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Assessment of myometrial invasion in endometrial cancer by transvaginal ultrasonography in women treated by preoperative brachytherapy

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ABSTRACT

Objectives: Preoperative transvaginal ultrasonographic assessment of myometrial invasion in 315 patients with endometrial cancer was performed and compared with histopathological findings.

Methods: Among 315 women examined, no echo of the endometrium was found in 9 cases. In the group of 306 women, 51 had primary surgical procedure and 255 underwent prior brachytherapy HDR followed by surgery. In all 306 patients, the following parameters were analysed: depth of myometrium infiltration, width of the endometrium, length of the endometrium circumference, the endometrium volume, volume of the uterine body, the proportion/ratio of volume of the endometrium and of the uterine body.

Results: Our study provided good results of ultrasonographic prediction of infiltration within uterine muscle in both groups of patients: after HDR-brachytherapy (efficacy 82.7%, sensitivity 60.3%, specificity 92.7%) and after the primary surgical procedure (respectively: 80.4%, 75%, 88.9%). Assessing the depth of infiltration in the myometrium in examined patients revealed: after HDR efficacy 89.4%, sensitivity 84.6%, and specificity 95.2% and after primary surgery respectively: 90.0%, 94.4%, 83.3%. Other parameters, despite increasing with the depth of myometrial involvement, were not of statistical significance.

Conclusions: Transvaginal ultrasonography is useful in detecting the presence of neoplastic infiItration and depth of such infiltration in the uterine muscle. Treatment by brachytherapy in the HDR mode does not impair the accuracy of this method.

Key words: endometrial cancer, transvaginal ultrasonography, brachytherapy, surgical treatment

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Introduction.

Ultrasonographic diagnostics may be of use for diagnosing the depth of neoplastic infiltration within the uterine muscle in patients with carcinoma of the endometrium. In the literature we can find reports about different degrees of correlation between the result of ultrasonographic assessment of the depth of neoplastic infiltration in the uterine muscle and the

result of histopathologic examination of the postoperative material. In early reports the accuracy of prediction of infiltration in the myometrium using transabdominal ultrasonic probes with frequencies of 2.5 - 5 MHz differed between 78% and 80%[1,2,3] when dividing the uterine muscle into three levels of depth. Most reports are based on studies comprising small groups of patients. The resulting values of efficacy in prediction of depth of inflitration in the myometrium amounted, respectively, to 69%[4], 76%[5], 78%[1,5,7,8] 80%[9,10], 91%[11], 92%[12], and in case of prediction of deep infiltration respectively 80.9%[13], 84%[4,14], 87% [10], 90%[15], and 100%[5].

In studies comprising larger groups of patients, not exceeding one hundred women however, similar results occur, which quote high average diagnostic values in recognition of the depth of neoplastic infiltration within the uterine muscle area of about 71.4%, with efficacy of 88.7%[1,16-19]. In the literature one can also come across reports on poor effectiveness of transvaginal ultrasonography for the assessment of infiltration within the [20,21] myometrium.

In all the above studies the patients in whom ultrasonographic diagnostics was performed were prepared for combined treatment, in which the first stage was a primary operation. The aim of such studies was the assessment of depth of the neoplastic infiltration in the uterine muscle directed for earlier planning of the extent of the surgical procedure.

Due to the fact that brachytherapy in the HDR mode is a method applied by some of the centres dealing in oncological treatment, the literature does not contain explicit information delineating the accuracy of ultrasonographic assessment of uterine muscle infiltration in patients for whom preoperative brachytherapy in the HDR mode has been applied.

Some authors attempted to correlate the infiltration with other parameters which can be identified during ultrasonographic examination of the uterus. The volume of the uterus, the volume of the endometrium, or that of the visible tumour, or else the proportion between those volumes, could be good indicators of the neoplastic infiltration within the uterine muscle, although reports in the literature concerning this are not so congruent[1,3, 4,22].

In patients for whom surgical procedure is for various reasons impossible, the assessment of risk factors for the neoplasm to spread could provide a correct evaluation of the probability of that process. In such patients, being acquainted with all prognostic factors would allow for a possible implementation of adjuvant treatment, thus enhancing the possibility of good prognosis and five-year survival rate.

The purpose of the study was to assess the usefulness of ultrasonographic measurement of depth of infiltration in the uterine muscle in relation endometrial carcinoma in patients after brachytherapy in the HDR mode and also to estimate other ultrasonographic indicators of infiltration in myometrium.

Methods

The study comprised 315 women patients diagnosed with endometrial cancer, treated surgically in the I st Clinic of Obstetrics and Gynecology of the Silesian Medical Academy in Bytom (Poland), between 1996 - 2002, during combined treatment carried out in cooperation with the Institute of Oncology in Gliwice (Poland).

In 9 patients no echo of the endometrium was found on ultrasonographic examination, and thus they were excluded from further stages. They amounted to 2.9% of all examined women patients, that percentage being similar to the data provided in the literature[23].

The remaining 306 patients were the subject of detailed analysis. In the group of 306 patients, 255 (83.3%) underwent brachytherapy in the HDR mode, while 51 (16.7%) patients did not undergo brachytherapy before the operation, due to contraindication (uterine myomas, tumours located in the uterine appendage area, acute or chronic inflammations within the pelvis minor). In all patients, I or II stage of clinical advancement of disease, according to FIGO 1971, had been detected.

The average age of the patients was 58.9 +/- 8.5 years (30 - 77 years of age). None of the patients from the whole examined group (n = 306) had been previously treated hormonally in connection with the primary disease, that is endometrial cancer. In order to carry out detailed analysis, the patients were divided into two groups: 1,255 patients during combined treatment, of which stage one was preoperative brachytherapy in the HDR mode, applying the after loading method. 251 patients during combined treatment, of which stage one was the primary operative procedure.

In all 306 patients ultrasonographic examination was carried out, applying the transvaginal technique, using the Siemens SI-200 model with transvaginal ultrasonic probe, with frequency of 5.0 to 7.5 MHz and the EUB-515 B model by Hitachi which has a transvaginal ultrasonic probe with a frequency of 6.5 MHz. All the ultrasonographic examinations were carried out between 3 and 5 days before the surgical procedure.

During examination, the ultrasonic probe was placed

in the posterior vaginal fornix, and the images obtained were in longitudinal followed by transverse cross-sections of the pelvis minor and organs located there.
The following were assessed during the examination:

1. length of the uterine body,
2. antero-posterior diameter of the uterus,
3. width of the uterus in the fundus,
4. width of the endometrium at the fundus level,
5. length of the endometrium at the fundus level,
6. thickness of the uterine muscle,
7. depth of infiltration within the uterine muscle, divided into:
   absence of infiltration,
   infiltration up to 50% of the thickness of the uterine muscle,
   infiltration exceeding 50% of the thickness of the uterine muscle,
8. length of the circumference of the endometrium in longitudinal cross-section.

On the basis of ultrasonographic examinations, the following parameters were included in the analysis:

I. depth of infiltration in the myometrium,
2. width of endometriurn at the fundus level,
3. length of endometrium circumference,
4. volume of endometrium, calculated according to the method developed by Shipley[14], which is the product of the width of endometrium, the length of endometrium at the level of the fundus, and the length of endometrium in longitudinal cross-section.
5. volume of the body of the uterus, calculated according to the formula where it is the product of the length of that body, its anteroposterior diameter, and width at fundus[19].
6. the proportion/ratio of volume of the endometrium and that of the body of the uterus.

In 29 patients with the first stage of clinical disease and G-I in histopathologic ripeness of the carcinoma hysterectomy was performed, with adnexectomy and removal of the vaginal cuff, and the pelvis minor and periaortal lymph nodes were assessed by palpation. Such a surgical procedure resulted from the fact that in no case were metastases found to be located in the lymphatic nodes excised from patients with stage endometrial cancer[23].
Hysterectomy was performed in 277 patients with adnexectomy and removal of the vaginal cuff, pelvic lymphadenectomy followed by assessment of the periaortal lymphatic nodes by palpation, while 2 patients had palpation lymphadenectomy detected on palpation. The extensiveness of the surgical procedure depended upon the degree of clinical advancement of the uterine body cancer and histopathologic finding of the endometrial carcinoma.

Table1: Data on the presence of endometrial invasion examined by ultrasound and pathological examination in group of patients after brachytherapy HDR mode(n=255)

		Results of ultrasound scan		All
		Deep or superficial invasion	No invasion	
Pathomorphological results	Deep or superficial invasion (+)	47 60.3% 78.3%	31 39.7% 15.9%	78 100% 30.6%
	No invasion (-)	13 7.3% 100%	164 92.7% 84.1%	177 100% 69.4%
All		60 23.5% 100%	195 76.5% 100%	255 100% 100%
		p<0.001		

Table2: Data on the presence of endometrial invasion examined by ultrasound and pathological examination in the group of patients without brachytherapy HDR mode(n=51)

		Results of ultrasound scan		All
		Deep or superficial invasion	No invasion	
Pathomorphological results	Deep or superficial invasion (+)	25 75.8% 92.6%	8 24.2% 33.3%	33 100% 64.7%
	No invasion (-)	2 11.1% 7.4%	16 88.9% 66.7%	18 100% 35.3%
All		27 52.9% 100%	24 47.1% 100%	51 100% 100%
		p<0.001		

Table 3: Depth of endometrial invasion compared by ultrasound and pathological examination in the group of patients after brachytherapy HDR mode (n=47 out of 255)

		Results of ultrasound scan		All
		Deep invasion	Superficial invasion	
Pathomorphological results	Deep invasion	22 84.6% 95.7%	4 15.4% 16.7%	26 100% 55.3%
	Superficial invasion	1 4.8% 4.3%	20 95.2% 83.3%	21 100% 44.7%
All		60 48.9% 100%	24 51.1% 100%	47 100% 100%
		p<0.001		

Table 4: Depth of endometrial invasion compared between ultrasound and pathological examination in the group of patients without brachytherapy HDR mode (n=25 out of 51)

		Results of ultrasound scan		All
		Deep invasion	Superficial invasion	
Pathomorphological results	Deep invasion	17 94.4% 94.4%	1 5.6% 16.7%	18 100% 72.0%
	Superficial invasion	1 16.7% 5.6%	6 83.3% 83.3%	7 100% 28.0%
All		18 72.0% 100%	7 28.0% 100%	25 100% 100%
		p<0.001		

The material removed underwent macroscopic assessment immediately after the procedure, and was subsequently fixed in formalin solution.

Histopathologic examination was used determine the degree to which the excised organs were affected by carcinoma as well as the depth of infiltration of the carcinoma within the uterine muscle (lack of infiltration, infiltration up to half the width of the uterine muscle, infiltration exceeding one half of the width of the uterine muscle), the degree to which the lymphatic system was affected by carcinoma (metastases of neoplastic cells to pelvic lymph nodes and possibly also to periaortal nodes). Changes in the neoplastic cells were also noted which could have been due to the preoperative radiotherapy applied. The neoplastic cells with radionecrosis were treated as neoplastically inactive, while those neoplastic cells which gave any other image were treated as surviving, neoplastically active cells.

The results of ultrasonographic and histopathologic examinations were subjected to statistical analysis with the aid of the Statistica Programme by Statsoft (USA).

Results

Results of this study are illustrated in tables 1-8.

The observed efficacy of the method amounted to 82.7%, the sensitivity was 60.3%, while the specificity was 92.7% in the group of patients after brachytherapy in the HDR mode (Table I).

The respective results obtained in the group of patients after primary surgical procedure, who did not receive radiotherapy were with an efficacy of 80.4%, sensitivity of 75%, and specificity of 88.9% (Table 2).

In assessing the depth of infiltration of the myometrium, which is of special importance for predicting the level of the lymphatic system affected by the neoplastic process, both groups of patients examined also revealed high levels of efficacy, sensitivity, and specificity. The respective results for the group of patients after brachytherapy in the HDR mode were as follows: efficacy of 89.4%, specificity of 95.2%, and sensitivity of 84.6% (Table 3). These results in the group of patients after primary surgical procedure were with efficacy of 90.0%, specificity of 83.3%, and sensitivity of 94.4% (Table 4).

Due to a possible variation of results of the predictions of myometrial infiltration, applying other ultrasonographic parameters available during examination of the uterus in reports issued so far, an attempt at their assessment and correlation has been undertaken, both for patients prepared for primary

surgical procedure, and of the possible influence of brachytherapy in the HDR mode applied before the procedure.

As the neoplastic process advances, of which infiltration of the myometrium is indicative, an increase of the size of the uterus itself and endometrium may be expected, the latter being the tissue where the neoplastic growth originated. Such an assumption, in accordance with reports of other authors[22], has been made in our study when assessing the usefulness of other ultrasonographic parameters such as width of the endometrium at the fundus level, length of the endometrial circumference, volume of the body of uterus, volume of endometrium, and the differences between them.

A statistically significant increase of the width of the endometrium was noted in the group of patients that underwent the surgical procedure primarily (n = 51), as the depth of infiltration in the myometrium increased. Such an association was not observed in patients after brachytherapy in the HDR mode. Other parameters, despite increasing with the depth of myometrial involvement, were not statistically significant (Tables 7. 8, 9).

Discussion

Endometrial cancer is currently the most common gynaecological malignancy in developed countries[26]. A number of reports have suggested that the incidence of carcinoma of the endometrium is increasing in the United States and other industrialised countries[27]. The American Cancer Society has estimated that the incidence of endometrial cancer is 2.5 times that of invasive carcinoma of the uterine cervix. According to the Finnish Cancer Registry[29] the ratio of endometrial cancer to cervical cancer was 4.0 in 1993. In contrast to cervical cancer, there are no routine mass screening programmes for the early detection of endometrial cancer, although many safe techniques are now available for detecting and diagnosing neoplastic lesions of the endometrium[30-34]. Since these methods are invasive, although safe and highly acceptable to the women[35,36], it might be preferable to first use some non-invasive method, such as ultrasound, to identify women at risk who should undergo endometrial biopsy.

Transabdominal sonography can be used to detect many forms of endometrial pathology including cancer. Transvaginal sonography yields even more detailed images of the uterus[37-39] and facilitates the measurement of endometrial thickness with good patient acceptance. The use of transvaginal sonography and colour flow imaging to detect endometrial cancer in women with postmenopausal

Table 5: Prevalence of myometrial invasion between ultrasound and pathological examination

		Prevalence of myometrial invasion between ultrasound and pathological examination		All
		Presence	Absence	
HDR	After HDR (+)	211 82.7%	44 17.3%	255 100%
	No HDR (-)	41 80.4%	10 19.6%	51 100%
All		252 82.4%		306 100%
		NS		

Table 6: The depth of myometrial invasion observed between ultrasound and pathological examination

		Accordance of Myometrial invasion depth in ultrasound and pathological examination		All
		Correlation	No correlation	
HDR	After HDR (+)	42 89.4%	5 10.6%	47 100%
	No HDR (-)	23 92.0%	2 8.0%	25 100%
All		65 90.3%	7 9.7%	72 100%
		NS		

Table 7: Comparsion of endometrial invasion depth after pathological examination with other ultrasound parameter in the group of patients after brachytherapy HDR mode

	Endometrial width [mm]	Endometrial circumference [mm]	Uterus trunk volume [ml]	Endometrial volume [ml]	Endometrial/ uterine trunk volume ratio
No invasion (A) n=177	8.85 ± 4.86	66.22 ± 23.31	115.88 ± 61.96	2.56 ± 2.54	0.021 ± 0.019
Superficial invasion (B) n=47	9.54 ± 5.71	63.83 ± 25.47	113.18 ± 65.38	2.36 ± 2.14	0.023 ± 0.019
Deep invasion (c) n=31	9.93 ± 4.90	70.14 ± 24.60	122.9 ± 56.34	3.82 ± 3.10	0.026 ± 0.024
A : B	NS	NS	NS	NS	NS
A : C	NS	NS	NS	NS	NS
B : C	NS	NS	NS	NS	NS

Table 8: Comparsion of endometrial invasion depth after pathological examination with other ultrasound parameter in group of patients without brachytherapy HDR mode

	Endometrial width [mm]	Endometrial circumference [mm]	Uterus trunk volume [ml]	Endometrial volume [ml]	Endometrial/ uterine trunk volume ratio
No invasion (A) n=18	10.89 ± 4.54	67.00 ± 20.68	139.38 ± 78.28	3.08 ± 2.74	0.022 ± 0.020
Superficial invasion (B) n=12	11.73 ± 5.23	69.40 ± 15.44	114.72 ± 52.54	2.20 ± 2.06	0.021 ± 0.021
Deep invasion (c) n=21	16.75 ± 6.17	80.78 ± 17.02	156.40 ± 65.52	4.66 ± 3.54	0.026 ± 0.025
A : B	p<0.05	NS	NS	NS	NS
A : C	p<0.05	NS	NS	NS	NS
B : C	NS	NS	NS	NS	NS

bleeding has been reported by Bourne et al[40].

Our results demonstrated a real effectiveness of ultrasonographic prediction of infiltration within uterine muscle, by assessment of the border between the neoplastic infiltration and myometrium, both in the group of patients after brachytherapy in HDR mode preceding the operation, and the group of patients prepared for the primary surgical procedure.

The obtained results of predictions of myometrial involvement in both groups of patients are comparable with reports by other authors, who conducted their studies using far smaller groups of patients prepared for primary surgical procedure [1, 4, 5, 7, 8, 10, 11, 12 l6, 17, 18, 24].

In case of assessing the depth of infiltration when the uterine muscle is divided into two levels: superficial - reaching to half the width/thickness of the muscle, and deep - exceeding half the width/thickness of the muscle, some other authors also reported similar results[4,5,10,13]. Those examinations were also carried out in patients who had not undergone brachytherapy in the HDR mode.

Comparing the efficacy of predictions of both the myometrial involvement as such, and its depth in both groups of patients, no statistically significant differences were found. This appears to be the evidence of lack of influence of brachytherapy in the HDR mode upon the accuracy of predictions that infiltration will be present in the myometrium, and the depth of that involvement, and to underline the high diagnostic value of transvaginal ultrasonography (Table 5).

The results presented above confirm the effectiveness of detecting infiltrations in the uterine muscle applying transvaginal ultrasonography in patients for whom the first stage of treatment consisted of a surgical procedure, in contrast with reports that shake such an opinion[20,21]. These results also prove that preoperative radiotherapy by means of HDR brachytherapy does not impair the accuracy of the ultrasonographic assessment of the depth of myometrial involvement[16], which is of great importance for the gynecologist-oncologist managing the case.

When assessing the advancement of the disease process, a substantial increase in the width of the endometrium and increasing depth of infiltration in myometrium were noted in the group of patients that underwent a surgical procedure primarily (n = 51), while no such dependence was noted in the group of patients who underwent brachytherapy in the HDR mode. The remaining parameters (length of endometrial circumference, volume of the body of uterus, volume of endometrium, and the mutual

relation between them) despite increasing with the depth of myometrial involvement, indicated no statistical significance (Tables 7, 8, 9).

These results however, differ from those reported by Shipley et al.[12] who found a significant increase of both the volume of endometrium, uterus, as well as the ratio of endometrium to uterus volume. Those authors found a statistically significant agreement between the volume of the uterus between 100 and 200 ml, and volume of endometrium between 12 and 20 ml, and deep infiltration. Similar statistically significant correlations were noted by Cacciatore et al.[1], but only for the volume of endometrium, where the average volume of the endometrium in cases where over 2/3 of the uterine muscle were affected amounting to 20 ml.

In our investigations we did not arrive at statistically significant correlations between volumes of the endometrium and the body of the uterus and depth of infiltration, and the volumes appeared to be much lower. For the whole group examined (n = 291) in case of deep infiltration the average volume of the body of uterus amounted to 134.72 ml, and the volume of the endometrium to 4.04 ml.

Also Lehtovirta et al. as well as Gordon et al.[3,4] found no correlations between the volume of the endometrium and the depth of infiltration. Lehtovirta assessed the average volume of uterus in his studies to be 196 ml, while the average volume of the endometrium or inner echo was 3.9 ml[3]. In the study by Gordon et al.[4] it was found that the volume of the endometrium in fact increases as the depth of myometrial involvement increases also, yet no statistically significant correlations were found to exist between those two.

Therefore, endometrial carcinoma is currently the most frequent gynecological cancer in western countries. Postmenopausal bleeding is usually the first symptom. Although only about 10-15% of women presenting with postmenopausal bleeding will actually have an endometrial cancer, definitive diagnosis in this clinical setting is warranted.

Transvaginal sonographic measurement of the endometrial thickness is a non-invasive method that has been demonstrated to be accurate enough to exclude endometrial malignancy in women with postmenopausal bleeding.
Smith-Bindman et al.[41] showed in their meta-analysis that, using an endometrial thickncss cut-off of ≥ 5mm, the false-negative rate in women with postmenopausal bleeding not taking hormone replacement therapy was as low 4%.

However, endometrial thickening is a non-specific finding that may be caused by a variety of conditions, such as carcinoma, polyps, hyperplasia, endometritis or cystic atrophy[42] although some authors have argued that endometrial echotexture may help to differentiate carcinoma from polyps and hyperplasia[43].

In our investigations no statistically significant differences were found between groups of patients, except for the endometrial thickness measured at fundus level, which appeared to be greater with statistical significance in patients that primarily underwent surgical procedures. Such an association has not been previously reported.

The obtained results seem to indicate that regardless of whether brachytherapy in the HDR mode had been applied before the operation or not, the dimensions of the uterus, its volume and the volume of endometrium do not differ significantly as the neoplastic process progresses in which myometrial involvement is indicated.

Thus the technique of transvaginal ultrasonography seems to be accurate, as well as an easily accessible and relatively cheap diagnostic method to be used in patients with endometrial carcinoma. In our experience, the main parameter which indicates myometrial involvement is the thickness/width of the endometrium at the level of fundus.

Conclusions:

1. Transvaginal ultrasonography is characterised by high efficacy in detecting the presence of neoplastic infitration and depth of such infitration in the uterine muscle. The basis for this is the assessment of the border between the neoplastic tissue and myometrium, while treatment by brachytherapy in the HDR mode does not alter the accuracy of this method.

2. Other ultrasonographic indications connected with the uterus do not provide a reliable method in detection of neoplastic infitration and its depth in the myometrium, except for the parameter of endometrium thickness/width at the fundus level. This is observed only in patients in whom preoperative intra-cavital radiotherapy has not been applied.

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