



Evaluation of adnexal masses: correlation between clinical, ultrasound and histopathological findings

Evaluacija adneksalnih masa: korelacija između kliničkih, ultrazvučnih i histopatoloških nalaza

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Abstract

Background/Aim. Concerning the growth of ovarian carcinoma incidence and bad prognosis for malignant forms, early and precise diagnostics is gaining in importance as a condition for precise and appropriate therapy for ovarian tumor masses. The aim of this study was to analyze pre- and postoperative findings of patients with adnexal masses in order to identify factors which could predict the nature and stage of the tumor prior to surgery. **Methods.** All patients with adnexal masses who were treated in a 6-month period in the Institute of Obstetrics and Gynecology, Clinical Center of Serbia, (IOG, CCS), Belgrade, had their epidemiologic and gynecologic anamnesis and standard laboratory analyses taken prior to surgery. Also, clinical and ultrasonographic check up of pelvic organs was performed, as well as calculation of body mass index (BMI) and risk of malignancy index (RMI). After surgery we analyzed histopathological (HP) findings of tumors as a mean of final diagnosis and staging. For statistical analysis, we used SPSS 15 program. **Results.** Throughout a 6-month period, we

examined 81 patients with adnexal masses treated in the IOG CCS. HP findings showed that there were significantly more benign ($n = 51$) than malignant ($n = 30$) tumors in all the patients ($\chi^2 = 5.512$). The patients with malignant HP findings were significantly older than those with benign adnexal masses ($t = 3.362$; $p = 0.001$). Significantly more patients with malignant HP findings were in menopause ($p = 0.034$). BMI values were highly significantly higher in the patients with malignant adnexal tumors ($t = 3.421$; $p = 0.001$). There was a statistically significant positive correlation between HP categories (benign, malignant) and RMI categories (low, intermediate and high risk) of all the patients (high risk, more malignant HP) ($R_{0xy} = 0.428$; $df = 78$; $p = 0.000$). **Conclusion.** Patients in menopause, especially older ones, with high BMI and RMI should immediately be referred to a tertiary level institution, where appropriate surgery could be performed.

Key words:

ovarian neoplasms; risk assessment; ultrasonography; body mass index; menopause; histological techniques.

Apstrakt

Uvod/Cilj. S obzirom na porast incidencije tumora jajnika u populaciji i lošu prognozu malignih promena, rana i precizna dijagnostika postaje sve značajnija kao preduslov za pravilnu i efikasnu terapiju tumorskih promena jajnika. Cilj studije bio je analiza pre- i postoperativnih nalaza kod bolesnica sa adneksalnim masama radi identifikacije faktora koji bi preoperativno mogli ukazati na prirodu i stadijum bolesti. **Metode.** Svim bolesnicama sa adneksalnim tumorima lečenim u Institutu za ginekologiju i akušerstvo Kliničkog centra Srbije (IGA, KCS), Beograd, tokom 6-mesečnog perioda uzete su preoperativno epidemiološka i ginekološka anam-

neza, urađene su standardne laboratorijske analize, klinički i ultrazvučni pregled organa male karlice, određen indeks telesne mase (BMI) i izračunat indeks rizika od malignosti (RMI). Posle operativnog zahvata analizirani su histopatološki (HP) nalazi odstranjenih adneksalnih tumora u cilju konačne dijagnostike i određivanja stadijuma bolesti. Za statističku analizu korišćen je statistički program SPSS 15. **Rezultati.** U toku 6-mesečnog ispitivanja u IGA KCS lečila se 81 bolesnica sa tumorom adneksa. Histopatološkim nalazom značajno češće je registrovan benigni ($n = 51$), nego maligni ($n = 30$) tumefakt kod svih ispitanica ($\chi^2 = 5,512$). Ispitanice sa malignim HP nalazom bile su visokoznačajno starije od ispitanica sa benignim promenama adneksa ($t = 3,362$; $p = 0,001$). Značajno više bilo je ispitanica u me-

nopauzi sa malignim HP nalazom ($p = 0,034$). Vrednosti BMI bile su visokoznačajno više kod ispitanica sa malignim tumorom ($t = 3,421$; $p = 0,001$). Postoji statistički značajna pozitivna povezanost kategorija HP nalaza (maligni, benigni) i kategorija rizika (nizak, srednji i visok) svih ispitanica (veći rizik, maligniji HP) ($R_{Oxy} = 0,428$; $df = 78$; $p = 0,000$).

Zaključak. Bolesnice u menopauzi, naročito starije, sa vi-

sokim BMI i RMI trebalo bi odmah uputiti u ustanovu tercijarnog nivoa, u kojoj se može sprovesti operativni zahvat neophodne opsežnosti.

Ključne reči: jajnik, neoplazme; rizik, procena; ultrasonografija, telesna masa, indeks; menopauza; histološke tehnike.

Introduction

Ovaries are highly capable of producing both benign and malignant tumors throughout a woman's life. Due to the complex ovarian structure, histopathological (HP) findings of adnexal tumors can be quite different¹. Although ovarian cancer is sixth in frequency among all malignant tumors, the mortality it takes has the leading place^{2,3}. Numerous factors influence the development and growth of adnexal tumors such as heritage, hormones, alimentation, surrounding, etc^{4,5}. Assuming that etiology and pathogenesis is complex and still not completely clarified, ovarian cancer presents a great diagnostic challenge. Early, correct and detailed diagnostics, adequate preoperative stage evaluation and preparation as well as up-to-date therapy are obligatory for adequate treatment of ovarian carcinoma².

The aim of the study was to analyze pre- and postoperative findings in patients with adnexal masses in order to identify factors which could preoperatively imply on the nature and stage of the tumor and in that way refer high-risk patients to a tertiary institution where appropriate (radical) operative procedures could be done.

Methods

The study included all consecutive patients with adnexal masses hospitalized at the Institute of Gynecology and Obstetrics, Clinical Center of Serbia during the first six months of 2010. Preoperatively, from all patients, basic epidemiological data (age, educational level, occupation, and residency) and gynecological anamnesis (menarche age, parity, last menstrual cycle, and symptoms) were taken, as well as the standard laboratory analysis (blood analysis, sedimentation, tumor marker levels). Furthermore, clinical and ultrasonographic examinations of pelvic organs (tumor dimensions, multilocular or bilateral tumor, solid/cystic components/ parts, metastasis and free fluid presence) were performed and body mass index (BMI) was assessed. Finally, risk of malignancy index (RMI) for all the patients was calculated, using the formula: $RMI = U \times M \times Ca125$. In the formula U represents the ultrasonographic index. Multilocular and bilateral tumors, the presence of solid parts in tumor, metastasis and ascites are marked with one point each. The sum of these points, are scored so that in the formula $U\ 0 = 0$ points, $U\ 1 = 1$ points, $U\ 2 - 5 = 3$ points. In the formula M represents menopausal status (1 for premenopausal and 3 for postmenopausal women). Values of Ca125 are calculated directly to the equation. The patients were divided into three groups according to the RMI values (low risk < 25 , interme-

diat risk 25–200, high risk > 200). After surgery, the HP findings of excised tumors were analyzed in order to make the final diagnosis and the stage of the disease. For statistical analysis of the achieved data we used: mean value, measurements of variability (confidence interval and standard deviation), Kolmogorov-Smirnov Z test, Friedman's parametric ANOVA, Kruskal – Wallis nonparametric ANOVA, Rank-sum test, χ^2 test, Fisher's test and Spearman's nonparametric rank correlation. For data analysis SPSS 15 computer program was used.

Results

During a 6-month investigation period at the Institute of Gynecology and Obstetrics there were 81 patients with adnexal tumors. Out of that number 51 (62.96%) patients were still in their reproductive period, while 30 (37.04%) women were already in menopause. The age of the women with adnexal masses was in the range of 66 years (min = 16, max = 82), with an average of 44.138 (SD = 14.496) years. The values of the patients' age correspond with the model of normal data division. The confidence interval of the age in which the investigated women had menarche was 7 years (min = 10, max = 17) and the average age was 13.188 (SD = 1.543) years. These values were also normally divided. BMI values of the patients range from minimal 19.0 kg/m² to maximal 37.1 kg/m² ($i = 18.1$), while the mean value was 24.805 (SD = 4.208) kg/m². The values of the women's BMI act according to the normal distribution model and age are presented in Figure 1. Minimal number of births, miscarriages and abortions was 0. The women maximally had 4 births, 3 miscarriages and 10 abortions. Tumor dimensions were in an interval from 1 to 20 cm ($i = 19$), with a mean value of 7.278 (SD = 3.787) cm. Sedimentation values varied from normal – referral to maximal 129 and the mean value was 21.675 (SD = 24.188). Ca125 values vary from minimal 2.4 do maximal 963.6 U/mL ($i = 960.6$), although, one extreme value Ca125 of 13,623.0 had to be excluded so that the statistical analysis could be more correct. The mean value was 120.343 (SD = 195.895) U/mL, median 30.700 U/mL, and mode 10.000 U/mL. The calculated RMI values range from 0.0 to 6,912 with the mean value of 407.776 (SD = 1,105.623), median of 37.400 and mode of 0.000. From this analysis one extreme RMI value of 122,607.00 was excluded.

Frequency in all the patients with adnexal masses does not differ significantly ($p > 0.05$) concerning the categories of these characteristics: educational level ($\chi^2 = 0.312$), biochemical analysis ($\chi^2 = 1.823$) and the presence of one

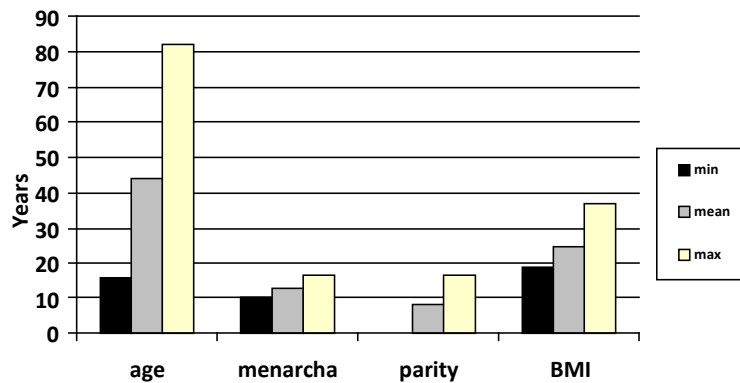


Fig. 1 – Minimal (min), maximal (max) and mean values of investigated parameters (BMI – Body Mass Index)

symptom ($\chi^2 = 2.112$). Frequency in all the patients with adnexal masses significantly differs ($p < 0.05$) concerning the categories of these characteristics: HP findings, menopausal status, RMI, symptoms type and highly significantly ($p < 0.01$) concerning the categories of these characteristics: residency, blood analysis, tumor dimensions and the presence of the symptoms. Frequencies in patients regarding the investigated parameters are shown in Table 1.

less frequent were the patients with high RMI and more frequent the patients with low RMI ($\chi^2 = 7.600$, $df = 2$). There were significantly less women with vaginal bleeding ($\chi^2 = 7.295$, $df = 2$) as well as with a symptom combination – pain and other symptoms ($\chi^2 = 8.001$, $df = 2$). Out of all the women with adnexal masses highly significantly more women ($\chi^2 = 26.406$) had referral blood analysis. Highly significantly more ($\chi^2 = 13.075$, $df = 2$) tumors had diameter

Table 1

Frequencies in patients regarding the investigated parameters

Parameter	Parameter categories	Frequencies in number (%) of patients		
		Total	Malignant	Benign
Educational level	Primary and secondary	44 (54.32)	23 (76.67)	21 (41.18)
	High school and university	37 (45.68)	7 (23.33)	30 (58.82)
Residency	Belgrade	61 (75.31)	19 (63.33)	42 (82.35)
	Other	20 (24.69)	11 (36.67)	9 (17.65)
	None	33 (40.75)	11 (36.67)	22 (43.14)
Symptoms	Pain	16 (19.75)	4 (13.33)	12 (23.53)
	Vaginal bleeding	4 (4.94)	2 (6.67)	2 (3.92)
	Waist diameter enlargement and appetite loss	14 (17.28)	7 (23.33)	7 (13.73)
	Pain and vaginal bleeding	3 (3.7)	2 (6.67)	1 (1.96)
	Pain, waist diameter enlargement and appetite loss	9 (11.11)	3 (10)	6 (11.77)
	Pain, vaginal bleeding, waist diameter enlargement and appetite loss	2 (2.47)	1 (3.33)	1 (1.96)
Tumor diameter	≤ 5 cm	41 (50.62)	7 (23.33)	34 (66.67)
	5.1–10	25 (30.86)	11 (36.67)	14 (27.45)
	≥ 10 cm	15 (18.52)	12 (40)	3 (5.88)
Blood analyses	Correct	73 (90.12)	25 (83.33)	48 (94.12)
	Incorrect	8 (9.88)	5 (16.67)	3 (5.88)
Biochemical analyses	Correct	47 (58.02)	17 (56.56)	30 (58.82)
	Incorrect	34 (41.98)	13 (43.33)	21 (41.18)
Risk regarding RMI values	Low	36 (44.44)	5 (16.67)	31 (60.79)
	Medium	29 (35.8)	12 (40)	17 (33.33)
	High	16 (19.75)	13 (43.33)	3 (5.88)

RMI – Risk of Malignancy Index

In the HP findings there were significantly more often registered benign ($n = 51$, 62.96%) than malignant ($n = 30$, 37.04%) tumors in all the investigated women ($\chi^2 = 5.512$). Adnexal masses were significantly more rare in the menopausal than in the younger women ($\chi^2 = 5.512$). Significantly

ranging from 5.1 cm to 10 cm, and less diameter bigger than 10 cm. A significant difference ($\chi^2 = 64.204$, $df = 6$) regarding the symptom presence categories is due to the high frequency in patients without symptoms and a low frequency in patients with vaginal bleeding and a symptoms combination.

There were highly significantly more ($\chi^2 = 8,511$) patients with only one (any one) symptom than those with a symptoms combination. Highly significantly more patients ($\chi^2 = 21,012$) lived in Belgrade than anywhere else in Serbia.

When the preoperatively obtained data were compared with the HP findings of excised tumors the following results were gained. Frequencies in patients regarding the categories of both educational level (primary, secondary or high school and university) and HP findings (benign, malignant) did not differ significantly ($\chi^2 = 0.252$; $df = 1$; $p = 0.616$). Frequencies in patients when assessed both categories of patient's residency and HP findings did not differ significantly ($\chi^2 = 3.000$; $df = 1$; $p = 0.083$). Also, there were no significant differences ($p > 0.05$) regarding both categories of HP findings and examined factors: age at which patients had menarche ($t = 1.054$; $p = 0.295$), number of births ($W = 1677.000$; $Z = 0.954$; $p = 0.340$), number of miscarriages ($W = 1709.000$; $Z = 0.823$; $p = 0.411$) and abortions ($W = 872.500$; $Z = 0.048$; $p = 0.961$). Frequencies in patients when examined categories of biochemical analyses (correct, incorrect) together with categories of HP findings did not differ significantly ($\chi^2 = 0.010$; $df = 1$; $p = 0.920$; $p > 0.05$). Frequencies in patients regarding the categories of blood analyses (correct, incorrect) and HP findings did not differ significantly ($P = 0.125$; $p > 0.05$). Sedimentation values of women with adnexal masses do not differ significantly regarding the factor of categories of HP findings (benign, malignant) ($W = 1599.500$; $Z = 1.824$; $p = 0.068$). Tumor diameters did not significantly differ regarding the categories of HP findings ($W = 1737.500$; $\chi = 0.174$; $p = 0.862$). The values of tumor marker Ca125 statistically significantly differed regarding the categories of HP findings (benign, malignant) ($p < 0.05$).

Frequencies in patients with adnexal masses assessed regarding both the symptom presence (present, not present) and HP categories (benign, malignant) significantly differed ($\chi^2 = 1.029$; $df = 1$; $p = 0.310$). However, a more detailed analysis shows that there are no differences neither in HP findings and symptom types (pain, vaginal bleeding, other) ($P_{1,2} = 0.397$; $P_{1,3} = 0.311$; $P_{2,3} = 0.440$), presence of one or more than one symptom ($P = 0.260$), nor in symptom combinations (pain and vaginal bleeding; pain and other symptoms; pain, vaginal bleeding and other symptoms) ($P_{1,2} = 0.061$; $P_{1,3} = 0.250$; $P_{2,3} = 0.778$).

The age of the patients with adnexal masses significantly differed regarding the factor of categories of HP findings ($t = 3.362$; $p = 0.001$). The patients with malignant HP findings were highly significantly older than patients with benign adnexal masses. Frequencies in women when categories of menopausal status (pre or post menopause) and HP findings were evaluated together, were significantly different ($p = 0.034$). There were significantly more postmenopausal women with malignant HP findings in comparison with premenopausal patients with benign adnexal masses.

BMI values of the patients with adnexal masses significantly differed concerning the factor of the HP findings categories ($t = 3.421$; $p = 0.001$). BMI values were significantly

higher in the patients with malignant HP findings than in those with benign adnexal tumors.

Frequencies in patients with adnexal masses when categories of HP findings (benign, malignant) and categories of the risk for malignant adnexal tumor (low, intermediate, high), achieved by calculating RMI, were evaluated together, significantly differed ($\chi^2 = 18.624$; $df = 2$; $p = 0.000$). This difference was due to the rare malignant HP findings in the patients with low and intermediate RMI and benign HP findings in patients with high RMI ($\chi^2_{1,2} = 1.379$; $df = 1$; $P_{1,2} = 0.118$; $P_{1,3} = 0.00004$; $P_{2,3} = 0.002$).

Correlation of categories of HP findings (benign, malignant) and categories of the risk (low, intermediate, high) of all the patients was positive (higher-risk, malignant HP) and of highly significant strength ($R_{oxy} = 0.428$; $df = 78$; $p = 0.000$).

Discussion

According to the literature one of the factors which could predict the stage and survival of patients as well as the tumors recurrence is their age. Older patients are under higher risk for worse outcome^{2,5}. These data correspond with the results of our study which has proven that patients with malignant tumors are significantly older than those who had benign masses.

Authors emphasize the significance of environmental factors for the development of malignant adnexal masses⁴. Regarding the results of our study, which evaluated educational level, occupation and residency, there were no statistical differences between patients with benign and malignant tumors. Furthermore, there were no correlations at all of these factors with tumor development. There were more patients from Belgrade only, but this could be explained by the fact that Belgrade was the place where this study was conducted.

Pregnancy is considered to have protective effect on the development of ovarian cancer^{2,6}. Contrary to what might be expected, in the examined population, the number of pregnancies (births, miscarriages and abortions) did not show a significantly different distribution between benign and malignant adnexal masses. Therefore, pregnancy cannot be considered a clear predictive factor that could help in preoperative evaluation of adnexal masses.

Symptoms linked to ovarian carcinoma usually are pelvic and abdominal pain, waist diameter enlargement, appetite loss, nausea and frequent urination over a prolonged period⁷. Although these symptoms, in some studies, have the incidence of even 90% in older women, in the population we investigated, most women from both groups of patients with benign and malignant tumors, had no symptoms at all. Besides, neither one of the symptoms nor their combination, have significantly proven to be a clear predictive factor for malignant nature of the adnexal tumor. When the achieved results are taken into consideration, it can be concluded that even the asymptomatic patients demand detailed diagnostics.

The very fact that a woman is in menopause presents a risk that the adnexal mass is of malignant nature⁸, which is

confirmed by the results of our study. On the other hand, patients in the reproductive period more often have benign adnexal masses.

High BMI values have been connected to the breast and endometrial carcinoma so far. Contemporary investigations show that obesity can be a risk factor also for ovarian carcinoma. It is considered that in the etiology of all of the above-mentioned carcinomas hormonal mechanisms have the leading role, but they should still be examined more thoroughly^{6, 9}. The results of our study correspond with the literature data, that there is a statistically highly significant correlation between higher values of BMI and malignant HP findings of adnexal masses.

For differentiation of benign and malignant adnexal masses the method of RMI calculation is usually done^{10, 11}. Numerous studies have shown that RMI has high sensitivity, specificity and predictive value for adnexal tumor evaluation¹²⁻¹⁴. RMI calculation is a swift and easy method that does not need special technical equipment and therefore it is considered a method of choice for preoperative screening of adnexal masses^{15, 16}. Moreover, the risk which is assessed by this method is more reliable than to evaluate separately menopausal status, ultrasonographic findings and Ca125 level^{8, 17, 18}. The results obtained in this investigation point out a significant diagnostic contributions that RMI calculation offers to a preoperative evaluation of adnexal masses.

Although contrary to usual findings^{17, 18} and our expectations, no other investigated parameter (blood analyses, sedimentation, biochemical analyses) in our population had a statistical significance as a risk factor that could imply to the

malignant nature of the tumor, so, in a preoperative tumor evaluation and in the process of deciding on the radicalism of the procedure, they cannot be considered reliable.

Conclusions

The average age of the women with adnexal masses was 44.138 years. Adnexal masses are more frequent in the younger women. On the other hand, the patients with malignant HP findings are highly significantly older and more often postmenopausal, than patients with benign adnexal masses. Regarding the fact that patients are usually asymptomatic, regular gynecological check-ups are needed in order to diagnose pathological changes in early stages. The time of the first menstrual cycle, parity, tumor diameter, blood and biochemical analyses, as well as symptomatology are not good indicators of the nature (benign, malignant) and the clinical stage of adnexal masses. Levels of Ca125 are high in patients with malignant adnexal tumors. BMI values correspond to the risk level (lower BMI is in benign and higher in malignant tumors), so in a preoperative evaluation of adnexal masses a patient's BMI should be taken into consideration. HP findings and the risk categories (RMI low, intermediate, high) are in a positive correlation. Therefore, it can be concluded that RMI presents a significant factor that could preoperatively imply to the diagnosis and the stage of adnexal masses and consequently it is recommended that RMI is always calculated. Patients in menopause, especially older, with high BMI and RMI values should be immediately referred to a tertiary institution where appropriate extensive operative procedure could be performed.

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