

## **REFERENCE**

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on the thesis of the

**DR. PAVEL IVELINOV ABUSHEV**

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on topic:

### **ROLE OF MULTIPARAMETRIC MAGNETIC RESONANCE IMAGING/ULTRASOUND GUIDED TRANSRECTAL FUSION BIOPSY FOR PROSTATE CANCER DIAGNOSTIC**

To award the scientific and educational degree

**„Doctor“**

Prostate cancer is one of the leading cancers worldwide. The scarce symptomatology and non-specific symptoms on the lower urinary tract side are very often the reason for its late diagnosis. Classical transrectal biopsy under ultrasound guidance is the standard diagnostic method for the diagnosis of prostate cancer in the setting of an elevated prostate specific antigen level or a positive finding on digital rectal examination. This method is based on the systematic collection of material from at least 12 symmetrical points. Ultrasound examination provides excellent information on the size and margins of the prostate. It does not, however, provide information on the structure of the gland or the presence of tumour lesions in the presence of clinical suspicion of prostate cancer.

All of this necessitates the search for new diagnostic methods that can successfully classify suspicious areas, provide information about their morphology and location within the gland, and enable precisely targeted biopsy. In this sense, multiparametric magnetic resonance imaging has significantly higher sensitivity and negative predictive value for clinically

significant prostate cancer. The method may reduce overdiagnosis of indolent prostate cancer and improve detection of clinically significant cancer. According to the recommendations of the European Association of Urology, target biopsy under MRI guidance should be recommended for persistent clinical suspicion of prostate cancer, even after a systemic biopsy with a benign histological result. Combined targeted and systemic biopsy has been shown to achieve the best outcome.

To this day, there is no dissertation in Bulgaria that has objectively and thoroughly investigated the importance and benefits of transrectal fusion biopsy in the diagnosis of prostate cancer. The present study is a real opportunity and an objective necessity for a generalized analysis of clinical, imaging, laboratory and histological results in a sufficient number of patients with fusion biopsy.

The present dissertation is written in 124 standard typescript pages. It includes 25 figures and 14 tables arranged sequentially in the text. The thesis has an acknowledgement of contributions. The bibliographical reference includes 194 titles, of which 19 are in Cyrillic. The bibliography is selected according to the topic of the thesis. It is written in clear and professional language.

The distribution of the material by chapters is as follows:

1. Introduction - 1 page
2. Literary review - 32 pages
3. Purpose and objectives - 1 page
4. Materials, subject and object of the research - 1 page
5. Method - description, comparative analysis and specifics - 33 pages
6. Results - 29 pages
7. Discussion - 5 pages
8. Conclusions – 1 page
9. Summary - 1 page
10. Scientific contributions - 1 page
11. Bibliography - 22 pages

**The literature review** is thorough and detailed. It is composed of 2 main chapters.

In the first chapter of the literature review Dr. Abushev analyzes the nature and specificity of prostate cancer. He describes in detail and in depth the symptomatology of the disease. He gives deserved attention to lower urinary tract symptoms, erectile dysfunction, pelvic pain, painful ejaculation and hematuria. These may be a clinical manifestation of prostatic carcinoma, but may also accompany other pathological conditions such as benign prostatic hyperplasia, bacterial and non-bacterial prostatitis, and some other forms of cancer. Unfortunately, there is no conclusive evidence of a relationship between the severity of lower urinary tract symptoms and the likelihood of prostate cancer or the stage at disease. The nonspecific nature of the symptoms listed clearly define some of the diagnostic difficulties for early detection of prostate cancer.

The author studied the incidence and etiology of the disease in Bulgaria and worldwide. He draws attention to the relationship between prostate cancer and familial burden of patients. He discusses in considerable detail germline mutations and pathogenic variants identified in tested genes. It vividly presents endogenous (age and race) and putative exogenous factors (diet,

overweight, smoking, alcohol consumption, sexual behaviour). The author pays and shows increased attention to the publications of Bulgarian authors in this field.

At the beginning of the second chapter, the author focuses on the diagnosis of prostate cancer. He explores the need for screening for early detection of prostate cancer and genetic testing for hereditary gland cancer.

In the next three subchapters of the literature review, the dissertation details the clinical diagnosis, as well as the role of digital rectal glandular tissue examination and prostate specific antigen testing (free fraction and total value) in the early diagnosis of prostate cancer.

Dr. P. Abushev also commented on the possibilities of new and modern biomarkers in urine and tissues, which would increase the effectiveness of the diagnosis of the disease.

In the remaining three subchapters, the author describes in depth the indications, benefits and drawbacks of various imaging tests. They are widely used in various diagnostic algorithms related to prostate cancer diagnosis and subsequent staging of the disease. The most commonly used diagnostic imaging modalities are transrectal ultrasonography, bone scintigraphy, multiparametric MRI and positron emission tomography.

In the last subchapter of the literature review, the dissertator describes fine needle aspiration biopsy and its historical value as well as modern puncture tru-cut biopsy.

In the literature review, Dr. Abushev highlights the most important points related to the diagnosis of prostate cancer and the necessary comprehensive approach, as well as the unresolved issues to date. The review is supported by a large number of bulgarian and foreign literature sources.

**The aim** of this thesis is to investigate the application of fusion biopsy in the diagnosis of prostate cancer. The dissertation formulates it accurately, and it corresponds to the title of the study.

In order to achieve the stated aim, Dr. Abushev set himself 5 tasks, which are clearly formulated, understandable and achievable. They fully correspond to the accumulated clinical experience on the problem.

In the chapter "**Material, subject and object of the study**" 167 men were included, analyzed and evaluated before and after fusion biopsy. The patients were hospitalized in the Clinic of Urology of St. Marina University Hospital, Varna for the period between 2019 - 2022. The author performs a comparative analysis of the results between fusion biopsy and classical ultrasound-guided prostate biopsy, highlights the specific features, benefits and risks of transrectal and transperineal biopsy approaches.

To develop the topic and fulfill the goals and objectives, Dr. Abushev performs a detailed analysis of anamnestic, clinical, laboratory, imaging, intraoperative and histological data. The sources of information include the available digital database, epicrises, case histories and operative journals of the Clinic of Urology of St. Marina University Hospital, Varna.

All patients with suspected prostate cancer underwent multiparametric MRI within three months prior to prostate fusion biopsy. Mandatory criteria were T2 images in at least two planes, one of which must be axial, diffusion-weighted images, and apparent diffusion coefficient images. The 2019 revision 2.1 of the PI-RADS system was used to interpret the images and classify the susceptible areas. Histologic outcomes in patients with prostate adenocarcinoma were evaluated against the revised Donald Gleason classification. They were divided into prognostic groups according to the International Society of Urologic Pathology (ISUP) classification.

Data were obtained from a sufficient number of patients. The different indicators are presented in all possible statistical scales (nominal, ordinal, rank and interval). The author has tested a significant number of statistical hypotheses. He has used regression analysis, general population, descriptive analysis and statistical observation analysis and synthesis in his study. Through correlation analysis he has established the strength of the relationships between them. Differences were considered significant at  $P < 0.05$ . The objective statistical methods used guarantee a scientific approach to the problem and reliable data processing and analysis.

In the chapter "**Results**", the set problems are solved in a sequential manner. The dissertant performs a detailed analysis of hospitalized patients with clinically suspected prostate gland malignancy according to a number of indicators. These are age, previous biopsy studies, total and free PSA, PSA density, anaesthetic risk by ASA, gland volume, palpatory findings by digital rectal examination, PI-RADS of the suspected lesion, and histological outcome, Gleason score and ISUP grade in patients with adenocarcinoma of the gland, ratio between systemic and referred puncture material, ratio between positive and negative biopsies, lesion size, clinical T stage, hospital stay and complications.

The "**Discussion**" chapter is presented in 5 pages. It is done competently, scientifically sound, and defined with an effort at objectivity. The author finds a correlation between high PI-RADS and high risk of prostate adenocarcinoma, but also one between high PI-RADS and high ISUP prognostic grade. This demonstrates the high precision and diagnostic value of fusion biopsy. It establishes that MRI is effective in the diagnosis of both large-sized tumors and tumors with a high degree of malignancy, which is directly relevant for demonstrating clinically significant disease. On the other hand, multiparametric MRI reduces unnecessary biopsies by a quarter, reduces overdiagnosis of clinically insignificant prostate cancer, and improves diagnosis of clinically significant cancer. According to Dr. P. Abushev, fusion biopsy is suitable both for repeat biopsy after previous negative systemic biopsies and for initial prostate biopsy in biopsy naive patients. In his opinion, it is suitable for biopsy of anterior and apical areas, although the latter are considered more difficult to reach when using a transrectal approach. The large percentage of patients with histologically verified adenocarcinoma of the prostate who have normal palpatory findings on digital rectal examination is definitely impressive. Modern diagnostics aims to distinguish clinically significant from clinically insignificant disease in order to maximize the benefit of definitive treatment and minimize complications from overtreatment of the disease. The author also comments on the rare cases of post-biopsy febrility and infection, and their management with a standard course of fluoroquinolone therapy. According to him, the method is also suitable for high-volume prostate glands, where there is even more need for needle guidance with great precision.

There are 10 **conclusions** at the end of the thesis. They objectively summarize the results obtained and are an excellent proof of the efforts made by Dr. Abushev.

The dissertation ends with a conclusion, in which again the dissertator emphasizes the possibilities of fusion biopsy for the collection of histological material according to an individual scheme for each patient from the specimen sites and provides a greater opportunity for early diagnosis of prostate cancer. According to him, the method is precise, safe and provides the possibility of histological verification of tumors regardless of their localization in the gland.

At the end of the thesis 4 scientific contributions are presented. They are the result of the author's in-depth efforts and are of high value for the early diagnosis, follow-up and prognosis of prostate cancer. They highlight once again the most important points of the study.

In my opinion, the most significant of these are:

1. The results of this study demonstrate the significant advantages of transrectal fusion biopsy for the early diagnosis of prostate cancer.
2. A correlation was found between PI-RADS category and pathological outcome after prostate fusion biopsy.

## CONCLUSION

Dr. Pavel Abushev was born on 07.11.1991. In 2016 he graduated medicine from Medical University "Prof. Dr. Paraskev Stoyanov", Varna. The same year he started working as a resident doctor at the Urology Clinic of St. Marina University Hospital, Varna. In 2017, he was appointed as a full-time assistant at the Department of Surgical Diseases, Urology Education Sector, Medical University, Varna. In 2017 he was appointed as a postgraduate fellow in urology at St. Marina University Hospital, Varna. In 2022 he passed the examination for specialty in urology.

In 2020, by order of the Rector No. P-109-29 / 30.01.2020, he was enrolled as a full-time PhD student at the Department of Surgical Diseases, Faculty of Medicine, Medical University, Varna. Pursuant to the Rector's Order No. P-109-160 / 24.02.2023 and on the basis of Art. 24, para. 6 and Art. 30, para. 68, par. 1 of the Regulations for the Development of the Academic Staff at the Medical University, Varna, Dr. Pavel Ivelinov Abushev is dismissed as a full-time doctoral student in the doctoral programme "Urology", professional field 7.1. Medicine with the right to defense. All requirements of the procedure have been met.

Dr. P. Abushev has a diagnostic, medical, surgical and teaching workload (full annual horary). He has versatile scientific interests. He is fluent in written and spoken English and German. He is computer literate. He has specialised at home and abroad in the problems of prostate cancer diagnosis and fusion biopsy of the prostate gland, urolithiasis, endourology, laparoscopic surgery, etc.

In conclusion, the presentation by Dr. Abushev's scientific work is dissertable and on a topical subject for urological practice. It is a modern scientific study on an innovative and precise method for early diagnosis of prostate cancer.

The number of fusion biopsy patients is sufficient to obtain scientifically valid results and reliable conclusions. The clinical material used, the interpretation of the clinical, imaging, laboratory and histological studies in the study is a real proof of the author's high awareness of the topic and a guarantee of a strong contribution of the study.

I know Dr. Pavel Abushev personally. He is a promising urologist. The presented great practical experience of the dissertator, the objective processing and interpretation of the results and the solution of the previously set tasks determine my highly positive assessment of the present dissertation.

All this gives me a moral ground to recommend the members of the honorable scientific jury to vote positively and to award Dr. Pavel Ivelinov Abushev the educational and scientific degree "Doctor".

01.04.2023

Reviewer:

Sofia

(Prof. D. Mladenov, MD, Phd, DMSc)

A handwritten signature in black ink, appearing to read 'D. Mladenov', written in a cursive style.