Histopathological diagnoses of adnexal masses: which parameters are relevant in preoperative assessment?

Histopatologiczne diagnozy jajnika: które parametry są istotne w ocenie przedoperacyjnej?

Milan Terzic[1,2], Jelena Dotlic[1], Natasa Brndusic[1], Nebojsa Arsenovic[3], Ivana Likic[1,2], Nebojsa Ladjevic[2,4], Sanja Maricic[5], Sasa Andrijasevic[1]

[1] Clinic of Obstetrics and Gynecology, Clinical Centre of Serbia, Dr Koste Todorovica 26, Belgrade, Serbia
[2] Department of Obstetrics and Gynecology, Faculty of Medicine, University of Belgrade, Dr Subotica 8, Belgrade, Serbia
[3] Department of Cellular Pathology, Path Links Pathology Services, Lincoln County Hospital, Greetwell Road, Lincoln LN2 5QY, UK
[4] Center for anesthesiology and resuscitation, Clinical Centre of Serbia, Pasterova 2, Belgrade, Serbia
[5] Occupational Health Department, General Health Centre "Savski Venac", Pasterova 1, Belgrade, Serbia

Abstract

Objective: *The aim of the study was to assess which clinical, laboratory and ultrasound characteristics of adnexal masses might predict the histopathological nature of the disease.*

Materials and Methods: *The study involved all women treated at the Clinic of Gynecology and Obstetrics Clinical Centre of Serbia for adnexal tumors between July 1, 2010 and December 31, 2011. On admission, detailed anamnestic and laboratory data were obtained, expert ultrasound scan performed and RMI was calculated for all patients. Data were related to histopathological findings and statistically analyzed.*

Results: *The study included 540 women out of which 85 had malignant (seven diagnoses), 435 benign (seven diagnoses) and 20 borderline tumors. All types of malignant and borderline tumors were more frequent in postmenopausal women (p=0.000). Only papillary adenocarcinoma significantly more often produced early metastases (p=0.000). Ascites is a common finding in Krukenberg tumors, granulose cell tumors and papillary adenocarcinomas. There were significant differences between tumor diagnoses regarding the levels of Ca 125 and CEA, erythrocyte sedimentation rate (ESR) and risk of malignancy index (RMI) (p<0.05). No significant differences were found within the group of malignant tumor types regarding the levels of all examined tumor markers, ESR as well as RMI (p>0.05).*

Conclusions: *In the light of our results, patient age, menopausal status, blood levels of Ca 125, CEA and ESR, as well as calculated RMI, can predict the nature of adnexal masses. Unfortunately, none of the examined parameters can accurately determine the exact histopathological diagnosis of the adnexal tumor.*

Key words: **histopathological diagnosis** / **adnexal masses** / **preoperative assessment** /

Corresponding author:
Milan M. Terzic
Clinic of Ob/Gyn, Clinical Centre of Serbia, Faculty of Medicine, University of Belgrade
Dr Koste Todorovica 26, 11000 Belgrade, Serbia
Tel: +381 11 361 5592, Fax: +381 11 361 5603
e-mail: terzicmilan@yahoo.co.uk

Otrzymano: **15.07.2012**
Zaakceptowano do druku: **10.06.2013**

Streszczenie

Cel: *Celem pracy była ocena, które cechy kliniczne, laboratoryjne i ultrasonograficzne guzów jajnika mogą pomóc przewidzieć histopatologiczny charakter choroby.*

Materiał i metoda: *Badaniem objęto wszystkie kobiety leczone w Klinice Ginekologii i Położnictwa w Centrum Klinicznym w Serbii z powodu guzów przydatków pomiędzy 1 lipca 2010 a 31 grudnia 2011. Przy przyjęciu uzyskano szczegółowe dane anamnestyczne i laboratoryjne, wykonano USG i obliczono RMI (indeks ryzyka złośliwości) dla wszystkich pacjentek. Uzyskane dane były powiązane z wynikami histopatologicznymi nowotworów i poddane analizie statystycznej.*

Wyniki: *Badaniem objęto 540 kobiet, z których 85 miało złośliwy nowotwór, 435 łagodny i 20 graniczny. Wszystkie rodzaje guzów złośliwych i granicznych były częstsze u kobiet po menopauzie (p=0,000). Tylko gruczolakorak brodawkowaty znacznie częściej dawał wczesne przerzuty (p=0,000). Wodobrzusze jest powszechnym zjawiskiem w nowotworach Krukenberga , guzach typu granulose-cell i w gruczolakoraku brodawkowatym. Nie było istotnych różnic w grupie nowotworów złośliwych dotyczących poziomu CA125 o CEA, szybkości sedymentacji erytrocytów (ESR) i indeksie ryzyka nowotworu złośliwego RMI (p>0,05).*

Wnioski: *Według naszych wyników, wiek chorych, status menopauzalny, poziom we krwi CA125, CEA i ESR a także obliczone RMI może pomóc przewidzieć charakter guza jajnika. Niestety, ani jeden z badanych parametrów nie może dokładnie określić rozpoznania histopatologicznego guza przydatków.*

Słowa kluczowe: **rozpoznanie histopatologiczne** / **guz jajnika** / / **ocena przedoperacyjna** /

Introduction

Ovarian cancer is the fourth most frequent cause of cancer death in women and the leading cause of gynecologic cancer mortality [1]. Several clinical factors such as surgery, patient age and tumor grade could influence the survival, even in advanced ovarian cancer. Histopathological subtypes have also been associated with different prognosis. In particular, clear cell and mucinous carcinomas have been identified as adverse prognostic features [2]. These tumors are associated with shorter time to progression and, consequently, a significantly worse prognosis when compared to serous tumors [3]. Furthermore, endometrioid or clear cell carcinoma can sometimes develop from previously benign ovarian endometriosis [4, 5]. Unfortunately, currently available screening test leave much to be desired and thus women are more frequently diagnosed with advanced cancer stages. The identification of factors that might predict tumor nature may aid us in selecting patients who might benefit from appropriate referral and different therapeutic approaches [6].

Objective

The aim of the study was to assess which clinical, laboratory and ultrasound characteristics of adnexal masses might predict the histopathological nature of the disease.

Material and methods

The study included all consecutive patients that were treated for adnexal tumors at the Clinic of Gynecology and Obstetrics, Clinical Centre of Serbia, during the period of 18 months (from July 1, 2010 up to December 31, 2011). The study was approved by the Clinic Board. All patients gave their written consent for the diagnostic procedures, surgery as well as inclusion in the study. On admission, detailed anamnesis and standard laboratory tests (blood analysis, erythrocyte sedimentation rate (ESR), and tumor marker levels) were taken from all women. Furthermore, expert clinical examinations and ultrasound scan of the pelvic organs (multilocular or bilateral tumor, solid/cystic components/ parts, metastases and ascites presence) were performed. Analyses were performed on IMMULITE® 2000 Immunoassay System (Siemens AG, Munich, Germany). Referral levels used in the study were: 0-35 IU/L for Ca 125; 0-33 IU/L for Ca 19.9; 0-38 IU/L for Ca 15.3; 0.21-4.8 IU/L for Carcino Embrio Antigen (CEA); and 10 for the first hour ESR. Finally, risk of malignancy index (RMI) was calculated for all patients using the formula: RMI = U x M x Ca125, where U represents the ultrasonographic index. Multilocular and bilateral tumors, the presence of solid parts in the tumor, metastasis and ascites are marked with one point each. These points are summed up, and then transformed so that in the formula U 0 = 0 points, U 1 = 1 points, U 2 - 5 = 3 points. In the formula, M stands for menopausal status, with 1 for premenopausal and 3 for postmenopausal women. Levels of Ca125 were calculated directly to the equation. The patients were divided into three groups according to the RMI values (low risk < 25, intermediate risk 25–250, and high risk > 250). Postoperatively, after extraction of adnexal masses, histopathological findings (HP) of the tumors were analyzed by a pathologist. The obtained HP diagnosis was then related to all anamnestic, laboratory and ultrasound parameters of the corresponding patient. We also tested the relationship between the groups of the investigated parameters (clinical: age, menopausal status, symptoms, RMI; laboratory: ESR, Ca 125, Ca 15.3, Ca 19.9, CEA; ultrasound: tumor dimensions, solid parts, ascites, bilaterality, multilocularity) and the histopathological diagnoses of registered adnexal masses in order to determine which of them might predict the histopathological nature of the disease. Finally, we tested whether all the examined parameters can discriminate well the histopathological diagnoses of adnexal tumors. The methods of descriptive and analytical statistics (Kolmogorov-Smirnov Z test, Friedman's parametric ANOVA, multivariate linear regression, discriminant analysis) and the SPSS 15 software were used for statistical analysis.

Results

There were 540 women involved in the study. Out of all cases, adnexal masses were malignant in 85, benign in 435, and borderline in 20 patients.

HP analysis revealed that there were 7 different malignant tumor diagnoses: serous adenocarcinoma, mucinous adenocarcinoma, endometrioid carcinoma, granulose cell tumor, papillary adenocarcinoma, Krukenberg tumor and other malignant diagnoses (clear cell tumor, mixed Mullerian tumor, etc.) present in less than 5 cases and therefore evaluated together. There were 7 different benign diagnoses: simple ovarian cyst, endometriotic cyst, hemorrhagic cyst, teratoma, benign ovarian cystadenoma, ovarian fibrothecoma and other diagnoses (corpus luteum, etc.) present in less than 5 cases and therefore evaluated together. Incidence of various histopathological diagnoses of adnexal masses is listed in Table I.

There were no significant differences between histopathological diagnoses of tumors regarding the presence of symptoms (F=0.729; p=0.394). Additionally, there were no significant differences within the group of various malignant tumor diagnoses (F=1.808; p=0.182), or within the benign tumors (F=2.537; p=0.112) regarding the presence of symptoms. (Table II).

When specific tumor diagnoses were evaluated, all malignant and borderline tumors turned out to be more frequent in postmenopausal women, while all benign tumor types were more common in premenopausal women (F=69.947; p=0.000). Endometrioid carcinoma (50%) and Krukenberg tumors (42.86%) were quite frequent in premenopausal women. On the other hand, there were no granulose cell tumors in that group of patients. Moreover, there were no significant differences within the group of malignant (F=0.359; p=0.550), and benign (F=0.236; p=0.628) diagnoses regarding the menopausal status of the patients. (Table I).

There were highly significant differences between tumor diagnoses regarding the tumor diameters (F=6.848; p=0.001). Endometrioid carcinomas were mostly larger than 10cm, while all benign lesions were predominantly from 5-10cm in diameter. (Table III).

There were no significant differences between specific malignant tumor types and production of metastases (F=1.433; p=0.234). Excluding metastatic Krukenberg tumors, only papillary adenocarcinoma produced early metastases significantly more often, while all other tumors were mostly diagnosed and operated before metastatic changes occurred. (Table III).

Significant differences between tumor diagnoses regarding the presence of ascites were found (F=169.115; p=0.000). However, there were no significant differences regarding the presence of ascites within the malignant (F=0.018; p=0.895), and benign (F=0.162; p=0.668) findings. Krukenberg tumor cases and almost all patients with granulosa cell tumors and papillary adenocarcinomas also had ascites. Moreover, almost all types of benign tumors were accompanied by ascites, but there were very few such cases. Less than 40% women with borderline tumors had ascites as well. (Table III).

In the majority of cases the changes were usually of the same histopathological type on either side (74%), but sometimes histopathology was different on the contralateral ovary (26%). Numerous endometriotic as well as simple ovarian cysts were bilateral. Furthermore, a considerable number of malignant tumors were bilateral. Consequently, there were no significant differences between tumor types regarding their bilaterality at all (F=0.011; p=0.917), nor were there any significant differences within the group of malignant (F=1.162; p=0.284) and benign (F=1.455; p=0.228) tumors. (Table IV).

Numerous simple and endometriotic cysts as well as malignant tumors were multilocular. Therefore, there were no significant differences between specific tumor diagnoses regarding their multilocularity (F=0.307; p=0.580). Moreover, there were no significant differences within the group of malignant (F=1.087; p=0.300) and benign (F=0.017; p=0.896) tumors regarding their multilocularity. (Table IV).

There were significant differences between tumor diagnoses regarding the blood level of Ca 125 (F=5.342; p=0.000). Ca 125 was the highest in serous adenocarcinomas, papillary adenocarcinomas as well as in the group of 'other malignant tumors'. However, there were no significant differences within the group of malignant tumors regarding the level of Ca 125 (F=0.898; p=0.511). (Table V).

When specific diagnoses were compared, Ca 19.9 was significantly higher in mucinous adenocarcinomas and lower in granulose cell tumors (F=3.833; p=0.000). Nevertheless, there were no significant differences within the group of malignant tumors regarding the levels of Ca 19.9 (F=1.940; p=0.081). (Table V).

Ca 15.3 was the highest in endometrioid carcinomas but, after all diagnoses were compared, no significant differences were found (F=1.572; p=0.115). Moreover, there were no significant differences within malignant tumors regarding the levels of Ca 15.3 (F=0.765; p=0.622). (Table V).

There were highly significant differences between tumor diagnoses regarding the blood levels of CEA (F=4.144; p=0.000). The highest levels of CEA were noted in women with mucinous adenocarcinomas and the group of 'other malignant tumors'. However, there were no significant differences within the malignant tumors regarding the levels of CEA (F=1.548; p=0.160). (Table V).

There were highly significant differences between tumor diagnoses regarding the ESR (F=6.173; p=0.000). The level of ESR was the highest in endometrioid carcinomas and the lowest in the group of 'other benign tumors'. However, there were no significant differences within the malignant tumors regarding the ESR (F=1.595; p=0.146). (Table V).

There were significant differences between tumor diagnoses regarding RMI (F=9.848; p=0.000). The highest RMI was noted in papillary adenocarcinomas and in the group of 'other malignant tumors', while fibrothecomas had the lowest RMI. However, there were no significant differences within the malignant tumors regarding RMI (F=1.561; p=0.156). There were highly significant differences in specific histopathological diagnoses and RMI categories (χ^2=184.202; p=0.000).

All benign diagnoses were found in all three risk categories (low, intermediate, high). On the other hand, only a few cases of serous and endometrioid adenocarcinomas and some tumors from the group of 'other malignant tumors' were assessed as low risk adnexal masses, while all other malignant tumors were in the intermediate or high risk groups. (Table V).

Table I. Distribution of histopathological diagnoses in pre- and postmenopausal patients with adnexal masses.

Diagnosis		Number		Menopausal status	
		Absolute	Relative	Pre-menopause	Post-menopause
Benign	Simple ovarian cyst	141	32.41	101	40
	Endometriotic cyst	110	25.29	86	24
	Hemorrhagic cyst	28	6.44	20	8
	Teratoma	61	14.02	47	14
	Benign ovarian cystadenoma	58	13.33	44	14
	Ovarian fibrothecoma	29	6.67	19	10
	Other diagnoses	8	1.82	8	0
Borderline		20	100	7	13
Malignant	Serous adenocarcinoma	23	27.06	4	19
	Mucinous adenocarcinoma	8	9.41	2	6
	Granulose cell tumor	6	7.06	0	6
	Endometriotic carcinoma	12	14.12	6	6
	Papillary adenocarcinoma	18	21.18	5	13
	Krukenberg tumors	7	8.24	3	4
	Other malignant diagnoses	11	12.94	4	7

Table II. Symptoms in patients with adnexal masses.

Diagnosis		Symptoms	
		Present	Absent
Benign	Simple ovarian cyst	61	80
	Endometriotic cyst	52	58
	Hemorrhagic cyst	8	20
	Teratoma	32	29
	Benign ovarian cystadenoma	32	26
	Ovarian fibrothecoma	14	15
	Other diagnoses	5	3
Borderline		12	8
Malignant	Serous adenocarcinoma	9	14
	Mucinous adenocarcinoma	5	3
	Granulose cell tumor	1	5
	Endometriotic carcinoma	7	5
	Papillary adenocarcinoma	13	5
	Krukenberg tumors	6	1
	Other malignant diagnoses	9	2

Statistically significant linear regression equations were obtained for all of the assessed groups using Enter method when all 14 registered diagnoses were evaluated together: clinical ($R=0.415$; $adjR^2=0.166$; $F=27.895$; $p=0.000$), laboratory ($R=0.580$; $adjR^2=0.286$; $F=6.596$; $p=0.000$), and ultrasound parameters ($R=0.604$; $adjR^2=0.358$; $F=50.900$; $p=0.000$):

HISTOPATHOLOGICAL DIAGNOSES= 14.624 – 1.803 x MENOPAUSE + 0.001 x RMI

HISTOPATHOLOGICAL DIAGNOSES= 11.947 + 0.001 x Ca 125 – 0.056 x ESR

HISTOPATHOLOGICAL DIAGNOSES= 12.806 + 0.849 x US TUMOR DIMENSIONS + 5.524 x METASTASES – 2.980 x ASCITES

Table III. Adnexal masses: diameter, metastases and ascites in various histopathological findings.

Diagnosis		Metastases		Ascites		Tumor diameters		
		Yes	No	Yes	No	<5cm	5-10cm	>10cm
Benign	Simple ovarian cyst	0	141	14	127	28	84	29
	Endometriotic cyst	0	110	10	100	27	68	15
	Hemorrhagic cyst	0	28	1	27	7	16	5
	Teratoma	0	61	1	60	18	34	9
	Benign ovarian cystadenoma	0	58	5	53	15	31	12
	Ovarian fibrothecoma	0	29	5	24	2	22	5
	Other diagnoses	0	8	0	8	1	7	0
Borderline		0	20	8	12	2	10	8
Malignant	Serous adenocarcinoma	9	14	14	9	4	15	4
	Mucinous adenocarcinoma	3	5	3	5	0	3	5
	Granulose cell tumor	2	4	5	1	2	4	0
	Endometrioid carcinoma	5	7	8	4	2	2	8
	Papillary adenocarcinoma	10	8	15	3	3	8	7
	Krukenberg tumors	7	0	7	0	2	5	0
	Other malignant diagnoses	5	6	8	3	1	5	5

Table IV. Adnexal masses: sonographic characterization.

Diagnosis		Multilocularity		Bilaterality	
		Yes	No	Yes	No
Benign	Simple ovarian cyst	103	38	55	86
	Endometriotic cyst	70	40	41	69
	Hemorrhagic cyst	18	10	10	18
	Teratoma	41	20	23	38
	Benign ovarian cystadenoma	40	18	30	28
	Ovarian fibrothecoma	21	8	13	16
	Other diagnoses	7	1	3	5
Borderline		16	4	6	14
Malignant	Serous adenocarcinoma	15	8	14	9
	Mucinous adenocarcinoma	7	1	1	7
	Granulose cell tumor	3	3	1	5
	Endometrioid carcinoma	9	3	5	7
	Papillary adenocarcinoma	15	3	9	9
	Krukenberg tumors	7	0	5	2
	Other malignant diagnoses	6	5	3	8

Most investigated parameters used in everyday triage of adnexal masses have again proved to predict the nature of adnexal tumors. Unfortunately, none of the examined parameters can accurately predict the exact diagnosis of the adnexal tumor, as no significant models were made for each specific histopathological diagnosis.

The studied parameters were good discriminating factors between histopathological diagnoses of adnexal tumors. We obtained one statistically significant function (eigenvalue =3.864; % of variance=48.6%; canonical correlation=0.891; Wilks λ=0.009; χ^2=262.450; p=0,000). From the largest group centroids for significant function, it can be concluded that metastases and

Table V. Mean levels of tumor markers, ESR and RMI in various histopathological findings of adnexal masses.

Diagnosis		Ca 125	Ca 19.9	CEA	Ca 15.3	ESR	RMI
Benign	Simple ovarian cyst	63.32	21.59	1.96	19.40	21.06	182.57
	Endometriotic cyst	79.96	28.01	1.72	19.56	17.59	185.22
	Hemorrhagic cyst	41.97	17.54	1.50	15.08	22.29	145.45
	Teratoma	37.64	27.57	2.24	21.19	18.07	111.03
	Benign ovarian cystadenoma	53.47	18.56	1.33	23.25	21.37	210.11
	Ovarian fibrothecoma	36.95	30.63	1.64	16.33	25.55	85.48
	Other benign diagnoses	62.40	7.11	1.47	0.00	9.00	158.12
Borderline		281.06	25.11	2.28	11.83	26.50	1708.39
Malignant	Serous adenocarcinoma	1255.53	10.66	1.38	156.12	47.78	4667.93
	Mucinous adenocarcinoma	55.85	376.67	13.27	15.63	31.13	372.25
	Granulose cell tumor	145.70	3.00	0.20	12.00	29.83	1242.68
	Endometrioid carcinoma	487.73	24.01	3.54	548.42	53.33	1154.95
	Papillary adenocarcinoma	1234.93	15.60	2.16	55.30	33.00	6433.36
	Krukenberg tumors	185.43	36.46	8.34	114.87	28.43	1215.00
	Other malignant diagnoses	2103.47	21.50	10.53	93.25	41.27	9299.21

ascites are the most expressed in the group of other malignant tumors, Krukenberg tumors, endometrioid tumors and serous adenocarcinomas. They are almost never present in fibrothecomas. Metastases and ascites discriminate the above mentioned tumors well from other histopathological diagnoses of adnexal masses (Table VI).

Discussion

According to the literature, papillary serous cystic adenocarcinoma is usually the most common type, followed by mucinous, endometrioid, yolk sac, dysgerminoma and adult granulose cell tumor [7]. In some populations, papillary serous adenocarcinoma was diagnosed in 25 - 54% of patients, endometrioid adenocarcinoma and mucinous tumor of low malignant potential in about 20%, poorly differentiated adenocarcinoma in 18%, granulose cells tumor in 5 - 7%, papillary adenocarcinoma and ring cell adenocarcinoma in 5%, endometrioid in 10.6%, dysgerminoma (4%), while yolk sac in just 2.6% [1,7]. The above mentioned distribution of the malignant tumors was confirmed in our study as well.

It is well known that malignant mixed Mullerian tumors are rare and usually occur in older women [8]. Mucinous, clear cell and transitional cell tumors are rare, comprising less than 10% of epithelial ovarian cancers [2]. In our study there were also only a few (less than 5) cases of these tumors.

The literature data show that the one-year incidence of new simple cysts is 8%. Simple ovarian cysts are fairly common among both pre- and postmenopausal women, and most appear stable or resolve by the next annual exam. Simple cysts were seen in 14% of women the first time their ovaries were visualized [9]. In some studies histopathology revealed 15.0% of functional cysts, 22.1% retention cysts, 6.4% endometriomas, 2.1% cystic teratomas, 8.6% undifferentiated cysts and 45.7% cystadenomas [10]. The incidence of these benign adnexal masses was similar in our study as well.

We found that ovarian masses usually have nonspecific symptoms or even are asymptomatic, what was also the finding of other investigations [7, 11].

Germ cell tumors are usually present in younger women [12, 13]. The relative risk for ovarian malignancy, among patients with ovarian malignant and benign (endometriotic cysts or physiological cysts) tumors, increased significantly after the age of 40 [14]. In some studies the average age of patients diagnosed with Krukenberg tumor was 48.6 years (range: 24 to 78 years) [15]. We found that although malignant tumors were more frequent in older women, endometriotic carcinoma and Krukenberg tumors were present in premenopausal women quite often.

The presence of ascites, abdominal distension, urinary complaints and loss of appetite and weight are considered to be significant individual risk factors indicating malignant potential. However, none of the individual risk factors is discriminatory between a benign and malignant cyst [14]. Furthermore, there are no specific ovarian carcinoma symptoms, either in early or later stages, to enable early diagnosis, but in the age group above 40 years persistent clinical symptoms should always be thoroughly investigated [7]. The risk of endometriosis increases in women with endometriosis-related symptoms. However, they are of limited predictive value for endometriosis, as only a small proportion of symptomatic patients are diagnosed with endometriosis in the follow-up [16]. In our study we also did not find any significant differences between tumor types regarding their symptoms and did not accurately determine factors that could predict the nature of the adnexal mass.

The literature presents cases where patients developed a Pseudo-Meigs syndrome consisting of a malignant ovarian tumor associated with ascites and pleural effusion without

Table VI. Relationship between discriminating variables and standardized canonical discriminant functions (variables ordered by absolute size of correlation within function).

Discriminant analysis		Significant function
		1
Examined parameters	Ascites	0.764(*)
	Metastases	0.631(*)
	Ca19.9	0.009
	RMI	0.271
	Bilaterality	0.074
	US dimensions	0.010
	Ca15.3	0.153
	Ca125	0.179
	Solid parts	0.171
	CEA	0.162
	Symptoms	-0.191
	Multilocularity	-0.014
	Menopause	0.136
	ESR	0.212
Functions at group centroids	Serous Adenocarcinoma	2.101
	Mucinous Adenocarcinoma	0.670
	Endometrioid Ca	2.223
	Other malignant diagnoses	3.340
	Krukenberg tumors	2.979
	Granulose cell tumors	0.604
	Papillary adenocarcinoma	1.902
	Other benign diagnoses	-0.678
	Simple ovarian cyst	-1.384
	Endometriotic cyst	-1.035
	Hemorrhagic cyst	-1.475
	Teratoma	-1.497
	Benign ovarian cystadenoma	-1.336
	Ovarian fibrothecoma	-1.767

* Largest absolute correlation between each variable and any discriminant function

malignant cells. Therefore, patients who present with ascites and benign pleural effusion should be first of all considered to have Krukenberg tumors [17]. This is consistent with our findings, and, moreover, all our patients with Krukenberg tumors had accompanying ascites.

Benign adnexal masses associated with ascites are unusual. Nevertheless, the literature reports cases of nulliparous women of childbearing age with abdominal distension and massive bloody ascites, a pelvic mass, dysmenorrhea, abdominal pain, weight loss, eventual pleural effusion, an increased Ca-125 level suggestive of ovarian cancer in which the final histological report showed endometriosis [18, 19]. Endometriosis-related ascites and/or pleural effusion is associated with extensive disease. Therefore, clinicians should consider endometriosis in differential diagnosis of pelvic masses and also include the disease in diagnostic workup of ascites or pleural effusion [20]. According to our results, ascites can be found in all types of tumor (benign, borderline and malignant).

Germ cell tumors, sex cord-stromal tumors, sarcomas and lymphomas are significantly more often unilateral [13]. Bilateral ovarian tumors, particularly in premenopausal women, must raise a high index of suspicion for Krukenberg tumors, before or during surgery [21]. Ovarian fibrothecomas are uncommon (3-4% of ovarian tumors) and unilateral in 90% of the cases. Nevertheless, rare reports of bilateral ovarian fibrothecomas in postmenopausal women [22], as well as a case of a woman with cystadenofibromas involving both ovaries [23], have been described in the literature. The results of our study show that there were no significant differences between tumor types regarding their multilocularity or bilaterality. Numerous simple and endometriotic cysts, as well as all malignant tumors, were multilocular. Also, all specific tumor types were present on both ovaries.

Serous ovarian carcinomas are much more prone to give metastases in lymph nodes than non-serous histological types (59.3% and 14.4%, respectively). In a study by Haller et al., early spread was predominantly found in the para-aortic region in both groups, serous and non-serous. Moreover, the pattern of lymph node distribution metastatic findings did not differ between the two groups and was similar in the pelvic and para-aortic regions [24]. In our study only papillary adenocarcinoma was found to produce early metastases.

Assessment for early detection of ovarian cancer can be achieved using tumor markers such as CEA, Ca 19.9, Ca 15.3 combined with Ca-125 levels. Levels of Ca-125 may indicate the disease extent and therefore the likelihood of successful cytoreductive surgery. Ca-125 efficiency for ovarian cancer has been previously reported between 70 and 90%. Screening with Ca-125 measurement and transvaginal ultrasonography every 6 months has been recommended for high-risk women, although evidence is insufficient to conclude that current screening methods improve their survival rates [6]. Moreover, somewhat elevated levels of Ca-125 can be detected in many non-malignant gynecological diseases, especially endometriosis, and even some physiological conditions. A combination of serum and molecular markers such as serum Ca125, Ca19 and mRNA for Survivin gene could allow a better triage between endometriosis and malignant adnexal masses [25]. In our study, women with malignant tumors had the highest levels of Ca 125, but there were no significant differences between women with benign and borderline tumors. There were also no significant differences between tumor types (benign, borderline, malignant) considering mean levels of Ca 19.9, Ca 15.3 and CEA. Furthermore, there were no significant differences within the malignant tumors regarding the levels of all examined tumor markers.

Serum levels of Ca-125 and ultrasound findings of ovarian tumors as the only criteria of malignancy prediction are not sufficiently precise and reliable. RMI calculation increases the accuracy of the preoperative diagnosis [26]. Jacobs et al., introduced the Risk of Malignancy Index (RMI) - the first diagnostic model that combined demographic, sonographic and biochemical parameters while investigating patients with adnexal masses. The RMI of 200 has been proven to be the best for

distinguishing between benign and malignant adnexal masses, with high level of sensitivity (51-90%) and specificity (51-97%) [27]. Studies have shown that the risk for malignancy of adnexal tumors based on RMI correlates with histopathological findings [27]. Moreover, RMI is a simple, easily applicable method in the primary evaluation of adnexal masses with high risk of malignancy, resulting in timely referral to gynecological oncology centers for suitable surgery [28].

Therefore, it is widely accepted that RMI presents the most reliable factor that could preoperatively predict the correct diagnosis and the stage of the adnexal masses [11]. According to our results, RMI remains the best preoperative triage tool for distinguishing between benign and malignant adnexal masses, but it could not differentiate between histopathological types of malignant or benign tumors. However, there are also new algorithms that contribute to preoperative triage of tumor masses such as the risk ovarian malignancy algorithm (ROMA). It is a logarithmic equation that combines levels of Ca 125 with a novel ovarian cancer tumor marker HE 4. Predictive index is calculated differently for pre- and postmenopausal women. The ROMA cutoff values for high-risk patients were ≥13.1% and ≥27.7% for pre-menopausal and post-menopausal women, respectively. Calculating ROMA index can improve the sensitivity of currently used serum Ca125 and RMI in differentiating ovarian cancer from other pelvic masses, even in early stages. ROMA performs equally well as the ultrasound depending RMI (sensitivity more than 80%) and might be valuable as the first line biomarker for selecting high risk patients for referral to a tertiary center and further ultrasound diagnostics and RMI calculations [29, 30]. Further studies ought to be undertaken in order to assess if ROMA can predict the exact histopathological diagnosis of adnexal masses.

Conclusion

All malignant and borderline tumors are more frequent in postmenopausal women, while all benign tumors types are more common in premenopausal women, although endometrioid carcinomas and Krukenberg tumors can often be found in younger women as well. Symptoms are not specific and reliable. Endometrioid carcinomas are mostly >10cm, while all benign diagnoses are mostly driven from tumors from 5-10cm. Only papillary adenocarcinoma significantly more often produces early metastases. Ascites is a usual finding in Krukenberg tumors, granulose cell tumors and papillary adenocarcinoma. Both simple and endometriotic cysts, as well as malignant tumors, can be multilocular and/or bilateral.

In our study, the Ca 125 level was the highest in serous adenocarcinoma, papillary adenocarcinoma and in the group of 'other malignant tumors'. Ca 19.9 was the highest in mucinous adenocarcinomas and the lowest in granulose cell tumors. Ca 15.3 was the highest in endometrioid carcinomas, while CEA in mucinous adenocarcinomas and the group of 'other malignant tumors'. ESR was the highest in endometrioid carcinomas and the lowest in the group of 'other benign tumors'. The highest RMI was calculated in papillary adenocarcinomas and in the group of 'other malignant tumors', while fibrothecomas had the lowest RMI. Only a few cases of serous and endometrioid adenocarcinomas, as well as some examples from the group of 'other malignant tumors', were assessed as low risk adnexal masses, while all other malignant tumors were in the groups of intermediate or high risk.

According to our results, patient age, menopausal status, blood levels of Ca 125, CEA and ESR, ultrasound scan and RMI can predict the nature of the adnexal tumor. Regardless, none of the examined parameters can accurately predict the exact diagnosis of adnexal masses.

Acknowledgement

This work was supported by Grant No 175062 from the Ministry of Science and Technological Development of the Republic of Serbia.

References

1. Rivas-Corchado L, González-Geroniz M, Hernández-Herrera R. Epidemiological profile of ovarian cancer. *Ginecol Obstet Mex.* 2011, 79, 558-564.
2. Bamias A, Psaltopoulou T, Sotiropoulou M, [et al.]. Mucinous but not clear cell histology is associated with inferior survival in patients with advanced stage ovarian carcinoma treated with platinum-paclitaxel chemotherapy. *Cancer.* 2010, 116, 1462–1468.
3. Mackay H, Brady M, Oza A, [et al.]. Prognostic relevance of uncommon ovarian histology in women with stage III/IV epithelial ovarian cancer. *Int J Gynecol Cancer.* 2010, 20, 945-952.
4. Munksgaard P, Blaakaer J. The association between endometriosis and ovarian cancer: a review of histological, genetic and molecular alterations. *Gynecol Oncol.* 2012, 124, 164-169.
5. Sekizawa A, Amemiya S, Otsuka J, [et al.]. Malignant transformation of endometriosis: application of laser microdissection for analysis of genetic alterations according to pathological changes. *Med Electron Microsc.* 2004, 37, 97-100.
6. American College of Obstetricians and Gynecologists. Committee Opinion No. 477. The role of the obstetrician–gynecologist in the early detection of epithelial ovarian cancer. *Obstet Gynecol.* 2011, 117, 742–746.
7. Khan A, Sultana K. Presenting signs and symptoms of ovarian cancer at a tertiary care hospital. *J Pak Med Assoc.* 2010, 60, 260-262.
8. Arora P, Rao S, Khurana N, [et al.]. Malignant mixed Mullerian tumor of broad ligament with synchronous ovarian and endometrial carcinoma: A rare association. *J Can Res Ther.* 2011, 7, 88-91.
9. Greenlee R, Kessel B, Williams C, [et al.]. Prevalence, incidence and natural history of simple ovarian cysts among women over age 55 in a large cancer screening trial. *Am J Obstet Gynecol.* 2010, 202, 373.e1–373.e9.
10. Gerber B, Müller H, Külz T, [et al.]. Simple ovarian cysts in premenopausal patients. *Int J Gynaecol Obstet.* 1997, 57, 49-55.
11. Dotlic J, Terzic M, Likic I, [et al.]. Evaluation of adnexal masses: correlation of clinical stage, ultrasound and hystopathological findings. *Vojnosanit Pregl.* 2011, 68, 861-866.
12. Guerriero S, Testa A, Timmerman D, [et al.]. Imaging of gynecological disease: clinical and ultrasound characteristics of ovarian dysgerminoma. *Ultrasound Obstet Gynecol.* 2011, 37, 596-602.
13. Alcázar J, Guerriero S, Pascual M, [et al.]. Clinical and sonographic features of uncommon primary ovarian malignancies. *J Clin Ultrasound.* 2011, 40, 323-329.
14. Tay SK, Tan YY. Risk factors and a risk scoring system for the prediction of malignancy in ovarian cysts. *Aust N Z J Obstet Gynaecol.* 1992, 32, 341-345.
15. Jun SY, Park JK. Metachronous Ovarian Metastases Following Resection of the Primary Gastric Cancer. *J Gastric Cancer.* 2011, 11, 31–37.
16. Abbas S, Ihle P, Köster I, Schubekt I. Prevalence and incidence of diagnosed endometriosis and risk of endometriosis in patients with endometriosis-related symptoms: findings from a statutory health insurance-based cohort in Germany. *Eur J Obstet Gynecol Reprod Biol.* 2012, 160, 79-83.
17. Bayod M, Carlón M, Idoate M. Pseudomeigs syndrome in a patient with Krukenberg's tumor. *Rev Med Univ Navarra.* 2007, 51, 19-22.
18. Sait K. Massive ascites as a presentation in a young woman with endometriosis: a case report. *Fertil Steril.* 2008, 90, e17-e19.
19. Dias C, Andrade J, Ferriani R, [et al.]. Hemorrhagic ascites associated with endometriosis. A case report. *J Reprod Med.* 2000, 45, 688-690.
20. Gungor T, Kanat-Pektas M, Ozat M, Zayifoglu Raaca M. A systematic review: endometriosis presenting with ascites. *Arch Gynecol Obstet.* 2011, 283, 513-518.
21. Mateş I, Iosif C, Bănceanu G, [et al.]. Features of Krukenberg-type tumors--clinical study and review. *Chirurgia.* 2008, 103, 23-38.

22. Salemis N, Panagiotopoulos N, Papamichail V, [et al.]. Bilateral ovarian fibrothecoma. An uncommon cause of a large pelvic mass. *Int J Surg Case Rep.* 2011, 2, 29-31.

23. Ewing T, Suh-Burgmann B. Preservation of fertility after partial resection of bilateral ovarian cystadenofibromas: a case report. *J Reprod Med.* 2011, 56, 364-365.

24. Haller H, Mamula O, Krasevic M, [et al.]. Frequency and distribution of lymph node metastases in epithelial ovarian cancer. *Int J Gynecol Cancer.* 2011, 21, 245-250.

25. Mabrouk M, Elmakky A, Caramelli E, [et al.]. Performance of peripheral (serum and molecular) blood markers for diagnosis of endometriosis. *Arch Gynecol Obstet.* 2012, 285, 1307-1312.

26. Antovska S, Bashevska N, Aleksioska N. Predictive Values of the Ultrasound Parameters, CA-125 and Risk of Malignancy Index in Patients with Ovarian Cancer. *Klin Onkol.* 2011, 24, 435-442.

27. Terzic M, Dotlic J, Likic Ladjevic I, [et al.]. Evaluation of the risk malignancy index diagnostic value in patients with adnexal masses. *Vojnosanit Pregl.* 2011, 68, 589-593.

28. Ashrafgangooei T, Rezaeezadeh M. Risk of malignancy index in preoperative evaluation of pelvic masses. *Asian Pac J Cancer Prev.* 2011, 12, 1727-1730.

29. Karlsen M, Sandhu N, Høgdall C[et al.]. Evaluation of HE4, CA125, risk of ovarian malignancy algorithm (ROMA) and risk of malignancy index (RMI) as diagnostic tools of epithelial ovarian cancer in patients with a pelvic mass. *Gynecol Oncol.* 2012, 127, 379-383.

30. Anton C, Carvalho F, Oliveira E, [et al.]. A comparison of CA125, HE4, risk ovarian malignancy algorithm (ROMA), and risk malignancy index (RMI) for the classification of ovarian masses. *Clinics* (Sao Paulo). 2012, 67, 437-441.