ABSTRACT

for the dissertation of Askar Eskhozhaevich Aidarov entitled «Personalized Diagnosis and Treatment of Ovarian Cancer», submitted for the degree of Doctor of Philosophy (PhD) in the Educational Program 8D10102 – "Medicine"

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Relevance of the Research Topic:

According to the International Agency for Research on Cancer (IARC), ovarian cancer (OC) ranks eighth in the structure of oncological diseases among women. According to GLOBOCAN 2022 data, 324,603 new cases of OC and 206,956 deaths attributable to the disease were recorded worldwide (Bray et al., 2024). The majority (75–80 %) of newly diagnosed OC cases are detected at advanced stages, while the overall 5-year survival rate remains at approximately 40 %, despite significant advances in surgical and systemic treatment. According to GLOBOCAN projections, by 2040 the incidence of OC is expected to increase to 428,000 new cases annually, while mortality is projected to reach 307,000 deaths per year, highlighting the need for further improvement of personalized diagnostic and treatment approaches for this disease (GLOBOCAN, 2022).

Research findings have confirmed the significant impact of BRCA1 and BRCA2 gene mutations on the risk of developing OC, breast cancer, and other malignancies (Akter et al., 2022; Chen et al., 2022). The lifetime risk of ovarian cancer is estimated at 40 – 60 % in BRCA1 mutation carriers (Kuchenbaecker et al., 2017; Lewis et al., 2018) and 10–30 % in BRCA2 mutation carriers (Talwar and Rauthan, 2022). BRCA-associated OC is characterized by increased sensitivity to platinum-based chemotherapy and PARP inhibitors, which is associated with more favorable overall survival outcomes (Hollis et al., 2019). The majority of BRCA-associated mutations occur in high-grade serous carcinoma (HGSC), the prevalence of which reaches up to 40 % according to the literature (Hollis et al., 2017; Kim et al., 2019). Large-scale studies have demonstrated high sensitivity to poly (ADP-ribose) polymerase inhibitors (PARPi) (Disilvestro et al., 2022). Clinical validation of this concept in OC was demonstrated in several large multicenter studies, including the SOLO-1 trial, in which the median progression-free survival reached 56 months in the PARPi (olaparib) group compared with 13.8 months in the placebo group. These findings confirm the clinical significance of PARPi in improving survival outcomes in patients with OC (Penson et al., 2020).

In the Republic of Kazakhstan (RK), OC remains one of the most significant oncological diseases among women, ranking fourth in incidence and fifth in mortality among malignant neoplasms of the female reproductive system. In 2023, 1,251 new cases of OC were registered in the country, while the mortality rate reached 5.3 per 100,000 female population (Kaidarova et al., 2025).

Despite the introduction of BRCA testing into clinical practice in the RK since 2022, its routine clinical application remains limited due to insufficient funding for molecular genetic testing within state healthcare programs. Expanding the use of BRCA1/2 sequencing in clinical practice would allow prediction of disease course, justification for PARP inhibitor therapy, and development of personalized treatment strategies. This approach is consistent with modern international standards of personalized oncology and is aimed at improving survival outcomes in patients with OC.

Objective of the Study: To improve personalized diagnosis and treatment of patients with OC based on the investigation of BRCA1 and BRCA2 gene mutations.

Objectives of the Study:

1. To analyze the incidence and mortality rates of OC in the RK during 2004–2024.
2. To evaluate the clinical and anamnestic characteristics of patients with OC.
3. To conduct a molecular genetic study of biological samples obtained from patients with OC using next-generation sequencing (NGS) in order to identify BRCA1/2 gene mutations.
4. To analyze the relationship between BRCA1/2 mutations and clinical characteristics of the disease, including disease stage, features of drug therapy, and overall survival outcomes in patients with OC.
5. To develop an algorithm for personalized diagnosis and treatment with prognostic assessment in BRCA-associated OC.

Materials and Methods:

The dissertation research was carried out as a multistage study, including a retrospective analysis of OC data in the RK for 2004–2024, a prospective clinical-anamnestic stage involving patient questionnaires, as well as a cross-sectional clinical and molecular study with retrospective analysis of clinical outcomes.

A retrospective analysis of data from the Electronic Cancer Registry of the RK for 2004–2024 was conducted to assess OC incidence, mortality, stage distribution, and age structure. The epidemiological stage of the study included data on 21,072 OC cases.

The clinical stage of the study was conducted prospectively within the framework of the international project The Every Woman Study™*:* LMIC Edition and was aimed at investigating the clinical-anamnestic, sociodemographic, and behavioral characteristics of patients with OC. Data collection was performed using the standardized The Every Woman Study™ questionnaire, adapted into Kazakh and Russian languages, consisting of 57 closed-ended and 2 open-ended questions. Data collection in the RK was carried out from October 7, 2022, to September 30, 2023. A total of 305 questionnaires were collected, of which 14 were excluded, resulting in the inclusion of 291 patients with morphologically confirmed OC in the study. Inclusion criteria were age between 18 and 99 years, morphologically confirmed diagnosis of OC, provision of informed consent, and completed questionnaire data. Exclusion criteria included lack of morphological verification of the diagnosis, incomplete questionnaire data, refusal to participate, or absence of informed consent. The study was approved by the Local Ethics Committee of the Joint Stock Company “Kazakh Institute of Oncology and Radiology” (Protocol No. IRB/2022/09-05 dated September 5, 2022).

The molecular-genetic stage of the study was conducted as a cross-sectional clinical and molecular study with retrospective assessment of clinical outcomes and was aimed at identifying somatic BRCA1/2 mutations using NGS. A total of 300 archived FFPE blocks of HGSOC tumor tissue obtained from oncology institutions of

the RK during 2017–2022 were used for analysis. The study included patients with newly diagnosed epithelial OC, histologically confirmed HGSOC, and a tumor cell content of at least 20 % in the sample. Exclusion criteria comprised non-epithelial ovarian tumors, other morphological variants of neoplasms, cases with discrepancies in identification documentation, and tumor cell content of less than 20 %. At the stage of verification and morphological quality control, 204 FFPE blocks were excluded, including 140 due to discrepancies in identification documentation and 64 due to non-compliance with morphological criteria. The final cohort for BRCA1/2 NGS analysis consisted of 96 samples. The obtained molecular-genetic data were correlated with the clinical and anamnestic characteristics of the patients and treatment modalities, including the use of PARP inhibitors, in order to evaluate the association between BRCA status and the clinical course of the disease. The study was approved by the Local Ethics Committee of the Kazakhstan-Russian Medical University (Protocol No. 19/107 dated January 6, 2023).

The subject of the study comprised the clinical-epidemiological and molecular-genetic characteristics of OC, the prevalence of somatic BRCA1/2 mutations, their relationship with clinical characteristics of the disease, survival outcomes, and the possibilities of personalized treatment.

Statistical analysis was performed using descriptive and analytical statistical methods, survival analysis (Kaplan–Meier method and log-rank test), as well as assessment of statistical significance between groups using the χ^2 test and correlation analysis to determine the prognostic significance of BRCA status and substantiate a personalized approach to OC treatment. Statistical significance was considered at $p < 0.05$.

Description of the Main Research Results:

The conducted epidemiological analysis demonstrated that OC remains one of the most significant oncological diseases among women in the RK, ranking fourth in incidence and fifth in mortality within the structure of gynecologic malignancies. During the period from 2004 to 2024, the incidence of OC increased from 10.2 to 12.1 per 100,000 female population (+18.6 %), while the mortality rate remained stable at 4.8 per 100,000 women. The overall 5-year survival rate was 20.3 %. The highest incidence rate was registered in the 55–69-year age group. The proportion of patients diagnosed with advanced disease stages (FIGO III–IV) was 59.5 %.

Clinical and anamnestic analysis of 291 patients demonstrated that the mean age at diagnosis was 54.2 years. HGSC predominated in the morphological structure (46.0%). Advanced stages of the disease (FIGO III–IV) were identified in 57.1 % of patients. The most frequently used diagnostic methods included CA-125 tumor marker assessment (99.3 %), magnetic resonance imaging (MRI) (93.8 %), and computed tomography (CT) (83.4 %). Complete cytoreduction was achieved in 67.0 % of patients, while chemotherapy was administered in 85.8 %, predominantly using carboplatin and paclitaxel regimens. Germline genetic testing was performed in 13.5% of patients, with pathogenic BRCA1 and BRCA2 variants identified in 2.1 % and 1.3% of the examined patients, respectively, indicating the limited availability of molecular genetic diagnostics in the clinical practice of the RK. Pronounced psycho-emotional,

social, and financial problems affecting quality of life were identified, including fear of treatment inefficacy (56.5 %), financial difficulties (54.5 %), and fear of death (51.0%).

Molecular genetic analysis using NGS was performed in 96 patients with HGSC. Somatic BRCA1/2 mutations were identified in 35.4 % of patients, including BRCA1 mutations in 24.0 % and BRCA2 mutations in 11.4 %. BRCA1 mutations occurred approximately twice as frequently as BRCA2 mutations. These findings confirm the high prevalence of BRCA-associated OC in the studied cohort and substantiate the need for expanded BRCA testing.

Analysis of the relationship between BRCA status and clinical characteristics demonstrated the predominance of advanced FIGO III–IV stages regardless of BRCA1/2 mutation status: 95.7 % in BRCA1-positive patients, 90.9 % in BRCA2-positive patients, and 77.5 % in BRCA-negative patients. A positive family history of breast cancer and OC was identified in 5.2 % of patients. Neoadjuvant polychemotherapy was administered in 56.2 % of patients, while adjuvant polychemotherapy was administered in 89.6 %. Overall survival was 67.3 months in the BRCA1 group, 59.8 months in the BRCA2 group, and 58.8 months in the BRCA-negative group. The mean time to recurrence was 16.9, 24.3, and 15.8 months, respectively. Determination of BRCA status allows optimization of therapeutic strategy selection in patients with OC. Maintenance therapy was associated with prolongation of progression-free survival to 16.8 months in BRCA1-positive patients and 27.5 months in BRCA2-positive patients compared with 15.9 months in BRCA-negative patients without maintenance treatment.

Based on the obtained clinical and molecular data, an algorithm for personalized diagnosis, treatment, and prognostic assessment of patients with BRCA-associated OC was developed and clinically substantiated. The algorithm includes optimal cytoreductive surgery, determination of BRCA status using NGS, platinum-based chemotherapy, and maintenance therapy with PARP inhibitors, taking into account the molecular genetic characteristics of the tumor.

Despite the implementation of BRCA testing into clinical practice in the RK since 2022, its accessibility remains limited due to insufficient funding for molecular genetic diagnostics. The results of the study confirmed the clinical significance of BRCA status determination for personalized treatment, prognostic assessment, and selection of maintenance therapy in patients with OC.

Scientific Novelty:

1. For the first time, a clinical and molecular analysis of the frequency of somatic BRCA1/2 mutations was performed in patients with high-grade serous ovarian carcinoma.
2. The features of clinical and morphological characteristics, treatment response, and survival outcomes depending on BRCA status in patients with OC were investigated.
3. The clinical significance of BRCA status in evaluating the effectiveness of PARP inhibitor therapy was established.

Main Provisions of the Dissertation Submitted for Defense:

1. During the period from 2004 to 2024, the incidence of OC in the RK increased from 10.2 to 12.1 per 100,000 women, corresponding to an 18.6 % increase, while maintaining a low survival rate (20.3 %), which emphasizes the need for further development of a molecular-oriented approach to diagnosis and treatment.
2. BRCA1/2 mutations were identified in 35.4 % of patients with HGSC in the studied cohort, confirming the feasibility of expanding molecular genetic testing.
3. A relationship between the clinical characteristics of the tumor and BRCA status in patients with OC was established, allowing prediction of disease course and optimization of treatment strategy.
4. The use of PARP inhibitors in the treatment of OC was associated with a trend toward improved progression-free and overall survival in patients with BRCA-associated OC.

Practical Significance of the Research Results: The practical significance of the obtained results lies in substantiating the need to expand the use of BRCA testing in patients with OC within the framework of a personalized approach to diagnosis and treatment selection. The developed recommendations for the diagnosis and treatment of BRCA-associated OC have been implemented into the practical activities of oncological institutions and are used in the educational process for training oncologists. Based on the results of the study, 2 copyright certificates were obtained, methodological recommendations were published, and 6 implementation acts were issued.

Personal Contribution of the Doctoral Student: The author independently formulated the aim and objectives of the study, determined the methodological approaches, and developed the study design. Collection, processing, and analysis of epidemiological, clinical, and molecular-genetic data were performed. The author conducted patient surveys, selection of tumor material, molecular genetic analysis using NGS, and interpretation of BRCA1/2 testing results. Statistical analysis, generalization of the study results, formulation of conclusions, and development of practical recommendations were also carried out by the author. All publications related to the dissertation topic were prepared in co-authorship with the direct participation of the author, while the concept, main content, and design of the works belong to the author.

Conclusions:

1. It was demonstrated that during the period from 2004 to 2024, the RK maintained a consistently high incidence rate of OC (from 10.2 to 12.1 per 100,000 women; +18.6 %), with a tendency toward increased detection at advanced stages (FIGO III–IV). Mortality rates remained stable (4.8 per 100,000 women), highlighting the need for improvement of early diagnostic methods and personalized therapy approaches.

2. The mean age of patients at the time of diagnosis was found to be 54.2 years. The clinical profile was characterized by a predominance of advanced disease stages (FIGO III–IV – 57.1 %) and dominance of the high-grade serous histological subtype (46.0 %). Despite the high coverage of instrumental diagnostic methods (MRI – 93.8%, CT – 83.4 %), a critically low level of molecular genetic testing (13.5 %) and use of targeted therapy with olaparib (0.7 %) was identified. In combination with the high frequency of cytoreductive surgery (67.0 %), these findings characterize the current management features of patients in the studied cohort.

3. The molecular genetic status of 96 patients with serous OC was determined using NGS. The overall frequency of BRCA1/2 gene mutations was 35.4 % (n=34). Among the identified alterations, BRCA1 mutations predominated at 24.0 % (n=23), whereas BRCA2 mutations accounted for 11.4 % (n=11). The high prevalence of BRCA-positive status (every third case) confirms the importance of genetic profiling in patients with serous ovarian carcinoma.

4. It was established that serous OC is diagnosed predominantly at advanced stages (FIGO III–IV) regardless of genetic status; however, the frequency of advanced disease was higher among mutation carriers (93.3 %) compared with the BRCA-negative group (77.5 %). The presence of BRCA1/2 mutations was associated with improved prognosis: the mean overall survival in BRCA-positive patients was 63.5 months, while the time to recurrence was 20.6 months (compared with 58.8 and 15.8 months, respectively, in the group without mutations). The survival advantage appears to be associated with high sensitivity to targeted therapy: in the subgroup of patients receiving maintenance therapy with PARP inhibitors, the mean progression-free survival increased to 22.2 months, exceeding the 15.9 months observed in patients with mutations who did not receive corresponding therapy.

5. Based on the results of the clinical and molecular study, an algorithm for the personalized treatment of patients with OC was developed. The algorithm is based on the findings of the present study and is consistent with the current recommendations of the United States National Comprehensive Cancer Network (NCCN Guidelines®, Version 2025) for molecularly guided OC treatment. The algorithm includes cytoreductive surgery, determination of BRCA1/2 status using NGS, administration of platinum-based chemotherapy, and the evidence-based use of maintenance therapy with PARP inhibitors in patients with identified BRCA mutations.

6.

Approbation of the Dissertation Results: The main provisions and results of the dissertation research were presented at international scientific and practical conferences and forums, including the Asian-American Symposium “Treatment of Gynecologic Tumors: Modern Approaches” (Almaty, 2023); the XIV Congress of Oncologists and Radiologists of the CIS and Eurasian Countries (Dushanbe, 2024); the International Forum “KazONCO: Oncourology. Oncogynecology” (Almaty, 2025); the Best of ASCO Kazakhstan 2025 Conference (Almaty, 2025); as well as at the extended meeting of the Department of Oncology with the Course of Radiology at the Kazakhstan-Russian Medical University (Almaty, 2026).

Publications Related to the Dissertation: A total of 9 scientific publications related to the dissertation topic have been published, including: 1 article published in an international peer-reviewed scientific journal indexed in the Scopus and Web of Science Core Collection databases (Q2, percentile – 56 % at the time of publication), 4 articles published in scientific journals recommended by the Committee for Quality Assurance in Science and Higher Education of the Ministry of Science and Higher Education of the RK, and 4 publications presented in the proceedings of international scientific and practical conferences and other scientific editions. Based on the results of the study, 1 methodological recommendation was developed and 2 copyright certificates were obtained.

Volume and Structure of the Dissertation: The dissertation is presented in 136 pages of typed text and is structured into the following main sections: introduction, literature review devoted to modern approaches to the diagnosis and treatment of OC, description of research materials and methods, chapters presenting the results and their discussion, conclusion, findings, practical recommendations, references, and appendices. The illustrative material includes 19 tables, 32 figures, and 6 appendices. The bibliography contains 107 references presented in both Russian and foreign languages.