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POLYAMINES AS NEW POTENTIAL BIOMARKERS FOR DIFFERENTIAL DIAGNOSIS OF PROSTATE CANCER AND ESTIMATION OF ITS AGGRESSIVENESS

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***Background*: Prostate cancer (PCa) is one of the most common malignancies in older men. The study of tissue markers of PCa can provide information about the state of proliferation and apoptosis in tumors, the susceptibility of tumor cells to metastasis and the mechanisms of resistance to therapy, which, in turn, can help predict the course of the disease and develop personalized treatment. Polyamines (PAs) spermine, spermidine, putrescine are of particular interest in terms of PCa tissue markers. *Aim*: To investigate the levels of basic and acetylated forms of PAs in the postoperative samples of malignant and benign tumors of the human prostate and evaluate the possibility of their use for differential diagnosis and assessment of the PCa aggressiveness. *Object and Methods:* 57 postoperative tumor samples from patients with prostate adenocarcinoma of different Gleason score (GS) and clinical stage (T1–T4) and 20 samples of tumors from patients with benign prostate hyperplasia (BPH) were studied. The content of PAs was determined by high performance liquid chromatography. *Results:* Among the studied PAs, the most significant difference between PCa and BPH was observed for spermine (Spm). The level of Spm in PCa samples was 16 times lower than in BPH samples ($p < 0.01$). We did not find a significant dependence of PAs levels, including Spm, on the clinical stage. The association between the Spm level and the GS was established. The indolent (GS6) tumors were characterized by the highest Spm level while in the most aggressive (GS9 and GS10) tumors Spm content was the lowest. *Conclusions:* A sharp decrease in Spm levels is probably a characteristic feature of prostate malignant tumors. The obtained results indicate an association of Spm levels in tumors with the GS. This may indicate Spm involvement in the formation of the aggressiveness of PCa. The results of the study can be further used for differential diagnosis of prostate tumors and for assessing the aggressiveness of PCa.**

***Key Words:* prostate cancer, benign prostatic hyperplasia, polyamines, spermine, tumor tissue.**

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Prostate cancer (PCa) is one of the most common cancers in older men. In recent years, the number of patients with PCa has been growing rapidly in most countries of the world [1]. In Ukraine, this pathology ranks second among all male cancers. According to the National Cancer Registry of Ukraine, the number of primary patients with PCa in 2020 was 6432 with the incidence amounting to 23.8 per 100 thousand and mortality — 10.8 per 100 thousand [2]. Judging by the recent trends, one might expect a two-fold increase of PCa incidence in Ukraine within the next 10 years. Such an intensive spread of PCa indicates that this disease is not only medical but also a topical social issue [3].

Currently, the complexes of biomarkers, such as the prostate health index (PHI) and 4KScore, are used for the differential diagnosis of PCa, and the products of genes associated with the development of PCa are determined in the urine of patients. The PHI-test combines the determination of total, free prostate-specific antigen (PSA) and proPSA. The 4KScore test includes serum biomarkers (PHI-test and kallikrein-2) and clinical data (age, digital rectal examination, and previous biopsy results). In patients with a previous negative biopsy, a ConfirmMDx test (a test to determine the degree of hypermethylation of certain genes) is also recommended for repeated biopsies.

It is known that in some patients the tumor develops slowly, the disease is sluggish (latent) and does not affect the life expectancy of patients. In other cases, the rapid growth of the tumor causes an aggressive course of the disease. At a latent course of an illness patients need active supervision, and at aggressive — radical treatment. At the same time, the lack of specific and reliable biomarkers for assessing the aggressiveness of tumors is the reason that in a significant number of men PCa is diagnosed when the disease has already spread beyond the prostate. The treatment in such cases is very complicated and rarely successful.

In addition, despite the possibility of local treatment (radical prostatectomy, radiation or hormone therapy), many patients develop recurrence after primary therapy. In general, according to various authors, recurrence of the disease after radical prostatectomy occurs in 27–53% of cases. The first sign of recurrence of prostate cancer is often an increase of PSA levels in serum, called “biochemical recurrence”. Subsequently, such patients develop clinical manifestations of the disease, which is often accompanied by the development of bone metastases. Accurate criteria

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Abbreviations used: BPH – benign prostate hyperplasia; Dns-Cl – dansyl chloride; GS – Gleason score; ODC – ornithine decarboxylase; PAs – polyamines; PCa – prostate cancer; PHI – prostate health index; Put – putrescine; Spd – spermidine; Spm – spermine; SSAT – spermine/spermidine-acetyltransferase.

for identifying patients at high risk of recurrence have not yet been fully developed, although some evaluation criteria exist. For example, the combined use of a Gleason grading system (ISUP grade), PSA level, and disease stage helps to predict the risk of recurrence. Nevertheless, in many cases, the use of these indicators also does not allow assessing correctly the degree of tumor aggressiveness and the risk of recurrence, which may be the cause of errors in choosing a treatment strategy [4, 5]. Therefore, the issue of identifying patients at high risk of recurrence after primary radical treatment is also very relevant.

It is known that the malignant tumors of the prostate are characterized by heterogeneity not only in morphological structure, but also in molecular and metabolic profile, which can cause different clinical course of the disease. Therefore, the search for the new cellular, molecular and metabolic markers that would predict the aggressive potential of tumors can be attributed, according to many researchers, to the most promising areas of research in modern oncourology [4, 6, 7].

Several authors believe that the detection of cell markers can provide objective information about the nature of the malignant process in the prostate, the state of proliferation and apoptosis in tumors, the predisposition of tumor cells to invasion and metastasis and mechanisms of developing resistance to hormone therapy. Such data will not only help to assess the degree of PCa aggressiveness more accurately but also will improve the prediction of the aggressiveness of the disease, and can become the basis for the development of new personalized treatment regimens [8–10].

Analyzing the literature on tissue markers of PCa, which are currently being studied and used to predict the course of the disease after radical surgery, one should take note of Ki-67, tumor suppressor p27, and the product of erythroblast transforming gene (ETS-related gene) — ERG protein involved in the regulation of embryonic development, cell proliferation, differentiation, angiogenesis, inflammation, apoptosis, etc. Currently, vast attention is devoted also to the studies of the expression of oncogenic miRNA, markers of tumor stem cells, NF-kB, lactoferrin, etc. [11–14].

Polyamines (PAs) deserve special attention as PCa tissue markers. PAs — spermine (Spm), spermidine (Spd), putrescine (Put) and cadaverine — endogenous polycations that play the key functions in the processes of proliferation and growth. The interest in studying PAs in tumors is not accidental, since cell proliferation and growth do not occur without certain PA species. It is known that the emergence and progression of malignant neoplasms is characterized by significant changes in PA metabolism.

In malignant tumors of different localizations, the level of PAs and the activity of the enzymes involved in their synthesis (ornithine decarboxylase — ODC and S-adenosylmethionine decarboxylase) increase significantly. Because PAs are directly involved in growth and proliferation, the differences in the concentration of individual PAs (in particular Spm and Spd) may be one of the causes of different proliferative activity of tumor cells, their growth rate and the ability of invasion [15–19].

It should be noted that the prostate and prostate secretion (prostatic fluid) played an important role in the modern understanding of the biological functions of PAs. Spm owes its name to the fact of its isolation from human sperm by Anthony Levenguk in 1677 [16]. Approximately 200 years later, after elucidating the chemical structure of PAs, the biochemical mechanisms of their action in living cells began to be widely studied. PAs has been shown to perform various regulatory functions in many critical metabolic processes, in particular in the synthesis of nucleic acids and protein. PAs are part of the protein-synthesizing apparatus and are involved in protein biosynthesis, manifesting their action both at the level of transcription and translation as well as posttranslational modification. PAs also stabilize the structure of ribosomes, polysomes and cell membranes and affect their functioning. PAs affects ion channels and hormone receptors, they are capable of inhibiting/blocking cation channels, reducing/enhancing the binding of growth hormone, follicle-stimulating hormone and insulin to their membrane receptors, affecting the binding of glycine to the glutamate receptor NMDA (N-methyl-D-aspartate) and activate estrogen receptors [17–19]. In addition, PAs are involved in the regulation of more than 300 genes [20, 21].

It is noteworthy that among other organs, the normal human prostate is characterized by the highest levels of PAs, especially Spm. In the prostate, PAs perform various functions. In particular, they are crucial for the regulation of cell proliferation and differentiation of prostate epithelial cells. The functions of individual PAs differ. Thus, Spd and Put are responsible for the proliferative activity of cells, and Spm — for the processes of differentiation. Spm also participates in maintaining the functional secretory state of the prostate epithelium, regulates the formation of a seminal clot, modulates the ability of sperm to fertilize, and others [22, 23].

Transformation of prostate cells is accompanied by the characteristic changes in the activity of metabolic enzymes of PAs and changes in their content [24–26]. There are literature data on the differences in the metabolism of PAs in prostate tumors in comparison not only with normal tissue but also with tumors of other localizations [10, 23]. PAs metabolism has been widely studied in recent decades *in vitro* in cultures of PCa cells and *in vivo* in experimental animals [22, 24, 27, 28]. Nevertheless, the studies on the postoperative samples of human prostate tumors are rather limited and their results are often contradictory.

At the same time, given the key role of PAs in the processes of growth and proliferation, the study of their metabolism in prostate tumors will provide valuable information about the peculiarities of the process of malignancy in this organ. The results of such studies can be used to assess the aggressiveness of malignant tumors of the prostate as well as to search for new

schemes of targeted therapy of PCa using modulators and inhibitors of PAs metabolism. Thus, there is already evidence that the inhibitor of the key enzyme ODC — α-difluoromethylornithine exhibits antitumor activity against PCa [29]. Other inhibitors of PAs metabolism were also studied. Recently published work presents encouraging results on the effect of various modulators and inhibitors of PA catabolism on the development of prostate tumors [30, 31]. All of the above mentioned indicates the prospects for studying the peculiarities of PAs metabolism in tumors of the human prostate.

The aim of the work was to investigate the levels of basic and acetylated forms of PAs in postoperative samples of malignant and benign tumors of the human prostate and evaluate the possibility of their use for differential diagnosis and assessment of the aggressiveness of PCa.

MATERIALS AND METHODS

The research was performed on 77 postoperative samples of tumors from patients with PCa (57 samples) and benign prostatic hyperplasia (BPH) (20 samples). Exclusion criteria were radiation therapy or chemotherapy before surgery. All patients were cured in the Department of Plastic and Reconstructive Oncourology of the National Cancer Institute (Kyiv, Ukraine) in 2018–2020. The average age of patients with PCa was 64.05 ± 0.72 (51–78) years; patients with BPH — 67.36 ± 1.50 (52–84) years.

Patients were examined in accordance with the standards of diagnosis and treatment of patients, approved by the orders of the Ministry of Health of Ukraine (Orders of the Ministry of Health of Ukraine № 135 of 04.03.2009 "On approval of the clinical protocol for the provision of medical care to patients with benign prostatic hyperplasia" and № 235 of 02.04.2014 "On approval and implementation of medical and technological documents for standardization of medical care for prostate cancer"). The research was conducted in accordance with the principles of the Helsinki Declaration of the World Medical Association. All patients were informed about the study and signed a consent form.

The stage of the tumor process was determined according to the International Classification of Malignant Tumors TNM8 (2017). Pathomorphological examination of histological sections of tumors was performed on paraffin blocks (staining of sections with hematoxylin and eosin). Morphological studies have shown that malignant tumors of the examined patients belong to adenocarcinoma. The grading of the PCa was done according to Gleason's score (GS). Measured GS ranged from 6 to 10. Among benign tumors were identified: atypical hyperplasia, nodular adenomatous, glandular-stromal and fibro-glandular forms of BPH.

Tumor material obtained after surgery was processed immediately or frozen in liquid nitrogen and stored at -80 °C until use. To determine the content of PAs, the modified method of high performance liquid chromatography was used [32]. Briefly, 30 mg of tumor tissue was taken, 1.5 M $HClO_4$ was added, homogenized carefully, left for 2 h in the refrigerator at 8 °C, then centrifuged for 30 min at 14,000 rpm. Aliquots of the supernatant were taken for further work, and a saturated solution of sodium carbonate was added. Then a solution of dansyl chloride (5-dimethylamino-1-naphthalene-sulfonyl chloride, Dns-Cl) (Serva, USA) in acetone at a concentration of 5 mg/ml was added. To obtain Dns-Cl-derivatized PAs, the samples were kept for 1 h at 40 °C. Then a solution of proline was added in order to remove excess of Dns-Cl and the samples were incubated again at 40 °C for 15 min. After the derivatization procedure with Dns-Cl, cyclohexane was added to the samples, shaken vigorously to extract the dansylated PAs, and then centrifuged for 10 min at 14,000 rpm. The cyclohexane fraction was collected and transferred to a crucible for vacuum drying. The procedure with cyclohexane was repeated twice. Cyclohexane fractions were dried in a vacuum dryer at room temperature in the dark. The remaining precipitate was dissolved in methanol and filtered through a Supelco PTFE filter — 25–2 with a pore size of 0.2 μm. After that, the samples were analyzed on a chromatograph. PAs hydrochlorides from Sigma Chemical Co., USA served as standards.

Statistical processing of the results was performed by methods of variation statistics using standard licensed computer programs STATISTICA 6.0, Microsoft Excel. Differences at $p \leqslant 0.05$ were considered as significant.

RESULTS AND DISCUSSION

PAs levels were determined in 57 postoperative samples of PCa and 20 samples of BPH. The distribution of patients by stage and gradation of tumors on the GS are presented in the Table.

We investigated and performed a comparative analysis of PAs levels in benign and malignant prostate tumors. The data presented in Fig. 1 shows the average values of PAs levels in malignant tumors without taking into account the stage of the disease and GS-gradation and in benign tumors.

The analysis of the obtained results showed that the levels of all studied PAs, except N^1-acetylspermidine and N^1, N^{12}-acetylspermine, in benign tumors significantly exceed that in malignant tumors. Thus, the levels of Spd and Put in benign tumors were 3 and 6.5 times higher than in malignant tumors, respectively. The level of N^1-acetylputrescine in benign tumors was also higher compared to PCa. At the same time, levels of N^1-acetylspermidine and N^1, N^{12}-acetylspermine in benign tumors were 3 and 3.4 times lower, respectively, than in malignant ones (Fig. 1).

In PCa and BPH cells, the ODC activity increased significantly [9, 10, 24] and Put levels should also be highly increased in both benign and malignant tumors. On the contrary, we observed a many-fold decrease in Put content in PCa cells, probably due to a sharp increase of Spd synthase in PCa [10].

Table. Distribution of PCa patients by clinical stages (category T) and GS

Clinical stage	Number of patients (n,%)	GS/Number of patients (n, %)				
		GS 6	GS 7	GS 8	GS 9	GS 10
T1	5 (8.77%)	4 (80.00%)	–	1 (20.00%)	–	–
T2	28 (49.12%)	5 (17.86%)	(42.86%)	9 (32.14%)	1 (3.57%)	1 (3.57%)
T3	14 (24.56%)	2 (14,29%)	1 (7.14%)	5 (35.71%)	6 (42.86%)	–
T4	10 (17.54%)	–	1 (10.00%)	4 (40.00%)	3 (30.00%)	2 (20.00%)
Total number of patients (n, %)	57 (100%)	11 (19.30%)	14 (24.56%)	19 (33.33%)	10 (17.54%)	3 (5.26%)

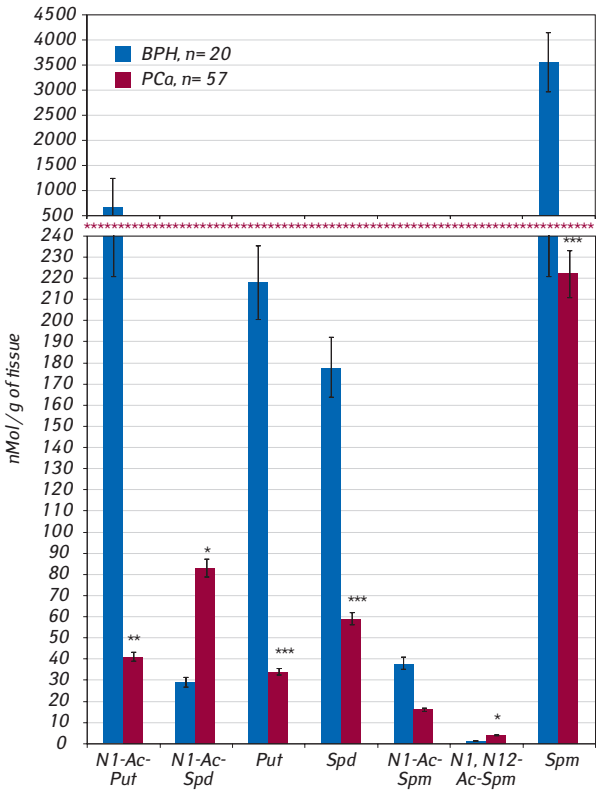

Fig. 1. Levels of PAs in BPH and PCa: N^1-Ac-Put — N^1–acetylputrescine; N^1-Ac-Spd — N1–acetylspermidine; Put — putrescine; N^1–Ac-Spm — N^1-acetylspermine; N^1,N^{12}-Ac-Spm — N^1,N^{12}–acetylspermine. The difference between the levels of PAs in malignant and benign tumors is significant at *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

Under conditions of Spd synthase upregulation, Put levels have to decrease. The decrease in Spd levels found in PCa cells, in turn, can be explained by upregulation of spermine/spermidine-acetyltransferase (SSAT), which directs Spd to acetyl-Spd production. Increased levels of acetylated forms of Spd (N^1-Ac-Spd) and Spm (N^1, N^{12}-Ac-Spm) in PCa cells, which was found in our study, apparently occurs due to the increased SSAT activity.

Among the studied PAs, the most significant difference between PCa and BPH was observed for Spm. Thus, the level of Spm in PCa samples was 16 times lower than in BPH samples. A sharp decrease in Spm in malignant tumors affected the value of the proliferation index — the molar ratio of Spd/Spm. The Spd/Spm value in PCa cells was 5.4 times higher than in BPH and amounted to 0.27 c.u., and in BPH — 0.05 c.u.

Our data are consistent with McDunn *et al.* [33] that in malignant tumors of the prostate a marked decrease in the number of metabolites that are synthesized in a healthy prostate is observed including Spm, simple sugars and citrate. Our results are also in line with the study suggesting that Spm depletion may indicate the transformation of prostate cells into a malignant phenotype [27, 28].

In addition, according to the literature [10, 30, 31, 34, 35] and the data from our own research [36], in PCa, in contrast to BPH, the activity of enzymes of PAs catabolism such as SSAT and Spm oxidase increases significantly. In this case, SSAT directs Spm and Spd to the production of their acetylated forms, and Spm oxidase catalyzes the conversion of Spm to toxic aldehyde 3-aminopropanol, H_2O_2 and Spd. Therefore, the dramatic depletion in Spm levels observed in PCa cells is apparently due to an increase in both SSAT1 and Spm oxidase activity.

The data on PA levels in PCa depending on GS grade are presented in Fig. 2 and 3. As can be seen, with the increase of GS grade of tumors, the levels of PAs undergo significant changes. In PCa cells with low GS-grade (GS6), the levels of Spm, Spd, and Put are significantly higher than in high GS-grade tumors (GS7, GS8, GS9-10). The association between GS-grade and Spm levels is especially noticeable. The highest Spm levels are specific for the least aggressive (GS6), and the lowest for the most aggressive tumors (GS9 and GS10) (Fig. 2). This may indicate the participation of Spm in the formation of aggressiveness of PCa.

At the same time, the levels of N^1-acetylspermidine in PCa cells increased with growth of the GS-grade of tumors. We also showed that with the increase of GS-grade in PCa cells, the value of the proliferation index increases significantly — the molar ratio Spd/Spm: GS6 → GS7 → GS8 → GS9 + GS10: 0.16 → 0.21 → 0.51 → 0.55) (Fig. 3).

Our data on the dependence of Spm levels on the CS grade of tumors are consistent with results obtained by Kdadra *et al.* [8], Andersen *et al*. [23], Peng *et al.* [34], Giskeødegård *et al*. [37], Braadland *et al*. [38] and data from other researchers.

The results of the study of PAs levels in PCa cells depending on the stage of the disease are presented in Fig. 4. In the case of disease stage progression, the levels of Ac-Put, Put, N^1-Ac-Spm and notably spermine were depleting. On the other hand, levels of N^1-Ac-Spd, Spd and N^1, N^{12}-Ac-Spm at different stages did not differ.

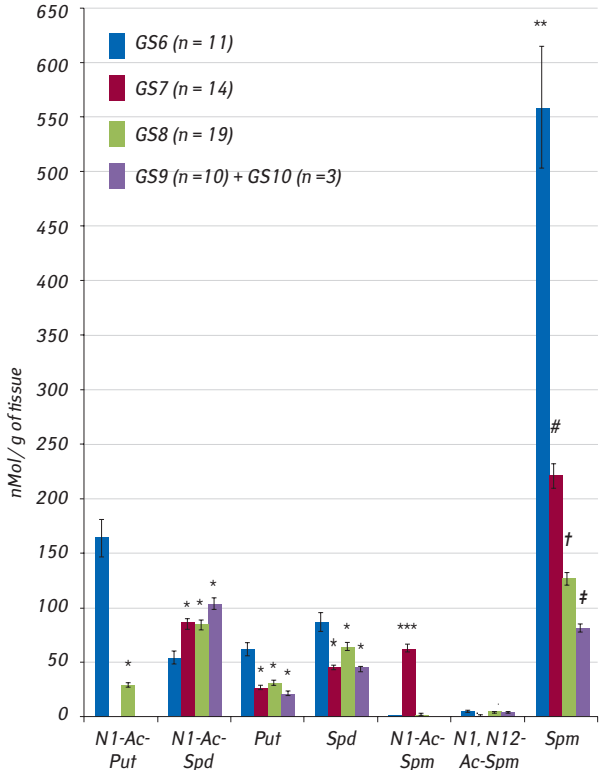

Fig. 2. PA levels in PCa depending on GS-grade: *$p < 0.05$ in comparison with GS6; **$p < 0.01$ in comparison with GS7, GS8 and GS9 + GS10; ***$p < 0.01$ in comparison with GS7, GS8 and GS9 + GS10; #$p < 0.05$ compared to GS8 and GS9 + GS10; †$p < 0.05$ compared to GS9 + GS10; ‡$p < 0.01$ in comparison with GS6, GS7 and GS8

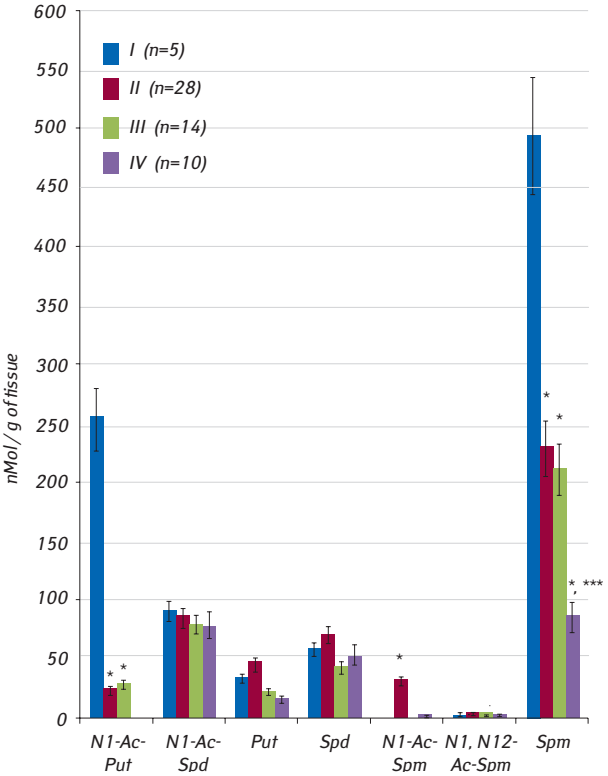

Fig. 4. PA levels in PCa depending on clinical stage of the disease: *$p < 0.05$ in comparison with stage I; ** $p > 0.05$ in comparison with stages II and III; *** $p < 0.01$ in comparison with stages I, II and III

We did not find a reliable dependence of PAs levels on the stage, including Spm. Thus, the difference in Spm levels in tumor samples of patients with stage II and III was insignificant ($p > 0.05$) (Fig. 4). The absence of such dependence may be a consequence of the fact that in stage II there were tumors with a high GS-grade (GS8, GS8, GS10), and in stage III — with less GS-grade (GS6 and GS7) (Table).

Direct dependence of the molar ratio Spd/Spm from stage was also not detected, although the lowest values of Spd/Spm were in stage I, and the highest — in stage IV (Fig. 5).

We have previously obtained the data on the levels of PAs in the blood and urine of patients with PCa and benign hyperplasia [39]. It should be noted that the levels of PA in the blood and urine are more integrated indicators and depend on the size of the tumor, the percentage of malignant and benign tissue in the tumor and so on. Nevertheless, when comparing the data on the levels of PA in the blood and urine described in the article [39], and the results obtained

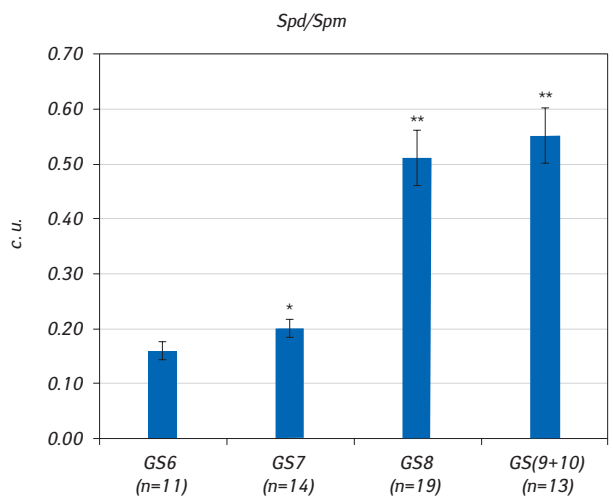

Fig. 3. The value of the molar ratio Spd/Spm in PCa with different GS-grade: *$p < 0.05$ in comparison with GS6, **$p < 0.01$ compared to GS6 and GS7

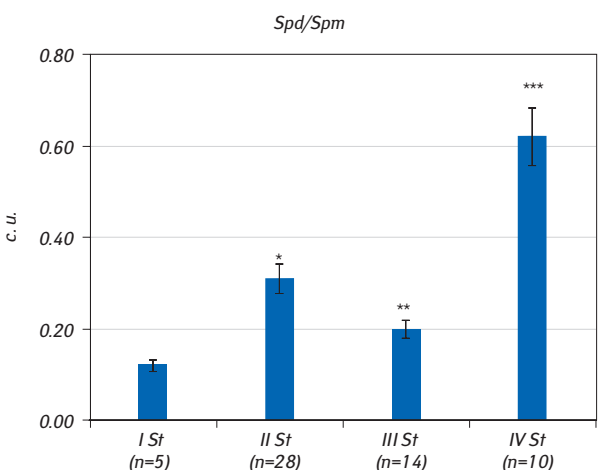

Fig. 5. The value of the molar ratio Spd/Spm in malignant tumors of the prostate depending on the stage of the disease: *$p < 0.05$ — in comparison with stages I and II; **$p < 0.05$ — in comparison with stages II and IV; ***$p < 0.001$ — in comparison with stages I, II and III

on tumor samples, we can see the relationship between these indicators. This relation is especially clear if traced between Spm levels in tumors and in body fluids.

Thus, we identified metabolic parameters of PAs metabolism in the clinical material (postoperative tumor samples), which vary depending on the gradation of PCa by the GS. It is established that the increase in the GS-grade of PCa is associated with sharply decreased levels of Put and especially Spm. Such changes in the metabolism of PAs, apparently, are characteristic of malignant tumors of the prostate, which distinguishes them not only from benign tumors of this organ, but also from malignant tumors of other localizations.

The data obtained may be important for the development of new criteria for assessing the aggressive potential of prostate tumors and for predicting the course of the disease. In addition, the data obtained can further serve as a scientific basis for the development of new schemes for targeted treatment of PCa with the inclusion of modulators and inhibitors of PAs metabolism.

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ПОЛІАМІНИ ЯК НОВІ ПОТЕНЦІЙНІ БІОМАРКЕРИ ДЛЯ ДИФЕРЕНЦІАЛЬНОЇ ДІАГНОСТИКИ ТА ОЦІНКИ АГРЕСИВНОСТІ РАКУ ПЕРЕДМІХУРОВОЇ ЗАЛОЗИ

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Резюме. Рак передміхурової залози (РПЗ) — одне з найбільш поширених злоякісних новоутворень у чоловіків старшого віку. Вивчення тканинних маркерів РПЗ може надати інформацію про стан процесів проліферації і апоптозу в пухлинах, схильність пухлинних клітин до метастазування та механізми розвитку резистентності до терапії, що, у свою чергу, може допомогти в прогнозуванні перебігу захворювання та розробці персоніфікованого лікування. На особливий інтерес в аспекті тканинних маркерів РПЗ заслуговують поліаміни (ПА) — спермін, спермідин, путресцин — речовини, що абсолютно необхідні для проліферації і росту клітин. ***Мета:*** Дослідити рівні основних та ацетильованих форм ПА в постопераційних зразках доброякісних і злоякісних пухлин передміхурової залози людини та оцінити можливість їх використання для диференціальної діагностики та оцінки агресивності РПЗ. ***Об'єкт і методи:*** Дослідження проведено на 57 постопераційних зразках хворих з аденокарциномою передміхурової залози з різним ступенем градації за шкалою Глісона (GS) та різною клінічною стадією (TI–TIV) та 20 зразках пухлин хворих на доброякісну гіперплазію передміхурової залози (ДГПЗ). Для визначення ПА використовували метод високоефективної рідинної хроматографії високого тиску. Значущість відмінностей між показниками у різних групах оцінювали за допомогою *t*-критерію Стьюдента. Відмінності вважалися достовірними за $p < 0,05$. ***Результати:*** Серед досліджених ПА найбільш суттєву різницю між РПЗ та ДГПЗ спостерігали для сперміну (Спн). Рівень Спн у зразках РПЗ був у 16 разів нижчий, ніж у ДГПЗ-зразках ($p < 0.01$). Достовірної залежності рівнів ПА, у тому числі і Спн, від клінічної стадії нами не виявлено. Встановлено зв'язок між рівнем Спн і градацією РПЗ за шкалою Глісона. Найвищі рівні Спн були характерні для індолентних (GS6), а найнижчі — для найбільш агресивних пухлин (GS9 та GS10). ***Висновки:*** Різке зниження рівня Спн, ймовірно, є характерною особливістю злоякісних пухлин передміхурової залози. Отримані результати свідчать про зв'язок Спн з градацією пухлин за шкалою Глісона. Це може свідчити про участь Спн у формуванні агресивності РПЗ. Результати дослідження в подальшому можуть бути використані для диференційної діагностики пухлин передміхурової залози та оцінки агресивності РПЗ.

Ключові слова: рак передміхурової залози, доброякісна гіперплазія передміхурової залози, поліаміни, спермін, пухлинна тканина.