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OVARIAN CANCER: A MODERN VIEW OF THE PROBLEM

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Abstract
This scientific and analytical work presents modern world and local-regional data on incidence, mortality, lethality and five-year survival rate of such a common oncological pathology as ovarian cancer. The issues of etiology and pathogenesis, modern approaches and principles of complex diagnostics, prospects for improving treatment results, as well as the prognosis are covered in detail. The epidemiological characteristics of this pathology in our republic are given in the context of the regions of the country.

Keywords: oncology, ovarian cancer, biomarkers, cancer antigen 125, human epididymis protein 4, BRCA1/2 mutation, DNA, RNA, epidemiology, incidence, mortality, lethality, five-year survival rate, prognosis.

Ovarian cancer (OC) is a malignant tumor that most often develops from the ovarian epithelium. Requirements for the pathomorphological conclusion in OC: 1) macroscopic description of the specimen separately for each ovary [size and weight, color, capsule condition, cross-sectional view, approximate ratio of cystic and solid components (in %), presence of papillary structures (if any, in % approximately), and other involved organs]; 2) tumor [total size (3 dimensions: height, width, length), location, type, invasion depth (in relation to the myometrium/endometrium border), myometrium thickness (mm), endometrium, involvement of the serous membrane of the uterus, involvement of the cervix, appendages)]; 3) other findings (presence of invasion into other organs); 4) lymph nodes (if present: size, location, size of the largest lymph node, number, number of cassettes); 5) microscopic description [primary tumor: histologic type, degree of differentiation, invasion, capsule/surface involvement, lymphovascular invasion, immunohistochemical (IHC) markers, metastases (preferably described separately): location of metastases (lymph nodes involved/number of nodes, size of largest metastasis, extension beyond lymph node)] [1].

The diagnostic criteria are as follows. Complaints and anamnesis: all patients are recommended to have a thorough collection of complaints and anamnesis; in the early stages, OC may be asymptomatic or cause minor discomfort; in the advanced stage, the disease manifests itself with non-specific symptoms: an increase in abdominal volume, dyspeptic symptoms, weight loss, loss of appetite, pain in the abdomen or pelvis, shortness of breath, general weakness. The level of evidence for recommendations is A (the level of evidence is 1). Comment: collecting information about complaints and anamnesis details, including family history, is carried out in order to identify factors that may influence the choice of treatment tactics.

Physical examination: a thorough physical examination is recommended; it includes a recto-vaginal examination, palpation of the abdominal organs and all groups of peripheral lymph nodes, auscultation and percussion of the lungs, palpation of the mammary glands. The level of evidence for recommendations is A (the level of reliability of evidence is 1). Comment: special attention should be paid to assessing the patient's condition according to the WHO/ECOG and/or Karnofsky scale, assessing nutritional status, pain syndrome, body temperature, hemodynamics, enlarged peripheral lymph nodes, and the presence of pleurisy and ascites.

Laboratory diagnostic tests: it is recommended to perform a complete general (clinical) blood test, a general therapeutic biochemical blood test with assessment of liver and kidney function, a complete (clinical) urine test, and a study of the blood coagulation system for all patients with OC in order to assess the patient's condition, determine the patient's treatment tactics and algorithm, and assess the prognosis of the disease. The level of evidence for recommendations is C (the level of reliability of evidence is 4). Comments: A complete

blood count is performed (repeated) at least 5 days before the start of the next course of chemotherapy; in a complete general (clinical) blood test, it is advisable to assess the following parameters: hemoglobin, hematocrit, erythrocytes, mean corpuscular volume, erythrocyte distribution by size, mean corpuscular hemoglobin content, mean corpuscular hemoglobin concentration, leukocyte platelets, leukocyte formula, erythrocyte sedimentation rate; in a general therapeutic biochemical blood test with an assessment of liver and kidney function indicators - total protein, glucose, bilirubin, creatinine, urea, iron, alanine aminotransferase, aspartate aminotransferase, total bilirubin, lactate aminotransferase, alkaline phosphatase, plasma electrolytes (potassium, sodium, chlorine), in a general (clinical) urine test - determination of color, transparency of urine, its specific gravity, protein in urine, pH, glucose, ketone bodies, urobilinogen, leukocyte esterase, by hardware microscopy of epithelial cells, erythrocytes, cylinders, salt, mucus, bacteria and fungi; as part of the study of the blood coagulation system, a coagulogram (an indicative study of the hemostasis system) is assessed (fibrinogen, prothrombin (according to Quick), international normalized ratio, prothrombin time, prothrombin index, activated partial thromboplastin time, thrombin time, if indicated, additionally - antithrombin III, D-dimer, plasminogen, % activity); it is recommended that all patients undergo a study of the level of adenogenic cancer antigen CA 125 in the blood in order to identify OC and its recurrence. The level of evidence for recommendations is A (the level of reliability of evidence is 1) [1].

In the absence of morphological verification of the diagnosis, it is recommended that all patients with suspected OC undergo determination of human epididymis protein 4 (HE4) in the blood and determination of the Risk of Ovarian Malignancy Algorithm (ROMA) index in order to assess the probability of OC. The strength of the recommendations is B (the level of evidence is 2). Comment: determination of HE4 in the blood and the ROMA index does not replace the need for morphological verification of the diagnosis, but an elevated HE4 level increases the specificity of OC diagnostics; if mucinous carcinoma is suspected, it is recommended, in addition to testing the level of adenogenic cancer antigen CA 125 in the blood, to test the level of adenogenic cancer antigen CA 19-9 in the blood and test the level of carcinoembryonic antigen (CEA) in the blood serum for the purpose of differential diagnosis. The strength of the recommendations is A (the level of evidence is 2). Comment: CEA and CA19-9 may increase in mucinous OC, which allows for subsequent monitoring of the effectiveness of the treatment; for women under 40, who have a high probability of non-epithelial tumors, it is recommended to perform a study of the alpha-fetoprotein level in the blood serum, a study of the level of chorionic gonadotropin in the blood, and a study of the level of inhibin B in the blood at the diagnostic stage. The level of evidence for recommendations is C (the level of reliability of evidence is 5). Comment: non-epithelial ovarian tumors predominate at a young age (detailed information is provided in the section on non-epithelial ovarian tumors). All patients with high-grade serous and endometrioid carcinomas are recommended to undergo molecular genetic testing for mutations in the BRCA1 and BRCA2 genes in the blood or by scraping the oral mucosa and/or in biopsy (surgical) material as predictors of the disease outcome and the choice of the patient's treatment algorithm. The level of evidence for recommendations is B (the level of reliability of evidence is 2). Comment: the frequency of mutations in the BRCA1 and BRCA 2 genes in the indicated histological types of tumors is about 15%. Information about the presence of a BRCA mutation is useful for determining a higher sensitivity of the tumor to therapy with alkylating agents, platinum derivatives and poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors [1].

1. All patients with OC or suspected OC are recommended to undergo computed tomography (CT) of the chest, abdominal cavity, retroperitoneal space, and kidneys at the diagnostic stage, with or without intravenous contrast in order to determine the extent of the tumor process and plan the treatment algorithm. The level of evidence for recommendations is A (the level of reliability of evidence is 1). Comment: CT allows (a) to visualize the primary tumor, (b) to identify metastases of the disease, (c) to assess the possibility of performing an optimal cytoreductive surgery. If CT is contraindicated or insufficiently informative, magnetic resonance imaging (MRI) with intravenous contrast may be performed. If distant metastasis is suspected, positron emission tomography (PET)/CT may be performed.

2. All patients with OC or suspected OC are recommended to undergo MRI of the pelvic organs with or without intravenous contrast at the diagnostic stage in order to determine the extent of the tumor process and plan the treatment algorithm. The strength of the recommendations is A (the level of evidence is 1). Comment: MRI allows (a) to visualize the primary tumor, (b) to identify metastases of the disease, (c) to assess the possibility of performing an optimal cytoreductive surgery. In case of contraindications to MRI examination or its insufficiently informativeness, as well as when it is not possible to perform MRI, CT with or without intravenous contrast is indicated. If distant metastasis is suspected, PET/CT can be performed.

3. All patients with OC or suspected OC are recommended to undergo chest X-ray at the diagnostic stage if CT of the chest is not possible. The strength of the recommendations is C (the level of evidence is 5). Comment: CT of the chest organs is more sensitive and specific in detecting metastases in the lungs and mediastinal lymph nodes.

4. All patients with OC or suspected OC are recommended to undergo ultrasound examination of the lymph nodes in the cervical-supraclavicular region, axillary, inguinal lymph nodes, ultrasound of the abdominal cavity, retroperitoneal space and pelvis at the diagnostic stage if CT/MRI/PET-CT cannot be performed in order to determine the prevalence of the tumor process and plan the treatment algorithm. The level of evidence for recommendations is B (the level of reliability of evidence is 2). Comment: Ultrasound is the simplest method for visualizing formations in the abdominal cavity, in the pelvic cavity, and secondary

lymph node damage. However, this method is significantly inferior to CT/MRI/PET-CT in terms of making a decision on the first stage of treatment. Evaluation of the effect of chemotherapy according to RECIST 1.1 criteria is also impossible based on the results of ultrasound.

5. All patients with OC or suspected OC at the diagnostic stage are recommended to undergo examination of the mammary glands in order to exclude secondary (metastatic) ovarian lesions or primary multiple malignant neoplasms. The level of evidence for the recommendations is A (the level of reliability of the evidence is 1). Comments: Women under 40 years of age undergo ultrasound examination of the mammary glands in the first phase of the menstrual cycle, if available; women over 40 years of age are recommended to undergo mammography in the first phase of the menstrual cycle, if available. Examination of the mammary glands is carried out in accordance with the principles set out in the clinical guidelines for malignant neoplasms of the mammary glands.

6. For patients with OC, diagnostic laparoscopy is recommended to clarify the extent of the process, morphologically verify the diagnosis and assess resectability, as well as in cases where the performance of optimal cytoreduction is questionable for staging or if it was not adequately performed during previous cytoreduction, as well as for morphological verification of the diagnosis if less invasive methods are not effective [1].

As noted by Zhu B. et al. [2] the incidence and mortality of gynaecological cancers (GCs) can significantly impact women's quality of life and increase the health care burden for organisations globally. The objective of study was to evaluate global inequalities in the incidence and mortality of GCs in 2022, based on The Global Cancer Observatory (GLOBOCAN) 2022 estimates. The future burden of GCs in 2050 was also projected. Data regarding to the total cases and deaths related to GCs, as well as cases and deaths pertaining to different subtypes of GCs, gathered from the GLOBOCAN database for the year 2022. Predictions for the number of cases and deaths in the year 2050 were derived from global demographic projections, categorised by world region and Human Development Index (HDI). In 2022, there were 1 473 427 new cases of GCs and 680 372 deaths. The incidence of gynecological cancer reached 30.3 per 100 000, and the mortality rate hit 13.2 per 100 000. The age-standardised incidence of GCs in Eastern Africa is higher than 50 per 100 000, whereas the age-standardised incidence in Northern Africa is 17.1 per 100 000. The highest mortality rates were found in East Africa (age-standardised mortality rates of 35.3 per 100 000) and the lowest in Australia and New Zealand (age-standardised mortality rates of 8.1 per 100 000). These are related to the endemic areas of HIV and HPV. Very high HDI countries had the highest incidence of GCs, with age-standardised incidence rates of 34.8 per 100 000, and low HDI countries had the second highest incidence rate, with an age-standardised incidence rates of 33.0 per 100 000. Eswatini had the highest incidence and mortality (105.4 per 100 000; 71.1 per 100 000) and Yemen the lowest (5.8 per 100 000; 4.4 per 100 000). If the current trends in incidence and mortality are maintained, number of new cases and deaths from female reproductive tract tumours is projected to increase over the next two decades. In conclusion, the authors point out that in 2022, GCs accounted for 1 473 427 new cases and 680 372 deaths globally, with significant regional disparities in incidence and mortality rates. The highest rates were observed in Eastern Africa and countries with very high and low HDI, with Eswatini recording the most severe statistics. If current trends continue, the number of new cases and deaths from GCs is expected to rise over the next two decades, highlighting the urgent need for effective interventions.

OC is a leading cause of death in women worldwide, with more than 300,000 new cases and nearly 200,000 deaths globally each year [3].

Medina J.E. et al. emphasize in their work that [4], OC is a leading cause of death for women worldwide, in part due to ineffective screening methods. Unfortunately, OC is usually detected in advanced stages (stages III and IV) due to nonspecific clinical symptoms at earlier stages and the lack of an effective screening approach. Consequently, there is a clear unmet clinical need for the development of highly specific and sensitive assays to detect OC in its earliest stages. In their study, the authors used whole-genome cell-free DNA (cfDNA) fragmentome and protein biomarker [cancer antigen 125 (CA-125) and HE4] analyses to evaluate 591 women with OC, with benign adnexal masses, or without ovarian lesions. Using a machine learning model with the combined features, researchers detected OC with specificity >99% and sensitivities of 72%, 69%, 87%, and 100% for stages I to IV, respectively. At the same specificity, CA-125 alone detected 34%, 62%, 63%, and 100%, and HE4 alone detected 28%, 27%, 67%, and 100% of OCs for stages I to IV, respectively. This approach differentiated benign masses from OCs with high accuracy (AUC = 0.88, 95% confidence interval, 0.83-0.92). These results were validated in an independent population. These findings show that integrated cfDNA fragmentome and protein analyses detect OCs with high performance, enabling a new accessible approach for noninvasive OC screening and diagnostic evaluation.

Qian F. et al. [5] in their study note that OC is the fifth leading cause of cancer deaths in US women, due to its typically advanced stage at presentation. Furthermore, unlike breast or colorectal cancer, there is no proven screening method for OC to identify early disease and initiate treatment to improve survival. Family history, oral contraceptive use, parity, body mass index (BMI), and genetic variants are potentially useful in estimating lifetime risk. Along with this, because of differences in age at onset and tumour histology/grade, risk factors for OC might be different for BRCA1/2 mutation carriers than women in the general population. Penetrance of BRCA1/2 mutations is likely modified by other genetic variants and lifestyle or reproductive factors. Investigation of these factors could aid in implementation of strategies to reduce OC risk among mutation carriers. In their work, the authors point out that height and BMI are associated with higher OC risk in the general population, but whether such associations

exist among BRCA1/2 mutation carriers is unknown. The researchers applied a Mendelian randomisation approach to examine height/BMI with OC risk using the Consortium of Investigators for the Modifiers of BRCA1/2 data set, comprising 14,676 BRCA1 and 7912 BRCA2 mutation carriers, with 2923 OC cases. They created a height genetic score using 586 height-associated variants and a BMI genetic score using 93 BMI-associated variants. Associations were assessed using weighted Cox models. Observed height was not associated with OC risk (hazard ratio [HR]: 1.07 per 10-cm increase in height, 95% confidence interval [CI]: 0.94-1.23). Height genetic score showed similar results (HR = 1.02, 95% CI: 0.85-1.23). Higher BMI was significantly associated with increased risk in premenopausal women with HR = 1.25 (95% CI: 1.06-1.48) and HR = 1.59 (95% CI: 1.08-2.33) per 5-kg/m2 increase in observed and genetically determined BMI, respectively. No association was found for postmenopausal women. Interaction between menopausal status and BMI was significant (pinteraction < 0.05). Our colleagues emphasize that the results of their observation of a positive association between BMI and OC risk in premenopausal BRCA1/2 mutation carriers is consistent with findings in the general population.

Jara-Rosales S. et al. [6] in their work they say that in 2020, OC ranked fourth in incidence among gynecological cancers worldwide, following breast cancer, cervical cancer, and uterine cancer. In terms of mortality, it ranked third, establishing itself as one of the most lethal gynecological cancers. A 2021 study revealed that the variability in the incidence depends on each country and region, but the mortality rate remains similar among the 185 countries included. This behavior is attributed to nonspecific symptoms and the lack of screening programs, leading to diagnoses at advanced stages with unfavorable prognoses for patients [7]. OC constitutes a group of diverse diseases, each characterized by its own morphology and biological behavior. This heterogeneity implies that different subtypes may respond differently to treatments and show variations in their progression rates [8]. It is therefore essential to recognize this diversity to effectively address the different manifestations of OC. The risk factors for OC are divided into two categories: modifiable and non-modifiable. Modifiable factors include smoking, hormone replacement therapy, and dietary elements, among others. Non-modifiable factors include heredity, mutations in the BRCA1 and BRCA2 genes, family history, Lynch syndrome, uninterrupted ovulation cycles, and the presence of endometriosis, among others [7].

Our colleagues conducted an exhaustive search was conducted to identify literature to describe the OC biology and physiopathology for new readers, in particular focused on clinical researchers. In addition, a more stringent search was performed to find studies related to the genetic components, social determinants, and comorbidities associated with OC in South America. The search was performed through PubMed and Google Scholar, using the MeSH descriptors and keywords such as “Hereditary Breast and Ovarian Cancer Syndrome”, “Latin America”, “BRCA1 Genes”, “BRCA2 Genes”, and “Ovarian Neoplasms”. Additionally, the keywords “Obesity”, “chronic disease”, “Comorbidity”, “poverty”, “education”, “race”, “ethnicity”, “menarche”, “menopause”, “multiparity”, “urbanization”, “epidemiology”, and “risk factors” were utilized to capture relevant studies. Due the reported disparities in clinical trials and other biomedical studies, the Latin American population is greatly underrepresented in most of the cancer and genomic databases, including local investigations. For this reason, the number of identified reports according to the specific topics was very small for further analysis. The revision of the literature was conducted based on original articles, including cohort studies, case-control studies, cross-sectional studies, and experimental research investigating the risk factors for OC in the South American population, and the selected articles were published within the last 10 years, with full-text availability, and were written in English or Spanish. The authors considered studies involving women from 12 South American countries, without age restrictions, focusing particularly on those analyzing genetic components, socioeconomic determinants, and comorbidities. Considering the main goal of this work, they excluded studies focused on OC treatment, research validating laboratory tests for detecting OC-related mutations, and non-original content such as reviews, opinions, editorials, letters to the editor, and conference abstracts. Articles that did not clearly specify the region or country of interest, or those centered on education about OC risk factors, were also excluded. [6].

In the conclusions following from the study, the researchers note that based on the revised articles, it can be concluded that although there are reports on the prevalence of mutations in the BRCA1 and BRCA2 genes in South American countries, such as Chile, Colombia, Argentina, Uruguay, and Brazil, including Mexico as Hispanic, the general prevalence is close to 15-20% in women with hereditary risk factors or those diagnosed with ovarian and/or breast cancer. However, it is important to highlight that the available studies are limited. More research is needed to accurately determine the prevalence of the punctual mutation in each country, as well as those mutational signatures that could be unique for the Latin American population. In terms of the social, demographic, and economic factors that influence the incidence of OC, these vary by country, but similarities are observed in age, being more prevalent in women over 50 years old, and in women with poor education and difficulties in accessing healthcare. Similarly, the absence of studies regarding the effect of contraception and hormone replacement therapy in the Latin American population is highlighted, despite being widely studied factors in the international scientific literature. This gap in the research underscores the need to address these aspects in future research in the region. This article has several limitations, starting with the very limited number of studies published and the number of participants in each study. The revised literature covers several years of research conducted in each country; these years may represent disparities in funding for biomedical research, the num-

ber and capabilities of each research group and the possibility of enrolling patients, and the access to technological facilities. For now, it is not possible to conduct a more comprehensive analysis; however, this work may promote the interest of other researchers to collaborate in the systematic revision of current and future data. Regarding the need to improve lifestyles as a preventive measure to reduce the possibility of morbidities and the concomitant development of OC, although the literature may not be sufficient to conclusively establish a direct link between obesity and/or diabetes and the development of OC, the indirect association suggests the importance of conducting additional clinical studies. These studies could confirm or dismiss the hypothesis that obesity and diabetes could be related to the risk of developing OC, thereby providing a more solid basis for future interventions and prevention strategies [6].

Bryant A. et al. [9] provide data showing that OC is the seventh most common cancer among women and a leading cause of death from gynaecological malignancies. Epithelial OC is the most common type, accounting for around 90% of all OCs. This specific type of OC starts in the surface layer covering the ovary or lining of the fallopian tube. Surgery is performed either before chemotherapy [upfront or primary debulking surgery (PDS)] or in the middle of a course of treatment with chemotherapy [neoadjuvant chemotherapy and interval debulking surgery (IDS)], with the aim of removing all visible tumour and achieving no macroscopic residual disease (NMRD). The aim of this study was to investigate the prognostic impact of size of residual disease (RD) nodules in women who received upfront or interval cytoreductive surgery for advanced (stage III and IV) epithelial OC (EOC). To assess the prognostic impact of RD after primary surgery on survival outcomes for advanced (stage III and IV) EOC. In separate analyses, primary surgery included both upfront PDS followed by adjuvant chemotherapy and neoadjuvant chemotherapy followed by IDS. Each RD threshold is considered as a separate prognostic factor. The authors searched CENTRAL (2021, Issue 8), MEDLINE via Ovid (to 30 August 2021) and Embase via Ovid (to 30 August 2021). Our colleagues included survival data from studies of at least 100 women with advanced EOC after primary surgery. RD was assessed as a prognostic factor in multivariate prognostic models. They excluded studies that reported fewer than 100 women, women with concurrent malignancies or studies that only reported unadjusted results. Women were included into two distinct groups: those who received PDS followed by platinum-based chemotherapy and those who received IDS, analysed separately. The researchers included studies that reported all RD thresholds after surgery, but the main thresholds of interest were microscopic RD (labelled NMRD), RD 0.1 cm to 1 cm [small-volume residual disease (SVRD)] and RD > 1 cm [large-volume residual disease (LVRD)]. Two review authors independently abstracted data and assessed risk of bias. Where possible, they synthesised the data in meta-analysis. To assess the adequacy of adjustment factors used in multivariate Cox models, authors used the 'adjustment for other prognostic factors' and 'statistical analysis and reporting' domains of the quality in prognosis studies tool.

Our colleagues also made judgements about the certainty of the evidence for each outcome in the main comparisons, using GRADE. The researchers examined differences between FIGO stages III and IV for different thresholds of RD after primary surgery. They considered factors such as age, grade, length of follow-up, type and experience of surgeon, and type of surgery in the interpretation of any heterogeneity. The authors also performed sensitivity analyses that distinguished between studies that included NMRD in RD categories of < 1 cm and those that did not. This was applicable to comparisons involving RD < 1 cm with the exception of RD < 1 cm versus NMRD. They evaluated women undergoing PDS and IDS in separate analyses. The researchers found 46 studies reporting multivariate prognostic analyses, including RD as a prognostic factor, which met inclusion criteria: 22,376 women who underwent PDS and 3697 who underwent IDS, all with varying levels of RD. While we identified a range of different RD thresholds, authors of the work mainly report on comparisons that are the focus of a key area of clinical uncertainty (involving NMRD, SVRD and LVRD). The comparison involving any visible disease (RD > 0 cm) and NMRD was also important. SVRD versus NMRD in a PDS setting In PDS studies, most showed an increased risk of death in all RD groups when those with macroscopic RD (MRD) were compared to NMRD. Women who had SVRD after PDS had more than twice the risk of death compared to women with NMRD (HR 2.03, 95% CI 1.80 to 2.29; I2 = 50%; 17 studies; 9404 participants; moderate-certainty). The analysis of progression-free survival found that women who had SVRD after PDS had nearly twice the risk of death compared to women with NMRD (HR 1.88, 95% CI 1.63 to 2.16; I2 = 63%; 10 studies; 6596 participants; moderate-certainty). LVRD versus SVRD in a PDS setting. When authors compared LVRD versus SVRD following surgery, the estimates were attenuated compared to NMRD comparisons. All analyses showed an overall survival benefit in women who had RD < 1 cm after surgery (HR 1.22, 95% CI 1.13 to 1.32; I2 = 0%; 5 studies; 6000 participants; moderate-certainty). The results were robust to analyses of progression-free survival. SVRD and LVRD versus NMRD in an IDS setting The one study that defined the categories as NMRD, SVRD and LVRD showed that women who had SVRD and LVRD after IDS had more than twice the risk of death compared to women who had NMRD (HR 2.09, 95% CI 1.20 to 3.66; 310 participants; I2 = 56%, and HR 2.23, 95% CI 1.49 to 3.34; 343 participants; I2 = 35%; very low-certainty, for SVRD versus NMRD and LVRD versus NMRD, respectively). LVRD versus SVRD + NMRD in an IDS setting meta-analysis found that women who had LVRD had a greater risk of death and disease progression compared to women who had either SVRD or NMRD (HR 1.60, 95% CI 1.21 to 2.11; 6 studies; 1572 participants; I2 = 58% for overall survival and HR 1.76, 95% CI 1.23 to 2.52; 1145 participants; I2 = 60% for progression-free survival; very low-certainty). However, this result is bi-

ased as in all but one study it was not possible to distinguish NMRD within the < 1 cm thresholds. Only one study separated NMRD from SVRD; all others included NMRD in the SVRD group, which may create bias when comparing with LVRD, making interpretation challenging. MRD versus NMRD in an IDS setting. Women who had any amount of MRD after IDS had more than twice the risk of death compared to women with NMRD (HR 2.11, 95% CI 1.35 to 3.29, I2 = 81%; 906 participants; very low-certainty). Summing up the results of the study, the authors point out that in a PDS setting, there is moderate-certainty evidence that the amount of RD after primary surgery is a prognostic factor for overall and progression-free survival in women with advanced OC. Our colleagues separated our analysis into three distinct categories for the survival outcome including NMRD, SVRD and LVRD. After IDS, there may be only two categories required, although this is based on very low-certainty evidence, as all but one study included NMRD in the SVRD category. The one study that separated NMRD from SVRD showed no improved survival outcome in the SVRD category, compared to LVRD. Further low-certainty evidence also supported restricting to two categories, where women who had any amount of MRD after IDS had a significantly greater risk of death compared to women with NMRD. Therefore, the evidence presented in this review cannot conclude that using three categories applies in an IDS setting (very low-certainty evidence), as was supported for PDS (which has convincing moderate-certainty evidence) [9].

What knowledge is available today about the specifics of OC treatment? Drug resistance is the bottleneck in OC treatment. The increasing use of novel drugs in clinical practice poses challenges for the treatment of drug-resistant OC. Although maintenance therapy with PARP inhibitors (PARPis) has prolonged progression-free survival and 5-year overall survival, unfortunately, many patients do not respond to PARPis treatment due to intrinsic or acquired resistance [10].

Wang L. et al. [11] indicate that despite receiving standard-of-care therapy (optimal cytoreductive surgery followed by adjuvant chemotherapy), most patients develop recurrent disease, which is resistant to chemotherapy, resulting in a 5-year survival rate of approximately 30-40% worldwide. Drug resistance is a formidable challenge in the treatment of OC and is the primary contributor to poor prognosis. According to the National Comprehensive Cancer Network guidelines (version 1.2023), there are many therapeutic regimens for resistant OC, including some novel agents. However, the objective remission rate is still low, and the median survival time is less than 12 months due to complicated resistance mechanisms. In resistant OC, the classical mechanisms of action of common drugs can be disrupted or altered, possibly resulting in impaired therapeutic effects. Thus, treatment regimens should not rely only on empirical options. As the number of categories of agents increases, after the development of multidrug resistance, the decision of appropriate later-line therapeutic regimens is very challenging. The authors reviewed the literature regarding various drug resistance mechanisms in OC and found that the main resistance mechanisms are as follows: abnormalities in transmembrane transport, alterations in DNA damage repair, dysregulation of cancer-associated signaling pathways, and epigenetic modifications. DNA methylation, histone modifications and noncoding RNA activity, three key classes of epigenetic modifications, constitute pivotal mechanisms of drug resistance. One drug can have multiple resistance mechanisms. Moreover, common chemotherapies and targeted drugs may have cross (overlapping) resistance mechanisms. MicroRNAs (miRNAs) can interfere with and thus regulate the abovementioned pathways. A subclass of miRNAs, “epi-miRNAs”, can modulate epigenetic regulators to impact therapeutic responses. Thus, they also reviewed the regulatory influence of miRNAs on resistance mechanisms. Moreover, researchers summarized recent phase I/II clinical trials of novel drugs for OC based on the abovementioned resistance mechanisms. A multitude of new therapies are under evaluation, and the preliminary results are encouraging. Summarizing the results of the study, our colleagues emphasize that with the increasing use of novel therapeutic drugs for OC, the development of later-line treatments has been under enormous pressure. Recently, resistance to a variety of therapeutic drugs, such as PARPis, angiogenesis inhibitors, and immune checkpoint inhibitors, has been found to occur. In the past, therapeutic agents for OC have been limited, and researchers have usually described the underlying mechanism and explored therapeutic strategies for overcoming resistance based on the drug classification. However, as increasing numbers of new agents are applied in clinical practice, the resistance mechanisms of these various new drugs must be identified, and these mechanisms may be similar or even identical to those of other drugs. Thus, the classification of drug resistance should not be confined to the drug category, and all should attempt to obtain insight into classification of resistance based on molecular mechanisms. The concept of drug resistance classification provides a sound basis for further research to develop more precise reversal strategies.

Instead of simply distinguishing resistance by agent, researchers attempted to classify drug resistance by mechanism. The authors summarized four major mechanisms from the published literature: 1) abnormalities in transmembrane transport, 2) alterations in DNA damage repair, 3) dysregulation of cancer-associated signaling pathways, and 4) epigenetic modifications. In the context of the increasing number of novel agents, summary of the four resistance mechanisms of OC provides a new concept for resistance classification by molecular mechanism, not by drug category. Given the intersections between drug resistance mechanisms, this concept is likely to result in the realization of “two birds with one stone” effects on the reversal of drug resistance in OC. Furthermore, these findings are anticipated to have broad implications for the development of precise therapeutic approaches for reversing drug resistance in OC. On this basis, umbrella trials can be carried out to explore the diagnostic and therapeutic targets of the four resistance mechanisms, and this may be a direction of future researches on drug resistance in

OC [11].

As Porter J.M. et al. [12] note in their study epithelial OC (ovarian carcinoma) is the most common form of the disease and comprises multiple histological types (histotypes): high-grade serous (70% of patients), endometrioid (10%), clear cell (10%), low-grade serous (≤5%), and mucinous (≤5%). Ovarian carcinosarcomas - previously considered a separate disease entity - are now recognized to represent metaplastic carcinomas and account for no more than 5% of diagnoses. A wealth of evidence now demonstrates that each histotype represents a unique disease entity, each with distinct developmental origins, molecular landscapes, intrinsic chemosensitivity, survival profile, and susceptibility to targeted molecular therapeutics.

The authors emphasize that complete macroscopic resection is a key factor associated with prolonged survival in OC. That being said, patients with clear cell ovarian carcinoma and low-grade serous ovarian carcinoma represent some of the groups that benefit most from achieving complete macroscopic resection; given that these cases are unlikely to respond well to neoadjuvant chemotherapy, complete primary cytoreduction is a major priority for these patients. Endometrioid ovarian carcinoma also represents a histotype in which complete macroscopic resection is associated with marked patient survival benefit. Engagement with multiple surgical teams to improve the likelihood of resecting disease at hepatobiliary, gastrointestinal, and other anatomical sites beyond the pelvis will be key for delivering optimal outcomes for such cases that present with extensive advanced-stage disease. More work is also required to understand the impact of resecting disease outside of the pelvis and abdomen. Achievement of complete macroscopic resection across the overall OC patient population is associated with markedly prolonged survival time, though differences in the degree of survival benefit are apparent across different histotypes. Patients with clear cell ovarian carcinoma derive one of the greatest survival benefits associated with complete macroscopic resection. High-grade serous ovarian carcinoma patients demonstrate highly clinically and statistically meaningful survival benefit, but the magnitude of benefit is lower than in some of the other histotypes. The extent of benefit from complete macroscopic resection does not appear to relate solely to levels of intrinsic chemosensitivity of each histotype [12].

Now, as for this pathology in our country at the republican level. The incidence of OC in the Republic of Kazakhstan in 2023 was 6.3 per 100 thousand population (6.2 in 2022) with a growth rate of 2.1% compared to the previous year, amounting to 1,251 people in absolute numbers (1,201 women a year earlier). The proportion of cases with a diagnosis established for the first time in life, recorded by oncological organizations, was 3.4%, as in the previous year in the general population, and 6.0% among women (in 2022 also 6.0%) and 4th rank place after breast cancer, cervical cancer and endometrial cancer [13].

Above the national average, OC was established in 8 regions of the country: the city of Almaty - 10.4 (maximum indicator); Pavlodar - 9.7; Karaganda - 8.6; Abay - 8.4; Akmola - 7.7; Kostanay - 7.6; North Kazakhstan - 7.5; West Kazakhstan - 7.2. Aktobe, Atyrau and Kyzylorda regions are on par with the national average. This indicator is lower than the national average in the remaining 9 regions: Turkestan - 2.9 (the lowest level); Mangistau - 3.5; Ulytau - 3.6; Almaty - 3.7; Zhambyl - 4.3; the city of Shymkent - 4.6; East Kazakhstan - 5.8; Zhetysu - 5.9 regions and the city of Astana - 6.2 per 100 thousand people. The mortality rate from this pathology in 2023 was 2.1, a year earlier - 2.4 per 100 thousand population. The regions where the mortality rate from OC is higher than the average in the republic (2.1 per 100 thousand population) include: Abay - 3.0 (maximum level); the city of Astana - 2.9; Karaganda and Pavlodar - 2.5; Kyzylorda - 2.4; Aktobe and the city of Almaty - 2.2. This indicator is at the same level with the national average in the East Kazakhstan region. The lowest rates were noted in Turkestan - 1.5 (minimum rate); Almaty and Atyrau - 1.6; Zhambyl - 1.7; Ulytau and Mangistau - 1.8; North Kazakhstan and Kostanay - 1.9; West Kazakhstan, Zhetysu, Akmola regions and the city of Shymkent - 2.0 per 100 thousand population [13].

The one-year mortality rate was 7.2% (7.9% in 2022). At the same time, the ratio between one-year mortality and neglect (stage IV) was quite high - 1.7 (a year earlier it was even higher - 2.1. At the same time, it should be noted that the farthest from "1" is the worst ratio between one-year mortality and neglect.

Now, regarding preventive examinations. It should be noted that during large-scale preventive examinations of the population in 2023, significantly more patients with malignant neoplasms were actively identified than in 2022. This is 25,193 patients against 23,623 patients identified in 2022, i.e. +6.6%. This is due to the further abatement of the epidemiological troubles due to coronavirus and the increased availability of preventive care for the population. The proportion of patients identified during preventive examinations increased from 62.0% to 62.4% of the total number of patients identified per year.

Of course, with in the analysis of the epidemiological situation, the indicators of early diagnostics are very important issues. In general, in terms of the amount of detected cases of cancer of all localizations, in 2023 the proportion of forms detected at early stages (0, I-II stages) increased from 66.3% to 67.9%. As for OC, the early detection of this pathology during preventive examinations increased from 40.5 to 44.8%. The number of newly diagnosed patients with OC registered with oncology organizations amounted to 1,218 people (1,173 - a year earlier). At the same time, the absolute number of cases detected during preventive examinations in 2023 was 863, in 2022 - 875; the proportion of cases detected during preventive examinations was 70.9% and 74.6%, respectively. Of these, patients with stages I-II - 387 in 2023 and 354 in 2022.

The regions where the proportion of patients with early stage I of the pathology in question is above the national average (31.0% and 9th place among all nosological forms of malignant neoplasms) include the following regions: the city of Almaty - 45.3%; (the best indicator); Zhetysu - 43.9%; the city of Astana - 42.2%;

Zhambyl - 38.5%; Kyzylorda - 35.8%; East Kazakhstan and Akmola - 35.0%; Kostanay - 33.9%; Almaty - 33.3%.

The lowest rates of early diagnosis were recorded in 11 regions. Against this background, two regions stand out - Aktobe and Turkestan, where stage I of the disease was established at only 5.2% and 6.5%, respectively (the worst rates in the republic). Next come: Mangistau - 16.0%; the city of Shymkent - 18.5%; Pavlodar - 23.3%; Abay - 23.4%; Ulytau and West Kazakhstan - 25.0%; Karaganda - 25.5%; Atyrau - 28.6% and North Kazakhstan - 30.8% of the region [13]. It should be noted that only two patients out of every five were detected in the early (I-II stages) of this pathology, making up 41.7% in the republic. The regions where the proportion of patients with OC detected at stages I-II is higher than the national average include the following regions. The best indicator is in the Zhetysu region - 51.2%. Then come two megacities - the cities of Almaty (51.6%) and Astana (50.6%); then - East Kazakhstan and Atyrau (50.0%); Akmola (48.3%); Mangistau (48.0%); Kostanay (45.2%); Zhambyl (44.2%); North Kazakhstan (43.6%); Karaganda (42.6%) regions. Low rates of early diagnosis were recorded in the following regions. Against the general background, the Aktobe region stands out negatively, where only every tenth patient was detected in the early stages of the disease - 10.3%. Then come the following regions: Turkestan (16.1%); Shymkent city (31.5%); West Kazakhstan (33.3%); Abay (34.0%); Almaty (37.0%); Ulytau (37.5%); Pavlodar (41.1%) and Kyzylorda (41.5%) regions [13].

As can be clearly seen from the above data, there is a very large spread in early diagnostic rates across the country, from good to disappointing. Of course, it is necessary to take into account migration processes and other factors that affect early diagnostic rates, but nevertheless, the results obtained give reason not to stop there, both for oncologists and gynecological oncologists, as well as for obstetricians and gynecologists, visual diagnostic doctors, and general practitioners, since improving the rates of early diagnostics of malignant tumors has remained one of the main postulates and one of the main tasks of medicine in general, and continues to be relevant today. The proportion of stage IV OC among all nosological forms of malignant neoplasms was 7.2%, and this is the 17th rank. In general, in 2023, the proportion of malignant neoplasms of stage IV in the republic for the sum of all nosologies decreased from 12.58 to 11.7% (from 4790 to 4735 patients).

As for the average national indicator of the proportion of stage IV (7.2%), Zhetysu and Mangistau regions stand out against this background - 0.0%. Then come: Kyzylorda and Zhambyl (1.9%); Atyrau (2.4%); North Kazakhstan (2.6%); the city of Almaty (3.6%); East Kazakhstan (5.0%); Pavlodar (5.5%). The city of Astana is on the same level with the average national indicator. The indicators are lower in the following regions. Abay region stands apart from all others, where every fifth patient is diagnosed in the terminal stage of the disease (21.3%). Next come: Turkestan (12.9%); Karaganda (12.8%); Ulytau (12.5%); Aktobe (12.1%); the city of Shymkent (11.1%); Akmola (10.0%); Kostanay (9.7%); West Kazakhstan (8.3%); Almaty (7.4%) regions.

The morphological verification rate of the disease in the country was 84.3%. In 5 regions out of 20, this is a 100% figure (East Kazakhstan, Zhambyl, Ulytau regions, as well as the cities of Astana and Shymkent). The lowest figure is in the Kyzylorda region (32.1%). Next on this list are the city of Almaty (55.2%); Zhetysu (78.0%); Mangistau and Akmola (80.0%); Aktobe (91.4%); Atyrau (92.9%); West Kazakhstan (93.8%); North Kazakhstan (94.9%); Turkestan and Kostanay (95.2%); Karaganda (95.7%); Pavlodar (95.9%); Almaty (96.3%) and Abay (97.9%) regions [13].

The total number of patients with malignant neoplasms, consisting of registered in specialized oncological organizations of the republic, continued to grow and by the end of 2023 amounted to 218,186 people, with an increase of 6.0% compared to the level of the previous year (2022 - 205,822, +5.8%). The overall incidence rate of malignant neoplasms increased by 3.9%, from 1055.3 to 1096.4 per 100 thousand population. The growth of this indicator is due to both the increase in the incidence and detection of pathology, and the increase in the survival rate of cancer patients. In addition, statistical data on patients diagnosed with malignant neoplasms, who have been under observation for 5 years or more, and continue to be observed in 2023, showed that the number of patients under observation by oncological organizations in Kazakhstan for over five years continued to grow and at the end of the reporting year amounted to 117,616 people, with an increase of 6.2% (2022 - 110,790 people, +6.6%) (form. No. 7).

It is impossible to ignore such an important clinical aspect as the coverage of patients with a first-ever diagnosis of OC in the Republic of Kazakhstan with specialized treatment.

In 2023, the number of hospitalizations for all nosological forms of malignant tumors in the country's oncology organizations amounted to 108,252 cases (2022 - 101,095), with an increase of 7.1% compared to the previous year, which is associated with a constant increase in the number of cancer patients, improved standardization of oncological care, and the development of palliative and restorative services.

At the end of 2023, the absolute number of patients with OC who completed specialized treatment amounted to 697 people, continuing treatment - 387 patients. The following results were obtained in percentage terms by methods and types of treatment. The overwhelming majority of patients received complex treatment - 68.4%, only surgical treatment - 21.1%, only drug treatment - 8.3%; combined - 0.3%, chemo-radiation - 0.1%.

Next, regarding the five-year survival rate of patients. As for OC, at the end of 2023, 8229 people or 41.4 per 100 thousand of the population were registered with the dispensary (at the end of 2022 - 7864 patients or 40.3 per 100 thousand of the population, respectively); and this is the 9th rank place among all nosological forms of malignant neoplasms.

At the same time, the mortality rate of the observed contingents in 2023 was 5.0% (6.0% - in 2022).

The five-year survival rate of patients with OC was 58.2% in 2023 (57.5% - a year earlier) [13].

Summarizing the above, we can conclude that OC occupies a significant place among all existing malignant tumors of other localizations. At the same time, despite the small percentage of patients detected at stage IV, taking into account a number of factors, the indicators of early diagnostics do not allow oncologists to "sleep peacefully", since the locally advanced stage III, which significantly prevails over all stages, in addition to the prevalence itself, gives a large number of complications and locoregional metastases, and these patients are subject to aggressive complex treatment, constituting the overwhelming percentage (68.4%) among all methods of treating this pathology. The variability and veiling of symptoms, its similarity with various non-core processes (sometimes the only symptom is a gradual increase in the abdomen due to ascites), leads to the neglect of the disease. All this requires both oncologists and gynecological oncologists, and, first of all, primary health care workers, as well as obstetricians and gynecologists and visual diagnostics doctors, to increase the level of cancer alertness, inform the population about early symptoms that may indicate this pathology or the onset of proliferative changes and conduct high-tech diagnostic measures and, as a result, timely treatment. Women at risk are advised to visit specialized specialists annually and, if necessary, undergo an examination.

An epidemiological assessment of the situation with OC in our country suggests that there are sometimes significant differences between regions not only in incidence rates, but also in the parameters of early diagnosis and mortality from this pathology. In connection with the above, this pathology continues to be a serious problem in modern clinical oncology.

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