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Prediction of Ovarian Tumor Malignancy

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A B S T R A C T

Ovarian cancer is the leading cause of mortality among gynecological cancers. The aim of the study was to form the decision rules for distinguishing benign from malignant ovary lesions. The research was conducted on 201 women with ovary tumor. Commonly used specific markers for ovarian cancer (biochemical marker Ca 125, ultrasound and vascular markers) were used. The signifficant differenece in the presence of an ultrasound and vascular markers between benign and malignant ovary changes along with the signifficantly different level of Ca 125 is confirmed. To a specific marker certain score number was appointed and the scoring system was formed. The incidence of benign/malignant ovary changes was observed in the researched group regarding anthropometric parameters (age, marital and menopausal status and number of deliveries). There is also signifficant difference in the incidence of benign/malignant ovary tumor regarding these parameters. Based on combination of the scoring system and anthropometric parameters the decision rules for distinguishing benign from malignant ovary tumors were formed. The logistic regression method was used. We proved that this method has higher accuracy in prediction of malignancy in women with ovary tumors than using morphological, doppler or anthropometric parameters separately.

Introduction

Ovarian cancer is the leading cause of mortality among gynecological cancers. Almost half (47%) women died from reproductive organs cancer had an ovary cancer[1]. The incidence of ovarian cancer is 17 in 100 000 in Croatian population with[2] the incidence slightly higher in the northern Croatian islands[3]. The disease is asymptomatic in earlier stages of disease. Two thirds of patients occur with already advanced disease. Epithelial ovarian tumors occur in 65–75% of all ovarian tumors, represent the most common types of all malignant ovarian neoplasm[4] and occur more frequently in older postmenopausal women[5]. Commonly used specific markers for ovarian cancer are: biochemical marker Ca 125, ultrasound markers (morphology of the ovaries) and vascular markers, with more or less success. Ca 125 has a high sensitivity, but low specificity and its value in early detection of epithelial ovarian cancer is limited[17]. Morphological markers are based on the »real-time« ultrasound, detect altered ovarian morphology. Most common scan protocols used for scoring systems or indexes include morphological changes associated with ovarian volume, its surface, the presence of papillae, the appearance of the complex cysts, fragmentation, thickness of the wall of the cyst, thickness of septa and echogenicity of the fluid[6] with large percentage of false positive results[7]. Colored and pulsed Doppler can be used separately to distinct benign from malignant lesions, but some authors believe that it does not reduce the percentage of false positive results[8]. Our aim is to form the decision rules for distinguishing benign from malignant lesions combining biochemical, morphological and vascular markers.

Materials and Methods

201 women with ovarian tumor treated in »Sestre milosrdnice« University Hospital Center participated in prospective study conducted during a period of three years. There were 120 patients (57.7%) with benign ovarian tumor and 81 patient (38.9%) with malignant ovarian tumor. The parameters obtained during the preoperative preparation were: a basic history and the serum level of

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CA 125 marker obtained using monoclonal antibodies (VITROS Immunodiagnostic Products CA 125 Reagent Pack II, Ortho Clinical Diagnostics). The cut off value for Ca125 in our laboratory was 21.0U/ml. Within 24 hours before te surgery every patient underwent transvaginal ultrasound, color and pulsed Doppler using ultrasound sonoline Antares Ultrasound Imaging System, Siemens, with a transvaginal transducer of 6.1 MHz. Parameters such as structure of the wall of the tumor, the existence of shadows or barriers, solid components and peritoneal fluid, changes in echogenicity and blood flow in tumor were detected. The blood flow was indirectly determined by measuring the resistance index RI (cut-off value to distinguish benign from malignant change was RI≤0.42).

We used an ultrasound scoring system showed in Table 1, obtained by modifying the ultrasound scoring system described by Dr Kupešić[9]. In every patient seven ultrasound parameters were studied. Certain number of points was assigned to every parameter (0–2). The final count of all obtained points presented the »score«. If the sum of changes (»score«) is less than 5 we presumed that the lesion is benign, and if the sum was equal or greater than 5 we presumed that the changes were more likely to be malignant.

TABLE 1
THE CRITERIA FOR DIAGNOSIS OF OVARIAN CANCER GAINED BY ULTRASOUND AND COLOR DOPPLER TEHNICQUE

		Points
The wall structure	a) smooth or irregular ≤3mm	0
	b) papillar growth >3mm	2
Shadow	a) YES	0
	b) NO	1
Septa/ Bariers	NO/thin ≤3mm	0
	thick >3mm	1
Solid components	0	0
	<1cm	1
	>1cm	2
Echogenicity	translucent or diminished	0
	mixed or high	2
Peritoneal fluid	No	0
	Yes	1
Tumor Vascularisation	RI>0.42	0
	RI≤0.42	2
Total	benign <5	malignant ≥5

Postoperatively, after the hystopatological analysis of the tumor we compared hystopatological findings with our preoperative evaluation of the tumor based on ultrasound scoring system and serum level of Ca 125.

We investigated the association of marital status, age, parity and menopausal status with the incidence of ovarian cancer. Patients were divided in two groups: patients with benign and malignant tumor. For comparation of these two groups, nonparametric Mann-Whitney test for numerical variables and χ^2 for qualitative variables was used. Since the numerical variables did not show normal distribution nonparametric test was applied. For creation of the model, the logistic regression,stepping logistic regression with the method of inclusion and exclusion of variables is applied, as well as Quinlanov C5.0 algorithm. The models are presented in tables, and the C5.0 algorithm graphically in form of decision trees. Both models were validated with absolute predictive accuracy. The method of cross validation was applied.

Results

The age of the patients ranged from 16 to 82 years. Younger women were more likely to develop benign ovarian tumors. The mean age in that group was 45.4. years with standard deviation of 12.68 and median of 46 years. In the group with malignant disease the mean age was 57.12 years with standard deviation 13:28 years and median of 55 years. The age difference between those two groups was statistically significant (p=0.001). The number of deliveries between two groups was also different with statistical significance (p=0.022).

The level of serum marker CA 125 in patients with benign ovarian tumors was significantly lower than in the patients with malignant ovary tumors (p=0.001, Table 2). In our study, sensitivity of CA125 marker was 85.19%, specificity 72.5%, the percentage of false positive results 32.35%, and the percentage of false negative results 12.12%. The score evaluation in patients with benign tumors and malignant tumors resulted with similar observation (p=0.001, Table 2). Sensitivity of the score was 82.72%, specificity 89.2%, the percentage of false positives 16.25%, and false negatives 11:57%. Resistance in-

TABLE 2
SERUM MARKER CA125, SCORE AND RESISTANCE INDEX (RI) IN PATIENTS WITH BENIGN AND MALIGNANT OVARY TUMORS

	Benign tumors			Malignant tumors			p
	$\overline{X}$*	SD**	Med***	$\overline{X}$*	SD**	Med***	
Ca 125 (U/ml)	24.79	37.59	12.47	748.11	1411.04	200	<0.001
Score	2.78	1.43	3	6.70	2.33	7	<0.001
RI	0.64	0.13	0.68	0.47	0.14	0.41	<0.001

* – Mean, ** – Standard deviation, *** – Median

TABLE 3
THE DIFFERENCES BETWEEN BENIGN AND MALIGNANT OVARY TUMORS BEFORE AND AFTER MENOPAUSIS

Postmenopausis	Benign tumor	Malignant tumor
Yes	46 (38.3%)	56 (69.1%)
No	74 (61.7%)	25 (30.9%)

TABLE 5
CLASSIFICATION MATRIX OF THE LOGISTIC REGRESSION MODELS

	Estimated benign	Estimated malignant	Sensitivity
Really benign	116	4	96.67%
Really malignant	14	67	82.72%

dex (RI) was also lower in patients with malignant tumors compared to those with benign tumors (p=0.001, Table 2). Sensitivity of resistance index measurement was 53.1%, specificity 92.5%, percentage of false positives 17.3% and false negatives 25.5%.

Analyzing the existence of menopause, 38.3% of patients with benign ovary tumor and 69.1% of patients with malignant ovary disease were menopaused. The difference between the groups is statistically significant (p=0.001, Table 3).

Predictive models for malignant ovary cancer: six independent predictors (age, Ca 125, score, menopausal status, number of deliveries and marital status) and the final histological diagnosis for each patient (criterion variable) were used for logistic regression. The resulting model is shown in Table 4.

The resulting model was statistically significant (–2 log likelihood=101.3, χ^2=169.7, df=5, p<0.0001). The absolute model classification accuracy is 91.04%. The classification is shown in Table 5.

Using Quinlan C5.0 algorithm multiple trials showed the decision tree to be the best stabile and acceptable model (Figure 1).

The resulting model evaluation was performed using the cross validation process in 10 steps. An average classification error in the decision tree was 11.5% and the standard error vas 2.1%.

Discussion

The ovarian cancer is the subject of multiple studies. Weiss and colleagues[10] found higher occurrence of ovarian cancer (60–70%) in women who have never been married 40 years ago. Women with ovarian cancer are significantly younger, have higher levels of education, better incomes, fewer children and more likely that they are not married in comparison to women with diagnosed colorectal carcinoma[11].

We observed the higher tendency for developing benign ovarian disease in unmarried group, and higher tendency for developing malignant ovary disease in divorced women group. It is presumed that the amount of stress in the life of divorced women, has some connection with the development of malignant disease, but unfortunately the overall number of divorced women in our study is 15. Due to the small sample of divorced women in our study, we cannot conduct valuable scientific conclusion regarding this observation but we conclude that it would be very interesting to continue the investigation in this direction. Most studies show that the risk for ovarian cancer decreases with the number of deliveries[2], with the explanation of longer anovulatory periods and reduced secretion of gonadotropins, which is considered to be a protective factor for ovarian cancer. The incidence of ovarian cancer in postmenopausis is significantly higher comparing to premenopausis[13], and is usually diagnosed in 5th, 6th and 7th decade of woman life[12]. In our study, we observed distribution toward malignant ovarian disease in the group of postmenopausal women, and toward benign ovarian changes in premenopausal women. The age of the patients is closely related to menopausal status. Our study showed statistically significant differences in the incidence of malignant or benign ovarian changes regarding age with higher incidence of benign tumors in younger group and higher incidence of malignant changes in older group. In the literature, the serum level of Ca 125 is most often mentioned marker for ovarian cancer. 83% of patients with epithelial ovarian cancer have Ca 125 serum level elevated. Ca 125 serum level is elevated in 50% of patients with the I stage of the dis-

TABLE 4
THE RESULTS OF LOGISTIC REGRESSION

Variables	B	S.E.	Wald	df	Sig	Odds Ratio	95% CI	
							Lower	Upper
Years	0.033	0.031	1.15	1	0.283	1.033	0.97	1.10
Ca125	0.012	0.004	7.49	1	0.006	1.012	1.00	1.02
Score	0.883	0.169	27.27	1	0.000	2.419	1.74	3.37
Number of deliveries	0.221	0.207	1.14	1	0.286	1.248	0.83	1.87
Menopausis	0.206	0.728	0.08	1	0.777	1.229	0.29	5.12
Constant	–7.25	1.502	23.27	1	0.000			

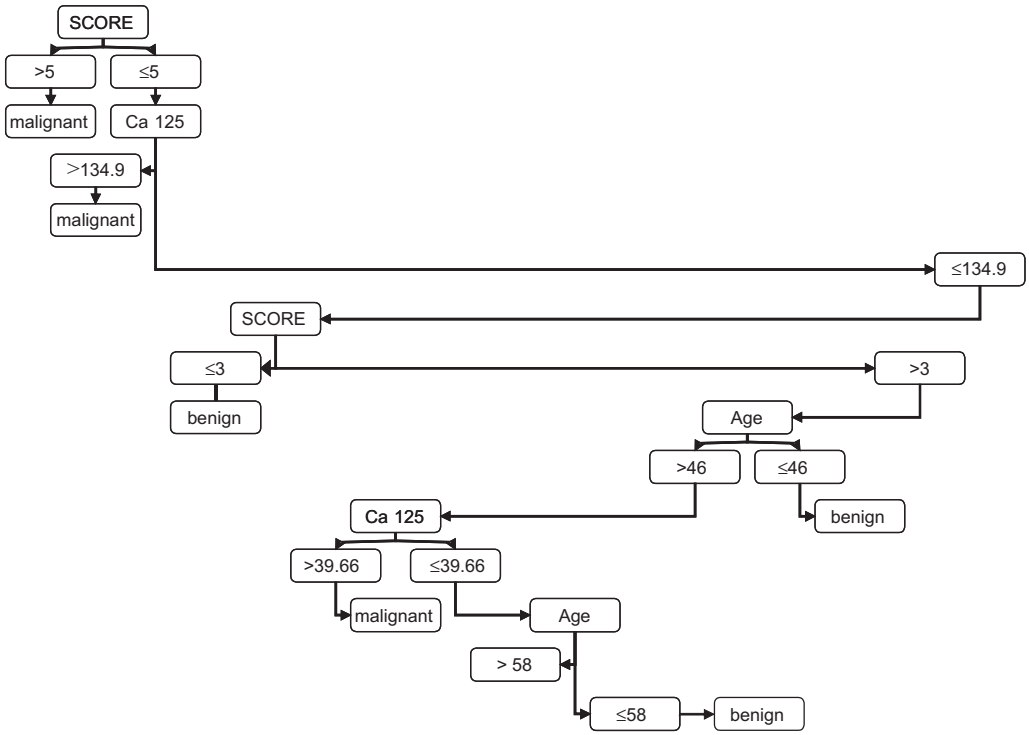

Fig. 1. The decision tree for prediction of malignant/ benign ovary changes.

ease, 60% of patients in the II stage of the disease, and over 90% of patients with advanced stages of the disease.

In this study, the serum level of CA 125 was significantly lower in the group with benign tumor in comparison to the patients with malignant ovary tumor. For better accuracy in prediction of benign or malignant tumors, some authors suggested combining ultrasonic parameters and the value of Ca 125 (13). Botsis and colleagues in the research on 62 women with ovarian masses showed significantly higher values of resistance index in benign ovarian changes comparing to malignant ovarian tumors (14). Sensitivity of Doppler analysis was significantly higher compared to the Ca 125 serum level, but combining these two methods the sensitivity in prediction of malignant pelvic masses increases. In accordance with the majority of statements from the literature, in our study, the value of resistance index (RI) was significantly lower in women with malignant tumors in comparison to those with benign tumors. An ultrasound observed parameters for identification of benign or malignant ovary tumors were: morphology of the masses with special reference to size changes, changes in echogenicity, presence of papillae, ascites, ovarian volume, thickness and regularity of the wall or other. Many authors formed a »scoring system« by associating to each parameter the number of points. Depending on the total score benign or malignant change was predicted[6,9]. The score which we describe in patients with malignant disease is statistically more sensitive than the score in patients with benign form of the disease. Many authors in hope for the better success in distinguishing benign from malignant ovary changes examined the concordance of individual reproductive, anthropometric, morphologic and color Doppler parameters obtained with the hystopatologic analysis, and tried to extract relevant parameters, with the attempt of creation more accurate model[15,16]. We conclude that the multivariant logistic regression analysis for calculation of the probability for malignancy in the patient with adnexal mass is fairly accurate. Its accuracy in prediction of malignancy appears to be higher than prediction of malignancy using morphological, doppler or anthropometric parameters separately.

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PREDVIDLJIVOST ZLOĆUDNOSTI RAKA JAJNIKA

S A Ž E T A K

Rak jajnika je po smrtnosti na vodećem mjestu među ginekološkim karcinomima. Cilj ove studije bio je konstruirati pravila odlučivanja za razlikovanje benignih od malignih promjena. Istraživanje je provedeno na uzorku od 201 žene. Promatrani su najčešće korišteni ultrazvučni, vaskularni markeri i biokemijski marker Ca 125 za detekciju ovarijskog karcinoma. Potvrđene su statistički značajne razlike u pojavnosti markera ovisno o malignosti promjene kao i koncentracije Ca 125. Svakom markeru pridodan je određeni broj koji u konačnici formira sistem bodovanja. Također je pojavnost benignih/malignih promjena promatrana obzirom na antropometrijske parametre (dob, bračni status, paritet, menopauza). Potvrđena je statistički značajno različita pojavnost benignih/malignih promjena obzirom na te parametre. Kombinacijom sistema bodovanja s antropometrijskim parametrima formirana su pravila odlučivanja za razlikovanje malignih od benignih promjena jajnika. Korištena je metoda logističke regresije za koju smo dokazali veću prediktivnost za maligne/benigne promjene jajnika od prediktivnosti koju daju navedeni paramtetri pojedinačno.