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“Prof. Dr Paraskev Stoyanov” - Varna

Faculty of Medicine

Deparment of General and Clinical pathology, Forensic medicine and Deontology

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EXPRESSION OF TETRASPANIN MARKERS IN BENIGN PROSTATE HYPERPLASIA AND IN PROSTATE CANCER

THESIS SUMMARY

of a dissertation for award

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Supervisor
Prof. Maria Tzaneva, MD, PhD

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The dissertation contains 133 standard pages and is illustrated with 48 tables and 38 figures. The literature includes 194 literature sources, of which 4 in Cyrillic and 190 in Latin.

The dissertation is discussed and directed to the defense of the Department Council of the Department of General and Clinical Pathology, Forensic Medicine and Deontology at MU "Prof. Dr. Paraskev Stoyanov ”- Varna on October 22, 2021.

The public defense of the dissertation will be held on 20.12.2021, Monday, at ..... h, before a scientific jury composed of:

External members:

1. Prof. Dr. Radina Ivanova

2. Assoc. Prof. Dr. Veselin Belovezhdov

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ABBREVIATIONS

AJCC – American joint committee of cancer
BPH – benign prostate hyperplasia
GP – Gleason pattern
ISUP – International society of urological pathology
PNI – perineural invasion
PSA – prostate specific antigen
WHO – Wrold health organization

INTRODUCTION

According to GLOBOCAN, in the world in 2020, prostate cancer is the second most common malignancy in men and is among the most common causes of death associated with neoplastic progression (Sung H et al., 2021). In some patients, this disease is detected at an early stage and has a favorable clinical course, but in many cases at the time of diagnosis, the tumor is locally advanced and has even metastasized to regional and distant lymph nodes, bones and rarely internal organs (Fedewa SA et al., 2020; Jemal A et al., 2020).

Very little is known about a malignant process of such magnitude and social significance in relation to its etiology. The main identified risk factors for the development of prostate cancer are age, family history, some genetic mutations and ethnicity (Kheirandish P and Chinegwundoh F, 2011; Rebbeck TR et al., 2013; Ferlay J EM et al., 2019). Some environmental factors, such as physical activity and nutrition, are also important, but their role is not yet well established (Chan JM et al., 2005).

Various clinical and morphological parameters are used to assess tumor progression in order to stratify patients for appropriate treatment. Of particular importance are the local spread of the tumor in the prostate gland and the metastatic status of the patient, categorized by TNM-classification (Moch H et al. 2016; Amin MB et al., 2017; van der Poel H et al., 2019; Cimadamore A et al. 2020). The degree of differentiation is categorized on the basis of different histological models of tumor growth and is determined by Gleason score. Based on Gleason score differentiation, tumors were divided into 5 different prognostic groups (Gnanapragasam VJ et al., 2018). Another important clinical and laboratory indicator is

preoperative PSA (prostate-specific antigen) values, which are used both to stratify the risk of recurrence and to monitor the effect of therapeutic interventions in the long term (Descotes JL., 2019; Iwamoto H et al., 2019).

Modern medicine is constantly striving to improve diagnostic and treatment methods by studying new molecules that would be important as prognostic factors for risk assessment and as potential target molecules for targeted therapy in oncology. In-depth analysis of the distribution and function of such molecules in tumor and non-tumor tissue can answer many questions related to the biology of neoplastic diseases and improve the survival and quality of life of patients by influencing key stages in oncogenesis, tumor progression and metastasis.

Molecules with such clinical potential are tetraspanin proteins. They are transmembrane proteins with diverse physiological functions and act as mediators in the processes of cell migration and complex cellular interactions with the extracellular matrix (Yunusova N.V et al., 2018). Research in recent years has revealed their importance in the processes of invasion and metastasis in a number of neoplastic diseases (Tokuhara T et al., 2001; Hashida H et al., 2003; Zhu GH, 2010; Suzuki S et al., 2010; Voss MA et al., 2011; Lorico A et al., 2021). Two members of this group, CD9 and CD151, have been considered in the light of suppressors and promoters of tumor progression, but the data for different neoplasms are very contradictory (Ang J et al., 2004; Detchokul S et al., 2013; Sadej R et al., 2014; Han R et al., 2020; Lorico A et al., 2021).

Their in-depth study in the context of prostate cancer would not only lead to a better understanding of the biological features of this disease, but would also allow the identification

of new prognostic and predictive factors, as well as new molecules for targeted therapy in oncology.

PURPOSE AND TASKS OF THE DISSERTATION WORK

Purpouse

The aim of the present study was to analyze the clinical and morphological parameters of patients with non-advanced and advanced prostate cancer in relation to the immunohistochemical expression of tetraspanins CD9 and CD151 and to elucidate their role in tumor progression.

Tasks

In connection with this goal, the following main tasks were formulated:

1. To study the clinical and morphological characteristics of patients with non-advanced and advanced prostate cancer.

2. To perform a comparative analysis between the different clinical and morphological parameters in patients with non-advanced and advanced prostate cancer.

3. To study the immunohistochemical expression of CD9 and CD151 in prostate cancer tumor tissue and to compare it with the expression in prostate hyperplasia.

4. To analyze the immunohistochemical expression of CD9 and CD151 in relation to clinical and morphological parameters in non-advanced and advanced prostate cancer.

MATERIALS AND METHODS FOR RESEARCH

Bases for realization of the dissertation work

- Department of General and Clinical Pathology, Forensic Medicine and Deontology, Faculty of Medicine, Medical University - Varna
- Clinic of General and Clinical Pathology at the University Hospital "St. Marina EAD – Varna

The study included prostate biopsy materials from a total of 101 patients, of which the target group was 91 patients diagnosed with prostate cancer and 10 patients had no tumor process and formed the control group.

Of all 91 patients, 50 had no distant metastases (M0) (non-advanced carcinomas) and 41 had cancers with distant metastases (M1) (advanced carcinomas).

The ten patients in the control group were diagnosed with BPH (benign prostatic hyperplasia). They were used to assess the expression of tetraspanin markers CD9 and CD151 in the prostate.

Histological materials were used from ready paraffin blocks from the histology of the Clinic of General and Clinical Pathology of UMHAT "St. Marina" - Varna, diagnosed with prostate cancer on thick needle biopsies, from radical prostate resections, and from transurethral resection of the prostate.

For the purposes of this study, the following clinical and morphological parameters were determined: histological type of tumor, TNM stage, degree of differentiation, perineural invasion, presence of tumor necrosis, presence of cribriform histological structure.

An indirect immunoperoxidase method was used for immunohistochemical analysis using the mini KIT high Ph DAKO K8024. The antibodies, staining reagents, and operating

concentrations used are presented in **Tables 1 and 2**. The following antibodies were used: Anti-CD151 murine monoclonal antibody cataloged №33315 and Anti-CD9 rabbit monoclonal antibody cataloged №92726. The antibodies are manufactured by ABCAM's RabMab technology.

In negative controls, instead of the primary antibody, sections of the paraffin blocks used were incubated with normal non-immune serum. Tonsil and colorectal carcinoma tissues stained for CD9 and CD151, respectively, were used for positive controls.

Table 1. *Reagents used*

Antibody	**Dilution**	**Positive control**	**Marker for**	**Manufacturer**
Anti-CD151 (ab33315)	1:200	Colorectal adenocarcinoma	Tetraspanin CD151	ABCAM
Anti-CD9 (ab92726)	1:600	Tonsillar tissue	Tetraspanin CD9	ABCAM

Table 2. *Staining systems and other reagents*

Product	**Application**	**Manufacturer**
HRP-DAB System	Original staining system	Dako
Mayer's hematoxylin	Counterstaining	Dako

Immunohistochemical expression of CD9 and CD151 was assessed using an H-score (histological score). For each

epithelial cell of the different gland types (tumor and non-tumor), the intensity of cytoplasmic expression was determined as follows:

• 0 in the absence of cytoplasmic expression, the cytoplasm is colorless

• 1+ with weak cytoplasmic expression - the cytoplasm is light yellow

• 2+ with moderate cytoplasmic expression - the cytoplasm is light brown

• 3+ in case of intensive cytoplasmic expression - the cytoplasm is dark brown

We determine the percentage of positive cells for each intensity, and finally the H-score is calculated by the following formula: 1x (% cells with 1+) + 2x (% cells with 2+) + 3x (% cells with 3+). Thus calculated, the range of H-score varies from 0 to 300.

Statistical methods

The used statistical methods are in accordance with the specifics of the set tasks, the type of the studied variables and the scales for their measurement.

Qualitative variables are represented by absolute number and relative share in the descriptive analysis of participants' demographic and clinical characteristics, and quantitative variables by mean and standard deviation / median and interquartile range depending on the distribution.

The chi - square test was used to test hypotheses for the relationship between two qualitative variables. Spearman's rank correlation was used to study the relationship between two quantities measured on the ordinal scale. The correlation between two quantitative variables was tested by Pearson's correlation analysis.

Comparisons between two quantitative variables were made with Student's t test, and when compared between more than two groups - with one-way analysis of ANOVA variance.

Each indicator is presented with a 95% confidence interval.

All statistical tests are two-way.

The results are reported as statistically significant at an allowable error level of alpha = 0.05.

The results are summarized in tables and illustrated with appropriate graphs.

Statistical analyzes were performed with the statistical package IBM SPSS ver. 21, and the graphs are built in Microsoft Excel for Winodws.

RESULTS

Clinical and morphological characteristics of patients with non-advanced and advanced prostate cancer

Biopsy materials

Of the 50 non-advanced cancers, 32 were diagnosed with resection and the remaining 18 with thick-needle biopsy. All 41 cases of advanced prostate cancer were evaluated on thick-needle biopsy material because patients did not undergo surgical treatment after imaging evidence of metastatic disease. Only conventional adenocarcinomas of the prostate were included in the study.

Age distribution of patients with non-advanced and advanced prostate cancer

In the present study, 91 patients with prostate cancer diagnosed at the Clinic of General and Clinical Pathology at the University Hospital "St. Marina EAD – Varna", as 50 (54.95%) have non-advanced cancer and 41 (45.05%) have advanced cancer. The mean age of the patients was 69.39 ± 7.98 years, with a minimum age of 45 years and a maximum age of 90 years. In the group selected by us, prostate cancer is most often found in the age groups 60-69 years and 70-79 years, respectively (37 (40.66%) and 38 (41.76%) cases, less common over 80 years of age - 10 (10.99%) cases, and under the age of 60 there are only 6 (6.59%) cases **(Figure 1)**.

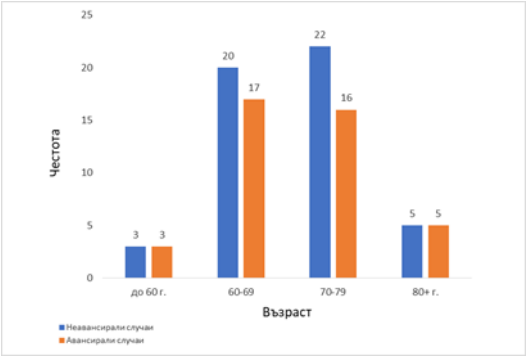

Figure 1. *Frequency of age distribution of patients with non-advanced and advanced prostate cancer*

The mean age of patients with non-advanced prostate cancer was 70.1 ± 7.12 years, and that of advanced cancer was 70.02 ± 8.93 years. **Figure 2** shows the relative proportion of patients by age, with this proportion for non-advanced and advanced cancer being highest in the 60-69 and 70-79 age groups. In the non-advanced 3 (6%) cases are in the age group up to 60 years, 20 (40%) are in the group from 60 to 69 years, 22 (44%) are aged from 70 to 79 years and 5 (10%) are at over 80 years of age. The distribution is similar in the group of advanced cancers - 7% of patients are under 60 years of age, 41% are aged from 60 to 69 years, 39% are aged from 70 to 79 years and 12% are over 80 years old.

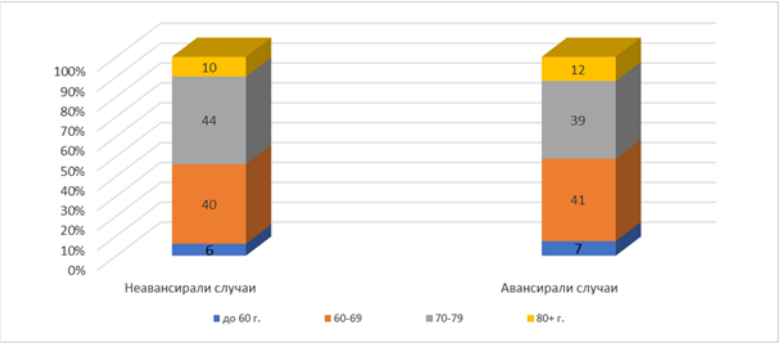

Figure 2. *Percentage distribution of non-advanced and advanced cases by age*

Clinical and morphological characteristics of patients with non-advanced prostate cancer

Of the 50 cases of non-advanced cancer, 46 had clinical and laboratory data on PSA values prior to histological examination. Of these 46 cases, 22 (47.83%) had a PSA below 10.00 ng / mL, 11 (23.91%) had a PSA between 10.00 and 20.00 ng / mL, 9 (19.57%).) between 20.01 and 50.00 ng / mL and 4 (8.70%) with a PSA above 50.00 ng / mL **(Figure 3)**.

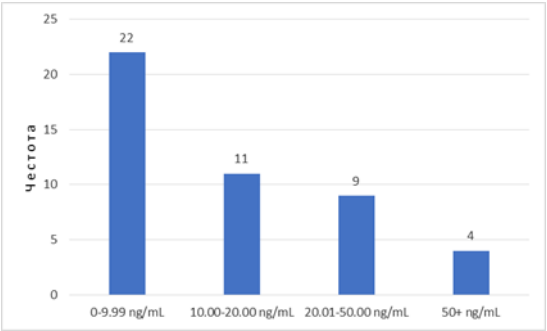

Figure 3. *Distribution of PSA values in patients with non-advanced cancer*

Of all the 50 non-advanced cancers studied, a cribriform growth pattern **(Figure 5)** was found in 27 (54%) cases, while in 23 (46%) cases it was absent **(Figure 4)**.

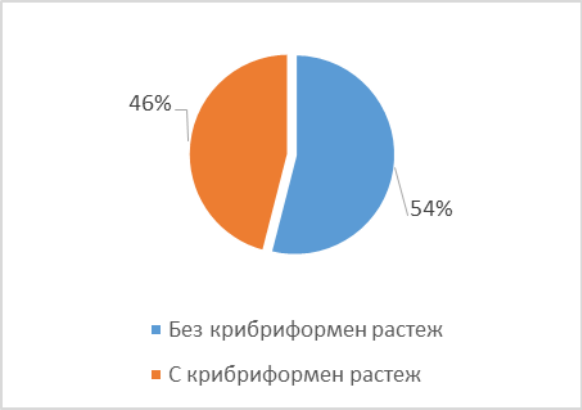

Figure 4. *Relative share of distribution of carcinomas with cribriform growth pattern in non-advanced prostate cancer*

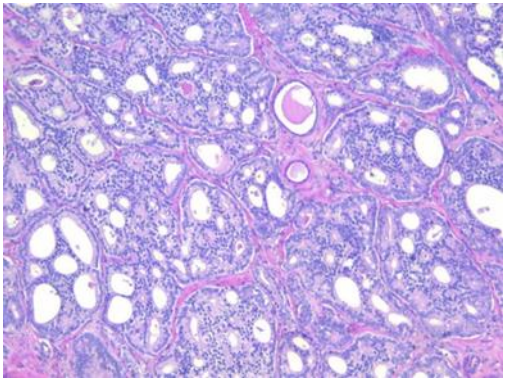

Figure 5. *Cribriform growth pattern in prostate cancer, x100*

In 12 (24%) of non-advanced cancers Gleason score is 6, in 22 (44%) is 7, in 9 (18%) is 8, in 6 (12%) is 9 and only in 1 (2%) is 10 **(Figure 6)**. When distributed by prognostic groups, they are 12 (24%) in Grade Group 1, 17 (34%) in Grade Group 2 and 7 (14%) in Grade group 3, 4 and 5, respectively **(Figure 7)**.

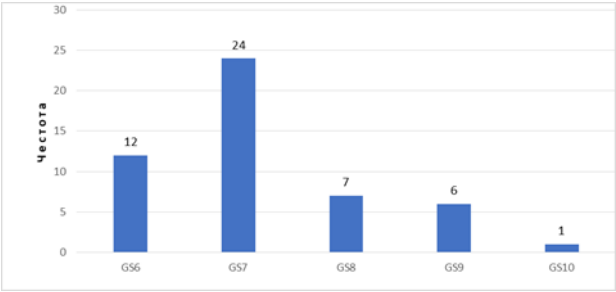

Figure 6. *Distribution of non-advanced prostate cancers according to Gleason score.*

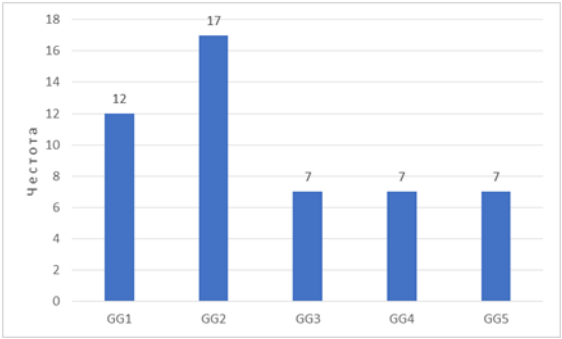

Figure 7. *Distribution of non-advanced prostate cancers according to Grade group.*

Perineural invasion was found in 35 (70%) of all non-advanced cancers, while in 15 (30%) of them it was absent **(Figure 8 and Figure 9)**.

Figure 8. *Number of cases of perineural invasion in the group of non-advanced carcinomas.*

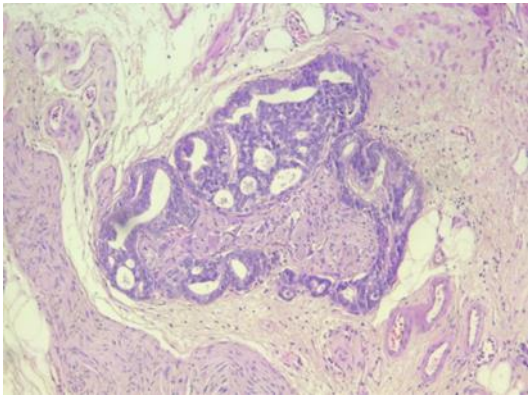

Figure 9. Focus of perineural and ganglion invasion of prostate cancer, x100

No tumor necrosis was found in any of the 50 cases of non-advanced prostate adenocarcinoma studied.

Taking into account the local progression of non-advanced carcinomas, 29 (58%) of them were confined to the prostate gland, 20 (40%) showed extraprostatic extension in the capsule or seminal vesicles, and only 1 (2%) involved adjacent prostate structures **(Table 3)**.

Table 3. *Distribution of cases with non-advanced cancer according to pathological T-stage*

T-stage	**Cases (n)**	**%**
2	29	58,0
3	20	40,0
4	1	2,0
Total	**50**	**100,0**

Advanced prostate cancer

PSA values in advanced carcinomas

From the group of advanced carcinomas (41 in number) for 35 patients there were clinical and laboratory data on PSA values before histological examination. Of these 35 cases, 2 (5.71%) had a PSA below 10.00 ng / mL, 2 (5.71%) had a PSA between 10.00 and 20.00 ng / mL, 4 (11.43%).) between 20.01 and 50.00 ng / mL and 27 (77.14%) with a PSA above 50.00 ng / mL **(Figure 10)**.

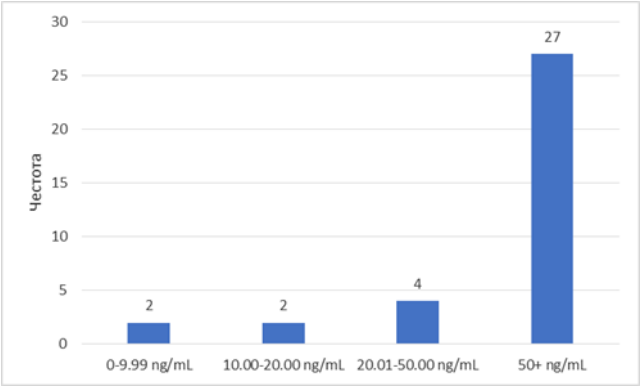

Figure 10. *PSA values in patients with advanced cancer*

Morphological characteristics of advanced prostate carcinomas

Of all 41 cases of advanced carcinomas, 30 (73.2%) had a cribriform growth pattern, while 11 (26.8%) had no cases **(Figure 11)**.

Figure 11. *Number of cases with cribriform growth pattern in advanced cancer*

In 1 (2.4%) of advanced cancers Gleason score is 6, in 4 (9.8%) is 7, in 15 (36.6%) is 8, in 16 (39%) is 9 and in 5 (12.2%) is 10 **(Figure 12)**. When distributed by prognostic groups, they are respectively 1 (2.4%) in Grade Group 1, 4 (9.8%) in Grade Group 2, 0 in Grade group 3, 15 (36.6%) in Grade group 4 and 21 (51.2%) in Grade group 5 **(Figure 13)**.

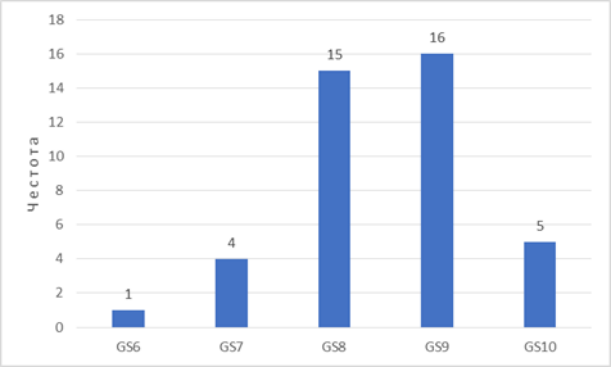

Figure 12. *Distribution of metastatic carcinomas according to Gleason score*

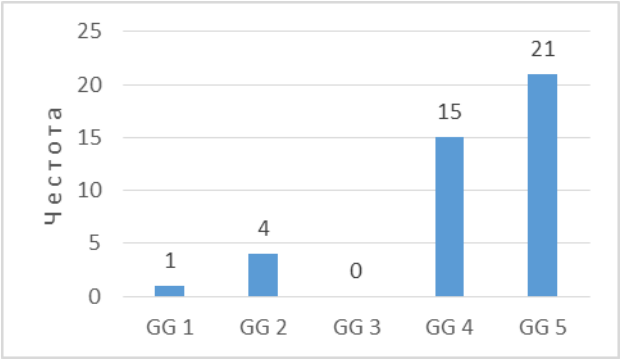

Figure 13. *Distribution of advanced carcinomas according to Grade group.*

In the group of advanced carcinomas, histological data for perineural invasion were found in 28 (68.3%) cases, and in 13 (31.7%) they were absent **(Figure 14)**.

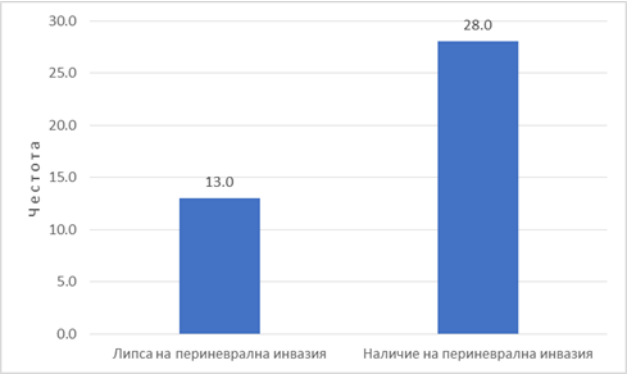

Figure 14. *Number of cases of perineural invasion in advanced carcinomas*

Histological data on tumor necrosis were found in 4 (9.8%) of all 41 cases of advanced cancer, and in 37 (90.2%) cases they were missing **(Figure 15)**.

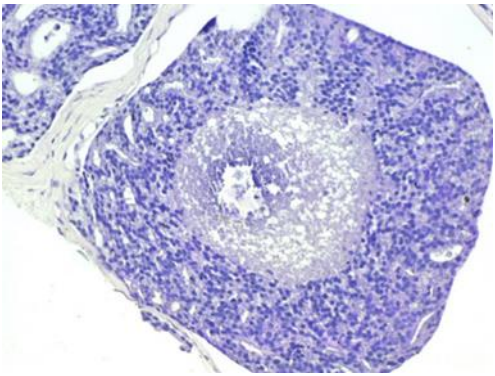

Figure 15. *Focus of comedonecrosis in a solid tumor nest, GP5, x200*

Taking into account the local progression of advanced carcinomas, 35 (85.4%) of them were restricted in the prostate gland, 3 (7.3%) showed extraprostatic extension in the capsule or seminal vesicles and 3 (7.3%) were engaged adjacent to the prostate structures **(Table 4)**.

Table 4. *Distribution of advanced carcinomas by stage*

T-stage	Cases (n)	%
2	35	85,4
3	3	7,3
4	3	7,3
Total	**41**	**100**

Of the studied 41 cases with metastases, 36 (87.80%) were only with bone metastases, in 2 (4.88%) cases there was involvement of bones and lungs, bones and distant lymph nodes in 1 (2.44%) case, 1 (2.44%) case was with bone and brain metastases. Isolated lung metastases were found in one (2.44%) case **(Table 5)**.

Table 5. *Distribution of advanced cases by localization of distant metastases*

Localisation	**Cases (n)**	**%**
Bones	36	87,80
Bones and lungs	2	4,88
Bones and distant LN	1	2,44
Lungs	1	2,44
Bones and CNS	1	2.44
Total	**41**	**100**

Comparative analysis of data between clinical and morphological parameters in patients with non-advanced and advanced prostate cancer

The comparative analysis of the variables up to and over 70 years of age and PSA did not reveal a statistically significant relationship between them, both in the group of non-advanced tumors (p = 0.275) and in the group of advanced carcinomas (p = 0.196) **(Table 6)**.

Table 6. *Relationship between the variables "PSA" and "age" in non-advanced and advanced tumors*

Group	**Cases (n)**	**PSA**	**p-value**
Non-advanced		Mean (SD)	
Up to 70 y	23	13,5 (8,01)	
70 y +	27	67,3 (228,06)	
Total	50	41,5 (165,4)	0,275
Advanced			
Up to 70 y	20	493,4 (1238,8)	
70 y +	21	117,0 (135,0)	0,196

Total	41	289,1 (850,2)	

Indicator: p = 0.275; p = 0.196

In the group of non-advanced tumors, patients under 70 years of age had a mean PSA value of 13.5 ng / mL, and those over 70 years of age had a mean PSA of 67.3 ng / mL at a markedly high standard deviation (228.06 ng / mL). . PSA levels were highest in younger patients with metastases at 493.4 ng / mL at a standard deviation of 1238.8 ng / mL. Elderly patients with advanced disease had a mean PSA level of 117.0 ng / mL. The comparative analysis between the age variables and the Gleason score showed that in the age groups 60-69 years and 70-79 years the patients with Gleason score <8 or ≥8 were the most numerous **(Table 7)**. No statistical relationship between age and Gleason score <8 or ≥8 was found (p = 0.202). There was also no statistical relationship between age and Gleason score (<8 and ≥8) in patients with non-advanced prostate cancer **(Table 8)**. In advanced carcinomas, a statistical relationship was found between age and Gleason score (p = 0.023). The Gleason score increases with age (80+ years) **(Table 9)**. All patients with distant metastases and over the age of 80 years had carcinoma with GS≥8.

Table 7. *Relationship between age variables and Gleason score in the studied patients with prostate cancer*

Age	**Gleason score < 8**	**Gleason score ≥ 8**
	Cases (%)	Cases (%)
Up to 59 y	5 (12,2)	1 (2,0)
60-69 y	17 (41,5)	20 (40,0)
70-79 y	16 (39,0)	22 (44,0)

80 y +	3 (7,3)	7 (14,0)
Total	**41 (100)**	**50 (100)**

Indicator: p = 0.202

Table 8. *Relationship between the variables Age and Gleason score in the group of non-advanced tumors*

Age	**Gleason score < 8**	**Gleason score ≥ 8**
	Cases (%)	Cases (%)
Up to 59 y	3 (8,3)	0 (0,0)
60-69 y	15 (41,7)	5 (35,7)
70-79 y	15 (41,7)	7 (50,0)
80 y +	3 (8,3)	2 (14,3)
Total	**36 (100,0)**	**14 (100,0)**

Indicator: p = 0.621

Table 9. *Relationship between age variables and Gleason score in the group of advanced tumors*

Age	**Gleason score < 8**	**Gleason score ≥ 8**
	Cases (%)	Cases (%)
Up to 59 y	2 (40,0)	1 (2,8)
60-69 y	2 (40,0)	15 (41,7)
70-79 y	1 (20,0)	15 (41,7)
80 y +	0 (0,0)	5 (13,9)
Total	**5 (100,0)**	**36 (100,0)**

Indicator: p = 0.023

Comparative analysis of data between PSA and clinical and morphological parameters in patients with non-advanced prostate cancer

The analysis between PSA values in the group of non-advanced carcinomas and cribriform histological growth showed that at high PSA values, tumors more often have cribriform structures (p = 0.017) **(Table 10)**.

Table 10. *Relationship between the cribriform growth model and PSA*

Cribriform structures	**Cases (n)**	**Mean ng/mL**	**SD ng/mL**
Present	26	11,59	8,37
Absent	20	24,37	23,92
Total	**46**	**17,27**	**18,07**

Indicator: p = 0.017

The comparative analysis of the mean PSA values in the groups with different Gleason score shows a tendency to increase PSA with increasing Gleason score (p = 0.002) **(Table 11)**.

Table 11. *Mean PSA value based on Gleason score in non-advanced cancer*

Gleason score	**Cases (n)**	**Mean ng/ML**	**SD**
6	10	8,7	4,36
7	24	13,9	11,67
8-9	11	32,5	27,43
Total	**45**	**17,3**	**18,08**

Indicator: p=0,002

The mean PSA value in patients with Gleason score 6 was 8.7 ng / mL, in Gleason score 7 - 13.9 ng / mL, and in patients with Gleason score - 32.5 ng / mL.

The mean PSA value for tumors with perineural invasion was 21.45 ± 20.77 ng / mL and was higher than that for carcinomas without evidence of perineural invasion - 8.93 ± 4.58 ng / mL and the difference was statistical. significant (p = 0.027) **(Table 12)**.

Table 12. *Mean PSA values depending on the presence of PNI in non-advanced carcinomas*

PNI	**Cases (n)**	**Mean (ng/mL)**	**SD (ng/mL)**
PNI (-)	15	8,93	4,58
PNI (+)	30	21,45	20,77
Total	**45**	**17,28**	**18,07**

Indicator: p = 0.027

Analysis of the relationship between PSA and T-stage in patients without metastases did not show a relationship between the two variables. The mean PSA value in lower T-stage tumors was 15.32 ± 19.40 ng / mL. Tumors with more advanced local stage had a mean PSA value of 19.71 ± 16.42 ng / mL **(Table 13)**.

Table 13. *Mean T-stage PSA values in non-advanced carcinomas.*

T-stage	**Брой (n)**	**Mean (ng/mL)**	**SD (ng/mL)**
T2	25	15,32	19,40
T3, T4	20	19,71	16,42
Total	**45**	**17,27**	**18,08**

Indicator: p = 0.424

Comparative analysis between PSA values and morphological parameters in patients with advanced prostate cancer

In advanced tumors, the mean PSA values in the cribriform growth model were higher (127.82 ng / mL) compared to the absence of a similar model (70.65 ng / mL), but the difference was not statistically significant (p = 0.217) **(Table 14)**.

Table 14. *Relationship between the "Cribriform Growth Model" and PSA in advanced tumors*

Cribriform structures	**Cases (n)**	**Mean (ng/mL)**	
Present	7	70,65	48,58
Absent	26	127,82	116,20
Total	**33**	**115,70**	**107,49**

Indicator: p = 0.217

The mean PSA values for tumors with a cribriform structure were 24.37 ± 23.92 ng / mL, which is more than twice the values for tumors without similar structures.

When analyzing the mean PSA values in the group of advanced tumors, no statistically significant relationship was found between PSA levels and Gleason score (p = 0.425) **(Table 15)**.

Table 15. *PSA mean values according to Gleason score*

Gleason score	**Cases (n)**	**Mean (ng/mL)**	**SD (ng/mL)**

6	1	44,1	0
7	3	39,6	52,27
8	10	103,4	52,98
9	19	137,9	130,32
Total	**33**	**115,7**	**107,50**

Indicator: p = 0.425

Despite the lack of dependence between the two indicators, a tendency to increase the average PSA values compared to the Gleason score was observed. At Gleason score 8 and 9, i.e. in low-grade tumors, the values were 103.4 ng / mL and 137.9 ng / mL, respectively, and they were higher than high- (Gleason score 6) and moderately differentiated carcinomas (Gleason score 7), 44.1 ng / mL, respectively. and 39.6 ng / mL.

When analyzing the mean PSA values in the group of metastatic tumors, no statistically significant relationship was found between PSA levels and the presence of perineural invasion (p = 0.731) **(Table 16)**.

Table 16. *Mean PSA values depending on the presence of PNI in metastatic carcinomas*

PNI	**Cases (n)**	**Mean (ng/mL)**	**SD (ng/mL)**
PNI (-)	10	105,73	50,47
PNI (+)	23	120,03	125,30
Total	**33**	**115,70**	**107,50**

Indicator: p = 0.731

Comparative analysis of the mean values of "PSA" versus "M-stage" in patients with prostate cancer

The analysis of the mean PSA values in the patients with prostate cancer showed a tendency to increase the PSA in the group of advanced tumors compared to the non-advanced ones. The mean PSA level in patients without distant metastases was 17.27 ± 18.07 ng / mL, while in metastatic cases it was significantly higher - 115.70 ± 107.49 ng / mL and the difference was statistically significant (p < 0.001) **(Table 17)**.

Table 17. *Mean values of PSA depending on the M-stage*

M-stage	**Cases (n)**	**Mean (ng/mL)**	**SD (ng/mL)**
M0	45	17,27	18,07
M1	33	115,70	107,49
Total	**78**	**58,91**	**85,93**

Indicator: p <0.001

Comparative analysis between morphological parameters in patients with non-advanced prostate cancer

Of the 15 non-advanced tumors without perineural invasion, only one (6.8%) had histological evidence of cribriform growth. Tumors with perineural invasion had cribriform structures in 22 (62.9%) cases and in the remaining 13 (37.1%) cases they were absent. Comparative analysis between the two variables showed that in non-advanced prostate carcinomas, a cribriform growth pattern was more commonly associated with perinerval invasion (p <0.001) **(Table 18)**.

Table 18. *Relationship between cribriform growth pattern and perineural invasion in non-advanced tumors.*

	ПНИ		
	ПНИ (-)	**ПНИ (+)**	**Общо**

Cribriform structures	Cases (%)	Cases (%)	Cases (%)
Present	14 (93,3)	13 (37,1)	27 (54,0)
Absent	1 (6,8)	22 (62,9)	23 (46,0)
Total	**15 (100,0)**	**35 (100,0)**	**50 (100,0)**

Indicator: p <0.001

Table 19. *Comparison between the degree of differentiation and perineural invasion in non-advanced carcinomas*

Gleason score	**ПНИ -**		**ПНИ +**		**Total**	
	Cases	%	Cases	%	Cases	%
6	7	46,7 %	3	8,6%	10	20,0 %
7	6	40,0 %	20	57,1 %	26	52,0 %
8	2	13,3 %	5	14,3 %	7	14,0 %
9 и 10	0	0,0%	7	20,0 %	7	14,0 %
Total	**15**	**100 %**	**35**	**100 %**	**50**	**100 %**

Indicator: p = 0.011

In the group of non-advanced carcinomas, the comparative analysis between Gleason score and perineural invasion showed a relationship between the two variables (p = 0.011). Of the 15 cases without perineural invasion, most were

those with Gleason score 6 - 7 (46.7%) cases, followed by those with Gleason score 7 - 6 (40.0%) cases and Gleason score 8 - 2 (13.3%) cases. In the group of carcinomas without PNI there were no cases with Gleason score 9 and 10. In non-advanced carcinomas with perineural invasion most were those with Gleason score 7 - 20 (57.1%), followed by the total Gleason score 9 and 10 - 7 (20.0%) of the case. Gleason score 8 was found in 5 (14.3%) cases and only 3 (8.6%) cases had Gleason score 6 **(Table 19)**.

In the majority of tumors - 18 (66.7%) cases, which were in pathological stage T2, there were no morphological data for a cribriform growth model. This growth model was not found in 9 (39.1%) of the tumors in -advanced pathological stage (T3 and T4), but the difference was not statistically significant (p = 0.052) **(Table 20)**.

Table 20. *Relationship between the cribriform growth pattern and the T-stage in non-advanced carcinomas*

	T-stage		
	T2	T3, T4	Total
Cribriform structures	Брой (%)	Брой (%)	Брой (%)
Present	18 (66,7)	9 (39,1)	27 (54,0)
Absent	9 (33,3)	14 (60,9)	23 (46,0)
Total	**27 (100,0)**	**23 (100,0)**	**50 (100,0)**

Indicator: p = 0.052

The comparative analysis between "Gleason score" and "T-stage" found a statistically significant difference between the two variables (p = 0.035). Gleason score 6 was more

common in stage T2 - 7 (25.9%) cases, while events in stage T3 + T4 were 3 (13.0%). Gleason scores 8 and 9 were more common in stage T3 + T4 than in stage T2, in 9 (39.1%) cases and 5 (18.1%) cases, respectively. Gleason score 7 in T2 stage was present in 15 (55.6%) cases and in 11 (47.8%) in T3 + T4 stage **(Table 21)**.

Table 21. *Degree of tumor differentiation "Gleason score" depending on "T-stage"*

	T-stage		
	T2	T3, T4	**Total**
Gleason score	Cases (%)	Cases (%)	Cases (%)
6	7 (25,9)	3 (13,0)	10 (20,0)
7	15 (55,6)	11 (47,8)	26 (52,0)
8, 9	5 (18,1)	9 (39,1)	14 (28,0)
Total	**27 (100,0)**	**23 (100,0)**	**50 (100,0)**

Indicator: p = 0.035

The study of the two variables in the group of non-advanced tumors showed that in carcinomas with more advanced T-stage the frequency of perineural invasion is 87.0% and it is significantly higher than in tumors with earlier T-stage (13,0%) **(Table 22)**.

Table 22. *Relationship between perineural invasion and T-stage in non-advanced carcinomas*

	T-stage		
	T2	T3, T4	Total
PNI	Cases (%)	Cases (%)	Cases (%)
PNI (-)	12 (44,4)	3 (13,0)	15 (30,0)

PNI (+)	15 (55,6)	20 (87,0)	35 (70,0)
Total	**(100,0)**	**(100,0)**	**50 (100,0)**

Indicator: p = 0.016

Comparative analysis between morphological parameters in patients with advanced prostate cancer

When comparing the two variables: "cribriform growth pattern" and "perineural invasion" in the group of advanced tumors, no statistically significant relationship was found between them. In the group of advanced prostate carcinomas, the presence of cribriform structures was more frequent compared to their absence, both in the 13 carcinomas without perineural invasion (61.5%) and in the 28 tumors with perineural invasion (78.6 %) **(Table 23)**.

Table 23. *Dependence between cribriform structure and PNI in advanced tumors*

	PNI		
	PNI (-)	**PNI (+)**	**Total**
Cribriform strucutres	Брой (%)	Брой (%)	Брой (%)
Present	5 (38,5)	6 (21,4)	11 (26,8)
Absent	8 (61,5)	22 (78,6)	30 (73,2)
Total	**13 (100,0)**	**28 (100,0)**	**41 (100,0)**

Indicator: p = 0.252

In advanced prostate cancer, a comparative analysis between Gleason score and perineural invasion showed no relationship between the two variables (p = 0.385). In tumors with perineural invasion and without perineural invasion, the high Gleason score of 9 and 10 prevailed, in 6 (46.2%) cases without perineural invasion and 15 (53.6%) cases with perineural invasion, respectively **(Table 24)**.

Table 24. *Comparison between Gleason score and perineural invasion in advanced carcinomas*

Gleason score	**PNI -**		**PNI +**		**Total**	
	Cases	%	Cases	%	Cases	%
6	1	7,7%	0	0,0%	1	2,4%
7	2	15,4%	2	7,1%	4	9,8%
8	4	30,8%	11	39,2%	15	36,6%
9 и 10	6	46,2%	15	53,6%	21	51,2%
Total	**13**	**100,0 %**	**28**	**100,0 %**	**41**	**100,0 %**

Value: p = 0.385

Comparative analysis of data between the variables "Cribriform growth model" and "M-stage" in non-advanced and advanced prostate cancers

The analysis of the data between the two variables showed that the frequency of the cribriform growth model was higher in advanced tumors than in non-advanced ones and the difference was statistically significant (p = 0.009). In non-advanced carcinomas, the lack of cribriform structures is more common than their presence (54% vs. 46%). In advanced tumors, tumors with a cribriform structure predominated

(73.2%) and they were almost 3 times more than tumors without such growth (26.8%) **(Table 25)**.

Table 25. *Relationship between the cribriform growth model and the M-stage*

	M-стадий		
	M0	M1	Total
Cribriform structures	Брой (%)	Брой (%)	Брой (%)
Present	27 (54,0)	11 (26,8)	38 (41,8)
Absent	23 (46,0)	30 (73,2)	53 (58,2)
Total	**50 (100,0)**	**41 (100,0)**	**91 (100,0)**

Indicator: p = 0.009

Comparative analysis between Gleason score and M status of patients with prostate cancer

The comparative analysis between Gleason score and M stage in patients with prostate cancer showed a statistically significant relationship between the two variables (p <0.001) **(Table 26)**.

Table 26. *Comparison between Gleason score and M1 status of patients with advanced prostate cancer*

Gleason score	**Cases M0**		**Cases M1**		**Total**	
	Cases	%	Cases	%	Cases	**%**
6	10	20,0%	1	2,4%	11	12,1%
7	26	52,0%	4	9,8%	30	33,0%

8	7	14,0%	15	36,6%	22	24,2%
9	6	12,0%	16	39%	22	24,2%
10	1	2,0%	5	12,2%	6	6,6%
Total	**50**	**100%**	**41**	**100%**	**91**	**100%**

Value: p <0.001

In non-advanced carcinomas Gleason score 7 - 26 (52.0%) cases predominate, while in patients with distant metastases the most common is Gleason score 9 - 16 (39.0%) cases, followed by Gleason score 8 - 15 (36, 6%) of the case. Gleason score 6 occurs in 10 (20.0%) cases with non-advanced cancer and only in 1 (2.4%) case the cancer is in M1 stage. Gleason score 8, 9 and 10 occur in non-advanced cancers in 7 (14.0%) cases, 6 (12.0%) cases and 1 (2.0%) case, respectively. Gleason score 7 and 10 in cancers with distant metastases were found in 4 (9.8%) and 5 (12.2%) cases, respectively.

Analysis of the relationship between perineural invasion and M-stage of patients

When analyzing the presence of perineural invasion in patients with prostate cancer, we did not find a relationship between perineural invasion and the presence of distant metastases. Perineural invasion had a similar predominance in both groups of tumors: it was reported in 70.0% of non-advanced tumors and in 68.3% of tumors with distant metastases **(Table 27)**.

Table 27. *Relationship between perineural invasion and M-stage*

	M-stage		
	M0	M1	Total
PNI	Cases (%)	Cases (%)	Cases (%)
PNI (-)	15 (30,0)	13 (31,7)	28 (30,8)
PNI (+)	35 (70,0)	28 (68,3)	63 (69,2)
Total	**50 (100,0)**	**41 (100,0)**	**91 (100,0)**

Indicator: p = 0.861

Analysis of the mean values of cytoplasmic expression of CD9 in non-advanced and advanced carcinoma and BPH

The highest mean levels of cytoplasmic expression of CD9 were found in the BPH group (91.40 ± 57.39). In carcinomas, the values were lower, respectively 91.40 ± 57.39 for non-advanced cancer and 96.95 ± 54.91 for advanced tumors, but there was no statistically significant difference (p = 0.314) **(Table 28, Figures 16-18)**.

Table 28. *Mean cytoplasmic expression of CD9 in the three study groups of patients*

Group	**Cases**	**Mean**	**SD**
M0	50	91,40	57,39
M1	41	96,95	54,97
BPH	10	120,00	18,71
Total	**101**	**96,49**	**54,06**

Value: p=0,314

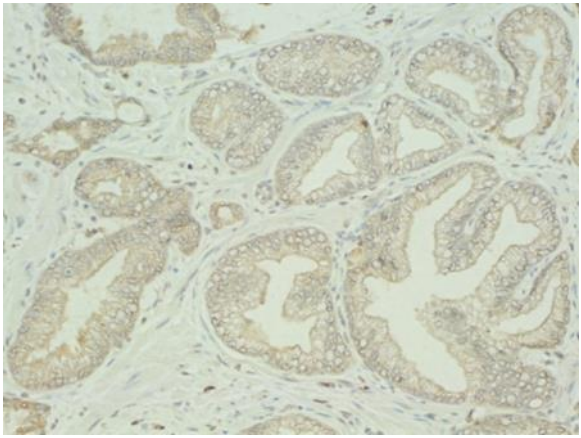

Figure 16. *Cytoplasmic expression of CD9 in non-advanced carcinoma, x100*

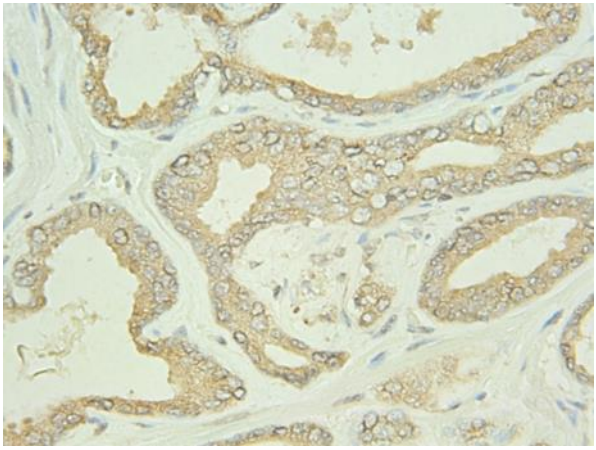

Figure 17. *Cytoplasmic expression of CD9 in advanced carcinoma, x200*

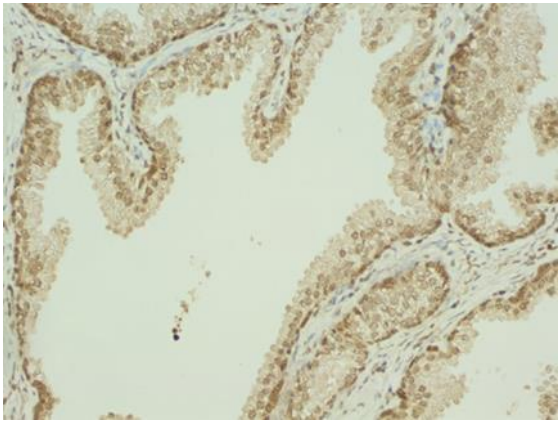

Figure 18. *Cytoplasmic expression in benign glands, x200*

Immunohistochemical expression of CD9 in non-advanced prostate cancer

The distribution of non-advanced prostate cancers according to CD9 expression levels calculated on the basis of H-score is as follows: 14 (28%) cases with H-score 0-50, 19 (38%) with 51-100, 11 (22%) with 101-150, 2 (4%) with 151-200, 4 (8%) with 201-250 **(Figure 19)**.

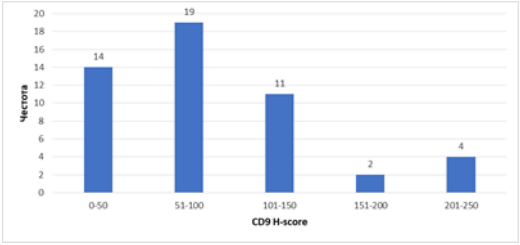

Figure 19. *CD9 expression levels in non-advanced H-score carcinomas.*

Immunohistochemical expression of CD9 in advanced prostate cancer

The distribution of advanced prostate cancers according to CD9 expression levels calculated on the basis of H-score is as follows: 13 (31.7%) cases with H-score 0-50, 11 (26.8%) with 51 -100.9 (22%) with 101-150.6 (14.6%) with 151-200.2 (4.9%) with 201-250 **(Figure 20)**.

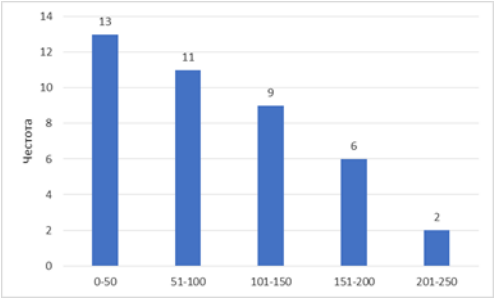

Figure 20. *CD9 expression levels in advanced H-score carcinomas.*

Analysis of mean cytoplasmic expression of CD151 in non-advanced and advanced carcinoma and BPH

The study of the mean values between these groups showed the highest levels in advanced carcinomas (203.05 ± 61.41), but the difference was not statistically significant (p = 0.325). The lowest level was in the BPH group - 181.50 ± 26.88 **(Table 29, Figures 21-23)**.

Table 29. *Mean cytoplasmic expression of CD151 in the three groups of patients*

Group	Cases	Mean	SD
M0	50	184,40	68,57

M1	41	203,05	61,41
BPH	10	181,50	26,88
Общо	**101**	**191,68**	**62,99**

Показател: p=0,325

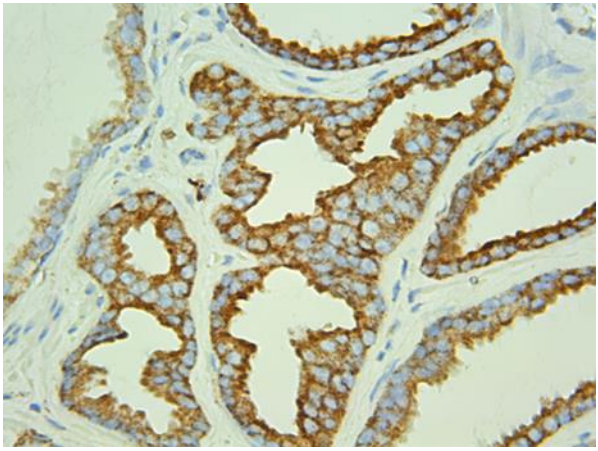

Figure 21. *Cytoplasmic expression of CD151 in advanced carcinoma, x200*

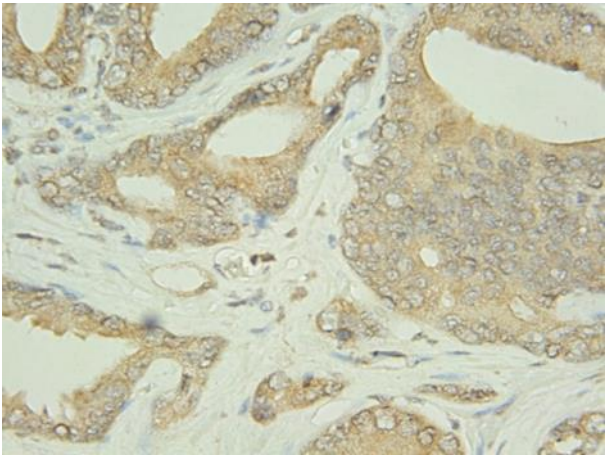

Figure 22. *Cytoplasmic expression of CD151 in non-advanced carcinoma, x200*

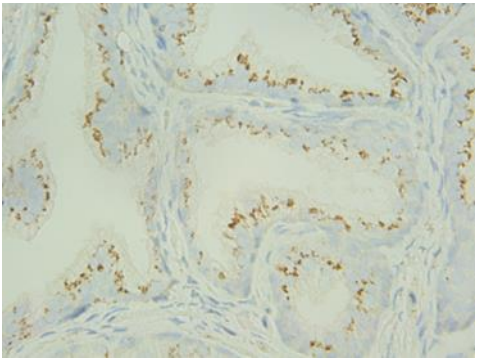

Figure 23. *Cytoplasmic expression of CD151 in benign glands, x200*

Immunohistochemical expression of CD151 in non-advanced prostate cancer

The CD151 expression study showed no expressionless carcinomas (0%), 7 (14%) had an H-score of 51-100, 14 (28%) had 101-150, and 10 (20%) had 151-200 , 9 (18%) with 201-250 and 10 (20%) with 250-300 **(Figure 24)**.

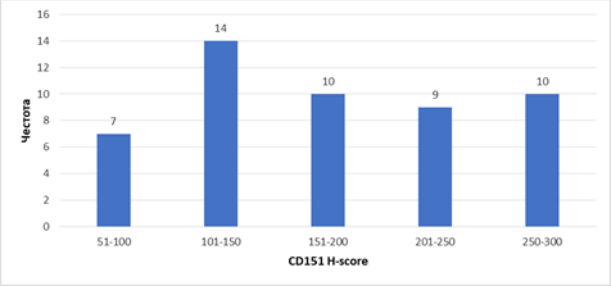

Figure 24. *CD151 expression levels in non-advanced H-score carcinomas.*

Immunohistochemical expression of CD151 in advanced prostate cancer

According to the evaluation of the expression of CD151 in the group of advanced carcinomas, the following distribution was found: there were no cases without expression, 1 (2.4%) had an H-score of 51-100, 10 (24.4%) with 101-150, 10 (24.4%) with 151-200, 10 (24.4%) with 201-250 and 10 (24.4%) with 250-300 **(Figure 25)**.

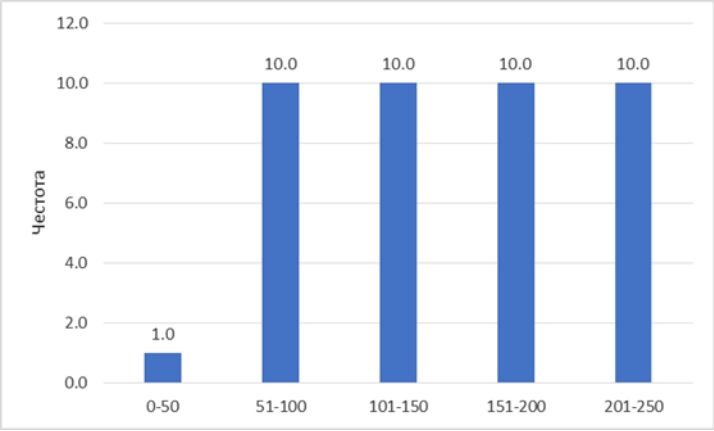

Figure 25. *CD151 expression levels in advanced H-score carcinomas.*

Immunohistochemical expression of CD9 and CD151 in relation to clinical and morphological parameters in non-advanced and advanced prostate cancer

Comparative analysis of data between age and CD9 expression

In the comparative analysis between the variables: age and CD9 expression in the group of non-advanced carcinomas, a decrease in CD9 values was found in patients over 70 years of age, which was statistically significant (p = 0.012). In carcinomas with distant metastases, no statistically significant dependence was found (p = 0.542) **(Table 30)**.

Table 30. *Relationship between the variables "age" and "CD9" in the groups of non-advanced and advanced carcinomas*

Group	**Cases**	**CD 9 score**	
Non-advanced		Средно (CO)	p-value
Up to 70 y	23	113,0 (64,49)	
70 y +	27	72,9 (43,84)	
Total	50	91,4 (57,4)	**0,012**
Advanced			
Up to 70 y	20	91,5 (54,0)	
70 y +	21	102,1 (56,7)	
Total	41	97,0 (55,0)	0,542

Indicators: p = 0.012; p = 0.542

The mean level of CD9 in the non-advanced group was 113.0 for patients under 70 years of age and 72.9 for patients over 70 years of age. In the advanced group, the distribution was 91.5 versus 102.1 in the two age groups, respectively.

Comparative analysis of data between age and CD151

expression

In the comparative analysis of the variables: age and CD151 H-score, no statistically significant relationship was found between the study groups **(Table 31).**

Table 31. *Relationship between the variables "age" and "CD151" in the groups of non-advanced and advanced carcinomas*

Group	**Cases**	**CD 151 score**	
Non-advanced		Средно (СО)	p
Up to 70 y	23	182,2 (66,7)	
70 y +	27	186,3 (71,4)	
Общо	50	184,4 (68,6)	0,835
Advanced			
Up to 70 y	20	201,8 (66,6)	
70 y +	21	204,3 (57,7)	
Total	41	203,1 (61,4)	0,897

Indicators: p = 0.835; p = 0.897

The mean value of CD151 in the group of non-advanced tumors in patients under 70 years of age was 182.2, while in older patients this value was slightly higher - 186.3 (p = 0.835). We found a similar distribution in the group of advanced cancers - 201.8 and 204.3, respectively (p = 0.897).
Immunohistochemical expression of CD9 in relation to morphological parameters in non-advanced prostate cancer

In the group of non-advanced carcinomas, no statistically significant relationship was found between the cribriform growth pattern and the levels of cytoplasmic expression of CD9 (p = 0.762). Mean CD9 levels were higher in tumors without cribriform structures (93.70 ± 57.79) than in those with a cribriform growth pattern (88.70 ± 58.10) **(Table 32)**.

Table 32. *Relationship between cribriform structure and cytoplasmic expression of CD9 in non-advanced tumors*

Cribriform structures	**Брой (n)**	**Mean**	**SD**
Absent	27	93,70	57,79
Present	23	88,70	58,10
Total	**50**	**91,40**	**57,39**

Indicator: p = 0.762

In the group of non-advanced carcinomas, no relationship was found between tumor differentiation by Gleason score and CD9 levels (p = 0.054) **(Table 33)**.

Table 33. *Mean CD9 value based on Gleason score in non-advanced cancer*

Gleason score	**Cases**	**Mean**	**SD**
6	10	64,00	25,91
7	26	112,31	65,13
8	7	67,14	37,29
9 и 10	7	77,14	52,51
Total	**50**	**91,40**	**57,39**

Indicator: p = 0.054

In tumors with PNI, mean CD9 expression values were higher (102.86 ± 57.12) compared to tumors without PNI (64.67 ± 50.12), and the difference was statistically significant (p = 0.030) **(Table 34)**.

Table 34. *Mean values of CD9 depending on perineural invasion in tumors without distant metastases*

PNI	**Cases**	**Mean**	**SD**
PNI (-)	15	64,67	50,12
PNI (+)	35	102,86	57,12
Total	**50**	**91,40**	**57,39**

Indicator: p = 0.030

Immunohistochemical expression of CD9 in relation to morphological parameters in advanced cancer

In advanced tumors, no relationship was found between the two variables: cribriform growth pattern and cytoplasmic expression of CD9 in prostate cancer tumor tissue. The mean value of CD9 in the 11 advanced tumors without cribriform model was 78.18 ± 54.73 and it was lower than in the 30 tumors with cribriform structures (103.83 ± 54.32), but the difference was not was statistically significant (p = 0.189) **(Table 35).**

Table 35*. Relationship between cribriform growth pattern and cytoplasmic expression of CD9 in advanced tumors.*

Cribriform structures	Cases	Mean	SD
Absent	11	78,18	54,73
Present	30	103,83	54,32
Total	**41**	**96,95**	**54,96**

Indicator: p = 0.189

In the group of advanced tumors, no relationship was found between the cytoplasmic expression of CD9 and the degree of tumor differentiation (p = 0.44) **(Table 36).**

Table 36. *Mean values of cytoplasmic expression of CD9 in according to the degree of differentiation in advanced carcinomas*

Gleason score	Cases	Mean	SD
6	1	20,00	
7	4	77,50	41,13
8	15	104,67	49,08
9 и 10	21	98,81	60,68
Total	**41**	**96,95**	**54,96**

Indicator: p = 0.44

Analysis of mean cytoplasmic CD9 expression in distant metastases showed no statistical dependence on perineural invasion (p = 0.488). The mean value of CD9 in the absence of perineural invasion was 88.08 ± 53.91, and in carcinomas with perineural invasion was 101.07 ± 55.93 **(Table 37)**.

Table 37. *Mean values of cytoplasmic expression levels of CD9 depending on perineural invasion in the group of advanced tumors*

PNI	**Cases**	**Mean**	**SD**
PNI (-)	13	88,08	53,91
PNI (+)	28	101,07	55,93
Total	**41**	**96,95**	**54,97**

Indicator: p = 0.488

Immunohistochemical expression of CD151 in relation to morphological parameters in non-advanced carcinoma

When comparing the variables "cribriform structure" and "CD151" in the group of tumors without distant metastases, a higher mean value of cytoplasmic expression was found in carcinomas with a cribriform model - 206.30 ± 67.25 than in those without such structures (165.74 ± 65.17) and the difference was statistically significant (p = 0.036) **(Table 38)**.

Table 38. *Relationship between cribriform structure and cytoplasmic expression of CD151 in non-advanced tumors*

Cribriform structures	**Cases**	**Mean**	**SD**
Absent	27	165,74	65,17
Present	23	206,30	67,25
Total	**50**	**184,40**	**68,56**

Indicator: p = 0.036

The comparative analysis between “Gleason score” and “CD151” showed a relationship between the two variables in

the group of non-advanced tumors (p = 0.045). In tumors with Gleason score 6, the mean value of CD151 was the lowest - 134.00. The highest was the average value for tumors with intermediate Gleason score - 203.85. In low-grade carcinomas, the mean values were 174.29 for Gleason score 8 and 194.29 for Gleason score 9 and 10 **(Table 39)**.

Table 39. *Mean value of CD151 depending on Gleason score in non-advanced cancer*

Gleason score	**Cases**	**Mean**	**SD**
6	10	134,00	55,01
7	26	203,85	55,62
8	7	174,29	75,24
9 и 10	7	194,29	95,89
Total	**50**	**184,40**	**68,56**

Indicator: p = 0.045

In tumors without distant metastases, the analysis showed a higher mean cytoplasmic expression of CD151 in carcinomas with perineural invasion (197.86 ± 69.08) than in carcinomas without a similar morphological finding (153.00 ± 57.94) and the difference was statistically significant (p = 0.033) **(Table 40)**.

Table 40. *Mean values of cytoplasmic expression of CD151 depending on perineural invasion in non-advanced tumors*

PNI	**Cases**	**Mean**	**SD**
PNI (-)	15	153,00	57,94
PNI (+)	35	197,86	69,08

Total	**50**	**184,40**	**68,57**

Indicator: p = 0.033

Immunohistochemical expression of CD151 in relation to morphological parameters in advanced prostate cancer

When comparing the two variables: growth model and cytoplasmic expression of CD151 in the group of tumors with distant metastases, no statistically significant relationship was found (p = 0.132). The mean value of CD151 expression in tumors without a cribriform model was 179.10 ± 46.78, and in advanced carcinomas with cribriform structures it was 211.8 ± 64.41 **(Table 41)**.

Table 41. *Relationship between cribriform growth pattern and cytoplasmic expression of CD151 in advanced tumors*

Cribriform structures	**Cases**	**Mean**	**SD**
Absent	11	179,10	46,78
Present	30	211,83	64,41
Total	**41**	**203,05**	**61,40**

Indicator: p = 0.132

In the group of advanced tumors, no relationship was found between the cytoplasmic expression of CD151 and the degree of tumor differentiation (p = 0.59) **(Table 42)**.

Table 42. *Mean values of cytoplasmic expression of CD151 according to the degree of differentiation in advanced tumors*

Gleason score	**Cases**	**Mean**	**SD**

6	1	160,00	
7	4	180,00	73,48
8	15	217,67	57,47
9 и 10	21	199,05	63,59
Total	**41**	**203,05**	**61,40**

Indicator: p = 0.59

In advanced carcinomas, CD9 showed more intense cytoplasmic expression (215.71 ± 67.57) in the presence of perineural invasion compared to cases where such a histological finding was absent (175.77 ± 67.570), but the difference was not statistically significant (p = 0.051) **(Table 43)**.

Table 43. *Mean values of cytoplasmic expression of CD151 according to perineural invasiveness in advanced tumors*

PNI	**Cases**	**Mean**	**SD**
PNI (-)	13	175,77	67,57
PNI (+)	28	215,71	55,07
Общо	**41**	**203,05**	**61,41**

Indicator: p = 0.051

DISCUSSION

In the present study, the mean age of patients with prostate cancer at the time of diagnosis was 69.39 ± 7.98 years. The data obtained from us do not differ from those of MacKintosh FR et al. (2016), who in a large-scale study involving 230,081 men with prostate cancer found an average age of their patients of 70.7 years. The distribution by age groups in their study is as follows: 70-79 years - 36%, 60-69 years - 32%, a smaller share falls on patients between 80 and 89 years - 17% and the least patients in interval 50-59 years - 15%. Despite the small number of patients analyzed, the present study showed a similar age distribution. The majority of patients were aged 70-79 and 60-69 years, respectively 41.76% and 40.66%, and the oldest and youngest patients had the lowest relative share in the study group: 10.99% of cancer patients were over 80 years of age and only 6.59% were under 60 years of age.

No statistical relationship between age and Gleason score <8 or ≥8 was found ($p = 0.202$). There was also no statistical relationship between age and Gleason score (<8 and ≥8) in patients with non-advanced prostate cancer. Only a relationship between the two variables was found in patients with advanced prostate cancer: Gleason score showed a tendency to increase with age ($p = 0.023$). In advanced prostate cancer Gleason score less than 8 occurs mainly in patients under 69 years (up to 59 years - 40% of cases, between 60-69 years 40% of cases, 20% at the age of 70-79 years). There was no Gleason score <8 in patients over 80 years of age. Carcinomas with a high Gleason score ≥8 and in M1 stage occurred mainly in older patients. In the age groups 60-69 years and 70-79 years, the patients with a high Gleason score were 41.7% each, and in the oldest patients the relative share was 13.9%.

Of the six prostate cancer patients under the age of 60, only one had a Gleason score of 9 and had distant metastases. Despite the small number of patients in the age group up to 60 years, the present study shows that at a young age, prostate cancer is detected at an earlier stage before giving distant metastases at the time of diagnosis. Similar results were obtained by Scosyrev E et al (2012), who found that compared to patients under 75 years of age, those over 75 years of age at the time of diagnosis had advanced disease and in almost half of the cases patients had distant metastases. The youngest patients in this study had a Gleason score below 8 and a significantly smaller proportion had GS≥8. In the current study, 12.2% of young patients under the age of 60 with low GS were 2.2% in the same age group with a high Gleason score, which supports the proposition that prostate cancers developed in early age, are more likely to have a lower Gleason score and show less aggressiveness.

The study by MacKintosh et al. (2016) showed that PSA at the time of diagnosis in men aged 70–89 years was higher (PSA = 33.3) than in men aged 50–69 years (PSA = 19.0). In the present study, in the group of non-advanced tumors, PSA was higher in patients over 70 years of age (67 ± 228.06 ng / mL) compared with patients under 70 years of age (13.5 ± 8.01 ng / mL). We also found that the mean PSA values in carcinomas with distant metastases were much higher than in non-advanced tumors (289.1 ± 850.2 ng / mL versus 41.5 ± 165.4 ng / mL). In our opinion, high PSA values occur in advanced prostate cancer and have prognostic significance. Our results do not differ from those of MacKintosh et al. (2016) who found that 54.6% of those who died of prostate cancer within 10 years of diagnosis had high PSA levels (≥10 ng / mL) and 39% had higher levels (≥20 ng / mL).

In the present study, patients with prostatic carcinoma with distant metastases had much higher mean PSA values (115.70 ± 107.49 ng / mL) than patients with non-advanced carcinomas (17.27 ± 18.07 ng / mL) ($p < 0.001$). No statistically significant difference between PSA and tumor stage in the group of non-advanced carcinomas was found ($p = 0.424$). The mean PSA values for T2-stage tumors were slightly lower than the mean serum marker values for neoplasms with more aggressive local distribution (T3 and T4 combined) (15.32 ng / mL vs. 19.71 ng / mL, respectively).

We found that the mean PSA values in non-advanced carcinomas correlated significantly with the degree of tumor differentiation ($p = 0.002$). In stage M1 tumors, no such dependence was found ($p = 0.425$), which was expected due to the relatively high PSA values among all advanced carcinomas. The results obtained by us differ from the data of Iwamoto H et al. (2018), who found a relationship between PSA and T-stage, but on the other hand they, like us, found a relationship between PSA and the degree of tumor differentiation. In our opinion, the lack of relationship between PSA and T stage of prostate cancer in the present study can be explained by the relatively small number of cases of prostate cancer included in the study. The study by Iwamoto H et al. (2018) was performed on 1873 patients with prostate cancer. According to the authors, PSA is a useful prognostic biomarker for overall survival in patients with prostate cancer at PSA levels between 20 and 70 ng / mL. At PSA values above 70 ng / mL the prognosis is extremely poor and above these PSA values there is no prognostic value. Similar to the authors, in stage M1 prostate cancer, we also found extremely high PSA values.

We found that in stage M1 the PSA values in 77.14% of cases were above 50.00 ng / mL, while in stage M0 they were only 8.70%. The comparative analysis of PSA in non-advanced

prostate cancer with clinical and morphological parameters showed dependence on a number of morphological categories such as the cribriform pattern of tumor growth ($p = 0.017$), Gleason score ($p = 0.002$) and perineural invasion ($p = 0.027$). PSA values increase in the presence of the cribriform tumor growth pattern, with an increase in the Gleason score, and with the onset of perineural invasion. In our opinion, high PSA values above 50.00 ng / mL in stage M0 of prostate cancer are indicative of other unfavorable morphological prognostic factors.

The model of tumor growth in prostate cancer was introduced in 1974 by Gleason (Gleason DF et al., 1974). This classification system is based on the architectonics of the tumor glands, which show marked morphological heterogeneity. The term "cribriform" is derived from the Latin word "cribrum" (ie "sieve") and was introduced by Gleason to characterize the histological finding of well-defined solid nest structures with lumen-like, "perforated" shapes without being surrounded. from the stroma. In determining the cribriform growth model, we relied on Gleason's criteria for cribriform growth, excluding from this category the so-called "fused glands" that resemble a cribriform pattern. The morphological criteria for "fused glands" are the communication of most of the tumor cells with the adjacent stroma and the linear orientation, instead of the ideal roundness of the lumens.

We found a cribriform growth model in 54% of cases of non-advanced prostate cancer and in 73.2% of cases of advanced cancer. There are studies according to which the model of cribriform growth has a worse prognosis and outcome than those of non-cribriform models (Iczkowski KA et al., 2011; Dong F et al., 2013; Kweldam CF et al., 2015; Iczkowski KA et al., 2018).

Among the various models of tumor growth, it is the cribriform model that is the subject of the widest discussion. Although there is currently a concept that the cribriform model is associated with poorer prognosis and clinical response, its significance and prognostic value have not yet been fully elucidated. One of the reasons is that GP4, in addition to the cribribriform model, also includes non-cribriform models: fused, poorly formed and glomeruloid glandular structures (Iczkowski KA et al., 2011; Dong F et al., 2013; Kweldam CF et al., 2015; Iczkowski KA et al., 2018). There are few studies that assess the individual prognostic value of the four growth modes related to GP4, in most cases they are considered and evaluated together (Efstathiou E et al., 2010; Epstein JI, 2010; Dong F et al. , 2013; Hoogland AM et al., 2014).

To assess the prognostic value of the cribriform growth model, we analyzed it in relation to the tumor stage. The results obtained by us show that in stage T2 the cribriform model occurs in 33.3% of cases, while in stages T3 + T4 it is 60.9%. The cribriform model was more widely represented among tumors with distant metastases than among non-advanced tumors ($p = 0.009$). We, like other authors, believe that cribriform structures are an unfavorable histological finding and a prognostic marker for distant metastases.

Literature data suggest that non-cribriform morphological models corresponding to Gleason pattern 4 may have indolent growth and this could affect future treatment. The multi-institutional and large-scale study by McKenney JK et al. (2016) on 1275 radical prostatectomies, shows that the cribriform model is associated with a significantly worse prognosis compared to other tumors with GP4. Kweldam CF et al. (2016) found that the survival of patients with tumors with Gleason score 3 + 4 without cribriform glands was similar to that of Gleason score 6. The presence of even a minimal amount

of cribriform model reduces the survival of patients with prostate cancer (Kweldam CF et al., 2016).

We found that in non-advanced carcinoma with a cribriform growth pattern, the mean PSA value was 24.37 ± 23.92 and it was significantly higher compared to cases where cribriform structures were absent - 11.59 ± 8.37 ($p = 0.017$). In the same group of tumors, we found a statistically significant relationship between the cribriform model and the presence of perineural invasion ($p = 0.001$). In our opinion, the cribriform model of tumor growth requires special attention and mandatory reflection in the biopsy response of prostate cancer, especially in core biopsies, even with a tumor area below 5% due to its unfavorable prognostic value.

According to Flood et al. (2016) perineural invasion in diagnostic prostate biopsy is a finding inherent in locally advanced cancer, but as a prognostic factor it is inferior to the cribriform growth model in assessing extraprostatic spread before radical prostatectomy. In the group of prostatic carcinomas with distant metastases, we did not find a relationship between the cribriform model and PSA levels ($p = 0.217$) and between the cribriform model and perineural invasion ($p = 0.252$). The cribriform model was more widely represented among tumors with distant metastases than among non-advanced tumors ($p = 0.009$).

Dong F et al. (2013) followed for 24 years 241 patients after radical prostatectomy for prostate cancer with Gleason grade 4 and found that 13% of patients with a cribriform model developed metastases, while metastases had only 2.6% of cases when there were no cribriform structures. The authors conclude that the cribriform model is an independent prognostic factor for biochemical recurrence, as well as for the appearance of metastases after radical prostatectomy. These results have been confirmed by other authors (Trudel D et al. (2014), Kir G et al.

2014 and Ku JY et al. 2017), who also support the thesis that even minimal cribriformity is associated with an increased risk of biochemical relapse. The results of the present study also support the thesis of a more aggressive course of prostate cancer in a cribriform growth model. This growth pattern was more prevalent among tumors with distant metastases than among non-advanced tumors, and the difference was statistically significant ($p = 0.009$).

In 2013, Kryvenko ON et al. analyzed the cribriform model of tumor growth in relation to the lymphonodular status and found that in the cribriform model the tumor volume is larger and there are lymphonodular metastases. Later, Harding-Jackson N and Kryvenko ON (2016) compared prostate cancers with Gleason score 4 + 4 and Gleason score 3 + 5 and found that there was no difference in survival between the two groups, but in the group of Gleason score 4 + 4, patients with the cribriform model have a lower 3-year survival compared to patients who do not have this model. In 2020, Bernardino RM et al. analyzed the relationship of the cribriform model with a number of clinical and morphological indicators and found that the cribriform model is associated with higher values of preoperative PSA levels, with extracapsular extension and invasion of the seminal vesicles and is an unfavorable prognostic factor for biochemical recurrence so the patients need more intensive adjuvant radiation therapy.

Not all authors accept that the cribriform model has a significant effect on prostate cancer. Flammia S et al. (2020) analyzed data from diagnostic biopsies and surgical resections of 210 GS $\geq$7 / ISUP grade $\geq$2 patients and found no relationship between cribriform structures and most parameters studied, such as age, preoperative PSA values, local stage, differentiation, and resection margins. The authors found only an inverse relationship between the presence of cribriform

structures and perineural invasion. Perineural invasion was higher in the group without cribriform structures than in the group with cribriform structure of prostate cancer. In patients with perineural invasion, free, non-biochemical recurrence survival was higher in patients with cribriform structures than in those who were absent.

Our results support the hypothesis that the cribriform pattern of tumor growth is an unfavorable prognostic factor because it is associated with high PSA values, perineural invasion, and distant metastases.

CD9 is a member of the tetraspanin family that is found on the cell surface, binds to various molecules, and modifies multiple cell events, such as cell adhesion, migration, invasion, and survival (Murayama Y et al, 2015; Lorico A et al. 2021). CD9 expression is thought to play a role in several stages of carcinogenesis, is involved in venous invasion, and is associated with poor prognosis (Murayama Y et al. 2015). Despite numerous reports of the effects of CD9 on cell migration, the molecular mechanisms governing this process stimulated by CD9 have not yet been fully elucidated.

Data from the literature indicate that in most malignant tumors, the expression of CD9 in tumor tissue has an inhibitory effect on carcinogenesis and the incidence of metastases. Decreased CD9 expression has been associated with a worse prognosis in a number of malignancies: lobular breast cancer, melanoma, lung and colorectal cancer, neoplasms of the pancreas, ovary and prostate (Si Z & Hersey P, 1993; Higashiyama M et al. 1995; Mori M et al.1998: Sho M et al. 1998; Houle CD et al. 2002; Wang JC et al. 2007; Murayama Y et al., 2015; Baek J et al. 2019).

In contrast to these tumors in squamous cell carcinoma of the esophagus, CD9 expression is increased compared to normal squamous epithelium of the esophagus (Huan J et al,

2015). In a mouse model of prostate cancer, ablation of endogenous CD9 had no effect on initiating a primary tumor de novo, but significantly increased liver metastases but not lung (Copeland BT et al, 2013).

The results of the present study showed that CD9 expression was higher in non-advanced prostate cancers in patients under 70 years of age compared with those over 70 years of age ($p = 0.012$). Not all authors have found a similar relationship between age and CD9 expression in malignant tumors. There is no relationship between CD9 expression and the age of patients with breast cancer and colorectal cancer, (Kim K et al. 2016; Baek J et al. 2019).

We found that BPH had the most intense cytoplasmic expression, and the expression levels in advanced versus non-advanced carcinomas were approximately the same. The differences between the three groups in this indicator were not statistically significant ($p = 0.314$).

The results obtained by us differ from those of Wang et al. (2007) who applied a four-point scale to assess immunohistochemical expression in adenocarcinoma of the prostate and found that loss of CD9 expression was associated with tumor progression and metastasis. CD9 expression is well expressed in non-metastatic disease, whereas in local cancer progression and in metastases, expression is reduced or absent. In our opinion, the possibility of reduced CD9 expression in the study of Wang et al. (2007) could be at least partly due to the preoperative hormonal treatment that was performed before prostatectomy.

CD9 expression did not show a dependence on the degree of tumor differentiation determined by the Gleason score in either non-advanced or advanced prostate cancer. The data obtained did not differ from those of Chuan Y et al., (2005), who examined the expression of CD9 on histological materials

from the prostate gland of 79 patients. The authors observed CD9 immunoreactivity primarily at the apical and lateral cell boundaries of benign glands, and basal cells were not stained. In carcinoma, luminal cells were stained both at the border and in the cytoplasm, and the staining was significantly heterogeneous, from very intense in some glands to complete absence in others. This pattern of uneven distribution was also observed in a large proportion of carcinoma cases, whereas in BPH the staining was predominantly uniform. Interesting are the results of the same authors who observed CD9 expression in patients undergoing antiandrogen therapy (Chuan Y et al., (2005). In these patients there was no expression of CD9 in luminal cells, but there was poor expression in the basal epithelium. Our study could not comment on these findings because the patient population did not include those who underwent androgen ablation.

An interesting and unexpected finding in the analysis of CD9 in tumor tissue is the more intense expression of the antibody in cases of perineural invasion in the group of non-advanced carcinomas compared to PNI-negative tumors ($p = 0.030$). There is no similar analysis in the literature for prostate cancer, but there is for colorectal cancer, although there is no statistically significant relationship (Kim KJ et al, 2016).

No dependence was found on CD9 expression in relation to the cribriform growth pattern in both advanced ($p = 0.189$) and non-advanced tumors ($p = 0.762$).

The lack of relationship between CD9 expression and histological differentiation determined by the Gleason score and the cribriform model supports the thesis that CD9 has little effect on tumor progression in prostate cancer.

We found that the highest expression of CD151 was in prostate carcinomas with distant metastases (203.05 ± 61.41), followed by prostate carcinomas without distant metastases

(184.40 ± 68.57) and the lowest in BPH (181.50 ± 26.88), but the difference was not statistically significant (p = 0.325). These data differ from those of Ang J et al. (2004) who examined the tissue expression of CD151 in 106 patients, of whom 30 with BPH and 76 with prostate cancer. The authors found that the expression in the cytoplasm of tumor cells was significantly more pronounced compared to the control group and the difference was statistically significant. In our opinion, the discrepancies in the results between the two studies may be due to the different target groups of patients. In the present study, patients were divided into three groups: BPH, tumors with M0 and M1, while in the study of Ang J et al. (2004) compared all prostate cancers with BPH expression.

Analyzing the expression of CD151 in tumor tissue by H-score, it was found that the tumor tissue of all carcinomas of non-advanced and advanced type was positive. CD151 is a cell membrane protein that is part of desmosomes, is associated with malignant tumors and is involved in all stages of malignant tumor progression and metastasis (Sadej R et al., 2014). Its involvement has been associated with many types of neoplasms, including breast, lung, endometrial, and prostate (Zhu, J et al., 2021; Li S et al., 2021; Sadej R et al., 2014; Voss MA et al., 2011). One of the reasons why CD151 may play a key role in tumor progression is its relationship to integrins: α3β1, α6β1 and α6β4, which bind to laminin, a key element of the extracellular matrix (Sadej R et al., 2014). This interaction allows CD151 to modulate integrin-dependent cell functions such as migration, signaling, and adhesion, enhance them, and they all play a key role in tumor progression (Sadej R et al., 2014). In addition to laminin-binding integrins, CD151 modulates tumor cell activity through matrix metalloproteinases and growth factor receptors, clearly demonstrating its multifaceted involvement in carcinogenesis.

Taken together, these data suggest the involvement of CD151 as a potential diagnostic, prognostic marker, as well as a target for the treatment of malignant tumors.

To elucidate the role of CD151 in prostate cancer, we analyzed the expression of CD151 in tumor tissue in relation to clinical and morphological parameters: age of patients with prostate cancer, cribriform growth pattern, Gleason score, perineural invasion in non-advanced and advanced prostate cancer. No statistically significant relationship was found between age and CD151 H-score in non-advanced prostate cancers. CD151 expression was not associated with age when patients were divided into two categories: under and over 70 years in both prostate cancer groups ($p = 0.835$). A similar lack of relationship between CD151 expression and age was found by Ang J et al. (2004), and found a lack of relationship between CD151 expression and preoperative PSA values.

A statistically significant difference was found between the cribriform growth pattern and the expression of CD151 in the tumor tissue of prostate carcinomas without distant metastases. The mean value of cytoplasmic expression of CD151 in carcinomas with a cribriform model was 206.30 ± 67.25, and when there was no similar model - 165.74 ± 65.17 and the difference was statistically significant ($p = 0.036$). Literature data indicate that the median survival of patients with high CD151 expression is 26 months, while it is 99 months with low CD151 expression (Ang J et al., 2004). The same authors found that low-grade tumors expressed CD151 more strongly than high-grade neoplasms. In the analysis of CD151 expression in relation to Gleason score, we found the lowest antibody expression at the lowest Gleason score 6, while at Gleason score 7 and above, the values were higher and the difference was statistically significant ($p = 0.045$). The results of the analysis of the cribriform model and the Gleason score in

relation to the expression of CD151, taken together, clearly show that in non-advanced prostate cancer, the expression of CD151 protein is positively associated with both indicators, which are established pathological criteria for assessing clinical stage and malignant progression of prostate cancer.

In tumors without distant metastases, the mean cytoplasmic expression of CD151 with perineural invasion was higher than in carcinomas in which it was absent and the difference was statistically significant ($p = 0.033$). Integrin α6 is known to promote the adhesion of prostate cancer cells to peripheral nerves, and perineural invasion is a key factor in the occurrence of bone metastases (Sroka IC et al. 2010). There is an increase in nerve fibers in the tumor tissue of prostate cancer, which means that perineural motility and invasiveness of neoplastic cells are not passive processes, but are the result of an interaction between nerve fibers and tumor cells. In our opinion, CD151 may play a key role in perineural invasion and tumor progression due to its association with integrins: α3β1, α6β1 and α6β4, which bind to laminin, a key element of the extracellular matrix (Sadej R et al., 2014).

Detchokul S et al. (2013) analyzed CD151 expression in a mouse model in relation to angiogenesis and metastatic potential of prostate cancer and concluded that CD151 has a prognostic role and may play a role in lymphangiogenesis. The expression of CD151 in M0 and M1 stage tumors did not show a statistically significant difference ($p = 0.325$). In our opinion, CD151 is more likely to play a role in communication between tumor cells themselves and between tumor cells with the tumor microenvironment than as a prognostic factor.

In advanced carcinomas, the expression of CD151 in prostate cancer tumor tissue showed no dependence on the age of patients under and over 70 years ($p = 0.897$), the cribriform

growth pattern (p = 0.132), the Gleason score (p = 0.59) and the perineural invasion. (p = 0.051).

Han R et al. (2020) analyzed the localization of CD151 expression, dividing it into two categories: predominantly diffuse cytoplasmic and focal, predominantly in intercellular contacts. They found that in non-tumor prostate tissue, CD151 expression was predominantly in intercellular contacts, whereas in carcinomas it was in the cell cytoplasm. The authors conclude that with the development of prostate cancer, there is a change in the distribution of CD151 from intercellular contacts to the cell cytoplasm.

In the present study, the isolated expression of CD151 in the area of intercellular contacts was not considered, and only diffuse cytoplasmic expression and study data support the thesis that the increase in cytosolic expression of CD151 occurs with deterioration of clinical and morphological tumor characteristics.

CD151 undoubtedly plays a role in tumor growth and metastasis, but given the complex and multifunctional role of protein, interaction with integrins, growth factors and receptors, it does not carry out these processes alone, but as a component of tetraspanin-integrin complexes interacting with other molecules. This requires more in-depth and comprehensive studies among a larger group of patients. The expression of CD151 has been studied mainly immunohistochemically by administering different antibodies, revealing different epitopes of the molecule, which is important for its cell distribution. Comparative immunohistochemical analysis of tissue expression with different CD151 antibodies would contribute to a more detailed specification of cell localization.

CONCLUSIONS

1. At high PSA values, the incidence of cribriform structures and perineural invasion is also high.

2. In non-advanced prostate cancer, there is no relationship between PSA and age, as well as between PSA and T-stage of prostate cancer.

3. Perineural invasion in non-advanced prostate cancer is common in the cribriform growth pattern and is associated with the T-stage.

4. The cribriform growth pattern does not show a T-stage dependence in non-advanced prostate cancer.

5. Advanced prostate cancer has high PSA values, but they do not show a dependence on the cribriform growth pattern and perineural invasion.

6. The cribriform growth pattern in advanced prostate cancer is 3 times more common than in non-advanced cancer.

7. In non-advanced carcinomas, cytoplasmic CD9 expression decreases after age 70 years.

8. In PNI, patients with prostate cancer without distant metastases have higher CD9 expression than patients with metastases.

9. In advanced carcinomas, the expression of CD9 does not show a dependence on morphological parameters: cribriform growth pattern, Gleason score and PNI.

10. High CD151 expression in stage M0 prostate cancer occurs in a cribriform growth pattern, high Gleason score, and perineural invasion.

11. In advanced carcinomas, the expression of CD151 in prostate cancer tumor tissue is independent of patient age, cribriform growth pattern, Gleason score, and perineural invasion.

CONCLUSION

In recent years, significant progress has been made in more precisely stratifying prostate cancer patients in order to avoid unnecessary therapeutic interventions or insufficient aggressive treatment for seemingly low-risk tumors. Despite the results achieved in elucidating the mechanisms of carcinogenesis, many issues related to the biology of neoplastic diseases remain unclear. Interest in proteins from the group of tetraspanins has increased and they are increasingly established as molecular biomarkers with pronounced prognostic and diagnostic potential. Their key role as coordinators of cellular motility and intercellular interactions in the extracellular matrix under physiological and pathological conditions has put them in the focus of a number of scientific studies related to the invasive and metastatic potential of malignant tumors. The study of these molecules gave many answers, but also led to many questions and controversies, as tetraspanins appear to play different roles depending on the organ location of the primary tumor process.

Therefore, in order to elucidate the molecular mechanisms of CD9 and CD151 and their role in the neoplastic process in prostate cancer, research and further studies are needed. This would clarify the relationship between these proteins and some of the most unfavorable clinomorphological parameters in prostate cancer such as perineural invasion, low tumor differentiation, and cribriform growth pattern. Future studies of CD9 and CD151 in the context of their interaction with their molecular partners in the processes of neoplastic progression and metastasis would clarify their complex image in terms of their prognostic significance.

CONTRIBUTIONS

Original contributions

1. Complex clinical-morphological and immunohistochemical analysis was performed for characterization of tetraspanins CD9 and CD151 in patients with prostate cancer.

2. An analysis of the immunohistochemical expression of CD9 and CD151 was performed in view of clarifying their role in the prognosis in patients with prostate cancer.

Practical contributions

1. For the first time in our country the prognostic value of the cribriform growth model in prostate cancer has been determined.

2. The different PSA values in relation to the clinical and morphological parameters were evaluated: age of the patients, the pattern of tumor growth, tumor differentiation, tumor stage and the presence of distant metastases.

3. CD9 expression was analyzed in relation to clinical and morphological parameters to determine the risk of distant metastases.

4. The expression of CD151 in tumor tissue was evaluated and its relationship with clinical and morphological parameters was clarified.

PUBLICATIONS

Articles

Stoev L. Contemporary recommendations and perspectives for the morphological evaluation of prostate gland adenocarcinoma. Varna Medical Forum, v.10, 2021

Stoev L., Stoeva M., Tzaneva M. Tetraspanin 151 and its role in carcinogenesis. Varna Medical Forum, v.10, 2021

Participations

Stoev L., Hinev A., Dzhenkov D. Pagetoid spread in prostate ducts of in situ transitional cell carcinoma with synchronous clinically insignificant prostate adenocarcinoma. 12th national congress of pathology, 11-13th May, 2017