Prostate Multiparametric MRI or how to find significant prostate cancer

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Take home messages

Significant prostate cancer can be accurately detected on mpMRI thanks to the functional sequences which increase the specificity of T2W-MRI

A PIRADS scoring system is available which allows for a consistent reporting across centers

MRI-targeted biopsies represent a technological development which allow for a precise sampling of the suspicious are achieving a detection rate of up to 80-95% in PIRADS 4-5 lesions

Owing the 90% negative predictive value of mpMRI, it may be time to consider MRI before the initial biopsy to increase the detection rate of significant tumors and to decrease overdiagnosis (and the burden of active surveillance) and possible overtreatment by deferring biopsin men with no MRI focal abnormality

Introduction

Taking a prostate biopsy decision is guided by the willingness to detect significant PCa in men with a reasonably long life expectancy and ideally harbouring a still curable tumor. It is thus admitted worldwilde that biopsy and further staging investigations should be indicated only if they affect the management of the patient.

The current biopsy decision making, based on PSA level and/or DRE findings, has several drawbacks. Over-diagnosis of insignificant tumors, potentially leading to an unnecessary radical treatment is a now an established finding (1). Under-diagnosis of aggressive tumor has also been well emphasized and fear for missing and/or underestimate tumor aggressiveness (2) often leads to repeat and saturation biopsies (3). A substantial increase in biopsy-induced morbidity has been thus observed, mainly represented by prostatitis, especially in patients with no cancer and those with repeat biopsies (4)

Therefore, it becomes legitimate to identify men with clinical significant PCa prior to biopsy and avoid detection of insignificant tumors by unnecessary biopsies. To achieve this goal, localisation of significant tumors by imaging is a pre-required step to allow for a targeted only biopsy strategy. With this regard, prostate magnetic resonance imaging (MRI) has undergone substantial technical improvements. In addition to morphological information provided by T2 weighted images, MRI allows for an estimation of physiological properties of tissues. Diffusion-weighted MRI (DWI) is sensitive to restriction of diffusion of water molecules (5), and dynamic contrast-enhanced (DCE) MRI can help estimate tumor angiogenesis (6). Spectroscopy, used in some centers, is sensitive to variations of the concentration of prostatic metabolites.

Moreover, scoring systems have been developed to allow for a standardization of MRI reporting (7). As a result, multiparametric MRI (mpMRI) can accurately localise tumor foci with a more consistent accuracy and suggest tumor aggressiveness (8, 9). However, once a target has been identified on MRI, the physician performing the biopsy must have this information available at the time of biopsy to match as accurately as possible the needle tract and the target, hence the concept of TRUS-MRI image registration (or image fusion) to plan and to guide the biopsy. Alternatively the biopsy can be performed under MRI guidance.

This article illustrates how mpMRI 1- can detect significant tumor foci of PCa according to a reproducible scoring system and therefore direct appropriate treatment. 2- can confirm the diagnosis with a great accuracy with MRI targeted biopsies either with TRUS-MRI image fusion or MRI guidance. 3- can exclude clinically significant disease thus enabling deferment of biopsy and therefore reduce overdiagnosis and overtreatment.

What is meant by significant cancer? A significant tumor poses a risk to the health and life expectancy of a patient. Prostate cancer is multifocal in 50-80% of cases (10), but it is now admitted that a single focus will be responsible for cell proliferation, extaprostatic spread and distant metastases (11). The so-called index tumor is the one which has to be detected by mpMRI. Most satellite tumors are indolent low volume low grade tumors which will not cause harm to the patient. According to some authors (12), low volume Gleason score 6 tumors may not have the hallmarks of malignancy and could be considered a benign epithelial condition.

Definition of significance has been established on the basis of tumor volume and percentage of Gleason grade 4. The threshold of significance is 0.2-0.5cc, but it has been suggested that clinically insignificant prostate cancer may include index Gleason score 6, pT2 tumors with volumes up to 1.3 ml (13). A progressive increase in the proportion of the Gleason 4 component is directly associated with significantly worse outcome (14). Even patients with only a tertiary Gleason 4 (ie 3+3+ ≤ 5% grade 4, pattern 1) were found to have a significantly worse outcome than those with pure Gleason 3+3 tumors (15). In addition, patients with a Gleason 3+4 (pattern 2) vs 4+3 (pattern 4) defined a primary Gleason score of 4 as an independent risk factor for a worse outcome (16), as well as those with a tertiary grade 5 component (pattern 5) (17). There are thus 5 different types of grade 4 pattern with a different significance for tumor aggressiveness and variations in mpMRI accuracy to detect them.

Accuracy of mpMRI to detect significant cancer: the PIRADS scoring system.

Visible lesions are characterized by mpMRI which reports on findings observed on several sequences. T2W-, DW- and DE-MRI represents the minimal requirement. Spectroscopic-MRI is optional. Recent guidelines of the European Society of Uro-Radiology (7) have recommended a scoring system, based on a five point scale from 1 to 5 for each of the three sequences (T2W, DW and DCE-MRI) to read MRI prostate examinations. A global subjective score is then assigned, similar to the Likert score and not made of the sum of the three individual scores, to establish a final diagnostic score out of 5 for tumor localisation. It can be anticipated from the forthcoming versions that the scoring will take into account a dominant sequence: DW-MRI in the peripheral zone which improves the specificity of T2W-MRI and T2W-MRI in the transition zone, because many benign nodules, which have a typical T2W appearance, show impeded diffusion and increased vascularisation (18).

Accuracy of mpMRI to detect tumor aggressiveness.

Gleason score. Tumor aggressiveness can be suggested by mpMRI in selected cases. On T2W-MRI, a study showed that higher Gleason grades were associated with lower tumor-muscle Signal Intensity Ratios (19), but no cut-off could be defined to consistenly suggest the presence of high grade foci and the amount of grade 4. Nevertheless, Signal Intensity evaluation on T2-weighted MR images may suggest tumor aggressiveness undetected on a first set of biopsies. On DW-MRI, numerous studies, using pathological examination of radical prostatectomy specimens as the reference standard (20-25) have demonstrated the

significant lower ADC value of Gleason 6 tumors compared to that of higher grade tumors. However, with regard to a more specific differentiation between low, intermediate and high tumor grade, only two studies found a significant correlation between ADC values and each of the three tumor groups (21, 23) of the peripheral zone. In our experience (unpublished data), the mean ADC value starts to decrease only in tumors with more than 20% grade 4 and the mean ADC value of tumors with more than 20% grade 4 is significantly lower that tumors with less than 20% grade 4. However, a difference between 20-50% and more than 50% grade 4 could not be found, due to a large overlap between values as histological tumor aggressiveness increased. Any ADC thresholds to stratify tumor grade may thus have a limited clinical relevance on an individual basis to rule in rule out tumor aggressiveness, but any visible tumor on MRI showing a "low" ADC value and a low grade tumor should have repeated biopsies to reevaluate the tumor risk.

Tumor volume. Evaluation of tumor volume with DW-MRI has been reported several times (26-29). Is is until now a subject of error with an underestimation rate of approximately 30-50% depending the combination of sequences used to measure the volume (26). It has been thus suggested that rather to try to measure the tumor volume itself (26), a target volume should be defined, in the perspective of focal therapy, which would cover the area to ablate without leaving tumor outside the tumor area.

MRI-targeted biopsies

They can be done under MRI-guidance or with TRUS-MRI image registration. Several methods of TRUS-MRI image fusion are available. One is cognitive and does not require any specific software. The others use a software to registrate MR and TRUS images. There are two different approaches. One consists of a rigid registration in real time with a navigation system (30, 31). It defines the sensor-based registration which tracks the TRUS probe and computes its position with a magnetic device placed on the probe or incorporated in a robotic arm (32). The other approach, defined as the organ based registration, coregistrates TRUS and MRI images with an organ-based tracking system, which takes into account prostate deformation and patient motion. Whatever the technique, most of the studies show an increase by approximately 40% of the detection rate of grade 4-5 tumors and a significant decrease in the detection of non significant cancer by approximately 15% (33, 34). In all studies, the degree of suspicion on MRI was the most powerful predictor of significant cancer on multivariate analysis, as cancer detection rate was 80-95% in patients with a highly suspicious MRI target (score 4-5) (33, 34).

Comparison of software vs cognitive registration shows discordant results, a study (30) showing a similar accuracy, while two others (35, 36) conclude to the superiority of software registration. It can be intuitively predicted that differences in slice orientation during acquisition between strictly axial MRI slices and the oblique scanning of end-fire TRUS probes explains why cognitive registration may fail to match with a sufficient accuracy the needle tract and the target. Moreover, the accuracy of cognitive registration also relies on the degree of expertise in prostate imaging.

Comparison of registration systems between them has not been thoroughly done. One study shows a trend towards a better accuracy of deformable (organ-based) registration over the non deformable (sensor-based) (36). The main limitation of sensor based registration with navigation systems is that it is not an organ-tracking technique, the sensors only allowing for a TRUS probe-tracking which does not take into account patient and/or prostate motion during the procedure (34). Improvements incorporated in the Artemis (33) or the Uronav (31) systems have been developed to circumvent this major limitation, but

accuracy may still be limited if patient and organ immobility, critical in sensor-based registration, are not consistently obtained. Moreover, a prostate deformation cannot be obtained related to the fact that the probe only performs an initial 3D acquisition during biopsy and the 2D scanning during the tracking phase cannot be registered in real time to the reference volume, explaining why a deformable TRUS-MRI image registration system may be preferred (34, 37).

Rationale for a TRUS-MRI image registration-based biopsy policy

Multiparametric MRI is an established accurate technique to localize prostate cancer and may be thus used as a test to detect significant tumors. This concept is gaining more and more widespread acceptance, as there is growing evidence that random biopsies in areas without MRI abnormality show no cancer or insignificant tumors (36, 38-40). It is now more and more widely accepted that MRI should be recommended before a second set of biopsies in patients with a persistent biological suspicion of prostate cancer and those under active surveillance to target a significant tumor missed and underestimated by the initial set of biopsies. Currently, the fear to miss a significant tumor generated the practice of a template biopsy scheme (one transperineal biopsy every 5 square mm using a brachytherapy grid), under general anesthesia. It is a complex procedure which entails a higher complication rate than sextant biopsies (10). Similarly, patients under active surveillance should have a repeat MRI before considering a second set of biopsies which would be only indicated if PSA level or MRI findings show signs of progression. In this setting, a study has shown that the negative predictive value of MRI for excluding significant cancer, defined by the presence of Grade 4 on any core and a cancer length >4mm was 90% (41).

Given the high predictive value of mpMRI, the question is actually whether mpMRI should be considered a triage test before initial biopsy to select patients requiring immediate targeted biopsies in case of a positive MRI, while biopsy could be deferred if MRI shows no suspicious area (38, 42).

Conclusion

Multiparametric MRI can detect significant tumors with a high accuracy. To detect the dominant tumor, the prostate should thus be imaged before biopsies and the accuracy of MRI-Targeted Biopsies should be utilized to target suspicious areas, like for other organs of the body. In this strategy, immediate sextant biopsies would be obviated (38, 42) and targeted biopsies would be performed under the guidance of DW-MRI abnormalities, to pick up the highest grade of the tumor, achieving a concordance of biopsy and surgical Gleason score in 84% cases (43). Given the high negative predictive value of a negative mpMRI, this policy would be helpful to decrease the overdiagnosis rate and thus the burden of active surveillance, while significant tumors would be diagnosed with a unique set of biopsies.

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