

A Role of Multifactorial Evaluation of Prostatic 3T MRI in Patients with Elevated Prostatic-specific Antigen Levels: Prospective Comparison with Ultrasound-guided Transrectal Biopsy

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Abstract. Aim: To assess the role of multiparametric 3T magnetic resonance (3TMRI) of the prostate in detection of the prostatic carcinoma in a male population with elevated prostatic-specific antigen (PSA) and to compare the results with those of transrectal biopsies. Materials and Methods: A prospectively collected cohort of 191 men underwent 3T MRI before transrectal biopsy. The evaluation consisted of the assessment of T2-weighted images, diffusion-weighted images, MR spectroscopy and the pharmacokinetic evaluation of the data obtained during the dynamic post-contrast T1 imaging. The assessment included the calculation of the blood volume and transfer constant evaluations. The diagnosis of prostate carcinoma was based on a minimum of three positive signs obtained from MR studies – hypointensive T2 lesion, diffusion restriction, elevated choline/creatine peak in spectrum and malignant type of saturation by contrast agents. All biopsies were evaluated by a specialist in uropathology. Results: 164 patients underwent biopsy, in 27 the biopsy was omitted due to a lack or low probability of carcinoma. Overall, 84 carcinomas were found. Based on the comparison of biopsy results, 3T MRI reached a sensitivity of 97.6%, specificity of 85.0%, positive predictive value of 74.6% and negative predictive value of 96.3% respectively. There were only three false negative findings. In three patients with very suspicious MRI findings and PSA levels over 30 ng/ml, the biopsy did not confirm carcinoma, even

though it was highly suspected. Conclusion: The implementation of 3T MRI in routine assessment of patients with elevated PSA should reduce the number of biopsies performed and improve the number of tumors detected due to better targeted biopsies.

Prostate carcinoma is the second most common cause of tumor death in the Western male population. Diagnostic algorithms in prostate carcinomas aim not only at the detection of the presence of a tumor and the assessment of its aggressiveness, but also at the localization of the tumor in the prostate and the evaluation of disease progression and response to therapy (1).

The development of magnetic resonance imaging (MRI) of the prostate has experienced considerable acceleration in the past decade, from records with T2-weighted MRI, supplemented with T1-weighted MRI before and after the administration of contrast agents, through diffusion weighting, ¹H-spectroscopy, right up to the most recent records with evaluation of pharmacodynamic parameters or hybrid imaging (2, 3). Apart from records, the equipment used for prostate imagery with magnetic resonance is also currently undergoing change discontinuing the use of dedicated endo-rectal coils and moving to the use of equipment with 3T magnetic field induction (4-7).

This study evaluated the experience with prostate imaging in patients indicated for prostate biopsy because of elevated levels of prostatic-specific antigen (PSA).

Materials and Methods

A prospectively acquired group of 191 men (of age between 47 and 79 years) indicated for prostate biopsy was procured from one urological department. All patients were investigated due to an elevated PSA level and decrease of the free to total PSA ratio. All investigations were carried out with the informed consent of each individual

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Key Words: 3T magnetic resonance, prostatic carcinoma, transrectal biopsy, PSA.

participant. In this group, the levels PSA were 4.2 – 123 ng/ml, with pathological values of free-to-total ratio below 20%. All these patients underwent complex prostate imaging using a 3T resonance system (Magnetom Skyra, Siemens, Erlangen, Germany). A superficial body 18-channel phased-array coil was used for the examination. The examination itself was preceded by cannulation of the ante-cubital vein with an 18-gauge plastic cannula.

The imaging protocol consisted of the imagery of T2-weighted images of fast spin echo (TSE T2) in three orthogonal levels, followed by T1-weighted images of gradient echo (volume interpolated breath-hold examination, VIBE). Another sequence represented the diffusion weighted images of echo-planar sequences with the calculation of the apparent diffuse coefficient (ADC) and the calculation of b-value quantifying charts. The next step was the performance of MR spectroscopy. Here we used the 3D chemical shift imaging version of data acquisition. Dynamic imaging followed after administration of a contrast agent. In all the examinations, a contrast agent with high relaxivity was used – ganobenat dimeglumine (Multihance; Bracco, Milan, Italy), at a dose of 0.5 mmol/kg. In the course of the application, data acquisition of 46 series of T1-weighted images of gradient echo was started (VIBE), covering the 60 seconds of the dynamic saturation of the tissues.

During the evaluation, the prostate volume was measured with calculation of the volume in milliliters, approximated from the calculation using half the multiple in orthogonal levels. In addition, the gland structure was evaluated in TSE T2 images, as well as from the presence of a high signal in T1-weighted images. During the evaluation of diffusion imaging non-homogeneities with signs of diffusivity restriction were searched. For the evaluation of spectroscopy the voxel-by-voxel analysis was chosen that of over the whole volume of the prostate. Those findings in voxels where choline/creatine peak reached more than half of that of the citrate were marked as pathological. During the pharmacodynamic evaluation the Tissue4D (Siemens, Erlangen, Germany) analytical software was used, making it possible to create, on the basis of the dynamic T1-weighted series analysis, a chart of blood volume in tissue (calculated by integral form of the dynamic curve, which is the area below the curve), then a transfer constant chart (K_{trans}), extracellular space volume (V_e) and finally a chart of the elimination constant (K_e). Apart from the evaluation of the charts, in suspicious areas the curve of contrast agent addition was evaluated, and curve with hypervascularization and fast wash-out was marked as a pathological finding.

The evaluation stating whether there were any signs of carcinoma in the prostate depended on a concordance of at least three out of the following four findings: hypointensive lesion in T2, lesion of diffuse restriction, positive finding on spectroscopy, pathological finding during pharmacodynamic analysis, pathological curve of contrast agent addition and lesion of hypervascularization together with increased K_{trans} .

Within the period of one to 92 days, a total of 164 patients underwent an ultrasound-guided transrectal biopsy. All biopsies were evaluated by an experienced uropathologist who performed the assessments of all bioptic samples including the Gleason score estimation. Biopsy findings were compared with MRI findings. Sensitivity, specificity, and negative and positive predictive MRI values were assessed in relation to the biopsy finding. The number of patients in whom the biopsy was omitted and who were scheduled for so-called watchful waiting was assessed.

Results

In the entire group, there were a total of 84 prostate carcinomas confirmed by biopsy. Derived from comparison of biopsies and MRI, statistical results are summarized in Table I and show that by data analysis of the group as a whole, a high sensitivity of 97.62% and high negative predictive value of 96.30% were achieved. Relatively high false-positivity was reflected in lower a specificity value of 65.00% and positive predictive value of 74.55%. Out of the false-positive findings we should mention two cases of prostatitis, high-grade prostatic intraepithelial neoplasia (PIN) in four cases and 23 findings where the biopsy identified adenomyomatous hyperplasia. In five cases, the MRI finding was highly probable for carcinoma; in one case, the patient's PSA values were 113 ng/ml.

On the other hand, the only two false-negative cases showed a very small carcinoma in a peripheral position, and diffuse infiltration of the central zone respectively. During their re-evaluation, a discrete finding in the charts of pharmacodynamic analysis and diffuse weighting was found in both cases.

In 27 patients, the biopsy was omitted due to the negative findings on MRI, all of these patients were scheduled for active watchful waiting program with monitoring of the PSA level. All patients with negative biopsy findings were also managed in the same way.

Discussion

Prostate imaging and prostate carcinoma detection represent a long-standing and very problematic matter with regard to imaging methods. Apart from magnetic resonance, other methods do not provide sufficient contrast resolution. For a long time, the method of magnetic resonance itself lacked sufficient technical properties to achieve a high quality signal-to-noise in an acceptable scanning time. In the first few years of the 21st century, endo-rectal dedicated coils were gradually introduced into clinical practice. Their purpose was to increase the contrast resolution and signal homogeneity in the near-field at the cost of increasing the invasiveness of the examination. Gradually, systems with higher magnetic induction were produced for clinical practice, and the 3T systems began to be employed instead of 1.5T systems in the imaging of the pelvis, including the prostate (8, 9). With the increase in the quality of resolution, subsequently, superficial coils were tested and an identical reproducibility of images and spectroscopic findings was demonstrated in both superficial and endo-rectal coils (4, 5, 7, 8).

With the development of scanning techniques, morphological records were gradually completed for molecular imaging with spectroscopy and diffuse imaging. Most recently, dynamic scanning records, which can be used as data source for pharmacodynamics analysis, have been

Table I. *Description of the cohort.*

	n
Watchful waiting	27
Biopsy	164
True-positive	82
True-negative	52
False-positive	28
False-negative	2
Repeated biopsy	3
Carcinoma	84
MRI versus biopsy	
Sensitivity (%)	97.62
Specificity (%)	65.00
Positive predictive value (%)	74.55
Negative predictive value (%)	96.30

introduced into clinical practice. The possibility of new analytical procedures for creating charts of contrast agent distribution parameters, undoubtedly represents a shift in evaluation (2, 6, 7, 10).

A typical prostate carcinoma, suggested by magnetic resonance, is a tumor that occurs in the peripheral area of the gland, hypointensive in T2 (3) and showing restriction of diffusion, which also contains high oscillation of choline and creatinine during spectroscopic finding. In the dynamic post-contrast imaging, the tumor is also saturated rapidly with the contrast agent, but at the same time it washes out quickly (2). Finding a typical image tends to be unambiguous, but there is a large group of images that differ considerably from the ideal one.

T2 hypointensive lesions in prostatic tissue in the transition area are very common in adenomyomatous transformation and also in calcification of the gland. Adenomyomatous hyperplasia often causes displacement of peripheral area tissue into the shape of a thin shell.

The problem in the evaluation of diffusion restriction lies in the presence of non-homogeneities caused by bleeding after a previous biopsy. Restriction of diffusivity also tends to be present in inflammatory infiltration with high cellularity (suppurating prostatitis), pronounced also in our two false-positive findings. Another problem can be artifacts in the prostate transition into the surrounding fatty tissue, or a thick layer of ligament on the surface, where through an incorrect evaluation, a lesion on the very periphery may be overlooked, as also happened in our one false-negative finding. For better orientation, a b-value chart can be used, as in our experience it is less sensitive to these artifacts.

Even spectroscopic evaluation is not completely trouble-free. In our experience the most significant problem is that of a partial volume. Since prostatic tumors often form a

nidus of its own size no more than several millimeters, and the voxel, which is created by the image used in the record, is a cube with an edge-length of 0.5 cm, this may be insufficient for an exact assessment of the choline level in tissue (10, 11). If a carcinoma represents only a smaller part of the measured voxel or if it even partially overlaps beyond it, then the acquired spectrum may not be determinant of the presence of a carcinoma. This problem is even greater in the area of hypertrophic tissue in the transition area, and at the prostate periphery (8).

Dynamic imaging after administration of the gadolinium contrast agent is a standard procedure in the imaging of many tumorous processes, breast imaging being one of many. There is a rule for carcinomas (except in relatively rare situations) that due to neovascularization, the neoplastic tissue fills with the administered contrast agent very quickly, but subsequently the contrast agent tends to be washed out early. It is possible to apply a compartmental model of substance distribution with extracellular distribution (2, 6) for the tumor tissue. Carcinomatous tissues consist of a vascular space and an extracellular space made up of intercellular spaces. In prostatic carcinoma, the acinar gland space is sometimes considered to be another space. In dynamic imaging, due to neovascularization, we register an early hypervascularization that is reflected in the enlarged volume of contrast agent in the tissue. The volume is calculated as the area below the curve that originated in every single voxel according to intensity. At the same time, however, since molecules permeate faster into the extracellular space through insufficiencies in the walls of neoplastic blood vessels, the contrast agent washes out faster into the extracellular space. The speed of the contrast agent transfer outside the vascular space is characterized by so-called transfer constant (K_{trans}). The elimination constant (K_e) characterizes rapid re-release of the molecule into the vascular space. The size of the extracellular volume (V_e) is dependant on tumor tissue cellularity. Generally it can be stated that pharmacodynamic parameter charts help to identify areas of hypervascularization in prostatic tissue, as well as those with faster transfer of the contrast agent into the interstitium and its faster elimination back into the blood circulation. These charts are, therefore, a good guide to enabling the evaluation of the tissue-saturating curve in the areas of interest. The evaluation itself of the character of the curve has a significant position in the differentiation of hypervascularization from neovascularization in carcinoma and knotty vascularized lesion of adenomyomatous hyperplasia.

For correct detection of an area suspected of having carcinoma it is not possible to use simply one positive symptom. Most authors give importance to when diffusion imaging pathological findings are combined with the findings of a pathological representation of choline in the spectrum and with a morphological finding in T2 images

(12-16). Our experience demonstrates the extreme importance of the finding of vascularization with rapid saturation and fast wash-out of a tissue, where pharmacokinetic charts show the suspected area, and the precise evaluation itself should be performed with the construction of a saturation curve. In the detection of carcinoma, an effective approach could be a comparison of the diffusion imaging and pharmacokinetic maps. The fusion of these images helps to detect *foci* suspected as being from carcinoma. The evaluation of perfusion both with the level of diffusion restriction seems important in the evaluation of the tumor aggressiveness (17)

The analyses of the group comparing findings of magnetic resonance with the assessment of biopsy samples, acquired by means of transrectal puncture, represent an interesting aspect of this study. The data, acquired in large cohorts of patients, stated that in patients with a pathological level of PSA, there were 66-71% negative biopsies and, moreover, that up to 23% of prostate carcinomas are not detected in the first biopsy. This fact is very significant in the so-called grey area, namely PSA values from 4 to 10 ng/ml (1). It is therefore difficult to take seriously the fact that almost every fourth case of a false-positive MRI finding may actually be a carcinoma undiagnosed by biopsy. This problem has been documented in our positive finding in a man with a PSA level of 113 ng/ml and a negative biopsy, even with targeting according to a clear highly positive finding in MRI, as well as in cases of five patients where prostate carcinoma was demonstrated only in a repeated biopsy.

A similarly serious problem to that of undetected prostate carcinomas can be its actual diagnosis. According to studies from the United States, positive diagnosis of prostate cancer leads to an increase in cardiovascular morbidity and mortality, as well as to an increase in the incidence of suicidal behavior (1). Since the risks resulting from prostate carcinoma depend on the aggressiveness of the process and also on the patient's age, in the future it will also be necessary to evaluate such risk as well. It might be possible in the future to quantify or suggest a score according to diffusivity restriction, character of neovascularization and the level of choline representation in the spectrum (10).

Conclusion

Our analysis of a relatively large prospectively monitored group of patients allows us to conclude that complex imaging of prostate on 3T MRI, including morphological imaging, imaging of water molecule diffusion, biochemical evaluation with MR spectroscopy and post-contrast saturation is a robust diagnostic method with very promising results in detecting prostate carcinoma in patients with pathological PSA values inclusive of a low free-to-total PSA ratio. This approach could reduce the number of biopsies performed and improve

the detectability of prostatic carcinoma. All non-biopsies patients and those with negative biopsies are under active follow up further to assess the long term efficacy of our approach to prostatic carcinoma detection.

Acknowledgements

This study was supported by the project of the Czech Ministry of Health: Conceptual development of the research institution 00669806 - FN Plzen and by the Charles University Research Fund (project number P36).

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Received April 3, 2013

Revised May 8, 2013

Accepted May 10, 2013