Ultrasound Diagnostics in Patients with Endometrial Carcinoma

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Abstract: *Introduction*: Endometrial carcinoma is diagnosed by histopathological assessment of the sampled endometrium. After establishing the diagnosis the patient needs to be further evaluated in order to establish an optimal treatment. The most important factors that determine the treatment plan include: age, reproduction status, the depth of myometrial invasion, cervical invasion, histopahological type of tumor, histological and nuclear grade. Surgery is the most common treatment. The choice of optimal surgical procedure may include various imaging methods.

Aim of the study: Testing the usefulness of applying the ultrasound diagnostics in preoperative evaluation of patients diagnosed with endometrial carcinoma.

Method: The prospective study included 61 patients diagnosed with endometrial carcinoma. The ultrasound was used to estimate the presence and depth of invasion of the uterine muscle and cervical inclusion. The obtained parameters were compared to histopathological findings from surgically removed uterus.

Results: The sensitivity of the ultrasound method in the estimation of myometrial invasion in the tested sample was 77.59%, specificity was 100.00%, predictive value of the positive test was 79.03%. The sensitivity of the ultrasound method in the estimation of cervical invasion in the tested sample was only 11.11%, specificity was 90.91%, predictive value of the positive test was 33.33%, predictive value of the negative test was 71.43%, whereas total accuracy of the method was 67.74%.

Conclusion: Ultrasound diagnostics can be used in the assessment of the depth myometrial invasion but not in the assessment of cervical inclusion.

Keywords: Endometrial carcinoma, ultrasound diagnostics, myometrial invasion, cervical inclusion.

INTRODUCTION

Endometrial carcinoma is one of the most common malignant tumors of female reproductive organs. About 200.000 women develop endometrial carcinoma every year, and about 50.000 women die [1]. The incidence of the uterine carcinoma in the developed countries is 12.9/100.000 (mortality 1.6/100.000), while in the undeveloped countries it is 5.7/100.000 (mortality 0.7/100.000) [2]. In Serbia, endometrial carcinoma is the fifth most common malignancies among women following breast cancer, colon cancer, rectal and cervical cancer [3]. The incidence of endometrial carcinoma increases with age (5-10 years before menopause) with peak incidence between 65 and 70 years of age [4].

The first and most common symptom of a malignant disease of the endometrium is abnormal postmenopausal bleeding [5]. The greatest number of patients was postmenopausal at the time of diagnosis and vaginal bleeding was considered a serious symptom. Out of all patients, 7% to 14% were premenopausal [6-9].

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Every abnormal genital bleeding demands careful examination. After taking the history and clinical examination (with a speculum, bimanual, rectovaginal) a number of diagnostic procedures are undertaken. The available procedures include: cytological diagnostics, ultrasound diagnosis and tumor markers.

Cytological diagnostics is not sensitive enough in the diagnosis of endometrial carcinoma [10] because the cells of endometrial carcinoma are rarely spontaneously desquamated [11] because they are submitted to changes when they pass through the reproductive tract [12], because cervical canal stenosis (in postmenopausal women) is common [10] and because the sample is most commonly indirectly taken. The sample taken directly (by washing out or by brush) is more reliable in the detection of endometrial pathology [12].

Transvaginal sonography is available, noninvasive and painless and it is often used in screening and in the evaluation of abnormal uterine bleeding. Majority of authors state that measuring the thickness of the endometrium, especially in postmenopausal women is a satisfactory method with high specificity in the detection of endometrial carcinoma and other endometrial abnormalities [13]. According to numerous

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authors, the critical depth of the endometrium is 5 mm and sampling of the endometrium is necessary as well as histopathological evaluation [14]. On the other hand, there are reports that with 5 mm endometrial thickness only 4% of patients with severe endometrial pathology will be registered with transvaginal sonography [15]. A study performed on a larger sample with histopathological evaluation of 6 mm thick endometrium showed that specificity of this test was 98% and sensitivity was 17%, so the conclusion of the study was that transvaginal sonography was not suitable for the screening of endometrial carcinoma [16].

Tumor markers are not elevated in the early phases of the disease and they are not endometrium-specific (CA 125), therefore, they are not suitable in establishing the diagnosis [17]. There are claims that in the future apolipoproteins A1 and C1 could be used in screening [18].

The diagnosis is established on the basis of fraction explorative curettage, hysteroscopically controlled biopsy or aspiration biopsy of the endometrium and histopathologic analysis of the obtained endometrium. The histopathology of the curettement and the findings in the surgically removed uterus usually show a significant match or the surgical findings are more severe [19-22].

In case recurrent bleeding is present with negative histopathological findings, hysteroscopically targeted biopsy should be performed. Hysteroscopy is not a replacement for transvaginal sonography and cytology because it is invasive and there is potential risk for transtubal dissemination process (due to the use of fluids) but is has significance especially in case of focal lesions. There is a good correlation between the visual impression of the hysteroscopically biopsied change and histopathological findings [23-25].

Endometrial carcinoma is a disease with good prognosis because most patients have the first stage of the disease at the time of diagnosis, and because it belongs to less aggressive tumors. However, it has been noticed that the patients who die from this neoplasm were also diagnosed and treated during early stages [26]. After establishing the diagnosis of malignant tumor of the corpus uteri, it is necessary to define the prognostic parameters and create a treatment plan.

The prognosis and treatment of endometrial carcinoma depend on several factors. The prognostic parameters are classified into nontumor (race, age, menopausal status) and tumor: uterine and extrauterine. The extrauterine prognostics factors include: adnexal involvement, intraperitoneal metastases, positive peritoneal fluid, metastases in the pelvic and paraaortic lymph nodes. The uterine prognostic parameters include; tumor size, histopathological tumor type, the degree of maturity, the depth of myometrial invasion, vascular invasion and DNA ploidy [27, 28].

The most important determinants in treatment plan include: probable disease stage, age, reproductive menopausal status, histopathological type of tumor, histological and nuclear grade, presence and degree of myometrial invasion and presence of cervical infiltration. [29,30].

There are two pathways of carcinogenesis and two types of endometrial cancer. The most common type of endometrial carcinoma is endometrioid type of adenocarcinoma which develops under the conditions of hyperplastic endometrium, it is hormone-dependent and has a good prognosis. Nonendometrioid types are more aggressive, they develop within atrophic endometrium, they spread more quickly and have a more negative prognosis [31,32].

Histologic grade represents represents the ration between solid parts and glandular tumor parts (Grade I includes the presence of solid parts up to 5%, Grade II includes the presence of solid parts up to 50% and Grade III comprises the percentage of solid parts above 50%). Higher grade of the disease is a negative prognostic parameter (deeper myometrial infiltration is more common, the incidence of pelvic and paraaortic metastases is higher) [30].

Nuclear grade is determined on the basis of the degree of nuclear atypia. Tumors with nuclear grade III have polymorphic, hyperchromatic nuclei with rough irregular chromatin and prominent nucleolus. Endometrial tumors are classified into three groups: well, averagely and badly differentiated or, according to some authors, into low grade and high grade. The last FIGO grading system revision and histopathological classification by the WHO suggests that tumors are graded according to both criteria, architectural and nuclear [33, 34].

The grade of endometrial carcinoma is surgically and histopathologically determined [35-38] and preoperative method may be used for determining only

the probable grade, using clinical examination, fractional curettage and modern imaging techniques.

Disease stadium determines survival which is reduced with higher grades [31, 32]. At the time of diagnosis, the greatest number of patients was able to undergo surgery and 10% had extrauterine disease [39]. The greatest number of patients will be treated surgically if there are no severe comorbidities which would present a contraindication. The choice of optimal surgical method includes modern imaging techniques (ultrasound diagnostics – US, computerized tomography – CT and magnetic resonance imaging – MR).

The application of ultrasound in patients diagnosed with endometrial carcinoma aims at: detecting tumor changes, estimating the myometrial invasion and detecting the cervical involvement [40-45]. Myometrial invasion is an independen prognostic parameter. The presence of deeper myometrial invasion increases the possibility of developing recurrent disease (locals recurrences, metastases in paraaortic and pelvic nodes [30]. The presence of the deep muscular invasion points to patients who require dissection of regional lymph glands [27,28,46-48]. The current histopathological grading obliges a surgeon to perform intraoperative estimation of the degree of muscular invasion and to decide on the type and invasiveness of the treatment depending on preoperatively known parameters (histopathological disease type, histological and nuclear grade, age, menopausal status) as well as on the parameters estimated intraoperatively (depth of muscular invasion, presence of cervical infiltration and extrauterine spread of the disease). Cervical infiltration is also an independent prognostic parameter and if it is present it is necessary to radicalize the operation and conduct dissection of reginal lymph nodes [49, 50].

Patients with the diagnosis of endometrial carcinoma may undergo preoperative evaluation by transvaginal sonography in order to plan the treatment: the choice of optimal procedure, surgeon and institution.

The aim of the study was to estimate the significance of preoperative ultrasound evaluation of patients diagnosed with endometrial carcinoma.

MATERIAL AND METHODS

The study was prospective. It included 62 patients diagnosed with endometrial carcinoma. The patients were admitted at the Clinic of Gynecology and Obstetrics for operative treatment after examination and approval from the consulting body of the Clinic of Oncology in Nis. The patients with severe comorbidities or with advanced and nonoperative disease were not referred to the Clinic of Gynecology and Obstetrics. The data were collected from January 2009 to February 2011. All patients had histopathological findings of endometrial carcinoma and they were prepared for surgery as outpatients. During immediate preoperative preparation, after admittance and with consent, the routine preparation for surgery (history, examination by a gynecologist and anesthesiologist) was followed by ultrasonic diagnostics.

Patients' age ranged from 35 to 79. Average age was 62. The greatest number of patients was postmenopausal – 57 (92%), whereas only 5 (8%) were premenopausal. An average postmenopausal patient was in the postmenopausal period for 11 years. Majority of patients were from urban areas 52 (84%), and 10 (16%) were form rural areas. There were 36 (58%) of patients with high school education, 20 (32%) with elementary school and 6 (10%) patients had higher education. Average menstrual cycle was 28 days, menarche in an average patient occurred at the age of 13. Average number of deliveries was 2.08, and the average number of miscarriages was 2.85. The comparison of the groups of premenopausal and postmenopausal women showed no statistical differences regarding education level, origin, menarche and parity status. The menstrual cycle was significantly longer in postmenopausal patients, compared to women who were not in the menopause (28.33±1.23:28.00±0.00 days; $t=2.05$ and $p<0.05$). The differences of other numerical characteristics, as well as the presence of some attributive features between premenopausal and postmenopausal patients were not statistically significant in the tested sample (Table **1**).

The patients who underwent explorative laparotomy was excluded from the study because it was not possible to compare the estimated parameters with the parameters measured ultrasonically (the uterus was not removed).

The most common comorbidities present in patients were: hypertension (85.5%), obesity (50%), diabetes (37%), thromboembolic diseases (8%) and gallbladder calculosis (14%) (Table **2**). Malignant diseases of other localities were registered in 3 patients (4.8%) and malignant diseases in immediate kin were present 6 (9.7%) patients (Graph **1**).

Table 1: Characteristics of Patients with Endometrial Carcinoma with Regard to Menopausal Status

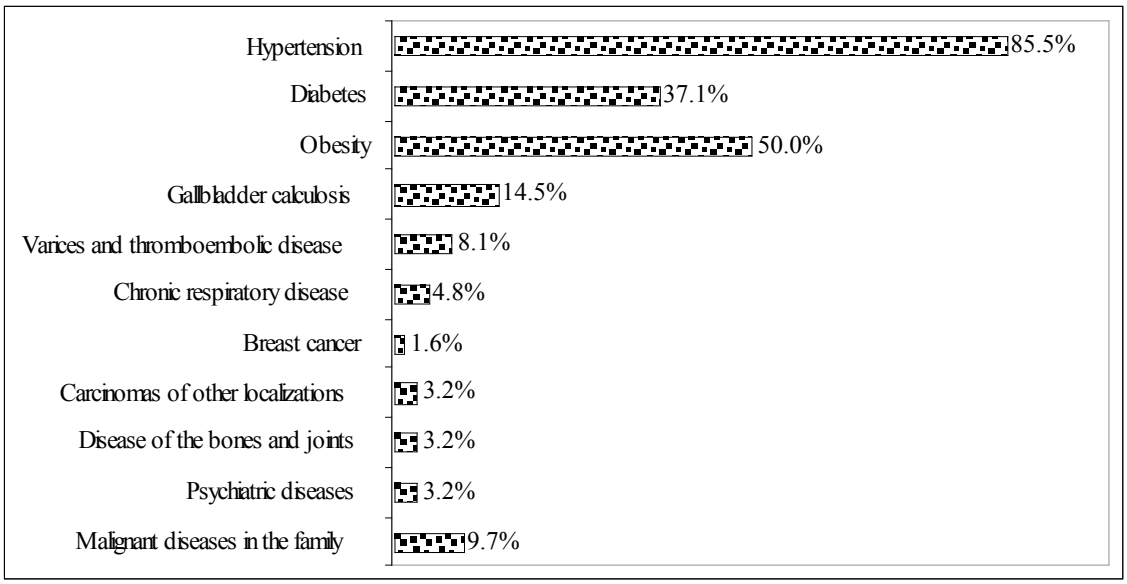
Observed characteristic	Menopause		Total (n=62)	Comparison among groups
	No (n=5)	Yes (n=57)		
Age	54.80±14,86	62,77±7,96	62,13±8,80	p=0,299 t=1,19
Duration of symptoms (months)	6.40±4,04	3,74±3,76	3,95±3,82	p=0,219 t=1,42
Menarche (age)	12,80±2,17	13,02±1,62	13,00±1,65	p=0,836 t=0,22
Duration of mensytrual cycle (days)	28,00±0,00	28,33±1,23	28,31±1,18	p=0,045 t=2,05
Number of deliveries	2,20±1,92	2,07±1,29	2,08±1,33	p=0,889 t=0,15
Number of miscarriages	2,00±1,58	2,93±4,09	2,85±3,95	p=0,322 t=1,04
Years after menopause	-	12,39±7,91	11,39±8,30	-
Education level				p=0,729 χ^2=0,63
Elementary	2 (40,0%)	18 (31,6%)	20 (32,3%)	
High school	3 (60,0%)	33 (57,9%)	36 (58,1%)	
Higher	-	6 (10,5%)	6 (9,7%)	
Residence				p=0,306 χ^2=1,04
Rural	-	10 (17,5%)	10 (16,1%)	
Urban	5 (100,0%)	47 (82,5%)	52 (83,9%)	

Table 2: Present Comorbidities in Patients Operated for Endometrial Carcinoma and Presence of Malignant Diseases in Next of Kin

Characteristic	Menopause		Total (n=62)	Comparison between groups
	No (n=5)	Yes (n=57)		
Hypertension				p=0,717
No	1 (20,0%)	8 (14,0%)	9 (14,5%)	
Yes	4 (80,0%)	49 (86,0%)	53 (85,5%)	
Diabetes				p=0,073
No	5 (100,0%)	34 (59,6%)	39 (62,9%)	
Yes	-	23 (40,4%)	23 (37,1%)	
Obesity				p=0,641
No	3 (60,0%)	28 (49,1%)	31 (50,0%)	
Yes	2 (40,0%)	29 (50,9%)	31 (50,0%)	
Gallbladder calculosis				p=0,717
No	4 (80,0%)	49 (86,0%)	53 (85,5%)	
Yes	1 (20,0%)	8 (14,0%)	9 (14,5%)	
Varices and thromboembolic disease				p=0,490
No	5 (100,0%)	52 (91,2%)	57 (91,9%)	
Yes	-	5 (8,8%)	5 (8,1%)	
Chronic respiratory disease				p=0,599
No	5 (100,0%)	54 (94,7%)	59 (95,2%)	
Yes	-	3 (5,3%)	3 (4,8%)	
Breast cancer				p=0,765
No	5 (100,0%)	56 (98,2%)	61 (98,4%)	
Yes	-	1 (1,8%)	1 (1,6%)	

(Table 2). Continued…..

Characteristic	Menopause		Total (n=62)	Comparison between groups
	No (n=5)	Yes (n=57)		
Carcinomas of other localizations				
No	5 (100,0%)	55 (96,5%)	60 (96,8%)	p=0,670
Yes	-	2 (3,5%)	2 (3,2%)	
Disease of the bones and joints				
No	5 (100,0%)	55 (96,5%)	60 (96,8%)	p=0,670
Yes	-	2 (3,5%)	2 (3,2%)	
Psychiatric diseases				
No	5 (100,0%)	55 (96,5%)	60 (96,8%)	p=0,670
Yes	-	2 (3,5%)	2 (3,2%)	
Malignant diseases in the family				
No	5 (100,0%)	51 (89,5%)	56 (90,3%)	p=0,445
Yes	-	6 (10,5%)	6 (9,7%)	



Graph 1: Present comorbidities in patients operated for endometrial carcinoma and presence of malignant diseases in next of kin.

The analysis of postoperative histopathological results showed that differences in representation of some histopathological types in menopausal and non-menopausal patients are statistically significant in the tested sample (χ^2=16.90; p=0.002) (Table **3**). The selected comparison did not confirm significant differences in representation of endometrioid type of cancer in menopausal and non-menopausal patients (Fisher's test: p=0.059) (Table **3**).

The analysis of histopathological report showed that in 6.6% of patients there was no invasion; myometrial invasion up to a half of the uterine wall was confirmed in 41.0% and more than a half was confirmed in 52.5%. invasion of the cervix was not confirmed in 71.0% of patients and it was present i 29.0% of patients (mucosa was included n only 8% while 21% had stromal infiltration). Metastatic disease (spread to the adnexa and regional nodes) was confirmed in 9.7% of patients. Histopathological findings of the surgically removed uteri showed no malignant processes in 3 patients 96.6%) (Table **4**).

According to the FIGO classification, patients with the disease limited to the body of the uterus have stage I of the disease. Depending on the degree of infiltration the stage is IA – disease is limited to the mucosa, IB – myometrial infiltration is less than a half and IC –

Table 3: Histopathological Results from Surgical Material with Regard to Menopausal Status

Characteristic	Menopause		Total (n=62)	Comparison between groups
	No (n=5)	Yes(n=57)		
Postperative histopathological type				
Negative results	1 (20,0%)	2 (3,5%)	3 (4,8%)	p=0,002 χ^2=16,90
Endometrioid	2 (40,0%)	50 (87,7%)	52 (83,9%)	
Papillary	-	2 (3,5%)	2 (3,2%)	
Serous	1 (20,0%)	3 (5,3%)	4 (6,5%)	
Villoglandular	1 (20,0%)	-	1 (1,6%)	
Endometrioid Ca				
Non-endometrioid type	2 (40,0%)	6 (10,5%)	8 (12,9%)	p=0,059
Endometrioid type	3 (60,0%)	51 (89,5%)	54 (87,1%)	

Table 4: Analysis of Postoperative Histopathological Findings with Regard to Menopausal Status

Characteristic	Menopause		Total (n=62)	Comparison between groups
	Ne (n=5)	Da (n=57)		
Myometrial invasion				
Absent	1 (25,0%)	3 (5,3%)	4 (6,6%)	p=0,059 χ^2=5,67
Up to a half	3 (75,0%)	22 (38,6%)	25 (41,0%)	
More than a half	-	32 (56,1%)	32 (52,5%)	
Parametrial invasion				
No	5 (100,0%)	54 (94,7%)	59 (95,2%)	p=0,599
Yes	-	3 (5,3%)	3 (4,8%)	
Extrauterine metastases				
No	5 (100,0%)	53(93%)	58 (93,5%)	p=0,999
Yes	-	4 (7,0%)	4 (6,5%)	
Cervical invasion				
Absent	5 (100,0%)	39 (68,4%)	44 (71,0%)	p=0,329 χ^2=2,22
Musoca	-	5 (8,8%)	5 (8,1%)	
Stroma	-	13 (22,8%)	13 (21,0%)	
Lymphovascular invasion				
No	5 (100,0%)	51 (89,5%)	56 (90,3%)	p=0,302
yes	-	6 (10,5%)	6 (9,7%)	

infiltration of the outer half of the myometrium). If the cervix is included it may be the case of cervical node infiltration – stage IIA or stromal invasion of the cervix – stage IIB) [35]. This classification provided the system for estimating the muscular and cervical invasion with transvaginal ultrasound examination. All the patients were preoperatively examined with ultrasound device Toshiba Nemio XG. The examination included transvaginal sonography using the endovaginal probe.

In the postmenopaus the endometrium is seen as a thin echogenous line surrounded by (sometimes hardly visible) hypoechoic halo [51, 52]. In transvaginal sonography, the probe is placed near the area of interest and the image is of better quality than the image obtained by transabdominal sonography. The visualization of both the depth and structural details of the endometrium is better with transvaginal sonography. Hypoechoic layer around the endometrium is composed of well vascularized compact zone [51].

Endometrial cancer is usually seen as a thickened, hypoechoic layer or as a layer of different echogenity.

In terms of differential diagnostics, it may be the image of hyperplasia or of endometrial polyp [43]. First, cross-sections are made and changes in the endometrium are monitored as well as the distance of the change from endo-myometrial border and outer borders of the uterus. The probe is then rotated in order to make cross sections from the fundus to the cervix [44]. The depth of the endometrium, echogenity of the endometrium and preservation of subendometrial hypoechoic zone are thereby estimated [43, 51, 52].

Stage IIA of cervical invasion includes the protrusion of the tumor into endocervical canal without inclusion of the stroma [43]. Stage IIB includes infiltration of cervical stroma which demands the application of radical hysterectomy and pelvic and paraaortic lymphadenectomy [43, 49]. Ultrasound examination of the cervix requires the probe to be moved backwards in order to visualize the cervix. The changes in echogenity of the cervical stroma are searched for as well as disturbances in the appearance of the cervical canal. Detection of cervical infiltration preoperatively enables planning, choosing the institution and surgeon trained in radical hysterectomy and lymphadenectomy.

Transvaginal ultrasound sonography estimates the depth of muscular invasion and presence and degree of cervical involvement. The aim of ultrasound examination is to detect tumor changes, visualize endometrium (hyperechogenic ring) and monitor the hyperechogenic layer under the endometrium (less echogenic myometrium). Penetration into this layer presents a myometrial invasion and the depth of the invasion is measured with respect to the depth of the overall uterine wall. Tumor protrusion and cervical infiltration are also monitored. Following hysterectomy, histological findings are compared to the findings obtained by ultrasound diagnostics. The findings obtained by hystopathological examination were considered gold standard.

The length, width and thickness of the uterus were measured by ultrasound. The volume of the uterus was calculated and the relationship between these parameters and the stage was monitored (patients with stage I of the disease). The measurement of the uterus and the calculated volume are not significantly associated with the stage of the disease. Average thickness of the endometrium in stage IA is 10.33mm, in stage IB it is 13.68mm,and in stage IC it is 15.67mm.The differences are not statistically significant. The length of the symptoms is also not correlated to the stage of the disease at the time of surgical treatment (Table **5**).

Localization of tumor changes could not be confirmed due to its spread to the whole uterus in 29% of patients, whereas in 25% of patients no tumor changes were detected. The most common localization of changes was the front wall of the uterus (22.6%). Myometrial invasion registered by ultrasound was present in 72.6% of patients. There was no myometrial invasion in 27.4% of patients, invasion less than 50% was observed in 51.6% and more than 50% invasion was present in 21% of patients. Cervical invasion was observed in 9.7% of patients. Average thickness of the endometrium was 14.34mm in patients with confirmed endometrial carcinoma. Average thickness of the endometrium in premenopausal patients was 14.60mm, while in postmenopausal patients it was 14.34 mm. The stages determined by ultrasound showed that 17 (27.4%) patients most probably had stage IA, 29 (46.8%) had stage IB, 10 (16.1%) had stage IC and 6 (9.7%) patients had stage IIB. Myomas were verified by ultrasound in 30% of patients, ascetic fluid was present in 6.5%, fluid in the uterine cavity was observed in 16.1% of patients. Differences in the

Table 5: Comparison of Ultrasound Measurements of the Uterus, Volume of the Uterus, Duration of Symptoms, Thickness of the Endometrium in Stages IA, IB and IC

Prameters measured by ultrasound	Stage IA (n=3)	Stage IB (n=22)	Stage IC (n=24)	Comparison
I measurement of the uterus (mm)	77,67±13,58	69,32±23,53	69,88±17,42	n.s.
II measurement of the uterus (mm)	57,33±16,62	48,95±16,5	50,75±12,22	n.s.
III measurement of the uterus (mm)	52,00±21,93	43,14±12,22	44,13±10,28	n.s.
Volume of the uterus (mm3)	261,02±206,31	174,36±156,89	176,33±140,08	n.s.
Duration of symptoms (months)	4,33±2,08	3,32±2,57	3,79±3,50	n.s.
Thickness of the endometrium (mm) US	10,33±6,51	13,68±5,52	15,67±8,03	n.s.

Table 6: Correlation of Parameters Determined by Ultrasound with Regard to Menopausal Status

Characteristic	Menopause		Total (n=62)	Comparison between groups
	Ne (n=5)	Da (n=57)		
Tumor localization by ultrasound				
No change	2 (40,0%)	14 (24,6%)	16 (25,8%)	p=0,356 χ^2=5,52
Anterior wall	-	14 (24,6%)	14 (22,6%)	
Posterior wall	-	9 (15,8%)	9 (14,5%)	
Bottom of uterus	-	5 (8,8%)	5 (8,1%)	
Complete uterus	3 (60,0%)	15 (26,3%)	18 (29,0%)	
Myometrial invasion by ultrasound				
No	2 (40,0%)	15 (26,3%)	17 (27,4%)	p=0,781
Yes	3 (60,0%)	42 (73,7%)	45 (72,6%)	
Cervical invasion by ultrasound				
No	5 (100,0%)	51 (89,5%)	56 (90,3%)	p=0,445
Yes	-	6 (10,5%)	6 (9,7%)	
Depth of myometrial invasion by ultrasound				
Absent	2 (40,0%)	15 (26,3%)	17 (27,4%)	p=0,795 χ^2=0,45
Up to a half	2 (40,0%)	30 (52,6%)	32 (51,6%)	
More than a half	1 (20,0%)	12 (21,1%)	13 (21%)	
Disease stage by ultrasound				
I A	2 (40,0%)	15 (26,3%)	17 (27,4%)	p=0,815 χ^2=0,94
I B	2 (40,0%)	27 (47,4%)	29 (46,8%)	
I C	1 (20,0%)	9 (15,8%)	10 (16,1%)	
II B	-	6 (10,5%)	6 (9,7%)	
Thickness of endometrium (mm) US	14,60±5,86	14,32±6,88	14,34±6,76	p=0,922 t=0,10
I measurement of the uterus (mm) US	74,40±26,37	69,26±18,89	69,68±19,37	p=0,690 t=0,43
II measurement of the uterus (mm) US	53,00±14,21	50,18±14,94	50,40±14,79	p=0,690 t=0,42
III measurement of the uterus (mm) US	47,80±20,52	45,00±12,60	45,23±13,19	p=0,778 t=0,30

values as well as the frequency of some categories in US findings among menopausal and non-menopausal patients are not statistically significant in the tested sample (Table **6**).

Myometrial invasion is classified into three categories: No myometrial invasion (the border between the endometrium and myometrium is clear and subendometrial hypoechogenic halo is preserved); Myometrial invasion is present but with less than 50% myometrial layer depth (the border between the myometrium and endometrium is disturbed and hyperechogenic tumor layer is present in the muscle) (Figure **1**): Myometrial invasion is present and it is above 50% (Figure **2**). Cervical infiltration is classified into two categories: No cervical infiltration and cervical infiltration is present.

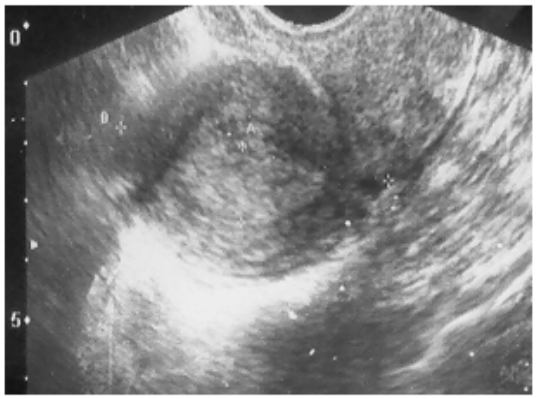


Figure 1: Myometrial infiltration, less than a half.

Figure 2: Myometrial infiltration, more than a half.

Statistical methods. The following statistical parameters were used for processing the data: arithmetic mean, standard deviation (SD) and structure index (%). Student t test was used for comparing numeric mean values between two groups of examinees. The comparison of the frequency of attributive features between the groups was done using Mantel-Haenszel Chi square test or Fisher's exact test when some of expected frequencies was less than five.

The determination of diagnostic parameters of the ultrasound method, compared to histopathological method was done by calculating sensitivity, specificity, postivie predictive value, negative predictive value and efficiency (accuracy) of the method. Sensitivity refers to accurate classificiation of positive findings, specificity is accurate classification of negative findings, positive predictive value is the possibility for the patient to have positive histopathological findings when ultrasound is positive, and negative predictive value is the possibility for the patient to have negative histopathological results when ultrasound results are negative and efficiency (accuaracy) of th emethod represents the total percentage of accurate results.

The estimation of the correlation of results between the ultrasound and histopathological findings on an operative preparation was calculated using Kappa coefficient. The threshold for statistical significance was the level estimation error less than 5% ($p<0.05$). The results of statistical analysis are presented in tables and graphs. Quantitative statistical analysis was done by a computer. Registering, grading, grouping, representation in tables and graphs was performed by Microsoft Office 2003. The estimations were performed by SPSS program 10.0 and Statcalc program EPI-INFO, version 6.

RESULTS

Myomertial invasion was confirmed by ultrasound in 77.6% cases and it was absent in 22.4%. Histopathological findings matched the ultrasound findings in 79% of cases, out of which in 100% (4 patients) invasion was absent and in 77.6% (45 patients) invasion was present (Table **1**). Compared to the estimation of invasion depth, ultrasound findings corresponded to histopatološkim findings in 47.5% (100% with invasion, 60% with invasion up to half and 31.3% with invasion more than a half) (Table **2**). Kappa coefficient value was statistically significant -0.303, P=0.001, but it points to a low degree of congruence between the ultrasound and histopathological findings. The sensitivity of the ultrasound method in the estimation of myometrial invasion in the tested sample was 77.59%, specificity was 100%, positive predictive value was 100%, and negative predictive value was 23.53%. The overall accuracy of the method was 79.03% (Table **3**).

In the estimation of the cervical infiltration, the ultrasonic findings were congruent with the histopathological findings in 67.7%, out of which invasion was absent in 90.9% (40) and present in 11.1% (Table **4**). The sensitivity of the ultrasound method in the estimation of cervical infiltration in the tested sample was 11.1%, specificity was 90.91%, positive predictive value was 33.33% and negative predictive value was 71.43%. The overall accuracy of the method was 67.74% (Table **5**).

DISCUSSION

Ultrasound diagnostics is not part of official grading system. In patients with endometrial carcinoma grading is performed surgically-histopathologically. There is a good correlation between visual estimation by the surgeon (regarding the depth of muscular invasion and cervical infiltration compared to histopathological findings [53]. The results of this estimation may be worse if tumors are of higher grade [54]. The results of intraoperative estimation may be more reliable if ex tempore diagnostics is applied [55].

Anyway, the knowledge of operative parameters (age, hitopathological type, grade) is significant in

Table 7: The Relation Between the Findings of Mometrial Invasion (Results Obtained by Ultrasound and Histopathologically)

Method	Myometrial Invasion	Histopathological findings of muscle infiltration	
		Absent (N) N	Present (N)
Ultrasound	Absent	4 (100%)	13 (22.4%)
	Present	-	45 (77.6%)

Table 8: The Relation Between the Findings Depth of Myometrial Invasion (Results Obtained by Ultrasound and Histopathologically)

Method	Depth of myometrial invasion	Histopathological findings of muscle infiltration		
		Absent(N)	Up to a half(N)	More than half(N)
Ultrasound	Absent	4 (100%)	8 (32%)	5 (15.6%)
	Up to a half	-	15 (60.0%)	17 (53.1%)
	More than a half	-	2 (8%)	10 (31.3%)

designing the operative plan. It should be remembered that there is a possibility that preoperative and postoperative findings do not correlate [56]. There is also possibility of more severe findings (curettage deals with superficial tumor parts).

Since there are no oncological centers, it is highly probable that patients from my country, who are diagnosed with endometrial carcinoma will be operated on in smaller centers or general hospital. These institutions provide standard extrafascial hysterectomy with bilateral adnexectomy with no regard to prognostic parameters which may be unfavorable for the patient.

The application of preoperative ultrasonic diagnostics and training of doctors who deal with ultrasonic diagnostics would, on a larger scale, enable the selection of patients who need a more radical operation, lymphadnectomy and a trained surgeon.

The depth of muscular invasion is a significant prognostic parameter. The possibility of the estimation

Table 9: Sensitivity, Specificity, Positive and Negative Predictive Value of Ultrasound Diagnostics in the Estimation of the Present Myometrial Invasion

Method	Sensitivity	Specificity	PPV	NPV	Accuracy	Kappa	p
Ultrasound	77.59	100.00	100.00	23.53	79.03	0.309	0.001

Table 10: The Relation Between the Findings of Cervical Infiltration (Histopathologic and Ultrasound Findings)

Method	Cervical invasion	Histopathologic findings	
		Absent (N)	Present (N)
Ultrasound findings	Absent	40 (90.9%)	16 (88.9%)
	Present	4 (9.1%)	2 (11.1%)

Table 11: Sensitivity, Specificity, Positive and Negative Predictive Value of Ultrasound Diagnostics in the Estimation of the Present Cervical Infiltration

Method	Sensitivity	Specificity	PPV	NPV	Accuracy	Kappa	p
Ultrasound findings	11.11	90.91	33.33	71.43	67.74	0.025	0.807

of the presence/absence of myometrial invasion is particularly significant in patients who have not yet reproduced and in whom conservative treatment can be performed [50]. The conservative treatement may be undertaken in patients who have not yet had deliveries and who have low grade endometrioid tumor type, without myometrial invasion. Medroxyprogesterone-acetate is administered for about three months and then curettage and histopathological evaluation are repeated. The response to this therapy is about 76%. After that, patients without residual tumor are submitted to assisted reproduction [50, 57, 58]. The increase in the depth of muscular invasion increases the frequency of lymph node metastases and shortens the survival rate [30].

In our study, the specificity and negative predictive value in the estimation of the presence/absence of invasion was 100%. This means that ultrasound would be very reliable if conservative treatment was chosen. The estimation of the degree of invasion was less accurate, sensitivity was 77.59%, negative predictive value was 23.53% and it decreased with the increase in the depth of the invasion. Relevant studies show that in the estimation of the myometrial depth the sensitivity is 69.4-92.3% and specificity 70.6-90% [28,44-48].

The estimation of the cervical infiltration is much more complex and problematic and in our study the sensitivity of the ultrasound method was 11.1%, whereas specificity was 90.91%. Savitski and Savelli reported that the sensitivity of the ultrasound method was 86.4-93%, whereas specificity was 92-93%. Ultrasonic diagnostics of cervical infiltration was more effective in distinguishing patients without infiltration but it was significantly less effective in estimating the presence of cervical infiltration. The ultrasonic diagnostics of our patients was performed by several diagnosticians, changes in cervical structure were discrete and detection of cervical infiltration by ultrasound is a new procedure in our practice. It is possible that the results would be better with a smaller number of diagnosticians and more examinations, greater number of patients and with more practice.

CONCLUSION

The ultrasound may be used in the estimation of the depth of myometrial invasion and there is significant congruence with the histopathological findings. There is no correlation between the ultrasound findings and the histopathological results concerning the cervical infiltration.

REFERENCES

[1] Sankaranarayanan R, Felay J. Word-wide burden of gynecological cancer: the size problem. Best Pract& res Clin Obstet Gynecol 2006; 20: 207-25.

[2] Jemal A, Bray F, Center M, Ferlay J, Ward E, Forman D. Global cancer statistics. CA:Cancer J Clin 2011; 61(2): 69-90. http://dx.doi.org/10.3322/caac.20107

[3] Cancer incidence and Mortality in Central Serbia 2004. Cancer registry of Central Serbia. Report No 5 Beograd, 2007.

[4] Milenković V, Sparić R, Atanacković J. Methods of screening for endometrial cancer. Srp Arh Celok Lek 2005; 133(3-4): 199-201.

[5] Stojanović S, Djorđević B, Ljubenović N, Pavlović Z. Preoperativni i postoperativni histopatološki nalaz kod pacijentkinja sa karcinomom endometrijuma. Apolinem medicum et aesculapium 2008; 3-4(6): 37-42.

[6] Schmeler K, Soliman P, Sun C, Slomovitz B, Gershenson, D, Lu K. Endometrial cancer in young, normal-weight women. Gynecol Oncol 2005; 99(2): 388-92. http://dx.doi.org/10.1016/j.ygyno.2005.06.029

[7] Parslov M, Lidegaard O, Klintorp S, *et al*. Risk factors among young women with endometrial cancer: a Danish case-control study. Am J Obstet Gynecol 2000; 182(1): 23-9. http://dx.doi.org/10.1016/S0002-9378(00)70486-8

[8] Manchana T, Khemapech N. Endometrial Adenocarcinoma in Young Thai Women. Asian Pacific J Cancer Prev 9: 283-86.

[9] Gallup DG, Stock RJ. Adenocarcinoma of the endometrium in women under 40 years ago and younger. Obstet Gynecol 1984; 64: 417-20.

[10] Mahovlić V. Endometrij U, Ćorušić A, Babić D, Šamija M, Šobat H. Ginekološka onkologija. Medicinska Naklada Zagreb 2005; 42-47.

[11] Pavlović S. Citopatologija tela materice. U:Pavlović S. Citopatologija ženskih genitalija. Niš 1980; pp. 218-34.

[12] Broso P. Cervico-vaginal and endometrial cytology in the screening for endometrial cancer. Minerva Ginecol 1995; 47(11): 503-7.

[13] Smith-Bindman R, Kerlikowske K, Feldstein VA, *et al*. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. JAMA 1998; 280(17): 1510-7. http://dx.doi.org/10.1001/jama.280.17.1510

[14] Ćurčić A, Đurđević S, Mladenović–Segedi LJ, Grujić Z, Višnjevac N. Ultrazvučni skrining karcinoma endometrijuma kod žena u postmenopauzi bez simptoma. Med Pregl 2009; LXII (5-6): 263-67.

[15] Langer RD, Pierce JJ, O Hanlan, Johnson S, *et al*. Transvaginal ultrasonography compared with endometrial biopsy for detection of endometrial disease. N Engl J Med 1997; 337: 1792-98. http://dx.doi.org/10.1056/NEJM199712183372502

[16] Fleischer AC, Wheeler JE, Lindsay Y, *et al*. An assesment of the value of ultrasonographic screening for endometrial disease in postmenopausal women without symptoms. Am J Obstet Gynecol 2001; 184: 70-75. http://dx.doi.org/10.1067/mob.2001.111088

[17] Lo SS, Cheng DK, NgTY,Wong LC, Ngan Hy. Prognostic significance of tumor markers in endometrial cancer. Tumor Biol 1997; 18 (4): 241-9. http://dx.doi.org/10.1159/000218037

[18] Takano M, Kikuchi Y, Asakawa T, *et al*. Identification of potential serum markers for endometrial cancer using protein expression profiling. J Canc Res Clin Oncol 2010; 136(3): 475-81. http://dx.doi.org/10.1007/s00432-009-0680-7

[19] Grahovac S. Komparacija pre-i postoperativnog histopatološkog nalaza kod pacijentkinja sa histerektomijom. Magistarski rad, Niš, Srbija. Univerzitet u Nišu, 2006.

[20] Kurman RJ, (Ed). Blaustein´ pathology of the female genital tract, 5th ed. New York:Springer-Verlag. 2002; pp. 501-56.

[21] Obermair A, Geramou M, Gucer F, *et al*. Endometrial cancer :accuracy of the finding of a well diferentiated tumor at dilatation and curettage compared to the findings at subsequent hysrectomy. Int J Gynecol Cancer 1999; 9: 383-6.
http://dx.doi.org/10.1046/j.1525-1438.1999.99050.x

[22] Ilić-Forko J. Karcinom trupa materice. U: Ćorušić A, Babić D, Šamija M, Šobat H. Ginekološka onkologija. Medicinska naklada Zagreb 2005; 229-34.

[23] Simonds I. Ultrasound, hysteroscopy and endometrial biopsy in the investigation of endometrial cancer. Rev Gynecol Perinatal Pract 2003; 3(1): 11-15.

[24] Bradley WH, Boente MP, Brooker D, *et al*. Hysteroscopy and cytology in endometrial cancer. Obstet Gynecol 2004; 104: 1030-3.
http://dx.doi.org/10.1097/01.AOG.0000143263.19732.18

[25] Gutman G, Almong B, Lessing J, Bar-Am A, Grisaru D. Diagnosis of endometrial cancer by hysteroscopy does not increase the risk for microscopic extrauterine spread in early-stage disease. Gynecolo Surg 2005; 2: 21-23.

[26] Kong A, Simera I, Collingwood M. Adjuvant radiotherapy for stage I endometrial cancer:systematic reiview and meta analysis. Ann Oncol 2007; 18: 1595-4.
http://dx.doi.org/10.1093/annonc/mdm066

[27] Ruangvutilert P, Sutanawibul A, Sunsaneevithayakul P, Borioonhirunsam D, Chuenchom T. Accuracy of transvaginal ultrasound for the evaluation of myometrial invasion in endometrial carcinoma. J Med Assos Thai 2004; 87(1): 47-52.

[28] Szabo I, Szantho A, Nemet J, Csapo Z, Szirmai K, Papp Z. Assessment of myometrial invasion in endometrial cancer by transvaginal ultarsonography. Orv Hetil 1997; 138(21): 1323-7.

[29] Creasman WT, Odicino F, Maisoneuve P, *et al*. 26 th Annual Report on the results of treatment in Gynecelogical cancer. Int J Gynecol obstetr 2006; 95(1): 105-44.

[30] Creasman WT, Morow CP, Bundy BN, Homesly HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer in the eldery. GOG 033. Cancer 1987; 60: 2035-41. 95

[31] Abeler WM, Kjorstad KE. Endometrial adenocarcinoma in Norway. A study of total population. Cancer 1991; 67: 3093-4003.
http://dx.doi.org/10.1002/1097-0142(19910615)67:12<3093::AID-CNCR2820671226>3.0.CO;2-L

[32] Stanojević Z. Maligni tumori genitalnih organa žene. U: Osnovi kliničke onkologije 2009; 196-206.

[33] Taylor RR, Zeller J, Lieberman RW, O Connor DM. An analysisis of the two versus three grades for Endometrial carcinoma. Gynecol Oncol 1999; 74: 3-6.
http://dx.doi.org/10.1006/gyno.1999.5422

[34] Scholten A, Creutyberg CL, Noordijk EM, Smit VM. Long term outcome in endometrial carcinoma favors a two -instead of three-tiered grading system. Int J Radiat Oncol Biol Phys 2002; 52 (4): 1067-74.
http://dx.doi.org/10.1016/S0360-3016(01)02710-9

[35] Creasmann WMD. Controversis in FIGO staging of corpus cancer. J Gynecol Oncol 2001; 6: 257-59.

[36] Kesić V. Određivanje stadijuma i prognostički faktori za endometrijalni karcinom. Zbornik predavanja Karcinom endometrijuma, 30 mart, 2007, Beograd Srbija.

[37] Aaron W, Sightler S, Markoe A, *et al*. The prognoctic significance of surgical staging for carcinoma of the endometrium. Gynecol Oncol 1992; 45(2): 142-46.
http://dx.doi.org/10.1016/0090-8258(92)90276-O

[38] Goff BA, Rise LW. Assesment of depht of myometrial invasion in endometrial adenocarcinoma. Gynecol Oncol 1990; 38: 46-48.

[39] Rose P. Endometrial carcinoma. N Engl J Med 1996; 9(335): 640-49.
http://dx.doi.org/10.1056/NEJM199608293350907

[40] Fleischer AC, Kalemeris GC, Machin JE, Entman SS, James JR. Sonographic deciption of normal and abnormal endometrium with histopathologic correlation. J Ultrasound Med 1986; 8(5): 445-52.

[41] Karlsson B, Granberg S, Wikland M, *et al*. Transvaginal ultrasonography of the endometrium in women with postmenopausal bleeding a Nordic multicenter study. Am J Obstet Gynecol 1995; 172: 1488-94.
http://dx.doi.org/10.1016/0002-9378(95)90483-2

[42] Goldstein SR. The role of transvaginal ultrasound or endometrial biopsy in the evaluation of the menopausal endometrium. Am J Obstet Gynecol 2009; 201(1): 5-11.
http://dx.doi.org/10.1016/j.ajog.2009.02.006

[43] Kurjak A, Kupešič S,Bauman R,eds. Zloćudni tumori materice u : Kurjak A i suradnici. Ultrazvuk u ginekologiji i porodništvu Zagreb 2000; pp. 43-58.

[44] Savelli L, Ceccarini M, Ludovisi M, *et al*. Preoperative local staging of endometrial cancer : transvaginal sonography vs. magnetic resonance imaging . Ultrasound Obstet Gynecol 2008; 31: 560-66.
http://dx.doi.org/10.1002/uog.5295

[45] MolinaG, Dell'Elce C, Libanori E, Preziuso F, Trompeo P. Transvaginal echographic evaluation of myometrial invasion in patients in patients with endometrial cancer. Minerva Ginecol 1996; 48(6): 239-42.

[46] Fishman A, Altaras M, Bernheim J, Cohen I, Beyth Y, Tepper R. The value of transvaginal sonography in the preoperative assesment of myometrial invasion in high and low grade endometrial cancer and in comparasion to frosen section in grade 1 disease. Eur J Gynaecol Oncol 2000; 21(2): 128-30.

[47] Sawicki W, Spiewankiewicz B, Steinmachow J, Cendrowski K. The value if ultrasonography in preoperative assessment of selected prognostic factor in endometrial cancer. Eur J Gynaecol Oncol 2001; 24(3-4): 293-8.

[48] Baekelandt M, Castiglione M. Endometrial carcinoma: ESMO Clinical recommendations for diagnosis, treatment and follow–up. Ann Oncol 2009; 20(4): 29-31.

[49] Ayhan A, Taskiran C, Celik C, Yuce K. The long term surwival of women with surgical stage II endometroid type endometrial cancer. Gynecol Oncol 2004; 93(1): 9-13.
http://dx.doi.org/10.1016/j.ygyno.2003.11.018

[50] Kaku T, Yoshikawa H, Tsuda H, *et al*. Conservative therapy for adenocarcinoma ans atypical endometrial hyperplasia of the endometrium in young women:central pathologic review and treatment outcome. Cancer Lett 2001; 167(1): 39-41.
http://dx.doi.org/10.1016/S0304-3835(01)00462-1

[51] Kurjak BF, Kupešić S, Kurjak A, Eds. Anatomija male zdjelice u žene. Ultrazvuk u ginekologiji i porodništvu Zagreb 200: 1-11.

[52] Davidson KG, Dubinsky TJ. Ultrasonographic evaluation of the endometrium in postmenopausal vaginal bleeding. Radiol Clin North Am 2003; 41(4): 769-80.
http://dx.doi.org/10.1016/S0033-8389(03)00060-5

[53] Teefey SA, Stahl JA, Middleton WD, *et al*. Local staging of transvaginal and intraoperative sonography and gross visual inspection. Am J Rentgenol 166: 547-52.

[54] Goff BA, Rise LW. Assesment of depht of myometrial invasion in endometrial adenocarcinoma. Gynecol Oncol 1990; 38: 46-48.

[55] Noumoff JS, Menzin A, Mikuta J, Lusk EJ, Morgan M, LiVolsi VA. The ability to evaluate prognostic variables on frozen section in hysterectomies performed for endometrial carcinoma. Gynecol Oncol 1991; 42: 202-208. http://dx.doi.org/10.1016/0090-8258(91)90346-7

[56] Eltabbakh GH, Shamonki J, Mount SL. Surgical stage, final grade, and survival of women with endometrial carcinoma whose preoperative endometrial biopsy shows well-differentiated tumors. Gynecol Oncol 2005; 99(2): 309-12. http://dx.doi.org/10.1016/j.ygyno.2005.06.010

[57] Ramirez PT, Frumovitz M, Budurka DC, Sun CC, Levenback C. Hormonal therapy for the management of grade 1 endometrial adenocarcinoma: a literature review. Gynecol Oncol 2004; 95(1): 133. http://dx.doi.org/10.1016/j.ygyno.2004.06.045

[58] Mao Y, Wan X, Chen Y, Lv W, Master XX. Outcomes of conservative therapy for young women with early endometrial adenocarcinoma. Fertylity and sterility 2010; 91(1): 283-85.

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http://dx.doi.org/10.6000/1927-7229.2012.01.01.4