ORIGINAL ARTICLE

Laboratory predictors of survival in ovarian cancer

Millena Prata Jammal[1]
Agrimaldo Martins Filho[1]
Guilherme Henrique Bandeira[1]
Beatriz Martins Tavares Murta[2]
Eddie Fernando Candido Murta[1]
Rosekeila Simões Nomelini[1]

1. Instituto de Pesquisa em Oncologia (IPON)/Departamento de Ginecologia e Obstetrícia; Universidade Federal do Triângulo Mineiro, Uberaba, MG, Brasil
2. Disciplina de Farmacologia; Universidade Federal do Triângulo Mineiro, Uberaba, MG, Brasil

http://dx.doi.org/10.1590/1806-9282.66.1.61

SUMMARY

OBJECTIVE: *To relate disease-free survival and overall survival with type I and type II ovarian cancer and preoperative laboratory parameters biomarkers.*

METHODS: *A retrospective study was carried out based on the collection of data from medical records of patients with ovarian tumors. Kaplan-Mayer curves were drawn based on the statistical analysis of the data and were compared using the Log-rank test.*

RESULTS: *Disease-free survival in type I ovarian cancer was significantly higher than in type II (p=0.0013), as well as in those with normal levels of CA-125 (p=0.0243) and with a platelet-lymphocyte ratio (PLR) lower than 200 (p=0.0038). The overall survival of patients with type I ovarian cancer was significantly higher than in patients with type II, as well as in patients with normal CA-125 serum levels (p=0.0039) and those with a preoperative fasting glucose of less than 100 mg/dL.*

CONCLUSION: *CA-125 levels may predict greater overall and disease-free survival. PLR < 200 may suggest greater disease-free survival, whereas normal fasting glucose may suggest greater overall survival.*

KEYWORDS: *survival, ovarian neoplasms, glucose, CA-125 Antigen.*

INTRODUCTION

Ovarian cancer is the fifth leading cause of cancer mortality in women[1]. According to data from Globocan[2], an estimated total of 238,719 new cases were diagnosed worldwide in 2012. Many studies have evaluated the clinical relevance of potential biomarkers, such as tissue or serum samples from patients with ovarian cancer, for their ability to predict either chemotherapy response or survival[3].

Both basic and translational research has shown that ovarian cancer includes several types of tumors with different phenotypes, molecular biology, etiology, progression, and even prognosis. In 2014, Shih & Kurman[4] proposed a classification system for ovarian tumorigenesis based on morphology and genetic molecular analysis. In this model, ovarian epithelial tumors are divided into two broad categories, designated as type I and type II. Type I tumors tend to be low grade, slow-growing neoplasms, and are associated with distinct molecular changes. They are relatively genetically stable and rarely have P53

DATE OF SUBMISSION: 15-Aug-2019
DATE OF ACCEPTANCE: 07-Oct-2019
CORRESPONDING AUTHOR: Rosekeila Simões Nomelini
Instituto de Pesquisa em Oncologia (IPON), Departamento de Ginecologia e Obstetrícia, UFTM
Av. Getúlio Guaritá, s/n, Bairro Abadia, 38025-440, Uberaba, MG - Brasil
E-mail: rosekeila@terra.com.br; rosekeila.nomelini@pq.cnpq.br

mutations. There have already been many studies of the mutations that typically occur in type I tumors, such as the BRAF and KRAS mutations for serous tumors, KRAS mutations for mucinous tumors, and β-catenin and PTEN mutations for endometrioid tumors. On the other hand, type II tumors are high-grade neoplasms with accelerated and disorganized growth, and very often, their precursor lesions have not been morphologically identified, so they tend to be diagnosed in more advanced stages. They are genetically unstable and have a high frequency of P53 mutations[5]; however, beyond that, the data on their molecular changes are still very limited. Thus, patients with type II tumors present a much higher chance of recurrent disease when compared to patients with type I tumors[6].

There is an important need for the development of new biomarkers for the diagnosis and prognosis of ovarian cancer, and ideally, these biomarkers would also serve as targets for new therapeutic modalities[7]. Systemic inflammatory response markers, such as absolute white blood cell count, neutrophil-lymphocyte ratio (NLR), and platelet- lymphocyte ratio (PLR), have been used as prognostic factors in patients with various types of tumors[8,9]. It is proposed that they can be used as significant predictors of malignancy for solid tumors originating from various tissues, also revealing that they can be used as a screening tool for these tumors as they are considered low cost and readily available tests. However, it is necessary to further research to evaluate the additional value of this finding to establish scores and indicate the potential predictive value of these markers in gynecological cancers[10].

Our study aims to correlate disease-free survival (DFS) and overall survival (OS) with type 1 and type 2 ovarian cancer and with preoperative laboratory parameters.

PATIENTS AND METHODS

This retrospective study was carried out using the medical records of patients with ovarian tumors being treated at the Pelvic Mass Ambulatory and undergoing surgical treatment by exploratory laparotomy according to pre-established criteria[11,12], and subsequently diagnosed with malignant ovarian neoplasia.

The inclusion criterion was a postoperative diagnosis of primary malignant ovarian neoplasia (epithelial or non-epithelial tumors) by anatomopathological paraffin analysis. Exclusion criteria were secondary malignant ovarian neoplasia (metastasis); torsion of the adnexal pedicle; treatment prior to surgery; recurrence; diseases that cause immunosuppression; treatment with immunosuppressive drugs.

The study was approved by the Research Ethics Committee (protocol number 2,061) and performed in accordance with the ethical standards as laid down in the 2013 Declaration of Helsinki. Informed consent was obtained from all participants.

Patients

Patients with confirmed histological diagnosis of ovarian cancer had the following data recorded: age, histological type, histological grade, staging (FIGO), type I/II classification (for epithelial tumors), lymph node metastases, OS, and DFS. Hemoglobin, absolute neutrophil and lymphocyte values, platelets, fasting glucose, and preoperative tumor markers (CA125, CA15.3, CA19.9) were also obtained from laboratory tests.

The NLR and PLR values were obtained by dividing the absolute number of neutrophils and platelets, respectively, by the absolute number of lymphocytes. The cut-off values used for NLR and PLR were 4 and 200, respectively[13,14].

DFS was considered from the date of histopathological diagnosis of ovarian cancer to the date of the first relapse. OS was calculated from the date of histopathological diagnosis of ovarian malignancy to death from any cause.

Statistical analysis

Data were analyzed in GraphPad Prism software 7. DFS and OS were assessed using Kaplan-Meier curves and compared using the log-rank test, with significance set at $p<0.05$. Considering the estimated proportion of death and relapse in the sample, at least 88 patients would be required to obtain a test power of 95%, at a significance level lower than 0.05 (www.lee.dante.br).

RESULTS

In total, the medical records of 110 patients diagnosed with malignant ovarian neoplasia were analyzed. The median age was 51 years (12-82). Results of preoperative laboratory tests are shown in Table I.

Serous cystadenocarcinomas represented the most common histological type, found in 30 (27.3%)

patients. There were 20 (18.9%) granulosa cell tumors, 16 (14.5%) borderline mucinous tumors, 10 (9.1%) borderline serous tumors, 6 (5.5%) mucinous cystadenocarcinomas, 4 (3.6%) endometrioid tumors, 4 (3.6%) adenocarcinomas, 4 (3.6%) dysgerminomas, 3 (2.7%) clear cell tumors, 2 (1.8%) carcinosarcomas, 2 (1.8%) endodermal sinus, 2 (1.8%) teratoma immature, 1 (0.9%) embryonal carcinoma, 1 (0.9%) borderline endometrioid, 1 (0.9%) undifferentiated stroma tumor, 1 (0.9%) poorly differentiated neoplasia, 1 (0.9%) Sertoli, 1 (0.9%) mucinous and serous, 1 (0.9%) clear cells + granulosa.

Regarding the type of carcinogenesis, 48 (43.6%) patients had ovarian cancer type I, 30 (27.2%) had ovarian cancer type II, and 32 (29.1%) were not classified because they were not epithelial cells. Regarding staging, 59 (53.6%) were in stage I, 5 (4.5%) in stage II, 36 (32.7%) in stage III, and 10 (9.1%) in stage IV. Thirty-three percent of the patients died.

DFS was significantly higher in type I than in type II ovarian cancer (p = 0.0013, Figure 1A) and was also higher in patients with levels of CA-125 lower than 35 U/ml (p = 0.0243, Figure 1B) and PLR lower than 200 (p = 0.0038, Figure 1C). There was no significant difference in DFS in relation to fasting glucose, hemoglobin, NLR, or serum levels of CA 19.9 and CA 15.3.

The OS of patients with type I ovarian cancer was significantly higher than that of patients with type 2 (p<0.0001, Figure 1D). In addition, OS was higher in patients with CA-125 serum levels lower than 35 U/ml (p = 0.0039, Figure 1E) and with preoperative fasting glucose lower than 100 mg/dL (p=0.0393, Figure 1F). There was no statistical significance regarding hemoglobin, serum levels of CA 19.9 and CA 15.3, NLR, or PLR.

DISCUSSION

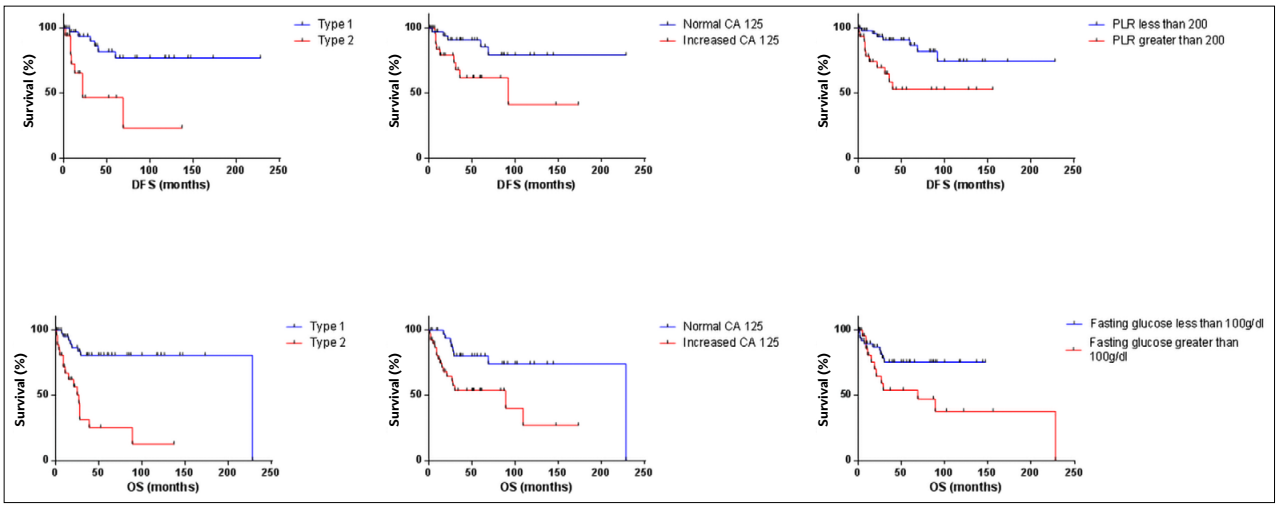
The identification of diagnostic markers for ovarian cancer, determination of prognosis, and treatment orientation is important. The most commonly used tumor marker in ovarian cancer is Serum Cancer Antigen 125 (CA-125). It was first identified by Bast, Knapp et al. in 1981[15]. CA125 is a high molecular weight glycoprotein expressed by 80% of ovarian cancers of epithelial origin and may be used to distinguish malignant pelvic masses from benign, monitor therapeutic response, and detect recurrent diseases[16,17].

TABLE 1. LABORATORIAL PARAMETERS.

	Median
Fasting glucose (mg/dl)	91.4 (48.0-379.1)
RBCs* (10^6uL)	4.3 (2.4-6.3)
Hemoglobin (g/dL)	12.4 (6.7-17)
Platelets (10^3uL)	291 (24-729)
Neutrophils (10^3uL)	5.487 (1.383-19.532)
Lymphocytes (10^3uL)	1.723 (336-4.068)
NLR	2.6 (0.5-31,66.6)
PLR	170.2 (13.5-1,827.3)
CA125 (U/ml)	54.4 (3.0-14,700)
CA-19.9 (U/ml)	11.8 (0.7-706.1)
CA-15.3 (U/ml)	22.9 (7.7-813)

*RBCs: red blood cells

FIGURE 1. DISEASE-FREE SURVIVAL AND OVERALL SURVIVAL CURVES (KAPLAN-MEIER AND LOG-RANK TEST).



a) DFS in type I ovarian cancer was significantly higher than in type II (p=0.0013); b) DFS was higher in patients with normal levels of CA-125 (p=0.0243); c) DFS was higher in patients with PLR less than 200 (p=0.0038); d) OS in type I ovarian cancer was significantly higher than in type II (p< 0,0001); e) OS was higher in patients with normal CA-125 serum levels) (p=0.0039); f) OS was higher in patients with fasting glucose lower than 100 mg/dL (p=0.0393).

Studies have evaluated the prognostic significance of CA-125 levels at different treatment times to determine their correlation with prognosis, but their role remains controversial[18]. Such results may be related to a failure to consider tumor grade and histological type[19]. Ovarian cancer is not a single entity disease but comprises a heterogeneous group of tumors with different histological types, with well-differentiated clinical-pathological characteristics and biological behavior[4,20].

Chen et al. (2013) found that baseline levels of CA-125 in serum were higher in patients with type II ovarian cancers, with a worse prognosis. They also found that CA-125 alone was not able to predict whether the tumor was a type I or type II[21]. Our results agreed with theirs, as patients with type I tumors showed better prognosis with higher DFS and OS, as well as lower levels of CA-125.

Cell growth is controlled by a coordinated response between growth factors and nutrients. Increased basal glucose may be involved in the carcinogenesis of gynecological tumors by acting as an energy source. There are many studies associating diabetes with the prognosis of gynecological cancer patients, glycemic rates with tumor progression, and overall survival since the most common alteration in the cellular metabolism of neoplastic cells involves increased glucose[22].

Malignant tumors require a high demand for glucose and alter cellular metabolism to maintain their survival. Metabolic changes are necessary to sustain cell division and unrestricted growth[23]. As tumor cells progress, they change their morphology and organization, increase their growth rate, and acquire an increasingly glycolytic phenotype[24]. Among the main metabolic alterations of cancer cells is the so-called Warburg effect, which consists of increasing glycolysis under aerobic conditions and uptake of glucose through an excessive expression of its transporters. The Warburg effect is a metabolic characteristic associated with cancer cells, in which they preferentially use glycolysis for energy production rather than oxidative phosphorylation to produce lactate[25,26]. Changes in glucose metabolism have also been associated with therapeutic resistance in the treatment of ovarian cancer[24]. This is in agreement with our findings, in which OS was higher in patients with normal fasting glucose.

Laboratory quantification of systemic inflammatory response markers such as NLR and PLR has been shown to be a useful prognostic factor in patients with various types of cancer, including ovarian[4]. Several inflammatory mediators are induced by inflammatory or tumor cells and participate in the formation of cancer, acting as growth factors or angiogenic. In addition, immune function is compromised by mediators of the systemic inflammatory response, which increases leukocyte, neutrophil, platelet, C-reactive protein, and fibrinogen levels and decreases lymphocyte concentrations[26]. Thrombocytosis is identified in 20% to 50% of cases of ovarian cancer. One retrospective study demonstrated that a high number of platelets is related to lower OS in ovarian cancer[17]. In our study, DFS was higher in patients with PLR lower than 200.

A study showed that preoperative PLR was an independent prognostic factor in patients with ovarian cancer[13]. PLR is a reproducible and cheap laboratory hematology marker that is being suggested as a marker of thrombotic and inflammatory conditions[26]. Preoperative thrombocytosis was an unfavorable predictor of survival in patients with ovarian cancer[27]. Platelet activation and aggregation occur in response to the release of inflammatory cytokines, and thrombocytosis not only promotes invasion and metastasis of tumor cells but may also reflect a state of systemic inflammation[28].

Since our sample included 110 patients, the test power was greater than 95%. Nevertheless, there is still no well-defined cutoff value in the literature that relates PLR and NLR to prognosis in ovarian cancer. Thus, additional studies are needed to elucidate the role of new predictors of DFS and OS in ovarian cancer.

CONCLUSIONS

Patients with type I ovarian cancer had greater DFS and OS (better prognosis) than patients with type II. CA-125 levels may be predictive of OS and DFS. PLR may suggest a higher DFS, and normal fasting glucose suggests a greater OS. Thus, low-cost and easy-to-use laboratory assessments could guide the oncologist to more appropriate treatment, and perhaps even point to future targets and novel approaches for treating ovarian cancer.

Acknowledgments

The authors wish to acknowledge the funding received from the National Council for Scientific and Technological Development (CNPq), the Foundation for Education and Research of Uberaba (FUNEPU), and the Research Foundation Support of the State of Minas Gerais (FAPEMIG).

Declaration of interest

The authors report no conflicts of interest. The manuscript has been read and approved by all the authors, the requirements for authorship as stated earlier in this document have been met, and each author believes that the manuscript represents honest work.

Authors contribuitions

Concepts, design, definition of intellectual content: Eddie Fernando Candido Murta, Rosekeila Simões Nomelini; Literature search: Millena Prata Jammal, Agrimaldo Martins Filho, Guilherme Henrique Bandeira; Data acquisition: Millena Prata Jammal, Agrimaldo Martins Filho, Guilherme Henrique Bandeira, Beatriz Martins Tavares Murta; Data analysis, statistical analysis: Millena Prata Jammal, Beatriz Martins Tavares Murta, Eddie Fernando Candido Murta, Rosekeila Simões Nomelini; Manuscript preparation, editing and manuscript review: Millena Prata Jammal, Beatriz Martins Tavares Murta, Eddie Fernando Candido Murta, Rosekeila Simões Nomelini; Guarantor: Rosekeila Simões Nomelini

RESUMO

OBJETIVO: *Relacionar a sobrevida livre de doença e sobrevida global com câncer de ovário tipos I e II, assim como com parâmetros laboratoriais pré-operatórios biomarcadores.*

MÉTODOS: *Estudo retrospectivo realizado com base na coleta de dados de prontuários de pacientes com tumor ovariano. As curvas de Kaplan-Mayer foram realizadas em relação à análise estatística dos dados, sendo comparadas pelo teste de Log-rank.*

RESULTADOS: *A sobrevida livre de doença nas pacientes com câncer de ovário tipo I foi significativamente maior do que nas pacientes com câncer de ovário tipo II (p = 0,0013), bem como maior naquelas com níveis normais de CA-125 (p = 0,0243) e com relação plaquetas-linfócitos (RPL) inferior a 200 (p = 0,0038). A sobrevida global de pacientes com câncer de ovário tipo I foi significativamente maior do que em pacientes com tipo II, maior em pacientes com níveis séricos normais de CA-125 (p = 0,0039) e naquelas com glicemia de jejum pré-operatória menor que 100 mg / dL.*

CONCLUSÃO: *Os níveis de CA-125 podem predizer uma sobrevida global e livre de doença. A RPL < 200 pode sugerir uma maior sobrevida livre de doença, enquanto uma glicemia normal de jejum, uma maior sobrevida global.*

PALAVRAS-CHAVE: *sobrevida, neoplasia ovariana, glicemia, biomarcadores.*

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018; 68(1):7-30.
2. Ferlay J, Soerjomataram I, Ervik M et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from: http://globocan.iarc.fr. Accessed on 04/07/2018.
3. Gadducci A, Cosio S, Tana R, Genazzani AR. Serum and tissue biomarkers as predictive and prognostic variables in epithelial ovarian cancer. Crit Rev Oncol Hematol 2009; 69(1):12-27. doi: 10.1016/j.critrevonc.2008.05.001.
4. Shih IeM, Kurman RJ. Ovarian tumorigenesis: a proposed model based on morphological and molecular genetic analysis. Am J Pathol 2004; 164(5):1511-8.
5. Rechsteiner M, Zimmermann AK, Wild PJ, Caduff R, von Teichman A, Fink D, et al. TP53 mutations are common in all subtypes of epithelial ovarian cancer and occur concomitantly with KRAS mutations in the mucinous type. Exp Mol Pathol 2013; 95:235-41. doi: 10.1016/j.yexmp.2013.08.004.
6. Skirnisdottir I, Seidal T, Åkerud H. Differences in Clinical and Biological Features Between Type I and Type II Tumors in FIGO Stages I-II Epithelial Ovarian Carcinoma. Int J Gynecol Cancer 2015; 25(7):1239-47. doi: 10.1097/IGC.0000000000000484.
7. Athanassiadou P, Grapsa D, Athanassiades P, et al: The prognostic significance of COX-2 and survivin expression in ovarian cancer. Pathol Res Pract. 204(4):241-9, 2008.
8. Bishara S, Griffin M, Cargill A, et al: Pre-treatment white blood cell subtypes as prognostic indicators in ovarian cancer. Eur. J. Obstet. Gynecol. Reprod. Biol. 138:71-75, 2008.
9. Hirashima K, Watanabe M, Shigaki H, et al: Prognostic significance of the modified Glasgow prognostic score in elderly patients with gastric cancer. J. Gastroenterol. (49)1040-1046, 2014.
10. Templeton AJ, McNamara MG, Šeruga B, et al: Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. J Natl Cancer Inst. 106(6):dju124, 2014.
11. Murta EF, da Silva CS, Gomes RA, Tavares-Murta BM, Melo AL. Ultrasonographic criteria and tumor marker assay are good procedures for the diagnosis of ovarian neoplasia in preselected outpatients. Eur J Gynaecol Oncol 2004; 25:707-12.
12. Murta EFC, Nomelini RS. Early diagnosis and predictors of malignancy in the evaluation of adnexal mass. Curr Opin Obstet Gynecol 2006; 18(1):14-19.

13. Dirican A, Kucukzeybek BB, Alacacioglu A, Kucukzeybek Y, Erten C, Varol U, et al. Do the derived neutrophil to lymphocyte ratio and the neutrophil to lymphocyte ratio predict prognosis in breast cancer? Int J Clin Oncol 2014; 20:70-81. doi: 10.1007/s10147-014-0672-8.

14. Ashrafganjoei T, Mohamadianamiri M, Farzaneh F, Hosseini MS, Arab M. Investigating Preoperative Hematologic Markers for Prediction of Ovarian Cancer Surgical Outcome. Asian Pac J Cancer Prev 2016; 17(3):1445-8.

15. Bast RC Jr, Feeney M, Lazarus H, Nadler LM, Colvin RB, Knapp RC. Reactivity of a monoclonal antibody with human ovarian carcinoma. J Clin Invest 1981; 68(5):1331-7. doi: 10.1172/JCI110380.

16. Gupta D, Lis CG. Role of CA125 in predicting ovarian cancer survival - a review of the epidemiological literature. Journal of Ovarian Research 2009; 2:13. doi: 10.1186/1757-2215-2-13.

17. Baert T, Van Camp J, Vanbrabant L, Busschaert P, Laenen A, Han S, et al. Influence of CA125, platelet count and neutrophil to lymphocyte ratio on the immune system of ovarian cancer patients. Gynecol Oncol 2018. doi: 10.1016/j.ygyno.2018.05.004.

18. Hogdall E. Cancer antigen 125 and prognosis. Curr Opin Obstet Gynecol 2008; 20(1):4-8. doi: 10.1097/GCO.0b013e3282f2b124.

19. Lu D, Kuhn E, Bristow RE, Giuntoli RL 2nd, Kjær SK, Shih IeM, et al. Comparison of candidate serologic markers for type I and type II ovarian cancer. Gynecol Oncol 2011; 122(3):560-6. doi: 10.1016/j.ygyno.2011.05.039.

20. Kurman RJ, Shih IeM. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. Am J Surg Pathol 2011; 34(3):433-43.

21. Chen X, Zhang J, Cheng W, Chang DY, Huang J, Wang X, et al. CA-125 Level as a Prognostic Indicator in Type I and Type II Epithelial Ovarian Cancer. Int J Gynecol Cancer 2013; 23(5):815-22. doi: 10.1097/IGC.0b013e31828f7a24.

22. Vrachnis N, Iavazzo C, Iliodromiti Z, Sifakis S, Alexandrou A, Siristatidis C, et al. Diabetes mellitus and gynecologic cancer: molecular mechanisms, epidemiological, clinical and prognostic perspectives. Arch Gynecol Obstet 2016; 293:239-46. doi: 10.1007/s00404-015-3858-z.

23. Creekmore AL, Heffron CL, Brayfield BP, Roberts PC, Schmelz EM. Regulation of cytoskeleton organization by sphingosine in a mouse cell model of progressive ovarian cancer. Biomolecules 2013; 3(3):386-407. doi: 10.3390/biom3030386.

24. Anderson AS, Roberts PC, Frisard MI, McMillan RP, Brown TJ, Lawless MH, et al. Metabolic changes during ovarian cancer progression as targets for sphingosine treatment. Exp Cell Res 2013; 319(10):1431-42. doi: 10.1016/j.yexcr.2013.02.017.

25. Warburg O. On the origin of cancer cells. Science 1956; 123(3191):309-14.

26. Zhang WW, Liu KJ, Hu GL, Liang WJ. Preoperative platelet/lymphocyte ratio is a superior prognostic factor compared to other systemic inflammatory response markers in ovarian cancer patients. Tumour Biol 2015; 36(11):8831-7. doi: 10.1007/s13277-015-3533-9.

27. Allensworth SK, Langstraat CL, Martin JR, Lemens MA, McGree ME, Weaver AL, et al. Evaluating the prognostic significance of preoperative thrombocytosis in epithelial ovarian cancer. Gynecol Oncol 2013;130:499-504. doi: 10.1016/j.ygyno.2013.05.038.

28. Alexandrakis MG, Passam FH, Moschandrea IA, et al. Levels of serum cytokines and acute phase proteins in patients with essential and cancer-related thrombocytosis. Am J Clin Oncol 2003; 26:135-40. doi: 10.1016/j.ygyno.2013.05.038.