METABOLIC SYNDROME INFLUENCE ON THE AGRESSIVENESS OF PROSTATE CANCER IN THE KAZAKH POPULATION

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Abstract: The effect of the metabolic syndrome on the course of prostate cancer (PCa) is increasingly becoming the subject of scientific discussion. However, there are practically no data on the clinical phenotype "prostate cancer + metabolic syndrome" (PCa + MS) in the Kazakh population. The study compared the signs characterizing the aggressiveness of prostate cancer in the Kazakh population between two clinical phenotypes: PCa + MS - the main group and PCa-MS - the comparison group. Potential participants of the study were of Kazakh patients with PCa who visited a urologist in oncological centers of Kazakhstan in the second half of 2018. After written consent, data were collected using specially designed questionnaires and a medical card. The differences between the two phenotypes were evaluated using x2 test, Student's test, Mann-Whitney and the relative risk was evaluated. The participants with the PCa + MS phenotype when making diagnosis of PCa were 4.47 years younger ($p < 0.05$), more often had PSA level above 20 ng / ml (41.8% vs 40.9%, $p < 0.05$), more often revealed metastatic form of the disease (57.69% vs 38.84%, $p < 0.05$). A year after radical prostatectomy, patients of the main group were more likely to have a biochemical recurrence of the disease: 4.8% vs 3.7% (relative risk 1.29). The study showed statistically significant aggressiveness of PCa+MS in the Kazakh population. At the same time, the study performed is not a direct evidence, but the results indicate the need to consider the inclusion of the clinical phenotype in PCa definition of prostate cancer for the Kazakh population, which will provide a more active position when monitoring patients with metabolic syndrome.

Keywords: prostate cancer, metabolic syndrome, clinical phenotype, Kazakh population.

Introduction

Prostate cancer is the second most frequent disease and the fifth most important cause of mortality among men from malignant neoplasms in the world [1]. The high PCa prevalence makes it one of the important social problems of our time. The highest prevalence rates of PCa are found in men of African descent in the USA and the Caribbean, which reflects ethnic and genetic predisposition [2]. In the Kazakh population, the role of PCa is not so high, according to the same estimates of GLOBALCAN 2018 in Kazakhstan, the incidence and mortality from PCa is on the third and eighth places respectively [1]. Nevertheless, national studies claim that PCa for Kazakh men is a disease which significance will only increase in the coming years. [3,4] This is due to the increase in life expectancy, urbanization of the population, spread of unhealthy lifestyle habits in the developed countries: insufficient mobility and diet, rich in calories and animal fats, but poor in vegetables and fruits. Given the growing number of substantiated evidence that excessive treatment due to PSA testing is significantly higher than necessary, incurs unreasonable financial, physical and psychological losses, it is necessary to look for alternative approaches to the management of PCa based on its clinical characteristics [5].

MS is a well-known group of cardiovascular risk factors, including arterial hypertension, central obesity, dysglycemia, elevated triglycerides and low cholesterol of high density lipoproteins. A possible relationship between MS and PCa was first described in 2004; several subsequent cohort studies have shown conflicting results. Nevertheless, the effect of the metabolic syndrome on the risk and aggressiveness of prostate cancer is increasingly becoming the subject of scientific discussion [6,7,8]. PCa and MS are widespread in the male population and demonstrate a significant relationship with age, which indicates the presence of common biological processes [9]. Unfortunately, in the available databases of scientific information there are no data on studies regarding the clinical phenotype of PCa + MS in the Kazakh population, this fact underlines the relevance of our study. As a result of the study, we expect to identify additional opportunities for the management of prostate cancer in Kazakhstan.

Currently, there is no way to completely cure prostate cancer, and the success of pharmacology in the development of antiandrogen drugs has not led to a noticeable decrease in mortality. In this regard, the difference between passive and aggressive forms of prostate cancer is a serious problem for diagnosis and treatment. In the case of accumulation of convincing data on the effect of MS on aggression of prostate cancer, it is possible that the practical healthcare of Kazakhstan will receive an additional tool in managing the risk and development of prostate cancer, since MS is a reversible pathophysiological state at the stage before the implementation of the diseases associated with it. The purpose of the study was to study the effect of MS on the course of prostate cancer in the Kazakh population. To achieve the goal, the transverse retrospective nature of the study was determined and secondary data evaluated.

Materials and methods

The study protocol was approved by the ethics committee of the Hospital (Figure 1).

Protocol of the study	
Studied group	
Patients diagnosed with prostate cancer who consulted an oncourologist in the second half of 2018 at least once. n = 5680	
Inclusion / Exclusion Criteria	
• verified diagnosis of C61 (ICD 10) for at least 1 year • Kazakh population • age • PSA level • Gleason biopsy scores • prevalence of the tumor process • risk of PCa (according to NICE) • Progression of PCa one year after RPE or RRT	
Road map	
• recruiting study participants • obtaining written informed consent • filling out a specialized questionnaire • access to personal medical records • entering information on 115 features into the database • assessment and selection of significant features • division of patients into 2 groups between two clinical phenotypes: □ PCa + MS - main group □ PCa-MS - comparison group • assessment of the received data	 n=234 n=121
Conclusions	
Conditional Abbreviations PCa - prostate cancer MS - metabolic syndrome PSA - prostate specific antigen RPE - radical prostatectomy DLT - remote radiation therapy NICE - National Institute for Health and Care Excellence, London, 2014	

Figure 1. Protocol of the study

Development of the database. Data on PCa in the Kazakh male population were used as a material for the study. Potential study participants were identified at the level of regional oncological centers in different regions of Kazakhstan. Each of them was randomly selected from the number of patients with PCa with a disease duration of at

least 1 year, who consulted a urologist during the second half of 2018. Identification criteria also served as self-determination by nationality and biological grandparents on the maternal and paternal side as "Kazakh". Persons meeting the criteria for inclusion in the study signed an informed consent to access to medical information, filled in a specialized questionnaire. As a result, data on 115 variables reflecting socio-demographic, anthropometric characteristics, family history of cancer, anamnesis of chronic diseases lasting for at least 1 year and the drugs used to treat them, clinical characteristics of prostate cancer were obtained. Information was also collected on lifestyle factors (physical activity, smoking, drinking, eating habits). In total, 355 participants were recruited as study participants. On January 1, 2018, 5680 men with prostate cancer were under the supervision of medical oncology centers, 2784 of them were Kazakhs (general population). The study included 355 patients (confidence), thus, with a sampling accuracy of 95%, the error was 5% (p = 0.05).

Identification of patients with PCa was consistent with European clinical guidelines [10]. Participants of the study were stratified by the PCa aggressiveness according to the 2014 NICE classification [11]: high risk - metastatic PCa, and also localized prostate cancer with any or more of the following characteristics: stage of the process T≥T2s; serum PSA levels> 20 ng / ml; results of histological analysis on the Gleason scale ≥ 8; □ medium risk - localized PCa without any signs of high risk and with a stage of the process ≤T2b, PSA 10-20 ng / ml and the result of a histological analysis on the Gleason scale = 7; □ low risk - localized PCa without any signs of high or medium risk.

Identification of MS was carried out according to MS criteria developed by the international federation IDF in 2005, due to which the main sign of MS is abdominal obesity: waist size for men ≥ 94 cm, for women ≥ 80 cm [12]. The presence of at least two of the following criteria was taken into account: • increased triglycerides (TG) level ≥ 1.7 mmol / L or normal TG levels with appropriate therapy; • reduced level of high density lipoprotein cholesterol (HDL-C) <1.03 mmol / L for men and <1.29 mmol / L for women or the normal level of HDL-C with appropriate therapy; • blood pressure (BP) ≥ 130/85 or antihypertensive therapy for previously detected hypertension (AH); • increased plasma glucose ≥ 5.6 mmol / L or the presence of a previously diagnosed type 2 diabetes.

The presence or absence of MS was the main condition for dividing the study participants (355 in total) into 2 groups PCa + MS (main group) and PCa-MS (comparison group). Considering the significant impact of specialized treatment on the MS prevalence in patients with PCa, the main group included patients with manifestations of MS before the PCa diagnosis. Among the compared patients symptoms were identified, evaluated during PCa diagnosis: average age of the group; group average PSA level and specific gravity of participants with PSA level of more than 20 ng / ml; proportion of participants having 8-10 points on the Glisson scale due to histological analysis; specific gravity of localized and metastatic PCa in the group; specific gravity of high and low risk of cancer malignancy (NICE criteria) in the group. Besides, incidence of PCa after radical prostatectomy (RPE) or radical remote radiation therapy (RRR) in a 1 year was estimated. There were no cases of true hereditary cancer among the participants (three or more relatives with PCa or at least 2 relatives with PCa diagnosed before the age of 55).

Statistical analysis. Differences between the two phenotypes were evaluated using x2 test, Student's test, Mann-Whitney test and the relative risk was evaluated.

Results

The studied phenotypes were compared by 10 parameters (Table 1). Clinical features of PCa in the Kazakh population depending on phenotype PCa+MS and PCa-MS.

№	Evaluation criteria	PCa+MS		PCa-MS		p
		abs	%	abs	%	
1.	Number of patients n=355	234	62.92	121	34.08	
2.	Mean age at diagnosis	69.13		73.6		p<0.05
3.	Median PCA value in blood serum	19.5		18.1		P=0.06
4.	Patients with PCA higher than 20 ng/ml at diagnosis	142	41.8	49	40.9	p<0.05
5.	Patients with metastatic PCa	135	57.69	47	38.84	p<0.05
6.	Patients with radical treatment	42	26,6	27	30,1	P=0,37
7.	Biochemical relapse in a year in patients with radical treatment	4	4.8	1	3.7	Relative risk =1.29
8.	Points on Glisson scale in biopsy 8-10	97	41.1	43	36.6	P=0.47
9	Stratification high risk group by NICE	117	50.0	53	44.1	P=0.37
10	Stratification of low risk group by NICE	22	8.2%	20	16.1	P=0.055

At the time of diagnosis, the mean age of patients with PCa + MS was 69.13 years compared to 73.6 years for PCa-MS. Patients with MS had higher mean PSA values than patients without MS, 19.5 and 18.1 ng / ml, respectively. Patients with MS at the time of diagnosis were also more likely to have metastatic PCa, 57.69% and 38.84%, respectively. Radical treatment (RT, RRT) in the main group was less frequent and was more often accompanied by biochemical relapse a year later: 26.6% of the participants underwent radical treatment, 4.8% of them had biochemical relapse one year after radical treatment. In the main group 30.1% received radical treatment, 3.7% had a relapse one year after radical treatment. It is necessary to mention the lack of facts of PCa biochemical recurrence during the first year after radical treatment. The relative risk was 1.29 (95% confidence interval from 0.122 to 13499). The stratification of NICE risk groups showed doubtful (p = 0.055) significance of PCa low risk and the lack of significance of PCa high risk (p = 0.37) at the time of diagnosis in the study groups.

Discussion

The study evaluates the Kazakh cohort with PCa. The results revealed connection between PCa and the presence of MS. The following conclusions are regarded as evidence of this connection.

1. PCa on the background of MS is diagnosed 4.47 years earlier (p <0.05). In a nationwide cohort study, Kim JW et al. obtained a similar result. In particular, the authors noted that a significant number of patients with MS are susceptible to PCa at a relatively

younger age [13]. The same conclusion was made by a team of researchers from Turkey Caliskah S. et all. Their conclusions are: in patients with MS PCa is more often diagnosed, develops at a younger age, at the level of higher PSA indicators, metastases appear earlier and more often [14].

2. PCa on the background of MS has a more aggressive course. Patients in the main group more often had a PSA level of more than 20 ng / ml (41.8% vs 40.9%, p <0.05) and more often had a metastatic form of the disease (57.69% vs 38.84%, p <0,05) at the time of registration. It should be noted that despite the statistically significant frequency of cases with a PSA level of more than 20 ng / ml in the MS + PCa group (main group), the median serum PSA values were less significant (p = 0.06). Probably, for the Kazakh population, the PSA level is not an absolute evidence of the PCa aggressive course, more targeted studies are necessary. Nevertheless, the data received confirm the conclusion of the REDUCE study on the association between a complex of at least three features of MS with aggressive PCa in some cases, regardless of PSA level [15].

3. PCa with MS is more often show relapse (relative risk = 1.29) after the first year after radical treatment (RPE, RRT): 4.8% versus 3.7%. And relapses of the disease are a direct threat to survival. The Italian researchers De Nunzio C et all in a multicenter cohort study also stress this fact [16]. Besides, Coliccia et all, in their retrospective study, noted that even in very low-risk PCa, patients with MS show a higher mortality rate and complication rate after radical treatment [17].

4. PCa on the background of MS is more often detected at the stage of metastasis (p <0.05). Canadian researchers also stressed the problem of untimely detection of PCa in patients with MS having a negative connection with the risk of developing and metastasizing prostate cancer [18]. In the present study, this conclusion can be repeated by the fact that the specific gravity of the initially diagnosed PCa in the metastatic stage with MS was 57.69% versus 38.84% without MS.

5. High prevalence of MS cases of primary diagnosis of PCa in the Kazakh population. The ratio of PCa + MS and PCa-MS as 67.52% and 38.84% suggests a significant role of MS as a risk factor for PCa for the Kazakh population. The predominance of PCa + MS was also described in the study of the Korean population, which showed higher prevalence of PCa among patients with MS [19]. The fact that in the study groups during the initial diagnosis of PCa dubious (p = 0.055) significance of low risk and the lack of significance of high risk (p = 0.37) of the disease according to NICE was found is regarded as a fact indicating possibly more pronounced negative effect of MS on subsequent aggression of PCa, regardless of the degree of initial risk. MS association with the worst results of prostate biopsy and relapse after radical prostatectomy was described by A. Sanchi-Bonet et all [20].

The present study did not confirm the significance of PCa cases having histological conclusion with Gleason scores of 8-10 in MS (p = 0.47). Probably this result is due to the limitations of the study. Nevertheless, it is possible to consider the obtained in the study result as indicating pronounced MS negative influence on the subsequent aggression of PCa, regardless of the initial differentiation of the oncological process. It is in this regard, considering biochemical recurrence of PCa after the first year after radical treatment, the fact of a relative risk of 1.29 was thought to be convincing. PCa is a genetic disease caused by activation of oncogenes and inactivation of tumor suppressors due to genomic

instability. Among the leading causes of genomic instability is MS, which acts as a link for the majority of age-associated diseases, including PCa [21,22].

According to the doctrine of cell biology proliferation, differentiation and death of human cells is regulated by the uniform molecular mechanisms. The development of the most common diseases associated with MS is regulated by the same mechanisms. In the course of its development from a normal to a malignant cell, it acquires new properties, among which self-sufficiency with mitogenic signals (growth signals), which regulate the transition of a cell from a resting state to a proliferative state, is of special significance. Mitogen-activated protein kinases (MAPKs) are integration points for a large number of biochemical signals associated with metabolic syndrome. Being involved in the process of phosphorylation of enzyme transcription factors, they affect the expression of genes, their metabolism, division, morphology and survival. Such participation ensures the effect of MAPK on various cellular processes: proliferation, differentiation, transcription regulation, development [23,24,25]. Thus, probably the influence of MS on aggression of PCa is ensured: aggressive PCa has a genetic component, and this component has a common relationship with MS. This study has a number of limitations, in particular, secondary data are retrospectively evaluated, in addition, the transverse nature does not provide high reliability of the results. Most of MS signs were diagnosed in patients with PCa over 60 years old and have already had the form of a specific disease: type 2 diabetes mellitus, arterial hypertension, coronary heart and / or brain disease. So, in most cases, these diseases were regarded as the main components of MS. Nevertheless, in this case the results were not overestimate, but underestimate, since in some studies the increased risk of PCa in the early stages was described [26, 27].

Despite limitations, our study showed a relationship between MS and PCa in the Kazakh population. Statistically significant differences were obtained between the compared groups. The analyzed data included detailed, in accordance with European recommendations, clinical information on PCa cancer, which allowed to assess the aggressiveness of PCa. MS in the study was determined by specific indicators corresponding to the internationally recognized international classification. Thus, complex metabolic disorders can be a risk factor for the aggressive course of PCa, and efforts to reduce the prevalence of MS can be justified.

Conclusion

The study revealed statistically significant signs of an PCA aggressive course in MS in the Kazakh population. Molecular basis of these associations is still to be understood, but today, MS should be regarded as a driver of PCa aggression. The study is not a direct evidence, but its results stress the necessity to consider the inclusion of the clinical phenotype in the definition of PCa for the Kazakh population, which will provide a more active position when monitoring patients with metabolic syndrome.

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