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ORNITHINE DECARBOXYLASE ACTIVITY IN PROSTATE CANCER

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Prostate cancer (PCa), the most common solid malignant neoplasm in men, is characterized using the Gleason score and diagnosed using prostate-specific antigen (PSA) biomarker. However, Gleason score and PSA-based diagnostics are not universal and have significant limitations. It is supposed that the ornithine decarboxylase activity (A_{ODC}) could be a suitable auxiliary biomarker for the PCa diagnosis or monitoring the therapeutic efficacy. ***Aim:*** **To assess the relation between A_{ODC} in PCa tissues and the level of serum PSA with the Gleason score (GS) and the clinical stage.** ***Materials and Methods:*** **29 patients (48 to 79 years old) with prostate adenocarcinoma of different GS (6 to 10) and clinical stage (T1 to T4) were enrolled in the study. The A_{ODC} was analyzed in the PCa tissues by the modified spectrophotometric assay.** ***Results:*** **The patients with PCa were distributed into two groups: with low $A_{ODC} < 0.3$ and high $A_{ODC} > 0.45$. In group with $A_{ODC} < 0.3$, the highest value of A_{ODC} was recorded in patients with the lowest GS (= 6), while in group with $A_{ODC} > 0.45$, the highest value of A_{ODC} was recorded in the patients with the highest GS (= 9–10). Furthermore, in group with $A_{ODC} > 0.45$, the highest value of A_{ODC} was registered in the patients with T1 or T4 stage. The highest levels of serum PSA were detected in T3–T4 cases and in cases with the highest GS.** ***Conclusion:*** **The patterns of A_{ODC} and serum PSA can be used as supplementary indices useful for monitoring PCa course.**

Key Words: **prostate cancer, Gleason score, prostate-specific antigen, ornithine decarboxylase activity, biomarkers.**

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Prostate cancer (PCa) is the second most frequent malignancy (after lung cancer) in men worldwide, accounting for 1,414,259 (7.3%) new cases and causing 375,304 (3.8% of all deaths caused by cancer) in 2020 [1, 2]. Commonly, the PCa rate is slow-growing, and standard surgical treatment (radical prostatectomy) is a recommended strategy [3, 4].

Four clinical stages (CS) of the PCa include the I stage (early-stage, small local cancer lesion), the II and III stages (larger tumor lesion invading into nearby tissues or lymph nodes), and the IV stage (cancer spread into the distant parts of the body) [5]. For characterization of PCa, the Gleason score (GS) (ranging from 6 to 10) is widely used [6]. The data on GS are obtained from the prostate biopsy analysis, and the score of 6 is related to low risk disease, and the score of 10 — to high risk disease. However, GS diagnostics is not universal and has significant limitations. For example, the relatively low GS (of 6 and 7) were observed in 60% of the patients with glandular tumors who died [7].

In the development of the PCa, a highly aggressive, high-risk form of cancer is possible with metastasizing to other tissues of the body, especially the lymph nodes and bones [8, 9]. Therefore, the accurate and early detection at a potentially curable stage is crucial for the improvement of the prognosis [10]. For the early diagnostic and prognostic insight into disease etiology and progression the different cancer biomarker tests can be used. Here, we can refer the PCa antigen 3 biomarker test [11], the Michigan Prostate Score test [12], the Prostate Health Index test [13, 14], the 4Kscore test [15]; the SelectMDx test [16]; the ConfirmMDx test [15, 17–19]. However, above biomarker tests either have a low level of evidence or can be used only for scientific purposes [20]. The rather popular is application of prostate-specific antigen (PSA) (also known as hK3) biomarker [21]. Commonly, the level of serum PSA correlates closely with prostatitis and benign prostatic hyperplasia [22]. It is used as the early standard screening diagnostic test of the PCa [23]. However, the sensitivity and specificity of the PSA test are not universal and clinically significant. In some cases, the test can provide the false positives or false negatives in the detection of small and low-grade lesions.

The ornithine decarboxylase (ODC, EC4.1.1.17) activity (A_{ODC}) can be also used for characterization of PCa. ODC is the key enzyme in polyamine biosynthesis. Activation of ODC and consequently increased concentrations of polyamines are related to tumor progression [24, 25]. A_{ODC} is also increased in PCa tissues and respective secretory fluids [26–29].

The relationship between metastatic properties of PCa cells and expression of ODC 1 gene has been recently demonstrated [30]. It can be speculated that A_{ODC} could be a suitable biomarker for

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Abbreviations used: A_{ODC} – ornithine decarboxylase activity; CS – clinical stage; GS – Gleason score; ODC – ornithine decarboxylase; PCa – prostate cancer; PSA – prostate-specific antigen.

the PCa diagnosis or monitoring the efficacy of the therapy. However, the correlations between the A_{ODC} and PSA patterns, as well as various clinical and pathological characteristics of the patients with the PCa have never been studied before.

The measurement of $^{14}CO_2$, that releases from ^{14}C-carboxyl-labeled ornithine is widely used as a method of assay for ODC activity [31]. However, the employment of this method is limited due to the use of radioactive tags, special detecting equipment and highly qualified personnel. In 2013, Luqman *et al.* [32] published a work in which the activity of ODC was determined by accumulation of the putrescine, which, when bound to picrylsulfonic acid, forms a yellow complex. Colored TNP-putrescine-TNP complex could be measured spectrophotometrically at 426 nm. This method is highly sensitive, does not require radioactive materials and special equipment.

The present work was aimed at the assessment of relationship between A_{ODC} and the serum PSA level with clinical parameters (CS and GS) and the evaluation of the possibile application of supplementary A_{ODC} and PSA tests for diagnostic and prognostic purposes.

MATERIALS AND METHODS

Patients. The patients with histologically confirmed PCa were cured in the National Cancer Institute (Kyiv, Ukraine) in the period between November 2017 and November 2018. The patients underwent radical prostatectomy and provided the consent on the use of their biological materials for the biochemical studies. The work was approved by the Ethics Committee of National Cancer Institute (Kyiv, Ukraine).

The study included 29 patients, 48 to 79 years old, the mean age of 65 years (Table). The prostate adenocarcinoma cases of different CS (T1–T4) and GS (ranged from 6 to 10) were studied. The stage of the tumor process was determined according to TNM classification of malignant tumors [5]. Exclusion criteria were radiation therapy or chemotherapy before surgery and the presence of medical problems such as diabetes, hypertension, and liver disease.

GS. Immediately after surgery, the fresh PCa specimens were fixed in 10% buffered neutral formalin (pH 7.2) overnight at room temperature, dehydrated in a graded series of ethanol and embedded in paraffin wax by standard procedure. The paraffin blocks were sectioned at 5 microns width. Every tenth section was stained with hematoxylin and eosin [33]. The grading of the PCa was done according to Gleason's system [6]. Measured GS ranged from 6 to 10 (Table). Depending on the GS, all patients were divided on four different groups (GS 6, 7, 8, and 9–10).

Table. Clinical data of patients after radical prostatectomy

Characteristic	Value			
Number of patients	29			
Age, mean and range, years	65 (48–79)			
Gleason scores,	6	7	8	9-10
Number of patients (%)	7 (24.1)	9 (31.1)	8 (27.6)	5 (17.2)
Clinical stage,	T1	T2	T3	T4
Number of patients (%)	2 (6.9)	17 (58.6)	6 (20.7)	4 (13.8)

PSA. The PSA levels (obtained from preoperative clinical assessments) were in the interval between 5.0 and 30.4 ng/ml with the mean of the 13.5 ng/ml.

A_{ODC}. The tumor material obtained after surgery was immediately frozen in liquid nitrogen and stored at –80 °C until use. The A_{ODC} was analyzed by the procedure described in [32]. Frozen tissue (200 mg) was ground to a fine powder with a mortar and pestle in liquid nitrogen. The powder was homogenized at 4 °C in a glass-to-glass homogenizer in 5 volumes of ODC buffer: 50 mM Tris-phosphate buffer (pH 7.5), containing 0.1 mM ethylenediaminetetraacetic acid, 0.1 mM pyridoxal-5-phosphate, 1 mM β-mercaptoethanol (all from Sigma-Aldrich, USA). The obtained tissue homogenate was centrifuged at 5,000 rpm for 5 min at 4 °C. Then supernatant was carefully aspirated and used for enzyme determination. Protein concentration was determined using spectrophotometer NanoDrop 2000c (Thermo Fisher Scientific, USA). For enzyme activity determination we used 5 µg of protein per 50 µl/sample. The 50 µl/sample was added to 400 µl of substrate reaction mixture (2.5 mM β-mercaptoethanol, 1.5 mM ethylenediaminetetraacetic acid, 2 µl of stock solution of pyridoxal-5-phosphate prepared in 150 mM phosphate buffer (75 nM) and 3 mM L-ornitine HCl in 150 mm phosphate buffer (pH 7.5) and incubated at 37 °C for 30 min. The reaction was terminated by the addition of 400 µl perchloric acid (1 M) and centrifugation at 5,000 rpm for 5 min at room temperature. 100 µl of supernatant was further mixed with 200 µl of 4N NaOH (supernatant was carefully pipetted), followed by the addition of 400 µl of 1-pentanol and centrifugation at 2000 rpm for 5 min. 200 µl of upper (organic) phase was transferred to a fresh tube containing 200 µl of sodium borate (0.1M, pH 8.0) and mixed. Then 200 µl (10 µM) of picrylsulfonic acid and 400 µl of dimethyl sulfoxide were added, followed by centrifugation at 3,000 rpm for 5 min. The supernatant was used to measure the enzyme activity by recording the absorbance at 426 nm with Synergy HT Microplate Reader (Bio-Tek Instruments, USA).

Statistical analysis. The tests were performed in triplicate for each sample and the mean values and standard errors were calculated. The significance of differences between the indices of different groups was estimated using Student's *t*-test. The differences were considered to be significant at $p < 0.05$.

Cumulative distribution functions, $I(x)$ were plotted for A_{ODC} in tissues and PSA in serum of PCa

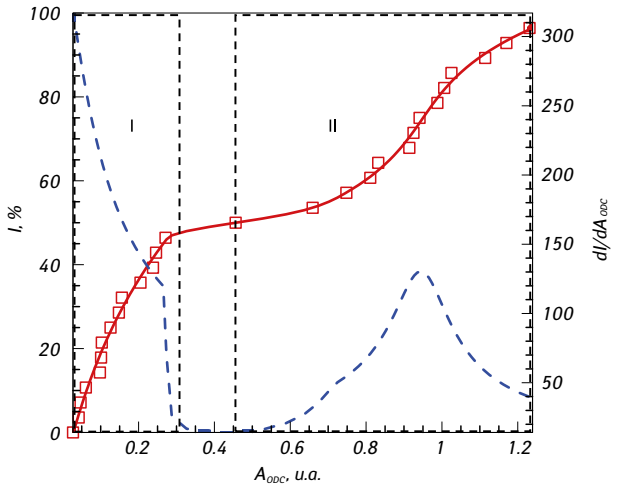

Fig. 1. Cumulative (integral) distribution function, *I*, of the measured values of A_{ODC} for all patients. Dash line corresponds to the differential function, dI/dA_{ODC}. The two groups of patients with small (14 patients in group 1, $A_{ODC} < 0.3$) and large (15 patients in group 2, $A_{ODC} > 0.45$) values of A_{ODC} are shown by filled areas

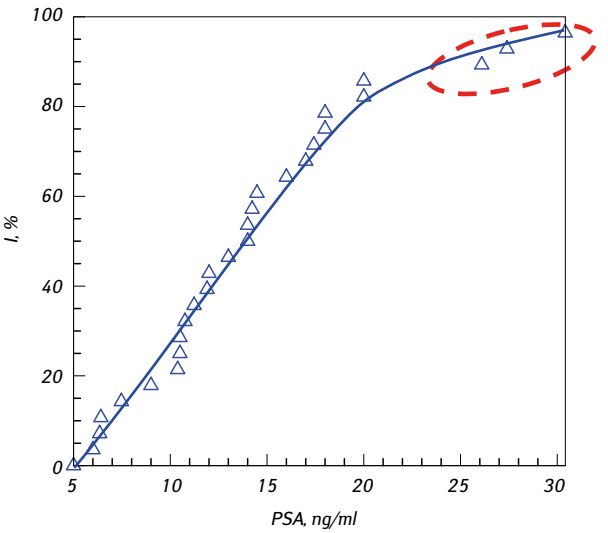

Fig. 3. Cumulative (integral) distribution function, I, of the measured level of serum PSA for all patients. Dashed area corresponds to the patients with high GS (GS = 9–10)

patients. The value *I(x)* was evaluated as the probability that a variate (A_{ODC} or PSA) takes on a value less than or equal to *x* [34].

RESULTS AND DISCUSSION

Fig. 1 presents cumulative distribution function, *I*, of the measured values of A_{ODC}, for all PCa patients. The value of *I* significantly increased up to ≈ 50% with increase of A_{ODC} in the interval between ≈ 0.1 and 0.3, then the significant growth of *I* was only observed at $A_{ODC} > 0.8$.

The two-peak differential distribution function, dI/dA_{ODC} (dashed line in Fig. 1) evidences the presence of two groups of PCa patients with low ($A_{ODC} < 0.3$, group 1, n = 14) and high ($A_{ODC} > 0.45$, group 2, n = 15) values of A_{ODC}. Accounting for these data, A_{ODC} in patients differed by GS (GS = 6, 7, 8, and 9–10) (Fig. 2, *a*) and CS (T1, T2, T3 and T4) (Fig. 2, *b*) were analyzed.

In group 1, the highest value of A_{ODC} ($A_{ODC} = 0.24 \pm 0.03$, $p < 0.05$) was only observed in the patients with the lowest GS (= 6), while in other patients with GS (= 7, 8, 9–10) the values of A_{ODC} were approximately the same ($A_{ODC} = 0.11 \pm 0.03$) (see Fig. 2, *a*). In this group, practically no association was observed between the values of A_{ODC} and CS (see Fig. 2, *b*). However, in group 2, the highest value of A_{ODC} ($A_{ODC} = 1.06 \pm 0.12$, $p < 0.05$) was only observed in the patients with the highest GS (= 9–10), and in other patients with GS (= 6, 7, 8), the values of A_{ODC} were approximately the same ($A_{ODC} = 0.85 \pm 0.10$) (see Fig. 2, *a*). In this group, the highest value of A_{ODC} in PCa tissues was observed at the initial stage of the disease (T1) (see Fig. 2, *b*).

Fig. 3 presents cumulative distribution function, *I*, of the measured level of serum PSA for all PCa patients. The minimum level of PSA was ≈ 5 ng/ml and the value of *I* practically linearly

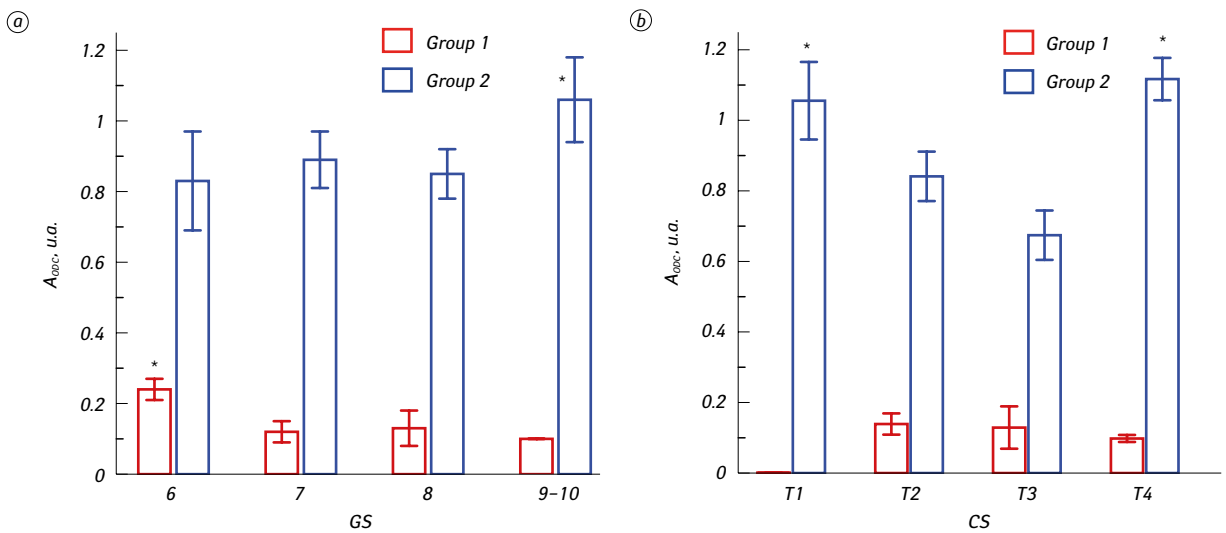

Fig. 2. A_{ODC} *vs* GS (*a*) and CS (*b*) for two groups of patients with low (14 patients in group 1, $A_{ODC} < 0.3$) and high (15 patients in group 2, $A_{ODC} > 0.45$) values of A_{ODC}. *$p < 0.05$ (in *a* — for GS 6 as compared to other GS subgroups in group 1 and for GS 9–10 as compared to other GS subgroups in group 2; in *b* — for T1 or T4 as compared to T2 or T3 for group 2)

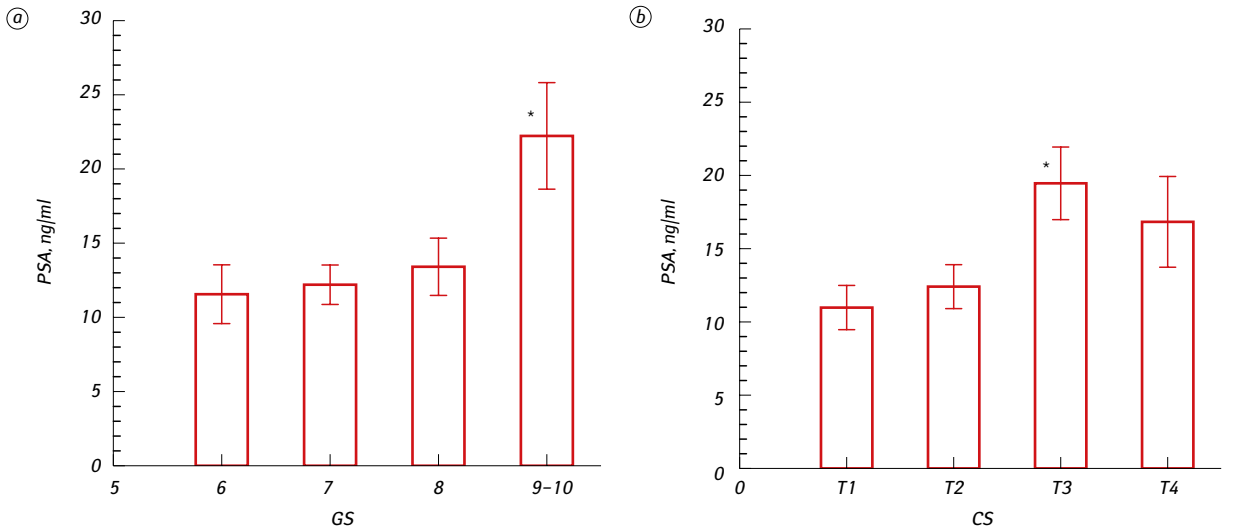

Fig. 4. The level of serum PSA *vs* GS (*a*) and CS (*b*) in all patients. In *a*, **p* < 0.01 for GS 9-10 as compared to other GS subgroups. In *b*, **p* < 0.05 for T3 as compared to T1 or T2

increased with increase of PSA in the interval between ≈ 5 and 20 ng/ml. The deviation from linear growth of *I* was only observed at the relatively large level of PSA (above 25 ng/ml) in three PCa patients with high GS grade (GS = 9–10) (dashed area).

The levels of serum PSA were assessed depending on GS (Fig. 4, *a*) and CS (Fig. 4, *b*). In the patients with GS (= 6, 7, and 8) the values of PSA were not significantly different (PSA ≈ 12.2 ± 1.5 ng/ml), whereas in the patients with GS (= 9–10) the PSA values were noticeably higher (PSA = 22.2 ± 3.6 ng/ml, $p < 0.05$) (see Fig. 4, *a*).

In the patients with T1 and T2 CS the values of PSA were not significantly different (PSA = 11.0 ± 1.5 (T1) and PSA = 12.4 ± 1.5 (T2)), whereas the PSA was noticeably higher in the patients with T3 and T4 stages (PSA = 19.5 ± 2.5 (T3), $p < 0.01$ and PSA = 16.8 ± 3.1 (T4)). The PSA levels in patients with T3–T4 stages were by ≈ 1.5 higher than in patients with T1–T2 stages (see Fig. 2, *b*). Thus, similar associations were found between the highest values of PSA and GS (= 9–10) (Fig. 4, *a*), and between the highest values of A_{ODC} in the second group ($A_{ODC} > 0.45$) and GS (= 9–10) (see Fig. 2, *a*).

The A_{ODC} can be regulated by different molecular biological processes. For example, ODC overexpression was observed as an early event in prostate carcinogenesis [36] and it stimulates cell proliferation at the initial stages of tumor growth [35]. The similar effect of ODC overexpression with increase of proliferation was observed in experiments with prostate tumorigenesis [26]. The malignant transformation of prostate epithelial cells seems to be accompanied by ODC overexpression.

The extent of A_{ODC} decreased with progression of cancer (at T2 and T3 stages) (see Fig. 2, *b*). The decrease in A_{ODC} at CS T2 and T3 may be associated with the accumulation of a certain amount of polyamines (e.g. putrescine, spermidine, and spermine) in the body. The synthesis of ODC is controlled by the level of polyamines and it decreased at high polyamine level [37]. For example, the experiments revealed that addition of a putrescine to the cultured H-35 cell induces the synthesis of antizyme that acts as ODC inhibitor [38].

At the terminal stages (T4), the level of ODC increases again (see Fig. 2, *b*). At this stage, the cancer cells migrate from prostate tissue and spread to the lymph nodes, bones, or liver. Investigations of the clinical and pathological data revealed that A_{ODC} was significantly higher in patients with deep tumor invasion [39].

In conclusion, the A_{ODC} and the serum PSA level can be used as supplementary indices useful for characterization of the PCa course.

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АКТИВНІСТЬ ОРНІТИНДЕКАРБОКСИЛАЗИ В ТКАНИНІ РАКУ ПЕРЕДМІХУРОВОЇ ЗАЛОЗИ

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Рак передміхурової залози є найбільш поширеним со-

лідним злоякісним новоутворенням у чоловіків. Його оцінюють за шкалою Глісона, а як біомаркер для діагностики застосовують визначення простато-специфічного антигену (ПСА). Разом з тим, як шкала Глісона, так і діагностика, що базується на визначенні ПСА, не є досконалими і мають певні обмеження. Вважають, що визначення активності орнітиндекарбоксилази (ОДК) може бути додатковим біомаркером для діагностики раку передміхурової залози або моніторингу ефективності лікування. ***Мета:*** Визначити зв'язок між активністю ОДК в тканині раку передміхурової залози та рівнем сироваткового ПСА з одного боку і показниками за шкалою Глісона та клінічною стадією, з іншого. ***Матеріали та методи:*** У дослідження були включені 29 хворих (віком від 48 до 79 років) з діагнозом раку передміхурової залози з різними показниками за шкалою Глісона (від 6 до 10) та різною клінічною стадією (від T1 до T4). Активність ОДК визначали в тканині раку передміхурової залози модифікованим спектрофотометричним методом. ***Результати:*** Хворих на рак передміхурової залози було розподілено на дві групи: з низьким (< 0.3) та високим (> 0.45) рівнем активності ОДК. У групі з низьким рівнем активності ОДК найвищі індивідуальні показники активності ОДК визначали у хворих із найнижчим показником за шкалою Глісона (= 6), у той час як у групі з високим рівнем активності ОДК найвищі індивідуальні показники активності ОДК визначали у хворих із найвищим показником за шкалою Глісона (= 9–10). У групі з високим рівнем активності ОДК (> 0.45) найвищі індивідуальні показники активності ОДК визначали у хворих з клінічними стадіями T1 або T4. Найвищі рівні сироваткового ПСА визначали у хворих з клінічними стадіями