Editorial

Role of magnetic resonance imaging in the diagnosis and treatment of prostate cancer

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Abstract

Prostate cancer is the second most common cause of oncological mortality in men. The screening based on digital rectal examination and determination of PSA level is still controversial because it has low specificity for clinically significant prostate cancer. Also, ultrasound-guided prostate biopsy is criticized due to its poor detection rate and many false negative results. In this context, magnetic resonance imaging comes as the missing puzzle piece because of the accurate information about the localization, characterization and staging of prostate cancer, the advantages of guiding prostate biopsy and focal therapy, and the possibility to assist and improve the surgical technique. The European Society of Urogenital Radiology argue cogently that magnetic resonance imaging should be an integral part of the diagnosis and treatment of prostate cancer.

Keywords: magnetic resonance imaging, MRI-guided interventions, prostate cancer

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Introduction

Prostate cancer (PC) is the second most common cause of oncological mortality in men. In Romania, the prevalence of prostate cancer reaches 3%, when using digital rectal examination and determination of PSA level for screening. As stated in the results of the CLOS-ER screening program that took place in Cluj-Napoca in 2005, the detection rate of localized PC is 41.9% [1]. The rise in the diagnosed number of patients with localized PC, not only in Romania, allowed for the development of new techniques for the diagnosis and curative treatment of the disease. Magnetic resonance imaging (MRI) is one of the most promising techniques that has been repeatedly proven to have a major importance in the diagnosis and treatment of PC.

• Value of prostate MRI in the diagnosis of prostate cancer

The diagnosis of PC is based nowadays on three steps: determination of PSA level, digital rectal examination and prostate biopsy. Even though it is used worldwide, the antigen screening still remains controversial, having poor specificity for significant cancer [2]; at least 60-70% of initial biopsies in patients with high PSA levels are negative and up to 45% of diagnosed PC are low-risk [3]. Digital rectal examination and transrectal ultrasound-guided prostate biopsy have also poor sensitivity for the diagnosis of PC. The main challenge that arises is to find the perfect balance between the overdiagnosis and overtreatment of patients with indolent PC that would be suitable for active surveillance, and the underdiagnosis and undertreatment of patients with aggressive PC.

Advances in magnetic resonance imaging show promise for improved detection and characterization of PC, using a multiparametric approach, which combines anatomical and functional data [4]. Multiparametric MRI (mpMRI) includes a combination of high-resolution T2-weighted images (T2WI), and at least two functional MRI techniques (dynamic contrast enhancement – DCE-MRI, diffusion-weighted imaging – DWI-MRI, and spectroscopy). **T2-weighted imaging** is the foundation of mpMRI, as it provides high-resolution anatomical images of the prostate. Normally, the peripheral zone of the prostate has high signal intensity in T2WI – if PC is present, it appears as a focus with low signal intensity. **Diffusion-weighted imaging** (DWI) measures the diffusion of water molecules through different tissues. Prostate cancer exhibits a reduced diffusion of water compared to normal prostate tissue due to its high cellularity and disruption of interstitial spaces and planes through which water normally diffuses – from this acquisition, apparent diffusion coefficient (ADC) maps of the prostate are then derived. **Dynamic contrast-enhanced imaging** (DCE-MRI) is based on the intravenous administration of gadolinium, followed by a series of rapid sequential scans. Each scan demonstrates a map of perfusion for every spatial region of the prostate at various moments in time. This information can be plotted graphically to create a perfusion vs time curve, which shows how rapidly the gadolinium uptake and the wash-out were. If PC is present, it will appear as a zone with early and intense contrast enhancement, followed by rapid wash-out. **Magnetic resonance spectroscopy** is a functional technique that measures metabolite levels in the prostate. Prostate cancer is characterized by a high concentration of choline and creatine, and low concentration of citrate – opposed to the normal tissues [5].

When combining at least three MRI sequences, the sensitivity and specificity for the detection of tumors larger than 0.2 mL can reach 75% and 94%, respectively, with more than 90% accuracy [6].

![Fig. 1 – T2WI – an area with low signal intensity in the peripheral zone of the prostate](image1)

![Fig. 2 – DWI – an area with low signal intensity in the left lobe because of the restricted water diffusion](image2)
In addition to the detection of prostate cancer, mpMRI shows to be a useful tool in evaluating the clinical importance of the diagnosed cancer. It has been stated many times that the ADC values, generated from the DWI-MRI acquisition, correlate with the Gleason score. By assessing the aggressiveness of PC, mpMRI before or even initial biopsy can accurately select patients who require immediate biopsies and those in whom biopsy could be deferred, can target prostate biopsies in order to have an accurate diagnosis and also can be a factor of importance when identifying patients suitable for active surveillance.

In 2012, the European Society of Urogenital Radiology formulated a series of guidelines for the MRI evaluation of the prostate. They suggest that the MRI data would be more helpful for the other specialities if presented as a score – PI-RADS (similar to BI-RADS, used for breast cancer), which estimates the probability of a lesion to be clinically significant (score 1: clinically significant disease is highly unlikely to be present, score 2: clinically significant cancer is unlikely to be present, score 3: clinically significant cancer is equivocal, score 4: clinically significant cancer is likely to be present, score 5: clinically significant cancer is highly likely to be present). The PI-RADS score has shown good to moderate interreader agreement and enables standardized evaluation of prostate mpMRI, with high sensitivity and negative predictive value [7]. It may also contribute to a more effective prostate MRI, improving the detection of clinically significant cancer [8].

• MRI for the staging of prostate cancer

When choosing the most suitable therapeutic option for a patient with diagnosed PC, a decisive information is the staging of the tumor. Multiparametric MRI has proven to be useful in evaluating the local staging of PC. When using multiplanar reconstruction and including both, direct and indirect signs of extracapsular extension, the sensitivity and specificity for T3a stage of T2WI reaches 84% and 89%, respectively [9]. Less experienced readers have been shown to benefit most from the use of 3D spectroscopy in association with T2WI, which significantly improved the accuracy of staging and the area under the ROC curve [10]. Also, the combination of DCE-MRI and T2WI has shown improved performance in predicting extracapsular extension than either technique alone [11]. But the best predictor of pT3 tumors is endorectal coil MRI [12].

Dynamic-contrast enhancement MRI and DWI-MRI, along with T2WI are used for detecting T3b stage and can add additional value to current nomogram for the prediction of seminal vesicle involvement [13].

Unfortunately, MRI remains disappointing regarding the lymph node staging of prostate cancer, with a sensitivity of only 30% [14]. Lately, a new technique for the MRI evaluation of lymph nodes in prostate cancer shows promising results, but it is not yet introduced in the clinical practice. Combined ultrasmall superparamagnetic particles of iron-oxide enhanced (USPIO) and DWI-MRI has been shown to be an accurate method for detecting metastases in normal-sized pelvic lymph nodes of patients with PC (sensitivity and specificity up to 75% and 96%, respectively [15].

• MRI and prostate biopsy

Ultrasound-guided prostate biopsy, either transrectal or perineal, is the method of choice for the confirmation of PC in patients with clinical (suggestive digital rectal examination) or biological suspicion (high level of PSA). Many professionals criticize this method because of the low detection rate (20-40%) [16] and of the false negative results (20%) [17]. The limitations of the ultrasound-guided prostate biopsy are due to the fact that it is based on an imaging technique (transrectal ultrasound) with low sensitivity and specificity in identifying the malignant prostate lesions [18], but also due to the fact that the choice of biopsied areas and the biopsy needle path are majorly biased by the
subjectivism of the medical examiner.

Therefore, the need for improved diagnosis in PC has become mandatory for two reasons: the first is the need for a better detection and localization of malignant areas of the prostate, and the second - the need for increased precision during the act of harvesting the tissue fragments by exact biopsy needle guidance in targeted areas. Magnetic resonance imaging is a technique that improves mostly the first aspect: the detection and localization of prostate cancer, as stated before in this review. This imaging method has the advantages of a high spatial resolution, excellent contrast for soft tissues and the possibility for volumetric images assessment [19]. The limitation of MRI is technical and related to the second aspect: does it have the ability to assist and guide the needle during prostate biopsy? As a result, most studies tried to develop various techniques to assist prostate biopsy by overlapping the MRI images with ultrasound, but many have found obstacles when superposing the prostate mapping. The first MRI-guided prostate biopsy was reported in 2000 and was performed transperineally, with the patient under general anesthesia, in lithotomy position [20].

There are three possibilities for performing prostate biopsy: targeted prostate biopsy (the biopsy is ultrasound-guided, but based on the coordinates offered by the MRI images), ultrasound-MRI fusion guided-biopsy (the biopsy is ultrasound-guided, but the archived MRI images are overlapped onto the ultrasound during biopsy) and MRI-guided prostate biopsy. Of all three possibilities, MRI-guided prostate biopsy has the highest detection rate (80%), in comparison with 46.2% for MRI-ultrasound fusion guided biopsy and 33.3% for MRI-targeted biopsy [21].

Probably the most efficient method is MRI-guided transperineal prostate biopsy, because it allows a more effective harvesting of tissue from areas with high incidence of cancer, but also from the anterior zone of the prostate, all these with a lower rate of septic complications. The disadvantages of this type of biopsy are: more intense pain, that usually requires general anesthesia, which involves a more complex logistics and higher costs of the procedure [22].

Prostate MRI might reduce the number of patients that should really undergo a prostate biopsy. The effectiveness of the method is defined by the ratio between the number of clinically relevant diagnosed PC patients and the number of biopsied cases. Targeted biopsy has been shown to have a higher accuracy (70%) than the standard (40%) [23].

There are two aspects that require standardization in order to have comparable reporting of the results of MRI-guided prostate biopsies:
1. Indication – which patients can benefit more from this biopsy?
2. The tissue harvesting technique

The MRI-guided tissue harvesting technique can lead to specific errors that can alter the quality of the histopathological outcome: imperfect overlay of MRI images with ultrasound (when performing ultrasound-guided biopsy) and the change in the position of the prostate due to the presence of the endorectal coil, to the movement of the biopsy needle and to the patient movement during the procedure.

In order to improve the tissue harvesting technique, there have been identified three types of biases that can alter the quality of the MRI targeted biopsies:
1. Target movement – the difference between planned and real time biopsy
2. Error in the positioning of biopsy needle – the difference between the planned targeted biopsy and the trajectory of the biopsy needle
3. Biopsy error – the difference between the targeted real biopsy and the trajectory of biopsy needle

The robotic system developed by Xu et al has reported the following results for the target movement, error of positioning and biopsy error: 5.4, 2.2 and 5.1 mm, respectively [24].

A prospective study evaluated the 12-core systematic prostate biopsy in comparison with mpMRI-targeted biopsy (cognitive and ultrasound-MRI fusion biopsy). The detection rate was 69% for systematic biopsy and 59% for MRI-targeted biopsy. However, when assessing the detection rate for the clinically significant PC (malignant tissue on any biopsy longer that 3 mm or with Gleason grade higher than 3), they noticed that the MRI-targeted biopsy detected 67% of cases, in comparison with 52% for systematic biopsy [25].

Another study reported also a detection rate for clinically significant PC of 87% for MRI-guided prostate biopsy, higher than of the systematic and targeted prostate biopsies [26].

A very useful application of MRI-guided prostate biopsy could be the biopsy of patients with previous negative ultrasound-guided biopsies, but high PSA values or abnormal digital rectal examination. In these cases, the confirmation rate for PC of MRI-guided biopsy can reach a sensitivity and specificity of 93% and 94.4%, respectively. This means an improvement in the detection rate for PC of 40%, in comparison to 20-35%
when performing the second ultrasound-guided biopsy [27] [28].

**MRI and focal therapy for prostate cancer**

Focal therapy represents the eradication of the malignant tissue inside the prostate and the preservation of the non-malignant tissue in order to maintain the genitourinary function as much as possible [29]. The efficiency of the focal therapy is majorly influenced by the exact mapping of the malignant areas. Multiparametric MRI allows a fair localization of cancer inside the prostate, so it can become a tool to assist the focal therapies: laser ablation, high-intensity focused ultrasound (HIFU), cryosurgery, brachytherapy, microwave ablation and radiofrequency ablation. The imaging method can allow the exact localization and the selective ablation of malignant areas inside the prostate [30].

Magnetic resonance imaging has four key roles in the guidance of focal therapy: identification and characterization of the neoplastic tissue inside the prostate, positioning of the device and monitoring the ablation of cancer nodules [31].

In 2012, the first case of focal therapy by MRI-guided HIFU was reported. The procedure was performed in one-day-surgery system, the patient was discharged the same day, without uretro-vesical catheter and post-procedural complications. The efficacy of the therapy was assessed by the identification of devascularized areas in the prostate. Before treatment, the same areas were positive at biopsy and identified on the MRI images. The follow-up implied a repeat biopsy at 6 months after the procedure [32].

Subsequently, there were published the results of a series of 26 patients with prostate cancer treated by HIFU, for whom the selection of the ablated areas was based on the information from transperineal biopsy and from mpMRI. Three types of focal ablation were performed: quadrant ablation, hemi-ablation and hemi-ablation with contralateral extension [33].

In another series, the efficiency of this method was assessed for 5 patients, that underwent radical prostatectomy after MRI-guided focal therapy. The histopathological examination showed no residual malignant tissue in the areas treated by HIFU. However, outside the treated areas the pathologist identified significant malignant tissue that was not reported by the pretreatment MRI examination [34].

The advantages of MRI localization of the malignant areas in the prostate were used also to assist cryotherapy. In 2012, the results of a series of 10 patients that underwent cryotherapy was published. For these patients, the procedure was monitored by real-time MRI. This technique seemed to be feasible, MRI allowed an exact positioning of the cryoprobes in real-time, but also an excellent monitoring of the developing ice ball [35].

Another MRI-guided focal therapy for PC is the transperineal laser ablation. In a study form 2013 on 9 patients with low-risk PC, this procedure was feasible and did not associate urinary complications. The MRI follow-up after the therapy showed a hipovascular defect of the treated areas for 8 patients and the MRI-guided biopsy of these areas revealed residual cancer for 2 patients [36].

**Role of prostate MRI in surgical planning**

According to the Guidelines of the European Association of Urology in 2013, the treatment of choice in localized PC is radical prostatectomy (RP), which can be performed by open, laparoscopic or robotic approach. Regardless the type of approach used, RP has three main challenges: to ensure the oncological control of the disease, but also to maintain the uro-genital functionality – potency and continence. In order to overcome these challenges, the surgeon must perform a very cautious dissection, with regard to the oncological principles, and also a high-quality nerve-sparing and uretro-vesical anastomosis.

Advances in prostate MRI may provide important information for the surgeon and can become a useful tool for pre-treatment surgical planning. There are at least 3 steps in which the information offered by MRI may improve the surgical decisions: predicting the surgical difficulty, assessing the extracapsular spread of PC/evaluation of neuro-vascular bundles involvement and prediction of post-operative continence.

1. **Predicting the surgical difficulty**

During RP, especially when performed by robotic approach, access to the deep pelvis and adequate exposure is critical, given the close proximity of vital and anatomic structures, on which the functional outcomes depend. The pelvis of the man is very narrow in most cases and, therefore, may restrict some of the important manoeuvres during RP. The limitations come from the pelvic anatomy, but also from the prostate dimensions [13].

Mason et al in 2010 [37] published a study on 76 patients evaluated by endorectal MRI before robotic RP.
The parameters used for predicting surgical difficulty were: estimated blood loss (EBL), transfusion rates, operative time (OT) and positive surgical margin status. Patients who underwent robotic RP with prostate volume < 35mL and with a PV-to-PCI (prostate volume-to-pelvic cavity index) ratio of < 6 had significantly less blood loss and shorter OT. Higher prostatic transverse diameter, prostate volume, and PV-to-PCI ratio were also significantly correlated with OT and increased EBL. This suggests that patients with small prostates within large pelvises are predicted to have an easier surgery than those with large prostates in small pelvises. Factors that were significantly correlated with positive surgical margins were PSA and pelvic cavity index, which acts as a surrogate for working space in the pelvis for robotic arms. Mason also observed that the patients with positive apical margins had a pelvic cavity index that was significantly smaller than those with positive margins at other sites (6.53 vs 8.24, Student’s t-test, P<.0085). In another study published by Matikainen et al in 2009, apical prostate depth (defined as the cranio-caudal distance from the most proximal margin of the symphysis pubis to the level of the distal margin of the prostatic apex as measured on the mid-sagittal T2-weighted sequence image) was found to be an independent risk factor for apical positive surgical margins at RP [38]. In other words, patients who had positive apical margins had more surgically challenging and deeper pelvises than those who had positive margins at other sites.

In conclusion, endorectal coil MRI can provide accurate information regarding the dimensions of the deep pelvis, the pelvic inlet, and the prostate. The MRI can act as a navigation tool intraoperatively using its anatomic information. Obtaining pre-operative MRI may help with surgical planning and may alert the surgeon to the difficulty of the case.

2. Evaluation of the neuro-vascular bundles involvement

In the last decades, the number of patients diagnosed with localized PC increased due to the introduction of screening programs (based mostly on determining the serum PSA levels) and the advances in imaging techniques. Nowadays, there are numerous options for curative treatment of localized PC, so efforts have been made to preserve also the sexual function after RP. Singer et al noted that men undergoing treatment for prostate cancer were willing to exchange an approximate 20% chance of cure for an increased prospect of remaining potent after therapy [39]. The surgeon must now find the perfect balance between performing nerve-sparing surgery and ensuring negative surgical margins. The decision on whether to preserve or not a neuro-vascular bundle is based mainly on the presence and location of extracapsular extension.

Multiparametric endorectal MRI, which combines the conventional and the functional techniques, has been proven to provide a very good depiction of pelvic anatomy and prostate, being useful in predicting the presence of cancer as well as extracapsular extension and involvement of the neuro-vascular bundles.

A study published by Labanaris et al in 2009 analyzed the role of multiparametric MRI in the decision on whether nerve-sparing should or should not be performed during RP. The sensitivity, specificity and accuracy rate of mpMRI were 92%, 100% and 100% for extracapsular extension, seminal vesicles involvement and neuro-vascular bundles involvement, respectively. The conventional and functional MRI favoured NVB preservation in 22 patients (67%) with a high clinical probability of extraprostatic disease, and opposed NVB preservation in 11 patients (33%) with a low clinical probability of extraprostatic disease. Based on the final histopathological findings, the surgical plan was successfully changed in all patients. These results were higher than other published international standards, but in the authors’ opinion this might be the result of the high experience of the reader [40].

In conclusion, multiparametric MRI is one of the most sensitive preoperative clinical staging methods for selective patients, and extremely useful for identifying candidates for nerve-sparing RP.

3. Prediction of post-operative continence

In addition to impotency, the urinary incontinence is another outcome that alters the quality of life of patients that undergo surgery for PC. Membranous urethral length, which can be measured using conventional endorectal MRI on the sagittal and coronal images, from the prostatic apex to the urethra at the level of the penile bulb, has been identified as a factor that may contribute to post-RP urinary continence. Paparel et al and Coakley et al published two studies that assessed the importance of urethral length (measured preoperatively and in some cases, post-operatively) in the regaining of continence after the surgery. Both studies suggest that longer membranous urethral length on
pre-operative MRI is associated with increased rate of recovery and overall continence [41] [42].

Fig. 5 Measurement of the membranous urethral length on T2WI in sagittal section

The assessment of urethral length using MRI is a tool that may assist the surgeon at the step of urethral incision. For patients with longer membranous urethra and the tumor localized at the apex of the prostate, the urethral incision may be performed at distance from the apex, in order to ensure the oncological control of PC with negative surgical margins, but also to preserve the functional outcomes.

Conclusion
In conclusion, mpMRI can offer much needed information about the presence, localization, aggressiveness and staging of prostate cancer, can assist prostate biopsy by selecting patients suitable for biopsy or by guiding of the biopsy needle, can also assist the focal therapies in order to preserve healthy tissue and urogenital functionality and can be an important factor when planning the surgery. Magnetic resonance imaging contributes to the decision of performing nerve-sparing or not and can designate the areas with high suspicion of extracapsular extension in order to retrieve tissue for frozen sections. The surgical planning assisted by MRI can predict and warn about the difficulty of the procedure, and also can improve the oncological (status of the surgical margins) and functional results (potency, continence). Latest advances in magnetic resonance imaging make this method a real necessity in the proper diagnosis and treatment of prostate cancer.

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