Universitatea Transilvania din Brașov

INTERDISCIPLINARY DOCTORAL SCHOOL

Faculty of MEDICINE

LAURIAN ȘTEFAN MAXIM

ULTRASOUND GUIDED TRANSPERINEAL PROSTATIC BIOPSY PUNCTURE IN THE DETECTION OF PROSTATE CANCER AND THE ROLE OF NUCLEAR MAGNETIC RESONANCE (MRI) AND TRANSRECTAL ULTRASOUND WITH ELASTOGRAPHY

-ABSTRACT-

Scientific coordinator

Prof. dr. IOAN SCÂRNECIU

BRAȘOV, 2023

Introduction

The changing environment of prostate cancer diagnosis has ramifications in the current clinical practice. Continuous improvement of prostate cancer diagnosis is imperatively necessary, especially of high risk prostate cancer discovered in a stage in which it is still curative, given the growing percentage of this type of cancer. This fact involves continuous development of existing imaging technologies, as well as a precise diagnosis, carried out by means of a prostatic biopsy with an increased detection ratio and at the same time being safe for the patient.

Despite the fact that within the last decades science has made progress in order to unveil molecular mechanisms and risk factors involved in prostate cancer, in year 2020 prostate cancer is the most diagnosed cancer for male gender patients at European level, under the circumstances that compared to Europe, were prostate cancer is the most diagnosed cancer, in Romania it is ranked on third position, after pulmonary and colorectal tumors, but experiences a continuous growth within the last three years.

This permanently increasing global incidence of prostate cancer, being the most diagnosed cancer at European level, led to a higher concentration in order to identify the risk factors of this disease and to develop and implement certain prevention measures which should be used especially within the areas which show an increased incidence of prostate cancer. The etiology of prostate cancer is unclear, but there are risk factors involved in prostate cancer. These are divided into unchangeable risk factors and changeable risk factors. In-depth understanding of changeable risk factors leads to an important prevention of prostate cancer and, by changing some of the factors, numerous benefits emerge, with a substantial impact on public health, including the prospect of reducing risks of developing prostate cancer in a lifetime, but also avoiding potential adverse reactions associated with an aggressive treatment, which can be of surgical nature or based on radiation therapy, in case of localized forms of prostate cancer or biological therapy, in advanced or metastatic cases.

Prostate cancer diagnosis can be suspected by means of o combination between different methods, such as: digital rectal examination, dosing of prostatic specific antigen (PSA), transrectal ultrasound with or without elastography, as well as multiparametric nuclear magnetic resonance (mpMRI). The final diagnosis however is always histopathological based, on collected biopsy fragments.

Prostate cancer diagnosis developed significantly within the last decades, based on progress of imaging investigations (transrectal ultrasound with elastography and multiparametric MRI), as well as of MRI or ultrasound with targeted elastography, prostate biopsies.

The role of imaging investigations is very important, as a high percentage of patients can avoid prostatic biopsy as well as associated risks, if performed pre-procedure imaging investigations do not reveal the suspicion of an obvious intra-prostatic lesion.

Histopathological diagnosis of prostate cancer has for 30 years primarily been based on transrectal approach in prostatic biopsy, for prostate cancer diagnosis. Compared to transperineal approach, there are several disadvantages of transrectal approach, such as diagnosis accuracy, which is suboptimal, as well as more frequent infectious complications. Taking into account all these inconveniences of the approach, ultrasound guided transperineal biopsy has in time gained importance all over the world, until it became to be recommended as first intention procedure for prostate cancer diagnosis within European Urology Association's guides.

At the same time, a way of approach should be used, which ensures the majority of benefits in terms of a high rate of detection of prostate cancer, due to easy access to the apex and to the front area of the prostate, but also a safe and comfortable procedure, that can be carried out under local anesthesia, thus minimizing adverse effects of anesthesic medication, as well as of antibiotics used in prostatic biopsy.

The topic which I am approaching within this doctoral thesis is of immediate relevance, as prostate cancer is the most diagnosed type of cancer in Europe. For prostate cancer diagnosis, the way of approach was transperineal and the used "free hand" biopsy technique, by means of a single incision, was extensively described within this paper, proving the fact that this type of biopsy fulfills the criteria of a superior biopsy compared to transrectal biopsy, ensuring a higher rate of clinically significant prostate cancer, with negligible complications. The study was performed on a number of 1674 patients, within a period of 5 years.

Personal contribution

1. Goals

This study aims to demonstrate the superiority of cognitive guided "free hand" transperineal prostate biopsy, through a single perineal path, compared to transrectal prostate biopsy, as well as the role of imaging investigations (mpMRI and transrectal ultrasound with elastography) in the detection of prostate cancer.

Secondary goals of the study were:

1. Evaluation of prostate cancer detection rate in the anterior area of the prostate
2. Detection of prostate cancer in early stages
3. Highlighting of localization, distribution and characteristics of prostate cancer diagnosed by transperineal biopsy
4. Role of imaging investigations in improving the detection of prostate cancer
5. Differences between detection using the two biopsy procedures and mpMRI or transrectal ultrasound with elastography
6. Influence of comorbidities with regard to post-biopsy complications
7. Evaluation of septic, hemorrhagic complications and acute urinary retention, compared to transrectal biopsy and data from literature

2. General methodology

The research was carried out at County Clinical Hospital Brașov and was based on a prospective study completed over a period of time from September 2015 to September 2020.

The work consists of four parts, a general part, which represents the theoretical base of the paper, it contains a series of information from the specialized literature, about the history of prostate cancer, its epidemiology, risk factors, histopathological classification, prostate cancer diagnosis, types of approach in prostatic biopsy and prostatic biopsy complications.

The special part consists of 3 sections which analyze the role of ultrasound guided "free hand" transperineal biopsy within current practice, as well as the role of imaging investigations in prostate cancer detection.

At the end of the special section 3 refers the last two chapters which contain discussions with regard to obtained results, by comparing these results with data from literature. We underlined elements of novelty and significance in order to prove the superiority of the procedure in cause, as well as the minimal risk of post-procedure complications, but also the personal contribution of experimental scientific nature.

.

Special Part I

In Study I, i described the technique of cognitive ultrasound guided "free hand" transperineal prostatic biopsy performed under local anesthesia, through a single incision. Preoperative patient preparation, preparation of instrumentation, preparation of patient with the operating room, operating technique with ultrasound anatomy of prostate and fragment collecting technique, identification of suspect lesions, artifacts occurred during procedure and post-op care, were described.

The particularity of ultrasound guided transperineal biopsy technique by means of the "free hand" method used within Urology Clinic Brașov is that this method is carried out under local anesthesia, while the feed of the puncture needle done through a single perineal puncture spot, by means of a minimal incision, without using a needle or another guiding system mounted on the ultrasound transducer. Once the needle has been fed through the incision area at the level of the perineum, the needle is being guided parallel with the transducer, towards each prostate lobe.

Special Part II

The second section of the special part refers to the role of imaging investigations within detection of prostate cancer, based on presentation of 5 cases in which a preoperative mpMRI was performed and 5 cases of transrectal ultrasound with elastography was performed, as well as presentation of obtained histopathological results.

Special Part III

The 3rd section of the special part is particularly extensive and it compares ultrasound guided "free hand" transperineal biopsy, with transrectal prostatic biopsy, in the detection of cancer prostate, patient's characteristics and complications of each procedure. At the same time the role of imaging investigations with regard to improvement of detection has been evaluated. The study included a number of 1674 patients, who met the requested criteria and who signed an informed written consent. The patients who were included in the study were divided in 2 groups, one group of 1161 patients, who underwent ultrasound guided transperineal biopsy and a number of 513 patients, who underwent transrectal biopsy. Out of the group of patients which went through transperineal biopsy, 644 were subjected to mpMRI and 453 were subjected to transrectal ultrasound with elastography.

In the group of patients who underwent transrectal biopsy, a number of 252 patients underwent mpMRI and 127 patients underwent transrectal ultrasound with elastography.

The group of patients who underwent preprocedural mpMRI, this was interpreted according to the reporting and data system for prostatic imaging (PIRADS v2). Results with a mpMRI score higher or equal to 3 were included, given the fact that this score indicates a positive MRI result. Scores of 1 or 2 were excluded, as this group of patients can avoid prostatic biopsy.

The interpretation of images was performed by MRI experienced radiologists, under the circumstances that this type of interpretation is part of their daily routine. For the group of patients who had prebiopsy transrectal ultrasound with elastography, this was performed out by a single radiologist, while interpretation of results was completed using an elastographic score for classifying discovered lesions.

All collected biopsy fragments were individually labelled, processed and analyzed by a group of pathologists, according to the standards of the International Society for Urologic Pathology.

Demographic and clinical data were extracted by means of reviewing patient's electronic medical files.

Baseline characteristics included age, prostate volume, PSA value, imaging investigations, number of performed biopsies, patient's comorbidities as well as classification of patients in groups, according to ISUP risk grouping.

Three weeks after the procedure, all patients were evaluated on an outpatient basis, in order to discuss the histopathological result and to evaluate any late complications related to the biopsy, such as urinary tract infections, macroscopic hematuria, urethrorrhagia, hemospermia, urinary retention.

All patients signed a surgical consent, after getting each procedure explained and after being told what possible complications might occur.

Patient's data were collected and stored using Excel.

The entire activity in these studies was carried out complying with conditions of medical deontology and ethics, as well as with conditions of scientific research. For statistical analysis, the software Statistical Package for Social Sciences (version 23.0, 2016, SPP, Inc., Chicago, IL, SUA) was used. To calculate the differences between the averages, we used the Student test for independent samples. A value $p < 0.05$ was considered as being statistically significant.

Results and conclusions

Few things are still known about the carcinogenesis of prostate cancer and additional epidemiological studies are needed in order to prevent the disease, but also for obtaining more information about its pathogenesis. The only risk factors that are significantly associated with prostate cancer development are: age, family history and race. The risk of developing prostate cancer increases by aging, generally after the age of 55 years. Age remains one of the strongest risk factors for developing prostate cancer. The risk of developing prostate cancer is very low for patients below the age of 50 (0,1% of cases). Within our study, out of 1674 patients suspected of prostate cancer, 4 patients (0,2%) were diagnosed with prostate cancer at an age below 50.

Regarding characteristics and age of patients included in the study, in the group with transrectal biopsy, we noticed a statistically significant older age, compared to the group of patients which went through transperineal biopsy (72.19 +/- 7.81 vs 69.87 +/- 7.71).

Patients in the transrectal biopsy had a significantly higher average PSA than those with transperineal biopsy (72.7547 +/- 162.23 ng/ml vs 53.8437 +/- 128.29). Transperineal biopsy patients were identified with prostate cancer at a lower PSA level, in a better tumor stage. The volume of prostate is important when deciding to collect a smaller number or a larger number of prostate fragments during biopsy, a bigger prostate needs a large number of collected fragments. Within our study, the volume of prostate showed no significant differences between the two analyzed groups of patients.

Even if no significant differences exist between the two procedures, regarding prostate volume we identified statistically significant differences concerning the number of collected fragments, a larger number of fragments was collected using transperineal approach (14.41 +/- 2.60; 13.96 +/- 2.03; < 0.001 Student).

The overal detection of prostate cancer was of 65,2% using the two types of approach, transperineal and transrectal, this value does not include only clinically significant and insignificant prostate cancer, but also possible precursor lesions of prostate cancer.

The detection rate of prostate cancer and possible malignant precursor lesions using transperineal "free hand" biopsy was of 67,8%, while detection of clinically significant and insignificant prostate cancer, by transperineal biopsy was of 65,7 %, with prostate cancer being identified at 763 patients. Out of 788 patients identified with prostate cancer by transperineal biopsy, 25 patients (2,1%) had possible precursor lesions of prostate cancer.

In the group of patients who had transrectal biopsy, the detection rate of prostate cancer, including possible precursor lesions of prostate cancer, was 59,4%, with prostate cancer based on a Gleason score being identified at 294 patients (57,3%).

We notice an important detection difference between transperineal biopsy and transrectal biopsy (67,8% vs 59,4%), with a better detection of prostate cancer by the transperineal approach.

The sextant protocol for collecting prostatic fragments is insufficient for prostate cancer diagnosis, therefore the number of systematically collected fragments, depending on template and the number of additional target collected number of fragments at the level of the imagistically described lesion is important concerning the detection rate. In our study, increasing the number of fragments led to increasing the detection rate only in case of using transperineal approach, not for patients who underwent transrectal biopsy. Using transperineal biopsy procedure in order to collect 24 fragments, cancer prostate detection rate increased by 13,3% compared to systematic biopsy.

Lesions which are located in the anterior zone of the prostate are less likely to be palpable and more likely not to be diagnosed by transrectal approach, in addition, tumors located in the anterior zone of prostate, are more difficult to be detected by imaging with mpMRI. To avoid multiple transrectal biopsies, especially due to difficult access, but also in order to avoid systematic transperineal biopsies, in case the patient shows biological suspicion, mpMRI is recommended before biopsy, to identify lesions located in the anterior zone of the prostate. Tumors identified later, on repeat prostate biopsy, are most frequently identified in the anterior zone of the prostate, which is difficult to be accessed by transrectal prostate biopsy and far easily accessible by transperineal approach. Detection rate for prostate adenocarcinoma in lesions located in the anterior zone of the prostate was of 93,1% for transperineal biopsy and of 47,1% for prostate acinar adenocarcinoma, which was identified by transrectal biopsy. The overall prostate cancer detection rate for lesions located in the anterior region of the prostate was statistically significant higher using transperineal biopsy,

compared to transrectal biopsy (94,1% vs 43,1%; p < 0,05). Due to the statistically significant difference between prostate cancer detection in the anterior zone of the prostate using he two procedures, in case of a negative transrectal prostate biopsy we recommend thus a transperineal biopsy, with prior performing of an mpMRI, in order to evaluate the front area of the prostate. Patients with lesions in the anterior zone of the prostate were split into risk groups, depending on the performed intervention. Patients with anterior zone lesions and transperineal biopsy were most frequently detected with a Gleason score of 8, while patients with transrectal biopsy were detected with a Gleason score of 7 (4+3).

Evaluation of clinically significant and insignificant prostate cancer was one of the secondary evaluation goals. Clinically insignificant prostate cancer was statistically significant more frequent in the group of patients with transperineal biopsy, compared to patients with transrectal biopsy (8,09% vs 4,2%; p < 0.05), whereas the number of collected fragments was higher in case of transperineal biopsy (14.41 +/- 2.60 vs 13.96 +/- 2.03). Due to the higher number of collected fragments and the fact that we predominantly used combined biopsy, the percentage of insignificant prostate cancer was higher than the one recorded within the literature. The greater number of collected fragments by transperineal biopsy also led to a more frequent detection of clinically insignificant prostate cancer. Patients must therefore be informed about the fact that a larger number of collected fragments increases the detection rate of clinically insignificant prostate cancer, which might affect the quality of life. Clinically significant prostate cancers are defined as cancers that have a Gleason score higher or equal to 7 (3+4), with a tumor volume higher than 0,2 cm3 or with extracapsular extension. Once these tumors have been diagnosed, immediate treatment is necessary, it can be curative or palliative, depending on tumor stage subsequent to prostate biopsy. In our study, clinically significant prostate cancer was identified differently, using the two types of biopsy. In the group of patients with transperineal biopsy, clinically significant prostate cancer was identified at 57,6% of patients, while in the group with transrectal biopsy this type of cancer was identified at 53% of patients. The transperineal procedure identified better the clinical significant prostate cancer. The most diagnosed histopathological type of prostate cancer was acinar adenocarcinoma, identified at 97,3% of patients with transperineal biopsy and at 97,1 % of patients with transrectal biopsy.

The analysis of histopathological forms identified by prostatic biopsy was carried out comparative, for each separate procedure. The most frequent histopathological type discovered in the transperineal biopsy was prostate acinar adenocarcinoma (63,8%). The most frequent histological subtype identified after acinar adenocarcinoma was ductal adenocarcinoma, at 1,6% of patients. Data from the literature identify ductal prostate adenocarcinoma subtype at a percentage of approximately 1%, the pure ductal adenocarcinoma subtype and at a percentage of approximately 5%, mixed subtype with acinar adenocarcinoma. Mucipar adenocarcinoma was identified in 0,3% of cases. In the group of patients with transrectal biopsy, 294 (57,3%) were diagnosed with prostate cancer. The most frequently diagnosed prostate cancer was prostate acinar adenocarcinoma, which was identified in 55,6% of cases, followed by ductal adenocarcinoma, in 1,8% of cases.

From the point of view of highlighted histopathological forms within both groups, we have not recorded significant differences between the two groups, prostate acinar adenocarcinoma being the most identified histopathological subtype by using the two types of biopsy.

Due to the fact that prostate cancer incidence is correlated with age, this is a first factor that has to be taken into account before performing a prostatic biopsy. The risk of death by prostate cancer is

higher at young patients, probably due life expectancy, which is higher and thus a long term evolution of clinically significant prostate cancer will lead to death. Out of patients diagnosed with prostate cancer within our study, using the two types of prostatic biopsy, we noticed that the average age was 70 years, with variations between 46 and 93 years. Very old patients underwent a prostate biopsy only in case their biological status was very good, for patients who needed a histopatholgical result in order to benefit of palliative treatment or in case symptoms the patient showed were not controllable.

The significance and impact of age on behavior and evolution of prostate cancer has for a long period of time been a subject of controversy. Older men are more frequently diagnosed with advanced tumor stages than young patients, therefore the chance of receiving curative therapy for their cancer is lower. Men diagnosed with prostate cancer have to be treated taking into account their health status at the moment of diagnosis, but also the life expectancy and not necessarily the age, healthy but aged patients should have the same treatment options as younger patients. The efficiency of prostate cancer detection within our study, for patients with transperineal biopsy, within the 3 age categories patients were divided into, was of 62,1%, for age 50-60, 63,5% for age 61-75 and 73,4% for age over 75.

Detection of prostate cancer for patients with transrectal biopsy, within the 3 age categories patients were divided into, was of 31,1%, for age 50-60, 83,2% for age 61-75 and 59,5% for age over 75. We noticed a much better detection of prostate cancer by means of transperineal biopsy at young patients, aged between 50-60, a high percentage of these patients can benefit of curative treatment. Transrectal biopsy shows an increased detection of prostate cancer only for the group of patients aged between 61-75.

We noticed a significantly improved detection at patients diagnosed with prostate cancer within the 50-60 years group, using transperineal approach (62,1% vs 31,1%), better even than data described with literature. In the age category over 75 years, if we classify the patients into risk groups, we noticed statistically significant more patients diagnosed by transperineal biopsy, with the group of intermediate risk. Patients aged over 75 of age were included in a large percentage in the high risk group and were better diagnosed by transrectal biopsy. Thus we noticed the influence of age on prostate cancer aggressiveness, the older the age, the more aggressive the prostate cancer. Within our study we also evaluated detection of clinically significant and insignificant prostate cancer depending on average age, of clients diagnosed with prostate cancer, for both procedures. We noticed statistically significant a lower average age for patients diagnosed with clinically significant prostate cancer by transperineal biopsy, than by transrectal biopsy (70,5 years vs 72,1 years; p=.004). In the group of patients diagnosed with clinically insignificant prostate cancer, the average age of the group with transperineal biopsy was lower than of the group with transrectal biopsy (69,3 years vs 72,1 years; p=098).

Metastatic prostate cancer is a finding that is expected to appear at older ages, it is less probable for younger men to be diagnosed with prostate cancer, and this undergo PSA testing, compared to elderly men who show associated urinary symptomatology at the moment of urological examination. However, older men may also be more likely to have metastatic disease, as by getting older the risk of having a potentially lethal cancer that has not been detected grows, as it has been asymptomatic.

In our analysis, for detection of prostate cancer depending on PSA value, patients were split into 3 PSA categories (category I with PSA below 10 ng/ml, category II with PSA between 10-20 ng/ml and

category III with PSA over 20 ng/ml). Detection rate of prostate cancer (p<0.05) was statistically significant better in the group with transperineal biopsy (p value <0,05), compared to transrectal biopsy, for all PSA categories (54% vs 37%; 59% vs 47%; 84% vs 75%). The most significant prostate cancer detection rate was at patients with PSA below 10 ng/ml (54% transperineal biopsy vs 37% transrectal biopsy, p < 0,05). The data obtained are similar to those in the specialized literature, which also reported the advantage of transperineal approach for patients with a PSA level between 4,01-10 ng/ml, this indicates the fact that by using this approach prostate cancers in localized stages are discovered, with reduced or intermediate risk, which can subsequently be suggested for curative treatment, by means of surgical treatment or curative radiation therapy. Other studies reported a prostate cancer detection rate by systematic biopsy, at a PSA level between 4-10 ng/ml, which varied from 30% to 50%. We found a higher detection rate than in literature data, for patients with PSA values between 4-10 ng/ml, the rate of our study being of 54%.

In the category of patients with PSA below 10 ng/ml who went through combined biopsy, we statistically significant identified more transperineal collected fragments than transrectal collected fragments (27,9% vs 17,1%; p<0.05).

Patients with PSA higher than 20 ng/ml show an increased risk of death by prostate cancer. For patients in the group with PSA level > 20 ng/ml, differences between detection rate using the two procedures are smaller, but statistically significant in favor of patients with transperineal biopsy (84% vs 75%, p < 0.05). The more aggressive prostate tumors are, the more transrectal biopsy gets closer to transperineal biopsy in terms of detection.

Depending on the three groups of PSA (<10 ng/ml, 10-20 ng/ml and >20 ng/ml) into which we divided the patients, they were classified into three risk groups, low, intermediate and high, according to prostate cancer diagnosis. Statistically significant (p<0,05) we noticed a better detection for the group of patients with intermediate risk, which who underwent transperineal biopsy, at PSA 10-20 ng/ml (35% vs 24,7; p<0,05).

By analyzing obtained data, we noticed that, using transperineal biopsy, we detected prostate adenocarcinoma as being the most frequent histopathological type, at a medium PSA of 74 ng/ml. HGPIN and ASAP were detected at a PSA of 14,3 ng/ml and 12,3 ng/ml.

By comparing the two procedures depending on PSA value, we also evaluated detection of clinically significant and insignificant prostate cancer. Statistically significant we noticed that by using transperineal approach we obtained a better detection of clinically significant prostate cancer, at medium PSA values lower than in case of using transrectal approach (80,8 ng/ml vs 114,7 ng/ml; p=.016). For clinically insignificant prostate cancer, transrectal approach recorded tumors at a medium PSA level lower than for patients with transperineal approach (14,7 ng/ml vs 20,6 ng/ml; p=0.80).

In our study, we identified by transperineal biopsy significantly more clinically insignificant prostate cancers, with a Gleason score equal to 6 (8,1% vs 4,3%). This is also based on different collecting mode of fragments between the two procedures, with a significant difference recorded for the transperineal group, where more prostate fragments were collected, compared to the transrectal group. The majority of clinically insignificant prostate cancers within the transperineal group were discovered by collecting 14-23 fragments, 76 out of 94 patients were identified with clinically insignificant prostate cancer. Prostate cancers with a Gleason score of 7 or higher are tumors that associate mortality and morbidity, therefore they must be treated. Within our study we were able to

evaluate just the Gleason score, in order to define clinically significant prostate cancers. We noticed a clinically significant prostate cancer detection rate (Gleason higher or equal to 7) of 56,1%, by using the two biopsy procedures, transperineal and transrectal. Clinically significant prostate cancer detection rate, for each procedure, is better by using transperineal biopsy than transrectal biopsy (57,6% vs 53%).

The most common Gleason score was 8, both for transperineal biopsy and for transrectal biopsy (22,5% and 18,7%). Aggressive and very aggressive prostate cancers, with a Gleason score of 9 or 10, were more frequently identified by using transrectal biopsy (2,7% vs 2,1% and 5,5% vs 3,1 %). By means of using transrectal approach, we identified more aggressive tumors which need oncological treatment.

The majority of patients were included in stage ISUP 4, both within the group with transperineal biopsy, and within the group with transrectal biopsy. Statistically significant, the ISUP 1 score was better detected by transperineal biopsy, than of transrectal biopsy (8,09% vs 4,2%; $p<0.05$). Aggressive prostate cancers, with ISUP scores of 4 and 5, were more frequently diagnosed using the two types of biopsies, compared to ISUP 2 or 3. We identified an important diagnosis difference for patients from group ISUP 1, transperineal biopsy identified patients to a better extent.

Prostate cancers in stage T1 were 11,2% discovered by transperineal biopsy and 8,5% by transrectal biopsy. Most frequently patients were diagnosed in tumor stage T2b (17,2% by transperineal biopsy and 15,2% by transrectal biopsy).

In our group, we recorded a higher detection rate by transrectal biopsy, compared to transperineal biopsy, for patients also included in tumor stages T3 and T4 (20,2% vs 16,7%).

To conclude, using transperineal biopsy, we identified more patients with localized stages of the disease, compared to transrectal biopsy, these patients are candidates for a curative treatment of prostate cancer.

The majority of patients identified within our study were patients classified in the high risk group, 447 patients, the intermediate risk group had 403 patients, while the low risk group had 175 patients. For patients within the high risk group we noticed the fact that detection was statistically significant superior by transrectal biopsy, compared to transperineal biopsy (51,6% vs 40,5%; $p<0,05$). Prostate cancers from intermediate and low risk groups were better diagnosed by transperineal biopsy, compared to transrectal biopsy.

Prostate cancer detection depending on prostate volume was intensively discussed, as prostate volume is a strong prediction factor for prostate cancer detection. The size of the gland can affect the efficiency of prostatic biopsy, in case of large size prostates, it can result into a higher rate of false negative results. For patients who were part of the group with transperineal biopsy, an average value of prostate volume of 67,72 cm3 was recorded for patients without prostate cancer, compared to 63,1 cm3 for patients diagnosed with prostate acinar adenocarcinoma. In the group with transrectal biopsy, patients without prostate cancer had a prostate volume of 62,3 cm3, lower than the transperineal group, while acinar adenocarcinoma was diagnosed for a prostate volume larger than the transperineal group (66,3 cm3 vs 63,1cm3).

We analyzed the detection of clinically insignificant prostate cancer depending on average prostate volume, for each performed procedure and we noticed clinically significant prostate cancer detection at a smaller prostate volume, in case of using transperineal prostate biopsy biopsy, compared to transrectal prostate biopsy biopsy (63,8 cm3 vs 65,7cm3; $p=.271$). For the group of patients

diagnosed with clinically insignificant prostate cancer, the average prostate volume was significantly smaller within the group of patients with transperineal biopsy (56,9 cm3 vs 65,7 cm3; p=.198).

The most diagnosed cancer was acinar adenocarcinoma (741 patients, 94,03%) and it was diagnosed at an average prostate volume of 63,12 cm3 in case of using transperineal approach, while within the group of patients with transrectal biopsy the most diagnosed cancer was also acinar adenocarcinoma (285 patients, 93,44%). For patients with transperineal biopsy, the largest average prostate volume was recorded for mucipar adenocarcinoma, while the smallest average prostate volume was recorded for ductal adenocarcinoma. In case of transrectal biopsy, the largest average prostate volume was recorded for acinar adenocarcinoma.

We noticed statistically significant differences between detection of clinically significant and clinically insignificant prostate cancer, depending on the performed procedure, but also on the number of collected fragments. We recorded a statistically significant higher average number of fragments collected in transperineal biopsy, compared to transrectal biopsy, for clinically significant prostate cancer detection (14,3 vs 13,8; p=0.02). For clinically insignificant prostate cancer, statistically significant more fragments were collected for detection by transperineal approach, than by transrectal approach (15,7 vs 14,2; p=.000). We also followed detection of diagnosed histopathological forms, depending on average value of number of collected fragments. The most frequent histopathological type of prostate cancer, acinar adenocarcinoma, was diagnosed by collecting an average number of 14,4 fragments, by transperineal biopsy and 13,8 fragments, by transrectal biopsy. Acinar adenocarcinoma needed more collected fragments for diagnosis, in case of using transperineal approach.

Depeding on the number of collected fragments by transperineal biopsy, prostate acinar adenocarcinoma was discovered by systematic biopsy in 52,8% of patients, in 66,1% of patients with combined bipopsy (systematic and targeted) and in 66,2% of patients who underwent a saturation biopsy. By transrectal approach, prostate acinar adenocarcinoma was diagnosed depending on the number of collected fragments (systematic, combined and saturated biopsy), at a level of 70,8%, 51,3% and 50%. We noticed a superior detection by combined and targeted biopsy, using transperineal approach, as well as a better detection for the group with transrectal biopsy, where fragments were systematically collected, according to the template. Depending on Gleason score and the number of collected fragments, we noticed the highest number of cases with Gleason score 8 at patients who underwent combined biopsy, and in case of transrectal biopsy the most frequent Gleason score was also 8, identified the best by combined biopsy. If we compare the two procedures depending on the number of collected fragments and Gleason score, we statistically significant notice a better detection of Gleason score 8 by combined transperineal collected fragments, compared to transrectal cores (23,2 % vs 14,6%; p<0.05), but also a better detection of Gleason score 8 by transrectal biopsy, case in which we collected fragments in a systematic way (31,9% vs 20,1%; p<0.05). Gleason score 9 score was better diagnosed by transrectal systematic biopsy (23,9% vs 15,0%; p<0.05). We identified a lower use of systematic biopsy in case of transperineal approach. Combined transperineal biopsy was more efficient in detecting clinically significant prostate cancer, with ISUP between 2 and 5, than transrectal biopsy (59,7% vs 47,6%; p<0.05). Systematic transrectal biopsy was also more efficient detecing prostate cancer, with ISUP between 2 and 5, than transperineal biopsy (71,6% vs 51,2%; p<0.05). Combined biopsy proved to be more efficient in our study, than transrectal biopsy, in the diagnosis of tumors in stages T1 and T2a (14,3% vs 11,2%;p>0.05 and 19,7% vs 11,5%; p>0.05).

By using combined systematic biopsy (14-23 fragments) and saturation biopsy (24 fragments), prostate cancer detection rate increased from 52,8% to 68,1% and to 72% with transperineal biopsy and to 71,6%, 53,1% and 56,2% by transrectal biopsy.

Localization of lesions in case of transperineal and transrectal biopsy is important in order to guide targeted biopsy in case of patients with performed imaging investigations. We highlighted the fact that mpMRI is superior in order to record lesions in the anterior zone of prostate (17% vs 0%), compared to transrectal ultrasound with elastography. For the anterior zone of the prostate, we noticed a detection of prostate cancer for patients with mpMRI before the procedure, of 94,1% by means of transperineal procedure and of 43,1%, the difference between the two groups being statistically significant (<0.05). The yield of prostate cancer is higher by using transperineal approach, which increases the rate of detection at transitional and anterior zone of the prostate, compared to transrectal approach. The transitional zone of the prostate is not included in the initial biopsy protocol of prostate cancer, the majority of prostate cancers in this zone are incidental discoveries after a transurethral prostate resection. The transitional area has different sizes, there are patients with a small size transitional area and patients with a large size transitional area which requires a number of additional fragments. Prostate cancers in the transitional area of the prostate are generally clinically insignificant. Within our study we noticed a more frequent of localization of lesions in the transitional area of the prostate by using transperineal biopsy, compared to transrectal biopsy (8,4% vs 0,8%). The transitional area of the prostate was more frequently submitted to transperineal biopsy than to transrectal biopsy, after imaging investigation of suspect lesions in the transitional area. As the transitional area of the prostate is not included in the standard biopsy protocol, due to a low risk of prostate cancer detection.

We also evaluated possible precursor lesions of prostate cancer, for each type of biopsy. High degree intraepithelial neoplasia (HGPIN) was accepted as being the most frequent precursor lesion of invasive prostate cancer, whereas low degree intraepithelial neoplasia (LGPIN) does not have a clearly established influence. In our study, we found possible precursor lesions of prostate cancer in 2,1% of cases, by transperineal biopsy and in 2,2% of cases, by transrectal biopsy.

HGPIN alone does not indicate any suspicion during rectal examination and does not change the PSA value. HGPIN was identified by means of transperineal biopsy and transrectal biopsy, in 0,2% and 0,6% of cases, whereas LGPIN was identified in 0,3% and 0,4% of cases.

Ductal adenocarcinoma is quite rare, at a percentage of 1,3%, usually being associated with acinar carcinoma and it is reported at a percentage of 2,6%-6,3% of cases and is considered as being a more aggressive disease than acinar adenocarcinoma. In our study we recorded ductal adenocarcinoma in 1,6% of cases.

In the group of patients with transperineal approach, the average diagnosis values of PSA in case of HGPIN was of 12,3 ng/ml, in case of LGPIN of 33,6 ng/ml and in case of ASAP of 14,3ng/ml, and in the case of combining PIN and ASAP, the average PSA value for which prostate cancer was diagnosed, was of 14,3 ng/ml. HGPIN is the lesion that is diagnosed at the smallest PSA value. In comparison, in the group of transrectal biopsy HGPIN was diagnosed at a PSA higher than 16,6 ng/ml, LGPIN at a much lower average PSA of 12 ng/ml, and ASAP was diagnosed at a higher average PSA of 28,8 ng/ml, compared to transrectal biopsy. The average number of collected fragments for HGPIN, LGPIN and ASAP was 14,5, 16,5 and 16,7. Compared in the group with transrectal biopsy, HGPIN, LGPIN and ASAP were discovered at an average number of 14, 14, and 16,6 fragments. We

noticed a better detection of LGPIN by means of transperineal biopsy, if the number of collected fragments is bigger.

Depending on the number of collected fragments, possible precursor lesions of prostate cancer were most frequently met by using combined biopsy by means of transperineal approach, in case of ASAP and by transrectal approach, in case of HGPIN and LGPIN. In our study, possible precursor lesions of prostate cancer were identified exclusively by combined collecting of fragments (systematic and targeted biopsy).

The role of imaging investigations in prostate cancer detection

In our study, patients who underwent imaging investigations were divided into two groups, a group who underwent mpMRI and a group of patients who underwent transrectal ultrasound with elastography. Of the group of patients who underwent transperineal biopsy, 55.5% underwent mpMRI and 39% underwent transrectal ultrasound with elastography. Of the group of patients who underwent transrectal biopsy, 49.1% underwent mpMRI and 24.8% underwent transrectal ultrasound with elastography. We observed that patients included in the transperineal biopsy group had more imaging investigations performed than those in the transrectal biopsy group.

A more contemporary and recommended approach by the guidelines of the European Association of Urology is to use mpMRI before making the decision to perform a prostate biopsy in a patient who has increased suspicion based on a positive digital rectal exam or on the basis of a persistently elevated PSA level.

In those with transrectal biopsy and who did or did not have mpMRI, we observed an increased detection rate in patients who had mpMRI compared to those who did not (65.8% vs 49%).

In the group of patients who underwent transrectal ultrasound with elastography and transperineal biopsy, detection increased from 61.8% without elastography, to 71.7%. And in patients with transrectal biopsy, transrectal ultrasound with elastography identified less prostate cancer than in the group that did not (48.8% vs 60.1%).

Comparing the characteristics of patients who underwent mpMRI and had a transperineal biopsy versus those who had a transrectal biopsy, we observed that patients in the transperineal biopsy group were statistically significantly younger than those in the transrectal biopsy group (69.3 % vs 72.2%; $p<0.05$). Prostate volume and PSA of patients with mpMRI and transperineal biopsy were lower than in the transrectal biopsy group. In patients who performed a preoperative transrectal ultrasound with elastography, we identified statistically significantly more younger patients in the group with transperineal biopsy (70.3 vs 72.3; $p<0.05$). Prostate volume and PSA were lower in the transrectal biopsy group of patients who had an elastography ultrasound performed before the intervention. Statistically significant, if we refer to the location of the lesions identified by imaging, they were more frequently described after transrectal ultrasound with elastography, in the right lobe, left lobe and both lobes in patients who performed a transrectal biopsy. In patients who underwent an mpMRI, we observed in our study a significantly better detection of tumors discovered in tumor stage T1, T2a and T2b by transperineal biopsy compared to transrectal biopsy (17.2% vs. 13.5%, $p>0.05$; 24.4% vs 15.1%; $p>0.05$ and 22% vs 21%; $p>0.05$). Comparatively, patients who performed transrectal ultrasound with elastography were more identified by transrectal biopsy in T1 tumor stage (7.1% vs 5.7%; $p>0.05$). Comparing patients who underwent mpMRI and were diagnosed with a prostate cancer classified using the ISUP score, we observed that transrectal biopsy better identified

only patients classified with an ISUP score of 5 (17.1% vs 13%; p>0.05). In the group of patients with transrectal ultrasound with elastography, transrectal biopsy better identified patients only from the ISUP 2 group (10.2% vs 7.9%). We highlighted significant differences in patients in the intermediate risk group and who performed an mpMRI; they were statistically significantly better diagnosed by transperineal biopsy (39% vs 29%; p<0.05). According to the data, patients with a PIRADS score of 5 are more often placed in very high risk groups (4 and 5).

Depending on the cores number and the ISUP scoring, we observed for patients diagnosed with clinically insignificant prostate cancer, in the case of PIRADS 3 lesions that it was only diagnosed by collecting more than 12 fragments. Patients who had described PIRADS scores of 4 and 5 were diagnosed in an important percentage also by systematic biopsy. Patients who underwent transrectal ultrasound with elastography and had an elastographic score of 3 were classified into lower risk groups as well as into the increased risk group. Patients who described an elastographic score of 4 most frequently were included in the high-risk group. According to the PIRADS score used in mpMRI and the elastographic score used in transrectal ultrasound with elastography, we performed a division of patients. Thus, at the PIRADS 3 score, the groups of patients were percentage equal in the two biopsy groups. Those who presented a PIRADS score of 4 were higher in percentage in the transrectal biopsy group (72.2% vs 64.4%). Patients with high suspicion of prostate cancer with a PIRADS score of 5 were found in a higher percentage in the transperineal biopsy group. In patients who had an elastographic score, significantly more patients were found with an elastographic score of 3 (16.9 vs 5.6%), and with elastographic scores of 4 and 5 more patients were found in the group of transrectal biopsy.

The prostate cancer detection rate for patients who had a positive mpMRI with a PIRADS score higher than or equal to 3 for the transperineal biopsy procedure was 23.9% for lesions classified as PIRADS 3, 57.8% for lesions classified PIRADS 4 and 70.9% for PIRADS5 lesions. In the group of patients in whom a transrectal ultrasound with elastography was performed preprocedural, the detection according to the elastographic score for the transperineal procedure was 28.5% in patients with an elastographic score of 3, 55.3% in elastographic score of 4 and the elastographic score of 5 is 81.9%.

To evaluate the detection of acinar adenocarcinoma of the prostate in those who performed mpMRI, according to age, we divided the patients into two age categories: under 65 years and over 65 years. We identified in the group of patients with transperineal biopsy a higher detection, in the age category over 65 years compared to under 65 years (75.5% vs 21.8%). In patients who underwent transrectal biopsy, the detection rate of acinar adenocarcinoma was higher in those over 65 years of age compared to the group under 65 years of age (79.1% vs 17.8%). In the group of patients who performed transrectal ultrasound with elastography, the detection of prostate adenocarcinoma was higher in the group of patients over 65 years old, using both transperineal and transrectal biopsy (76.5% vs 73.9%).

Evaluation of the detection of statistically significant and insignificant prostate cancer for patients who underwent preprocedural imaging investigations was one of the objectives of the present study. For clinically significant prostate cancer, we observed a superior detection in patients who underwent transperineal biopsy, both for those who performed mpMRI and those who performed transrectal ultrasound with elastography (63% vs 57.9%; p> 0.05 and 61.5% vs 46.4%; p>0.05). The detection of clinically insignificant prostate cancer was higher in the group of patients who underwent a

transperineal biopsy and who underwent mpMRI and transrectal ultrasound with elastography compared to those who had a transrectal biopsy (10.7% vs 7.9%; p>0.05 and 10.2% vs 2.4%; p>0.05). The group of patients who had a transperineal biopsy and imaging investigations performed before the procedure had a better detection of prostate cancer compared to the group of patients who had a transrectal biopsy and imaging investigations performed.

The most common were T1 and T2 tumor stages in the anterior area of the prostate according to the TNM classification, both for the transperineal biopsy and for the transrectal biopsy. The percentage of tumors in stage T1 and T2 was revealed for transperineal and transrectal puncture, statistically significantly more in transperineal biopsy (86.2% vs 51%; p<0.05). The classification of patients who underwent mpMRI and presented comorbidities before surgery revealed in our study a higher percentage of patients who underwent transperineal biopsy and had diabetes. Also in the patients who performed transperineal biopsy, there were more who had obesity and performed mpRMN. In transrectal biopsy patients, most were not overweight or with grade I obesity. Compared to the group of patients who underwent transrectal ultrasound with elastography, in the case of the transperineal approach, there were more patients with diabetes. Overweight patients who underwent transrectal ultrasound with elastography and had a transperineal biopsy were more than those who did not undergo ultrasound with elastography. In transrectally biopsied patients, more patients with grade II obesity were diagnosed in the ultrasound group. In the group of patients who performed mpMRI, anticoagulant consumption was more common in those who performed transperineal biopsy (34% vs 26.2%; p>0.05).

Patient comorbidities in biopsy groups

On patients included in our study, we evaluated, as a secondary objective, in addition to the detection rate of prostate cancer by transperineal biopsy and the role of imaging investigations in prostate cancer detection, the influence of comorbidities such as obesity, diabetes and the consumption of anticoagulants or antiplatelets platelets in prostate cancer, diagnosed by transperineal or transrectal biopsy

The risk factors for the development of prostate cancer were analyzed for the purpose of prevention. A popular risk factor that has been studied in the literature but also described in our study due to its prevalence in the Western world was obesity involving diet, physical activity and body size change. A Western diet also involves an increased intake of calories and fat. In our study according to body mass index, patients were divided according to the procedure performed.

We did not observe a significant percentage difference between the group of patients with increased body mass index who underwent transperineal biopsy or transrectal biopsy. According to body mass index, obese patients were divided into risk groups according to the procedure performed. Patients that were included in the low and intermediate risk group with transperineal biopsy had more frequent obesity than those included in the same risk groups but with transrectal biopsy (11.5% vs 5.7%; p>0.05 and 27, 7% vs 19.2% p>0.05). We observed that in the group of patients with transperineal biopsy, obesity was a risk factor for placing patients in the high-risk group, with more patients being identified with obesity and an aggressive prostate cancer than those who did not have obesity.

In patients on anticoagulant or antiplatelet treatment before biopsy, more were assigned to the low and intermediate risk group by performing prostate biopsy through the transperineal versus

transrectal approach (15% vs 9.3%; p.0.05; 28 % vs 20.5%; p<0.05). Patients who were placed in the high-risk group and had anticoagulant treatment were more frequently identified using the transrectal approach (29.8% vs 26.8%; p>0.05). We observed in patients who had a transperineal biopsy and were placed in the low-risk group that those who were on anticoagulation were more common than those who were not on anticoagulation.

In our study, patients who had diabetes and had a transperineal biopsy performed were more frequently in the intermediate and high risk group, compared to patients who did not have diabetes (27.7% vs 27.2%; 29, 7% vs. 25%). For patients with transrectal biopsy, diabetes mellitus diagnosed preoperatively was a risk factor for intermediate or high risk groups (23.5% vs 17.5%; 30.1% vs 29.7%). In contrast, we observed that patients who presented diabetes and were assigned by transperineal or transrectal biopsy were also included to the low-risk group. We observed that diabetes is a risk factor for the diagnosis of more aggressive tumors in intermediate and high risk groups.

In our study in the group of patients who underwent transperineal biopsy the most common complications encountered were urethrorrhagia (9.5%), macroscopic hematuria (5.9%) and dysuria (5%). Compared with the transperineal biopsy group, in the transrectal biopsy group, the most common complications encountered were rectal bleeding (5.5%), fever (4.3%), and macroscopic hematuria (3.7%). If we compare the first three complications occurring for each procedure we notice that they are different, the only common complication encountered is macroscopic hematuria, which is more common in the transperineal biopsy group (5.9% vs 3.7%). The febrile syndrome also appeared in the transrectal biopsy, quite frequently compared to the transperineal biopsy, where we did not record any case of postoperative fever.

The perineal skin can be prepared with antiseptic solutions, which the rectal mucosa cannot.

We observed in patients who had diabetes and had a transperineal biopsy that diabetes did not influence the increase in the risk of infectious complications, thus no patient was registered with urosepsis, fever or lower urinary tract infection. In the group of patients with transrectal biopsy, the rate of infectious complications is significantly higher than in the group with transperineal biopsy, but we observed that diabetes mellitus was not a risk factor for the occurrence of infectious complications. The rate of infectious complications in patients with diabetes was 0% in the transperineal biopsy group and 9.6% for the transrectal biopsy group, lower results than those described in the literature. Assessed perineal pain was more common in patients with transperineal approach who had diabetes compared to those with transrectal approach and had diabetes (3.6% vs 0%). In patients with diabetes who had transrectal biopsy, significantly more were identified with postoperative urinary infection than those who had transrectal biopsy (7.4% vs 0%).

Patients with a higher body mass index were evaluated in our study for complications. In the group of patients with transperineal biopsy in patients who presented different degrees of obesity, the risk of bleeding complications, like macroscopic hematuria, urethrorrhagia or rectal bleeding was higher than in those who were normoweight (6.1% vs 5.6 %; 10.9% vs 7.9% and 0.7% vs 0.4%). Obesity, from the data analyzed in our study, is a risk factor for the more frequent occurrence of bleeding complications than in normal weight subjects. Analyzing the group of patients with transrectal biopsy, we observed that obesity may favor the more frequent occurrence of infectious complications, such as febrile syndrome and lower urinary tract infection compared to the group of normal weight patients (6% vs 2.5% and 3.8% vs 1 .6%). Patients with an increased body mass index should be proposed for prostate biopsy through the transperineal approach to reduce the risk of developing a septic complication,

which may be of low grade but which may be serious, requiring aggressive antibiotic therapy or even hospitalization on intensive care unit.

Patients with anticoagulant or antiplatelet treatment were also evaluated for complications in those two groups. In the transperineal biopsy group we observed an increase in hemorrhagic complications such as macroscopic hematuria, urethrorrhagia, rectal bleeding and hemospermia in those who used anticoagulant treatment compared to those who did not use anticoagulant treatment (9.8% vs 3.7%; 18 .2% vs 4.8%; 1% vs 0.3% and 7.6% vs 2.1%). Chronic use of anticoagulants increases the risk of bleeding using the transperineal approach, the most important difference is in those who have anticoagulant treatment and had urethrorrhagia. In patients in the transrectal biopsy group, the anticoagulant did not influence the risk of bleeding.

Acute urinary retention is a complication that can occur postoperatively after prostate biopsy. Risk factors for acute urinary retention after prostate biopsy have been reported, including increased prostate volume, large transitional zone, and a high International Prostate Symptom Score (IPSS).

The incidence of acute urinary retention in our study was 2.4%, 0.3% for transperineal biopsy, and 2.1% for transrectal biopsy. Acute urinary retention was more frequently observed in the group of patients with transrectal biopsy. Routine catheterization was not performed for patients included in the study. The mounting of a urethrovesical probe was used only if the patient had a lesion located in the anterior prostate or periurethral area described in the mpRMN examination, a difficult lesion to approach. The ureterovesical probe was removed immediately after the prostatic biopsy was performed.

According to the number of collected fragments and acute urinary retention, patients were divided into the group in which fragments were collected systematically, the group with combined fragment collection, and the group of patients in which fragments were collected by saturation biopsy with collection of 24 fragments. Accordingly, we observed a small risk of acute urinary retention for transperineal biopsy patients with the collection of 12-23 fragments, and the collection of 24 fragments (0.3%; 1.5%) compared to the group who performed transrectal biopsy with 13-23 fragments and 24 fragments (2.6%; 6.3%). In patients who had a systematic transrectal or transperineal biopsy, we did not identify any cases of acute urinary retention. The increase in the number of fragments also increases the risk of acute urinary retention, in our study the most cases were recorded in the transrectal biopsy group after the collection of 24 fragments.

Patients were divided into 4 categories to evaluate the complications that occurred according to the volume of the prostate and the type of biopsy performed. In patients with prostate volume below 50 cm3, with transperineal biopsy, acute urinary retention occurred in 2 patients (0.4%) and in the group with transrectal biopsy also in 2 patients (0.3%). In transrectal biopsy patients, the risk of acute urinary retention was increased in those with prostate volume below 50 cm3 compared to those with prostate volume above 50 cm3 (2.6% vs 1.6%). Only in the group of patients with prostatic volume over 50 cm3 or over 60 cm3, acute urinary retention is more common. In the group of patients with transrectal biopsy, we did not reveal an increase in the rate of acute urine retention correlated with the increased prostate volume.

General Conclusions

Prostate cancer diagnosis has been based for 30 years on the transrectal approach. There are many disadvantages to it, such as the diagnostic accuracy which is suboptimal but also the more frequent infectious complications that can occur much often than in the case of using the transperineal approach. Given these drawbacks of the transrectal approach, transperineal ultrasound guided, gradually gained importance worldwide until it came to be recommended as a fist-line procedure in the diagnostic of prostate cancer in the guidelines of the European Association of Urology.

The optimal diagnostic pathway for men with persistent clinical suspicion of prostate cancer must be found, also biopsies must be performed as targeted as possible to increase the detection rate of prostate cancer and reduce the psychological stress of the patient associated with repeated biopsies. An important thing to consider is related to the overall costs per patient, which may be higher if the detection rate is lower and the patient requires one or more repeats of the prostate biopsy. The increased rate of infectious complications also lead to an exponential increase in costs if the patient develops septic complications after biopsy, complications that are financially ineffective, through increased consumption of expensive antibiotics, and eventually if the patient requires admission to intensive care unit, they increase even more. Transperineal prostate biopsy performed "free hand", guided cognitive, mostly solves the problems presented above and thus leads to lower costs for patients who had a prostate biopsy.

A number of publications suggest that transperineal prostate biopsy offers a higher detection rate of prostate cancer, fewer complications and a technique with increased feasibility. These features were exposed and studied in this thesis, on a large number of patients. The ultrasound guided transperineal biopsy approach is also useful to better characterize the suspicious tumors discovered by ultrasound and after that direct the needle to the suspicious areas, and performing target biopsy. The use of the brachytherapy template limited the transperineal biopsy procedure because it could not be performed under local anesthesia, thus increasing the costs of the intervention as well as the surgical risks. Giving up to the perineal brachytherapy template has opened new horizons in performing the intervention in the ambulatory field, under local anesthesia, a procedure that does not require additional equipment, being usually performed through two perineal paths.

Our clinic experience from everyday practice can prove with this thesis the superiority of the transperineal approach compared to the transrectal one, but also the very important role of imaging investigations in the detection of prostatic tumors by performing ultrasound guided cognitive biopsy.

This thesis describes a „free hand" transperineal biopsy technique, with cognitive guidance performed under local anesthesia that presents an increased detection rate compared to transrectal prostate biopsy but also compared to existing data in the literature. The procedure is well tolerated by patients with a low complications rate, especially septic complications.

This thesis also indentifies patients who are candidates for prostate biopsy based on imaging investigations but may also identify groups of patients who are with aggressive disease and need to be treated more aggressively.

The role of imaging investigations such as mpMRI and transrectal ultrasound with elastography as tools used to supplement the PSA test and also for the cognitive guidance of transperineal prostate biopsies was investigated in this thesis. MRI technology is in a continuous development, both in

terms of evolution of MRI machines and also accessibility. A well performed MRI leads to greater diagnostic accuracy and leads to targeted biopsies that are combined with systematic biopsies to detect clinically significant prostate cancer. The increased use of mpMRI for the diagnosis of prostate cancer increases the demands on radiologists to meet the additional clinical demands of the most diagnosed type of cancer in men.

The role of transrectal ultrasound with elastography remains modern because it is a non-invasive, inexpensive method that brings important benefits in describing suspicious lesions that are then to be biopsied transperineally with cognitive guidance.

That is why increasingly advanced imaging investigations and transperineal prostate biopsy that increase accuracy in hard to reach areas of the prostate, with a very low risk of complications, must be used in daily practice in order to have the most accurate diagnosis, a classification of patients in risk groups and after that, a more effective treatment.

In conclusion, we need to use a method of biopsy that increases the detection rate of significant prostate cancer, stratifies patients into risk groups and decreases the risk of complications, some of the them very serious, is a cost effective strategy because it leads to the use a treatment corresponding to the tumor stage in which the patient is discovered.

The most important aspect discovered in this thesis were summarized as follows:

1. Overall prostate cancer detection rate using both procedures was 65,2%.
2. We noticed an important difference in cancer detection rate between transperineal biopsy and transrectal biopsy (67,8% vs 59,4%).
3. Collecting fragments was performed systematically, combined and by saturation biopsy, and the detection rate when using saturation biopsy increased to 66,2% from 52,8% when using systematic biopsy.
4. We observed more patients in our study who had a transperineal prostate rebiopsy. A significant number of those who initially underwent transrectal prostate biopsy subsequently underwent transperineal prostate biopsy, due to the overall higher detection rate on prostate cancer, but also due the approach to the anterior area of the prostate, which is easily approached transperineally.
5. The overall detection rate of prostate cancer for lesions located in the anterior area of the prostate was statistically significantly higher using transperineal biopsy versus transrectal biopsy (94,1% vs 43,1%; $p<0,05$).
6. Clinically insignificant prostate cancer was statistically significantly more frequent in the group of patients with transperineal prostate biopsy compared to those with transrectal prostate biopsy (8,09% vs 4,2%; $p<0.05$), and the number of prostate cores was higher in the case of transperineal prostate biopsy (14.41+/- 2.60 vs 13.96+/- 2.03).
7. Much better detection rate of prostate cancer by transperineal biopsy in young patients aged 50-60 years old, a large percentage of these patients can benefit of curative treatment (62,1% vs 31,1%).
8. The most significant prostate cancer detection rate was in patients with PSA below 10 ng/ml (54% transperineal biopsy versus 37% by transrectal biopsy, $p<0.05$).
9. Aggressive and very aggressive prostate cancers with a Gleason score of 9 or 10 were more frequently identified using transrectal prostate biopsy (2,7% vs 2,1% and 5,5% vs 3,1 %).

10. Score ISUP 1 was statistically significant, better detected by transperineal biopsy than transrectal biopsy (8,09% vs 4,2%; p<0.05).

11. The higher the ISUP score is, the older the patients are, patients with ISUP score of 1 had an average age of 69 years, compared to those with an ISUP score of 5, who had an average age of 73 years old, aggressive prostate cancer being discovered at an older age.

12. In our study, using transperineal prostate biopsy we identified more patients with localized stages of the disease than with transrectal prostate biopsy, patients who are candidates for curative treatment of prostate cancer.

13. We observed a superior cancer detection rate by systematic and targeted biopsy using the transperineal approach and better cancer detection in the transrectal group in which the cores biopsy samples were systematically collected according to the template.

14. Combined transperineal prostate biopsy was more effective in detecting clinically significant prostate cancer, classified ISUP between 2 and 5, than transrectal prostate biopsy (59,7% vs 47,6%; p<0.05)

15. Using systematic biopsy, combined biopsy (14-23 fragments) and saturation biopsy (24 fragments), the detection rate of prostate cancer increased from 52,8% to 68,1% and to 72% with transperineal prostate biopsy and 71,6%, 53,1% and 56,2% by transrectal prostate biopsy.

16. Prostate cancer detection rates in patients who underwent mpMRI and transperineal prostate biopsy versus those who did not have a mpMRI and transperineal prostate biopsy is 73,7% vs 55,7%.

17. In the group of patients who underwent transrectal ultrasound with elastography and transperineal biopsy, the detection rate increased from 61,8%, without elastography to 71,7% (65,8% vs 49% for transrectal prostate biopsy).

18. Significantly better detection rate of stage T1, T2a and T2b tumors by using transperineal prostate biopsy compared to transrectal prostate biopsy (17,2% vs13,5%, p>0.05; 24,4% vs 15,1%; p>0.05 and 22% vs 21%; p>0.05).

19. We did not observe major differences between the prostate cancer detection rate using transperineal approach, in patients with PIRADS score and elastographic score. In patients with a PIRADS or elastographic score of 4, the detection rate was better in those with mpMRI. At PIRADS score of 4, detection was better using transrectal ultrasound with elastography.

20. The rate of infectious complications in the patients with diabetes was 0% in the transperineal group and 9,6% for the transrectal biopsy group. We observed in our study that diabetes is not a risk factor for the development of infectious complications.

21. The most common complications in the group with transperineal biopsy were hemorrhagic complications (urethrorrhagia, macroscopic hematuria), and in the group of patients with transrectal biopsy the most common complications were infectious complications (febrile syndrome, lower urinary tract infection) and rectal bleeding.

22. Obesity, from the data analyzed in our study, is a risk factor for the more frequent occurrence of hemorrhagic complication than in normal weight patients.

23. Performing transperineal prostate biopsy we observed an increase number of hemorrhagic complications such as macroscopic hematuria, urethrorrhagia, rectal bleeding and hemospermia in those who used anticoagulant treatment compared to those who did not use anticoagulant treatment (9,8% vs 3,7%; 18,2% vs 4,8%; 1% vs 0,3% and 7,6% vs 2,1%).

24. The incidence of acute urinary retention in our study was 2,4%, 0,3% for transperineal biopsy and 2,1% for transrectal biopsy. Acute urinary retention was more frequently observed in the group of patients with transrectal biopsy.

Originality and Innovative contributions of the thesis

This study exposes and tries to solve the dilemma in choosing the biopsy modality between transperineal prostate biopsy and transrectal prostate biopsy as the detection rate of prostate cancer but also the very important role of imaging investigations in the detection of prostate cancer and to avoid or reduction of the rate of prostate complications associated with prostate biopsy. The transition from transrectal biopsy to transperineal biopsy can be difficult to implement as a change, because involves a change of the existing equipment from the Clinic of Urology, improve communication with radiologist who perform mpMRI and who perform transrectal ultrasound with elastography and also allocation of a period of time required for courses for the learning curve of the biopsy procedure.

The present thesis is, from our knowledge, the first doctoral thesis from the country that analyzes and describes in detail a particular transperineal biopsy technique, comparing the results obtained on a large group of patients with those obtained by transrectal biopsy and with the data from literature.

I have described in this PhD thesis, as the originality of the thesis, a technique of „free hand" transperineal biopsy, cognitive, under local anesthesia performed using a single incision. The particularity consist in the fact that in the literature the studies published on transperineal biopsy performed under local anesthesia, describe the biopsy made with an incision made for each prostatic lobe or with an guidance system placed on the ultrasound transducer. In our study the needle core were collected through a single perineal route.