და, რაც ძალიან მნიშვნელოვანია, ინარჩუნებს და/ან აღადგენს მუცლის წინა კედლის კუნთების მოქნილობას.

როგორც კვლევებითაა ნაჩვენები, Chevrell onlay მეთოდი ხასიათდება პოსტოპერაციული ჭრილობის გართულების ბევრად უფრო მაღალი მაჩვენებლით და სერომის წარმოქმნით, ვიდრე პროცედურა Rives-Stoppa. დიდი ინციზიური თიაქრების მკურნალობა მოითხოვს გარკვეულ გამოცდილებას ამ სფეროში და მულტიდისციპლინურ მიდგომას; მიზანშეწონილია, რომ მკურნალობა ჩატარდეს სპეციალიზებულ სამედიცინო ცენტრებში.

OVARIAN CANCER TREATMENT OPTIMIZATION: THE COMPLEX ANALYSIS OF THE RESULTS OF CYTOREDUCTIVE SURGERY, MICROSCOPIC MALIGNANCY AND T-LYMPHOCYTIC INFILTRATION OF THE TUMOR

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Ovarian cancer ranks 7th among the most common cancers in the world and 8th among the causes of death [1-3].

The high mortality rate is due to the absence of effective screening methods and the indolent course of the disease. About 70-80% of the cases of ovarian cancer are diagnosed on the advanced stages (III or IV) of the disease, and the recurrence rate is 75%, while the five-year disease-free survival period is observed in only 35% of patients [4].

Today, the complete cytoreduction of the tumor - the "debulking" surgery – has established itself as a leading choice in the treatment of ovarian cancer.

The main point of cytoreductive surgery is the complete elimination of the macroscopic tumor, which often requires intervention on several organs of the abdominal cavity (resection of the peritoneum, diaphragm (stripping), liver, pancreas, intestine (especially rectosigmoid, which is required in 30-50% of cases of disseminated ovarian cancer), splenectomy, cholecystectomy, appendectomy, omentectomy, salpingo-oophorectomy, hysterectomy) [5-7].

It is important that the complications, associated with the debulking surgery do not increase the mortality rate [8,9].

It is known that the prognosis of ovarian carcinomas is significantly determined by their histological types and the grade of microscopical malignancy. Besides, according to the data of recent years, the clinical outcome and prognosis of ovarian cancer are closely correlated with the presence of tumor-infiltrating lymphocytes (TILs) in the microenvironment of the tumor.

The importance of TILs has been already established in melanomas, non-small-cell lung cancers, "triple-negative" forms of breast cancer, while in cases of the prostate, kidney, esophagus and colorectal carcinomas TILs are being actively studied and the obtained results are being used for choosing a course of immunotherapy [10-12]. The study of TILs has been started in ovarian tumors as well. However, their diagnostic value is not thoroughly clear. Data on their importance in ovarian tumors of various morphological forms are particularly poor [13-15].

The study aimed to investigate the association of accumulation of Infiltrating T-lymphocytes and their subtypes with histology of ovarian cancer tissue excised during debulking surgeries considering the microscopic malignancy grade and the clinical stage.

Material and methods. The present multicenter, retrospective-prospective study involves 64 ovarian cancer patients. It is noteworthy that in advanced cases of ovarian cancer, generally the treatment was started with neoadjuvant chemotherapy, and subsequent surgical treatment prevalently included a total hysterectomy and omentectomy. Since 2016, we have started the treatment recognized as the gold standard: debulking surgery with adjuvant platinum-taxane-based chemotherapy. The patients were selected on the basis of anamnesis and clinical and instrumental examinations, considering the age and comorbidities.

Patients' including criteria were the following: diagnosis of ovarian cancer, adult age, performed treatment (total hysterectomy, omentectomy, debulking surgery with adjuvant chemotherapy [primary cytoreduction] or neoadjuvant chemotherapy with subsequent debulking surgery and adjuvant chemotherapy [interval cytoreduction] or secondary cytoreduction in case of recurrent tumor. Patients' excluding criteria were the following: age 80 years and older, acute hypoalbuminemia and hypoproteinemia, a severe rise of the liver enzymes, the presence of radiologically confirmed distant methastasis. All patients had signed the informed consent form. The patients were divided according to age, clinical diagnosis and scale of surgery, stage of the disease, microscopic malignancy of the tumor, location, histology and lymphocyte infiltration.

Material obtained from 64 surgeries of the ovarian cancer was examined by standard histological (H&E) and immunohistochemical (IHC) technique. Initially, the tumor tissue was fixed in 10% buffer formalin for 6-12 hours. This time is perfect for retaining the antigen in the tissue and preventing the false-negative results of IHC. After fixation, the material was proceeded in the «Leica Bond Max» device and embedded into paraffin. Paraffin blocks were cut into 3 μm thick slices for standard histology and IHC. Shimizu/Silverberg systems as well as "two-tier" grading systems were used to determine the tumor differentiation grade in serous carcinomas. The malignancy grade was determined by the application of an immunohistochemical study technique using the oncoprotein p53 marker. Each specimen was analyzed by two morphologists independently. In the case of two different interpretations of the results, a joint discussion was held until a consensus was reached.

TILs were detected by applying immunohistochemistry using "Novocastra" antibodies: CD2, CD3, CD4, CD8. The markers' expression was studied separately in the stromal and parenchymal components. The percentage of $CD2^+$, $CD3^+$, $CD4^+$, $CD8^+$ lymphocytes in the tumor tissue was calculated by the "ImageJ" software.

All scices were studied be means of the light microscope - Leica DM 750.

The survival of patients with ovarian cancer was examined by using the Kaplan-Meier curves and calculations of Cox Hazard Ratio (HR). Quantitative parameters were presented as average ± standard deviation; Comparative analysis of such data of each group was performed by using Student's t-test, while qualitative parameters were statistically analyzed by using the $\chi 2$ test. Correlations were studied by using the Pearson coefficient (r). Multiple regression analyses of factors influencing surgical intervention was performed by a logarithmic regression method. This method excluded the most unreliable factors step-by-step. Finally, when all the factors in the set of factors showed a reliable correlation, the method ended the analysis. Statistical processing of the results was performed by the statistical software IBM SPSS Statistics V22.0. As a difference reliability criterion there was used (to reject the null hypothesis) $p<0.05$.

Results and discussion. Of all 64 incidents, there were 42 cases of the serous carcinoma, 6 cases of the endometrioid carcinoma, 6 cases of clear cell carcinoma, 6 cases of the mucinous carcinoma. Three patients were diagnosed with a primary peritoneal tumor, and one patient was diagnosed with malignant Struma Ovarii (papillary thyroid carcinoma in Struma Ovarii).

41 out of 64 patients were undergone the primary cytoreduction with the following adjuvant platinum-based chemotherapy, and 19 - underwent neoadjuvant chemotherapy. Secondary cytoreduction was performed in 10 cases out of 64. The patient, diagnosed with malignant Struma Ovarii underwent the total hysterectomy, bilateral adnexectomy, omentectomy; later the total thyroidectomy, followed by radioactive iodine therapy.

The detailed charasteristcs of the included in study patients according to age, clinical diagnosis and scale of surgery, stage of disease, microscopic malignancy of the tumor, location, histology and lymphocyte infiltration is provided in Table 1.

The grade of differentiation along with the histological type was determined in all 64 cases of ovarian cancer. Serous carcinoma was diagnosed in 42 cases (66%), 30 patients (71%) from them had high-grade form, 5 patients (12%) had highly differentiated (low-grade) form, and 7 (17%) patients had moderately differentiated form of serous carcinoma.

Out of the 42 invasive ovarian carcinomas, studied by us with Shimizu/Silverberg grading system, there was observed a poorly differentiated option of the serous carcinoma (G3) in 30 cases, a moderately differentiated –(G2) - in 7 cases and a highly differentiated(G1) - in 5 cases. By a "two-tier" system, 37 cases of high-grade and 5 cases of low-grade malignancy of serous invasive cancer were observed.

As it is known, a tissue of the carcinoma is generally characterized by histological diversity, where different histostructural and differentiation sites interchange; however, it is noteworthy, that in none of the cases of the serous carcinoma of high-grade malignancy, studied by us, was observed the coexistence of sites with borderline malignant and/or low-grade serous carcinoma.

Thus, research has focused on various theories of cancer carcinogenesis. According to one of the theories, the development of serous ovarian cancer is a gradual process: the borderline tumor progresses to low- grade and then high-grade serous carcinoma [16,17]. Upon this theory, low- and high-grade serous carcinomas have a single origin. A markedly different approach to the mentioned is a dualistic theory, arguing that the histogenesis of high-grade and low-grade serous carcinomas are significantly different and their development is resulted by two completely different geneses [18].

The results of the multiple morphological examinations, obtained by us, suggest that the histogenesis of high-grade malignancies of the ovary and low-grade malignancy potential tumors is different. We couldn't find any transformation of low-grade malignancies into high-grade malignancies. Therefore, if there are two interdependent ways of formation of the serous ovarian cancer, we suggest that the "two-tier system" for grading the microscopic malignancy of ovarian serous carcinomas more accurately reflects the biology of the tumor and the mechanism of its formation. Besides, in some cases assigning the moderate malignancy grade (Grade 2) according to the "three-tier" system, may complicate the clinical approach and explicit treatment strategy planning.

The grade of tumor differentiation was determined by the application of the IHC. Oncoprotein p53 expression (monoclonal, Novocastra). was analyzed immunohistochemically according to the tumor differentiation grade."Wild" type p53 is a product of the mutated suppressor gene and is accumulated in most tumor cells as an oncoprotein (oncoprotein p53). It also represents certain molecular features of tumor anaplasia [19].

In those seven cases, in which the «universal» grading system provided by Shimizu/Silverberg diagnosed moderately differentiated serous carcinoma, the tumor differentiation grading was determined immunohistochemically by using oncoprotein p53. It should be noted that even in 30 cases of high-grade serous carcinomas, the marker expression accounted for 90%; nuclear expression of oncoprotein p53 is sharp, in addition, it allows outlining incorrect nuclear contours, which is one of the features of poorly-differentiated carcinomas.

In seven cases, which were classified as moderately differentiated forms (according to the Shimizu/Silverberg scheme), the percentage of marker expression varied in the range of 49.2 -58.0%, while the sharpness in the case of p53 involvement ranged from moderate to strong expression.

As for 5 cases of a highly differentiated serous carcinoma (G1), the expression intensity of oncoprotein p53 was from poor to moderate. Their involvement varied from 22.9 to 41.2%. We made an effort to provide insight into the microscopic malignancy grading of the tumors and evaluate it in terms of tumor cell carcinogenesis. According to one of the hypotheses - "dualistic concept" - the formation of serous carcinoma malignancies with low-grade and high-grade differentiation is by different mechanisms.

In our study, we analyzed to what extent the formation mechanisms of highly differentiated serous and poorly differentiated serous carcinomas differ.

According to our data, none of the cases of high-grade malignancy (poorly differentiated) serous carcinomas were associated with highly differentiated carcinoma structures. The coexistence of the histostructure of a borderline malignant tumor with a serous cancer with a high-grade malignancy was not revealed.

Therefore, we might conclude that the theory on the different histogenesis of low-grade and high-grade malignancies of serous carcinomas is right. We believe that their formation is possible in two different ways. Serous carcinomas with low malignant potential are associated with a relatively better prognosis. They are characterized by indolent disease progression. In many cases, we face all three morphologies simultaneously: benign, borderline malignant tumor and highly differentiated serous carcinoma.

Table 1. Data of the patients included in the study

Age group	**< 60 Yrs.**		**60-65 Yrs.**		**> 65 Yrs.**	
n	28		18		18	
	Medium±SD		Medium±SD		Medium±SD	
Age	49,14±8,42		62,94±1,95		70,89±3,89	
	n	**%**	**n**	**%**	**n**	**%**
Conducted treatment						
First chemotherapy / then surgery	5	17,9	6	33,3	8	44,4
First surgery / then chemotherapy	23	82,1	12	66,7	10	55,6
	Chi2=3.8698 (p=0.1444, NS)					
Morphological type:						
High-grade serous carcinoma- HGSOC	11	39,3	13	72,2	16	83,3
Low-grade serous carcinoma- LGSOC	2	7,1	1	5,6	2	11,1
Mucinous carcinoma – MOC	5	17,9	0	0,0	1	5,6
Endometrioid carcinoma – ENOC	5	21,4	1	5,6	0	0,0
Clear cell carcinoma – CCOC	3	10,7	3	16,7	0	0,0
	Chi2=7.0054 (p=0.0301)					
The degree of tumor malignancy: G1	2	10,7	1	5,6	2	11,1
G2	7	25,0	4	22,2	2	11,1
G3	18	64,3	13	72,2	14	77,8
	Chi2 = 1.7737 (p = 0.7773, NS)					
Stage: 1	6	21,4	0	0,0	2	11,1
2	2	7,1	1	5,6	2	11,1
3	20	71,4	15	83,3	14	77,8
4	0	0,0	2	11,1	0	0,0
	Chi2 = 3.718 (p = 0.7148, NS)					
Lethal Outcome: Dead	3	10,7	7	38,9	3	16,7
Alive	25	89,3	11	61,1	15	83,3
	Chi2 = 5.579 (p = 0.0614, NS)					
Lymphocyte infiltration: Low	17	60,7	5	27,8	3	16,7
High	11	39,3	13	72,2	15	83,3
	Chi2 = 10.2702 (p = 0.0059)					
Metastases / Invasion:						
Metastases	10	35,7	6	33,3	4	22,2
Invasion of nearby organs	6	21,4	5	27,8	8	44,4
Metastases / without invasion	12	42,9	7	38,9	6	33,3
	Chi2 = 2.9134 (p = 0.5724, NS)					
Operations performed due to recurrence						
Yes	5	17,9	4	22,2	1	5,6
	Chi2 = 2.0844 (p = 0.3527, NS)					

According to our data, low-malignant serous carcinomas are predominantly associated with serous cystadenoma and cystadenofibroma, and in the case of low-malignant serous carcinomas, the borderline malignant tumor foci almost always are observed.

As mentioned previously, based on our data, low-malignant serous invasive carcinomas are predominantly associated with cystadenoma and borderline serous malignant processes. In terms of immunohistochemistry, the intensity of oncoprotein p53 expression is poor or moderate in highly differentiated serous cancer, whereas it is weakly positive in serous cystadenoma; the intensity and percentage of marker involvement in cystadenofibroma is increased. It is noteworthy that in some cases routine morphological examination makes it difficult to differentiate the benign processes - serous cystadenoma or serous cystadenofi-

broma - from serous malignant formations with the borderline malignancy, especially when the slice is tangential. Therefore, we assume it would be important to separate these two biologically different processes with additional immunohistochemical analysis by using oncoprotein p53 in serous carcinomas with borderline malignancy.

The expression of $CD2^+$, $CD3^+$, $CD4^+$, $CD8^+$ T-lymphocytes in the tissue of ovarian cancer, as well as in metastases in the omentum, peritoneum and other organs was analyzed.

Tumor-infiltrating T cells ($CD2^+$, $CD3^+$, $CD4^+$, $CD8^+$) are almost absent in the parenchyma of endometrioid carcinoma formed at the background of ovarian endometriosis. In addition, CD3 expression in stroma is detected in less than 1% of lymphocytes. CD4/CD8 positive cells are present in equal amounts (0.9/1%); CD2 expression is not observed.

The expression of CD2, CD3, CD4, and CD8 in ovarian endometrioid carcinomas did not differ according to tumor differentiation grading. A statistically significant difference between bilateral ovarian endometrioid carcinomas and unilateral forms also was not revealed. This suggests that the antineoplastic role of tumor-infiltrating T-lymphocytes is minimal in case of the indolent progression of ovarian cancer. It may be assumed that the indolent tumors «exhaust» the local immunity.

Expression of CD2, CD3, CD4, and CD8 markers in both primary serous ovarian carcinomas and metastatic lesions in the case of highly differentiated forms, is almost absent in the parenchyma of tumor cells, while in the stroma the T-cells involvement is ranging from 0.8 to 6.2%.

In the case of high-grade serous carcinomas, the expression of CD2, CD4, and CD8 markers was equal in the stromal component of the tumor. In contrast to the low-grade forms of serous carcinomas (where, in the parenchyma of the cancer, TILs were either absent or in low amounts), the percentage of TILs distribution in the high-grade forms ranges from 36.4% to 37.5% in the parenchyma and from 9.5 to -12.4% - in the stroma.

It should be noted that there was observed a significant difference between CD4+/CD8+ lymphocytic infiltrations in high-grade serous carcinoma.

The involvement of TILs in serous carcinoma metastases is not significantly different from their quantitative-qualitative distribution in the primary tumor tissue. In addition, the percentage of expression of CD4/CD8 markers is more or less equal.

It is interesting that, in the case of clear cell carcinomas and mucinous carcinomas, an only a single occurrence of CD3, CD4, and CD8 positive TILs are detected in the tumor stroma while they are not observed in the tumor parenchyma. It should be mentioned that the quantitative-qualitative rate of TILs in parenchyma and stroma of ovarian endometrioid, mucinous and clear cell carcinomas does not exceed 1%.

Statistical analysis. A) Influence of morphological type on the outcome of ovarian cancer treatment.

The 3-year survival rate in patients with high-grade serous adenocarcinomas is 41.5% lower than in patients with other morphological types of ovarian cancer, i.e. the probability of a lethal outcome in patients with high-grade serous adenocarcinomas is 41.5% 3 years after surgery. This is higher compared to the mortality of patients with other morphological types of ovarian cancer (Diagram 1, Table 2).

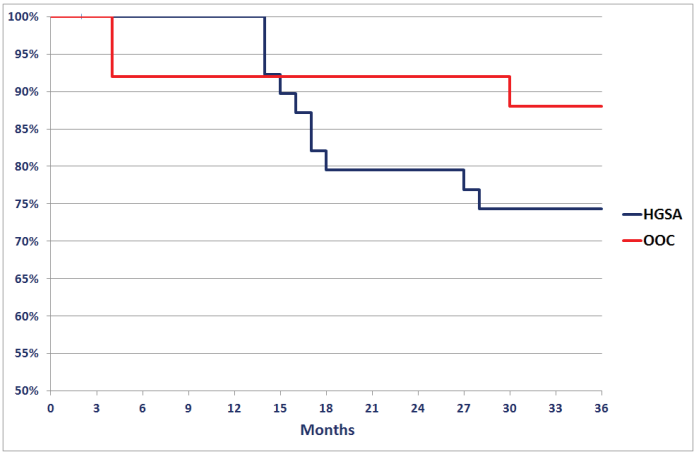

Diagram 1. Kaplan-Meyer curves obtained by survival analysis for the following groups: Group 1 - High-grade serous carcinoma (HGSOC) (dark blue line); Group 2 - Other morphological types of ovarian cancer (OOC) (red line)

Table 2. Comparative analysis of Kaplan-Meyer curve results for groups: Group 1 - High-grade serous carcinoma (HGSOC); Group 2 - Other morphological types of ovarian cancer (OOC)

Survival rate 3 years after surgery	
Group 1 – HGSOC	74.4%
Group 2 – OOC	88.0%
Cox Hazard Ratio (**HR**)	**1.710**
95% confidence intervals for HR (Confidense intervals – 95%CI)	**[1.277, 2.290]**
Chi2-test	**11.401**
P-value	**0.0007**

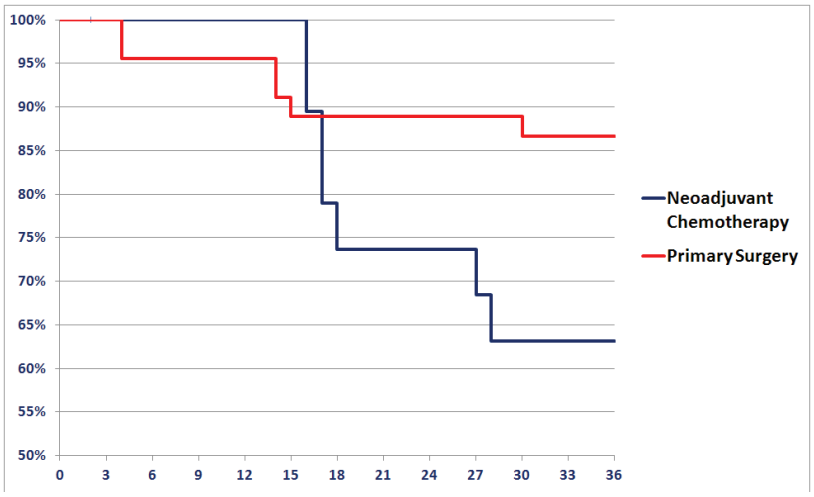

Diagram 2. Kaplan-Meyer curves obtained by survival analysis for the following groups: Group 1 - neoadjuvant chemotherapy (dark blue line); Group 2 – Primary Surgery (red line)

Table 3. Comparative analysis of results obtained by Kaplan-Meyer curves for groups: Group 1 - neoadjuvant chemotherapy; Group 2 - Primary Surgery

Survival rate 3 years after surgery	
Group 1 - Neoadjuvant chemotherapy	63.2%
Group 2 - Primary Surgery	86.7%
Cox Hazard Ratio (**HR**)	**2.064**
95% confidence intervals for HR (Confidense intervals – 95%CI)	**[1.492, 2.854]**
Chi2-test	**25.206**
P-value	**0.0001**

B) The impact of treatment tactics on the treatment outcome of ovarian cancer.

The 3-year survival rate in patients who underwent chemotherapy first and then surgery, was lower by 51.6% than in patients for whom surgical treatment was selected as the primary treatment method; i.e. the probability of a lethal outcome in patients of the initial neoadjuvant chemotherapy group within 3 years after surgery is 51.6% higher than in patients of the primary surgery group (Diagram 2, Table 3).

Multiple regression analysis was performed for the following risk factors (variables) affecting the effectiveness of ovarian cancer surgical treatment (assessed by the lethal outcome).

Pearson correlation coefficient r = 0.3758 (p=0.009).

Therefore, based on the obtained results, it can be concluded that from the combination of risk factors defining the effectiveness of ovarian cancer surgical treatment (lethal outcome) the presence of chemotherapy prior to surgery (neoadjuvant chemotherapy) and high-grade (G3) have a significant impact.

Conclusion. According to the obtained data, the carcinogenesis of high-grade and low-grade serous ovarian carcinoma is different. Low-grade forms are always preceded by serous cystadenoma and/or serous cystadenofibroma, which progresses to borderline serous carcinomas and then to low-grade invasive carcinoma. High-grade serous carcinomas are not developed from the progression of low-grade invasive carcinomas and are the product of the de novo formation.

Based on our study, there was not revealed a statistically significant difference between the universal system, provided by Shimizu/Silverberg and the "two-tier" system - in grading the microscopic malignancy of serous ovarian carcinomas.

Besides, the involvement of oncoprotein p53 in poorly differentiated serous carcinomas of the ovary is more intense compared to highly differentiated serous carcinomas and it is advisable to use it as an additional molecular-biological feature for specifying the grade of microscopic malignancy of the tumor.

The antineoplastic and/or prognostic role of the tumor-infiltrating T lymphocytes is not fully evident and needs further investigation.

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SUMMARY

OVARIAN CANCER TREATMENT OPTIMIZATION: THE COMPLEX ANALYSIS OF THE RESULTS OF CYTOREDUCTIVE SURGERY, MICROSCOPIC MALIGNANCY AND T-LYMPHOCYTIC INFILTRATION OF THE TUMOR

[1,3]Khatchapuridze Kh., [4]Tananashvili D., [3]Todua K., [1,3]Kekelidze N., [3]Tsitsishvili Z., [1,2]Mchedlishvili M., [1,2]Kordzaia D.

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The paper discusses 64 cases of ovarian cancer (observed in 2016-2019). Patients underwent cytoreductive surgery. Both Shimizu/Silverberg system and the "Two-tier" system were used to grade the tumor differentiation of serous carcinomas. The grade of the differentiation was specified by expression of oncoprotein p53.

The tumor infiltrating lymphocytes (TILs) labeled with immunohistochemical markers - CD2, CD3, CD4, CD8 - were evaluated for the intensity of expression in both - the ovarian tumor parenchyma and stroma. Quantitative assessment of expression was performed by a computer program ImageJ.

The survival of patients with ovarian cancer was examined by using the Kaplan-Meier curves and calculations of Cox Hazard Ratio (HR). Multiple regression analyses of factors influencing surgical intervention was performed by a logarithmic regression method.

According to the obtained data, the carcinogenesis of high-grade and low-grade serous ovarian carcinoma is different: low-grade forms are always preceded by serous cystadenoma and/or serous cystadenofibroma, which progresses to borderline serous carcinomas and then to low-grade invasive carcinoma; high-grade serous carcinomas are not developed from the progression of low-grade invasive carcinomas and are the product of the de novo formation.

p53 may be used as an additional molecular-biological feature for specifying the grade of microscopic malignancy of the tumor in the cases, when the moderate differentiation is established by Shimizu/Silverberg system.

The antineoplastic and/or prognostic role of the tumor-infiltrating T lymphocytes is not fully evident and needs further investigation.

High-grade (G3) of ovarian carcinoma and the neoadjuvant chemotherapy are the factors having a significant impact in defining the effectiveness of the surgical treatment of ovarian cancer.

Keywords: epithelial ovarian cancer, cytoreduction, grading system. TILs.

РЕЗЮМЕ

ОПТИМИЗАЦИЯ ЛЕЧЕНИЯ РАКА ЯИЧНИКОВ: КОМПЛЕКСНЫЙ АНАЛИЗ РЕЗУЛЬТАТОВ ЦИТОРЕДУКЦИИ, МИКРОСКОПИЧЕСКОЙ ЗЛОКАЧЕСТВЕННОСТИ И ИНФИЛЬТРАЦИИ ОПУХОЛИ Т-ЛИМФОЦИТАМИ

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В статье рассматриваются 64 случая рака яичников (наблюдавшихся в 2016-2019 гг.). Пациентам проведена циторедуктивная операция. Как система Симидзу/Сильверберга, так и двухуровневая система использовались для гистологической классификации серозных карцином. Степень дифференцировки дополнительно уточнялась экспрессией онкопротеина p53.

Интенсивность экспрессии инфильтрирующих опухоль лимфоцитов (ОИЛ) как в паренхиме, так и в строме опухоли яичника оценивали с помощью иммуногистохимического исследования. Количественную оценку выполняли с помощью компьютерной программы ImageJ.

Выживаемость пациенток с раком яичников оценивалась с использованием кривых Каплана-Мейера и расчетов коэффициента риска Кокса (HR). Множественный регрессионный анализ факторов, влияющих на хирургическое вмешательство, проводился методом логарифмической регрессии.

Согласно полученным данным, канцерогенез серозной карциномы яичников высокой и низкой степени злокачественности различен: низкостепенным формам всегда предшествует серозная цистаденома и/или серозная цистаденофиброма, которая прогрессирует до пограничной, а затем до инвазивной серозной карциномы низкой степени злокачественности; серозные карциномы высокой степени злокачественности не развиваются в результате прогрессирования инвазивных карцином низкой степени злокачественности и являются продуктом образования de novo.

p53 может быть использован как дополнительный молекулярно-биологический маркер для определения степени микроскопической злокачественности опухоли в тех случаях, когда по системе Симидзу/Сильверберга установлена умеренная дифференцировка.

Противоопухолевая и/или прогностическая роль ОИЛ не полностью очевидна и требует дальнейшего изучения.

Высокая степень (G3) карциномы яичников и неоадъювантная химиотерапия являются факторами, оказывающими значительное влияние на эффективность хирургического лечения рака яичников.

რეზიუმე

საკვერცხის კიბოს მკურნალობის ოპტიმიზაცია: ციტორედუქციის შედეგების, მიკროსკოპიული ავთვისებიანობის და სიმსივნის T-ლიმფოციტებით ინფილტრაციის კომპლექსური ანალიზი

[1,3]ხ. ხაჭაპურიძე, [4]დ.თანანაშვილი, [3]კ.თოდუა, [3]ნ.კეკელიძე, [3]ზ.ციციშვილი, [1,2]მ.მჭედლიშვილი, [1,2]დ.კორძაია

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ნაშრომში განხილულია საკვერცხის კიბოს 64 შემთხვევა (პაციენტებზე დაკვირვება ხდებოდა 2016-2019 წლებში). პაციენტებს უტარდებოდათ ციტორედუქციული ოპერაციები. სიმსივნის დიფერენციაციის ხარისხის განსაზღვრის მიზნით სეროზულ კარცინომებში, გამოყენებული იყო როგორც Shimizu/Silverberg-ის, ასევე „Two tier" სისტემა, ხოლო დიფერენციაციის ხარისხის დაზუსტება ხდებოდა ონკოპროტეინ p53 ექსპრესიის მეშვეობით.

სიმსივნის მაინფილტრირებელი ლიმფოციტების (TILs) ექსპრესიის ინტენსივობის შეფასება ხდებოდა როგორც საკვერცხის სიმსივნის პარენქიმაში, ასევე სიმსივნური ქსოვილის სტრომაში - იმუნოჰისტოქიმიური კვლევის მეთოდით. რაოდენობრივი შეფასება ხორციელდებოდა კომპიუტერული პროგრამით ImageJ.

გადარჩენადობის ანალიზი ჩატარდა კაპლან-მეიერის მრუდების გამოყენებით და კოქსის საფრთხეთა ფარდობის (Hazard Ratio - HR) გამოთვლებით. ქირურგიულ ჩარევაზე გავლენის მქონე ფაქტორების მრავლობითი რეგრესიული ანალიზი ჩატარდა ლოგარითმული რეგრესიის მეთოდით.

კვლევის საფუძველზე დადგინდა, რომ:

-საკვერცხის დაბალდიფერენცირებული და მაღალდიფერენცირებული სეროზული კარცინომების კარცინოგენეზი განსხვავებულია. დაბალი ავთვისებიანობის (low-grade) ფორმებს ყოველთვის წინ უძღვის სეროზული ცისტადენომა და/ან სეროზული ცისტადენოფიბრომა, რომლებმაც შეიძლება ტრანსფორმაცია განიცადოს მოსაზღვრე ავთვისებიან სეროზულ კარცინომად და შემდეგ low-grade ინვაზიურ კარცინომად. ამასთანავე, მაღალი ავთვისებიანობის (high-grade) სეროზული კარცინომები არ წარმოიქმნება low-grade ინვაზიურ კარცინომებისაგან და de novo განითარების შედეგია.

საკვერცხის დაბალდიფერენცირებულ სეროზულ კარცინომებში ონკოპროტეინ p53 ჩართვა ინტენსიური იყო მაღალდიფერენცირებულ სეროზულ კარცინომებთან შედარებით. აღნიშნულის გამო, p53 შეიძლება გამოყენებულ იქნას როგორც დამატებითი მოლეკულურ-ბიოლოგიური მახასიათებელი სიმსივნის მიკროსკოპული ავთვისებიანობის ხარისხის დასაზუსტებლად იმ შემთხვევებში, როდესაც Shimizu/Silverberg სისტემის მიხედვით დგინდება სიმსივნის ზომიერად დიფერენცირებული ფორმა.

- საჭიროა სიმსივნის მაინფილტრირებელი T-ლიმფოციტების ანტინეოპლაზიური და/ან პროგნოზული როლის შემდგომი შესწავლა.
- საკვერცხეების სიმსივნის ოპერაციული მკურნალობის ეფექტურობაზე (ლეტალურ გამოსავალზე) გავლენის მქონე სარწმუნო ფაქტორებად გვევლინებიან ნეოადიუვანტური ქიმიოთერაპია და სიმსივნის დიფერენციაციის დაბალი ხარისხი.

ЯТРОГЕННЫЕ ПОВРЕЖДЕНИЯ ПРИ ВЫПОЛНЕНИИ ПРЕДОПЕРАЦИОННОЙ МАРКИРОВКИ НЕПАЛЬПИРУЕМЫХ ПАТОЛОГИЧЕСКИХ УЧАСТКОВ МОЛОЧНЫХ ЖЕЛЕЗ

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На протяжении длительного времени заболеваемость и смертность от рака молочной железы у женщин в развитых странах мира и на территории РФ не уступают свои лидирующие позиции среди всей онкологической патологии [2,5,6,8,10,11,13,15]. Выживаемость при раке молочной железы и дальнейшее качество жизни пациентов во многом зависят от стадии, на которой выявлено и пролечено заболевание [12]. Именно поэтому принципиальной задачей лучевой диагностики и онкологии остается выявление злокачественного процесса в молочных железах на доклинических стадиях развития болезни [1,7,9]. Для постановки корректного диагноза, при наличии узлового образования в молочной железе категории BI-RADS 4 и 5, помимо стандартных исследований (рентгеновская маммография и ультразвуковое сканирование) в обязательном порядке проводится морфологическая верификация выявленных патологических участков вне зависимости от их размеров. Минимальные (непальпируемые) изменения в тканях молочной железы, подозрительные в отношении злокачественного процесса, требуют перед началом хирургического лечения предоперационной маркировки [17,19]. Для этого используются такие способы навигационной разметки, как проводниковые, ультразвуковые, радионуклидные. Несмотря на наличие выбора, на практике с целью разметки непальпируемых участков молочных желез чаще всего применяются проволочные иглы, устанавливающиеся под рентгенологическим стереотаксическим контролем [14,18]. Однако вне зависимости от развития научно-технического прогресса и появления новых методов и методик, а также подходов к диагностике и лечению, человеческий фактор способен косвенно или напрямую влиять на количественный показатель ятрогений [4]. Основа принципа улучшения качества диагностики гласит, что не возможно исправить то, что не измеряется. Именно поэтому все мероприятия по минимизации диагностических ошибок должны состоять из трех этапов: выявления, анализа и устранения [3,16].

Цель исследования - выявить характер, частоту и виды ошибок врачей-рентгенологов, совершаемых при выполнении предоперационной разметки непальпируемых патологических участков молочных желез.

Материал и методы. Проанализировано 60 клинических наблюдений пациенток в возрастной группе от 40 до 85 лет с выявленными непальпируемыми патологическими участками в тканях молочных желез. Всем больным до начала хирургического лечения выполнено комплексное лучевое обследование молочных желез, включающее в себя проведение обзорной цифровой маммографии в двух стандартных проекциях, ультразвуковое исследование в В-режиме, а также в режиме цветового допплеровского картирования, и морфологическую верификацию посредством трепанобиопсии, преимущественно, под рентгенологическим контролем. Распределение нозологических форм патологических процессов в молочных железах в зависимости от результатов морфологического исследования биоптатов, полученных в процессе проведения трепанобиопсии на догоспитальном этапе, представлено на рис. 1.

Рис. 1. Распределение нозологических форм непальпируемых патологических участков молочных желез после проведения трепанобиопсии (n=60)

Таким образом, на амбулаторном этапе до начала хирургического лечения рак молочной железы морфологически подтвержден у 10 (16,7%) женщин. В 18 (30%) наблюдениях по данным гистологии имела место пролиферативная форма узловой фиброзно-кистозной мастопатии. У 32 (53,3%) обследуемых выявленные при лучевом обследовании подозрительные в отношении рака молочной железы изменения (участки микрокальцинатов, тяжистые перестройки структуры ткани) не имели морфологически доказанных признаков злокачественности.

Всем 60 пациенткам на первом этапе выполнена секторальная резекция молочной железы с проведением внутритканевой маркировки патологического новообразования иглой-проводником «гарпунного» типа под рентгенологическим контро-