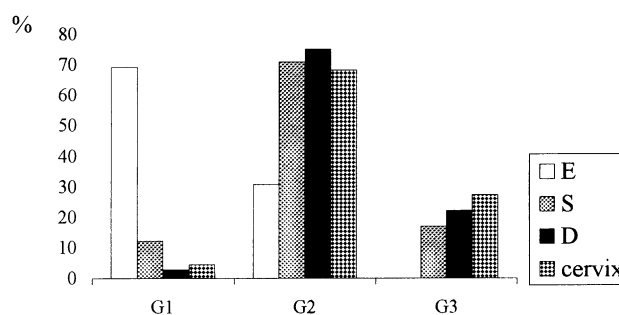


Figure 1. — Histological maturity in each type of uterine invasion.

The endometrium was visible and measurable in all cases. The median thickness of malignant endometrium was 19.5 ± 9.6 (range 7 to 54 mm). In *type E* the median thickness was 11.76 ± 4.2 , in *type S* 17.3 ± 7.6 , in *type D* 24.8 ± 9.8 and in cases with cervical involvement 23.2 ± 11 mm (Figure 2).

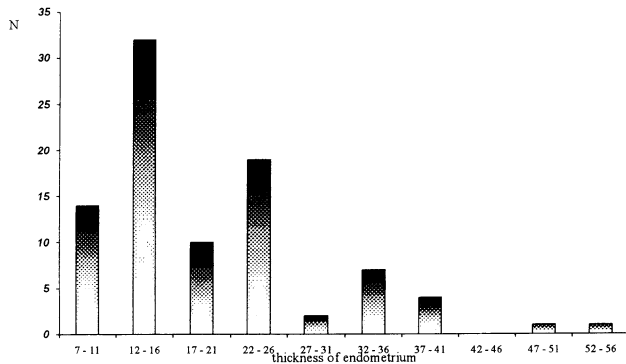


Figure 2. — Thickness of endometrium measured by TVS.

Histologically adnexal and omental metastases were determined in 12.2% (11/90) and in 2.2% (2/90) of cases, respectively. Ultrasonographically, preoperatively adnexal metastasis was correctly diagnosed in eight of 11 cases in which it was present (sensitivity 72.7%, specificity 97.5%, positive predictive value 80%, negative predictive value 96.3), whereas omental infiltration was overdiagnosed in one case (false positive) (Table 3).

Table 3. — Adnexal metastases - correlation of TVS and histology.

TVS	Histology		Total
	meta+	meta-	
meta+	8	2	10
meta-	3	77	80
Total	11	79	90

meta = metastasis.

There were two false positive diagnoses: in a 78-year-old patient with an ovary 44 x 30 mm of mixed echogenicity, and volume 12.3 cm³ (out of norm), however without color-coded areas inside, and in a 72-year-old woman with a mixed, solid cystic tumor 75 mm in diameter which finally turned out to be a post-inflammatory process. In three false negative diagnoses histologically micro invasion of ovarian stroma was established. In cases with a correct diagnosis, 75% had neoplastic cervical involvement and at least 50% or more of uterine invasion (*type S and D*). In 50% of these cases histological malignancy was G₂.

Omental metastases occurred in two grade III carcinoma cases correctly diagnosed by ultrasound. One of the false positives was caused by fatty tissue in the great omentum in a very obese woman (135 kg).

Lymph-node metastasis was found in 16.6% (15/90) of cases. Among them 6.7% (1/15) in *type E*, 26.7% (4/15) in *type S* and 66.6% (10/15) in *type D*. Therein in four (26.7%) cases with neoplastic cervical involvement. In this group histologic grading was as follows: G₁ in 13.3% (2/15), G₂ in 46.7% (7/15) and G₃ in 40% (6/15) of cases. Mean diameter of the endometrium in these women was 23.1 mm and was not statistically significant from the mean diameter of the patients' entire endometrium (23.1

vs. 19.5 mm). By ultrasound, lymph-node metastases was diagnosed in only five of 15 cases (sensitivity 33.3%, specificity 100%, positive predictive value 100%, negative predictive value 88.2%). False negative diagnoses were made in ten, i.e., 66.7% of cases (Table 4).

Table 4. — Lymph-node metastases - correlation of TVS and histology.

TVS	Histology		Total
	meta+	meta-	
meta+	5	—	5
meta-	10	75	85
Total	15	75	90

meta = metastasis.

Neoplastic infiltration of the cervical canal was seen in 24.4% (22/90), whereas endosonographically was properly assessed in 19 of 22 women in which it was present (sensitivity 86.4%, specificity 85.3%, positive predictive value 85.5%, negative predictive value 95.1%). There were 13.6% (3/22) false negative and 14.7% (10/68) false positive diagnoses (Table 5).

Table 5. — Cervical extension (c. ex.) - correlation of TVS and histology.

TVS	Histology		Total
	c. ex.+	c. ex.-	
c. ex.+	19	10	29
c. ex.-	3	58	61
Total	22	68	90

In this group mean diameter of the endometrium was 23.2 mm and was not statistically significant from the mean diameter of the patients' whole endometrium (19.5 mm). In 72.3% (16/22) of cases there was deep (*type D*), and in 27.7% (6/22) superficial (*type S*) uterine invasion. There were no cases where cancer concerned only the endometrium (*type E*). Grade G₃ was ascertained in 27.3% (6/22), G₂ in 68.2% (15/22) and G₁ only in 4.5% (1/22) of cases. In three false negatives only invasion of the cervical glands (micro invasion) was found. False positives were made in ten cases. In five there were cervical polyps and in others inflammation of the cervical mucosa was diagnosed.

Discussion

The most important prognostic factors of endometrial carcinoma include stage, grade of tumor, depth of myometrial invasion, histologic subtype, and presence of nodal metastases. Determination of factors such as the depth of invasion, extent of the disease in the uterus (endocervical extension), extrauterine extent (e.g., nodal involvement, adnexal metastases, and intra-abdominal disease) is attempted preoperatively by US. Therefore US staging would give the clinician a more accurate

method of determining the extent of disease. More appropriately definitive optimal therapy could then be given.

Achiron *et al.* [7] stated that in women with a mean age of 57 years (53-65) in 94.4% of cases cancer developed in endometrial thickness above 6 mm, whereof in 68.2% when it had outrun 11 mm. On the basis of this data they concluded that when the thickness of the endometrium is ≤ 4 mm the likelihood coefficient of cancer development is 0.05, however when it exceeds 11 mm, it reaches 3.87. Gull *et al.* [8] think that frequency of endometrial cancer in women up to 40 years is quite low, and fiercely increases after 50 years with acme between 65 and 74 years. This data has been acknowledged in our material, wherein only 7.8% of cancers were in women up to 40 years, mean age amounted to 63.3 ± 12.3 years (32-86) and 88.9% of women exceeded 50 years. Mean endometrial thickness was 19.5 ± 9.6 (range 7-54 mm). In endometrial thickness less than 7 mm we did not observe malignant processes, and in the range 7-10 mm, only 15.5% of cancers were detected. Similar data was provided by Sheth *et al.* [9] where mean thickness of neoplastic endometrium was 22.5 mm versus 18.2 mm in benign lesions.

Ambrose and Kurman [10] reported that depth of myometrial invasion and the presence of changes associated with vascular invasion (perivascular lymphocytic infiltrates) were the best indicators of prognosis for patients with Stage I endometrial carcinoma. Vascular invasion is the mechanism by which metastatic disease occurs in many patients with recurrent endometrial carcinoma.

High resolution images obtained with transvaginal sonography (TVS) enable the detection of endometrial abnormalities ranging from simple increased endometrial thickness measurements to sophisticated morphologic evaluation of complex endometrial architecture. After screening for endometrial hyperplasia and carcinoma in postmenopausal women, sonography may also be used to assess the depth of myometrial invasion in patients already diagnosed histologically with endometrial carcinoma. In recent studies [11, 12] transvaginal sonography has been used to assess myometrial infiltration of endometrial carcinoma and has been shown to have high sensitivity and specificity. Osmers and co-workers [13] stated that women with asymptomatic endometrial carcinomas detected by TVS exhibited significantly less myometrial tumor infiltration and more well-differentiated tumors than those who initially presented with atypical bleeding. The authors conclude that asymptomatic endometrial carcinomas screened by TVS are likely to have a better prognosis than symptomatic carcinomas, and that TVS may be used as a reliable tool for tumor staging before surgery or radiotherapy [13]. Weber *et al.* [14] in a prospective study stated that assessments of depth of tumor invasion and staging obtained by TVS were found to correlate with the histologic findings in 85% and 88% of the cases, respectively. This group concludes that in cases of endometrial carcinoma, TVS has an essential preoperative role in devising an individualized treatment

program that takes into account the extent, spread, and stage of the tumor.

Karlsson *et al.* in 1992 [12] evaluated the ability of TVS to characterize myometrial infiltration as more or less than 50% in women admitted for primary surgery for endometrial carcinoma diagnosed by curettage. Using TVS, the sensitivity of detecting myometrial invasion of less than 50% was 79%. The positive predictive value, however, was 100% in all cases when ultrasound suggested myometrial invasion of greater than 50%. These data are accordant with ours in which accuracy reached 84.4%, sensitivity of detecting infiltration of type E and S was 92.3% and 78.0%. In deep myometrial invasion sensitivity, specificity, PPV and NPV also was high and reached 88.9%, 92.6%, 88.9% and 100.0%, respectively. Sensitivity, specificity and negative predictive values of endosonography were similar in each type of infiltration. Statistically significant differences were noted in positive predictive value. It means that the deeper the uterine muscle infiltration the more correct the endosonography, however more false positive diagnoses are made in superficial cases. The degree of invasion was overdiagnosed in 4.4% and underdiagnosed in 11.1% of cases. In the former, in three cases there were endometrial polyps that changed the thickness of the endometrium, and in one case adenomyosis of the posterior uterine wall that made the junctional zone indistinct.

In the underdiagnosed group there were four cases of microinvasion and three with adenomyosis. In another three cases small myomas (up to 18 mm in diameter) were the reason. More of these cases involved myometrial invasion of less than 50% (*type S*). For that reason sensitivity of endosonography in assessment of the average grade of invasion achieved a rather low value equal to 78.0%.

As mentioned above a very important role in the treatment of endometrial cancer includes accurate preoperative assessment of disease, e.g., in cases with deep myometrial invasion (*type D*) total abdominal hysterectomy with salpingo-oophorectomy with pelvic and paraaortic lymphadenectomy and peritoneal cytology would be an adequate procedure. This mode of treatment – besides removal of the primal focus – enables further diagnostics, on which initiation of additional treatment depends (chemo, radio, hormonotherapy). On the other hand in cases with deep myometrial invasion preoperative radiotherapy should be performed reduce the number of relapses [15]. Gusberg [16] stated in cases with myometrial invasion of less than 50% there is 70% 5-year survival. This percentage goes down to 34% in deep infiltration (*type D*). It is associated with the fact that deep invasion favors formation of metastases by lymph or blood routes. In cancers with no myometrial invasion (*type E*) frequency of lymph-node metastases does not exceed 4%, in *type S* it reaches 10-18%, whereas in *type D* it amounts to 30-60% of cases and additionally paraaortic metastases are seen (88). These are in agreement with our data, where in types E, S and D we found lymph-node metastases in 6.7%, 26.7% and 66.6%,

respectively. We noted that the deeper the neoplastic infiltration the lower the histologic grading (Figure 1). Accordingly throughout the estimation of the deepness of infiltration, the degree of cancer invasiveness, and then, potentiality of metastases can be indirectly qualified.

Histologic maturity of neoplastic cells is consecutive, which is a very important prognostic factor. The opinion that faster development, bigger disposition to deeper infiltration and sparing of metastases of cancer is closely associated with its grading dominates. Highly mature forms (G_1) occupy only the endometrium or superficial layer of the uterine muscle for a long time (type E, S). As histologic malignancy of cancer increases (G_2 , G_3) its ability for deeper infiltration also grows. In highly mature cancers myometrial invasion is seen in 20%, whereas in the least mature it exceeds 50% [16]. In our material in type E high maturity (G_1) of cancer was found in nearly 75% of cases, whereas in type S and D low maturity dominated (G_2), respectively in 70.8% and 75% of cases (Figure 1). It is considered that the more clinical advancement of disease the more distinct is the adverse importance of low grading. Prognosis in grade 1, highly mature (G_1) endometrial cancer is good, with 95% of 5-year survival. In grade 2 5-year survival reaches < 60%, and in 3 grade (G_3) it is only 16.7% [17].

Lymph-node metastasis considerably worsens the prognosis [18, 19]. Some authors attempt to have an accurate definition of extensiveness of disease through ultrasonographic (TAS, TVS) assessment of paraaortic (TAS) and pelvic (TVS) lymph nodes to search for metastases. It is considered that sensitivity of ultrasonography in that field does not exceed 25% [20]. In our paper we achieved similar, rather low sensitivity equal to 33.3%, however positive predictive value and specificity were high, equal to 100% (Table 4). Such low sensitivity is often associated with microinvasion to the lymph nodes, which are not adequately enlarged to be seen in ultrasound. Furthermore, patient physique (patients with endometrial carcinoma are often obese and have short stature) makes the precise evaluation of the retroperitoneal space of the minor pelvis difficult, even when high resolution equipment is used. However the overall accuracy of ultrasonography in the preoperative assessment of lymph nodes approached lymphography, CT and MRI and amounted to 78-87% [21]. In our material accuracy achieved 88.9%. However above the mentioned low sensitivity of endosonography considerably restrains its application. It seems that endosonographic assessment of myometrial invasion could be a parameter that facilitates diagnosis. It could be approved as an indirect factor of the potential ability of lymphnode metastases, because it was found that the deeper the myometrial invasion and lower histologic maturity, the more the percentage of lymph-node metastases increases. In type E it was 6.7%, in S – 26%, D – 66.6%, and in G_1 , G_2 , G_3 13.3%, 46.7%, 40%, respectively.

Frequently we met with difficulties in assessing tumor extension into the cervix. The basic technique is fractional curettage, which is weighted with numerous false

positive diagnoses (low specificity) [22, 23]. Analysis of our material revealed that endosonography has a rather high sensitivity and specificity, respectively 86.4% and 85.3%. Thus in assessing neoplastic infiltration of the cervical canal the application should be an easy and low cost procedure. Most difficulties exist in cases of microinvasion (tumor invasion confined only to the glandular elements of the cervix) which do not give the image of changed echogenicity, tissue ridges or liquid reservoirs - characteristics which are possible to recognize in ultrasonography, as in cases of infiltration of the cervical stroma. Similar difficulties were found by Gabrieli *et al.* [24], Gordon *et al.* [25], Lehtovirta i Ylostalo [26] and Artner *et al.* [27].

Transvaginal sonographic evaluation of the endometrium might also have revealed other pelvic abnormalities that probably would not have been diagnosed as early if TVS had not been performed. Granberg *et al.* [28] encountered 24 incidental findings in their study of 205 women (11.7%) with postmenopausal bleeding, including five bladder tumors, three ovarian carcinomas, and one cancer of the colon. In our material metastatic adnexal tumors were revealed in 12.2% of cases, the majority of which (75%) were deep myometrial invasion (type S and D) and cervical canal infiltration. Sensitivity of TVS in diagnosing adnexal metastases was 72.2%, thus in over 25% of cases imaging of adnexal lesions was not successful. Similar problems arise from neoplastic microinvasion to the ovary. Therefore in cases with deep myometrial invasion, even without an ultrasonographic image of adnexal tumor, microinvasion of ovarian stroma can be highly suspected.

Conclusion

These results suggest that 2D TAS and TVS evaluation of endometrial cancer are reliable methods for preoperative assessment of selected prognostic factors, e.g. myometrial invasion, cervical involvement and adnexal metastases. However in assessing lymph-node metastases TVS, with its low sensitivity, did not provide additional information. Preoperative ultrasound examination should be speculated as an important tool in the establishment of different surgical choices which can be made after correct pretreatment prognosis, and can be recommended as the primary imaging approach. Moreover this study confirms the importance of assessing prognostic factors in the treatment of endometrial adenocarcinoma. Ultrasound is an excellent first step for evaluating endometrial carcinoma because it is less invasive, less expensive, just as sensitive and has additional benefits such as visualizing the other abdominal organs. Its use in patients undergoing evaluation for endometrial carcinoma may reveal other pelvic abnormalities such as ovarian or omental lesions that would not be encountered as early if the scan is not performed. The most significant prognostic factors for positive pelvic nodes were found to be the depth of myometrial invasion and grade of tumor.

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