

1. Introduction

Ovarian cancer is one of the most fatal female reproductive system cancers [1]. Based on data provided by the WHO, 225,500 cases of ovarian cancer are diagnosed worldwide each year and 140,200 deaths are reported. Among the female population, according to world statistics, ovarian cancer ranks 7th in the structure of morbidity and 8th in the structure of mortality [2, 3]. According to the Ukraine National Cancer Registry (2019), ovarian cancer occupies the 6th position both in the morbidity and mortality structure of women population [4].

Epithelial malignant neoplasms of the ovaries account for 40 % of all oncopathology [5], with SOC being the leading histotype and covering 68–71 % of epithelial neoplasms [6]. There are 2 types of SOC, which differ in origin, biological behavior and prognosis for patients. Type I is represented by serous carcinoma of low malignancy (LGSC), and type II – serous carcinoma of high malignancy (HGSC). [7] Although LGSC accounts for only 5 % of all SOCs, and the leading role is played by HGSC [8], the study of molecular genetic and biological features of LGSC is extremely important for the ability to predict tumor behavior and selection of targeted therapy.

In recent years, much attention has been paid to the study of CSCS population and their role in the cancer progression. Numerous studies have shown that although CSCS account for only a few percent of tumor mass, they are one of the leading predictors of chemoresistance, recurrence and metastasis of SOC [9, 10]. The population of CSCS in ovarian tumor tissue is determined by a number of surfaces IHC-markers (CD44, CD117, CD133) and intracellular markers (Nanog, Oct4 and Sox2) [11, 12]. The origin of CSCS is also debatable: according to some data, normal stem cells can become a source of the CSCS pool, according to other data, stem tumor cells are transformed from carcinoma cells. In addition, many studies have focused on the plasticity properties of CSCS and their relationship to EMT. According to some researchers, carcinoma phenotype changes dynamically from epithelial to mesenchymal depending on disease stage and presence of metastases, and it correlates with increased levels of CSCS expression and worsening prognosis [13].

The aim of our research was studying of expression surface CSCS markers CD44 and CD117 in LGSC with subsequent re-

PROGNOSIS ROLE OF EPITHELIAL-MESENCHYMAL TRANSFORMATION MARKERS AND SURFACE STEM TUMOR CELLS IN THE RECURRENCE OF SEROUS LOW GRADE OVARIAN CARCINOMAS

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Abstract: Ovarian cancer remains one of the most fatal pathologies among women around the world due to late diagnosis on the advanced stages of the tumor process. Serous ovarian carcinomas (SOC) often recur, which worsens the prognosis for patients' recovery and survival. The identification of prognostic clinical and morphological factors that predict the appearance of recurrence remains an urgent problem.

The aim of the research was studying relationships between the phenomenon of epithelial-mesenchymal transformation (EMT) and the expression of surface cancer stem cells (CSCS) markers to identify recurrence predictors among women with low grade serous ovarian carcinomas (LGSC).

The material were paraffin blocks and slides of 43 patients with LGSC I-IV FIGO stage. The study included 30 cancers without recurrence and 13 tumors with it within 24 months. The expression of E-cadherin, Vimentin, CD44 and CD117 was studied using immunohistochemical (IHC) method.

Results. Development of recurrence is typical for women with stage III-IV ($p=0.01$), the expression of Vimentin at level 51–100 % ($p=0.001$) and E-cadherin at 10–50 % ($p=0.04$). CD44 was expressed in 51.16 % of tumors and level didn't depend on age, recurrence, but depended on disease stage ($p=0.001$). Recurrent LGSCs are characterized by the expression of CD117>10 % ($p=0.0001$), its direct correlation with the stage ($p=0.0001$) and the recurrence ($p=0.0001$). A direct relationship was found between the CD117 and Vimentin expression.

Conclusions. Prognostic markers of recurrence should be considered stage III-IV, levels of Vimentin 51–100 %, E-cadherin 10–50 % and CD117>10 %. A correlation between CD117 and Vimentin expression indicates the commonality of EMT and CSCS in progression and recur. CD44 has no independent prognostic role.

Keywords: LGSC, Vimentin, E-cadherin, EMT, CSCS, CD44, CD117, ovarian cancer, FIGO stage, IHC, immunohistochemistry, IHC markers.

currence and without it, as well as the relationship between the expression of CSCS and EMT markers to identify possible predictors of recurrence in patients.

2. Materials and methods

The material for our research were case histories, paraffin blocks and slides of 43 patients with LGSC who underwent surgery in the amount of bilateral salpingo-oophorectomy and hysterectomy with resection or extirpation of the large omentum with subsequent adjuvant chemotherapy and previous neoadjuvant chemotherapy in cases of advanced stages. Surgical interventions were performed at the Institute of Medical Radiology and Oncology. S. P. Grigoriev, Regional Clinical Oncology Center (Kharkov) in the period from 2013 to 2018. The prevalence of the tumor process was assessed according to the FIGO classification. The study included LGSC with disease stage I-IV: 30 cancers without recurrence over the next 24 months (main group) and 13 cancers with recurrence (comparison group) in the specified time interval. The age of the patients varied from 28 to 56 years (average age 42.7 ± 0.91). Histological type of tumors was determined during examination of slides stained with hematoxylin-eosin. From each clinical case, 1 paraffin block was selected for IHC-study.

All patients signed informed consent for the using their information from case histories, paraffin blocks and slides in our study.

For the IHC study, the material was fixed with 10 % neutral formalin for 24 h, embedded in paraffin, prepared 4 μ m thick sections, which were applied to highly adhesive Super Frost slides and dried at 37 °C for 18 hours.

Unmasking heat treatment was performed by boiling the sections in citrate buffer (pH 6.0). UltraVision Quanto Detection Systems HRP Polymer (Thermo scientific) was used to visualize primary antibodies. DAB (diaminobenzidine) was used as the chromogen.

Primary monoclonal antibodies (MCAT) from DAKO (Denmark), ThermoScientific (Germany) and Diagnostic BioSystems (USA) were used. The expression of the following markers was studied: E-cadherin (EP7004, Thermo Scientific), Vimentin (Diagnostic BioSystems), CD117 (Diagnostic BioSystems), CD44 (Clone: 156-3C11, Dako Cytomation).

To assess the intensity of IHC mark used a semi-quantitative scale 0–3 +: 0 – no expression, + – weak, ++ – moderate, +++ – a pronounced reaction. To quantify the IHC mark, E-cadherin

and Vimentin took into account the percentage of staining: 0 – no staining, <10 % of nuclei – weak, 10–50 % – moderate, 51–100 % – high expression. To assess the immunohistochemical label CD117 and CD44, the level of staining >10 % was considered high, ≤10 % – low, 0 – no staining. Only cells with moderate (++) and high (+++) color intensity were taken into account.

Statistical analysis was performed using the Mann-Whitney test to assess differences between two groups on the level of trait. Spearman's rank correlation method was used to assess the correlation. Pearson's Yets-corrected test was used to assess differences between the study groups. The level of significance ≤0.05 was considered significant.

3. Results

Analysis of general clinical characteristics showed that age of patients in the main group ranged from 35 to 51 years (median=42.97±0.81 years), and in the comparison group age fluctuations ranged from 28 to 56 years (median=42.08±2.43 years). Age differences of the compared groups are statistically insignificant ($U_{emp}=191$ at $U_{crit}=132$). Menopause occurred in 23.08 % (3/13) of patients from the group of recurrent LGSCs, in the group of LGSCs without recurrence menopause was recorded in 13.33 % (4/30) cases. For LGSCs without recurrence are typical initial (I–II) stages of the disease with no terminal (IV) stage, while recurrent LGSCs are characterized by disease stage III–IV with no cases diagnosed in stage I ($\chi^2=20.95, p=0.0051$) and a significant decreasing of cases diagnosed in stage II ($\chi^2=14.37, p=0.0059$) (Table 1).

Table 1

Distribution of tumors (n=43) depending on the stage of the disease according to FIGO

FIGO stage	Main group n=30 (%)	Comparison group n=13 (%)
I	6 (20)*	0*
II	20 (66,67)**	1 (7,69)
III	4 (13,33)***	10 (76,92)
IV	0	2 (15,38)

Note: * – insignificant difference between I and II stages ($\chi^2=0.46, p=0.5$), III and IV stages ($\chi^2=0, p=1$); ** – significant difference between II and III stages ($\chi^2=14.37, p=0.0002$); *** – significant difference between I–II and III–IV stages of the disease ($\chi^2=20.95, p=0.0001$)

The study did not show association between the patients' age and disease recurrence in the control group ($r=0.402, p=0.0049$) and the study ($r=0.159, p=0.07$). At the same time Fig. 1 shows a direct strong correlation between FIGO stage and development of recurrence of SOC ($r=0.69, p=0.00039$).

Analyzing the expression of EMT markers (Table 2), it was found that both carcinoma groups are characterized by Vimentin expression at ≥10 %. The control group is typical for a moderate expression level (median 35.27 %±1.93) with increasing number of cases of high level of marker expression in the comparison group ($\chi^2=16.21, p=0.006$), where the average level expression reached 61.15 %±3.95. Analyzing the expression of Vimentin depending on stage, it was noticed that in both LGSC groups moderate expression of Vimentin is typical for I–II stage of the disease ($\chi^2=15.13, p=0.0001$), while for III–IV is typical expression level >50 %.

Regarding the expression of E-cadherin, statistically significant differences between moderate and high levels of expression in tumors with recurrence and without were not detected ($\chi^2=2.6, p=0.1$), while for both groups the expression level was ≥10 %. In the control group, the expression level acquired values from 26 % to 68 % (median=30.15 %±2.78), and in the comparison group the

values ranged from 11 % to 47 % (median=46.57±1.77 %). Interestingly, despite the lack of differences in the levels of E-cadherin expression, in tumors with recurrence there is a tend to decrease the level of IHC-mark ($U_{emp}=43$ at $U_{crit}=132$). It was found that LGSC III–IV stages are characterized by a moderate level of E-cadherin expression ($\chi^2=4.03, p=0.04$) with a decrease in the number of cases of high marker expression in the control group and the absence of such cases in recurrence LGSC. There is an inverse relationship between E-cadherin expression and FIGO stage ($r=0.32, p=0.034$) and development of recurrence ($r=0.62, p=0.00031$) (Fig. 2).

Table 2

Distribution of tumors (n=43) depending on the level of expression of IHC markers of EMT and the disease stage by FIGO

Expression level	Main group n=30				Comparison group n=13				
	E-cadherin	I	II	III	IV	I	II	III	IV
0 %	-	-	-	-	-	-	-	-	-
<10 %	-	-	-	-	-	-	-	-	-
10–50 %	-	18	4	-	-	1	10	2	-
51–100 %	6	2	-	-	-	-	-	-	-
Vimentin									
0 %	-	-	-	-	-	-	-	-	-
<10 %	-	-	-	-	-	-	-	-	-
10–50 %	6	19	2	-	-	-	3	-	-
51–100 %	-	1	2	-	-	1	7	2	-

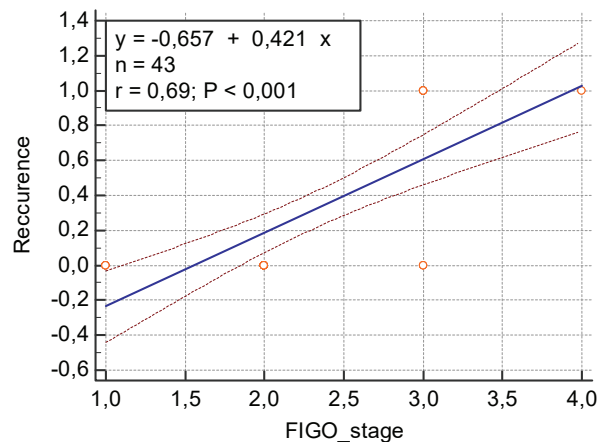


Fig. 1. Graphical representation of the relationship between FIGO stage and LGSC recurrence

Considering the expression of surface CSCS markers (Table 3), it was found that CD44 +– status had 51.16 % (22/43) of all tumors: in the comparison group CD44 + tumors were observed in 69.23 % (9/13) cases, and in the control group in 43.33 % (13/30) of the studied tumors. In LGSC with recurrence, the level of CD44 expression ranged from 8 % to 14 % with an average value of 7.46 %±1.49, in LGSC without reoccur, the IHC-index varied between 6–14 % with a median of 4.13 %±0.91. No statistically significant differences between marker expression levels in the study groups were found ($\chi^2=2.74, p=0.098$).

The dependence of marker expression on age ($r_s=0.128, p=0.41$) and the presence of recurrence ($r_s=0.29, p=0.057$) was not detected, while the dependence of CD44 expression on the FIGO stage was found ($r_s=0.483, p=0.001$) (Fig. 3).

Regarding the CD117 expression, it should be noted that 39.53 % (17/43) of tumors had CD117-negative status: 7.69 % (1/13) belonged to the comparison group and 53.33 % (16/30) to the main group. The control group was characterized by marker

expression at the level of 0–10 % with a median of 5.37 %±1.19 and a range of values from 6 % to 19 % with a statistically significant ($\chi^2=14.81, p=0.00043$) increase in the number of cases of high expression level in comparison group (median 13.85 %±1.55) and the increase of expression level in the group of recurrent LGSC ($U_{emp}=62$ at $U_{krit}=132$). For stage III–IV there is a tend to increase number of cases with expression > 10 %, while for the initial stages more typical expression at the level of 0–10 % ($\chi^2=26.68, p=0.00067$). A strong correlation was found between the CD117 expression and stage of the disease ($r_s=0.84, p=0.0002$), the presence of recurrence ($r_s=0.54, p=0.00033$). At the same time, there is no relationship between CD117 + tumor status and patient’s age ($r_s=0.183, p=0.24$) (Fig. 4).

Coexpression of markers, studied in our study, revealed a direct correlation between CD117 and CD44 expression ($r_s=0.73, p=0.001$), as well as between Vimentin expression ($r_s=0.64, p=0.0006$), the inverse correlation between E-cadherin and Vimentin expression

($r_s=-0.32, p=0.038$). Coexpression of CD44 and E-cadherin shows no dependence ($r_s=0.08, p=0.615$). Results are displayed in Fig. 5.

Table 3

Distribution of tumors ($n=43$) depending on the level of CSCS markers and the stage of the disease according to FIGO

Expression level	Main group $n=30$				Comparison group $n=13$			
CD44	I	II	III	IV	I	II	III	IV
0 %	3	14	–	–	–	–	–	4
≤10 %	2	4	2	–	–	1	2	–
>10 %	1	2	2	–	–	–	4	2
CD117								
0 %	6	10	–	–	–	1	–	–
≤10 %	–	7	–	–	–	–	–	–
>10 %	–	3	4	–	–	–	10	2

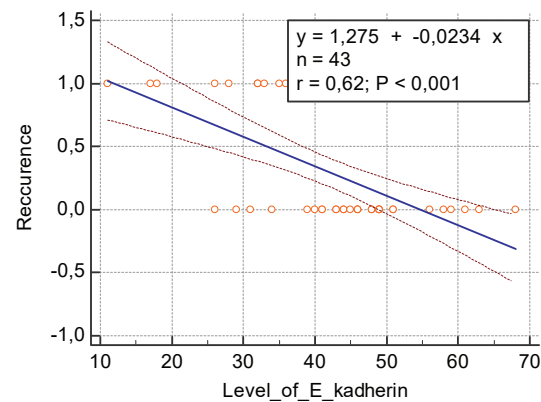
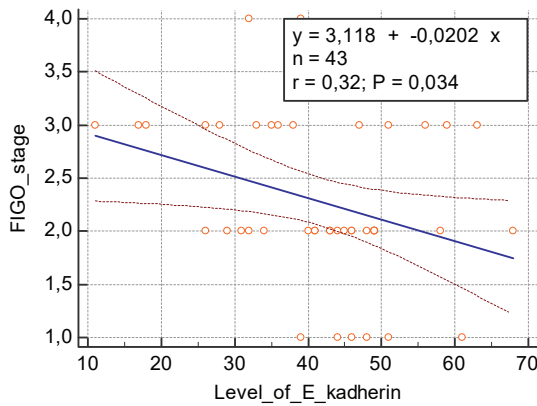


Fig. 2. Graphic representation of the relationship between E-cadherin expression and disease stage (left) and relapse (right)

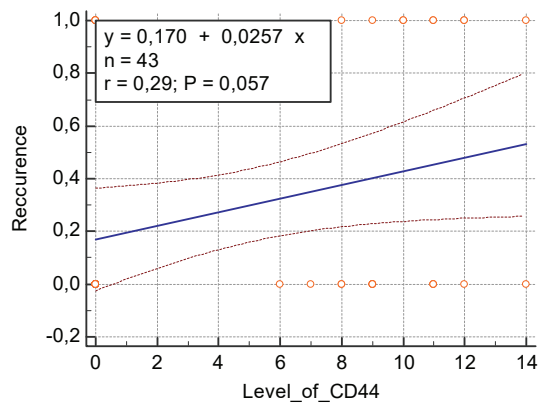
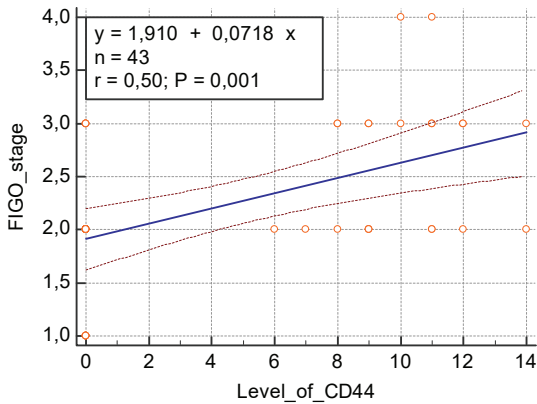


Fig. 3. Graphic representation of the relationship between CD44 expression and disease stage (left) and relapse (right)

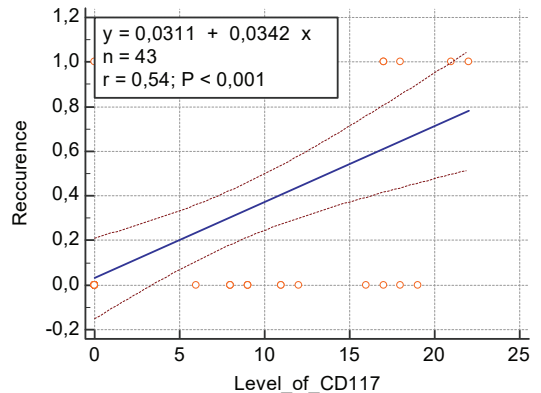
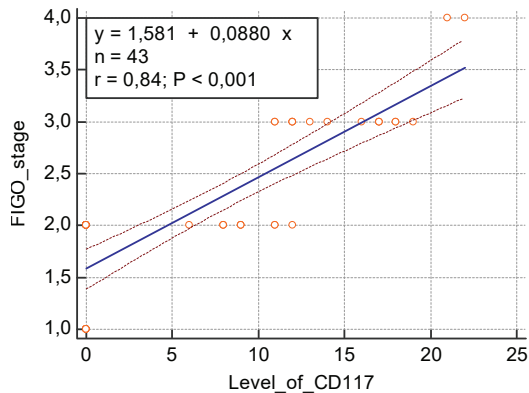


Fig. 4. Graphic representation of the relationship between CD117 expression and disease stage (left) and relapse (right)

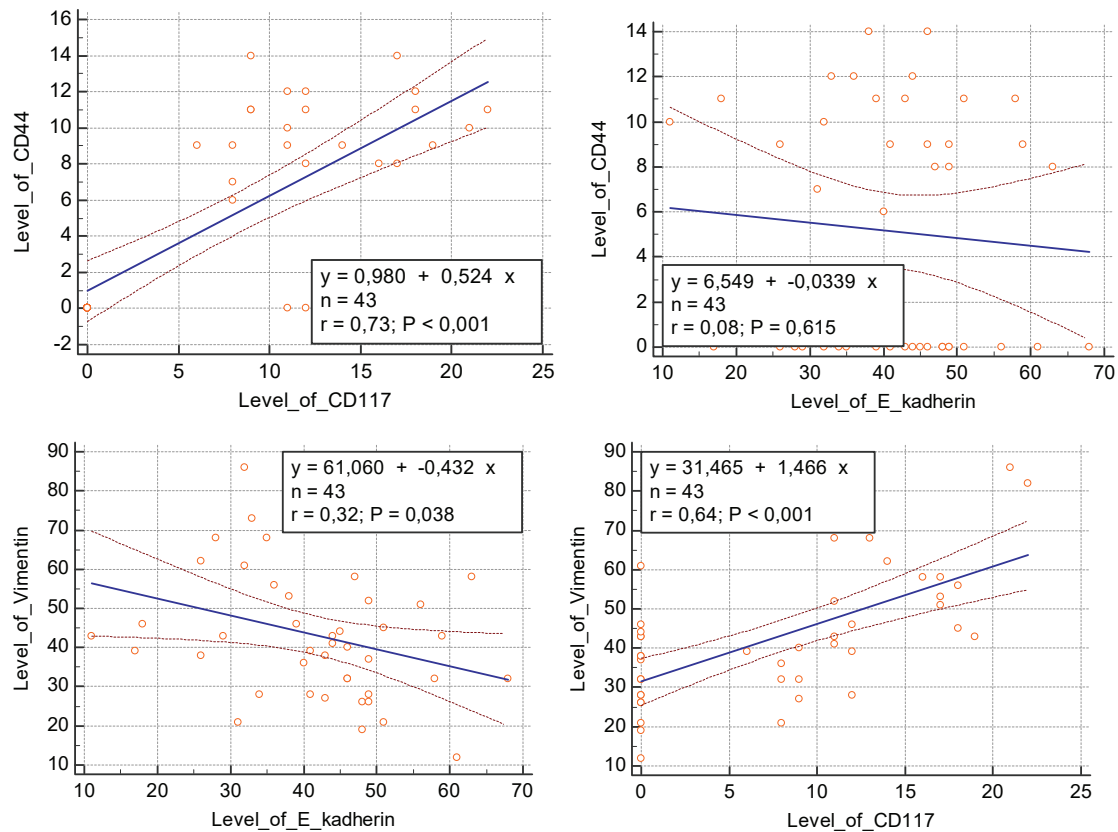


Fig. 5. Graphical representation of the correlations between the studied markers of EMT and CSCS

4. Discussion

Clinical data of our study show that recurrence of LGSC occur in patients with stage III–IV disease by FIGO ($p=0.0051$) and were not detected in stage I, although according to the literature LGSC have an indolent course, less often diagnosed on advanced stages and have more favourable prognosis [7, 14]. The relationship is confirmed by a direct correlation between disease stage and reoccur ($p=0.00039$). The presence of large number of patients with stage III–IV in the study, in our view, is due to untimely treatment of patients, because in the early stages ovarian tumors are mostly asymptomatic. An additional adverse factor for early detection of SOC is the low consciousness of women, who neglect preventive gynecological examinations. Detection of recur in the neglected stages is due to the prevalence of the tumor process, which is less susceptible to cytoreduction and treatment. The age of onset of LGSCs in two comparable groups didn't differ: sick patients aged 42 years, which coincides with data of other studies and the average age of onset of LGSCs according to the WHO (43 years) [8, 14, 15].

Results of IHC studies show that recurrent LGSCs ($p=0.006$) and tumors detected in stages III–IV ($p=0.0001$) are characterized by the expression level of Vimentin 51–100 %. The expression of E-cadherin in stages III–IV tends to remain at 10–50 % ($p=0.04$) in both groups with a relative decrease in all stages in the recurrent LGSCs. It was also observed that with a decrease of E-cadherin expression, the FIGO stage worsens ($p=0.034$) and the probability of recurrence increases ($p=0.00031$), with a decrease of marker expression decreases the adhesion properties of tumors and increases their ability to invade and metastasize, which will indicate a deterioration of the stage by FIGO. At the same time, in our study, all tumors showed the phenomenon of EMT with the acquisition of a pronounced mesenchymal phenotype and loss of epithelial phenotype in tumors with disease

stage III–IV ($p=0.038$). The obtained data do not contradict the literature about the key role of EMT in tumor metastasis and progression [16].

CD44 expression was observed in 51.16 % of all tumors, and level of expression in the study groups did not change significantly ($p=0.098$). CD44 +-status didn't depend on age ($p=0.41$) and recurrence ($p=0.057$), but there was a direct correlation with the FIGO stage ($p=0.001$). Similar data were obtained in other studies [17, 18], at the same time in the work of Sillanpää S. et al. there is controversy about a direct correlation between CD44 expression and highly differentiated tumors detected in the early stages and long-term recurrence-free survival of patients [19]. CD117 + - status had 60.47 % of all tumors, recurrent LGSCs were characterized by an expression level >10 % ($p=0.00067$) with increasing values of the IHC mark. The frequency of expression according to the literature reaches 40 % [9], and the difference with our data can be explained by the characteristics of a particular sample. For the initial stages of the disease according to FIGO, the typical level of CD117 expression was 0–10 % ($p=0.00043$) with an increase of cases number of high expression in stages III–IV. As for CD44, the CD117 marker did not show a dependence on the age of patients ($p=0.24$), but there is a strong correlation between the FIGO stage ($p=0.0002$) and tumor recurrence ($p=0.00033$), which supported by data from another study [9]. At the same time, it was found that the level of CD44 expression increases with increasing expression level of CD117, which confirms the phenotype of ovarian CSCS, because to verify this pool itself, the coexpression of these two markers is always studied [9]. There is also a direct correlation between the expression level of CD117 and Vimentin, which, in our opinion, indicates the commonality of EMT and CSCS in progression and recurrence of ovarian cancer. Coexpression of CD44 and E-cadherin was not found in our study ($p=0.615$),

which is somewhat unexpected, because CD44 is a transmembrane glycoprotein, which, like E-cadherin, is involved in intercellular adhesion. The heterogeneity of the expression of the two markers can be explained by the complexity of the mechanisms of intercellular adhesion and the peculiarities of the microenvironment of tumor cells, because CD44 has many functions and can function as a signalling transmitter, which is also involved in invasion and migration of tumor cells [20].

Study limitations. The study analyzed 43 carcinomas, which is a sufficient reference sample. However, it should be borne in mind that obtained results are specific only for LGSC and may lose their relevance and informativeness when applied to high-grade serous ovarian carcinomas due to the different biological origins of two groups of tumors.

Prospects for further research. Given the relevance and prospects of studying the role of CSCS in tumor progression, metastasis and recurrence, it is interesting to study the relationship of other CSCS markers (Sox2, CD133, Oct4) with the onset of recurrence of SOC, as well as their relationship with EMT.

6. Conclusions

Based on the data of our study, in the risk group for recurrence of LGSC are women with stage III-IV disease according to FIGO, and the likelihood of recurrence increases with increasing stage. Recurrent carcinomas are also characterized by EMT phenomenon with expression level of Vimentin 51–100 % and expression of E-cadherin at level of ≤ 50 %. In our study, we did not find a prognostic role of the CD44 marker as a predictor of recurrence or worsening of the SOC stage, it should be used, in our opinion, as an additional marker that identifies pool of ovarian CSCS. A prognostic role in the deterioration of the stage and appearance of recurrence was found for CD117, for recurrent LGSC typical expression level > 10 %. The direct correlation between CD117 expression and Vimentin proves the common role of EMT process and CSCS in recur and progression of LGSC.

Conflict of interests

The author declares no conflict of interests.

References

1. Klemba, A., Purzycka-Olewiecka, J. K., Wcisło, G., Czarnecka, A. M., Lewicki, S., Lesyng, B. et al. (2018). Surface markers of cancer stem-like cells of ovarian cancer and their clinical relevance. *Współczesna Onkologia*, 2018 (1), 48–55. doi: <http://doi.org/10.5114/wo.2018.73885>
2. Ahmed, N., Kadife, E., Raza, A., Short, M., Jubinsky, P. T., Kannourakis, G. (2020). Ovarian Cancer, Cancer Stem Cells and Current Treatment Strategies: A Potential Role of Magmas in the Current Treatment Methods. *Cells*, 9 (3), 719. doi: <http://doi.org/10.3390/cells9030719>
3. Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, 68 (6), 394–424. doi: <http://doi.org/10.3322/caac.21492>
4. Cancer in Ukraine, 2019–2020. (2021). National Cancer Institute. Kyiv. Available at: http://www.ncru.inf.ua/publications/BULL_22/index.htm
5. Cannistra, S. A., Abu-Jawdeh, G., Niloff, J., Strobel, T., Swanson, L., Andersen, J., Ottensmeier, C. (1995). CD44 variant expression is a common feature of epithelial ovarian cancer: lack of association with standard prognostic factors. *Journal of Clinical Oncology*, 13 (8), 1912–1921. doi: <http://doi.org/10.1200/jco.1995.13.8.1912>
6. Sillanpää, S., Anttila, M. A., Voutilainen, K., Tammi, R. H., Tammi, M. I., Saarikoski, S. V., Kosma, V. M. (2003). CD44 Expression Indicates Favorable Prognosis in Epithelial Ovarian Cancer. *Clinical Cancer Research*, 9 (14), 5318–5324.
7. Goulding, E. A., Simcock, B., McLachlan, J., Griend, R., Sykes, P. (2019). Low-grade serous ovarian carcinoma: A comprehensive literature review. *Australian and New Zealand Journal of Obstetrics and Gynaecology*, 60 (1), 27–33. doi: <http://doi.org/10.1111/ajog.13105>
8. Eun, K., Ham, S. W., Kim, H. (2017). Cancer stem cell heterogeneity: origin and new perspectives on CSC targeting. *BMB Reports*, 50 (3), 117–125. doi: <http://doi.org/10.5483/bmbrep.2017.50.3.222>
9. Garson, K., Vanderhyden, B. C. (2015). Epithelial ovarian cancer stem cells: underlying complexity of a simple paradigm. *Reproduction*, 149 (2), R59–R70. doi: <http://doi.org/10.1530/rep-14-0234>
10. Kaldawy, A., Segev, Y., Lavie, O., Auslender, R., Sopik, V., Narod, S. A. (2016). Low-grade serous ovarian cancer: A review. *Gynecologic Oncology*, 143 (2), 433–438. doi: <http://doi.org/10.1016/j.ygyno.2016.08.320>
11. Katsoulis, M., Lekka, J., Vlachonikolis, I., Delides, G. (1995). The prognostic value of morphometry in advanced epithelial ovarian cancers. *British Journal of Cancer*, 72 (4), 958–963. doi: <http://doi.org/10.1038/bjc.1995.441>
12. Karan Križanac, D., Krasić Arapović, A., Skočibušić, S., Pintarić, I., Trgo, G., Tomić, S. (2018). CD44 Immunoexpression is Unfavorable Predictor in Ovarian Serous Cancer. *Applied Immunohistochemistry & Molecular Morphology*, 26 (6), 398–402. doi: <http://doi.org/10.1097/pai.0000000000000427>
13. Lisio, M.-A., Fu, L., Goyeneche, A., Gao, Z., Telleria, C. (2019). High-Grade Serous Ovarian Cancer: Basic Sciences, Clinical and Therapeutic Standpoints. *International Journal of Molecular Sciences*, 20 (4), 952. doi: <http://doi.org/10.3390/ijms20040952>
14. Muñoz-Galván, S., Carnero, A. (2020). Targeting Cancer Stem Cells to Overcome Therapy Resistance in Ovarian Cancer. *Cells*, 9 (6), 1402. doi: <http://doi.org/10.3390/cells9061402>

15. Pastushenko, I., Blanpain, C. (2019). EMT Transition States during Tumor Progression and Metastasis. *Trends in Cell Biology*, 29 (3), 212–226. doi: <http://doi.org/10.1016/j.tcb.2018.12.001>
16. Rosso, M., Majem, B., Devis, L., Lapyckyj, L., Besso, M. J., Llauroadó, M. et. al. (2017). E-cadherin: A determinant molecule associated with ovarian cancer progression, dissemination and aggressiveness. *PLOS ONE*, 12 (9), e0184439. doi: <http://doi.org/10.1371/journal.pone.0184439>
17. Solopova, A. G., Bitsadze, V. O., Solopova, A. E., Makatsariya, A. D., Rozanov, I. A. (2017). Ovarian cancer: current approaches to classification, diagnostics, staging and differential management of patients. *Journal of Obstetrics and Women's Diseases*, 66 (2), 55–66. doi: <http://doi.org/10.17816/jowd66255-66>
18. Suster, N. K., Virant-Klun, I. (2019). Presence and role of stem cells in ovarian cancer. *World Journal of Stem Cells*, 11 (7), 383–397. doi: <http://doi.org/10.4252/wjsc.v11.i7.383>
19. Herrington, C. S. (Ed.) (2020). *WHO Classification of Tumours Female Genital Tumours*. Lyon: International Agency for Research on Cancer, 44–46.
20. Ryabtseva, O. D., Antipova, S. V., Lukyanova, N. Yu., Nadirashvili, M. A., Polishchuk, L. Z., Chekhun, V. F. (2014). Individual prognosis of serous ovarian cancer survival patients based on adhesion and proliferation of tumor cells. *Oncology*, 16 (1). Available at: <https://www.oncology.kiev.ua/ru/article/6303/individualnij-prognoz-vizhivanosti-xvorix-z-uraxuvannyam-proliferacii-ta-adeziii-puxlinnix-klitin-u-xvorix-na-seroznij-rak-yayehnika-2>

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