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AND TECHNOLOGY OF TARGU MURES

**SCHOOL OF DOCTORAL STUDIES**
**UROLOGY CLINIC TARGU MURES**

DOCTORAL THESIS SUMMARY

# Clinical, biological and pathological factors in the diagnosis and prognosis of prostate cancer

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TÎRGU MUREȘ 2022

UNIVERSITATEA DE MEDICINĂ,
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**Introduction**

Prostate cancer is a major health problem for all health systems in the world, being the third cancer diagnosed globally in men. An important aspect of prostate cancer management is the possibility to identify and stratify the evolutionary risk of the prostate cancer patients and who might optimally benefit from existing treatments through the use of diagnostic and prognostic biomarkers. Until now, no marker capable of detecting and offering an absolute prognostic role in prostate cancer has been identified. A number of biomarkers have been discovered and studied for their diagnostic role, for prognosis, treatment and follow-up of patients after treatment, but current studies cannot determine their recommendation with a high level of evidence and high discriminatory power by current guidelines. Research continues to identify biomarkers with increased sensitivity and specificity for prostate cancer.

The aim of this doctoral research was to elucidate the diagnostic or prognostic potential of a serum biomarker, unstudied so far, in prostate cancer. We looked at the presence and serum levels in healthy men, comparing levels between patients without prostate cancer and prostate cancer, correlation with age, PSA, PSA density, prostate volume, and Gleason group scores, exploring transcriptomic data available online and evaluating findings in The Genome Atlas Program (TGCA) dataset of prostate cancer patients. Also, we studied in two reviews of the specialized literature, the role of artificial intelligence and radiogenomics in the diagnosis and prognosis of prostate cancer.

**Research methodology**

The doctoral study was a pilot study, followed by a prospective, case-control study, conducted in the period 2016-2018, with a total number of 46 patients included in the study in study 1, 123 patients in study 2, hospitalized within the Urology Clinic of the Târgu Mureș County Clinical Hospital, Romania. For the review studies we used the international databases Web of Science, PubMed/Medline, Science Direct to identify research on artificial intelligence and radiogenomics in prostate cancer.

**Study 1 Fascin is secreted in men's serum: results from a pilot study**

The serum level of Fascin-1 is low or almost absent in normal epithelium, but high levels of Fascin-1 have been identified in various types of cancer, with important roles in progression, invasion and metastasis. We performed a study to identify the presence of Fascin-1 levels in the serum of different age groups in men without neoplastic pathology with the objective being to see if Fascin-1 is secreted in the serum and to compare the serum levels according to age. We collected blood from 46 men who were included in the prostate cancer screening group in the Urology clinic. The included patients were divided into three subgroups: the first group aged between 51 and 60 years (11 patients), the second group included patients aged between 61 and 70 years (25 patients), and the third group included patients aged 71 to 80 years (ten patients). We did not identify any statistical difference in the serum level of Fascin-1 between groups ($p=0.65$). Our results are similar to those in the literature that measured serum Fascin-1 in control patients. The limitations of this study are those of a pilot study. Although a larger number of subjects could increase the statistical power of the study, we still report the largest group of men in which serum Fascin-1 was determined and confirmed that Fascin-1 is secreted in the serum of healthy men. Thus, Fascin-1 could play a role as a serum biomarker in metastatic cancer and could be a target for therapy. At this point we can say that Fascin-1 is indeed secreted in the serum of healthy men, with no statistical significance between age groups.

**Study 2 Fascin-1 and its role as a serological marker in prostate cancer: a prospective case-control study**

In prostate cancer patients, the presence of Fascin-1 was investigated experimentally by immunohistochemistry techniques and was found to be highly expressed in localized and hormone-resistant prostate cancer, and not statistically significantly associated with Gleason score, pathological stage or recurrence biochemistry. This research is the first to investigate changes in serum Fascin-1 levels in prostate cancer patients compared to a control group, aiming to identify the role of Fascin-1 as a circulating marker in prostate cancer and to support previously inconclusive claims on the presence of Fascin-1 based on immunohistochemistry data by using Fascin-1 mRNA data from analysis of publicly available transcriptomic data. Our study is a prospective case-control study with the final study groups included 62 men, aged between 55 and 75 years, diagnosed with prostate cancer and 61 men of similar age were enrolled as a control group. The public, online resource (CANCERTOOL) was explored for analysis of available transcriptomic data. The Gene Expression Profile Interactive Analysis 2 (GEPIA2) database was used to assess the presence of the Fascin-1 gene in a large cohort of prostate cancer patients.

The group of prostate cancer specimens includes data from 492 subjects and 152 normal prostate specimens. Analyzes for the subgroup of patients with prostate adenocarcinoma (PRAD)-TGCA (Gleason score and presence of lymph node metastases) were performed using the UALCAN portal. The age of the patients did not differ between the two studied groups with p=0.06. No differences were identified for prostate volume among prostate cancer patients and controls p=0.18. A statistically significant difference for PSA (p<0.0001) and PSA density (p<0.0001) was identified. No statistically significant difference (p=0.20) between serum Fascin-1 levels of prostate cancer patients and controls was identified. Grasso, Taylor and Varambally's data showed a high presence of Fascin-1 mRNA in the tissue of patients with prostate cancer compared to controls, especially in metastatic samples. We evaluated these findings in the TGCA dataset of prostate cancer patients and found no statistically significant difference between the two groups (p > 0.05), although Fascin-1 was overexpressed in tumors with lymph node metastases and scores Large Gleasons. Finally we can say that our results regarding Fascin-1 as a new biomarker in prostate cancer patients must be seen as having limited potential and although the serum values of Fascin-1 were different in the two groups of patients, the difference was not statistically significant. Serum Fascin-1 values stratified by Gleason score were not significantly changed. A statistically significant negative correlation was identified between the presence of Fascin-1 and age (rho =-0,331; p=0,009).

**Study 3 Artificial Intelligence and Machine Learning in Prostate Cancer Patient Management-Current Currents and Future Perspectives**

In recent years, research has focused on diagnosis, prognosis and outcome prediction using artificial intelligence in prostate cancer. Several new tools are available for prostate cancer screening and diagnosis such as genomics, MRI imaging, and molecular biomarkers. Artificial intelligence can play a key role, first in interpreting this enormous amount of data, second in developing machine learning algorithms that can help urologists reduce the number of unnecessary prostate biopsies without missing the diagnosis of aggressive prostate cancer. The aim was to provide an overview of the current evidence and future directions of artificial intelligence in the clinical management of prostate cancer patients. Artificial intelligence and artificial neural network algorithms (especially deep learning) show promise for diagnosis and can play a predictive role for the evolution of the disease. The need for further studies is real, as current evidence is scant to support full integration into everyday practice. The potential of imaging for diagnostic, histopathological and genomic evaluation may hold great promise for the future for individualized treatment.

**Study 4 Radiogenomics in prostate cancer – from imaging to molecular characterization**

Current research indicates that radiogenomics is a part of precision medicine. In recent years, the introduction of advanced imaging techniques, such as multiparametric prostate magnetic resonance imaging and prostate-specific membrane antigen positron emission computed tomography, have changed the understanding of prostate cancer screening, diagnosis, and treatment. Radiogenomics is an entirely new area of research, for which research is ongoing both to identify the more precise role of radiomics and in combination with genomics. The mechanisms by which radiomics and genomics work are poorly known and adapted for urological clinical practice, and poorly understood by practitioners. We designed this review to provide an overview of the current evidence and future directions of radiogenomics in prostate cancer diagnosis and prognosis. The combination of radiomics and genomics in the detection and follow-up of prostate cancer patients after treatment is important to be studied in the future. Early radiogenomics research comes with a limited amount of literature data in the study of prostate cancer. No prospective randomized studies have been published. At this time, we do not have any approval or validation for the use of radiogenomics in clinical practice. The use of models that combine or not clinical, radiomic and genomic biomarkers will improve the predictive or prognostic role. The role of artificial intelligence will help to overcome these limitations and may enable the clinical implementation of radiogenomics.

**General conclusions**

Fascin-1 is secreted in the serum of healthy men with no statistical significance between age groups, and these results may be a stable reference point when measuring serum Fascin-1 levels in men. In the prospective case-control study, the serum values of Fascin-1 were different in the two groups of patients, but the difference was not statistically significant, making it unlikely that Fascin-1 could be regarded as a diagnostic biomarker. Artificial intelligence is promising for diagnosis and can play a predictive role for disease progression. Early radiogenomics research comes with a limited amount of literature data in the study of prostate cancer, and for translation into clinical practice large, prospective, randomized trials are needed in the future as well as for analysis of the diagnostic or prognostic role of radiogenomics. At this time, we have no approval or validation for the use of radiogenomics in clinical practice, only a recent exception of the US Food and Drug Administration's

approval of a software for the histopathological diagnosis of prostate cancer. The use of diagnostic and prognostic models, which may or may not combine clinical, radiomic and genomic biomarkers, will improve the predictive or prognostic role. It is predicted that artificial intelligence, especially deep learning techniques, will overcome the current limitations and may enable the clinical implementation of radiogenomics.

**The originality of the thesis**

The main note of originality of the doctoral thesis is given by the fact that no paper has followed until the moment of publication of the results in specialized journals, how the role of the Fascin-1 biomarker in prostate cancer patients is understood. The research was the first in the world to establish the role of Fascin-1 as a diagnostic or prognostic biomarker in prostate cancer. Also, the doctoral research followed the literature review of studies and was designed to maximize current knowledge regarding the role of artificial intelligence and radiogenomics in the present and future identification of new biomarkers with a diagnostic and prognostic role in prostate cancer.