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Modern Molecular Diagnostic of Prostate Cancer in Young Men

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ABSTRACT

Prostate cancer (PCa) is a public health problem. Among malignant neoplasms, it is the second most common (in 105 out of 185 countries of the world) and the main cause of death from cancer in men from 46 countries. In some cases, pathology is verified in men under 50 years of age, including at the stage of the metastatic process. Common methods of diagnosis of prostate cancer, including assessment of the PSA level, are not always accurate, and the algorithm for their use has not been finalized.

The Purpose of the Study: To determine a set of new molecular-genetic and histological research methods for early diagnosis of prostate cancer in young men (under 50 years of age).

Materials and Methods: Micro-preparations were studied and an IHC study of 10 samples of patients with prostate cancer aged 40-51 years after radical surgical treatment was performed. The tumor stages of the subjects (pT1cN0M0-pT2cN0M0), PSA level (3.5-9.86 ng/ml), malignancy criteria (4 – ISUP-1, 4 – ISUP-2, 2 – ISUP-3). All patients underwent robot-assisted radical prostatectomies.

Results: Reviewing the micropreparations by a third-party morphologist, all the ISUP criteria of the samples obtained were confirmed: a tumor in the apex of the gland was absent in 1 probe (10%), both lobes of the gland were represented in all samples, without perineural lymphovascular invasion and urethral lesions. The positive board of surgical resection – in 1 case (0.2 cm). During the IHC it was found: *Ki*-67 in 1-5% of samples, *b-catenin* – 3 points with membrane staining up to 100%, *e-cadherin* – from 1 to 3 points (pT1cN0M0 ISUP-1). Mutations of *EGFR*, *TP-53* and *BCL*-2 were not detected. Losses of heterozygosity by *BRCA2* – 1 case (pT2cN0M0 ISUP-2), RB-1 – in 1 (pT2aN0M0 ISUP-3), PTEN – in 2 samples (pT2cN0M0 ISUP-1 and ISUP-2).

Conclusion: A preliminary complex of molecular genetic and histological markers for early diagnosis of prostate cancer has been determined. Problems of early diagnosis are associated with a lack of sampling among young men, as well as the high cost of the proposed genetic studies.

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Relevance

Prostate cancer (PCa) is a major public health problem around the world [1]. In 2018, 1.3 million new cases of the disease and 359 000 deaths were registered worldwide, PCa is the second most common, one of the most inherited cancers and the fifth leading cause of death from malignant neoplasms (MN) in men [2,3]. It is the most common type of MN in men in more than half of the countries in the world (105 out of 185) and the leading cause of cancer death in 46 countries. The incidence of PCa has increased in men aged 15 to 40 years, with an increase of up to 2% per year since 1990 ($p < 0.01$) [4]. In the USA, locally advanced prostate carcinoma is more than 6 times more common in patients under the age of 50 than in probands over the age of 50. The overall 5-year survival rates for patients with PCa aged 40 to 80 years ranged from 95% to 100%, between 15 and 24 years - 30%, and in the ranges of 20-29 years and 25-34 years - 50% and 80%, respectively.

Studying information from scientific literature publications on the peculiarities of early diagnostics of PCa in young men (PubMed, CrossRef and Scopus databases for 1997-2021), data on the probable causal relationship of a number of factors potentially influencing the development of this MN were obtained.

One of the key factors is a burdened hereditary history. Rare mutations caused by DNA repair affect the stage of PCa, risk of detection at screening, cancer mortality and response to treatment [5-9]. According to the data of a multicenter study [10], it has been proven that in the presence of familial prostate cancer (PCa) and breast cancer (BCa) the risk of prostate cancer development increases 2-3 times. Genetic alterations in *BRCA2, CHEK2, ATM*, *HOXB13* and *BRCA1* genes are common in 4.6% of cases with local and in 11.8-16.2% with metastatic PCa.

One of the key factors predisposing to the development of PCa is a burdened hereditary history. Rare mutations caused by DNA repair affect the stage of PCa, risk of detection at screening, cancer mortality and response to treatment [5-9]. According to the data of a multicenter study, it has been proven that in the presence of familial prostate cancer (PCa) and breast cancer (BCa) the risk of prostate cancer development increases 2-3 times [10]. Genetic alterations in *BRCA2, CHEK2, ATM, HOXB13* and *BRCA1* genes are common in 4.6% of cases with local and in 11.8-16.2% with metastatic PCa.

The study, conducted from 2014 to 2020 by a group of authors led by Clements M.B. (2022), involved 20 323 men with verified prostate cancer [10]. In 22% (n=4524) of the subjects studied, there was no burdened heredity for this disease, in the remaining patients, detailed family information was revealed only in 29.2% of cases. In one first-line relative with prostate cancer, the probability of developing high-grade carcinoma was determined to be 1.77 times higher than the normal threshold (95% CI1.57-2.0, p <0.001). The influence of multiple first-line relatives with PCa on the chance of developing carcinoma was determined as a ratio of 1.92:1.54. When studying the influence of second-line relatives on the development of prostate cancer, a positive anamnesis exceeded the risk of developing pathology (95% CI 1.07-1.77, p = 0.011). The presence of a first-line relative with breast cancer was also associated with the development of prostate cancer (95% CI 1.01-1.67, p= 0.040). When adjusted for the family history of PCa, the relationship between family history of these two tumors was clinically insignificant (95% CI, 0.96-1.60, p=0.093). A statistically significant relationship between burdened heredity and the level of prostate-specific antigen (PSA) was not been established [10].

To date, there is no generally accepted strategy for PCa screening described in world practice. To determine the risk of developing prostate cancer based on the results of PSA screening, the PROBASE randomized trial from 2014 to 2019, 46 642 men aged 45 years were divided into 3 groups according to the level of PSA: low (<1.5 ng/ml), intermediate (1.5-2.99 ng/ml) and high (≥3 ng/ml) risk [11]. When PSA ≥3 ng/ml, MRI and prostate biopsy were recommended. Half of the men (23 341) were offered PSA screening and the rest (23 301) - digital rectal examination (FRE), with delayed screening upon reaching the age of 50. Of the 21 301 screening participants, 1.5% (344) were in the high-risk group for PCa. With repeated PSA measurement, a high risk was confirmed in 186 men (0.8%), of whom 120 (64.5%) underwent prostate biopsy. In total, 48 cases of prostate cancer were detected (overall prevalence of 0.2%). PSA blood test in men at a young age was not effective in terms of early detection of PCa, in accordance with the results of the study.

Numerous studies are being conducted worldwide to investigate new biomarkers of PCa. This will not reduce the need for invasive diagnostic methods, but can be used for early and accurate diagnosis, which will simplify the choice of appropriate treatment, reduce the likelihood of side effects, as well as the cost of therapy [12].

According to the data of domestic and foreign publications, the authors analyzed information about changes in the structure of genes (*BRCA1, BRCA2, Ki 67, BCL-2, P53, b-catenin, E-cadherin, EGFR, RB1, PTEN*) with prostate cancer in men older than 50 years [13-20]. There is very little information in the medical literature regarding the examination of young patients (40-50 years of age) with suspected PCa.

Common methods of diagnosing prostate cancer in population, including the assessment of serum PSA levels, are not always accurate, and the algorithm for their use has not been finalized. It is advisable to optimize the early diagnosis of PCa in men aged 40-50 years, taking into account risk factors for the development of the disease, based on the morphological features of cellular and genomic composition, reproductive characteristics of a young man. These issues are of great medical and social importance in connection with the examination of the able-bodied part of the population of reproductive age.

The Purpose of the Study

To determine a set of new molecular-genetic and histological research methods for early diagnosis of PCa in young men (under 50 years of age).

Materials and Methods

The histological structure of micropreparations of 10 patients aged 40 to 50 years with verified PCa after radical surgical treatment in one clinic (I.M. Sechenov First Moscow State Medical University, Ministry of Health of Russian Federation) for 2016-2019 was studied. All patients underwent robot-assisted radical prostatectomies without complications of the immediate postoperative period. A retrospective analysis of patients' medical records was performed to assess their somatic pathology: 20% of patients were found to have comorbidities (arterial hypertension, aortic atherosclerosis, 2-stage atrioventricular block, pacemaker), the remaining patients were somatically healthy. Preoperative PSA levels (3.5-9.86 ng/ml), malignancy criteria (4 - ISUP-1, 4 - ISUP-2, 2 - ISUP-3), tumor stage (3-pT1cN0M0, 4-pT2aN0M0, 3-pT2cN0M0) were studied. Immunohistochemical (IHC) examination and molecular genetic analysis of postoperative material from each patient was performed. The analysis for the presence of mutations by the IHC method in the genes: *Ki 67*, *P53*, *b-catenin, E-cadherin, BCL-2*, and molecular genetic analysis: *BRCA1, BRCA2, EGFR, TP53, RB1, PTEN* was conducted.

The study was conducted within the framework of the joint research program "Opportunities for early detection of prostate cancer in young men" of two state medical universities (FSFEI HE "St. Petersburg State Pediatric Medical University" of the Ministry of Health of the Russian Federation and FSAEI HE "I.M. Sechenov First Moscow State Medical University" of the Ministry of Health of the Russian Federation).

Results

Comparison of parameters in patients of the study group, considering the distribution of tumor cases in accordance with the criteria of histological classification and international clinical classification TNM, is shown in Figure 1.

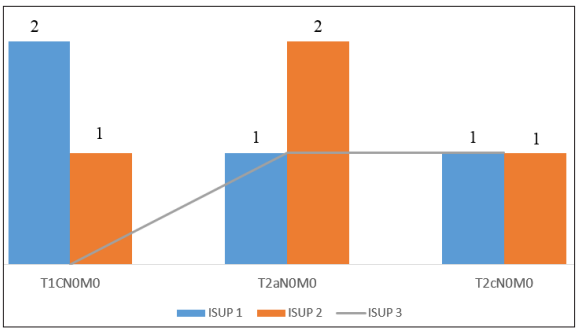

Figure 1: Comparison of Patients in the Study Group According to TNM and ISUP

When reviewing the micrographs by a third-party morphologist, all the ISUP criteria were confirmed: tumor at the apex of the gland was absent in 1 specimen (10%), both lobes of the gland were represented in all specimens, without perineural lymphovascular invasion or urethral lesions. The positive edge of surgical resection is in 1 case (0.2 cm).

Additionally, when performing IHC by a specialist morphologist, it was found: Ki-67 was detected in all samples according to the degree of staining from 1-5% (4 – 1%, 1 – 2%, 1 – 4%, 4 – 5%), b-catenin – 3 points with 100% membrane staining in all patients, e-cadherin – from 1 to, maximum, 3 points with staining from 50 to 100% in all patients (50% - 1 ISUP-1 T1cN0M0; 70% - 2 ISUP 1 – 1 T2cN0M0, 1 T2aN0M0, 1 ISUP 3 - T2cN0M0; 80% - 1 ISUP 2 – 1 T1cN0M0; 100% - 1 ISUP 1 - T1cN0M0, 3 ISUP 2 – 1 T2cN0M0, 2 T2aN0M0, 1 ISUP 3 – T2aN0M0). Mutations of BRCA1, EGFR, TP-53, P-53 and BCL-2 were not detected. Losses of heterozygosity by *BRCA2* were verified in 1 case pT2cN0M0 ISUP-2, by *RB*-1 – in 1 case pT2aN0M0 ISUP-3, by *PTEN* – in samples of 2 patients pT2cN0M0 ISUP-1 and ISUP-2. No mutations were identified in 20% of patients with concomitant pathology (arterial hypertension, aortic atherosclerosis, atrio-ventricular block II, pacemaker).

Interpretation

A number of large studies have shown a negative prognostic value of the loss of heterozygosity of *RB1*, *TP53* and *BRCA1/2*: loss of heterozygosity of the *PTEN* gene occurs in 20% of cases in post-radical prostatectomy PCa specimens and in 50% of castration-resistant tumors [21-24]. The presence of *PTEN* aberration is associated with unfavorable prognosis, in particular an increased risk of biochemical relapse. Determination of the status of this gene is recommended for patients with localized and locally advanced PCa for risk stratification of relapse/prognosis and personalization of surveillance tactics [25].

The presence of *PTEN* aberration in biopsy samples with grade I group (Gleason 6=3+3) is associated with carcinoma progression and a change in the Gleason pattern in tumor material after radical prostatectomy, up to grade IV (Gleason 8=4+4; 3+5; 5+3).

BRCA2 mutations occur in 3% of cases of prostate cancer, and in metastatic disease – in 5% of cases [21]. The presence of mutations in the *BRCA2* gene is an indication for the use of the olaparib PARP inhibitor in patients with metastatic castration-resistant prostate cancer [26]. The presence of TP53 gene aberration is associated with an unfavorable prognosis, and loss of *RB-1* gene heterozygosity occurs in ~15% of cases of localized carcinoma [21,23,27]. This aberration is also much more common in castration-resistant PCa and in tumors with neuroendocrine differentiation, but this is a separate topic for study and discussion [21]. A number of studies have shown that the presence of *RB1* aberration is associated with an unfavorable prognosis [21, 23]. In general, in IHC studies and molecular genetic analysis, it is advisable to use a sequencing panel, especially in patients younger than 50 years.

Prediction of PCa genetic risk is one of the key objectives to reduce prostate cancer mortality through early detection and prevention [28]. Rare pathogenic mutations, especially in genes responsible for repairing damaged DNA sites (*BRCA2*), increase the risk of developing PCa by 2-8.6 times and lead to the development of a more aggressive form of the disease. Common genetic variants can be combined into a genetic risk scale (GRS). With high GRS (20-25% of the population), the risk of developing prostate carcinoma is 2-3 times higher than with the average. With a very high GRS (1-5% of the population), the variant of the development of prostate cancer increases by 6-8 times. It is difficult to separate genetic predisposition from ethnicity, social characteristics and health status to understand the cause of cancer development.

Given the multifactorial nature of prostate cancer development, the decrease in local immune regulation in inflammatory diseases of the urinary tract cannot be ignored. In a retrospective study, it was found that patients with prostate cancer had a history of more frequent episodes of urinary tract inflammation [29]. Risk factors were: pyelonephritis - 2.3 (95% CI = 1.36-3.88), prostatitis - 2.04 (95% CI = 1.03-4.05), cystitis - 4.02 (95% CI = 2.11-7.66).

Data from some studies indicate that genetic predisposition to the development of PCa is not a factor that determines an unfavorable outcome of the disease [30]. A healthy lifestyle (normal weight, regular physical activity, smoking cessation and a healthy diet) allowed patients with a high genetic risk of prostate carcinoma to reduce the number of deaths and the development of common forms of the disease. Among men from the high-risk group of prostate cancer, adherence to a healthy lifestyle resulted in fewer deaths (HR, 0.55; 95% CI, 0.36-0.86). At the same time, adherence to a healthy lifestyle was not associated with a reduction in the overall risk of developing this aggressive tumor, which is important for modeling the algorithm for early PCa diagnosis.

In recent years, tumor molecular characteristics have gradually been integrated into the clinical management of patients with localized prostate cancer, in which high genomic heterogeneity is observed [31]. Recent advances in treatment personalization lead to an increased need for genomic profiling: gene expression analyses may influence clinical decisions regarding active follow-up or adjuvant therapy for localized and metastatic forms of prostate cancer. Therefore, the expansion and continuation of the research described in this paper is extremely important for clinical oncology.

In clinical practice, when treating patients with prostate cancer, it is necessary to understand the relevance of identifying hereditary (embryonic) and acquired (somatic) mutations, which in certain patients affect the risk of developing prostate cancer and its course [32]. In the late stages of the disease, mutations in homologous recombination repair genes (for example, *BRCA1, BRCA2, ATM, CHEK2, PALB2*) suggest chemotherapy with platinum preparations and testing of the enzyme poly ADP-ribose polymerase (PARP) inhibitors. In turn, microsatellite instability and deficiency of mismatch repair, which can occur with mutations of *MLH1*, *MSH2, MSH6* and *PMS2*, suggest potential vulnerability to PD-1 inhibitors. Genetic testing of the germ line is potentially important in the treatment and assessment of the hereditary risk of developing prostate cancer. Tumor-targeted somatic sequencing can help in making decisions about individual treatment tactics.

The issues of diagnosis and treatment of young men (younger than 50 years) with prostate cancer are of great medical, social and economic importance. The problems of untimely diagnosis in men of this age group are associated with the lack of an algorithm for PCa diagnosis based on the results of PSA level determination. A more detailed analysis of morphological changes in the prostate tissues affected by the tumor can be carried out with a comparative assessment of the results obtained with genomic sequencing data in a cohort of elderly patients (over 65 years old), the most vulnerable

to this tumor. The study of the totality of risk factors for the development of prostate cancer in young, able-bodied patients will make it possible to formulate a diagnostic approach, taking into account personal molecular genetic information.

Conclusion

Molecular genetic analysis and examination of histological samples from patients with verified PCa showed heterogeneous results. Based on the results of the pilot study, the authors plan to increase the sample of patients, compare the obtained data of molecular genetic analysis and IHC with the further fate of patients under the age of 50: with indicators of general and cancer-specific survival, treatment frequency, PSA dynamics, etc. It is supposed to compare the results obtained with the data of the study in the control group (patients with prostate cancer in the age category over 65 years).

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