MRI and surveillance

Adil Ouzzane[a,b], *Philippe Puech*[b,c], *and Arnauld Villers*[a,b]

Purpose of review
In this review, we summarize the recent advances in modern imaging, particularly multiparametric (mp) MRI and its role in the selection and monitoring of patients on active surveillance.

Recent findings
Current diagnostic pathway has some limitations in selecting patients with insignificant prostate cancer for active surveillance. Hence, percentage of men under active surveillance for insignificant prostate cancer and reclassified as significant cancer at 2 years is 20–30%. It is mainly because of anterior cancer underdiagnosis by systematic posterior biopsies. mp-MRI is accurate for significant cancer detection and staging, including anterior cancers, which represent 20% of cancers in an unselected population of men with suspicious prostate-specific antigen elevation. One way to reduce the risk of underestimation is to target the needle on significant cancer identified at prebiopsy anatomical and functional imaging, so that detection and personalized risk stratification can be improved. MRI reveals greater volume of cancers and higher grade than systematic 12-core biopsies. MRI 95% negative predictive value has the potential to avoid biopsy series for monitoring patients under active surveillance.

Summary
Upon confirmation of these results, MRI may be used to better select patients for active surveillance inclusion. Incorporation of mp-MRI into active surveillance selection criterias for patients with low-risk prostate cancer can reduce the number of patients reclassified at subsequent biopsies because of better initial prognosis evaluation. In addition to additional cost, MRI requires a highly skilled team to obtain information adequate to drive clinical decisions.

Keywords
biopsy, detection, imaging, MRI, natural history, pathology, prostate neoplasm

INTRODUCTION

The introduction of prostate-specific antigen (PSA) screening has led to an increasing number of newly diagnosed localized low-risk prostate cancer and growing interest for active surveillance as an alternative to immediate radical therapy to reduce the risk of overtreatment. The aim of this approach is to follow patients with insignificant low-risk prostate cancer and to treat with a curative intent only in case of progression during follow-up. The current definition of insignificant prostate cancer is based on the pathologic assessment of the radical prostatectomy specimen: tumor volume less than 0.5 cm^3 and Gleason score *or less* 6 without any Gleason pattern 4 or 5 [1]. The issue with active surveillance is how to be confident in the absence of significant cancer in the prostate, whereas the biological rationale for not treating insignificant cancers is largely accepted.

The preoperative assessment of prognosis is mainly based on clinical variables (digital rectal examination and PSA level) and systematic biopsy results (number of positive cores, cancer length and Gleason score) to predict pathologically insignificant prostate cancer. However, this diagnostic pathway has some limitations which can lead to reclassification in significant cancer that can involve 20–30% of patients [2,3▪▪]. Recently, a new monogram for predicting pathologically insignificant prostate cancer was proposed incorporating clinical data, biopsy results and MRI findings [4▪]. In this study, 27% of patients had insignificant prostate cancer at pathology and MRI models did

[a]Department of Urology, Hospital Huriez, University Lille Nord de France, Lille, [b]INSERM U703, CHRU Lille, Univ Lille Nord de France, Loos and [c]Department of Radiology, Hospital Huriez, University Lille Nord de France, Lille, France

Correspondence to Professor Arnauld Villers, Department of Urology, Hôpital Huriez, Centre Hospitalier Regional Universitaire, 59037 Lille, France. Tel: +33 3 20 44 42 35; fax: +33 3 20 44 51 43; e-mail: arnauld.villers@wanadoo.fr

Curr Opin Urol 2012, 22:231–236
DOI:10.1097/MOU.0b013e328351dcf7

KEY POINTS

- The current diagnostic pathway can lead to reclassification in significant cancer of 20–30% of patients under active surveillance.
- Most reclassified cancers in active surveillance series are the missed anterior cancers that represent 20% of cases.
- Multiparametric MRI and targeted biopsies are very effective for posterior and anterior prostate significant cancer detection and should be part of the workup before referring a patient for active surveillance.
- Multiparametric MRI is very effective for ruling out significant cancers and can be useful for monitoring patients under active surveillance, reducing the need for prostate biopsies.

significantly better than the clinical models ($P < 0.05$). One thing that should be kept in mind is that most reclassification of men fulfilling active surveillance criteria at initial biopsy occurs at immediate repeat biopsy or 1–2 years after diagnosis, suggesting undersampling of significant tumors at the time of initial biopsy, rather than progression of indolent tumors [2,5▪▪]. In a large series of 377 men with low-risk prostate cancer managed with active surveillance, 34% experienced Gleason upgrading and the majority of them (81%) did so by their second repeat biopsy [6]. This suggests that systematic biopsies are carried out blind to the location of the cancer and there are parts of the prostate where the needle cannot reach, even with an extended biopsy scheme, so biopsy results can be misleading. One way to reduce the risk of underestimation is to target the needle on significant cancer 'detected' on prebiopsy anatomical and functional imaging, so that detection and personalized risk stratification can be improved. In this review, we summarize the recent advances in imaging, particularly MRI and its role in the management of patients on active surveillance.

MRI IS ACCURATE FOR SIGNIFICANT CANCER IDENTIFICATION

MRI is accurate for significant cancer identification, particularly anterior cancers missed by current standard diagnostic pathway and which should be excluded from active surveillance protocols [7,8]. Multiparametric (mp) MRI is currently the most established imaging modality for significant prostate cancer diagnosis, and yields high sensitivity and specificity for the detection of anterior and posterior cancers [9▪▪,10▪,11]. At tumor volume greater than 0.5 cm^3, sensitivity and specificity were 86 and 94% [area under receiver operating characteristic curve (AUC) 0.874] in correlation with radical prostatectomy pathology as reference standard [9▪▪]. Negative predictive value (NPV) was 95%. Mean cancer volume detected at MRI was 2.44 cm^3 (0.02–14.5) and those lesions not detected at MRI were mean 0.16 cm^3 (0.01–2.4) in size. In a recent work by Haffner *et al.* [12▪▪], sensitivity, specificity and accuracy of MRI and targeted biopsies for significant cancer detection were 0.95, 1 and 0.98, respectively. In another study including 101 patients, fusion MRI/ultrasound guided biopsy detected overall more cancers and more cancer per core than systematic 12-core transrectal ultrasound (TRUS)-guided biopsy [13]. Roethke *et al.* [14] reported a detection rate of 52% for magnetic resonance (MR)-guided biopsies among 100 patients with one or more previous negative systematic biopsy series and persistent suspicion of prostate cancer. Overall, 80.8% of the patients in that series revealed a clinically significant prostate cancer. Correlation between cancer volumes using T1-weighted MRI sequences with dynamic gadolinium contrast sequences and histopathology for large tumors (>0.2 cm^3) detected by MRI ($n = 30$) is good ($r^2 = 0.530741$) [15]. A good correlation was also reported in a study including 27 patients with predominant anterior prostate cancer ($r^2 = 0.69$) [10▪].

In addition to cancer volume, cancer grade is strongly associated with prognosis. However, sampling error in biopsy specimens obtained at systematic biopsy occurs in approximately 23–35% of procedures [16] and results in a changed Gleason score at histopathologic evaluation of the prostatectomy specimen. Increasingly, functional imaging techniques provide information not just about tumor location and volume, but also about cancer behavior [17]. For instance, degree of enhancement on T1-weighted sequences with gadolinium may be related to Gleason grade [18]. In a series of 93 patients, AUC for detection of cancers with Gleason grade 4 or 5 at dynamic contrast enhancement MRI was 0.819 [9▪▪]. Additionally, several studies have documented reliable correlations between apparent diffusion coefficient (ADC) values obtained with diffusion-weighted MR imaging and Gleason scores [19,20]. Less differentiated and dense cancers are associated with lower ADC values, better contrast and higher detection rate at diffusion-weighted imaging [21–23]. In a study with cases performed at 3.0 T, ADC values showed an inverse relationship to Gleason grades for peripheral zone prostate cancer. A high discriminatory performance was achieved in the

differentiation of low-grade, intermediate-grade, and high-grade cancer [24▪]. Significant differences between the ADC values of low-risk and intermediate-risk prostate cancer have been found, and in a cohort of patients on active surveillance, the baseline ADC value was an independent predictor of both adverse repeat biopsy findings and time to radical treatment [22,25]. So, MRI can be useful before inclusion of patients in active surveillance protocols because it is the most reliable tool to exclude those harboring significant cancer. Another interesting point is MRI accuracy for predicting reclassification among men already under active surveillance. In a cohort of 110 patients on active surveillance with a median follow-up of 59 months, patients with suspicious lesion for malignancy at MRI had a greater risk of Gleason score upgrading at subsequent biopsy (hazard ratio 4.0; 95% confidence interval 1.1–14.9) comparatively to those without such lesion [26▪]. Hence, men wishing to start or remain on active surveillance might benefit by having potentially lethal cancers excluded with MRI before choosing this management strategy. It should be noted that MRI application requires a degree of discipline in its conduct, reporting and evaluation to obtain homogenous results among centers as emphasized by a recent European consensus meeting [27▪▪].

CURRENT STANDARD DIAGNOSTIC PATHWAY IS INACCURATE

The current diagnostic process is to use TRUS guidance to take 10–12 transrectal needle biopsies from different parts of the prostate in a systematic fashion which has inherent random and systematic errors related to the biopsy technique, underestimates the true cancer grade in up to one-third and the cancer burden in up to one-half of men diagnosed with low-risk disease [28]. As a result of these errors, localization of individual tumors within the prostate is poor, whereas mp-MRI is very sensitive for both anterior and posterior cancer detection; recently published data support the concept of MRI-targeted biopsy [29,30▪▪]. TRUS is used to locate the prostate gland itself, but otherwise plays little part in guiding the biopsy procedure. Consequently, random error occurs, as the operator has no knowledge of where the cancerous areas may be. In addition, systematic error occurs because only the peripheral zone is sampled during an initial biopsy, and sampling of the anterior peripheral and transition zones is inadequate [31], whereas extreme anterior apical biopsies were shown to improve detection [32]. One way to overcome these errors is to sample the gland using more and more biopsies. Saturation TRUS biopsies have shown minimal utility in this regard [33]. Three-dimensional (3D) transperineal template prostate mapping biopsies provide several benefits compared to the conventional TRUS-guided biopsy. First, it is able to detect disease with greater accuracy by overcoming random and systematic errors of TRUS-guided biopsy as it fixes the sampling frame to 5 mm and samples the whole gland [34,35]. Although 3D transperineal mapping biopsy is a reliable and detailed method of mapping individual prostate tumors, it may remain a temporary step in our quest for image-guided diagnosis and treatment, as it has several disadvantages that may limit its long-term use.

CANCERS MISSED BY STANDARD DIAGNOSTIC PATHWAY ARE THE ANTERIOR CANCERS

The anterior prostate gland is a challenging anatomical area for diagnosing prostate cancer. Anterior cancers represent 20% of the largest cancers in unselected patients suspected to have prostate cancer [30▪▪]. It is a difficult area to sample by a routine 12-core, TRUS biopsy approach, currently the standard scheme used by most urologists. Targeting biopsies to an MRI-suspicious area was proven to be very effective in improving detection of anterior located cancers, beyond the area sampled by posterior biopsies, This was true when tissue biopsy was performed under TRUS guidance with MRI 'cognitive' co-registration [10▪]. In a study of 46 anterior cancer cases, median cancer length of the most involved core in targeted compared to systematic biopsies was 8 vs. 1 mm ($P < 0.001$), respectively, for the 25 cases sampled by both targeted and systematic biopsies [30▪▪]. Sensitivity of biopsy for high-grade disease was also improved with biopsies targeted to MRI lesion. Significant Gleason score upgrading was observed in 11 of 25 (44%) cases.

MOST RECLASSIFIED CANCERS IN ACTIVE SURVEILLANCE SERIES ARE THE MISSED ANTERIOR CANCERS

When diagnosed by 12-core TRUS-guided systematic biopsy, anterior tumors had fewer cores with tumor involvement and less summated tumor length than had posterior cancers [36]. This makes the assessment of tumor volume inaccurate and cannot be taken as reference for establishing prognosis and treatment strategy decision. In a series of radical prostatectomy in patients with failure of active surveillance, 10 of the 48 tumors on histopathology were greater than 1 cm^3 in volume and were all anteriorly located [5▪▪]. In a retrospective

study involving 31 patients with previous negative biopsy or low-volume disease and considered for active surveillance (14 cases), predominant anterior tumor was identified on prebiopsy MRI and confirmed with targeted biopsy in 27 cases (89%) [8]. Among the 13 patients who had radical prostatectomy in this study, pathological stage was pT2 in three, pT3 in seven and pT4 in three cases. The authors proposed the entity of 'prostatic evasive anterior tumors' that should be excluded before embarking patients on active surveillance.

PERSPECTIVES AND FUTURE STUDIES

Use of prebiopsy mp-MRI has the potential to decrease the number of insignificant cancers diagnosed and therefore the number of men referred for active surveillance. Targeted biopsies-only strategy without systematic biopsies was retrospectively studied in a series of 555 men referred for elevated PSA [12▪▪]. MRI was positive in 351 (63%) patients and overall 302 (54%) had cancer at systematic biopsies and/or targeted biopsies. This 54% detection rate is consistent with the average 50% detection rate observed in a European population of unselected newly screened patients with no history of biopsy and a median PSA of 6.75 (0.18–100). Detection accuracy of significant prostate cancer by targeted biopsies was higher than systematic biopsies ($P < 0.001$). Furthermore, targeted biopsies detected 16% more Gleason grade 4 or 5 cancers and better quantified the burden of cancer than systematic biopsies, with a cancer core length involvement of 5.56 vs. 4.70 mm ($P = 0.001$). It was also demonstrated in a study by Rouse *et al.* [37] that mp-MRI have a role in ruling-in and ruling-out clinically significant prostate cancer in men at risk prior to biopsy. Hence, NPV of 94% is high enough for ruling out clinically significant disease and may act as triage test for biopsy (re-biopsy) indication and may result in fewer men needing to undergo further biopsy [12▪▪]. These results demonstrate the role of prebiopsy MRI with targeted biopsies and support the use of MRI before active surveillance inclusion. Moreover, the use of targeted biopsies only can avoid the detection of insignificant prostate cancer and lead to a lower number of men being managed with active surveillance.

MRI CAN BE USEFUL FOR MONITORING PATIENTS UNDER ACTIVE SURVEILLANCE, REDUCING THE NEED FOR PROSTATE BIOPSIES

Recently, Giles *et al.* [38] showed that ADC values at repeat biopsy were significantly lower in patients with Gleason score increased than in those with a stable score ($P = 0.001$). In that study, both tumor volume ($P = 0.002$) and ADC values calculated from diffusion-weighted imaging (300–800 s/mm^2) ($P = 0.02$) were significant independent predictors of progression of active surveillance patients. In another active surveillance study in 86 patients with a mean follow-up of 29 months [39], diffusion-weighted imaging tumor ADC data were significant predictors of a Gleason score 4 component at repeat biopsy ($A_Z = 0.70$, $P = 0.001$) and of the need for initiation of radical treatment during follow-up ($A_Z = 0.83$, $P = 0.001$). The same finding was corroborated by Morgan *et al.* [40] studying 50 patients managed by active surveillance.

THE ECONOMIC IMPLICATIONS

The economic implications for carrying out MRI in every man who requires a prostate biopsy need careful consideration. This prebiopsy MRI strategy involves economic and resources realities as MRI costs about 300€ in Europe and 2–3000 USD in the USA, and necessitates available MRI and experienced radiologists. In most settings, prebiopsy MRI which studies the pelvic nodes is, in case of cancer, the only imaging modality for pretreatment evaluation, in addition a bone scan indicated a PSA greater than 10 ng/ml or the presence of Gleason grade 4. In addition, negative MRI may rule out significant cancer and avoid a second biopsy series in case of persistent elevated PSA. Ultimately, cost-utility and cost-effectiveness of incorporating imaging into the diagnostic pathway in this manner may be associated to downstream savings that result from not biopsying every man and thus reducing over-diagnosis and over-treatment may be substantial.

CONCLUSION

There is clear evidence that targeting biopsies to areas suspicious for malignancy at multiparametric prostate MRI can reveal a greater volume of cancers and a higher grade than systematic 12-core biopsies. Incorporation of mp-MRI into active surveillance selection criterias for patients with low-risk prostate cancer can reduce the number of patients reclassified at subsequent biopsies because of better initial prognosis evaluation and can lead to a lower number of patients needing repeat prostate biopsies because of its promising role in monitoring cancer progression. Large prospective clinical trials are urgently needed to assess the stronger evidence regarding the use of mp-MRI in active surveillance. Limitations of this MRI-based approach are that in addition to additional cost, MRI requires a highly

skilled team to obtain information adequate to drive clinical decisions.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 261).

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