

THE ROLE OF SERUM LEVEL OF TUMOR MARKER CA 125 IN DISTINGUISHING BENIGN FROM MALIGNANT OVARIAN TUMORS IN POSTMENOPUSUAL WOMEN AND CORRELATION WITH SONOGRAPHIC FINDING

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Malignant ovarian tumors occur at all ages, including early childhood, but also advanced old age, with the total incidence dramatically increasing with age. Tumor markers for early detection of ovarian carcinoma are used in ovarian cancer examination.

The aim of the study was to examine the degree of correlation between sonographic findings and the levels of serum tumor marker Ca 125, and to study a correlation of preoperative sonographic findings and serum marker level CA 125 with intraoperative finding and patohistopathological results.

The study was based on the prospective-retrospective study model involving 60 postmenopausal women diagnosed with the presence of ovarian tumor.

The following medical tests and examinations were performed for all patients: anamnesic analysis of the medical record, that is the history of the disease with the data on age, parity, duration of menopause, the use of oral contraceptives and symptomatology, small pelvis sonography, lab parameters - Ca 125 with referent ranges up to 35 ml/U. Laparotomy was used as an operative procedure in all patients. All material obtained operatively underwent histopathological treatment.

The group of patients with malignant tumors of high statistical significance showed considerably higher average CA125 values.

Among subjects with benign tumors, the dominant tumor structure was cystic, as opposed to the mixed-type tumors in malignant tumors. To this effect, the parameter of tumor structure is a serious factor in distinguishing between benign and malignant ovarian tumors.

Tumor location is, with high statistical significance, more often bilateral in subjects with histopathologically proven malignant tumors, while it is predominantly unilateral in benign tumors.

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Key words: CA125, ovarian tumors, postmenopausal, sonographic finding

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Introduction

Malignant ovarian tumors occur at all ages, including early childhood, but also advanced old age, with the total incidence dramatically increasing with age. The risk of ovarian carcinoma formation increa-

ses after the age of 40, with the incidence peak between 50 – 55 years of age. Ovarian carcinoma is in the fifth place immediately behind breast, lung, rectosigmoid colon and lymphoma cancer, with the highest mortality rate among the gynecologic cancers (1, 2).

Survival rate for ovarian cancer depends on the stage when the disease is detected. In this respect, survival is 93% in stage I, 70% in stage II, 37% in stage III and 20% in stage IV. Three-quarters of newly discovered ovarian carcinomas are in stage III and IV, where the five-year survival rate is below 50%. This leads to the conclusion how important early detection and treatment of ovarian cancer are.

The development of ovarian cancers is influenced by many factors. First of all, hereditary, environmental factors, prior pregnancies, breast feeding, oral contraceptives, infertility, substitution hormone therapy, oncogenic viruses, etc.

It is thought that malignant tumors can develop in many ways. The most likely path of development is by means of a benign epithelial neoplasm developed from serous inclusion cyst, developed again by the invagination of the serosa. This is followed by the malignant transformation into epithelium of the benign cyst or the epithelium in serous inclusion cyst can turn malignant without a previous benign phase or, in turn, ovarian serous cells may develop into epithelial malignancy de novo without the formation of the serous inclusion cyst. For a long time, it has been widely accepted that, in time, benign epithelial ovarian cysts may turn malignant (3).

Precisely, due to this complex and insufficiently clarified pathogenesis and unknown etiology, the incidence of malignant ovarian tumors cannot be prevented. Only early diagnosis in asymptomatic women and modern therapeutic approach have proven effective in this serious illness.

Tumor markers for early detection of ovarian carcinoma are used in ovarian tumor examination.

In the past 20 years, various methods for ovarian cancer detection (Papanicolaou test, peritoneal cytology examination, etc.) have been applied, but have not proven to be good enough. The latest methods of immunoscintigraphy, nuclear magnetic resonance and computed tomography may detect small cancers, but their invasiveness and price prevent them from becoming the main screening tests. The methods examined today as screening methods are: bimanual gynecological examination, ultrasound, tumor markers.

Bimanual examination has its advantages: it is relatively easy, it can fit into the already existing cervical screening program, and it does not require special equipment, thus the costs are low. However, neither the sensitivity nor the specificity of this test has been known so far.

The majority of studies looking into the value of ultrasound in the diagnosis of ovarian tumors included women with symptoms who were about to undergo the laparotomy due to suspected ovarian masses. They confirmed the concurrence between ultrasonography and operative findings regarding the size, position and characteristics of the ovarian tumor. Many researchers have tried to use the ultrasound to characterize benign and malignant tumors. However, a criterion with 100% specificity for malignant ovarian tumors has not been described so far. With all this in mind, Sassone and associates published a study in 1991 presenting a scoring system for an objective description of pelvic disease based on the transvaginal ultrasonographic characterization of the alteration (4). The proposed scoring system, used both for ovaries and extrauterine pelvic masses of unknown origin, is based on the following four criteria: the structure of interior tumor wall (1-4 points), thickness of the tumor wall (1-3 points), the presence and thickness of septa (1-3 points), 4 echogenicity (1-5 points). In order to obtain a scoring threshold that best separates malignant ovaries from the rest, the sensitivity and specificity for each score from 5-13 is calculated, based on which the curve is formed, the shape of which showed that the total

score of 9 points best distinguishes between benign and malignant lesions.

Primarily those are serum levels of alpha-feto-protein markers (AFP), CA 125, lactate dehydrogenase (LDH), CEA, and inhibin B. If there is suspicion that the tumor is hormone active and produces certain hormones, hormone analyses are performed and they serve as tumor markers. The most common are β HCG, estradiol and testosterone. In addition, tumor markers are used to monitor the effect of the therapy, as well as for the early detection of the recurrence of certain ovarian tumors (5).

CA 125 is antigenic determinant of high molecular weight glycoprotein recognized by the monoclonal antibody OC125. CA 125 is highly sensitive, but not a specific marker for tumors of ovarian epithelial cells. It may have elevated values in many intraperitoneal processes such as endometriosis, pregnancy, small pelvis inflammatory disease, Crohn's disease or other malignant abdominal tumors.

Ca 125 antigen may be detected in serum using radioimmunoassay, and serum levels are higher than 35 ml/U in over 80% of women with ovarian cancer (5). Bast and associates (6) also showed that only 1 % of healthy women had serum Ca 125 levels higher than 35 ml/U (6). Elevated levels may, however, be related to a benign gynecological pathology. However, the incidence of these benign conditions in postmenopausal women, the group that is most at risk of getting ovarian cancer, is low. A more detailed analysis however shows dependence on the stage of the disease. The disease spread outside the ovary is associated with the elevated levels of CA 125 in the serum in over 90% of cases. In the case where the tumor is restricted to ovarian tissue, CA 125 levels in the serum are increased only in 50% of cases (6).

Given that a high degree of specificity is required for the prospective screening program for ovarian cancer and given the link between CA 125 and non-malignant pathology, the positive predictive value of elevated serum CA 125 for this disease is considered too small to use only CA 125 as a screening test. The specificity could be enough if CA 125 were combined with ultrasonography. Such screening program is used in large centers worldwide, including the Royal London Hospital since 1985 (6).

Aims

The aim of this study was to examine the degree of correlation between the ultrasound finding with respect to the level of serum tumor marker Ca 125 and the correlation of preoperative ultrasonography and the level of serum CA 125 marker with intraoperative finding and pathohistopathological results.

Material and methods

The study was based on the prospective-retrospective study models involving 60 postmenopausal women diagnosed with the presence of ovarian tumor.

The research was carried out in the following

institutions: Clinic for Gynecology and Obstetrics at the Clinical Center Niš, Women's Health Service of the Health Center Niš, Clinic for Gynecology and Obstetrics of the Clinical Center Kragujevac, and Clinic for Gynecology and Obstetrics „Narodni front“ from Belgrade.

All patients underwent the following tests and examinations:

- Anamnestic health card analysis, history of the disease with the data on age, parity, duration of menopause, the use of oral contraceptives and symptomatology;

- Ultrasonography of the small pelvis;

- Lab parameters - Ca 125 with reference range up to 35 ml/U.

Laparotomy was used as an operative procedure in all patients. All material obtained operatively has undergone histopathological treatment.

The standard descriptive statistical methods were used in statistical data processing (mean value, standard deviation, representation in percentages, degrees of freedom). The assessment of the distribution type was carried out using Kolmogorov-Smirnov test. The assessment of the distribution significance

was carried out using the parametric t-test and non-parametric χ^2 statistical test, using a standard significance level.

Results

The reference ranges of all laboratories where the levels of serum Ca 125 tumor markers were tested are up to 35 U/L. Average Ca 125 values in the group of benign ovarian tumors amounted to 39.67 U/L, while in the group of women with malignant ones they amounted to 556.6 U/L, which is a difference in values with outstandingly high statistical significance.

In over one half of the subjects with benign tumors, Ca 125 levels were within the reference ranges up to 35 U/L. High marker values (over 100 U/L) were determined in 4 women from this category, whereby the presence of endometrial tumors was found in histopathological preparations after the laparotomy. Simultaneously, similar marker values were also found in the category of malignant tumors in 9 out of 15 subjects, as shown in Table 1 and 2.

Table 1. Distribution of values of CA 125 tumor marker

CA 125 m/U	Benign tumors	Malignant tumors
< 17.4	14	0
17.5 - 35	13	0
36 - 52.5	7	0
52.6 - 99	7	2
100 - 999	4	9
1000 >	0	4
Σ	45	15

Table 2. A correlation between the levels of tumor markers Ca 125 measured in benign and malignant tumors, with standard deviations in both categories

	\bar{X}	SD	Σ
Benign	39.67	± 34.8	45
Malignant	556.6	± 499.3	15

*T - test = - 7.08; $p < 0.01$ - significantly high statistical significance, $df = 58$

Tumor location is predominantly bilateral in the case of malignant tumors, while unilateral in benign ones, resulting in high statistical significance as shown in Table 3. The size of benign tumors is 7 cm on aver-

age, while the malignant tumors in the examined group of patients were over 9 cm, which makes high statistical significance, as shown in Tables 4 and 5.

Table 3. A correlation between the location of benign and malignant tumors, with standard deviations in both categories

	\bar{X}	SD	Σ
Benign	4.4	1	45
Malignant	2	13	15

$\chi^2 \rightarrow \infty$; $p > 0.001$ – high significance, $df = 1$

Table 4. The size of the tumor in the examined group of women

Tumor size in cm	Benign tumors	Malignant tumors
< 3 cm	0	0
4 – 5	8	0
6 – 7	23	2
8 – 9	7	5
> 10	7	8
Σ	45	15

Table 5. A correlation between the size of benign and malignant tumors, with standard deviations in both categories

	\bar{X}	SD	Σ
Benign	6.96	± 3.11	45
Malignant	9.04	± 4.12	15

T test = -2.8: $p = 0.006$ – high statistical significance, $df = 58$

The wall was significantly thicker in benign changes in 39 subjects and it amounted to 3 and more millimeters. In contrast, in malignant tumors, the thick-

ness of the tumor wall in 13 out of 15 subjects was 2 and below 2 mm, which has high statistical significance, as shown in Table 6.

Table 6. A correlation between the wall thickness of benign and malignant tumors, with standard deviations in both categories

	≤ 2 mm	≥ 3 mm	Σ
Benign	6	39	45
Malignant	13	2	15

$\chi^2 = \infty$; $p < 0.001$ – high statistical significance, $df = 1$

There are significant differences in the appearance of the wall of the change. While in benign ovarian tumors the interior of the wall is smooth, in malig-

nant tumors the interior of the wall is uneven and with numerous excrescences, as shown in Table 7.

Table 7. A correlation between the wall structure of benign and malignant tumors, with standard deviations in both categories

	Smooth	Uneven	Σ
Benign	40	5	45
Malignant	7	8	15

$$\chi^2 = 11.8, p < 0.001 - \text{high statistical significance, } df = 1$$

Discussion

A large number of previously conducted studies (7-9) showed that Ca 125 tumor marker was not specific enough in the differentiation of benign from malignant ovarian tumors. Van Calster and associates point out in their paper that serum Ca 125 value are more often false positive in premenopausal women compared to postmenopausal women, but that in both groups the ultrasonographic classification of changes in the ovary is by far a more reliable criterion for distinguishing between benign and malignant tumors (7). The average Ca 125 values in the examined population were considerably higher in the group of patients with malignant tumors $X = 556.6$ U/L versus $X = 39.6$ U/L in benign tumors. Hence, there is a high statistical significance. The results of this study are complementary to the results of the study led by Dr. Edward E. Partridge, University of Alabama and Birmingham (10). This study showed that Ca 125 values of more than 35 U/L could be considered suspicious (indicative of tumor), and that values greater than 65 U/L were a reliable predictor for tumor malignancy in asymptomatic menopausal women in combination with transvaginal ultrasound examination.

Differentiation between benign and malignant ovarian tumors is most important both for the patient and the physician. In most institutions, the operative procedure (laparoscopy or laparotomy) depends on the assessment of the malignancy of the change, but malignancy can be safely excluded by histopathological confirmation only (11, 12). Therefore, many prognostic models for the differentiation of malignant from nonmalignant ovarian tumors, including Doppler criteria, have been published so far and show significant validity (12-15).

In ultrasound diagnostics and in estimation of malignant potential for ovarian tumors, many scoring systems have been created that did not find broad application in clinical practice (10, 16). However, all data suggest that in terms of location in malignant tumor processes, the tumor is most often bilateral, in contrast to dominant one-sidedness in benign conditions. It is that assumption that was proven in the presented study. In addition, the size of benign tumors is up to 70 mm, while the malignant tumors in the examined group of patients are over 90 mm.

Benign ovarian tumors are primarily cystic in structure, in contrast to the mixed-type structure in malignant tumors. The thickness of the ovarian tumor wall is considerably higher in benign tumors,

which speaks in favor of their cystic and clearly limited structure. There are also significant differences in the appearance of the wall of the tumor alteration. While the interior of the wall is smooth in benign tumors, it is uneven and with numerous excrescences in malignant tumors. Papillary projection is a significant ultrasound sign of tumor malignancy. The degree of malignancy is proportional to the number of these papillary formations (16). Granberget al. showed that the risk of malignancy is 3-6 times higher in unilateral cysts with papillary formations compared to unilateral cysts without these formations, which makes the conservative tracking of these cysts unacceptable (16).

As an addition to the ultrasonographic morphological image of the tumor, other factors such as family history, the presence of free fluid in the pouch of Douglas and the presence of subjective symptoms should be taken into account when deciding on the optimal treatment. When it comes to benign alterations in the conducted study, the presence of free fluid in the pouch of Douglas was sporadically determined, while in malignant ovarian conditions this is one of almost regular clinical and ultrasound findings.

Conclusion

Average Ca 125 values were far higher in the group of patients with malignant tumors with high statistical significance. Among subjects with benign tumors, the dominant tumor structure was cystic, as opposed to mixed-type structure tumors in the malignant ones. In that sense, the parameter of tumor structure was a significant factor in distinguishing between malignant ovarian tumors.

Tumor location is, with high statistical significance, more often bilateral in subjects with histopathologically proven malignant tumors, while it is predominantly unilateral in benign tumors.

The size of benign tumors was around 70 mm on average, while the malignant tumors in the examined group of patients were over 90 mm. Based on this, tumor size is a reliable factor in distinguishing between benign and malignant ovarian tumors. The thickness of the wall of benign tumors is higher in relation to that of malignant ones, and this is a parameter of high statistical significance.

The presence of free fluid in the pouch of Douglas is rare in benign ovarian tumors, and as a rule, where determined, it is associated with the ruptures of the tumor wall (cyst) and most often it is below 50 ml, while in malignant ovarian tumors the

presence of free fluid is quite frequent, whereby the quantity is multiple times higher, and often filling the entire volume of Douglas.

The obtained results clearly demonstrated that detailed ultrasonography of the small pelvis and ad-

nexa and the levels of serum tumor marker Ca 125 are reliable parameters for the differentiation of benign from malignant ovarian tumors in postmenopausal women.

References

1. Silverberg E. Cancer statistics, 1985. *CA Cancer J Clin* 1985; 35(1): 19-35. [[PubMed](#)]
2. Chen KTK, Schooley JL, Flam MS. Peritoneal carcinomatosis after prophylactic oophorectomy in familial ovarian cancer syndrome. *Obstet Gynecol* 1985; 66(3): 93S-94S. [[CrossRef](#)][[PubMed](#)]
3. Radosavljević A, Stanković A, Petković S, Argirović R, Stefanović A, Plešinac S, et al. Palpabilni ovarijum u postmenopauzi – rizik od malignoma. XXXV ginekološko-akušerska nedelja SLD. Beograd, 1991: 244-8.
4. Vasilev S, Schlaerth J, Campeau J, Morrow P. Serum Ca-125 levels in preoperative evaluation of pelvic masses. *Obstet Gynecol* 1988; 71(5): 751-6. [[PubMed](#)]
5. Zurawski WR, Orjaseter H, Andersen A, Jellum E. Elevated serum CA 125 levels prior to diagnosis of ovarianneoplasia: relevance for early detection of ovarian cancer. *Int J Cancer* 1988; 42(5): 677-80. [[CrossRef](#)][[PubMed](#)]
6. Wolf SI, Gosnik BB, Feldsman MR, Lin MC, Stuenkel CA, Braly PS, et al. Prevalence of simple adnexal cysts in postmenopausal women. *Radiology* 1991; 180(1): 65-71. [[CrossRef](#)][[PubMed](#)]
7. Timmerman D, Van Calster B, Jurković D, Valentin L, Testa AC, Bernard JP. The inclusion of CA-125 does not improve mathematical models developed to distinguish between benign and malignant adnexal tumors. *J Clin Oncol* 2007; 25(27): 4197-200. [[CrossRef](#)][[PubMed](#)]
8. Kitawaki J, Ishihara H, Koshiba H, Kiyomizu M, Toramoto M, Kitaoka Y. Usefulness and limits of CA-125 in diagnosis of endometriosis without associated ovarian endometriomas. *Hum Reprod* 2005; 20(7): 1999-2003. [[CrossRef](#)][[PubMed](#)]
9. Valentin L, Akrawi D. The natural history of adnexal cysts incidentally detected at transvaginal ultrasound-examination in postmenopausal women. *Ultrasound Obstet Gynecol* 2002; 20(2): 174-80. [[CrossRef](#)][[PubMed](#)]
10. Gadducci A, Casio S, Capri A, Nicolina A. Serum tumor markers in the management of ovarian, endometrial and cervical cancer. *Biomed Pharmacolther* 2004; 58(1): 24-38. [[CrossRef](#)][[PubMed](#)]
11. Timmerman D, Schwarzler P, Collins WP, Clearhout F, Coenen M, Amant F, et al. Subjective assessment of adnexal masses with the use of ultrasonography: an analysis of interobserver variability and experience. *Ultrasound Obstet Gynecol* 1999; 13(1): 11-6. [[CrossRef](#)][[PubMed](#)]
12. Rottem S, Levit N, Thaler I, Yoffe N, Bronshtein M, Manor D, et al. Classification of ovarian lesions by high-frequency transvaginalsonography. *J Clin Ultrasound* 1990; 18(4): 359-63. [[CrossRef](#)][[PubMed](#)]
13. Brown DL, Doubelet PM, Miller FH, Frates MC, Laing FC, DiSalvo DN, et al. Benign and malignant ovarian masses: selection of the most discriminating grayscale and Doppler sonographic features. *Radiology* 1998; 208(1): 103-10. [[CrossRef](#)][[PubMed](#)]
14. Timmerman D, Testa AC, Bourne T, Ferrazzi E, Ameye L, Konstantinovic ML, et al. International ovarian tumor analysis group. Logistic regression model to distinguish between the benign and malignant adnexal mass before surgery: a multicenter study by the International Ovarian Tumor Analysis Group. *J Clin Oncol* 2005; 23(34): 8794-801. [[CrossRef](#)][[PubMed](#)]
15. Bret-Guibaud L, Atri M, Gillett P, Seymour R, Senterman M. Transvaginal US-guided aspiration of ovarian cysts and solid pelvic masses. *Radiology* 1992; 185(2): 377-80. [[CrossRef](#)][[PubMed](#)]
16. Granberg S, Norstorm A, Wikland M. Tumor in the Lower pelvis as imaged by vaginal sonography. *Gynecol Oncol* 1990; 37(2): 224-9. [[CrossRef](#)][[PubMed](#)]

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ULOGA SERUMSKOG NIVOVA TUMORSKOG MARKERA CA 125 U RAZLIKOVANJU BENIGNIH OD MALIGNIH TUMORA JAJNIKA KOD ŽENA U POSTMENOPAUI I KORELACIJA SA ULTRAZVUČNIM NALAZOM

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Maligni tumori jajnika javljaju se u svim životnim dobima, uključujući i rano detinjstvo, ali i duboku starost, pri čemu ukupna incidencija dramatično raste sa godinama života. U ispitivanju tumora jajnika koriste se tumorski markeri za njihovo rano otkrivanje.

Cilj rada bio je ispitivanje stepena korelacije ultrazvučnog nalaza u odnosu na nivoe serumskog tumorskog markera Ca 125 i ispitivanje korelacije preoperativnih ultrasonografskih nalaza i nivoa serumskog markera CA 125 sa intraoperativnim nalazom i patohistopatološkim rezultatima.

Istraživanje je definisano po modelima prospektivno-retrospektivne studije, koja obuhvata 60 žena u postmenopauzi kod kojih je postavljena dijagnoza postojanja tumora jajnika.

Svim bolesnicama su urađene sledeće pretrage i pregledi: anamnestička analiza kartona, odnosno, istorije bolesti sa podacima o godinama starosti, paritetu, trajanju menopauze, upotrebi oralnih kontraceptiva i simptomatologiji, ultrasonografski pregled male karlice, laboratorijski parametri: Ca 125 sa referentnim vrednostima do 35 ml/U. Kod svih bolesnica primenjena je laparotomija kao operativna procedura. Operativno dobijen material je histopatološki obrađen.

Prosečne vrednosti CA125 bile su daleko veće u grupi bolesnica sa malignim tumorima, sa visokom statističkom značajnošću.

Među ispitanicama sa benignim tumorima dominantna građa tumora bila je cistična, nasuprot tumorima mešovite građe kod malignih tumora. U tom smislu, parametar građe tumora je ozbiljan činiac u razlikovanju benignih od malignih tumora jajnika.

Lokalizacija tumora je sa visokom statističkom značajnošću češće bilateralna kod ispitanica sa histopatološki dokazanim malignim tumorima, dok je kod benignih tumora pretežno unilateralna.

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Ključne reči: CA 125, tumori jajnika, postmenopauza, ultrazvučni nalaz