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RISK FACTORS FOR PERITONEAL DISSEMINATION OF OVARIAN CANCER

FAKTORI RIZIKA ZA POJAVU PERITONEALNE DISEMINACIJE KARCINOMA JAJNIKA

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Summary

Introduction. Ovarian epithelial tumors constitute 60% of all ovarian tumors and approximately 90% of primary ovarian tumors. Most patients are diagnosed at an advanced stage of the disease. Epithelial ovarian tumors typically spread via transcoelomic dissemination, with about 70% of patients presenting with peritoneal metastases. Additionally, cancers can metastasize to the pelvic lymph nodes. The objective of this study was to identify which clinical characteristics of malignant ovarian cancer might influence the occurrence of peritoneal metastases. **Material and Methods.** This retrospective study involved histopathological analysis of 99 malignant ovarian tumors treated at the Institute of Oncology of Vojvodina between January 1, 2018 and December 31, 2020. The analysis included patient age, referral and final diagnosis, dimensions of ovaries, fallopian tubes, and tumor tissue, tumor bilaterality, histological type and grade, Tumor-Node-Metastasis classification, International Federation of Gynecology and Obstetrics stages of the tumor, ovarian capsule involvement, fallopian tube involvement, and presence of peritoneal implants. Patients were categorized into two groups: one with peritoneal dissemination of cancer and the other without peritoneal metastasis. **Results.** A statistically significant difference was observed between the presence of peritoneal dissemination and tumor bilaterality ($p \leq 0.05$), as well as capsular invasion by the primary tumor ($p \leq 0.05$). **Conclusion.** Specific clinical characteristics of ovarian cancer can aid in assessing the extent of primary ovarian tumor involvement and guide the selection of appropriate therapeutic interventions.

Key words: Ovarian Neoplasms; Carcinoma, Ovarian Epithelial; Risk Factors; Neoplasm Metastasis; Peritoneum

Sažetak

Uvod. Tumori epitela koji pokrivaju jajnike čine 60% svih tumora jajnika i oko 90% primarnih tumora jajnika. Većina pacijentkinja u trenutku postavljanja dijagnoze nalazi se u uznapredovalom stadijumu bolesti. Epitelni tumori jajnika se najčešće šire transcelomskim putem. Oko 70% pacijentkinja ima rezvijene peritonealne metastaze. Mnogi od ovih karcinoma imaju metastaze i u pelvičnim limfnim čvorovima. Cilj istraživanja bio je da se utvrdi koje kliničke karakteristike malignog tumora jajnika mogu uticati na pojavu peritonealnih metastaza ovarijalnog karcinoma. **Materijal i metode.** Studija je bila retrospektivna; obuhvatila je patohistološku analizu 99 malignih tumora jajnika, u periodu od 1. januara 2018. godine do 31. decembra 2020. godine, na Institutu za onkologiju Vojvodine. Analizirani su sledeći kliničko-demografski podaci: starost pacijentkinja, uputna i konačna dijagnoza, dimenzije jajnika, jajovoda i tumorskog tkiva, bilateralnost tumora, histološki tip i gradus tumora, klasifikacija: *Tumor*, *Čvor*, *Metastaze* i stadijumi tumora prema Međunarodnoj federaciji ginekologije i akušerstva, zahvatanje kapsule jajnika, zahvatanje jajovoda, prisustvo peritonealnih implanata. Pacijentkinje su podeljene u dve grupe. Prvu grupu su činile žene sa peritonealnom diseminacijom karcinoma, dok su drugu grupu činile žene bez peritonealnih metastaza. **Rezultati.** Postoji statistički značajna razlika ($p \leq 0,05$) između postojanja peritonealne diseminacije bolesti u odnosu na postojanje bilateralnosti malignog procesa, kao i u odnosu na kapsularnu invaziju primarnog tumora ($p \leq 0,05$). **Zaključak.** Odgovarajuće kliničke karakteristike ovarijalnog karcinoma mogu se koristiti u proceni proširenosti primarne ovarijalne tumorske promene, kao i u izboru adekvatnog terapijskog postupka.

Ključne reči: tumori jajnika; epitelni karcinom jajnika; faktori rizika; metastaze; peritoneum

Introduction

Ovarian epithelial tumors comprise of 60% of all ovarian tumors and around 90% of primary ovarian tumors [1, 2]. Malignant epithelial tumors are rare before the age of 40 and become more prevalent after menopause, similar to breast and endometrial tumors [1]. Ovarian cancer is the fifth leading cause of cancer-related deaths among women. In Serbia, approximately 820 cases of ovarian cancers are diagnosed each year [3].

The majority of patients are diagnosed with the disease at advanced stages, commonly in the third and fourth stages, due to the absence of early symptoms, leading to a poorer prognosis [2]. According to Juliette et al., 80% of patients present with advanced primary disease [4]. Despite therapeutic interventions, the five-year survival rate is 50%, indicating widespread disease in most patients. If metastases involve distant organs, even with surgical and chemotherapy treatments, the five-year survival rate decreases to 30% [5].

Ovarian epithelial tumors are heterogeneous in nature. Based on their origin, genetic characteristics,

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Abbreviations

TNM – Tumor, Node, Metastasis
FIGO – International Federation of Gynecology and Obstetrics
VEGF – vascular endothelial growth factor

and disease aggressiveness, tumors are classified into type I and type II. Type I tumors are genetically more stable, exhibiting slower growth and progression. Tumors in this category include low-grade serous carcinoma, endometrioid carcinoma, mucinous carcinoma, Brenner carcinoma, and clear cell carcinoma. In contracts, type II tumors demonstrate more aggressive behavior and higher mortality rates. Tumors in this group include high-grade serous carcinoma, carcinosarcoma, and undifferentiated carcinoma [6].

The ovarian surface epithelium shares the same embryonic origin as the coelomic mesothelium. Ovarian epithelial tumors typically spread via transcoelomic dissemination. About 70% of patients develop peritoneal metastasis, often involving omental metastasis assessed during diagnostic laparotomy to evaluate disease extent. Many of these cancers also exhibit metastasis in pelvic lymph nodes, highlighting a strong association between peritoneal and nodal metastasis [2, 7].

There are two hypotheses regarding the mechanism of peritoneal dissemination in primary ovarian disease. The first model, often referred to as the "seed and soil" hypothesis, suggests that tumors as genetically heterogeneous, and metastases originate from clones that have acquired a metastatic phenotype [8]. The genotype of the clone determines the tissue in which the cells will metastasize. According to the other theory, metastasis is a stochastic event, suggesting a small but real possibility that tumor cells will metastasize, and all tumor cells are homogeneous [9].

The process of metastasis in malignant ovarian carcinoma involves several key steps. Firstly, malignant cells must evade anoikis, a process in which cells undergo apoptosis when they lose contact with the extracellular matrix [10]. An important event in the development of metastatic potential is epithelial-mesenchymal transition, during which epithelial cells depolarize, intracellular connections are disrupted, and cells acquire morphological characteristics of fibroblasts, enabling adaptive migratory potential [2, 11]. This transition leads to the overexpression of endothelin 1 and its receptors, and reduced expression of E-cadherin [12].

Further evidence enhancing our understanding of adaptive metastasis involves the existence of spheroids, which represent aggregated malignant cells in malignant ascites [13]. In in vitro studies have shown that spheroids exhibit greater resistance to the component complement system, as antibodies and component complements struggle to penetrate cell clusters [14].

Peritoneal metastasis can manifest as either microscopic or macroscopic. It has been established that complete surgical removal of macroscopic peritoneal implants significantly prolongs overall survival and disease-free survival [15]. Amate et al. reported that peritoneum is the most common site of recurrence following treatment for ovarian malignancy [16]. When considering micrometastases, Schroff et al. identified their presence in 5% of cases on seemingly healthy peritoneum. The five-year survival for patients with micrometastases was 61.83% compared to 88.25% for patients without occult dissemination [17, 18].

This study was prompted by the high incidence of ovarian cancer among female patients and the presence of peritoneal metastasis at the time of diagnosis. Our aim was to investigate which clinical characteristic of malignant ovarian tumors influence the occurrence of peritoneal metastasis.

Material and Methods

The research was conducted retrospectively, involving the histopathological examination of 99 malignant ovarian tumors from January 1, 2018, to December 31, 2020, at the Oncology Institute of Vojvodina, following ovarian and fallopian tube surgeries. The histopathological analysis adhered to the protocol outlined by the College of American Pathologists (CAP) in 2018.

The methods used during the histopathological analysis of the ovarian tumors included:

1. Macroscopic analysis including the description of the received resected one or both ovaries with or without the fallopian tubes, uterus, lymph nodes and peritoneum; measurement of dimensions of ovaries, fallopian tubes, and tumor tissue (cm); description of the appearance of tumor tissue (shape, size, and color), localization, and edges (limits, presence of the tumor capsule, invasive growth, infiltration of ovarian capsule, fallopian tubes, uterus, or surrounding peritoneum); serial cutting of resected material perpendicularly along the longest axis into 3 mm thick slices.
2. Tissues were fixed in 10% neutral formalin, dehydrated in increasing concentrations of ethanol (70%, 80%, 96%, 100%), embedded in paraffin, and cut into 4 μm thick sections using a rotary microtome (Leica). All sections were stained with hematoxylin-eosin.
3. Microscopic histopathology examination was performed by pathologist using a light microscope to determine a definitive histopathological diagnosis based on histomorphological characteristics of tumor tissue.

All patients with complete medical history, including present symptoms, comorbidities, family history, allergies, and chronic therapies (if any), were included in this study. Additionally, each patient needed to have a noted final histopathological diagnosis and indication of peritoneal dissemination of carcinoma. Patients with incomplete medical histories and verified benign tumor masses were excluded from this research. After conducting macroscopic and microscopic analysis of the tissue samples obtained, the following data was analyzed: age of the patient, referral and final diagnosis, dimensions of the ovaries, fallopian tubes, and tumor tissue, bilaterality of the tumor, histologic type and grade, according to the tumor-node-metastasis (TNM) (AJCC 8th Edition) and the International Federation of Gynecology and Obstetrics (FIGO) tumor stages, ovary capsule involvement, fallopian tubes involvement, presence of peritoneal implants.

Patients with histopathologically confirmed ovarian cancer were divided into two groups based on the presence or absence of peritoneal dissemination of ovarian carcinoma. We recorded the number of patients younger than 50 years and those older than 50 years of age. Descriptive statistics were employed to ascertain the mean age of patients, distribution of carcinoma grade, disease stage, bilaterality, ovarian capsule invasion, uterine tubal involvement, and the utilization of neoadjuvant therapy. To investigate the relationship between the existence of peritoneal dissemination and patient age, we used a T-test to determine statistical significance. Chi square (χ^2) tests were used to assess whether there was a statistically significant association between peritoneal dissemination of the primary tumor and malignancy grade, disease stage, bilaterality, ovarian capsule invasion, and fallopian tube involvement. Differences in the number of removed lymph nodes and lymph nodes with metastatic deposits between groups with and without peritoneal dissemination were analyzed using the Mann-Whitney U test. The staging of ovarian tumors was determined according to the TNM classification [19] and FIGO criteria [20].

Results

The mean age of patients was 58.66±11.75 years, with the youngest patient being 27 years old and the oldest patient 87 years old. Among all patients, 19.20% were younger than 50 years, while 80.80% were older. Positive peritoneal lavage or peritoneal implants were found in 83.80% of cases. The histological types of tumors and their representation in the examined histopathological sample are shown in **Table 1**.

Regarding malignancy grade, tumors were categorized as high or low grade (G1, G2, G3). Among the examined samples, 17.17% were classified using the three-tier grading system (G1: 17.65%, G2: 47.06%, G3: 35.29%). The remaining tumors (67.68%) were classified using the two-tier system (high/low grade), with the majority of tumors (91.04%) being high grade and the rest (8.96%) low

Table 1. Presentation of histological types of ovarian cancers in the examined sample
Tabela 1. *Prikaz histoloških tipova ovarijalnih karcinoma u ispitivanom uzorku*

		N/*Br.*	%
Histological types of cancer *Histološki tipovi karcinoma*	Serous carcinoma/*Serozni karcinom*	71	71.72
	Mucinous carcinoma/*Mucinozni karcinom*	11	11.11
	Endometrioid carcinoma/*Endometrioidni karcinom*	6	6.06
	Mucinous borderline tumor/*Mucinozni 'borderline' tumor*	4	4.04
	Serous borderline tumor/*Serozni 'borderline' tumor*	2	2.02
	Clear cell carcinoma/*'Svetloćelijski' karcinom*	2	2.02
	Seromucinous borderline tumor/*Seromucinozni 'borderline' tumor*	1	1.01
	Undifferentiated or dedifferentiated carcinoma *Nediferentovani ili dediferentovani karcinom*	1	1.01
	Carcinosarcoma/*Karcionosarkom*	1	1.01
	Total/*Ukupno*	99	100

Table 2. Absolute and percentage values of carcinoma bilaterality, ovarian capsule involvement, uterine tube involvement, and application of neoadjuvant therapy
Tabela 2. *Prikaz apsolutnih i procentualnih vrednosti bilateralnosti karcinoma, zahvaćenosti kapsule jajnika, jajovoda i primene neoadjuvantne terapije*

		N/*Br.*	%
Bilaterality/*Bilateralnost*	No/*Ne*	44	44.40%
	Yes/*Da*	55	55.60%
	Total/*Ukupno*	99	100%
Capsule involvement/*Zahvaćenost kapsule*	No/*Ne*	40	40.40%
	Yes/*Da*	59	59.60%
	Total/*Ukupno*	99	100%
Tube involvement/*Zahvaćenost jajovoda*	No/*Ne*	72	72.70%
	Yes/*Da*	27	27.30%
	Total/*Ukupno*	99	100%
Neoadjuvant therapy/*Neoadjuvantna terapija*	No/*Ne*	95	96%
	Yes/*Da*	4	4%
	Total/*Ukupno*	99	100%

Table 3. Peritoneal dissemination rate depending on tumor bilaterality and ovarian capsule involvement
Tabela 3. *Učestalost peritonealne diseminacije bolesti u zavisnosti od bilateralnosti tumora i prisustva kapsularne invazije*

		Bilaterality/*Bilateralnost*						p/*p*
		No/*Ne*		Yes/*Da*		Total/*Ukupno*		
		N/*Br.*	%	N/*Br.*	%	N/*Br.*	%	
Peritoneal dissemination of the disease *Peritonealna diseminacija bolesti*	No/*Ne*	14	31.80	2	3.60	16	16.20	≤0.05
	Yes/*Da*	30	68.20	53	96.40	83	83.80	
	Total/*Ukupno*	44	100	55	100	99	100	
		Ovarian capsule involvement *Zahvaćenost kapsule jajnika*						p/*p*
		No/*Ne*		Yes/*Da*		Total/*Ukupno*		
		N/*Br.*	%	N/*Br.*	%	N/*Br.*	%	
Peritoneal dissemination of the disease *Peritonealna diseminacija bolesti*	No/*Ne*	14	35	2	3.40	16	16.20	≤0.05
	Yes/*Da*	26	65	57	96.60	83	83.80	
	Total/*Ukupno*	40	100	59	100	99	100	

Table 4. Analysis of the differences between peritoneal dissemination of the disease and the number of removed lymph nodes. Analysis of the differences between peritoneal dissemination of the disease and the number of lymph nodes exhibiting metastatic changes
Tabela 4. *Ispitivanje postojanja razlike između peritonealne diseminacije bolesti i broja odstranjenih limfnih čvorova. Ispitivanje postojanja razlike između peritonealne diseminacije bolesti i broja metastatski izmenjenih limfnih čvorova*

Average number of removed lymph nodes in regard to peritoneal dissemination of primary disease *Prosečan broj odstranjenih limfnih čvorova u odnosu na peritonealnu diseminaciju primarne bolesti*			
Peritoneal dissemination of the disease *Peritonealna diseminacija bolesti*	Average number of removed lymph nodes *Prosečan broj odstranjenih limfnih čvorova*	Mann Whitney *Man-Vitnijev test* (U)	p/*p*
Yes/*Da*	3.27	1057.500	0.510
No/*Ne*	1.92		
Peritoneal dissemination of the disease *Peritonealna diseminacija bolesti*	Average number of removed lymph nodes with confirmed metastasis/*Prosečan broj odstranjenih limfnih čvorova sa potvrđenim metastatskim promenama*	Mann Whitney *Man-Vitnijev test* (U)	p/*p*
Yes/*Da*	2.00	896.000	0.01
No/*Ne*	0.06		

grade. Fifteen tumors did not have an indicated malignancy grade. When comparing disease staging, the most prevalent stage was T3 (50%), followed by T1 (30.00%), and T2 (18.90%). T4 stage was the least represented (1.10%). Nine tumors did not have an indicated T stage in the medical records.

Table 2 presents absolute and percentage values of bilateral tumor presence, capsule involvement, uterine tubal involvement, and application of neoadjuvant therapy in the examined sample.

There was no statistically significant difference between the age groups (cutoff 50 years) and positive peritoneal lavage/implants (p=0.620). Patients with G1 malignancy grade did not have peritoneal disease expansion, whereas in patients with G3 grade, only one patient did not have peritoneal dissemination. Among patients with G2 malignancy grade, 62.50% had peritoneal dissemination. In stages T2, T3, and T4, no patients were without peritoneal dissemination, making it impossible to determine statistical significance.

Table 3 shows the frequency of peritoneal dissemination in relation to tumor bilaterality and ovarian capsule involvement.

Table 4 examines statistically significant differences in the existence of peritoneal dissemination and the number of the removed lymph nodes, as well as the number of lymph nodes with metastatic changes.

Discussion

The mean age of patients in our study was 58.66 years. Among the examined sample, 19.20% were younger than 50 years, while 80.80% were 50 years of age and older. Antonijević et al. [21] noted a rapid increase in new cases of ovarian cancer after the age of 40, with 78.80% of new patients falling between the ages of 40 to 74 years, 9.00% below 40 years, and 12.30% older than 75 years.

In our study, 83.80% of the patients tested positive for peritoneal expansion of malignancy, while 16.20% tested negative. Ayhan et al. reported that 31.40% of

patients initially diagnosed with early stage carcinoma were subsequently reclassified to higher stages due to findings of the occult peritoneal metastasis [18]. Serous carcinoma was more commonly associated with positive peritoneal cytology (76.90%) compared to the mucinous and endometrioid types (44% and 25%, respectively) [22]. The most prevalent histological type of carcinoma in our study was serous ovarian adenocarcinoma, accounting for 59.60% of cases. Similar percentage for serous adenocarcinoma (52%) was reported in the investigation by Torre et al. [23].

Regarding the histological grade, high-grade carcinomas were far more common in our study (91.04%), with low-grade tumors present in 8.96% of cases. Among the three-tier grading system, G2 histological grade was most prevalent at 47.06%, followed by G1 at 17.65% and G3 at 35.29%. In contrast, Plaxe reported different proportions in a study of 12,400 women, with G1 grade at 6.30%, G2 at 23.10%, and G3 at 57.50% of ovarian cancers, indicating a notable difference compared to our findings [24].

Regarding the bilateral presence of tumors on the ovaries, our study found that the tumor process was bilateral in 55 patients (55.60%), while in 44 patients, the malignant process affected only one ovary (44.40%). Boger-Megiddo et al. reported that serous ovarian adenocarcinoma is bilateral in 57.50% of cases [25]. In our study, 40 patients (40.40%) exhibited tumors affecting the ovarian capsule, while in slightly more cases (59.60%), there was no invasion of the ovarian capsule by the primary tumor. Naz et al. noted tumors on the ovarian capsule in 61.00% of medical findings, with omental metastasis observed in 51% of cases [22]. Examining fallopian tube involvement in ovarian carcinoma, it was determined that in most cases, there was no expansion to the fallopian tube. A higher percentage of tumor involvement in the fallopian tubes was described in a study conducted by Seidman et al. [26].

Regarding differences in peritoneal spread of the disease in relation to the age of patients, we found no statistically significant differences between peritoneal spread and patient age. The mean age of patients with low-grade carcinoma in study by Wafa et al. was 48 years (ranging from 26 to 76 years) [27].

In cases when the tumor process was bilateral, we observed a statistically significant relationship between peritoneal dissemination of the disease and the presence of bilateral ovarian tumor masses. We arrived at a similar conclusion when comparing peritoneal dissemination of the disease with invasion of the ovarian capsule by primary carcinoma. Naz et al. also determined a statistically significant correlation of capsular invasion with the presence of malignant peritoneal dissemination [22].

When comparing the differences in the number of extirpated lymph nodes and the number of lymph nodes with metastatic deposits in case of peritoneal dissemination of the disease, we observed no statistically significant difference in the former (Mann-Whitney test; U=1057.500; p=0.510). However, there was significant difference in the average number of removed lymph nodes with verified metastasis (Mann-Whitney test; U=896.000; p=0.01). Tsuruchi et al. concluded that there is a strong correlation between intraperitoneal dissemination and lymph node involvement [7].

It is evident that the process of malignant cell metastasis from the surface of the ovary to the peritoneal mesothelium is complex [28]. High concentrations of the vascular endothelial growth factor (VEGF) are found in peritoneal effusion of patients with ovarian cancer [29]. The expression of VEGF is also associated with ovarian carcinoma, secretion, matrix metalloproteinase (MMP) activity, tumor growth, invasion, and worse prognosis [30].

E-cadherin is an intracellular molecule that maintains and stabilizes intercellular connections [31]. Decreased expression of E-cadherin is associated with metastatic disease and increased mortality from ovarian carcinoma [32]. Cancer antigen 125, a glycoprotein overexpressed on malignant cells, it is known to bind to mesothelin expressed on mesothelial cells [33]. E-cadherin is again overexpressed during the implantation of malignant cells into the peritoneum, whereas its expression is reduced during cell detachment from the primary tumor mass [34].

Mesothelial cells respond to inflammation and malignant cell activity by secreting reactive forms of oxygen, interleukin 1, interleukin 6, and interleukin 8 [35]. Interleukin 1β can contribute to tumor angiogenesis and increased formation of peritoneal effusion by stimulating VEGF secretion [36]. Interleukin 6 can promote tumor migration, adhesion to mesothelium, and proliferation of malignant cells. It is also associated with shortened disease remission and overall worse prognosis [37]. Interleukin 8 is a proinflammatory mediator with proangiogenic effects that may stimulate tumor growth and invasiveness [38].

Conclusion

Based on our examined data and statistical analysis of the study, we can conclude that the occurrence of positive peritoneal lavage or peritoneal implantations is not dependent on the age of the participants. Additionally, we found no correlation between peritoneal dissemination of the carcinoma and the histological grade of malignancy. While there was no significant difference observed in the number of extirpated lymph nodes between patients with or without peritoneal dissemination, there was a significant difference in the average number of removed lymph nodes with verified metastasis in patients with positive peritoneal dissemination of the disease. However, several markers suggest that clinicians should persist in testing and obtaining information to determine if the carcinoma has peritoneally disseminated. The presence of bilateral tumor process and invasion of the ovarian capsule strongly indicate peritoneal dissemination of the disease. Early diagnosis is often challenging but should be a priority, similar to other malignant diseases, as it facilitates early initiation of therapy and improves survival rates.

References

1. Atanacković M, Bacetić D, Basta-Jovanović G, Begić-Janeva A, Boričić I, Brašanac D, et al. Patologija. Beograd: Medicinski fakultet; 2015.

2. Tan DS, Agarwal R, Kaye AB. Mechanisms of transcoelomic metastasis in ovarian cancer. Lancet Oncol. 2006;7(11):925-34.

3. Đurđević S, Stojanović S, Basta Nikolić M, Nikolić D. Novel diagnostic and therapeutic approaches to the treatment of ovarian cancer. Med Pregl. 2019;72(1-2):11-6.

4. van Baal JOAM, van Norden CJF, Nieuwland R, Van de Vijver KK, Sturk A, van Driel WJ, et al. Development of peritoneal carcinomatosis in epithelial ovarian cancer: a review. J Histochem Cytochem. 2018;66(2):67-83.

5. Cancer stat facts: ovarian cancer [Internet]. 2019 [cited 2019 Jun 15]. Available from: https://seer.cancer.gov/statfacts/html/ovary.html

6. Romero I, Bast RC Jr. Minireview: human ovarian cancer: biology, current management, and paths to personalizing therapy. Endocrinology. 2012;153(4):1593-602.

7. Tsuruchi N, Kamura T, Tsukamoto N, Akazawa K, Saito T, Kaku T, et al. Relationship between paraaortic lymph node involvement and intraperitoneal spread in patients with ovarian cancer-a multivariate analysis. Gynecol Oncol. 1993;49(1):51-5.

8. Fidler IJ. The pathogenesis of cancer metastasis: the 'seed and soil' hypothesis revisited. Nat Rev Cancer. 2003;3(6):453-8.

9. Bernards R, Weinberg RA. A progression puzzle. Nature. 2002;418(6900):823.

10. Reddig PJ, Juliano RL. Clinging to life: cell to matrix adhesion and cell survival. Cancer Metastasis Rev. 2005;24(3):425-39.

11. Rosano L, Spinella F, Di Castro V, Nicotra MR, Dedhar S, de Herreros AG, et al. Endothelin-1 promotes epithelial-to-mesenchymal transition in human ovarian cancer cells. Cancer Res. 2005;65(24):11649-57.

12. Patel IS, Madan P, Getsios S, Bertrand MA, MacCalman CD. Cadherin switching in ovarian cancer progression. Int J Cancer. 2003;106(2):172-7.

13. Neufeld G, Cohen T, Gengrinovitch S, Poltorak Z. Vascular endothelial growth factor (VEGF) and its receptors. FASEB J. 1999;13(1):9-22.

14. Bjorge L, Junnikkala S, Kristoffersen EK, Hakulinen J, Matre R, Meri S. Resistance of ovarian teratocarcinoma cell spheroids to complement-mediated lysis. Br J Cancer. 1997;75(9):1247-55.

15. Azaïs H, Estevez JP, Foucher P, Kerbage Y, Mordon S, Collinet P. Dealing with microscopic peritoneal metastasis of epithelial ovarian cancer. A surgical challenge. Surg Oncol. 2017;26(1):46-52.

16. Amate P, Huchon C, Dessapt AL, Bensaid C, Medioni J, Le Frère Belda MA, et al. Ovarian cancer: sites of recurrence. Int J Gynecol Cancer. 2013;23(9):1590-6.

17. Shroff R, Brooks RA, Zighelboim I, Powell MA, Thaker PH, Mutch PH. The utility of peritoneal biopsy and omentectomy in the upstaging of apparent early ovarian cancer. Int J Gynecol Cancer. 2011;21(7):1208-12.

18. Ayhan A, Gultekin M, Celik NY, Dursun P, Taskiran C, Aksan G, et al. Occult metastasis in early ovarian cancer: risk factors and associated prognosis. Am J Obstet Gynecol. 2007;196(1):81.e1-6.

19. Krishnamurti UG, Crothers BA, Otis CN, Birdsong GG, Movahedi-Lankarani S, Klepeis V. Protocol for the examination of specimens from patients with primary tumors of the ovary, fallopian tube, or peritoneum [Internet]. 2021 [cited 2024 Jan 15]. Available from: https://documents.cap.org/protocols/Ovary_FT_Perit_1.3.0.1.REL_CAPCP.pdf

20. Đurđević S, Mandić A. Ginekološka onkologija. In: Đurđević S, editor. Ginekologija. 3rd ed. Novi Sad: Medicinski fakultet; 2019. p. 297.

21. Antonijević A, Rančić N, Ilić M, Todorović B, Stojanović M, Stefanović J. Incidence and mortality trends of ovarian cancer in central Serbia. J BUON. 2017;22(2):508-12.

22. Naz S, Hashmi AA, Ali R, Faridi N, Hussian SD, Edhi MM, et al. Role of peritoneal washing cytology in ovarian malignancies: correlation with histopathological parameters. World J Surg Oncol. 2015;13:315.

23. Torre LA, Trabert B, DeSantis CE, Miller KD, Samimi G, Runowicz CD, et al. Ovarian cancer statistic, 2018. CA Cancer J Clin. 2018;68(4):284-96.

24. Plaxe SC. Epidemiology of low-grade serous ovarian cancer. Am J Obstet Gynecol. 2008;198(4):459.e1-8.

25. Boger-Megiddo I, Weiss NS. Histologic subtypes and laterality of primary epithelial ovarian tumors. Gynecol Oncol. 2005;97(1):80-3.

26. Seidman JD. Serous tubal intraepithelial carcinoma localizes to the tubal-peritoneal junction: a pivotal clue to the site of origin of extrauterine high-grade serous carcinoma (ovarian cancer). Int J Gynecol Pathol. 2015;34(2):112-20.

27. Wafa M, Braicu EI, Muallem MZ, Richter R, Taube E, Sehouli J, et al. Incidence and pattern of spread of lymph node metastasis in patients with low-grade serous ovarian cancer. Anticancer Res. 2019;39(10):5617-21.

28. Adam RA, Adam YG. Malignant ascites: past, present and future. J Am Coll Surg. 2004;198(6):999-1011.

29. Zebrowski BK, Liu W, Ramirez K, Akagi Y, Mills GB, Ellis LM. Markedly elevated levels of vascular endothelial growth factor in malignant ascites. Ann Surg Oncol.1999;6(4):373-8.

30. Wang FQ, So J, Reierstad S, Fishman DA. Vascular endothelial growth factor-regulated ovarian cancer invasion and migration involves expression and activation of matrix matalloproteinases. Int J Cancer. 2006;118(4):879-88.

31. Burleson KM, Casey RC, Skubitz KM, Pambuccian SE, Oegema TR Jr, Skubitz AP. Ovarian carcinoma ascites spheroids adhere to extracellular matrix components and mesothelial cell monolayers. Gynecol Oncol. 2004;93(1):170-81.

32. Faleiro-Rodrigues C, Macedo-Pinto I, Pereira D, Ferreira VM, Lopes CS. Association of E-cadherin and beta-catenin immunoexpression with clinicopathologic features in primary ovarian carcinomas. Hum Pathol. 2004;35(6):663-9.

33. Rump A, Morikawa Y, Tanaka M, Minami S, Umesaki N, Takeuchi M, et al. Binding of ovarian cancer antigen CA125/MUC16 to mesothelin mediates cell adhesion. J Biol Chem. 2004;279(10):9190-8.

34. Imai T, Horiuchi A, Shiozawa T, Osada R, Kikuchi N, Ohira S, et al. Elevated expression of E-cadherin and alpha-, beta-, and gamma-catenins in metastatic lesions compared with primary epithelial ovarian carcinomas. Hum Pathol. 2004;35(12):1469-76.

35. Freedman RS, Deavers M, Liu J, Wang E. Peritoneal inflammation: a microenvironment for epithelial ovarian cancer (EOC). J Transl Med. 2004;2(1):23.

36. Standlmann S, Amberger A, Pollheimer J, Gastl G, Offner FA, Margreiter R, et al. Ovarian carcinoma cells and IL-1beta-activated human peritoneal mesothelial cells are possible sources

of vascular endothelial growth factor in inflammatory and malignant peritoneal efussions. Gynecol Oncol. 2005;97(3):784-9.

37. Tempfer C, Zeisler H, Sliutz G, Haeusler G, Hanzal E, Kainz C. Serum evaluation of interleukin 6 in ovarian cancer patients. Gynecol Oncol. 1997;66(1):27-30.

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38. So J, Navari J, Wang FQ, Fishman DA. Lysophosphatidic acid enhances epithelial ovarian carcinoma invasion through the increased expression of interleukin-8. Gynecol Oncol. 2004;95(2):314-22.