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MRI in addition to or as a substitute for prostate biopsy: The clinician’s point of view

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Abstract This paper aims to argue the advantages of using routine multiparametric MRI (mp-MRI) prior to the first series of biopsies in patients with suspected cancer of the prostate indicated by a rise in Prostatic Specific Antigen (PSA). Using biopsy targeted onto a lesion seen by MRI, this diagnostic strategy could increase detection of significant cancers and improve evaluation of their grade and size. This strategy would also mean that the detection of insignificant cancers (microfoci detected by chance during systematic biopsy) would decrease, since if the mp-MRI did not give rise to suspicion, the indications for biopsy would be reduced. It could also reduce the number of biopsies to be performed even when the mp-MRI is suspicious, by resorting solely to targeted biopsies. This review does not evaluate the role of mp-MRI in locoregional staging.

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The traditional diagnostic strategy for cancer of the prostate, based on a threshold Prostatic Specific Antigen (PSA) value along with performing systematic transrectal ultrasound-guided biopsy (12 biopsies sampling the 17 mm of the posterior part of the gland), is associated with diagnostic errors. This method is indeed producing over-diagnosis of clinically insignificant cancers and failing to detect certain cancers, which are clinically significant. There are in fact (anterior) areas of the prostate gland that are not sampled by systematic standard biopsies, even with the extended plan, which makes the results of them unreliable.

An alternative to this traditional strategy is to add multiparametric MRI (mp-MRI) to biopsy or to substitute it for the latter, thus providing the best diagnostic sequence. Mp-MRI is an accessible imaging technique, but performing it, interpreting it and evaluating it require considerable expertise [1]. One of the arguments in favour of using pre-biopsy

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mp-MRI is based on the principle of guiding biopsies according to abnormalities seen on imaging, rather than mapping from a pre-established diagram of part of the gland. This principle, of performing biopsies targeted on abnormalities detected clinically or on imaging, is the norm for all solid organs.

The economic impact of performing an mp-MRI in all men in whom a prostate biopsy is indicated should be evaluated. Pre-biopsy mp-MRI naturally implies adapting resources, both in terms of staff and of equipment, and requires initial investment.

**Pre-biopsy mp-MRI improves identification and characterisation of cancer of the prostate**

Mp-MRI is effective for studying the anterior and posterior regions of the prostate in patients presenting lesions suspected of being neoplastic.

A European consensus group of MRI experts recently recommended that this modern imaging technique should be performed as an examination prior to biopsy [1]. It is however necessary for the MRI to be performed in a standard way in all centres. The experts agreed on 67% of the 260 items related to the imaging sequences necessary, and decided for example, that the MRI sequences necessary are T2-weighted, dynamic T1 contrast-enhanced and diffusion-weighted sequences, whereas spectroscopy is not recommended. The experts also agreed on 54% of the 260 issues concerning interpreting the images. At least 16 and up to 27 prostate zones where cancer may occur must be described (Fig. 1.) A suspected cancer scale from 1 to 5 was approved to harmonise communication in describing the lesions observed. Because of increase in the signal-to-noise ratio, 3 Tesla MRI decidedly improves spatial, temporal and spectral resolution of the prostate in all imaging sequences. Nevertheless, 1.5 Tesla with a pelvic coil can be used to provide interpretation of the signals observed in suspect areas that is similar to 3 T MRI. It has, indeed, been decided that this use of 1.5 T MRI with a pelvic coil is adequate for standard clinical practice. An endorectal coil is no longer necessary for performing prostate MRI to detect cancer.

Mp-MRI is very sensitive and specific for detecting anterior and posterior cancers [2—5]. It has been shown that for a volume greater than 0.5 cm³, sensitivity and specificity are 86% and 94%, respectively. The negative predictive value is 95%. The mean volume of cancers detected using MRI is 2.44 mL (0.02—14.5) and the mean volume of lesions not detected by MRI is 0.16 mL (0.01—2.4). For tumours larger than 0.2 cm³, there is good correlation between assessment of the tumour volume using T1-weighted dynamic MRI with injection of gadolinium and the tumour volume found from histopathological analysis of ablated tissue.

Functional imaging techniques help characterise the cancer (Fig. 2). The degree of enhancement on the T1 sequences with injection of gadolinium and restriction of diffusion, for example, seem to be related to the Gleason score [6—8].

![Twelve seven Regions of Interest](image)

Figure 1. Standard scheme of 27 zones for locating suspect lesions seen on MRI. Sections of the base, the middle and the apex of the prostate. Sagittal and frontal section. Each section is subdivided into four posterior regions (p) (mid-lobar and lateral), four anterior regions (a) (mid lobar and lateral) and three regions of the anterior stroma (as), in the centre, in front of the glandular zones. The standard 12 biopsy plan samples the 12 posterior regions, 17 mm anteroposteriorly. VS: seminal vesicles. Adapted from Dickinson et al. [1].

**The role of pre-biopsy MRI with targeted biopsies**

**Current diagnostic strategy based on systematic biopsy**

With the current strategy, the real grade of the tumour is underestimated in a third of cases and the extent underestimated in more than 50% of the patients whose tumour is low risk [9]. Consequently, locating an individual tumour focus in the prostate is rather unlikely, whereas the sensitivity of mp-MRI for detecting anterior and posterior cancers is high. Recent publications have therefore backed the idea of targeted biopsy.

Current practice is still to take ten to 12 transrectal ultrasound-guided biopsies following a standard plan. Endorectal ultrasonography is used to define the contours of the prostate gland and, to a lesser degree, to guide the biopsies. Sampling is therefore done randomly, the operator often not having any idea of the location of tumorous areas if no suspect lesions can be seen on the ultrasound image. In addition, these biopsies are basically concerned with the peripheral area; sampling the anterior and transition areas is inadequate [10], whereas it has been shown that when biopsies are guided to the anterior apex, detection is increased [11]. One of the possible ways of overcoming this sampling inadequacy is to increase the number of biopsies. However, transrectal ultrasound-guided saturation biopsy strategies have not been found to be advantageous in this context. Transperineal mapping biopsies (40 to 50 samples), with a
placement grid, have not been reported in the experience of French centres.

**The mp-MRI/guided biopsy combination**

This combination improves biopsy performance by increasing detection of significant cancers, reducing detection of insignificant cancers and allowing better sampling (core length and cancer grade from the biopsies). The result is improved evaluation and therefore, a more accurate prognosis. This would also mean that the number of biopsies per patient could be reduced. For example, a great many centres have independently reported detection rates, in men with suspected cancer of the prostate and a first series of negative biopsies, that vary from 30% to 59% (mostly anterior cancers), by using biopsies targeted on lesions detected by MRI [12–17]. In addition, assessment of the size and grade of the tumours were improved by 44% using guided biopsy, compared with systematic biopsy [18]. It has also been shown that targeting biopsies uniquely on lesions detected by MRI is more effective for detecting significant cancers than systematic transrectal ultrasound-guided biopsy. It is associated with less detection of insignificant cancers and less biopsies overall and per patient [19]. Biopsies targeted on areas that appear suspect on MR images improve detection of anterior cancers (which are located beyond the area sampled by posterior biopsies). These anterior cancers make up 20% of the significant cancers in an unscreened population of patients suspected of having prostate cancer [18].

**The role of targeted biopsy without systematic biopsy**

This was studied retrospectively in a series of 555 men with raised PSA [19]. Mp-MRI was positive in 351 patients (63%), and 302 patients (54%) had a cancer detected at the time of systematic and/or guided biopsy. This 54% detection rate is consistent with the average detection rate of 50% observed in a European population of newly screened patients with no history of biopsy and a mean PSA level of 6.75. The rate of

![Figure 2. Multiparametric 1.5 T MRI with pelvic coil. Axial slices at the junction of the inferior 1/3 with the middle 1/3: a: T2-weighted sequence. Suspect lesion in T2 hypointense signal affecting the right transition area and the right anterolateral strip of the peripheral area, measuring 16 mm across its largest diameter. No signs of extraprostatic extension; b: diffusion map: very suspect lesion with strong diffusion restriction at the location of the lesion previously described; c: dynamic sequence with subtraction, at T0; d: MRI of prostate: dynamic sequence with subtraction, at T= 30s: very suspect lesion, with intense hypersignal from the area already described.](image-url)
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detection of significant cancers of the prostate was higher by guided biopsy than by systematic biopsy \((p < 0.01)\) and the quality of the sampling was better than with systematic biopsy. In a series of cancers irrespective of location, the mean length of invasion of targeted biopsies was 5.56 mm as against 4.70 mm for systematic biopsies \((p = 0.018)\).

In a study of 46 anterior cancers, the mean invasion of targeted biopsies was 8 mm compared with 1 mm for systematic biopsies \((p < 0.001)\) [18]. In addition, targeted biopsies helped detect higher grade tumours, with respectively 16% more grade 4 or 5 cancers compared with all location systematic biopsies and 44% for anterior cancers [18, 19].

These results demonstrate the role of pre-biopsy mp-MRI associated with targeted biopsy.

Not only does MRI detect intraprostatic targets towards which biopsies can be directed, but because of MRI, performing a biopsy in men with a low probability of having a clinically significant cancer can be deferred. For significant cancers Mp-MRI indeed has a negative predictive value greater than 90%. It could therefore be used as a screening examination to avoid biopsy if it does not reveal any abnormalities, just as a normal mammography result is used for not biopsying women whose risk of having breast cancer is low. In cooperation with the team from Cleveland, we demonstrated in this study the potential benefit of this diagnostic strategy [19]. Prostate biopsy can be avoided in a little under half of men (47%) who have a non-suspect mp-MRI. This would reduce the rate of detection of insignificant cancers by 13%, as has been shown in the study by Rouse et al. in which mp-MRI was used for pre-biopsy selection [20]. The negative predictive value of MRI of 94% for detecting cancer is high enough for it to be used as a screening test before biopsy or before indications for re-biopsy, resulting in a reduction in the number of men requiring several series of biopsies.

This has already been described but has not yet been widely accepted by the urology community. Ahmed et al. recommended increasing use of mp-MRI before prostate biopsy but recognised that the expertise required is only available in a limited number of centres [21]. The authors also emphasized that the effectiveness of mp-MRI may be limited by haemorrhagic artefacts if it is performed in the six to eight weeks following biopsy.

Different biopsy techniques targeted on areas seen as suspect in MRI

Ultrasound-controlled freehand targeted biopsies

These biopsies are easy to perform. Nevertheless, a biopsy targeted on a suspect area detected by mp-MRI is not, in this case, really guided by the MRI. A process of mental reconstruction is used to locate the suspect area, detected by mp-MRI, on the ultrasound image, with the help of standardised report diagrams.

The accuracy of these biopsies targeted by mental reconstruction has been evaluated. The coefficient of correlation between the length of the tumour on the targeted biopsies (median 8 mm, confidence interval: 7—12 mm) and the greatest anteroposterior diameter of the lesion considered on mp-MRI to be suspect (median 10 mm, confidence interval 8—14 mm) is \(r^2 = 0.6\) \((p < 0.01)\) [18]. There are therefore strong arguments in favour of this simple pinpointing technique, based on the zonal anatomy of the prostate and on standardised reports, in which two core biopsies are taken from the area determined as suspect. In this study, mp-MRI was performed prior to any series of biopsies. For each suspect area (anterior or posterior), 2 to 4 additional targeted biopsies were taken. Each mp-MRI was simultaneously evaluated by a radiologist and a urologist, which meant that the urologist could thus locate the suspect areas during the endorectal ultrasound. The targeted biopsies were taken freehand.

The suspect lesions detected by MRI within the posterior area of the prostate were generally associated with hypoechoic areas on transrectal ultrasound images, so that biopsies could be better targeted. In contrast, lesions in the anterior area could not be identified by ultrasound in all cases, because of the heterogeneity of the transition area and hypoechogeticity of the anterior fibromuscular stroma.

MRI-guided biopsies in real time

This method of biopsy has also shown improvement in the detection of cancer [12—17]. In these studies on patients with a first series of negative biopsies, the rate of detection by MRI-guided biopsy was 59%, 30%, 52%, 41%, 45.5% and 31.5% respectively. However, such real-time MRI-guided biopsy requires expert teams and equipment to be available.

Fusing MR and ultrasound images

This is done at the time of biopsy using virtual navigation in real time, with rigid registration, or by 3D acquisition with non-rigid or elastic registration, and is currently being evaluated. The technique has proved feasible. [22]. It requires thin slice images to be imported with the location of the suspect area clearly identified.

Mp-MRI could be added to active surveillance to replace biopsy

It can be envisaged that mp-MRI could be substituted for the series of biopsies performed during active surveil-

lance, completed, if need be, by targeted biopsies. In a meta-analysis, it has been shown that MRI combined with spectroscopy could be used in monitoring low risk patients. This result needs to be verified in larger studies and the cost/effectiveness ratio must be established [23].

If we wish to use imaging as a patient monitoring tool for active surveillance, we must study the ability of this imaging examination to predict the histopathological results of specimens from radical prostatectomy. Since these results do not however always reflect the long-term evolution of the disease, it would be preferable to compare the images made during diagnosis with the long-term results of the disease, whether treated or not. For example, recent work suggests that the values of the apparent diffusion coefficient predict clinical evolution better than the Gleason score [8].
TAKE-HOME MESSAGES

- Multi-parametric MRI is the only examination with which tumour foci in all areas of the prostate gland can be detected and characterised.
- MRI as an addition to prostate biopsies:
  - Ultrasound-guided prostate biopsy underestimates the grade and size of the cancer in more than a third of cases and samples the anterior and apical regions poorly.
  - The sensitivity and specificity of multi-parametric MRI performed before biopsy is respectively 86% and 94% for identifying a cancer of significant size, i.e. > 0.5 cm³. The negative predictive value is 95%.
  - Biopsies targeted on suspect areas detected by MRI permit better detection and characterisation of the size of the lesion and the grade of the cancer.
  - A strategy of biopsy solely targeted on lesions that appear suspect in MRI, without associated systematic biopsy, would reduce the detection of insignificant cancers by 13% and decrease the number of biopsies per patient. In addition, 42% of patients with an MRI clear of suspicion would not have any biopsies.
- MRI as a substitute for biopsy: the negative predictive value of MRI for detecting significant cancers is > 90%. The absence of an initial suspect lesion or of such a lesion in the course of monitoring patients under active surveillance would mean biopsy would be avoided.

Clinical case

This patient, aged 64, consulted owing to an increase in PSA to 6.61, whereas it was 3.64 three years ago. The prostate is not suspect on DRE.

Questions

1. What is the procedure to follow?
2. What MRI sequences should be systematically performed on the prostate?
3. What biopsy protocol should be applied?
4. What is the risk of not performing MRI, or of not performing targeted biopsy of an abnormality seen in an MRI?

Answers

1. A series of prostate biopsies preceded by MRI. Multiparametric MRI is performed before the prostate biopsies using 1.5 T equipment with a pelvic coil.
2. The protocol for the prostate should systematically include three types of sequence: T2-weighted axial and coronal sequences, diffusion and perfusion sequences (acquired every 10 to 15 seconds, with subtraction).
3. Twelve systematic biopsies must be taken, as well as two biopsies targeted on the very suspect right transition area, with an anteroposterior axis in MRI of 12 mm (Fig. 2).

During these prostate biopsies, a suspect nodule was detected by ultrasound in the right peripheral area. Two targeted biopsies of the suspect nodule of the right peripheral area were therefore also taken. Histopathological analysis of the biopsy cores showed 1 systematic biopsy in 12 invaded for 2 mm by an adenocarcinoma with a Gleason score of 3 + 3 = 6 in the right lateral mid zone. The biopsies targeted on the suspect area in the MRI were both invaded for 8 and 9 mm by an adenocarcinoma scoring 3 + 5 = 8. The biopsies targeted on the suspect nodule in the ultrasound were negative.

4. If only systematic biopsies had been done, the patient would have been considered as having a well differentiated microfocus with a low risk of progression (PSA < 10 ng/mL) and could have been included in a protocol of active surveillance. The biopsies targeted on the MRI suspect areas helped class the patient immediately as being at high risk of progression and requiring curative treatment without delay.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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