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Transperineal Template-Guided Mapping Biopsy and Multiparametric MRI for Detection of Clinically Significant Prostate Cancer in Patients after Initial Negative Transrectal Ultrasound-Guided Biopsy

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Abstract

Objectives: To evaluate the significance of mpMRI on detecting prostate cancer on repeat biopsy if transperineal prostate mapping (TPM) technique is applied.

Methods: Prospective clinical data of 72 patients with prior negative prostate biopsy and rising PSA level were collected. Patients underwent 1.5T mpMRI with subsequent 20 core transperineal prostate biopsy. Radiological examination was performed according PIRADS 2.0 version. Radiologist scores and location were matched with TPM histopathology of the prostate. The positive (PPV) and negative (NPV) predictive values of mpMRI for ruling out any PCa and clinical significant PCa were calculated.

Results: PCa was detected in 37 (51.4%) and clinically significant PCa in 24 (33.3%) patients. Calculated PPV and NPV of mpMRI to detect PCa were 45.45% and 39.29% with specificity and sensitivity of 54.05% and 31.43% respectively.

Conclusions: TPM biopsies detect prostate cancer in over half of the patients with one or more initially negative prostate biopsies and mpMRI is helpful in identifying prostate lesions suggestive of cancer.

Keywords: Prostate cancer; Transperineal prostate biopsy; mpMRI

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Introduction

Prostate cancer is one of oncological diseases, which is the most frequently diagnosed among males in the world and most European countries [1]. Despite improvement of diagnostic and therapeutic potentials, the survival rate of the patients with prostate cancer still remains low due to frequent recrudescence of the disease, which is not observed or observed too late. Similarly, patients with prostate cancer are quite often treated when they should not be treated at all overtreated when it is sufficient observe it. Consequently, it is critical to distinguish between clinically significant prostate cancer and clinically insignificant one because clinically insignificant prostate gland cancer progresses slowly and does not cause any threat to patient's life [2].

Because of the increase in prostate cancer morbidity, in 2006, Lithuanian launched the "Lithuanian Early Prostate Cancer Detection Programme" [3]. Taking the programme recommendations into consideration, more detailed examination of a patient is recommended when PSA level in the blood exceeds 3mg/mL. After carrying out of patient's urological check-up, digital rectal and echoscopic examinations, a transrectal ultrasound (TRUS) examination of the prostate gland is done to the patient. TRUS-guided biopsies help in detecting up to 70% of prostate cancer cases. However, during taking samples of TRUS-guided biopsy, the mucous membrane of the rectum is affected; therefore, it may cause certain complications such as bleeding, acute inflammation of the prostate gland, urinary retention or sepsis. [4,5]. For a repeated examination of the prostate gland, it is recommended to do transperineal biopsies because by applying this method risk of complications is lower while its diagnostic value amounts up to 85-90% [5]. Besides, research data indicates that the frequency rate of detection of prostate cancer increases by carrying out repeated transperineal biopsies to those patients who received negative findings from the initial TRUS biopsy [5,6]. Transperineal biopsy

with a template grid detects prostate cancer as well as localises it. The template grid is divided by 5mm segments; therefore, shots can be performed with a 5mm bias. It should be noted that this method of biopsy detects more accurately cancer sites existing in the apex area of the prostate gland, which is hardly accessed by applying TRUS biopsy [6]. Tumours in the apex area are detected in up to 30% cases of prostate cancer. TRUS biopsy does not indicate effectiveness of repeated biopsies of the prostate for clinically-significant verification of prostate cancer. Barzell et al. [7] have examined 124 patients who had repeated biopsy of the prostate and compared the diagnostic accuracy of TRUS-guided and transperineal biopsies. Research data has indicated that 76–80% of clinically-significant cases of prostate cancer were not detected if repeated biopsy was done by using TRUS method.

It is appropriate to involve new perspective methods of diagnostics if performing biopsies such as an algorithmic analysing system of 3D ultrasound imaging or examinations of multiparametric magnetic resonance imaging, and to reduce this way the number of insufficiently reasoned blind biopsies and to accelerate diagnostics of prostate gland cancer.

Algorithmic analysing system of 3D ultrasound imaging

An algorithmic analysing system of 3D ultrasound imaging is a diagnostic method of prostate cancer based on the system of three-dimensional (3D) ultrasonic waves for identification of the impairment of prostate tissue integrity. This is a non-invasive technology, which allows an accurate detection of very small cancer sites. The first clinical findings using this method were described in 2008 [8].

For examining the patient, a rectal 3D probe with a magnetic rotator, which angle of rotation goes to 180°, is used. The data of the rectal probe is transferred to the computing system, the basis of which is substantiated by the postoperative histologic findings of radical surgeries. The records of the algorithmic analysing system of 3D ultrasound imaging are substantiated by the impairments of prostate tissue integrity, which can be both as of inflammatory and tumorous origin. Evaluation of the sites within the prostate depends on a size of the site. Although findings of different studies indicate that specificity and responsiveness of the algorithmic analysing system of 3D ultrasound imaging of the site, the volume size of which is 0.2cm^3, amount to 60–75%, while, in case of a 0.5cm^3 site size, specificity and responsiveness is 85–95% when diagnosing tumorous lesions of the prostate [9,10]; however, there is still lack of large-scale studies evaluating the clinical value of this new technology.

Multiparametric magnetic resonance imagining in accordance with PI-RADS system

Multiparametric magnetic resonance imaging (mpMRI) of the prostate is able to identify prostate tumour sites on the basis of changes in the signal in the prostate tissue [14]. mpMRI examination is performed by a MR device of at least 1.5-Tesla (T) field strength using a pelvic coil. During the mpMRI examination, at least one anatomic sequence (T2) and at least 2 functional sequences (mostly the ones of diffusion-weighted and dynamic contrast-enhanced) are evaluated. Basing on mpMRI images, prostate lesions are evaluated by applying a PI-RADS system in accordance with the guidelines updated by the European Society of Urogenital Radiology in 2015 [15].

The mpMRI examination is valuable for detecting clinically-significant tumorous sites in the prostate, especially in those parts of the prostate (in the anterior part, especially within transition zone, and in the distal part of the apex), which are hardly accessed or cannot be accessed at all during the TRUS-guided biopsy [14].

Materials and Methods

The study involved NCI (National Cancer Institution) patients who signed an informed person's consent form and satisfied the enrolment criteria specified in the protocol.

Patients' enrolment criteria:

- Signed informed subject's consent form for participation in the study.
- Patients who are diagnosed with an increase of PSA level in the blood after at least 4 months from the date of transrectal biopsy of the prostate gland.
- Patients' age must not exceed 75 years old.

Patients' exclusion criteria:

- Patients' refusal to participate in the study.
- The patient is after surgical prostate operations (TUR-P, adenomectomy, suprapubic fistulas).
- The patients who are diagnosed with acute urinary tract inflammation, acute or chronic bacterial prostatitis.
- Malignant tumour of another localisation at the same time, except for dermal tumours in case if less than 5 years passed from its treatment.
- 2-3 scores of ECOG.
- The patients whom mpMRI cannot be performed due to renal function insufficiency, metal implants, pacemakers, subcutaneous cardiac defibrillators, any other non-mentioned electronic, mechanic or magnetic implant.

The patients participated in the study for five weeks, which involved five visits.

During the first visit, the patients were informed about the study being. In case of patient's consent to participate in the study, his/her demographic information and other data required to the study were registered: patients' diseases (IDC, histologic assessment of biopsies, Gleason's Score, etc.) and life anamnesis (age, cancer diagnosis in the family, accompanying diseases, administrated medicines). Besides, blood and urine samples were taken during this visit as well.

During the second visit, digital rectal (finger) examination of the prostate is carried out. The patient is investigated by using an algorithmic analysing system of 3D ultrasound imaging.

During the third visit, mpMRI examination was performed to the patient, and prostate lesions were evaluated in accordance with PI-RADS system.

During the fourth visit, for clinically-significant/insignificant histologic verification of prostate the patient was hospitalised in NCI Oncourologic Department in order to carry out transperineal biopsy of the prostate.

During the fifth visit, the examination findings were assessed, and tactical decisions on further follow-up (clinically-insignificant cancer) or treatment (clinically-significant cancer) of the patient were

Table 1: Examination plan of the patients participating in the study.

Data and examinations	Visit				
	Visit 1 (Week 0)	Visit 2 (Week 1)	Visit 3 (Week 2)	Visit 4 (Week 3)	Visit 5 (Week 5)
Informed person's consent form	x				
Demographic data	x				
Accompanying diseases and administrated medicines for BPH treatment	x				
Digital rectal examination		x			
Transrectal ultrasound imaging		x			
Algorithmic analysing system of 3D ultrasound imaging		x			
Transperineal prostate biopsy by using template grid				x	
mpMRI			x		
Blood examination (creatinine*, K, Na, glucose, CBT, coagulation indicators)	x*			x	
Analysis of molecular-markers (*CRISP3*, *EPCA*, *MSMB)*	x				
PSA examination results	x				
Urinal examination (and urinal culture sample in case of nitrite presence)	x				
IPSS scale	x				x
Evaluation of patient's examination findings and complications					x

Notes: CBT: Common Blood Test; dpMRI: Multiparametric Magnetic Resonance Imaging; BPH: Benign Prostate Hyperplasia; K: Potassium; Na: Sodium; IPSS: International Prostate Symptome Score.
*During the first visit, only a creatinine test is carried out prior to mpMRI imaging examination.

made.

An examination plan of the patients participating in the study is provided in Table 1.

Statistical data analysis

A statistical data analysis was performed by using a package of data analysing software SPSS. Quantitative features were evaluated by calculating averages, standard deviations, median, minimal and maximal values; qualitative – by calculation frequencies and percentages. Correlation of the research parameters with clinical pathological parameters was estimated by using $\chi 2$ or Fisher's Exact Test (in case if the number of cases in the group is less than 5). Differences among the groups were considered statistically significant when $p<0.05$.

Probability of the impact of the research parameters was assessed by applying a model of multifactor logistic regression, which involved statistically-significant parameters established during the one-factor analysis.

To determine diagnostic accuracy of the study ROC curves representing the dependence of study responsiveness on its specificity and displaying the value of the study, were used. The meanings of responsiveness, specificity, accuracy, positive and negative prognoses of every research method were calculated.

Results

Patient's median age at the time of TPM biopsy was 62.3±6.3 years, PSA 8.41±4.2ng/ml PSA density 0.203±0.18. Almost two thirds of patients underwent first repeat biopsy, 30.4% and 5.7% second and third repeat biopsy, respectively. PCa was detected in 37 (51.4%) and clinically significant PCa in 24 (33.3%) patients (Table 2).

Calculated positive predictive values (PPV) and negative predictive values (NPV) of mpMRI to detect PCa were 45.45% and 39.29% with specificity and sensitivity of 54.05% and 31.43% respectively. PPV and NPV of mpMRI for clinically significant PCa were smaller and reached 27.08% and 57.14% respectively, with sensitivity of 59.1% and specificity of 25.5% (Table 3).

Discussion

There are a lot of research and comparative projects carried out in order to assess the accuracy and sensitivity of mpMRI. It is stated that mpMRI applied to the patients may diagnose up to 33.27% of the clinically-significant focus in the prostate, which have not been diagnosed during the TRUS biopsy [16]. MpMRI sensitivity increases during diagnosing tumorous focuses in the prostate in case of a larger volume and/or malignancy of the tumour [17]. Moreover, it has established an opposite correlation between malignancy of the tumour (Gleason score) and the numerical value ADC of the sequence of diffusion restrictions [18].

Our research carried out also assesses mpMRI accuracy and sensitivity in order to find clinically-significant focuses in the prostate, which have not been diagnosed during the TRUS biopsy. Our attained results have indicated that calculated PPV and NPV of mpMRI to detect PCa were 45.45% and 39.29% with specificity and sensitivity of 54.05% and 31.43% respectively, was for clinically significant PCa they were smaller. Despite perspective results of our research, routine application of mpMRI is restricted by wide limits of the sensitivity and specificity provided by different researches. MpMRI sensitivity and specificity (T2, diffusion restriction and dynamic contrast-enhancement) for diagnosing the focus of a tumour in the prostate amounts to 0.74 (95% PI, 0,66–0,81) and 0.88 (95% PI, 0,82–0,92) while a negative predictive value is from 0.65 to 0.94 and a positive predictive value is from 0.31 to 0.95 [19].

However, it should be noted that mpMRI is not the only tool, which can be used in order to diagnose clinically-significant cancer of the prostate, but also there is an algorithmic analysing system of 3D ultrasound imagining. The first clinical studies, which applied this system, were published in 2008 and 2012 and showed good results. Braeckman J et al. [8] involved 29 patients in the study, who had been diagnosed with clinically-significant prostate cancer (cT1, cT2). The

Table 2: PCa and clinically significant PCa found inpatients.

Detected Pca	37 (51.4%)
Clinically significant PCa	24 (33.3%)

Table 3: PPV and NPV of mpMRI in detecting PCa and clinically significant Pca.

	PPV	NPV	Sensitivity	Specificity
Prostate Cancer	45,45%	39,23%	31,43%	54,05%
Clinically Significant PCa	27,08%	57,14%	59,09%	25,53%

authors indicated that the data attained by an algorithmic analysing system of 3D ultrasound imagining and a histological examination match by 100% ($p<0.001$). After Simmons LA et al. [9] had studied 27 patients suffering from prostate, they established that the specificity of an examination by an algorithmic analysing system of 3D ultrasound imagining amounted to 72% while its sensitivity did to 90% in case of examining the focuses of a 0.2cm^3 size in the prostate. De Coninck V et al. [11] have applied an algorithmic analysing system of 3D ultrasound imagining to 97 patients, 57 ones of them were diagnosed with suspect focuses. Repeated biopsies were carried out to the patients. The examination has indicated that an applicable biopsy based on the data of an algorithmic analysing system of 3D ultrasound imagining increases the efficiency of prostate cancer detection by 4.48 time ($p<0.0001$). Sivaraman A et al. [12] have studied 43 patients by carrying out TRUS and applicable biopsies. Positive applicable biopsies were more frequent in comparison with TRUS biopsies (55.4% vs. 37.5%, $p<0.05$ respectively). However, other examiners provide contradictory results concerning to the application of an algorithmic analysing system of 3D ultrasound imagining in diagnostics. Javed S et al. [13] conducted three independent studies to assess the significance of the algorithmic 3D ultrasound imaging analysis system in determining and characterizing prostate cancer. In the first study, an examination of the algorithmic 3D ultrasound imaging analysis system was performed for 24 patients who were suspected of having prostate cancer due to an elevated PSA level and/or a digital rectal exam. In patients with positive TRUS biopsy results, the adaptive algorithmic 3D ultrasound imaging analysis system-based biopsy also disclosed a positive result, and no new cases of cancer were detected. In the second study, an examination of the algorithmic 3D ultrasound imaging analysis system was performed for 57 patients and the results of this study were compared to the results of transperineal biopsy. The incidence of prostate was 13.4% for the algorithmic 3D ultrasound imaging analysis system and 54.4% – for transperineal biopsy. In the third study, before radical prostatectomy, an examination of the algorithmic 3D ultrasound imaging analysis system was performed for 24 patients with histologically confirmed and previously untreated adenocarcinoma of the bladder. No statistically significant correlation between the tumour volume measured by the algorithmic 3D ultrasound imaging analysis system and the pathological research methods was found (Pearson correlation coefficient -0,096). The authors of the research claim that an examination of the algorithmic 3D ultrasound imaging analysis system is a method which is not sensitive enough to be applied in routine clinical practice.

Conclusions

This study showed that TPM biopsies detect prostate cancer in over half of the patients with one or more initially negative prostate biopsies and mpMRI is helpful in identifying prostate lesions suggestive of cancer.

Acknowledgments

The Scientific Council of the National Cancer Institute (NCI) has allowed to carry out a biomedical study and to provide the necessary documentation for obtaining permission from the Bioethics Committee. The quality control of the biomedical research implementation is organized and controlled by the NCI Deputy Director in the fields of science and education, as well as by the Scientific Secretary. The main investigator should be able to control biomedical research, conduct audits, ethical supervision and inspection, while providing a direct access to the source documentation.

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