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Preoperative differentiation of malignant from benign ovarian tumors: the efficacy of morphology indexing and Doppler flow sonography☆

F.R. Ueland, M.D.,[a,b,*] P.D. DePriest, M.D.,[a,b] E.J. Pavlik, Ph.D.,[a,b] R.J. Kryscio, Ph.D.,[c] and J.R. van Nagell Jr., M.D.[a,b,1]

[a] *Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Kentucky Chandler Medical Center, Lexington, KY 40536-0298, USA*

[b] *Markey Cancer Center, University of Kentucky Chandler Medical Center, Lexington, KY 40536-0298, USA*

[c] *Department of Statistics, University of Kentucky Chandler Medical Center, Lexington, KY 40536-0298, USA*

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Abstract

Objective. The goal of this study was to determine the efficacy of morphology indexing and Doppler flow sonography as methods to predict risk of malignancy in sonographically confirmed ovarian tumors.

Methods. Risk of malignancy was assessed preoperatively in 442 ovarian tumors using a new morphology index (MI) based on tumor volume and wall structure. Each tumor was assigned a score of 0 to 10 based on increasing volume and morphologic complexity. Doppler flow studies were performed on 371 of these tumors. Following morphologic evaluation, all ovarian tumors were removed surgically.

Results. Of 315 tumors with a MI < 5 there was only 1 malignancy (a stage IA granulosa cell tumor <2 cm in diameter) whereas there were 52 malignancies in 127 tumors with a MI ≥ 5. Stage of disease was as follows: stage I, 33; stage II, 6; stage III, 14. Risk of malignancy was related directly to MI score, varying from 0.3% in tumors with a MI < 5 to 84% in tumors with a MI ≥ 8. A MI value of ≥ 5 as indicative of malignancy was associated with the following statistical parameters: sensitivity 0.981, specificity 0.808, PPV 0.409, NPV 0.997. A pulsatility index (PI) < 1.0 as indicative of malignancy was associated with: sensitivity 0.528, specificity 0.776, PPV 0.288, NPV 0.906. A resistive index (RI) < 0.4 as indicative of malignancy was associated with: sensitivity 0.222, specificity 0.867, PPV 0.222, and NPV 0.867. The addition of Doppler flow indices to MI did not improve the accuracy of predicting malignancy. Likewise, the absence or presence of ovarian tumor blood flow was not reliable as a means to differentiate benign from malignant ovarian tumors.

Conclusions. Morphology indexing is an accurate and inexpensive method of differentiating benign from malignant ovarian tumors, and can be a valuable adjunct in treatment planning. The addition of Doppler flow studies did not improve diagnostic accuracy of MI.
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Introduction

Ovarian cancer is the fifth leading cause of cancer death among women in the United States [1]. Unfortunately, most women continue to present with advanced disease where the prognosis is poor. In contrast, the survival rate of women with early-stage ovarian cancer is excellent. As a result, there has been increased interest in the development of methods that can detect ovarian cancer when it is curable. Although transvaginal sonography has been shown to be a sensitive method for detecting ovarian tumors, its positive predictive value (PPV) in identifying ovarian cancer has been relatively low [2]. Therefore, other adjuvant methods have been proposed to differentiate benign from malignant ovarian tumors. The present investigation was undertaken to evaluate the efficacy of morphology indexing and Doppler flow sonography as methods to predict risk of malignancy in sonographically confirmed ovarian tumors.

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* Corresponding author. University of Kentucky Medical Center, Department of Ob/Gyn, Division of Gynecologic Oncology, 800 Rose Street, 333 Whitney-Hendrickson Building, Lexington, KY 40536-0298, USA. Fax: +1-859-323-1018.

E-mail address: fredueland@yahoo.com (F.R. Ueland).

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Table 1
Sonographic morphology index for ovarian tumors

	Category					
	0	1	2	3	4	5
Volume[a] (cm^3)	<10	10–50	>50–100	>100–200	>200–500	>500
Structure	Smooth wall, sonolucent	Smooth wall, diffuse echogenicity	Wall thickening, <3-mm fine septa	Papillary projection ≥ 3 mm	Complex, predominantly solid	Complex, solid and cystic areas with extratumoral fluid

[a] Calculated using prolate ellipsoid formula ($L \times W \times H \times 0.523$).

Materals and methods

Subjects for this investigation included 442 women with an ovarian tumor confirmed on vaginal ultrasound referred to the University of Kentucky Medical Center from 1987 to 2000. Transvaginal sonography (TVS) was performed using Aloka 620 and GE LOGIQ 200 units with a 5.0-MHz vaginal transducer. Each ovary was measured in three dimensions, and ovarian volume was calculated using the prolate ellipsoid formula (length × width × height × 0.523). Criteria for abnormality included ovarian volumes in excess of 10 cm^3 for postmenopausal women and 20 cm^3 for premenopausal women. These values were defined by being more than two standard deviations above the mean normal ovarian volume for premenopausal and postmenopausal women [3]. In addition, any cystic ovarian tumor with a solid or papillary projection into its lumen was considered abnormal. Morphology indexing was performed according to a modification of the classification reported by DePriest and colleagues [4]. Two descriptive components were evaluated: tumor volume and morphologic structure. A point scale (0–5) was developed within each category, with total points varying between 0 and 10 for each tumor (Table 1). Septal structure, which was a standard variable in the original index, was not included as a major morphologic component, since it was shown to be less related to risk of malignancy than either wall structure or tumor volume. Rather, observations of diffuse echogenicity, tumor septa, and extratumoral free fluid were added as separate findings within the category of tumor structure (Fig. 1).

Color Doppler was performed using either an Aloka 680 unit with a 5.0-MHz vaginal transducer or a GE LOGIQ 400 unit with a 6.5-MHz transducer. Pulsed Doppler was used to evaluate intratumoral (central) blood flow. Peripheral tumoral blood flow was recorded if central blood flow was absent. When Doppler flow was present, both the pulsatility index (PI) and resistive index (RI) were documented. PI and RI were calculated as follows: PI = peak systolic flow − end-diastolic flow/mean systolic flow, and RI = peak systolic flow − end-diastolic flow/peak systolic flow. At least two readings were taken for each vessel and the lowest value was used for statistical analysis. A PI < 1.0 [5] or a RI < 0.4 [6] was considered abnormal.

Following sonographic evaluation and morphology indexing, each tumor was removed surgically. After removal, ovarian tumors were photographed, measured in three dimensions, and examined for areas of morphologic abnormality. Frozen-section histologic examination was performed on all areas suspicious for malignancy. Patients with ovarian cancer on frozen section underwent immediate staging laparotomy with total abdominal hysterectomy, bilateral salpingo-oophorectomy, retroperitoneal lymph node sampling, tumor debulking, and omentectomy. Tumors were classified histologically according to the World Health Organization (WHO) System, and were staged according to the International Federation of Gynecology and Obstetrics (FIGO) System. These data were entered into a Medlog database on a local network.

Statistical evaluation of the data was performed using univariate and multivariate analyses. Proportions were compared using the χ^2 statistic from the corresponding contingency tables. Means were compared using the two-tailed t statistic. Logistic regression was used for the multivariate analyses. Statistical significance was determined at the 0.05 level.

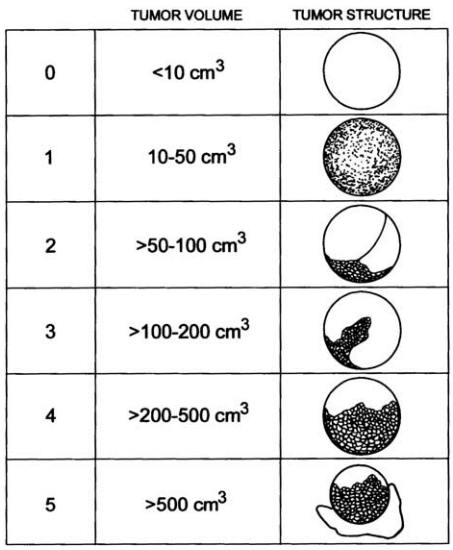

Fig. 1. Pictorial representation of morphology index for ovarian tumors.

Table 2
Histologic diagnosis of ovarian tumors ($N = 442$)

Malignant ovarian tumor	39
Ovarian tumor of low malignant potential	14
Serous cystadenoma	130
Mucinous cystadenoma	23
Endometrioma	57
Simple cyst	62
Cystic teratoma	36
Fibroma/thecoma	35
Hemorrhagic cyst	23
Other benign tumors	23

Results

Clinical characteristics of the patients evaluated are as follows: mean age 50 years (range, 18–85 years); mean height 64 in. (range, 48–74 in.); and mean weight 150 lb (range, 80–368 lb). Two hundred and twenty-five patients were 50 years of age or older and 217 were under the age of 50. Histologic diagnoses of the 442 ovarian tumors are illustrated in Table 2. There were 53 ovarian cancers, including 14 ovarian tumors of low malignant potential, and 389 benign ovarian tumors. The stages of the ovarian malignancies were as follows: stage I, 33; stage II, 6; stage III, 14.

The modified MI was easy to interpret, and each structural category was distinct. As a result, the interobserver variation in morphology scoring was minimal. In a blinded comparison of the MI score by two of the authors (J.R.v.N., E.J.P.), the identical score was recorded in 437 of 442 cases (98.8%). In the remaining 5 cases, the morphology score varied only by ±1. Risk of malignancy in an ovarian tumor was related directly to structural complexity ($P < 0.001$), tumor volume ($P < 0.001$), and total MI score ($P < 0.001$) (Table 3). There was only one malignancy in 315 ovarian tumors (0.3%) with a MI < 5. This patient had a stage IA granulosa cell tumor 2 cm in diameter. In contrast, there were 52 malignancies in 127 ovarian tumors (41%) with a MI ≥ 5 ($P < 0.01$). Risk of malignancy varied from 0.3% in ovarian tumors having a MI < 5 to 84% in tumors with a MI > 7 (Table 4). This relationship was essentially the same in women < 50 years of age and in women ≥50 years. A MI value of ≥ 5 as indicative of malignancy was associated with the following statistical parameters: sensitivity 0.981, specificity 0.807, positive predictive value (PPV) 0.409, negative predictive value (NPV) 0.997, and accuracy 0.828 (Table 5).

Doppler flow studies were performed on 371 of these tumors. Intratumoral blood flow was present in 246 tumors and was absent in 125. The frequency of malignancy was higher in ovarian tumors with (1) blood flow demonstrable by color Doppler and (2) a PI < 1.0 (Table 6). The rate of malignancy was 15% in ovarian tumors with blood flow and 6% in tumors without detectable blood flow ($P < 0.01$). A PI < 1.0 was observed in 66 tumors and 19 (29%) were malignant. In contrast, a PI ≥ 1.0 was demonstrated in 180 tumors and 17 (9.4%) were malignant ($P < 0.001$). The mean PI was 1.41 in 210 benign ovarian tumors and 1.15 in 36 ovarian cancers ($P < 0.01$). Nevertheless, a cutoff PI

Table 3
Morphology index components related to tumor histology ($N = 442$)

	N	Benign	Malignant
Structural score			
0	144	144 (100%)	0 (0%)
1	93	91 (98%)	2 (2%)
2	84	80 (95%)	4 (5%)
3	59	51 (86%)	8 (14%)
4	33	18 (54%)	15 (45%)
5	29	5 (17%)	24 (83%)
Total	442	389 (88%)	53 (12%)
Volume score			
0 (< 10 cm^3)	28	27 (96%)	1 (4%)
1 (10–50 cm^3)	201	192 (95%)	9 (5%)
2 (> 50–100 cm^3)	74	64 (86%)	10 (14%)
3 (> 100–200 cm^3)	59	55 (93%)	4 (7%)
4 (> 200–500 cm^3)	56	38 (68%)	18 (32%)
5 (> 500 cm^3)	24	13 (54%)	11 (46%)
Total	442	389 (88%)	53 (12%)

Table 4
Total morphology index score related to tumor histology ($N = 442$)

Morphology index score	*N*	Benign	Malignant
0	10	10 (100%)	0 (0%)
1	65	65 (100%)	0 (0%)
2	79	78 (99%)	1 (1.0%)
3	88	88 (100%)	0 (0%)
4	73	73 (100%)	0 (0%)
5	54	43 (80%)	11 (20%)
6	28	19 (60%)	9 (32%)
7	13	8 (62%)	5 (38%)
8	13	1 (8%)	12 (92%)
9	13	3 (23%)	10 (77%)
10	6	1 (17%)	5 (83%)
Total	442	389 (88%)	53 (12%)

Table 5
Statistical parameters associated with a morphology index value ≥5 predictive of ovarian malignancy

Sensitivity	$\frac{TP}{TP + FN}$	$\frac{52}{52 + 1}$	0.981
Specificity	$\frac{TN}{TN + FP}$	$\frac{314}{314 + 75}$	0.807
PPV	$\frac{TP}{TP + FP}$	$\frac{52}{52 + 75}$	0.409
NPV	$\frac{TN}{TN + FN}$	$\frac{314}{314 + 1}$	0.997
Accuracy	$\frac{TP + TN}{TP + TN + FN + FP}$	$\frac{52 + 314}{52 + 314 + 1 + 75}$	0.828

Note. TP, true positive; TN, true negative; FP, false positive; FN, false negative; PPV, positive predictive value; NPV, negative predictive value.

Table 6
Frequency of malignancy according to Doppler flow studies

	Benign	Malignant	Significance
PI < 1.00	47 (71%)	19 (29%)	$P < 0.001$
PI ≥ 1.00	163 (91%)	17 (9%)	
RI < 0.40	28 (78/%)	8 (22%)	NS
RI ≥ 0.40	182 (87%)	28 (13%)	
No blood flow	118 (94%)	7 (6%)	$P < 0.01$
Blood flow	210 (85%)	36 (15%)	

value of < 1.0 did not reliably separate malignant from benign ovarian tumors. A PI < 1.0 as indicative of ovarian malignancy was associated with the following statistical variables: sensitivity 0.528, specificity 0.776, PPV 0.288, and NPV 0.906 (Table 7). A RI < 0.4 was observed in 36 ovarian tumors and 8 (22%) were malignant, whereas a RI ≥ 0.4 was present in 210 tumors and 28 (13%) were malignant ($P = 0.19$). Likewise, a cutoff RI value of < 0.4 did not reliably separate malignant from benign ovarian tumors. A RI < 0.4 as indicative of malignancy was associated with the following statistical variables: sensitivity 0.222, specificity 0.867, PPV 0.222, and NPV 0.867. The addition of PI or RI to morphology indexing did not increase its accuracy in predicting ovarian malignancy.

Discussion

With the present emphasis on outcome-based medicine and the documentation of increased survival of ovarian cancer patients treated by gynecologic oncologists [7], it is important to develop a system that can predict risk of malignancy in ovarian tumors prior to operative intervention. Ideally, such a system should be time efficient, accurate, and of minimal cost to the patient. Its use should facilitate triage of high-risk patients to a gynecologic oncologist, while allowing low-risk patients either to be treated locally or to defer surgery entirely.

Since most ovarian tumors are now confirmed sonographically, several investigators [4,8,9] have proposed scoring systems relating morphologic complexity to the risk of malignancy. The challenge has been to design a system that will be easy to interpret, associated with minimal interobserver variation, and able to separate benign from malignant ovarian tumors. The present MI is a modification of the system first proposed by DePriest and colleagues [4]. By incorporating findings of intratumoral septa, diffuse echogenicity, and extratumoral free fluid into structural evaluation, the sensitivity, specificity, PPV, and NPV of the modified MI all increased, and its overall accuracy improved from 0.695 to 0.828.

Most importantly, using a MI value <5 as indicative of benign disease was associated with only one false positive in 315 ovarian tumors. This patient had a small (<2 cm diameter) solid tumor which on histologic review was a well-differentiated granulosa cell tumor. These findings confirm the observations of Bailey and co-workers [10] who noted no malignancies in 45 women who underwent surgery for persisting unilocular cystic ovarian tumors <5 cm in diameter. Likewise, no ovarian cancers developed in 86 women with cystic ovarian tumors <5 cm in diameter who elected to be followed without surgery. These authors concluded that unilocular cystic ovarian tumors <5 cm in diameter could be followed periodically with ultrasound examinations rather than being removed surgically, whereas complex ovarian tumors should undergo immediate surgical removal. The findings of the present investigation support these conclusions in that there were no cases of ovarian cancer in 144 unilocular cystic tumors removed surgically. In contrast, 41% of complex ovarian tumors with a MI ≥ 5 were malignant.

The use of Doppler flow studies of ovarian vasculature as a means to differentiate benign from malignant ovarian tumors is based on the observed difference in resistance to flow between vessels supplying normal ovarian tissue and those associated with ovarian malignancies [11]. A number of studies [5,6,12,13] have documented that resistance to flow is lower in vessels supplying ovarian cancers than in those supplying benign ovarian tumors. However, establishing an exact value for PI or RI that can reliably separate benign from malignant ovarian tumors has been difficult [14]. Data from the present study demonstrate that the mean PI of vessels supplying ovarian cancers is lower than that of vessels supplying benign ovarian tumors. Nevertheless, the overlap in vascular resistance between these two groups prevents reliable separation of malignant from benign ovarian tumors. Finally, Timor-Tritsch and colleagues [15] have reported that lack of blood flow in an ovarian tumor as detected by color Doppler may preclude cancer. This was not substantiated in the present study since 6% of ovarian tumors without blood flow were malignant. When PI or RI were added to morphology indexing, there was no increase in the accuracy of predicting ovarian malignancy. This is consistent with the prior observations of Roman and colleagues [16] and is important because the financial cost of Doppler flow studies is significant.

Conclusions

The findings of the present investigation indicate that morphologic indexing based on sonographically determined

Table 7
Statistical parameters of Doppler flow variables related to prediction of malignancy in ovarian tumors

	Sensitivity	Specificity	PPV	NPV
PI < 1.00	0.528	0.776	0.288	0.906
RI < 0.4	0.222	0.867	0.222	0.867
No blood flow	0.163	0.640	0.056	0.854

structure and volume is an accurate method to predict risk of malignancy in ovarian tumors. It is easy to perform, subject to minimal interobserver variation [17], and associated with little cost to the patient. The use of morphology indexing preoperatively can identify ovarian tumors at high risk for malignancy and allow appropriate triage of these patients to a gynecologic oncologist.

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