Preoperative discrimination between malignant and benign adnexal masses with transvaginal ultrasonography and colour blood flow imaging

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Summary

Background: Ovarian cancer is one of the causes of death in women, and in about 70% of cases is recognized only in advanced stages. This study was undertaken to evaluate distinctive values of transvaginal and color Doppler ultrasonography in differentiating malignant and benign adnexal masses through analysis of ultrasonic morphological features of malignancy and estimation of location and intensification of angiogenesis as well as values of resistance of flow in examined masses.

Patients and methods: 329 women with malignant and benign adnexal masses underwent ultrasonographic and colour Doppler examination 1-5 days before surgery (laparotomy, laparoscopy) thus allowing histological verification of diagnosis. The ultrasonographic structure was assessed using a morphological scoring system devised by Sassone [4], Jain [5] and Benacerraf [6]. Regions showing vasculature, especially within septae and solid parts of tumours were examined by means of transvaginal colour Doppler. Location and intensification of angiogenesis as well as resistance index (RI) were investigated. Sensitivity, specificity, PPV and NPV of both techniques were assessed. Statistical analysis of obtained data were based on the Student's t test; $p < 0.05$ level was considered significant.

Results: Postoperatively 255 (77.5%) benign and 74 (22.5%) malignant tumours were seen. In the group of benign masses the average age of women was 42.6±12.3 and in the malignant it was 53.1±12.6 ($p<0.0001$). The transverse dimension of benign lesions was 77.2±19, whereas for malignant it was 107.0±31 ($p<0.0001$). Benign tumours in 63.0% were cystic, in 26.0% mixed cystic-solid and in 11.0% solid echostructures while in malignant they were respectively, 6.8%, 56.8% and 36.4% ($p<0.0001$). Doppler flow within the tumour was 74.5% in benign and 98.6% in malignant masses ($p<0.0001$). In benign lesions homogenous superficial or peripheral vasculature was visualized, and in the majority of cases (82.7%) it was of medium intensification. However in malignant central, peripheral or mixed vascularisation, in the majority intensified character was found. Average value of the resistance index in all benign masses amounted to 0.77±0.14, however in malignant it was 0.39±0.07 ($p<0.0001$).

Conclusions: We contend that complete ultrasonographic estimation of ovarian neoplasms outside the qualification of structural details should include Doppler analysis of vasculature parameters. Most important is the qualification of resistance of flow, and location and intensification of vascularisation in examined masses which permit the differentiation of malignant and benign lesions. Preoperatively recognizing malignant processes with colour Doppler ultrasonography shows higher accuracy, specificity and PPV.

Key words: Ovarian cancer; Transvaginal ultrasonography; Colour blood flow imaging.

Introduction

Among all malignant neoplasms of the female genital tract ovarian carcinoma constitutes the main cause of death, and the general 5-year survival amounts to approximately 35%. Length of survival depends on the extensiveness of disease from the time of beginning medication. General mortality exceeds 80%, and bad outcomes are due to late detection [1]. About 70% of the cases of ovarian cancer are diagnosed in advanced stage, when intraperitoneal spread, oppressing signs, and infiltration of other organs occur. Therefore early detection of ovarian tumors and the possibility of preoperative differentiation are extremely important to improve this situation.

Among the methods that currently may detect ovarian cancer in an early period, the most important are: serum CA 125 levels and modern imaging techniques, especially transvaginal ultrasonography and color Doppler ultrasonography (recently with the application of ultrasound contrast agents).

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The main problem in ultrasound screening of ovarian cancer is detection of large numbers of benign lesions (false positive diagnosis), causing approximately 1-5% of these women to be operated on, while cancer is detected in only 0.1% of cases. Regarding the risk of surgical complications it seems that benefit of such procedure is somewhat doubtful. The proper approach is to operate on only highly suspected lesions. Thus we utilize all preoperative techniques, and most of all, the least invasive i.e., ultrasonography. Introduction of colour Doppler ultrasonography has permitted the improvement of diagnostic specificity. Besides certain characteristic tumor morphology, it renders visualization and determination of characteristics of neovascularization in the septae and solid elements. Transvaginal ultrasonography (TVS) especially in association with colour Doppler (TVCD) has high sensitivity, which fluctuates between 80%-100% [2]. Diagnostic specificity of endosonography alone amounts to 80%-85% [3]. The addition of colour Doppler upgrades it, and reaches even 100% according to some authors [2].

The aim of our study was to compare the diagnostic value of "grey scale" transvaginal ultrasonography and the colour Doppler modality in the differentiation of benign and malignant adnexal tumors throughout the analysis of morphologic, ultrasonic characteristics of malignancy and estimation of localization, intensity of angiogenesis and resistance index in vessels inside the tumor.

Materials and Methods

Three hundred and twenty-nine patients with adnexal masses were examined by transvaginal "grey scale" ultrasonography and with color Doppler imaging. All patients were scanned by the same ultrasonographer (W.S.) with a Siemens Sonoline Versa Pro ultrasonographic system equipped for color Doppler imaging. A 6.5-MHz intravaginal probe was used, incorporating a field of view of 90°. The wall filter was set at 50 Hz and the pulsed Doppler sample volume size was set at 2 mm. Initially an extensive gray-scale morphologic examination with attention to different morphologic criteria was performed. Women in premenopausal age were examined on the 7.8 day of cycle (2-14 days) to exclude luteal flow in the corpus luteum. Examinations were performed 1-5 days before surgery (laparoscopy, laparotomy). Ultrasonic morphology was assessed by incorporating a scoring system devised by Sassone [4], Jain [5] and Benacerraf [6]. Malignancy was suspected in tumors with solid or mixed, cystic-solid echotexture, faded borders, thick (> 3 mm) septa and solid papillary projections into the cyst cavity from the cyst wall of > 3.0 mm in length. Ascertainment of free fluid in the peritoneal cavity was the sufficient parameter to diagnose a malignant process. Ascites was judged to be present if there was ≥ 50 mm free fluid in the pouch of Douglas. Subsequently the entire tumor was surveyed by color Doppler imaging. The power, gain, and pulse repetition frequency were initially adjusted for maximum sensitivity of low blood flow states. The lowest velocity signals were filtered out by gradually increasing the pulse repetition frequency, and flow analysis was concentrated on the signals of highest velocity. A pulsed Doppler range gate was placed over these areas to obtain flow velocity waveforms. Minute adjustments were made to the angle of the probe until the audible and visible signal was optimal. This was considered to be the optimal angle for the probe at that particular location, and no angle correction was made. Recorded parameters included resistance index, localization, and intensity of vascularisation. Superficial vascularization meant the presence of blood vessels on the tumor capsule, peripherally, where a Doppler signal was detected within the solid tumor areas or within the septae. A subjective semiquantitative assessment of the amount of blood flow (area and color scale) within the septa, cyst walls, solid tumor areas, or ovarian stroma was made. We looked for such a cross-section, wherein the number of focuses revealing colored Doppler signals within the lesion was the biggest. It permitted determination of vascular intensity which responded to the mean number of focused colored Doppler signals within one of the ultrasonic cross-sections. Vascularization was considered intense when the number of focused images revealing colored signals was more than five (moderate flow or highly vascular, with marked blood flow according to color Doppler imaging) and mediocre when below or equal to 5 (no flow or minimal blood flow). The cut-off point value of the resistance index for discrimination of malignancy was set at 0.50. Additional Doppler criterion of malignancy was ascertainment of intense, peripheral or central angiogenesis within the septa or solid parts of a tumour. Obtained data were correlated with histopathological surgical findings. Multiple photographic prints were made of relevant structures and Doppler signals. Sensitivity, specificity, accuracy, positive and negative predictive values (PPV, NPV) of both ultrasonographic methods was estimated. Statistical calculations were carried out with the software package *STATISTICA* version *5* (by StatSoft) for Windows. Analysis of results was performed by calculation of the relevant difference among percentage values with the Yates corrected chi-square test or the Fischer exact test. The means of unpaired groups (benign versus malignant) were compared with the Mann-Whitney U test or the Student's t test.

Results

Postoperatively 329 masses were analyzed. At surgery 255 (77.5%) masses were found to be benign, and 74 (22.5%) were malignant. Characteristics of scrutinized tumours are given in Table 1.

Among malignant neoplasms first stage was ascertained in 20 (27.0%) cases, second in nine (12.2%), third in 42 (56.7%), and fourth stage in three (4.1%) cases (Figure 1). The patient's age with benign masses ranged from 15 to 88 years with a mean of 42.6±12.3, and malignant from 19 to 81, 53.1±12.6, respectively. Patients with malignant masses were significantly older than patients with benign masses. The diameter of benign lesions ranged from 35 to 260 mm, with a mean of 77.2±19, and malignant from 36 to 368 mm, with a mean of 107.0±31 (significantly different, $p<0.0001$).

Benign masses were cystic (unilocular or multilocular with smooth internal walls or with minute solid elements < 3 mm in length) in 63% of cases, however 26% were multilocular cystic-solid, compared with 56.8% of malignant masses ($p<.0001$) and only 11% were solid compared with 36.4% of malignant lesions ($p<.0001$). Only 6.8% of malignant masses had cystic echostructures (multilocular, with minute solid projections < 3 mm in length - two cases of serous and one of endometrioid cystadenocarcinoma.). The presence of measurable arterial blood flow within the tumor was found in 74.5% of benign adnexal tumours, whereas in 98.6% of malignant masses ($p<.0004$). In benign masses most often superficial and peripheral vascularization were visualized, accordingly 51.7% and 45.4% of cases, in the majority (82.7%) with mediocre intensity. Whereas among 74 malignant masses in 98.6% of cases vascularization of at least one kind was found: central or peripheral. In 37.2% of malignant masses one of these two kinds of vasculari-

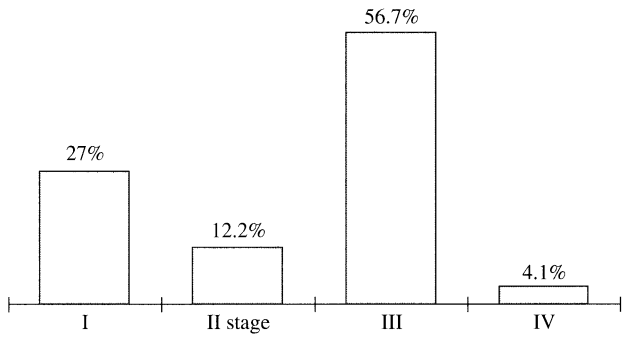

Figure 1. — FIGO stages of analysed adnexal malignant masses.

Table 1. — *Pathological diagnoses of benign and malignant neoplasms.*

Histologic diagnosis	N	%
Benign		
Simple serous cyst	72	28.2
Endometrial cyst	44	17.3
Dermoid cyst/cystic teratoma	39	15.3
Hemorrhagic cyst	27	10.6
Hydrosalpinx	26	10.2
Mucinous cystadenoma	20	7.8
Serous cystadenoma	12	4.7
Fibroma	7	2.7
Brenner tumor	6	2.4
Fibrothecoma	2	0.8
Total benign	255	100.0
Malignant		
Serous cystadenocarcinoma	30	40.5
Endometrioidal cystadenocarcinoma	21	28.4
Granulosa cell tumor	8	10.8
Mucinous cystadenocarcinoma	7	9.5
Dysgerminoma	5	6.7
Immature teratoma	3	4.1
Total malignant	74	100.0

Table 2. — *Age of patients and ultrasonographic parameters of examined adnexal masses.*

Analysed parameter	Benign (n=255)	Malignant (n=74)	p
Age (mean±SD)	42.6±12.3	53.1±12.6	<0.0001
Diameter (mm, mean±SD)	77.2±19	107±31	<0.0001
Unilocular-entirely cystic (%)	32.3	0	–
Multilocular-entirely cystic (%)	7.8	0	–
Unilocular-cystic with minute solid elements (%)	9.9	6.8	=0.2699
Multilocular. cystic with minute solid elements (%)	13.0	0	–
Cystic-solid with papillary projections (%)	26.0	56.8	<0.0001
Solid (%)	11.0	36.4	<0.0001
Presence of vascularisation (%)	74.5	98.6	<0.0004
Superficial vascularisation (%)	51.7	0	–
Peripheral vascularisation (%)	45.4	90.7	<0.0001
Central vascularisation (%)	11.9	72.1	<0.0001
Mixed vascularisation (%)	9.0	62.8	<0.0001
Weak and medium intensification of vasculature	82.7	15.7	<0.0001
Intense vascularisation	17.3	84.3	<0.0001
RI (mean±SD range)	0.77±0.14 (0.32-1.00)	0.39±0.07 (9.20-0.78)	<0.0001

zation was displayed, and in 62.8% of cases mixed vascularization was ascertained. Peripheral localization of angiogenesis was visualized most often (90.7% of malignant cases), whereas it was central in 72.1%, and in 84.3% of intense character. In this group of tumours no superficial vascularization was recorded. In contrast to benign masses malignant tumours significantly more often showed mixed vascularization respectively, 9% and 62.8%, p<0.0001. An average value of the Pourcelot index in benign masses amounted to 0.77(0.14, however in malignant masses it was 0.39±0.07 (p<0.0001) (Table 2).

Mathematical analysis comparing distinctive indices of both ultrasonic techniques revealed absence of any statistically significant differences between sensitivity and negative predictive value of malignant processes. It means that the value of grey scale ultrasonography and coloured techniques in affirming malignant processes – also in setting probabilities of absence of malignancy in negative outcome examinations – is approximate (similarly, low numbers of false negative errors). Statistically significant differences were ascertained in relation to the distinctive accuracy, specificity and positive predictive value of both methods. They varied markedly (in favour of TVCD) in excluding malignant processes and also in setting probabilities; patients with positive Doppler examination results (present Doppler malignancy attributes) had ovarian cancer (fewer false positive errors in TVCD) (Table 3).

Table 3. — *Composition of statistical coefficients comparing both ultrasonographic methods in diagnosing malignant adnexal masses.*

Statistical coefficient	TVS	TVCD
Sensitivity (%)	86.5	93.2 †
Specificity (%)	67.5	94.5 *
Accuracy (%)	71.7	94.2 *
PPV (%)	44.7	83.1 *
NPV (%)	96.1	98.0 †

† - NS; * - p < 0.005.

Comment

High-resolution transvaginal ultrasonography allows precise visualization of many tumoural structure details, which are utilized in the elaboration of ultrasonic morphological malignancy criteria of masses. They comprise multilocularity, mixed solid-cystic echostructures, faded outlines, huggermugger architecture, septae of distinct thicknesses (usually above 3 mm) and echogenicity, and solid hyperechogenic inner wall papillary projections. Tumours revealing at least two of the foregoing characteristics qualify as suspected lesions. Rottem *et al.* [7] advocated conformity of purely morphological criteria, suggesting that malignancy is closely associated with a solid or mixed cystic-solid echostructure, occurring in papillary projections and that diameters of tumours are over 100 mm. However thin septa, below 3 mm in thickness and multilocularity are significantly more often observed in benign lesions.

It is known that because of the considerable changeability of ultrasonic morphology of adnexal masses, many benign lesions reveal morphological attributes of malignancy, making a comparatively big number of false positive diagnoses unavoidable (which lowers specificity). Therefore frequent problems with ultrasonographic differentiation between malignant and benign lesions have occurred. However some ultrasonic parameters are rather characteristic of malignant masses. For example, a tumor diameter above 100 mm, except unilocular cysts, usually betrays its malignant character [8]. Analysis of our mate-

rials revealed that malignant masses more significantly showed larger diameters. The mean diameter of benign masses was 77.2 (range 35-260) and of malignant 107 mm (range 36-368). Similar data have been published by Anandakumar *et al.* [9]. In their investigations the mean diameter of benign tumours was 85.7 mm, whereas for malignant it was 152 mm (range 84-270).

Malignant lesions often revealed mixed cystic-solid or solid structures, with hypoechogenic foci coming from edematous tissue, bloody effusions and necrosis. In our material malignant masses compared to benign revealed significantly more complex cystic-solid and solid structures (respectively 93.2% and 37%). Solid papillary projections, particularly well visible endosonographically, with the exception of dermoid cysts, usually betrays malignancy [10]. There is an opinion that these structures frequently can not be viewed even in KTP and NMR and the newest publications comparing transvaginal ultrasonography and NMR in the diagnosis of ovarian cancer reveal superior specificity of the former [11, 12]. Benign tumours have mostly cystic echostructures, with thin septa. It should be noted that in our material benign masses revealed predominantly (63%) cystic echostructures. To make ultrasonic criteria of malignancy most objective, Sassone *et al.* [4], and Benacerraf *et al.* [6] devised a morphological scoring system for estimations of adnexal masses. These parameters included inner structures and thickness of walls and septa as well as the echogenicity of lesions. Employing that system they correctly diagnosed all malignant adnexal masses, attaining a sensitivity of 100%, a specificity of 83%, and positive and negative predictive value accordingly of 37% and 100%. Kurjak and Predanic [2] using a similar scoring system relying on the estimation of internal borders, presence and character of septa, presence of papillary projections, echogenicity of tumor tissue and its volume with a cut-off value for postmenopausal women equal to 9 cm^3 achieved a sensitivity of 92% and a specificity of 94.8%. Despite such perfect capabilities of precise estimations of tumour morphology in endosonography we still cannot distinguish masses of borderline malignancy from cystadenocarcinoma, or differentiate epithelial tumours from those coming from procreative cells, particularly when they reveal a complex structure. Ascertainment of exact diagnosis is difficult in cases of borderline masses as well as dermoid and hemorrhagic cysts, which frequently reveal all ultrasonographic attributes of malignancy.

Doppler ultrasonography can be a technique, which permits specific diagnosis in cases where an ultrasonic, morphological scoring system is inadequate. Kurjak [13] first used it in the estimation of circulation in the small pelvis, and in differentiating adnexal lesions by measuring vascular resistance. Bourne *et al.* [14] to measure circumferential resistance, first used the pulsatility index - PI. Fleischer [15] which showed a correlation between vasculature of ovarian cancer with the result of the histologic investigation. He states that in most malignant masses the PI value is below 1.0 (in his own investigations such value was ascertained in 80% of malignant masses).

Kurjak [16], for estimations of tumour vasculature, prefers the Pourcelot Index - RI. A value ≤ 0.40 is a useful coefficient to estimate malignancy. Among benign masses (RI below 0,40) he ascertained only in 0.16% of lesions, instead in 96.4% in malignant. Similarly Hata [17] showed low RI values, equal to 0.46 ± 0.11 in all ovarian cancers. A little higher value was ascertained by Hamper [18]. In benign lesions he reached a RI value $\geq 0.77\pm0.22$, whereas in malignant lesions it was $\leq 0.50\pm0.17$. These deviations point out the existence of certain common values in malignant and benign masses that can influence preoperative estimations of tumour. Also it could be the source of error, both false positive and negative, especially if we rely on only one flow parameter. Low pressure wave-forms sometimes are encountered in dermoids, endometrial and hemorrhagic cysts, thecomas and in inflammatory lesions.

During analysis of the above indices of flow it should be remembered that examinations of premenopausal women should be performed in the follicular phase of the menstrual cycle (first 10 days, best between 3-10 days to avoid measurement of luteal flow). Data quoted from the literature have been covered and found in our own investigations. Among benign ovarian masses the average value of RI was 0.77 (0.32-1.00) and for malignant 0.39 (0.20-0.78), and it was statistically significant; somehow in each type of tumour these values showed large variability.

Most authors lean towards the belief that connecting the results of transvaginal "grey scale" ultrasonography with the estimation of Doppler flow permits better qualification of the kind of examined ovarian mass and in most cases a specific diagnosis. Kurjak and Predanić [2] in 1992 proposed a scoring system of estimation which uses both techniques. In their investigations they reached a sensitivity of 97.3% and a specificity of 100%. Their system embraced qualification of vascular location. They proved that malignant lesions in comparison to benign more often showed central vasculature. Timor-Tritsch *et al.* [19] used the morphological estimation proposed by Sassone [4] and colour Doppler and reached a sensitivity of 87.5% and a specificity of 100%. Of much importance was the ascertainment that all masses with no vascularization were benign. We take the position that it is better not to comply stiff RI or PI values as the only parameter differentiating benign and malignant lesions. Rather estimation of flow should be analysed together with morphological criteria.

Numerous authors examining adnexal masses warn that appraisal for surgery should not be based exclusively on Doppler parameters of flow. To improve the preoperative estimation Fleischer *et al.* [20] proposed Doppler multifactor analysis in adnexal mass assessment. Besides qualification of PI and RI it stresses intensification and location of pathological vasculature, presence or lack of diastolic notch in Doppler waveforms, and also measurement of speed of flow (PSV – peak systolic velocity, TAMX – time averaged maximum velocity). He proved that a broader, multifactor analysis permits identification of malignant processes in 90%, with a sensitivity of 83%

and a specificity of 95%. Many authors introduced the above criteria and proved that benign lesions show largely peripherial and superficial vasculature with the presence of a diastolic notch, whereas malignant masses show scattered vasculature (often central), situated in the septa and solid elements [21]. The average value of RI in benign masses usually reveals a score of 0.56 and in malignant 0.33. At cut-off values of RI $\leq$ 0.40 diagnostic sensitivity was 82.1% with specificity 97.4%, whereas positive predictive value was 94.1% and negative predictive value 91.6%. These data are confirmed in our study, in which 51.7% of benign tumours showed superficial vasculature, and 45.4% peripherial vasculature.

Alcazar *et al.* [22] in benign and malignant lesions registered angiogenesis respectively in 64.8% and 95.7%. Most (77.3%) malignant masses showed central vasculature. Among 87.7% of benign tumours he determined peripheral vasculature. Investigating intensification of angiogenesis in malignant lesions, he detected an average of 7.5 colour coded areas within one section of the ultrasound image, instead in benign only of 1.4 (over a fivefold difference). Similar values were noted in our study, in which we showed vasculature in 74.5% of benign and in 98.6% of malignant masses (a significant difference). Central location of vasculature was identified in 72.1% of malignant and in only 11.9% of benign lesions, which was also statistically significant. Intensification of vascularization in malignant masses was significantly higher. In Alcazar's *et al.* investigations [22] the average RI value in malignant lesions was 0.39 and in benign 0.64. Thus confirming our coefficients, respectively 0.39 and 0.77 ($p < 0.0001$).

It appears that the colour Doppler technique due to high specificity (in our own study reaching 94.5%) and negative prognostic value equal to 98.0%, permits us to sort out cases of minimal probability of malignancy. Due to these suitable operating techniques (laparoscopy, laparotomy) can be choosen. It follows that in unilocular cysts of diameters up to 50 mm, the risk of malignancy is very low. Additionally if pathological vasculature is not determined, they can be safely undergo laparoscopy [23]. In our study we did not register one case of cancer in this type of lesion.

Similarly Levine *et al.* [24] showed that anechoic, smooth-walled cysts without septa, or with thin (not exceeding 3 mm) non vascularised septa, and with CA 125 serum levels within normal limits, occurring even in postmenopausal women – that for different reasons cannot be operated on – can safely be observed by endosonography. In our study a negative prognostic value of colour Doppler ultrasonography reached 98.0%, which means that only 2.0% of patients, in spite of negative results of Doppler examination, were detected with malignant processes. Estimation of statistical coefficients in our study showed a lack of significance between sensitivity and negative predictive value for both analysed ultrasonographic methods. This means that their value in confirming malignant growth or also to establish it's lack is similar.

Significant differences were ascertained in the specificity and positive predictive value of both methods. They clearly differ (an advantage of the Doppler technique) in excluding malignant processes (endosonographically a significantly greater number of false positive errors), and also in establishing probabilities that a patient with a mass showing Doppler features of malignancy has ovarian cancer.

Due to both techniques, we can today make important decisions regarding manner and time of treatment. For women in reproductive age, even masses containing solid elements, in which Doppler examination does not reveal peripheral and central vascularisation, could undergo spontaneous resorption. It happens in luteinized unruptured follicles, hemorrhagic and follicular cysts. Instead in cases suspected of malignant growth, when within the tumour papillary projections and thick abundantly vascularized walls with low resistance flow is detected, they should immediately undergo surgery maintaining oncological protocols. These, like masses, even in young women, should not be operated on by laparoscopy. Therefore the great usefulness of colour Doppler ultrasonography is seen first of all in selecting cases for endoscopic operations.

In our study Doppler analysis of vasculature in comparison to conventional endosonography permited improvement of: specificity from 67.5% to 94.5% and PPV from 44.7% to 83.1% (both significantly different). One of the pioneers of these investigations, Fleischer [25] in a group of postmenopausal women reached a PPV of 98% and NPV of 99%. He expressed the opinion that the use of Doppler ultrasonography, in spite of numerous criticisms is an invaluable technique in early recognition of ovarian cancer. He describes 17 cases of stage I ovarian cancer identified due to this method. He suggests that it should be diffused as widely as possible in gynaecological oncology. This belief is shared by Tepper *et al.* [26] in expressing the opinion that propagation of this method will permit the practice of individual cut-off values of flow independent of the equipment's technical possibilities and the experience of examiners.

Conclusions

We believe that complete ultrasonographic estimation of ovarian neoplasms outside the qualification of structural details should include analysis of Doppler vasculature parameters. Most important is the qualification of resistance of flow, and location and intensification of vascularisation in examined masses which permits the differentiation of malignant and benign lesions. Preoperatively identifying malignant processes by colour Doppler ultrasonography shows higher accuracy, specificity and PPV.

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