ABSTRACT

of the dissertation work by Gassanov Ziyo Bakhshievich on the topic
"Optimization of diagnostics of aggressive forms of prostate cancer",
submitted for the degree of Doctor of Philosophy (PhD) in the specialty
6D110100 – Medicine

Relevance of the research topic

Prostate cancer (PCa) is currently one of the most significant medical and social challenges in male oncology. According to the Globocan project of the International Agency for Research on Cancer (IARC, WHO), this disease ranks second among all malignant neoplasms in men – surpassed only by lung cancer and is the sixth leading cause of cancer-related mortality (Bray F., Global Cancer Statistics 2022: GLOBOCAN). The scale of its spread is striking: in 2022 alone, approximately 1.5 million new cases of prostate cancer were recorded worldwide, and the upward trend in incidence continues.

The epidemiological profile of prostate cancer shows pronounced geographic variation. The highest incidence rates are observed in industrially developed countries – primarily in North America, Northern and Western Europe, as well as Australia and New Zealand – where the figures reach, and often exceed, 70 cases per 100,000 men. In contrast, in several countries of Asia and North Africa, the frequency of diagnosed cases is significantly lower and generally does not exceed 25 per 100,000 male population.

Before the introduction of the screening program in the Republic of Kazakhstan, prostate cancer ranked only 14th in the overall structure of oncological morbidity and 15th among the causes of cancer-related mortality. The incidence and mortality rates were merely 3.7 and 2.1 cases per 100,000 population, respectively, while the mortality-to-incidence ratio reached 56.8%. This situation indicated that, despite the relatively low number of newly registered cases, lethality among diagnosed patients remained extremely high, reflecting late-stage detection and limited therapeutic options available at that time (Umurzakov K.T., Shalgumbayeva G.M., Kaidarova D.R., 2022).

The obtained data suggest that the prostate cancer screening program implemented in Kazakhstan from 2013 to 2017 did not lead to the expected reduction in mortality, while incidence trends remained unstable. The absence of a screening effect may reflect several systemic healthcare issues: insufficient standardization of diagnostic protocols, limited availability of modern imaging and molecular diagnostic methods, as well as heterogeneous treatment approaches across different regions of the country. The identified interregional differences in incidence and mortality further point to disparities in the quality of medical care.

Particular concern arises from the lower five-year survival rates among Kazakhstani patients with prostate cancer compared to international data, which may be associated with late-stage diagnosis, insufficient oncologic vigilance at the primary care level, and the limited implementation of personalized therapeutic strategies. Taken together, these factors underscore the need to revise existing programs for early detection and treatment of prostate cancer, as well as to conduct a comprehensive analysis of clinical practices in the country's onco-urological centers in order to optimize patient pathways and improve clinical outcomes (Umurzakov K.T., Shalgumbayeva G.M., 2022).

In Kazakhstan, the association between prostate cancer incidence and ethnicity has not been thoroughly investigated previously. This study retrospectively included 7,082 patients diagnosed with prostate cancer during the period 2015-2019. In analyzing the cohort, the distribution of patients was stratified by ethnicity (Slavic group, representatives of Central Asian nationalities, and others) and by age categories. The results showed that the highest incidence of prostate cancer was observed among men of Slavic origin, with a statistically significant predominance in the 60-69 year age group. The mean age at diagnosis in the total sample was 69 years. Stage II disease was the most prevalent, and adenocarcinoma was the most frequently identified morphological type (97.4%). These findings indicate the need to strengthen measures for early disease detection in high-risk groups and to adapt screening programs with consideration of ethnic characteristics (Gassanov Ziyo, Kaidarova Dilyara, Ismailov Zhumagali, 2020).

Studies of hereditary mutations are well established in breast cancer, ovarian cancer, and colorectal cancer; however, similar research has not previously been conducted in the male population of Kazakhstan with respect to prostate cancer, which underscores the high relevance of the present study.

Moreover, a thorough analysis of the diagnostic and treatment strategies for aggressive and advanced forms of prostate cancer used in Kazakhstan is necessary in order to reduce mortality.

Purpose of the study:

To improve early diagnostics of aggressive forms of prostate cancer in the Republic of Kazakhstan.

Research objectives:

1) To analyze the distribution of aggressive forms of prostate cancer among newly diagnosed patients in Kazakhstan, considering the country's diverse ethnic groups.
2) To perform a comprehensive analysis of clinical and morphological characteristics that influence the prognosis and progression of prostate cancer.
3) To conduct a cohort study of BRCA1 and BRCA2 mutations in patients with aggressive forms of prostate cancer.

4) To develop a diagnostic algorithm for identifying aggressive forms of prostate cancer.

Research methods:

This dissertation was carried out within the framework of the grant-funded project "Development of New Molecular-Genetic Methods for Preclinical Diagnostics of Aggressive Forms of Prostate Cancer, 2018–2020" (Grant No. AR05135402).

Clinical, instrumental, genetic, survey-based, and statistical methods were employed.

Data processing and analysis were performed using SPSS Statistics v.15 (SPSS Inc., Chicago, IL, USA). Categorical variables were described using absolute and relative frequencies, and comparisons between groups were conducted using the χ^2 test with a statistical significance level of $p<0.05$. For quantitative variables, the mean (M) and standard deviation (SD) were calculated.

Object and subject of the study:

The present study was conducted in two stages – retrospective and prospective.

The retrospective part of the study aimed to analyze the epidemiological, clinical, and molecular-genetic aspects of aggressive forms of prostate cancer (PCa) in Kazakhstan, taking into account regional and ethnocultural characteristics. A large dataset from 2013-2019 was used, including:

- 84 regional oncology reports (Form No. 7) for assessing primary PCa incidence.
- 9,595 individual medical notifications (Form No. 090/u) on newly diagnosed PCa cases.
- A database of 2,577 patients who died within the first year after diagnosis (based on Form No. 035).
- Official regional demographic indicators from the Agency for Statistics of the Republic of Kazakhstan.
- Results of national prostate cancer early detection programs (2013-2017), provided by Medinform LLP from the "Polyclinic" database.

The prospective analysis included 157 participants, divided into two key groups: 107 patients with a confirmed diagnosis of PCa and 50 men in the control group who had benign prostatic diseases and no oncological history.

The first subgroup consisted of men with aggressive forms of the disease – tumors classified as high-risk for progression according to the d'Amico classification, as well as castration-resistant variants of PCa. The second subgroup included patients with tumors of moderate or low risk of progression.

The formation of the control cohort was carried out on the basis of thorough and comprehensive evaluation. It included laboratory and instrumental methods: determination of prostate-specific antigen (PSA) levels, calculation of the Prostate Health Index (PHI), transrectal ultrasound (TRUS), and, when clinically indicated, multiparametric prostate biopsy and/or magnetic resonance imaging (MRI) with PI-RADS scoring. Malignant prostate neoplasms were excluded in all men in the control group.

The inclusion criteria were: age over 45 years, provision of written informed consent, and willingness to supply information regarding family cancer history to assess hereditary predisposition. All participants completed a standardized questionnaire that included questions about cases of malignant tumors among close relatives.

The men were aged 51 to 92 years. Following the comprehensive evaluation, the patients were divided into the following groups:

- Group 1 (n =58): patients with aggressive prostate cancer (adenocarcinoma; tumors classified as high-risk for progression according to the d'Amico classification, as well as castration-resistant forms of PCa).
- Group 2 (n=49): patients with moderately aggressive prostate cancer (adenocarcinoma).
- Group 3 (n=50): patients with benign prostatic hyperplasia (BPH).

The mean age of participants was 71.5 ± years.

Pathogenic BRCA1 (5382insC and 185delAG) and BRCA2 (617delT) mutations were assessed in all 157 participants.

The main theses of the dissertation submitted for defense:

1. To investigate the ethnic characteristics of prostate cancer (PCa) distribution in Kazakhstan, an analysis was conducted on patients diagnosed between 2013 and 2019. The data were obtained from the Unified Cancer Registry (EROB), ensuring representativeness of the sample and high reliability of the results. All cases were classified into three major ethnic categories: European nationalities, Asian populations (including Kazakhs), and Caucasian ethnic groups. For the first time, a comprehensive epidemiological assessment of aggressive forms of prostate cancer in the Republic of Kazakhstan was performed with consideration of ethnic groups, revealing a statistically significant predominance of aggressive disease among patients of Asian origin compared with European and Caucasian populations.

2. The prognostic significance of clinical and morphological factors—including PSA level, Prostate Health Index (PHI), Gleason score ≥8, perineural invasion, and lymphovascular invasion—has been scientifically substantiated as independent predictors of adverse clinical course and reduced survival in patients with PCa.

3. For the first time in the Kazakhstani population, a cohort analysis of BRCA1/2 gene mutations was conducted, demonstrating their strong association with aggressive clinical and morphological forms of PCa, thereby confirming the need for genetic testing in high-risk patients.

4. An algorithm for the early diagnosis of aggressive forms of PCa has been developed, integrating clinical and morphological assessment, multiparametric MRI, and BRCA1/2 genetic testing. This approach enhances the accuracy of risk stratification and optimizes patient management pathways.

The proposed algorithm has been implemented in clinical practice at oncology centers (implementation acts), resulting in improved early detection rates of

aggressive PCa and providing a basis for national recommendations on personalized oncological diagnostics.

Description of the key findings of the study

A comprehensive analysis of the clinical, morphological, and molecular-genetic characteristics of patients with aggressive forms of prostate cancer in the Republic of Kazakhstan was conducted. The study established that:

Based on the analysis of patients with newly diagnosed prostate cancer, clear ethnic differences in disease patterns were identified: a higher frequency of aggressive forms was characteristic of individuals of European origin, whereas Asian patients tended to present at a younger age and exhibited more pronounced tumor aggressiveness.

Clinical and morphological indicators, including PSA levels > 20 ng/mL, Gleason score ≥ 8, and stages T3–T4, were significantly associated with poorer survival outcomes ($p < 0.05$).

Genetic testing using next-generation sequencing allowed determination of the frequency and spectrum of BRCA1/2 mutations. BRCA2 mutations were found to be the most significant, demonstrating strong associations with poor tumor differentiation and unfavorable prognosis.

An improved diagnostic algorithm for aggressive prostate cancer was developed, integrating clinical data, multiparametric MRI (mpMRI), morphological criteria, and BRCA1/2 mutation analysis.

Implementation of this algorithm in the practice of onco-urological centers enhances the accuracy of early detection of aggressive prostate cancer and optimizes patient management pathways.

Scientific novelty of the work

1. This study represents the first large-scale project in Kazakhstan dedicated to a comprehensive analysis of the prevalence and molecular-genetic characteristics of aggressive forms of prostate cancer (PCa), taking into account the ethnocultural diversity of the male population.

The work generated new, previously unavailable data on differences in the frequency of aggressive PCa variants among representatives of various ethnic groups. These findings have substantial practical value, as they provide a foundation for the development of targeted screening initiatives and early diagnostic programs tailored to high-risk populations and aligned with ethnic patterns of disease prevalence.

2. A comprehensive analysis of clinical, morphological, and molecular-genetic factors associated with an unfavorable prognosis and aggressive disease course in PCa was performed.

3. The novelty of the findings lies in determining the prevalence of BRCA1 and BRCA2 gene mutations among different population groups and identifying their association with aggressive PCa in Kazakhstan. These data will support the development of personalized PCa screening approaches and improve early detection of aggressive disease, offering significant socio-economic benefits.

4. Moreover, the study established a clear association between the presence of pathogenic and likely pathogenic BRCA1/2 mutations and several clinical and

morphological characteristics of aggressive PCa, including disease stage, prostate-specific antigen (PSA) level, Gleason score, and extent of metastatic involvement. This finding opens new opportunities for implementing personalized approaches in diagnosis, prognosis, and selection of optimal therapeutic strategies for individual patients.

Practical significance of the study:

1. Recommendations have been developed for risk stratification of aggressive forms of prostate cancer (PCa), as well as for personalized screening and therapy in the Republic of Kazakhstan, including prevention of complications associated with prostate biopsy.

2. Assessing the prevalence of aggressive PCa based on clinical, morphological, and molecular-genetic data allows forecasting the need for pharmacological and antitumor therapies and justifies the establishment of a multidisciplinary team—including a urologist, oncologist, geneticist, and other specialists—for dynamic monitoring and comprehensive management of PCa patients.

3. The findings are expected to improve the current state of early PCa detection in Kazakhstan, which represents an important socio-economic challenge.

4. The results have high practical significance: they can be used in the development of national clinical guidelines, design of algorithms for early diagnosis and prognostic stratification, as well as in defining indications for targeted therapy and genetic counseling of relatives.

Thus, this study makes a substantial contribution to the advancement of molecular oncourology in Kazakhstan and provides a scientific and methodological basis for enhancing the effectiveness of management of aggressive PCa and improving patient survival outcomes.

Personal contribution of the doctoral candidate:

All results presented in this dissertation and possessing scientific novelty were obtained personally by the author. The author personally collected the clinical material, processed and analyzed the data, interpreted the findings, and described the results with formulation of conclusions (Appendix A). The study results have been implemented in the practical activities of oncology centers in the Republic of Kazakhstan (Appendix B). The author has also prepared and published articles, patent descriptions, as well as the manuscript of the present dissertation.

In accordance with the dissertation topic, a methodological guideline entitled “Complications Associated with Prostate Biopsy and Their Prevention” was developed and approved (Appendix C).

The author obtained a utility model patent: “Method for Predicting the Risk of Developing Aggressive Forms of Prostate Cancer” №5964 (Appendix D).

Conclusions:

1. Analysis of the epidemiological structure of prostate cancer (PCa) incidence in the Republic of Kazakhstan revealed clear ethnic differences. The

highest proportion of registered aggressive PCa cases was observed among men of European origin (57.4-66.2%), with a mean age of 70.6 years. In contrast, among men of Asian origin (40.7%), tumors were more frequently diagnosed at a younger age (mean age 64.8 years) and at later stages, which is associated with a poor prognosis. For individuals of Caucasian descent, the mean age was 70.2 years, and incidence rates fluctuated significantly – from 1.3% to 2.8% in different years – reflecting statistical instability due to the small population size.

2. Integration of clinical and morphological data with imaging results (transrectal ultrasound, multiparametric MRI, PET-CT using radiopharmaceuticals), as well as laboratory indicators (PHI, total and free PSA, PSA density, PSA velocity, etc.), allowed estimation of the likelihood of aggressive PCa, with higher values indicating a more aggressive tumor course and worse survival prognosis. In 100% of aggressive tumors, the PHI index was ≥25, which can predict unfavorable survival outcomes in PCa. Implementation of a PHI threshold ≥30 correlated with the probability of detecting aggressive PCa in more than 20% of the male population. The most prognostically unfavorable factors were PSA levels above 20 ng/mL, Gleason score ≥8, and the presence of perineural and lymphovascular invasion. These parameters were significantly associated with higher rates of metastatic progression and reduced overall and recurrence-free survival.

3. Genetic testing effectively identified aggressive forms of PCa in a cohort analysis of patients with a positive family history, particularly with mutations NM_000059.4:c.7008-2A>G (rs81002823) in the BRCA1 and BRCA2 genes. The use of next-generation sequencing (NGS) technologies for clinically significant mutation detection allows more accurate prediction of disease course and determination of patient management strategies compared with PCR-based methods.

4. Based on these findings, a clinical diagnostic algorithm for aggressive PCa, incorporating the detection of pathogenic BRCA1 and BRCA2 mutations (“Diagnostic Algorithm for Aggressive Prostate Cancer Considering BRCA Mutations”), was proposed and implemented. This approach integrates epidemiological, clinical, and molecular-genetic data, enabling the identification of aggressive forms in 25% of men, facilitating personalized decision-making, and improving the effectiveness of early detection.

Approbation of the dissertation results:

The main findings and conclusions of the dissertation were presented at the following scientific events:

- The section of young scientists on the topic "Possibilities of preclinical diagnostics of aggressive prostate cancer" of the ROOU at the XIV congress in Moscow on October 3-4, 2019.
- Oncourology section on the topic: “Modern aspects of prostate cancer diagnostics” VII Congress of Oncologists and Radiologists of Kazakhstan, Nur-Sultan October 17-18, 2019

- Oncourology section on the topic: "Prostate cancer. Diagnostics" I CENTRAL ASIAN CONGRESS OF UROLOGISTS CACU (Central Asia Congress of urology) October 25-26, 2019 Almaty

- Oncourology section on the topic: "Prostate cancer diagnostics. Comparative analysis of transrectal multifocal biopsy from 8 and 12 points, importance in detecting early prostate cancer" December 10-11, 2020 in honor of the 60th anniversary of KazIOR. International conference "Oncology of Kazakhstan. Yesterday. Today. Tomorrow".

- Oncourology section on the topic: "Prostate cancer diagnostics issues" Conference on modern diagnostic and treatment options for genitourinary tumors July 2, 2021 Almaty

- Oncourology section on the topic: "Comparative analysis of transrectal multifocal biopsy from 8 and 12 points, importance in detecting early prostate cancer" Own experience.

- Scientific and Practical Conference "Urology of Kazakhstan, from history to prospects" May 13, 2022 Almaty

- Oncourology section on the topic: Comparative analysis of transrectal multifocal biopsy from 8 and 12 points, importance in detecting early prostate cancer" XIII Congress of oncologists and radiologists of the CIS countries ADIOR April 28, 2022 Kazakhstan Nur-Sultan.

Publications on the topic of the dissertation

Based on the dissertation materials, 16 publications have been produced, including:

- 1 article with an impact factor, indexed in Scopus Q2 and Q3, Web of Science Core Collection, and in the Russian Science Citation Index (RSCI);
- 6 articles in journals recommended by the Committee for Quality Assurance in Science and Higher Education of the Ministry of Education and Science of the Republic of Kazakhstan;
- 6 abstracts presented at international and 1 at national scientific-practical conferences (Russia, CIS countries, Kazakhstan);
- 1 article in other scientific journals;
- 1 utility model patent: “Method for Predicting the Risk of Developing Aggressive Forms of Prostate Cancer” №5964;
- 1 methodological guideline: “Complications Associated with Prostate Biopsy and Their Prevention.”

Implementation:

The results of this research have been implemented in the practical activities of oncology centers in the Republic of Kazakhstan. Implementation acts are attached.

Volume and structure of the dissertation:

The dissertation comprises 149 pages of typescript text and includes 24 figures and 23 tables illustrating the main findings. The bibliography contains 219 references.