

DIAGNOSTIC IMPORTANCE OF CA-125 IN DETECTION OF RECURRENCE AND PROGRESS OF THE DISEASE IN STAGES III AND IV OF EPITHELIAL OVARIAN CARCINOMA

DIJAGNOSTIČKI ZNAČAJ CA-125 U DETEKCIJI RECIDIVA I PROGRESIJE BOLESTI U STADIJUMU III – IV EPITELIJALNIH KARCINOMA JAJNIKA

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Summary: In 60 patients operated in stages III and IV of epithelial ovarian carcinoma continuous determination of CA 125 from serum was done during the following 2 years. The main condition for entering the survey were elevated values of CA 125 in serum > 35 U/mL and histologically verified epithelial ovarian carcinoma. The aim of the survey was to perform statistical assessment of serum CA 125 determination in diagnostics of recurrence and progression of the disease in stages III and IV of epithelial ovarian carcinoma, and percentage (%) of false positive and negative results. Determination of CA 125 from serum during 2 postoperative years is a reliable but not completely certain diagnostic parameter in detection of the disease progression in stages III and IV of epithelial ovarian carcinoma (sensitivity 79.3%, specificity 97.1%, positive predictive value 91.2%, negative predictive value 92.4%, test accuracy 92.1%). False positive (0.7%) and false negative results (4.7%) of individual tests were present in 5.4% of all samples.

Keywords: CA 125, ovarian carcinoma, recurrence, diagnostic importance

Introduction

Determination of CA 125 started in 1981, when Bast et al. (1) discovered the monoclonal antibody OC-125 belonging to immunoglobulin G class

Kratak sadržaj: Kod 60 pacijentkinja koje su operisane u stadijumu III i IV epitelijalnih karcinoma jajnika vršeno je kontinuirano određivanje CA 125 iz seruma tokom naredne 2 godine. Osnovni uslov za ulazak u istraživanje bilo je prisustvo preoperativno povišenih vrednosti CA 125 u serumu > 35 U/mL i histološki potvrđen epitelijalni karcinom jajnika. Cilj rada je bio da se izvrši statistička ocena određivanja CA 125 u serumu u dijagnostici recidiva i progresije bolesti u stadijumima III i IV epitelijalnih karcinoma jajnika i procenat (%) lažno pozitivnih i negativnih rezultata. Određivanje koncentracije CA 125 u serumu tokom 2 postoperativne godine predstavlja pouzdan ali ne i apsolutno siguran dijagnostički parametar u detekciji progresije bolesti u stadijumu III i IV epitelijalnih karcinoma jajnika (senzitivnost 79,3%, specifičnost 97,1%, pozitivna prediktivna vrednost 91,2%, negativna prediktivna vrednost 92,4%, tačnost testa 92,1%). Lažno pozitivni (0,7%) i lažno negativni rezultati (4,7%) pojedinačnih određivanja prisutni su ukupno kod 5,4 % svih uzoraka određivanja.

Ključne reči: CA 125, karcinom jajnika, recidiv, dijagnostički značaj.

(IgG₁) using Köhler and Milstein's technique of hybridization.

CA 125 antigen is produced in amniotic cells of the 7 weeks old embryo, while in adults it can be detected in the epithelium of most organs which originate from Müller ducts. Its presence is confirmed in placental tissue, mothers' milk after childbirth, bronchopulmonal and cervical mucus, pleural exudates, semen, content of benign and malignant ovarian tumors. It is released in blood circulation by different tissues sheathed by peritoneum, especially in the presence of inflammation with adhesion creation (2,

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3). The upper level of referent values for CA 125 in serum is 35 U/mL and can be seen in about 99% of healthy people. More than 83% of patients with epithelial ovarian carcinoma have elevated values of CA 125 higher than 35 U/mL at the moment of diagnosing the disease. Elevated values are present in about 50% of patients in stage I, and in over 90% of patients in advanced stages III and IV of ovarian carcinoma (4). In cases of ovarian carcinoma, preoperatively determined values of CA 125 in serum are correlated with the extent of the expansion of the disease (St, stage), histological type of tumor and degree of differentiation of malignant cells (Gr, gradus) (5). Elevated values of up to 65 U/mL in serum can also be found in other malignant tumors (pancreas, breast, colon, bladder, lungs, liver) and in different benign diseases (diverticulosis of colon, uterine myoma, endometriosis, benign ovarian cysts, tuboovarian abscess, ectopic pregnancy, ovarian hyperstimulation syndrome) as well (6).

The level of serum CA 125 which indisputably confirms a malignant process in the organism is quite debatable, and according to various authors, ranges from 65 to 200 U/mL (7, 8). The role of serum CA 125 as a biochemical parameter in the initial phase of the disease has not provided desired results (9). Level of serum CA 125 after the surgery can indicate regression or progression of ovarian carcinoma in over 90% of the patients who had had elevated values of CA 125 prior to the surgery. Elevated values of CA 125 immediately after the surgery can result from the surgery itself, so determination should be postponed for one month, when normal values after complete surgical reduction of tumor can last for weeks (10). Postoperative levels of CA 125 >35 U/mL in patients with no residual tumor and values > 65 U/mL in those with residual tumor implants represent a separate prognostic factor in the further course of the disease. Before the »second look« surgery, which confirmed the recurrence or progression of the disease, 62–88% of the patients had elevated values of CA 125, and values of Ca 125 < 35 U/mL cannot definitely rule out the presence of the tumor (11).

The importance of continuous determination of CA 125 tumor marker has not been precisely defined and has to be adjusted to each single case (12). The aim of the survey was to make a statistic evaluation of the continuous postoperative determination of CA 125 levels in diagnosing progression of the disease in stages III and IV of epithelial ovarian carcinoma, as well as percentage (%) of false positive and false negative results. Diagnostic importance of CA 125 in detection of recurrence of serous and other histological subgroups of epithelial ovarian carcinoma (mucinous, endometrioid, clear cell) has been examined in this study.

Patients and Methods

The survey involved 60 patients operated on at the Clinic for Gynecology and Obstetrics, Clinical Center of Vojvodina. All patients were operated in stages III and IV of epithelial ovarian carcinoma, according to the present FIGO classification. Patients were 21–80 years old (47.8 on average). There were 37 (61.6%) patients in stage III and 23 (38.4%) patients in stage IV. Distribution according to histological group of malignant epithelial ovarian tumors was: serous (38), mucinous (12), endometrioid (8), clear cell carcinoma (2). Complete surgical reduction, without residual tumor tissue, was done in 37 (61.6%) patients, while partial reduction with residual implants smaller than 5 mm in the longest diameter was done in 23 (38.4%) patients. Postoperatively, 6 cycles of chemotherapy in accordance with current protocols for epithelial ovarian carcinoma (Taxol, Carboplatin) were ordained. Basic conditions for entering the survey were elevated values of serum CA 125, more than 35 U/mL, prior to the surgery, and histologically confirmed ovarian carcinoma belonging to the group of epithelial tumors. In 4 patients in stage IV, who died 12 months after the beginning of the survey, determination of CA 125 was not conducted after that period. Control clinical examinations were done 30 days after the surgery, and then once every 3 months during the following 2 postoperative years, when determination of the levels of CA 125 from blood samples was also done. Control examination consisted of detailed anamnestic questioning, general physical, gynecologic examination, ultrasound examination of upper abdominal organs as well as basic laboratory blood analyses. Control CT scan of abdominal and pelvic organs was performed in all patients with complete reduction of the tumor, without residual implants on peritoneum and intra-abdominal organs, at the end of the first and the second postoperative years. When any suspicion on recurrence, based on conducted examinations, arose, additional examinations, or »second look« surgery, were done. Tumor recurrences were confirmed by pathohistological examination of bioptic or intraoperatively taken samples of tumor tissue, which were microscopically the same as the primary tumor. Patients with partial tumor reduction and residual implants after chemotherapy were reoperated (second look surgery). Activation of residual tumor was confirmed if during the »second look« surgery implants were larger than 5 mm, or new metastases in the abdomen were found, compared to primary operative reports.

When processing the results, we divided all patients into 3 subgroups according to Schegel's degree of tumor activity: A0 – complete remission (stable course of the disease), A2 – partial remission (appearance of the recurrence) and A3 – disease progression (activation of the residual tumor) (13). Patients from subgroup A0 with stable course of the

disease were the control group, with emersion of truly negative and false positive results according to upper limit of referent values for CA 125 (35 U/mL). Patients from A2 and A3 subgroups were the examined group with truly positive and false negative results. In each case when elevated levels of serum CA 125 were found, we performed a control CA 125 determination in 7 days, and if the values were still elevated, we considered it to be a truly positive result, while in cases when repeated testing showed results within the referent range, we considered previous elevated values of CA 125 as a false positive result. Every time we proved the recurrence or the progression of the disease during the patient's follow up, we also noted the values of serum CA 125. If they were <35 U/mL, we considered it as a false negative CA 125 result, while if they were elevated as a truly positive result.

For determining the tumor marker CA 125 concentration in blood, we used serum obtained from 5 mL of venous blood. Carbohydrate antigen CA 125 was determined by a commercial Abbott CA 125-EIA Monoclonal test produced by Abbott Company, on Abbott's company EIA spectrometer (14). Upper level of referent values for CA 125 tumor marker was 35 U/mL.

Statistics

All results from the survey were shown in tables and graphically. When evaluating diagnostic significance of CA 125 in detection of the recurrence and progression of the disease after the surgery, we were monitoring the period from the 3rd to the 24th month. For evaluating the diagnostic significance of tumor markers, we used methodology for calculating diagnostic significance of tests in medicine (15, 16).

Results and Discussion

Preoperatively, all patients had elevated values of blood CA 125 compared to the upper level of referent values (35 U/mL), ranging from 41 to 860 U/mL (\bar{x} = 352.2 U/mL, SD ± 267.8, CV 76.0). Distribution of the patients according to the degree of the tumor activity after the surgery was as follows: A0 (stable course of the disease) – 30 (50 %), A2 (appearance of the recurrence) – 15 (25 %), and A3 (progression of the residual tumor) – 15 (25 %).

Figure 1 shows the distribution of arithmetic means during two-year serum CA 125 determination according to degrees of tumor activity (A0, A2, and A3). Diagnostic significance of continuous postoperative determination of tumor marker CA 125 in the detection of recurrence and progression of the disease in stages III and IV of epithelial ovarian carcinoma is shown in Table I. Table II shows statistical the evaluation (T test) of applying CA 125 in detection of the

disease progression in different histological subgroups of epithelial ovarian carcinoma.

During the continuous determination of the tumor marker there were 448 single determinations of CA 125 blood concentration (subgroup A0 – 240, subgroups A2 and A3 – 208 tests). False positive results appeared in 24 (5.3 %) tests: false positive in 3 (0.7 %) and false negative in 21 (4.7 %) cases. Serial postoperative CA 125 determination in controlling the state of operated patients with ovarian carcinoma is a standard procedure applied in most countries. The aim of these controls is to discover the recurrence or progression of carcinoma during the post-

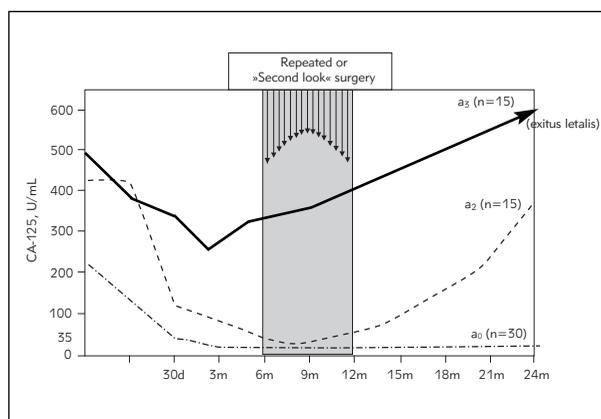


Figure 1 Medium CA 125 serum levels in correlation with the extent of tumor activity during the two-year period of follow up

Table I Diagnostic importance of CA 125 in postoperative detection of the disease progression in stages III and IV of epithelial ovarian carcinoma.

Diagnostic importance (%)	CA 125 (35 U/mL)
Sensitivity	79.3
Specificity	97.1
Positive predictive value	91.2
Negative predictive value	92.4
Test accuracy	92.1

Table II Statistical evaluation (T-test) of CA 125 usage in detection of recurrence and progression of the disease in different histological groups of epithelial ovarian carcinoma.

Evaluation of statistical significance	Histological sort of epithelial ovarian cancer	
	Serous carcinoma	Mucinous, endometrioid and clear cell
T test	0.74	0
p	0.45	1.00

operative period in the pre-clinical phase of the disease, and prescribe the second line of chemotherapy as soon as possible in order to prolong life expectancy (4, 5). Different authors say that the average time from elevation of CA 125 values to clinical progression of the disease is 3 to 4 months (17, 18). Recurrence of the disease after chemotherapy is incurable in most cases. Objectively, we can only speak about qualitative life prolonging, where patients in whom progression of the disease is very early detected, when no clinical symptoms and signs of the disease have appeared, have highest chances (11). In order to precisely evaluate the success of second line chemotherapy, administration based on elevated values of CA 125 and its effects on the outcome of the disease in patients with ovarian carcinoma who underwent surgery, multicentric randomized study, organized by 'The Medical Research Council (UK) and the European Organisation for Research and Treatment of Cancer', was conducted (19). This study shows that postoperative determination of CA 125 should not be done in all patients treated because of ovarian carcinoma, but only in cases of clinical suspicion that the recurrence of the disease really occurred. It has also been shown that chemotherapy administration in asymptomatic patients with elevated values of CA 125 does not have any significant impact on the course of the disease. However, patients with ovarian carcinoma cannot be deprived of control of the physical state and the course of the disease, nor the possibility to prove the recurrence by measuring CA 125 and administer proper treatment. Tuxen et al. (20) conducted a study on 225 patients in stages I c – IV of ovarian carcinoma, and found the CA 125 sensitivity of 76% and false positive results in 1% of the cases in detection of the disease progression after the first line of chemotherapy. Rustin et al. (21) showed that double rise of serum CA 125 values above the level of referent values stands as a stand-alone parameter which indicates progression of the disease (sensitivity 84 %, false positive results < 2%). Murakami et al. (22) examined the possibility of combined usage of PET-scan and tumor marker CA 125 in detection of epithelial ovarian tumor recurrence. Sensitivity of combined usage of PET scan and CA 125 is 97.8 %, with only one false negative case, where these two methods have complementary influence in detection of epithelial ovarian tumor recurrence.

Different authors showed that serial determination of CA 125 after the primary therapy indicates early detection of tumor recurrence, although elevated values of CA 125 are less present in mucous and light cell than serous ovarian carcinoma (23). During continuous determination of CA 125, Meyer et al. (24) noted false positive results in 3% and false negative in up to 20% of the samples. In our survey, sensitivity of serum CA 125 (>35 U/mL) in detection of recurrence and progression of the disease in stages III and IV of epithelial ovarian carcinoma is 79.3% and is similar to the results of other authors (Tuxen, Rustin), even though in these studies, heterogeneous groups of ovarian carcinoma regarding histology and stages were dealt with (5, 17, 20, 21). Specificity, positive and negative predictive value and test accuracy are high, over 90%. False negative results of determination were recorded in 0.7% of CA 125 processed samples, which is slightly lower than the other authors' results, where this percentage is 1–3%.

After diagnosing the recurrence or activation of the residual tumor during or after chemotherapy, levels of serum CA 125 in our survey show continuous and progressive rise regardless of treatment. Usage of CA 125 in detection of recurrence and progression of the disease between serous and other groups of epithelial ovarian carcinoma (mucinous, endometrioid, clear cell) does not show a statistically relevant difference ($p > 0.05$). The combined usage of PET scan and CA 125 has a higher sensitivity level in detection of the recurrence of epithelial ovarian carcinoma (97.8 %), compared to standalone determination of serum CA 125 (22). Unfortunately, usage of PET scan significantly rises the price of the whole procedure, and is not yet available for mass usage, especially in economically poor and developing countries.

In our study, false negative results percentage of CA 125 determination (4.7%) was lower, compared to the works of other authors (24, 25). Continuous determination of serum CA 125 concentration during the first 2 postoperative years is a reliable, but not completely certain diagnostic parameter in the detection of recurrence and progression of the disease in patients in stages III and IV of epithelial ovarian carcinoma (sensitivity 79.3%, specificity 97.1%, test accuracy 92.1%).

References

- Bast RC, Feeney M, Lazarus H. ET, Nadler L, Colvin R, Knapp R. Reactivity of a monoclonal antibody with human ovarian carcinoma. *J Clin Invest* 1981; 68: 1331–7.
- Barlow TS, Przybylski M, Schilder JM, Moore DH, Look KY. The utility of presurgical CA 125 to predict optimal tumor cytoreduction of epithelial ovarian cancer. *Int J Gynecol Cancer* 2006; 16, 496–500.
- Cooper BC, Sood AK, Davis CS, Berliare M, Brady MF. Preoperative CA 125 levels: an independent prognostic factor for epithelial ovarian cancer. *Obstet Gynecol* 2002; 100: 59–64.
- Duffy MJ, Bonfrer JM, Kulpa J, Rustin GJS, Sokletormos G, Torre GC, Tuxen MK, Zwirner M. CA 125 in Ovarian Cancer: European Group On Tumor Markers: Guidelines for Clinical Use. *Int J Gynecol Cancer* 2005; 15, 679–91.
- Tuxen MK, Soletormos G, Dombernowsky P. Serum tumour marker CA 125 in monitoring of ovarian cancer during first-line chemotherapy. *Br J Cancer* 2001; 84: 1301–7.
- Đurđević S, Đurđević J. Tumorski markeri u ginekološkoj onkologiji. 1. izd. Beograd: Društvo medicinskih biohemičara Jugoslavije, 1998; 118.
- Sevinc A, Camci C, Turk HM, Buyukberber S. How to interpret serum CA 125 levels in patients with serosal involvement? A clinical dilemma. *Oncology* 2003; 65: 1–6.
- Majkić-Singh N. Tumorski markeri: biohemija i klasifikacija. *Jugoslav Med Biochem* 2006; 25 (2): 79.
- Jacobs I, Skates SJ, MacDonald N, Bridges J, Davies AP. Screening for ovarian cancer: a pilot randomised controlled trial. *Lancet* 1999; 353: 1207–10.
- ACOG Committee Opinion. The role of the generalist obstetrician-gynecologist in the early detection of ovarian cancer. *Obstet Gynecol* 2002; 100: 1413–6.
- Board RE, Brujins CTPH, Pronk AE, Ryder WDJ, Wilkinson PM, Welch R, Shanks JH, Connolly G, Slade RJ, Reynolds K, Kitchener HC, Jayson GC. Stage and CA 125 related survival in patients with epithelial ovarian cancer treated at a cancer center. *Int J Gynecol Cancer* 2006; 16 (Suppl.1), 18–24.
- Skates SJ, Menon U, MacDonald N. Calculation of the risk of ovarian cancer from serial CA 125 values for preclinical detection in postmenopausal women. *J Clin Oncol* 2003; 21: 206–10.
- Schlegel G, Luthagens M. Assessment of marker results. In: Luthagens M, Schlegel G. Clinical use of the tumor marker system CEA-TPA. 1. ed. Stuttgart: Tumour Diagnostik Verlag, 1989: 1–10.
- Stanković S. Tumorski markeri: metode određivanja. *Jugoslav Med Biochem* 2006; 25 (2): 89–101.
- Sheps BS, Schechter T. The assesment of diagnostic test. *JAMA YU.* 1985; 1(2): 204–8.
- Aslan D, Sandberg S. Simple statistics in diagnostic tests. *Journal Medical Biochem* 2007; 26 (4): 309–13.
- Rustin GJS. Use of CA125 to assess response to new agents in ovarian cancer trials. *J Clin Oncol* 2003; 21: 187s–93s.
- Rim SY, Kim SM, Choi HS. Struma ovarii showing clinical characteristics of ovarian malignancy. *Int J Gynecol Cancer* 2005; 15, 1156–9.
- Eisenhauer EA, Vermorken JB, Van Glabbeke M. Predictors of response to subsequent chemotherapy in platinum pretreated ovarian cancer: a multivariate analysis of 704 patients. *Ann Oncol* 1997; 8: 963–8.
- Tuxen MK, Soletormos G, Dombernowsky P. Serum tumor marker CA 125 for monitoring ovarian cancer during follow up. *Scand J Clin Lab Invest* 2002; 62: 177–88.
- Rustin GJS, Marples M, Nelstrop EA, Tuxen MK, Lambert HE. Use of CA 125 to define progression of ovarian cancer in patients with persistently elevated levels. *J Clin Oncol* 2001; 10: 4054–7.
- Murakami M, Miyamoto T, Iida T, Tsukada H, Watanabe M, Shida M, Maeda H, Nasu S, Yasuda S, Yasuda M, Ide M. Whole-body positron emission tomography and tumor marker CA 125 for detection of recurrence in epithelial ovarian cancer. *Int J Gynecol Cancer* 2006, 16 (Suppl.1), 99–107.
- Skates SJ, Menon U, MacDonald N, Xy FJ, YU YH. Calculation of the risk of ovarian cancer from serial CA-125 values for preclinical detection in postmenopausal women. *J Clin Oncol* 2003; 21: 206–10.
- Mayer T, Rustin GJ. Role of the Tumour Markers in monitoring Epithelial Ovarian Cancer. *Br J Cancer* 2000; 82: 1535–8.
- Mousavi AS, Borna S, Moeinoddini S. Estimation of probability of malignancy using a logistic model combining color Doppler ultrasonography, serum CA 125 level in women with a pelvic mass. *Int J Gynecol Cancer* 2006; 16 (Suppl.1): 92–98.

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