

## CLINICAL STUDY

# Transvaginal ultrasound examination of myometrial infiltration by endometrial cancer

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**Abstract:** The depth of myometrial infiltration by endometrial cancer is an important prognostic factor. The examination of the depth of infiltration classifies the patients in the low- and high-risk groups, which influences the therapeutic approach. Transvaginal ultrasonography represents a first-choice diagnostic test for the assessment of the depth of myometrial infiltration as the time consumption and financial demands of magnetic resonance imaging need to be taken into account. In comparison with the MRI, the diagnostic accuracy of the transvaginal ultrasound depends more on the individual experience and professional potential of the examining physician. This fact can contribute to the heterogeneity of published results of transvaginal ultrasound on the determination of infiltration depth. Having in mind the aim to verify these indicators in our local conditions and environment, we decided to prospectively study 150 endometrial cancer patients who were examined with the transvaginal ultrasound in the period 1/2009 – 10/ 2011. Correlated firstly with the preoperative and then secondly with the definitive histopathological examination was the depth-of-infiltration-related data that had been taken from the ultrasound findings. The output being monitored was the exclusion or confirmation of the invasion exceeding half the thickness of myometrium. In our study, the diagnostic accuracy of the method reached 82.67 %, while the other indicators were as follows: sensitivity 92.31 %, specificity 79.28 %, positive predictive value (PPV) 61.02 %, negative predictive value (NPV) 96.7 %, the likelihood ratio of a positive test 4.455 and the likelihood ratio of a negative test 0.097. The results of the depth of myometrial infiltration examination and their comparison with the data from similarly oriented clinical studies entitle us to include this examination in the set of standard preoperative methods used for the examination of patients with endometrial cancer (Tab. 3, Fig. 5, Ref. 20). Text in PDF [www.elis.sk](http://www.elis.sk). Key words: endometrial cancer, depth of infiltration, transvaginal ultrasonography, diagnostic accuracy.

Endometrial cancer is a relatively common gynecologic cancer, in 2008 worldwide it was estimated to be the 6th most common cancer among females and the 13th most common cause of death from malignancy (non-melanoma skin cancer excluded) (1). In 2007, the number of endometrial cancer cases in females diagnosed in the Slovak Republic was 901, which represented crude incidence rate of 32.4/100,000 and the standardized incidence (to the World Standard Population) of 20.2/100 000 (2). In the same year, 223 females with endometrial cancer died in the Slovak Republic, which represented a crude mortality rate of 8.3/100,000, and standardized mortality 4.2/100,000. Endometrial cancer was the 3rd most common malignancy in Slovak females and the 9th most common cause of death. The incidence of this disease has been slightly rising during the last decades, while the mortality has remained approximately the same (3). Often causing a therapeutic problem and limiting the therapy possibilities, endometrial carcinoma occurs mainly in elderly polymorbid patients. The en-

dometrial cancer prognosis is determined by the stage of disease, the histological type of tumour, the depth of myometrial infiltration and by whether and how far the lymph nodes are afflicted. The depth of myometrial infiltration, which is considered to be one of the most important prognostic factors, highly correlates with lymph node metastases and the 5-year survival rate (4, 5). The preoperative assessment of the depth of infiltration is cru-

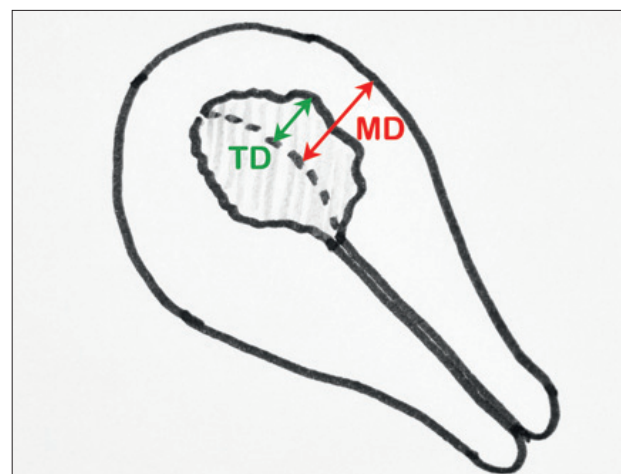


Fig. 1. Myometrial infiltration measurement. Myometrial depth MD, Tumor depth TD

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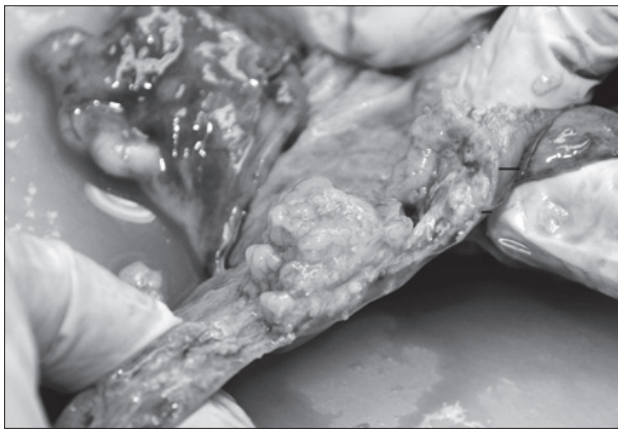


Fig. 2. Pathological specimen. Myometrial infiltration more than 50 %.

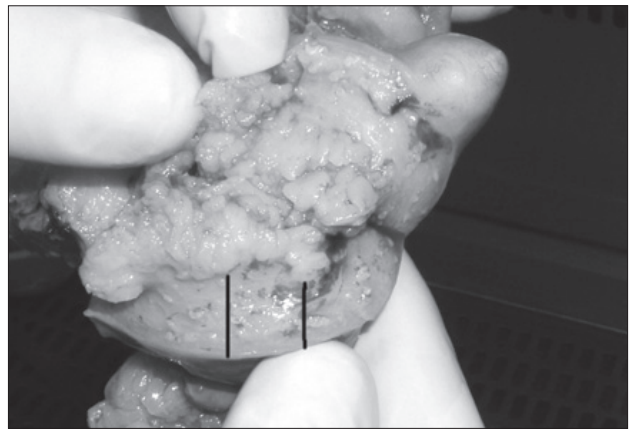


Fig. 4. Pathological specimen. Myometrial infiltration less than 50 %.



Fig. 3. Ultrasonography examination. Myometrial infiltration more than 50 %.

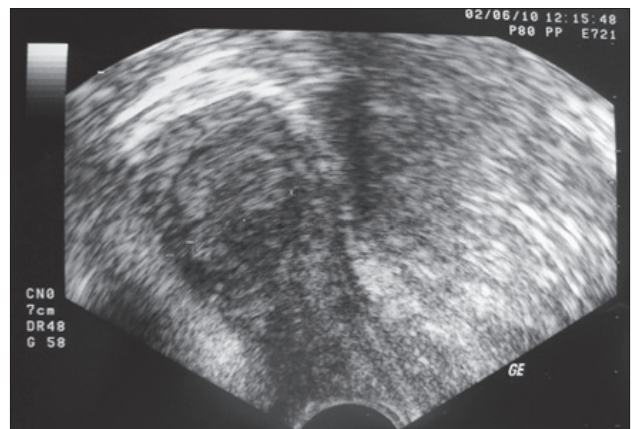


Fig. 5. Ultrasonography examination. Myometrial infiltration less than 50 %.

cial to determining the most effective therapeutic approach and to deciding whether the patient should be referred for systematic pelvic and paraaortic lymphadenectomy. The depth of myometrial infiltration can be evaluated by a number of methods. These are magnetic resonance imaging (MRI), computer tomography (CT) and ultrasonography (USG), among which the best results can be achieved by the MRI (6, 7). The goal of our project was to determine the accuracy of preoperative transvaginal ultrasonography (TVS) for the classification of myometrial infiltration depth in endometrial cancer patients, while definitive histological finding served as a reference method. The fact was kept in mind that TVS exemplifies a widely accessible but relatively cheap method for determining the depth of myometrial invasion, albeit it has been shown to produce heterogeneous diagnostic results.

#### Materials and methods

There were 150 patients with endometrial cancer examined by a single physician utilizing TVS, the 700 MHz GE probe Logiq 400 Pro in the period of 1/2009 – 10/2011. The endometrial cancer diagnosis was determined on the basis of material incoming from the preceding curettage or hysteroscopy. The results were categorized

into two groups: invasion to less and to more than half the thickness of the myometrium. The depth of invasion was measured as the ratio of the distance between endometrium-myometrium interface and maximum tumour depth to the total myometrial thickness (Figs 1–5). The patients were subsequently indicated for total abdominal hysterectomy with bilateral adnexectomy. Their uterus was sent to preoperative biopsy, where the depth of myometrial invasion was determined. Depending on the results, pelvic and paraaortic lymphadenectomy was added in the high-risk group (infiltration to more than half the depth of myometrium, grading 3, unfavourable histotype, infiltration of the cervix). In the end, the results of the preoperative examination of the infiltration depth via the TVS method were correlated with the definitive histopathological examination and the data that we obtained were then statistically evaluated by tools for the analysis of 2x2 contingency tables. The estimations of diagnostic indicators for the classification of myoinvasion degree with the TVS are given with the respective 95% confidence intervals (95% CI). Differences and associations were tested with the exact tests at the 0.05 level of significance ( $\alpha$ ). All the analyses were made in the following environment: Microsoft Office Excel 2007 (Microsoft Corporation), HP Compaq NX6310 and StatsDirect 2.6.8 (Stats Direct Ltd., Cheshire, UK).

## Results

The sample of 150 examined patients with endometrial cancer had the following descriptive characteristics.

The average age was 63.2, the minimum age was 43 and the maximum one was 92 years. Stage I was determined in 114 (76 %) patients, stage II in 12 (8 %) patients and stage III in 24 (16 %) patients. Stage IV was determined in none of the patients. Endometrioid adenocarcinoma was determined in 139 (92.7 %) cases, clear cell in 7 (4.6 %), mucinous papillary histotype in 1 (0.7 %) and serous papillary histotype in 3 (2 %) cases. Histological grading G1 was determined in 79 (52.7 %) cases, G2 in 40 (26.6 %) and G3 in 31 (20.7 %) cases (Tab. 1). In the assessment

**Tab. 1. Patient characteristics.**

		n	%
FIGO stage	I	114	76 %
	II	12	8 %
	III	24	16 %
	IV	0	0 %
Histotype	Endometrioid	139	92.7 %
	Clear cell	7	4.6 %
	Mucinous	1	0.7 %
	Serous papillary	3	2 %
Grading	1	79	52.7 %
	2	40	26.6 %
	3	31	20.7 %

**Tab. 2a. A summary of the ultrasonographic measurements.**

Sonographic finding	Histopathological measurement	
	< 50%	> 50%
< 50%	88	3
> 50%	23	36

**Tab. 2b. Diagnostic performance of transvaginal ultrasonography.**

Diagnostic test measure	Estimated value	95% CI
Sensitivity	92.31%	79.13%–98.38%
Specificity	79.28%	70.55%–86.39%
Positive Predictive Value	61.02%	47.44%–73.45%
Negative Predictive Value	96.7%	90.67%–99.31%
Likelihood Ratio of a Positive Test	4.455	3.107–6.545
Likelihood Ratio of a Negative Test	0.097	0.033–0.258

The estimates are stated along with the 95% confidence intervals (95% CI).

**Tab. 3. List of studies considering the effectiveness of transvaginal ultrasonography in the preoperative assessment of myoinvasion.**

	Number of patients	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy %
Karlsson (12)	30	79	100	100	73	87
Prompeler (15)	96	93	72	73	93	81
Kim (9)	26	50	81	75	67	69
Szabo (18)	52	86	90	92	83	88
Develioglu (13)	39	37	90	78	60	64
Fishman (16)	91	88	83	74	92	82
Valenzano (14)	24	88	100	100	33	88
Szantho (19)	52	86	90	92	83	88
Kose (20)	47	92	64	89	70	85
Kanat-Pektas (17)	120	66	72	60	75	69
This study	150	92	79	61	97	83

of the depth of invasion in the group with infiltration to half the thickness of myometrium, agreement between the assessed (TVS) method and the reference method was found in 88 (79.28 %) patients with the confirmed lower degree of myoinvasion (correctly “negative” patients) and disagreement was found in 23 (20.72 %) cases (false “positive” patients). In the group with infiltration to more than half the thickness of myometrium, 36 (92.31 %) cases were classified properly (correctly “positive” patients) while the disagreement was found in three (7.69 %) cases (Tab. 2a). Sensitivity, specificity and the other indicators of TVS efficiency in the assessment of myometrial infiltration depth can be found in Table 2b. The contingency table analysis revealed that the reference histopathological examination had a significantly different proportion of results ( $p=0.0002$ ). The reason for this result is the higher number of false “positive” results within the classification with the TVS. This number exceeded the number of false “negative” results with a borderline probability value ( $p=0.055$ ) and thus we cannot exclude the possibility that, among cases incorrectly classified by the TVS, the cases with the overrated degree of myoinvasion would predominate. However, in both patient categories (invasion to less and to more than half the thickness of myometrium) the proportions of the cases correctly classified as “negative” and “positive” do substantially prevail over the proportions of the incorrectly classified patients ( $p<0.0001$  in both cases). The overall diagnostic accuracy of the classification with the TVS method reached 82.67 % and the diagnostic odds ratio was 45.91 (Fisher’s exact 95% CI: 12.41–245.09,  $p<0.0001$ ).

## Discussion

Preoperative examination of the myometrial invasion depth in endometrial cancer patients plays an important therapeutic and prognostic role. It splits the patients into the low- and high-risk groups each being submitted to its own specific treatment, where the major difference is the necessity to perform lymph node dissection (LND). Owing to the fact that the patients are mostly obese, polymorbid and elderly, the LND is linked with an increased perioperative and postoperative morbidity. This is why leaving the LND out, if based on the determination of myometrial infiltration depth, represents one of the possibilities to decrease the perioperative morbidity of these patients. There are several methods that can be used for the determination of myometrial in-



filtration depth (CT, MRI, TVS), but the price and availability of the equipment do often disqualify them (6, 7). At present, the TVS represents one of the best achievable low-cost imaging techniques. Besides its wide availability and cost effectiveness, its further advantages are that the examination can be done quickly, reliably, safely and without additional stress for the patient. The advantages of TVS over the transabdominal one are well known. Not only do both the application of a high-frequency probe and the nearness of the probe to the myometrium increase the resolution in general, but they also minimise the problems with the resolution under conditions of poor visualisation like obesity, meteorism and empty urinary bladder (8). An agreement between ultrasound examination and definitive histopathological examination is being reported in 68–88 % of the cases (Tab. 3). The reliability of the method depends on the quality of the ultrasound device and the erudition and experience of the examining physician. The presence of adenomyosis, leiomyomata or endometrial polyps can be an obstacle here.

Some authors (9, 10, 11) prefer the MRI examination to ultrasonography resulting from the significantly higher diagnostic accuracy of the MRI in determining the myometrial infiltration and cervix affliction, which reached 88.5 % and 86.7 %, respectively. On the contrary, costs and availability of the examination disadvantage this method against ultrasound. The overall accuracy of the correct classification of myometrial infiltration depth that was reached within our study (82.67 %) is, on average, comparable with the results being reported by other authors (Tab. 3). But these published results, when seen from the practical and clinical point of view, do represent unreliable information for the simple reason that they do not specify the confidence limits related to the diagnostic indicators and do concentrate all the attention to just one, though representative, value. Presenting results in that way is not acceptable, the rationale being that they are confusing as single performance scores are difficult to interpret. Especially, the results of studies that were based on a low number of cases (9, 12, 13, 14) must be interpreted with caution. In the study (15) based on 96 patients, Prompeler et al reached a sensitivity of 93 %, specificity 72 %, NPV 93 %, PPV 73 %, overall accuracy 81 %; and they consider the TVS to be a valuable method for the preoperative assessment of invasion depth especially in a combination with other preoperative techniques. Fishman et al (16) reports similar results. The relatively low values of sensitivity, specificity, NPV, PPV and accuracy (66 %, 72 %, 75 %, 60 % and 69 %) presented in the study by Kanat-Pektas et al (17)), are considered by us to represent threshold results limiting the applicability of the TVS for determining the depth of invasion. The studies by Szabo et al (18) and Szantho et al (19) came to equal results. An assumption can be expressed that both studies may have been based on an identical sample of patients. The study by Kose et al (20), based on the sample of 47 patients, reports rather balanced proportions of undervalued findings (in four patients, i.e. 8.5 %) and overvalued findings (in 3, i.e. 6.4 %), which represent better results in comparison with ours – undervalued (in three patients, i.e. 2 %) and overvalued (in 23, i.e. 15.3 %). But the number of patients in their sample was lower, what may distort the results,

because the 95% CIs for their estimates are very wide (after our reanalysis, in which their number of cases was taken into account, these intervals are 78–98 % for the sensitivity and 31–89 % for the specificity). On the other hand, Kanat-Pektas et al (17) reached an overvaluation that is similar to the results we got in our study – 20 (16.7 %) vs 23 (15.3 %) out of the total 120, however their final undervaluation was worse than ours – 17 (14.2 %) vs three (2 %), what is considered to have more serious consequences related to the further management of patients.

The values of sensitivity, specificity, NPV, PPV, diagnostic accuracy and especially the number of undervalued results – three (2 %) that were achieved within our study, empower us to integrate the TVS examination into the standard preoperative algorithm for the patients with endometrial cancer. The rationale here is that it provides information based on which we are able to take a correct decision about what type of surgical treatment to perform, increasing thus the patient survival rates and overall therapeutic benefits.

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