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ORIGINAL ARTICLE

Diagnostic significance of ultrasound and magnetic resonance imaging scan in the presurgical determination of FIGO stage of endometrial cancer

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Summary

Purpose: *To compare the presurgically determined FIGO (Federation International Gynaecology Obstetrics) stage of endometrial cancer based on ultrasound (US) and magnetic resonance imaging (MRI) with the surgico-pathological disease stage.*

Methods: *60 patients with histopathologically proven endometrial cancer were prospectively studied. Prior to surgical treatment, all patients underwent abdominal US and MRI. The imaging results were compared with the surgical histopathological findings.*

Results: *Imaging (US, MRI) staging accuracy for stage I identification was higher than the accuracy of advanced FIGO stages of endometrial cancer. Total accuracy of determination of all disease stages was significantly higher using MRI.*

Conclusion: *US is not adequate for overall presurgical FIGO stage assessment, but does have satisfactory accuracy in determining tumor spread in the uterus itself and can be applied when MRI scanner is not available and when the risk of extrauterine disease expansion is low. MRI examination should be applied in all cases when there is suspicion for extrauterine spread into other pelvic and abdominal organs.*

Key words: endometrial carcinoma, FIGO stage, MRI, presurgical examination, ultrasound

Introduction

In economically developed countries, endometrial cancer is the most common malignant tumor of the female genital system, while in Serbia it is second to cervical carcinoma [1,2]. Eighty percent of patients with endometrial cancer are diagnosed in stage I. Due to early symptoms and timely diagnosis, this malignant tumor is not the leading cause of mortality among the malignancies of the female genital system [3]. Prognosis depends on the tumor histological type, cell differentiation, depth of myometrial and cervical invasion, penetration of malignant cells into the lymphovascular spaces, lymph node metastasis and patient's age [4,5].

A number of patients with endometrial cancer belongs to the group with poor prognosis in which treatment has not been clearly defined yet [6]. When planning a therapeutic approach, FIGO stage and different prognostic factors should be taken into consideration. Modern imaging technologies help determine pre-therapy disease extension and contribute to optimal treatment planning [7-9].

This research was based on the assumption that US and MRI enable the presurgical determination of FIGO stage of endometrial cancer, and therefore allow the choice of the most appropriate therapeutic approach. According to FIGO recommendations, definite stage determination of endometrial cancer is done after surgery and includes assessment of disease extent during the operation, and histopathological examination of the removed material [10,11].

The aim of this study was to compare the presurgically determined FIGO stage based on US and MRI, and the definite stage of endometrial cancer found during surgery and based on histopathological examination of the surgically removed material.

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Methods

This was a prospective clinico-pathological study done at the Vojvodina Institute of Oncology in Sremska Kamenica in the period 2007 - 2009. Included were 60 patients with histopathologically proven endometrial cancer.

Inclusion / Exclusion criteria

Inclusion criterion was diagnosis of endometrial cancer based on histopathological examination of the removed material after endometrial biopsy or fractional curettage.

Exclusion criteria were the presence of severe chronic conditions (respiratory and renal insufficiency, congestive heart failure and severe diabetes) preventing a patient from surgical treatment, and active malignancy in other systems or organs.

All patients were given a written explanation about the planned diagnostic and therapeutic procedures and they signed an informed consent allowing the use of information from their medical records.

Before surgical treatment, all patients were examined by Siemens Sienna ultrasound using 7 MHz endovaginal probe. MRI examination was performed by Siemens Magnetom SP 6300 machine, field strength of 1.5T, using body coil according to the protocol for endometrial carcinoma patients. Preparation of patients before MRI included 3-6 h period without food to reduce bowel peristalsis and artifact prevention, as well as bladder emptying just prior the scan.

Hysterectomy with bilateral salpingoophorectomy and selective or complete pelvic lymphadenectomy was performed on all patients. In cases of suspected extension to the cervix, radical hysterectomy with pelvic lymphadenectomy was performed. In cases of enlarged paraaortic lymph nodes, paraaortic lymphadenectomy was carried out.

After opening of the abdomen with upper middle and paraumbilical incision, a detailed inspection and palpation of the pelvic and abdominal organs was performed, with sampling of peritoneal fluid (if present) or washings for cytological examination. Based on the surgico-pathological findings, the stage of endometrial cancer was determined according to the current FIGO classification [11]. The parameters studied included: histological type of the tumor, grade of cell differentiation (G), size of the tumor and depth of myometrial invasion, presence of invasion to the cervical epithelium or stroma, presence of lymphovascular invasion, number of removed lymph nodes, cytological examination of ascites or peritoneal washings. Relevant parameters for disease stage determination obtained by US and MRI were compared with the parameters of the surgico-pathological results (Tables 1 and 2).

Table 1. Parameters of myometrial invasion measured during US examination

1. No invasion - when the border between endometrium and myometrium is even and clear and the subendometrial hyperechogenic (halo) zone is visible.
2. Invasion < 50% of the myometrial wall - partially broken or uneven border between endometrium and myometrium with hyperechogenic signal of tumor in the outer half of myometrium, without invasion outside the uterine serosa.
3. Invasion > 50% of the myometrial wall - partially broken or uneven border between endometrium and myometrium with hyperechogenic signal of tumor in the outer half of myometrium, without invasion outside the uterine serosa.

Invasion of cervical mucosa - thick, inhomogeneous mucous membrane.
Invasion of cervical stroma - hyperechogenic, inhomogeneous, not clearly confined area in cervical stroma.
Ovary penetration - enlarged ovary, cystic, solid or mixed texture which differs from normal ovary echostructure.
Ascites - non-echogenic fluid in Douglas space and/or abdomen.

Table 2. Parameters of myometrial invasion measured during MRI examination

1. No invasion - when the "junction zone" is clearly identified on T2W shots, and the border between endometrium and myometrium is clear and even.
2. Invasion < 50% of the myometrial wall - partially broken "junction zone" or uneven border between endometrium and myometrium with tumor signal in the internal half of the myometrium.
3. Invasion > 50% of the myometrial wall - partially broken "junction zone" or uneven border between endometrium and myometrium with tumor signal in the external half of myometrium.

Invasion of cervical mucosa - thick, inhomogeneous mucous membrane.
Invasion of cervical stroma - area of low or high signal intensity, inhomogeneous, not clearly confined area in the cervix stroma.
Ovary penetration - enlarged ovary, cystic, solid or mixed texture which differs from normal ovary MRI appearance.
Ascites - non-echogenic fluid in Douglas space and/or abdomen.
Metastasis in lymph node - diameter > 1 cm

Statistical methods

Statistical methods included paired t-test for two independent groups with different number of cases, and x^2 test. For multivariate analysis of quantitative features MANOVA was applied, which confirms or rejects the hypothesis (Ho) that there are no significant differences between arithmetical means for levels defined by criteria features [12]. For determination of the diagnostic significance of certain parameters sensitivity, specificity, positive and negative predictive value and test accuracy were used [13].

Results

The median patient age was 59.7 years (range 44-80), and at the time of diagnosis 48 (80%) patients were postmenopausal and 12 (20%) premenopausal. Adenocarcinoma was the most common histological type (51 patients or 84.5%), and included endometrioid adenocarcinoma (36 patients or 60%), villoglandular adenocarcinoma (11 patients or 18%), serous adenocarcinoma (4 patients or 6.7%), and also other types (clear cell, mucinous, undifferentiated carcinoma; 9 patients or 15.3%). Based on the final histopathological findings and current FIGO classification, 39 (65%) patients were in stage I, 5 (8.3%) in stage II and 16 (26.7%) in stage III. Table 3 shows the prevalence of myometrial invasion obtained by US and MRI, compared with the histopathological findings.

Table 4 shows no significant differences between US and histopathology (myometrial infiltration <50%, p=0.712 and >50%, p=0.275) and MRI and histopathology (<50%, p=0.712 and >50%, p=0.303) concerning the estimation of myometrial depth infiltration obtained by MANOVA.

Positive results for cervical mucosa infiltration were most often found by histopathology (5 or 8.3%) compared to US (2 or 3.3%) and MRI (1 or 1.7%). Chi-square test did not establish connection between cervical mucosa infiltration findings with histopathological examination using US (p=0.243), while MRI showed only a trend for significance (p=0.096). Positive results of cervical strom-

Table 3. Prevalence of myometrial invasion using US and MRI examination compared to histological findings

Myometrial invasion < 50%						
Type of exam	*Negative*		*Positive*		*Total*	
	Patients, no.	*%*	*Patients, no.*	*%*	*Patients, no.*	*%*
US	35	58	25	41.7	60	100
MRI	35	58.3	25	41.7	60	100
Histology	37	61.7	23	38.3	60	100
Myometrial invasion > 50%						
Type of exam	*Negative*		*Positive*		*Total*	
	Patients, no.	*%*	*Patients, no.*	*%*	*Patients, no.*	*%*
US	35	58.4	25	41.6	60	100
MRI	33	55	27	45	60	100
Histology	31	51.7	29	48.3	60	100

x^2 test (p=0.709) did not establish differences between myometrial invasion < 50% using US, MRI, and histopathological findings. Also, x^2 test did not confirm differences between myometrial invasion > 50% and findings of US and histopathological findings (p=0.545), nor between MRI and histopathological findings (p=0.583). This Table shows the lack of statistically significant differences in myometrial infiltration depth findings using US, histopathological studies and MRI.

Table 4. Multivariate analysis of variance/MANOVA in myometrial infiltration depth findings using US, MRI and histology

US and histological results				
Myometrial infiltration (%)	*x*[§]	*R**	*F*[†]	*p-value*
< 50	0.034	0.034	0.137	0.712
> 50	0.100	0.101	1.204	0.275
MRI and histological results				
Myometrial infiltration (%)	*x*	*R*	*F*	*p-value*
< 50	0.034	0.034	0.137	0.712
> 50	0.094	0.095	1.072	0.303

[§]Pearson coefficient contingency, *Coefficient of multiple correlation, [†]Fisher's distribution

Table 5. Multivariate analysis of variance/MANOVA, between cervical mucosa infiltration and cervical stromal findings using US, MRI and histology

Cervical infiltration	*Ultrasound and histological results* $x^{\S}$	*R**	$F^{\dagger}$	*p-value*
Cervical mucosa	0.106	0.107	0.370	0.244
Stroma	0.025	0.025	0.076	0.784
Cervical infiltration	*MRI and histological results* x	R	F	*p-value*
Cervical mucosa	0.151	0.153	2.850	0.094
Stroma	0.072	0.072	0.615	0.435

§Pearson coefficient contingency, *Coefficient of multiple correlation, †Fisher's distribution

al infiltration were more common in US (8 or 13.3%) compared to histopathological findings (7 or 11.7%), but without statistical significance (p=0.783). MRI was more sensitive in revealing cervical stromal infiltration (10 or 16.7%) compared to histopathological findings (7 or 11.7%), but without statistical significance (p=0.432). Table 5 shows no significant differences of cervical mucosa infiltration and cervical stromal findings using US, MRI and histopathology obtained by multivariate analysis of variance (MANOVA).

There was a trend for significance between MRI results and histopathological findings of cervical mucosa infiltration, which was not recorded for infiltration of cervical stroma (p=0.096). Table 6 shows the results obtained by multivariate analysis/MANOVA. Positive findings of ovary and fallopian tubes infiltration prevailed in histological findings (5 or 8.3%) compared to US findings (3 or 5%), but without statistical significance (p=0.467). Positive findings of ovary and fallopian tubes infiltration prevailed in MRI results (8 or 13.3%) compared to histological findings (5 or 8.3%), again without statistical significance (p=0.380). Presence of ascites was more often seen during intraoperative examination of the abdomen (7 or 11.7%), than during US examination (3 or 5%) (p=0.188). Presence of ascites was more often recorded during surgery (7 or 11.67%), than by MRI (6 or 10%) (p=0.770). Positive findings of lymph nodes infiltration were more evident with MRI (10 or 16.67%), than with histopathology (9 or 15%) (p=0.611).

Table 7 shows the diagnostic value of US and MRI in the assessment of local extent of endometrial carcinoma in FIGO stage I, and Table 8 shows the frequency of endometrial carcinoma stages obtained by US, histological and MRI examinations.

Discussion

Information on morphologic prognostic parameters and their application in treatment planning are important factors for improvement of endometrial cancer prognosis and treatment. In the group of prognostic factors which influence the choice of treatment, tumor expansion and stage of disease stand out [14,15]. In early-stage endometrial cancer, where the risk of nodal involvement and distant metastatic disease is relatively low, surgical stage determination and removal of lymph nodes are questionable [16]. Another reason to omit lymphadenectomy is the presence of distinctive operative risk factors in women with endometrial cancer (old-

Table 6. Statistical significance of the differences between results for ovarian and fallopian tubes infiltration, ascites presence, and lymph nodes infiltration using multivariate analysis of variance/MANOVA

	US, histological and intraoperative findings $x^{\S}$	*R**	$F^{\dagger}$	*p-value*
Infiltration of ovaries and fallopian tubes	0.067	0.067	0.534	0.467
Presence of ascites	0.120	0.121	1.756	0.188
	MRI, histological and intraoperative findings x	R	F	*p-value*
Infiltration of ovaries and fallopian tubes	0.080	0.080	0.775	0.380
Presence of ascites	0.027	0.027	0.086	0.770
Lymph nodes infiltration	0.047	0.047	0.260	0.611

§Pearson coefficient contingency, *Coefficient of multiple correlation, †Fisher's distribution

Table 7. Diagnostic value of US and MRI in the assessment of extent of FIGO stage I endometrial carcinoma

Parameters	*Sensitivity*		*Specificity*		*Positive predictive value*		*Negative predictive value*		*Test accuracy*	
	US	*MRI*	*US*	*MRI*	*US*	*MRI*	*US*	*MRI*	*US*	*MRI*
Myometrial infiltration < 50%	0.82	0.86	0.84	0.91	0.76	0.80	0.88	0.91	0.85	0.86
Myometrial infiltration > 50%	0.75	0.82	0.87	0.90	0.84	0.88	0.79	0.84	0.81	0.86
Total determination FIGO stage I	0.71	0.82	0.83	0.81	0.93	0.88	0.47	0.71	0.63	0.81

Table 8. Disease stage determined by US, MRI and histology

	US		*MRI*		*Histology*	
FIGO stage	*N*	*%*	*N*	*%*	*N*	*%*
I A	9	15.0	7	11.7	6	10.0
I B	20	33.3	16	26.7	17	28.3
I C	19	31.7	13	21.7	16	26.7
II A	1	1.7	1	1.7	0	0
II B	6	10.0	5	8.3	5	8.3
III A	5	8.3	8	13.3	7	11.7
III C	0	0	10	16.7	9	15.0
Total	60	100.0	60	100.0	60	100.0

er age and associated diseases: diabetes, hypertension, obesity) [17]. Presurgical knowledge of myometrial and cervical invasion influences the decision on performing or the extent of lymphadenectomy, while cervix infiltration influences the type of hysterectomy. Despite the abundance of information offered by modern imaging methods, there are no precise protocols for presurgical evaluation of endometrial cancer [18-20].

US and MRI have overestimated initial infiltration, while deeper infiltration of the myometrium has been underestimated. The causes of underestimation of infiltration in early-stages (FIGO I A-B) include existence of large tumor volume which reduces the thickness of the uterine wall, and presence of myoma or adenomyosis. The cause of underestimation in FIGO stage I C is isoechogenic tissue and weak contrast between tumor and the myometrium. US shows falsely positive results of cervical mucosa infiltration more often. Cervical mucosa infiltration was more often overlooked by MRI. Falsely negative results were obtained due to the very early mucosal infiltration. The cause of wrong results in both cases was presence of polyps in the cervical canal or prominence of tumor, which did not infiltrate the cervix but did expand to the cervical canal from the uterine cavity. US overlooked expansion of tumor outside of uterus more often. The cause of false negative results for ovaries and Fallopian tubes infiltration was the presence of micrometastases in the ovaries. US can not detect tumor expansion outside the uterus precisely enough, although accuracy in determining parameters for the body of the uterus (depth of myometrial and cervical infiltration) was high. Application of MRI showed false positive results for ovarian and Fallopian tubes infiltration more often. Falsely positive results were obtained in women who had old inflammatory changes and benign cysts. The cause of false negative results for ovarian infiltration was the presence of micrometastases in the ovaries.

Analysis of results for disease stages did not prove statistically significant difference between the frequency of individual stages obtained by MRI and histopathological examination. Up until now, many studies show that the accuracy of MRI in differentiating invasive from noninvasive endometrial carcinoma ranges between 0.69 to 0.88 [21-24]. In our study, in stage IB patients with <50% myometrial infiltration false negative results were obtained by US in 4, and by MRI in 3 patients. Infiltration was not detected owing to the lack of contrast between tumor tissue and myometrium, and microscopic invasion. In 6 cases infiltration was overestimated by US, and in 5 cases by MRI. The causes of such findings were adenomyosis [1], myoma [1], distension of myometrium by large tumor volume [2], and weak contrast in 2 patients. In the literature, the absence of junction zone is cited as such a cause as well [25]. In the present study, when examining patients with myometrial infiltration >50%, US findings were falsely negative in 7, and MRI in 5 cases. Infiltration was not seen because of weak contrast between tumor tissue and myometrium.

Total accuracy of stage I determination by US and MRI is lower than accuracy of individual parameters determination of myometrial infiltration. Our results showed that accuracy of stage I determination was higher compared to more advanced stages. Confirmatory to this conclusion are the results of accuracy for parameters of infiltration of tissues and organs outside the uterus. Similar values were obtained in the Morales-Olaya et al. study, where accuracy of determination of deep myome-

trial invasion (sensitivity 0.94, specificity 0.84, and accuracy 0.88) was higher than total accuracy of US in determining disease stage (sensitivity 0.66, specificity 0.83, and accuracy 0.77) [26]. According to several authors, ultrasonographic accuracy in differentiating disease stages IA-C ranges between 0.66 and 0.100 [27]. MRI accuracy on T2W images regarding depth of myometrial invasion ranges from 0.68 to 0.80 [28,29]. Application of dynamic studies increases the contrast between tumor and surrounding tissues, as well as accuracy which ranges from 0.83 to 0.92 [30,31]. If we consider the total accuracy for all disease stages determination, MRI accuracy is significantly higher. In the present study there was statistically significant difference between findings obtained by US and histopathological examination (p=0.002), while no significant difference between MRI and histopathological examination was proven (p=0.957). When determining stages by US, the accuracy rate was 53.3 and by MRI 63.3. In a large scale multi-institutional research of the American National Cancer Institute, total accuracy of MRI in determining endometrial cancer stages was 0.85 [32]. In that study, 68% of patients were in stage I. Analysis of the findings for advanced stages (FIGO II - IV) revealed significant fall of accuracy to 0.57.

The predominant topic of most trials was the accuracy of cervical and uterine body infiltration. The accuracy of expansion to other tissues is evaluated through analysis of total accuracy of stages determination. Analysis of findings for disease stages in this study revealed that there is a significant difference between disease stages obtained by US and histopathological examination. Stages I A-C and II A-B (55 patients-91.7%) were determined by US more often, while stage III A (ovaries and fallopian tubes, and positive cytology) and III C (metastasis to lymph nodes;18 patients-30%) were determined more often by MRI. US is not precise enough for detecting tumor expansion outside the uterus. However, the accuracy of determining parameters of the expansion to the body of the uterus (depth of cervix and myometrial infiltration) is high using MRI.

Conclusion

Total accuracy of FIGO stage I endometrial cancer determination using US and MRI is lower than the accuracy of individual parameters of the depth of myometrial infiltration determination, because - when determining the total stage - other parameters which define each of the stages are also taken into account. Results showed that the accuracy of stage I determination is higher compared with advanced FIGO II and III stages. Regarding the total accuracy in determining all stages, MRI accuracy is significantly higher. Based on current knowledge, transvaginal sonography can be accepted as the method of choice in early evaluation of endometrial changes. Its advantages are that it is widely accessible, relatively low-priced, non-invasive, simple and harmless. Application of US is not suitable for the complete presurgical staging, but it is accurate enough for determining tumor expansion in the uterus itself and can be applied in cases when MRI is not available and when the risk of extrauterine expansion is low. MRI should be applied in all cases where advanced stages of endometrial cancer with expansion to other organs of the pelvis and abdomen are suspected.

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