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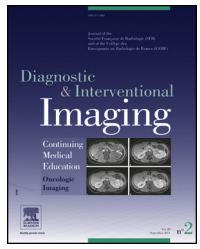

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Prostate MRI: Can we do without DCE sequences in 2013?

P. Puech[a,*,b,c], **A. Sufana-Iancu**[a,c], **B. Renard**[a], **L. Lemaitre**[a,b,c]

[a] *Department of Uroradiology, Lille Hospital, 1, rue Michel-Polonovski, 59037 Lille cedex, France*
[b] *University of Lille Nord de France, Lille 59800, France*
[c] *Inserm U703, 59120 Loos, France*

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Abstract Multiparametric MRI (mp-MRI) of the prostate currently provides stable and reproducible performances. The usefulness of dynamic contrast-enhanced (DCE) sequences is currently challenged, as they sometimes only confirm what has already been observed on diffusion-weighted imaging (DWI) and require the additional purchase of a contrast agent. Eliminating these sequences may help accelerate the use of MRI in addition to, or in lieu of, prostate biopsies in selected patients. However, many studies show that these sequences can detect lesions invisible on T2-weighted and diffusion-weighted images, better assess cancer extension and aggressiveness, and finally help detecting recurrence after treatment. We present the various applications of dynamic MRI and discuss the possible consequences of its omission from the current protocol.

Imaging of the prostate is often a controversial field. One subject under debate is perfusion imaging (DCE-MRI), i.e. T1-weighted imaging after injection of a contrast agent, to locate intraprostatic cancer foci. The question posed during the French of Radiology Day Conference 2012 is therefore topical.

For about five years, diffusion sequences have been incorporated in the standard prostate MRI protocol. They have been shown to improve detection of intraprostatic tumor foci and often provide information that is simply confirmed by the dynamic sequences (location of a lesion, size, confirmation of neoplastic nature). This rapidly led to a discussion of need for DCE-MRI sequences in the standard imaging protocol, despite numerous studies demonstrating their added value for the detection and evaluation of lesions [1—6], as in other indications (staging, detection of relapse, follow-up of focal treatment etc.), which have not been contradicted to date. However, this issue has rapidly developed with a proposal to only omit these contrast-enhanced sequences in a single indication:

* Corresponding author.
E-mail address: puech@dicomworks.com (P. Puech).

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''tumor detection'' MRI, reserving contrast-enhanced sequences for other indications (staging, detection of a local recurrence, follow-up during treatment etc.).

We briefly present here the physiological basis of contrast-enhanced MRI and its application in prostate imaging and then discuss the usefulness of contrast-enhanced sequences during prostate MRI.

Dynamic Contrast-Enhanced MRI (DCE-MRI)

Principles

Most neoplastic lesions greater than 200 μm induce neoangiogenesis which is essential for their growth and responsible for an increase in the microvasculature [7]. This microvasculature mainly differs from that of normal tissue by an increased permeability of the endothelial barrier that can be demonstrated by Dynamic Contrast-Enhanced T1-weighted MRI after injection of gadolinium (DCE-MRI) [8—12]. This involves an analysis of the signal measured as a function of time after an intravenous bolus injection of a low molecular weight paramagnetic contrast agent (gadolinium chelate) that freely diffuses into the EES (Extravascular Extracellular Space) with a rate that increases with the impairment in the integrity of the endothelial barrier. The first phase of enhancement called ''wash-in'' or ''filling'' is observed when the contrast agent fills the vascular compartment and rapidly diffuses into the EES [13]. This is a good reflection of the microvessel density in the region of interest. When enhancement has reached its peak intensity and there is an equilibrium concentration between the vascular compartment and the EES, the contrast returns to the vascular compartment as its intravascular concentration decreases after passage of the bolus. A second elimination phase, called ''wash-out'' begins, reflecting the displacement of contrast agent in the opposite direction from the EES into the vascular compartment. The wash-out rate increases with damage to the endothelial barrier. These phenomenons can be studied in three different ways:

- by direct examination of images and looking on the dynamic series for areas where the contrast appears first in the most intense areas which are considered to be those where the wash-in is the most important (Figs. 1—3);
- using the contrast agent time/intensity curve in a region of interest so that the reading permits an assessment

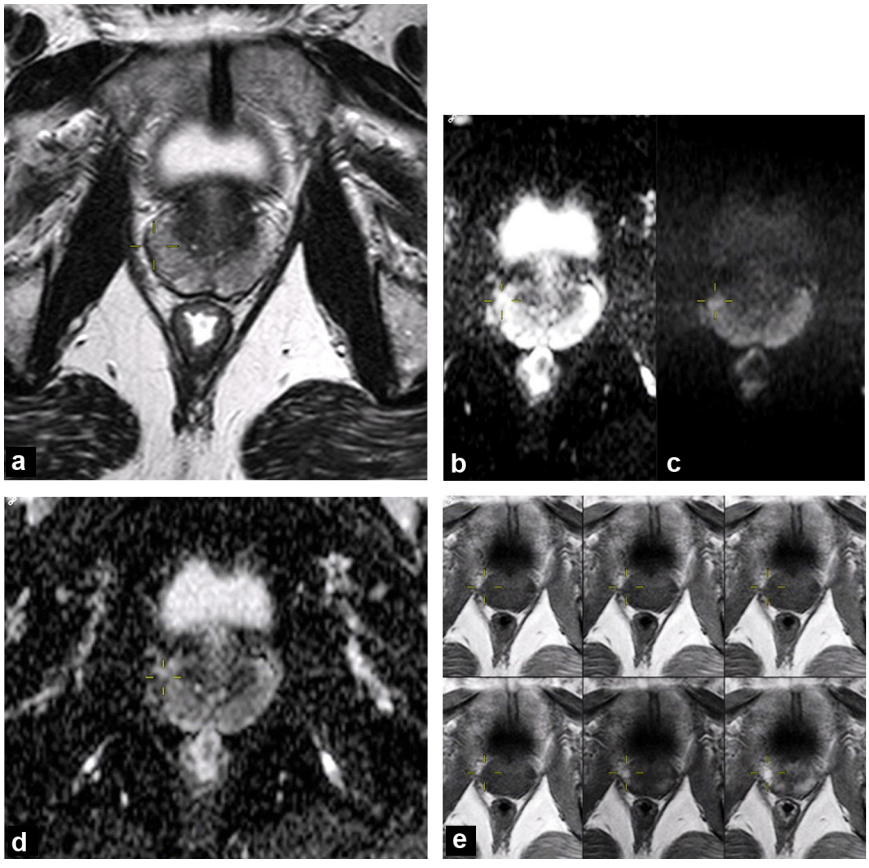

Figure 1. Lesion in the peripheral zone that is only detectable by dynamic sequences. 59-year-old patient with elevated PSA of 6.5 ng/mL. Two series of biopsies performed 3 (PSA: 4.4 ng/mL) and 4 years previously (PSA: 3.7 ng/mL) were negative. Multiparametric MRI performed before the 3rd series of biopsies, showed a nodular lesion of 13 mm in longest diameter in the middle and basal areas of the right lateral lobe of the prostate gland (yellow target on the five sequences: a) T2 TSE axial image, b) DWI with b = 0, c) DWI with b = 600, d) ADC map (b = 0—600), e) contrast-enhanced T1-weighted sequence at the 6 earliest times without subtraction. The lesion is only visible on the dynamic contrast-enhanced series (e), appearing at the fifth time of the injection. It was not detectable on the T2-WI sequence (a) or the ADC map (d). It was barely visible on the DWI with b = 600. After prostatectomy, this was found to be a pT3aNxR0 cancer of 15 mm, Gleason 4 + 3 = 7 with 70% grade 4 and focal extraprostatic extension.

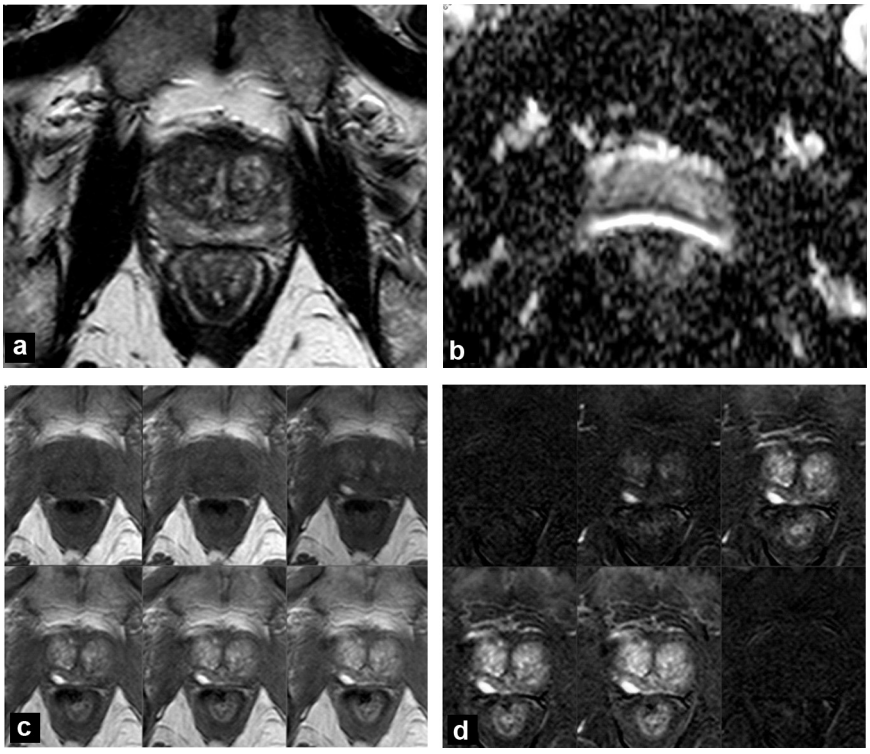

Figure 2. Lesion of the peripheral zone only detectable on contrast-enhanced sequences. 70-year-old patient with elevated PSA of 5.6 ng/mL and right induration during DRE. MRI performed before a second series of biopsies, as the first series had diagnosed a microfocus of 2 mm on the right. Given the discrepancy between the biopsies and the DRE, the urologist requested an MRI. a) axial T2 TSE image, b) ADC map (b = 0—600), c) dynamic, contrast-enhanced T1-weighted imaging at the 6 earliest times without subtraction, d) dynamic, contrast-enhanced T1-weighted imaging at the 6 earliest times with subtraction. The examination showed a prostate with multiple abnormalities on T2-WI (a). The diffusion sequence (b) showed no lesion. It was very difficult to read due to an artifact associated with intrarectal air. The perfusion sequence (c and d) clearly showed a nodular contrast enhancement of 10 mm in longest diameter in the mid region of the right lateral lobe with no direct evidence of extraprostatic extension. This image was best seen on the reconstructed series with subtraction. Directed biopsy established its neoplastic nature with Gleason grade 3 + 3 = 6, as did prostatectomy (pT2N0MxR0).

of the wash-out phenomenon: rapid, plateau, or absent during the acquisition time (usually 5 minutes to study it properly) [14]. These curves may be studied on a computer to obtain ''semi-quantitative'' values: wash-in/wash-out rates per second; peak amplitude; relative enhancement, time to peak, area under the curve of the first 90 seconds etc. [15];

- ''quantitative'' values are then obtained by trying to fit the measured signal to a theoretical signal with a mathematical formula incorporating a permeability factor between two or more compartments such as the Tofts, extended Tofts or Brix models etc. The most well known parameters are K-trans (endothelial barrier permeability coefficient), Ve (extravascular—extracellular volume fraction) and Vp (plasma volume). These ''quantitative'' calculations require the integration of many technical constraints, including in particular the transformation of the absolute signal measured by the gadolinium concentration in the region of interest and taking into account the arterial input function of the organ which is very difficult to estimate accurately.

Application to prostate cancer

Prostate tumors are hypervascularized [16]. Moreover it has been shown that the microvessel density is a prognostic factor independent of stage and probably of tumor aggressiveness [17] and subsequently that MRI is able to quantify the microvessel density [18] and, therefore, these prognostic factors. In theory, prostate cancers therefore present more rapid wash-in and wash-out phases than healthy zones but there are many false positives (inflammatory tissue, fibromuscular component of BPH [Benign Prostatic Hyperplasia], stromal nodules) and false negatives (cancers with low enhancement). The main task of the radiologist is therefore to distinguish areas where enhancements can be considered suspicious for cancer. For this, certain findings are more useful than others. A recent study based on the analysis of 53 prostatectomy specimens showed that the maximum concentration peak and wash-in parameters were constantly increased in case of cancer and that a combination of wash-in and wash-out alone gave the best diagnostic accuracy, measured with an area under the ROC curve of 0.86 [19].

Clinical applications

Lesion detection

It is now nearly 20 years since dynamic contrast-enhanced sequences were first described for the investigation of the prostate. Their added value in purely ''morphological''

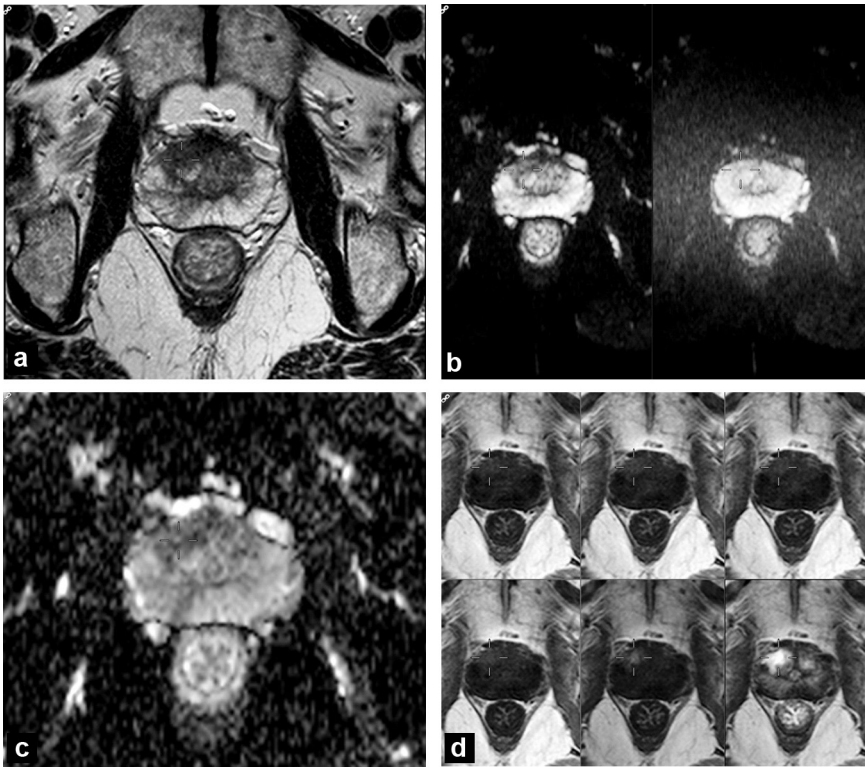

Figure 3. Aggressive transition zone lesion only detectable on contrast-enhanced images and undetectable by DWI. This 63-year-old patient had an elevated PSA of 6.61 ng/mL versus 3.64 ng/mL 3 years previously. DRE firm on the right. MRI performed before a first series of biopsies. a) axial T2 TSE image, b) DWI with b = 0 (left) and b = 600 (right), c) ADC map (b = 0—600), d) dynamic contrast-enhanced, T1-weighted sequence at the 6 earliest times without subtraction. A hypervascular lesion in the anterior, right and middle part of the gland was detected on the dynamic sequence (d). It measured approximately 16 mm and showed no direct evidence of extracapsular extension. It was only visible retrospectively on T2-weighted images (a) and was not detectable on the diffusion-weighted images (b and c). One systematic biopsy was positive (3 mm Gleason 3 + 3 = 6) in the right mid lateral region, but four biopsies were positive between 1 and 11 mm (Gleason 4 + 3 = 7 and 3 + 5 = 8).

imaging protocols including only T2-weighted sequences has been repeatedly demonstrated [18,20—31], though this has also been shown for protocols including combined T2-weighted imaging (T2-WI) and diffusion-weighted imaging (DWI) [1,32—37] and T2-WI, DWI and spectroscopy [38], whether the images were interpreted on the console, or using a Computer Assisted Design (CAD) system [39,40].

In general, these studies have shown that DCE-MRI improves the sensitivity of detection of lesions by about 10 to 15%, with no significant decrease in specificity [1—6,35—37]. The study of Kozlowski et al. (on 32 tumors), showed that the sensitivity in detecting lesions improved from 54% to 87% (+33%) when diffusion and perfusion sequences were combined [32]. The study by Tanimoto et al. of 88 prostatectomy specimens showed an improvement in detection sensitivity from 84 to 95% (+11%) and in accuracy from an area under the ROC curve of 0.905 to 0.966 ($P < 0.01$) by using the same combination [1].

This gain is all the greater for anterior lesions that are hidden in a transition zone that naturally consists of areas of myomatous, fibrous or calcified tissue with a low T2 and diffusion signal (Fig. 3). MRI can detect those hypervascular lesions that asymmetrically alter the structure of the adenoma or are localized in specific areas (anterior fibromuscular stroma, anterior part of the gland). Lesions of the anterior fibromuscular stroma, which are usually hidden in a fibrous tissue (hypo-intense signal on T2-WI and DWI and on the ADC map), are easily detectable on dynamic sequences. In the peripheral zone, DCE sequences are mainly effective in detecting non-nodular, infiltrating vascular lesions, which are poorly visible on T2-WI or DWI [41] (Figs. 1 and 2).

Evaluation of aggressiveness of lesions

Several studies have highlighted the relationship between dynamic imaging parameters and certain markers of the aggressiveness of prostate lesions: microvessel tissue density [42], Gleason score [43,44]. At macroscopic level, extracapsular (extraprostatic) extension and seminal vesicle invasion are other findings demonstrating the aggressiveness of lesions that we will describe separately.

Extracapsular extension

The accuracy of morphological MRI to evaluate the extracapsular extension of a lesion is very variable and mainly depends on the experience of readers and the semiotics used, with a sensitivity of about 33—50%, but a specificity of more than 80% in most studies [45—50]. Sensitivity is increased by the injection of contrast material that can improve the visibility of direct signs of extension, by showing contrast enhancement beyond the prostate surface or in the

periprostatic fat [51]. This contrast enhancement may, however, be linked to other processes (inflammatory) and cause false positives, probably explaining the discordant results described in the literature on this subject [20,52—57], although only a few specific studies are available.

Seminal vesicle invasion

The MRI evaluation of the seminal vesicles is facilitated by contrast-enhanced sequences that improve their visualization and study in approximately 23% of cases, especially for inexperienced readers [24]. As for direct extraprostatic extension, these results are debatable in certain series [57,58]. Evidence for seminal vesicle invasion is based on two signs, whose reliability is even better when combined [59]: filling of the seminal lumen and presence of asymmetrical or nodular seminal enhancement (Fig. 4). Unlike direct extraprostatic extension, the evaluation of seminal vesicle invasion is of great importance as its presence is directly correlated with prognosis and may lead to a change in treatment [60,61].

Detection of recurrence after prostatectomy

PSA rising after prostatectomy (theoretically zero three months after surgery) is a marker of biochemical recurrence. In most cases, surgeons wait until this PSA reaches a certain value (0.2 ng/mL on two consecutive assays) before declaring the recurrence and the question is then raised about its location and the need for additional treatment. This will be different whether the recurrence is localized in the prostatectomy bed, or if patient has lymph nodes or metastases. Pelvic MRI is increasingly requested to assess the prostatectomy bed because it is currently more effective than choline PET when the PSA is low (<1 ng/mL) and effective therapy is still possible. Several studies have shown that DCE-MRI sequences are particularly useful for the detection of recurrences as [62—64], in most cases, they lead to enhancement within the scar tissue.

Detection of recurrence after radiotherapy

Radiation induces changes in prostate tissue (atrophy, diffuse reduction in T2- and diffusion-weighted signal) that hinder the detection of recurrences on morphological sequences. Fibrosis and the decreased microvasculature of atrophic tissue will increase the contrast of a potential tumor recurrence which in most cases will be hypervascularized like the initial lesion. This makes the dynamic contrast-enhanced series a key element in the detection of recurrences, and MRI an excellent examination for this indication [65—69].

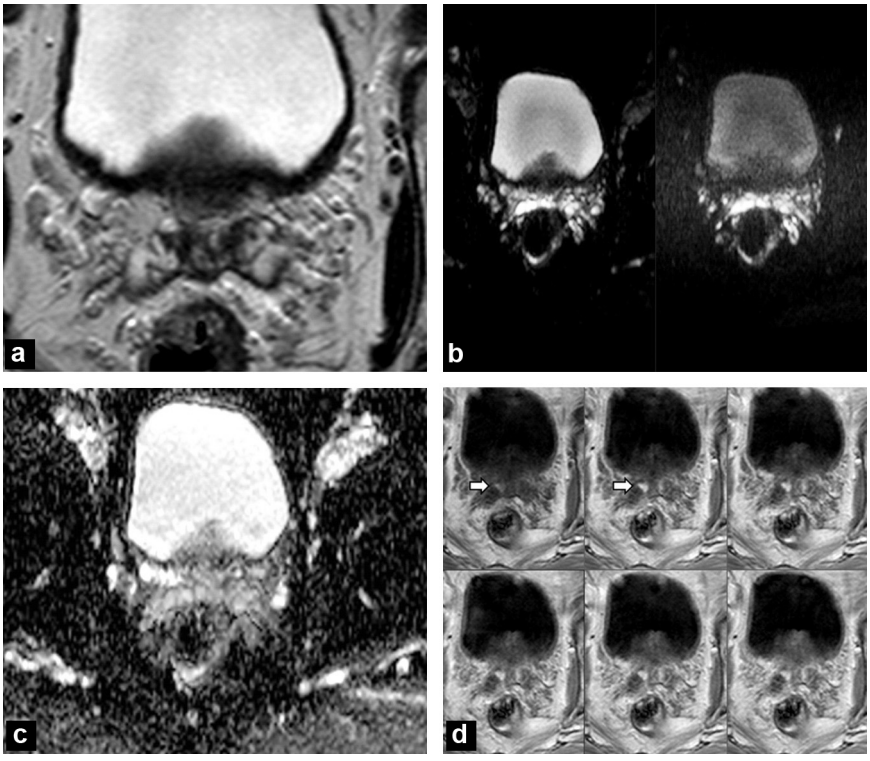

Figure 4. Value of the injection of contrast for the detection of initial seminal vesicle invasion. 66-year-old patient with elevated PSA of 35 ng/mL. MRI performed before a first series of biopsies, also showing a large lesion of the middle basal region (later found to be an aggressive lesion Gleason 4 + 3 = 7), for which an evaluation of seminal vesicle invasion is paramount. a) T2 TSE axial image through the lower part of the vesicles, b) DWI with b = 0 (left) and b = 600 (right), c) ADC map, b = 0—600, d) dynamic contrast-enhanced T1-weighted sequence at 6 earliest times, without subtraction. The dynamic sequence (d) showed early nodular contrast enhancement in the right seminal vesicle (white arrow), which was not detectable on the T2 sequence (a), where the vesicles appeared perfectly symmetric. There was no significant abnormality on DWI, which is usually unhelpful in this indication due to its low spatial resolution, frequent artifacts and noise.

Monitoring of focal treatments

New therapeutic options for prostate cancer (cryotherapy, vascular phototherapy, hi-intensity focused ultrasound, laser thermotherapy, etc.) usually require early monitoring of their efficacy (after 8 days in most protocols) and follow-up during time to detect any recurrence after treatment [52,70]. In these two cases, alterations on T2-WI and DWI sequences are not specific, whereas dynamic imaging is very informative: it shows hypovascular or necrotic areas, and allows the description of their topography, volume, and extension. Recurrences take the form of plaques of local contrast enhancement in the treated area or at its periphery, as seen after radiotherapy.

Why omit contrast-enhanced sequences? Plea for a ''standardized'' protocol

The omission of sequences with injection of a contrast agent is currently supported by four arguments:

- they do not provide a significant diagnostic gain and are therefore useless;
- they generate unjustified extra costs by making patients purchase a gadolinium-based contrast agent;
- the risks associated with the injection of this contrast agent are not justified;
- they increase the duration of the examination and make it less accessible.

However, this question has only really been raised because of the growing willingness of the urological and radiological communities to use MRI more broadly as a complement to prostate biopsy, for the benefit of patients who more easily accept screening (no endorectal insertion, pain, rectal bleeding, risk of infection etc.). For this, we must justify the medical economic benefit, as although there is a clear medical benefit [71,72] (Figs. 2 and 3), the additional cost of including MRI in the standard individual prostate cancer screening program remains open to question. We must therefore find new savings.

We have already discussed the significant contribution of contrast-enhanced sequences to the detection, localization, characterization, assessment of aggressiveness and staging of prostate lesions and we will not mention the increased duration of the examination which is negligible (5 minutes). Concerning the ''risk'' of the injection for patients, it may also be considered very low, as systemic nephrogenic fibrosis has become very rare since certain precautionary measures are taken and hypersensitivity reactions are rare [73–75]. We can therefore reassure patients about this.

The question of the additional cost is, however more concerning, because the cost of contrast agents is relatively high (about 80€, 20 to 30% of the total cost of the exam) and hampers the possibility of reimbursing the whole ''screened'' population, and consequently the indication of MRI for individual detection. We will not enter into a debate about a comparison of the cost of DCE-MRI with that of MRI a few years ago (with endorectal coil, longer exams etc, or with the new laboratory techniques that are already widely prescribed and much more expensive for a controversial benefit (PCA3). If this MRI screening is applied to the same population that currently undergoing transrectal biopsies, we can relativize the additional cost of contrast products by pointing out the potential savings that can made by including contrast-enhanced sequences:

- reduction in the number of unnecessary biopsy series after obtaining a more accurate diagnosis with optimal negative predictive value as the injection of contrast improves the detectability of lesions and diagnostic accuracy. How could the idea of a better quality examination than biopsies to detect significant cancer and exclude non-significant cancer, be defended without providing the means to obtain an optimum performance [1,6]? This might unnecessarily discredit MRI with urologists and patients and could be considered a backward step;
- a reduction in biopsy series during active surveillance, for the same reasons;
- the possibility of performing the whole preoperative assessment in a single session without repeating the examination if there really is a cancer at the end of this detection stage (staging requires a second MRI to assess ''extension''). The relevance of a two-stage imaging evaluation, may be asked with respect to the actual benefit for urologists and radiotherapists during the diagnosis disclosure visit, as they may not being able to propose a clear approach to their patients, due to suboptimal information (number of lesions, presence of other lesions modifying the therapeutic approach, and extracapsular extension and seminal vesicle invasion). The same is true for patients, some of whom may, by own their will or that of the therapist, not benefit from a more comprehensive assessment to further accelerate their management. This would again be a probably damaging backward step.

Standardization of protocols is one of the main strengths of prostate imaging at present. It is currently possible to perform a work-up to detect lesions and staging during a single examination under optimum conditions. The currently most widely used multiparametric protocol (T2, diffusion, perfusion) facilitates the implementation of the examination by teams of varying experience by harmonizing their performance and quality of service, increases the accessibility of the examination, the power of multicenter studies, the trust of urologists and patients by providing a reproducible assessment of their disease. The omission of DCE sequences within a brand new specific indication (called ''detection'' MRI) must be rigorously analyzed before being proposed as the medical risk may outweigh the supposed savings, especially as this diagnostic pathway would involve the performance of another complementary MRI if cancer is established and may, in case of sub-optimal performance, lead to the repetition of the examination and its discredit, reducing its readability (multiplication and complexity of protocols).

Conclusion

DCE-MRI is one of the cornerstones of the multiparametric MRI of the prostate. Its value to improve the detection and evaluation of the aggressiveness of the cancer has never been questioned in the literature simply because it highlights different histological features from those observed by T2-WI or DWI. It is also essential in the multiple indications

occurring during the management of prostate cancer by imaging (detection of recurrences, staging, follow-up of focused therapies etc.).

TAKE-HOME MESSAGES

- Multiparametric MRI of the prostate comprises complementary and synergistic T2, diffusion and perfusion sequences.
- Contrast-enhanced sequences significantly improve the accuracy of the examination for the detection and evaluation of intraprostatic tumor lesions.
- Omitting them increases the risk of not detecting some aggressive lesions and therefore discrediting prostate imaging by MRI.
- Contrast-enhanced sequences are essential in the following indications: detection of recurrences and follow-up after treatment.

Clinical case

This 66-year-old patient had an elevated PSA of 4.59 ng/mL versus 4.11 ng/mL 1 year previously. There were mild urinary functional signs. No history of urinary tract infection. The digital rectal examination found a soft prostate. MRI was performed before the first series of prostate biopsies. You do not know if the patient has cancer or not. Here is an image of a prostate axial section (Fig. 5).

Questions

1) How would you describe the images (use the Pi-RADS score if possible)?
2) Do you think this image is suspicious?
3) Why is this lesion not visible (or barely) on the T2-WI and DWI sequences?

Response

1) According to the ESUR 2012 guidelines, describing the first version of the Pi-RADS score [75], the lesion is located in the mid portion of the right lateral lobe (area 04p) (Fig. 6) [76,77], measures about 20 mm and has a Pi-RADS score of 6 or 7 out of 15 points; scored 2 points on the T2-WI (''poorly-defined hypo-intense T2 area'') + 1 point by DWI (''no signal reduction in ADC or increase in imaging with b-value > 800'') + 3 points by DCE (''type 3 enhancement − 3 points with focal appearance − + point''). Type 2 enhancement is possible (2 points), as the wash-out phenomenon is poor. The likelihood of extraprostatic tumor invasion is low (1 in 5), as there is no anomaly or irregularity of the prostate surface. Note the progressive enhancement (type 1) of the contralateral healthy prostate.
2) Despite the relatively indecisive nature of the Pi-RADS ''objective'' score, we can give the lesion a ''subjective'' score of 5 out of 5 (Fig. 7), as the contrast enhancement is very suspicious, asymmetrical, nodular and focal. There is no upper limit for the Pi-RADS score, which describes the sequences. Its prospective clinical validation is in progress. If the patient had a past history of urinary tract infection or clear functional signs a score of 4 out of 5 could be considered as a hypothetical focus of prostatitis could not be ruled out. Prostate biopsies showed two positive cores in the mid lateral and mid regions of the right lobe (4 and 8 mm Gleason adenocarcinoma 3 + 4 = 7 on two cores of 12 mm each). The guided biopsies were also positive and also showed perineural extension. All the other biopsies (10 cores out of 14) were negative.
3) Prostate tumor lesions have variable histological characteristics (degree of infiltration of the stroma, homogeneity, microvasculature, cell density, architecture, histological grade etc.) which are not always homogeneously visible on all sequences. Rosenkrantz et al. recently demonstrated that lesions visible on diffusion-weighted images were those that were hard to see on DCE images and vice versa. In general, lesions visible on T2-WI are also detectable on DWI, but their behaviour on DCE series is variable. Certain lesions are visible on T2-WI and DWI but not on dynamic series whereas, on the contrary, others that are only visible on the dynamic series, are almost invisible on non-contrast-enhanced sequences. The visibility of lesions also depends on the contrast with the surrounding tissue. When the prostate has a low T2 (chronic inflammation etc.), nodules are less contrasted and more difficult to detect. This case illustrates the importance of perfusion sequences for the detection of prostate lesions, particularly in the peripheral zone, and shows that diffusion-weighted imaging may not detect lesions of significant size and aggressiveness (Gleason 3 + 4 = 7 on 4 biopsies).

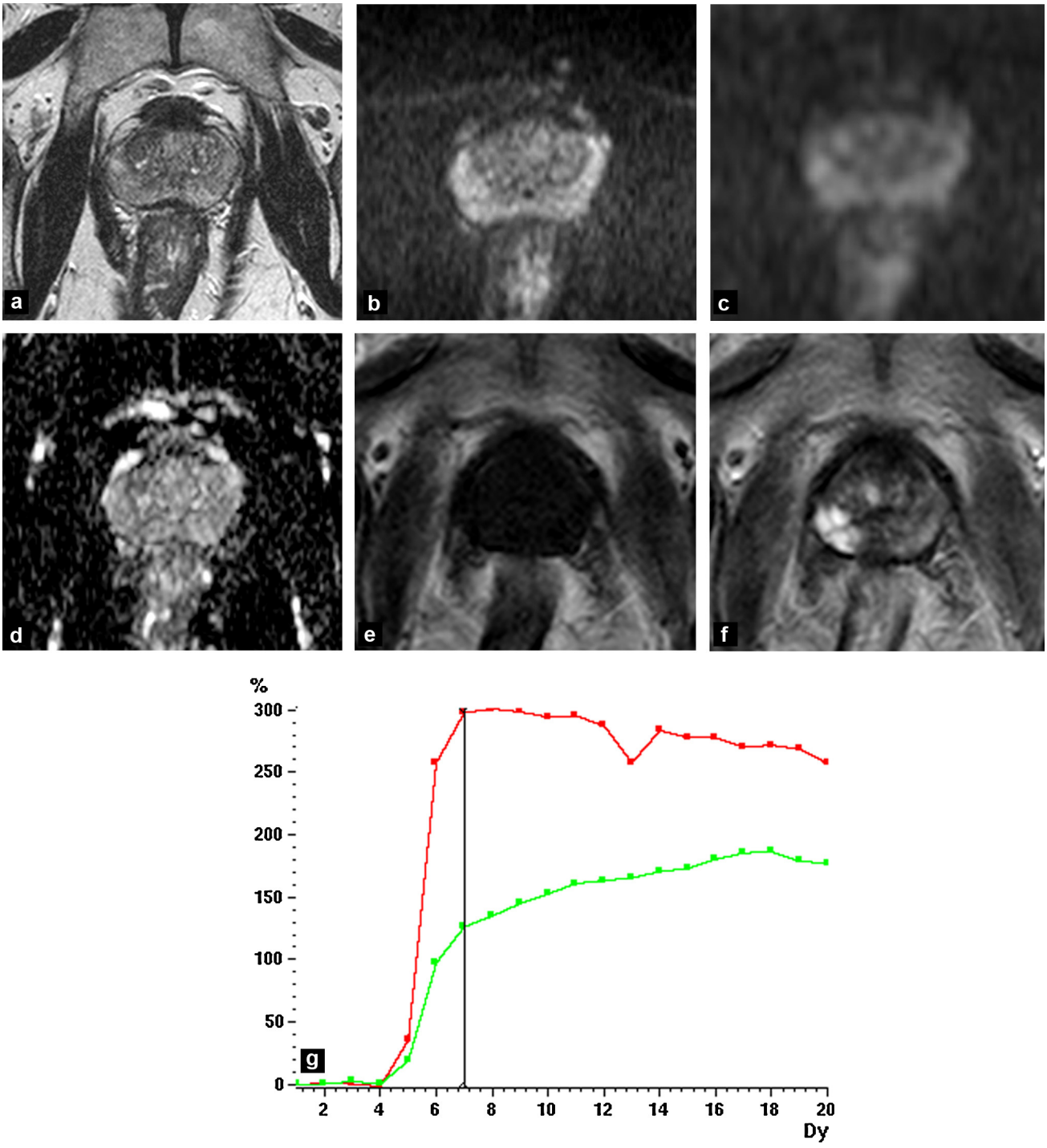

Figure 5. a) T2-weighted axial image. b) Diffusion-weighted axial image obtained with gradient b = 600, same slice. c) Diffusion-weighted axial image obtained with diffusion gradient b = 1000, same slice. d) Reconstructed ADC image with b = 0—600, same slice. e) Non-contrast-enhanced T1-weighted image; same slice. f) Dynamic contrast-enhanced T1-weighted image on the second series where the contrast is visible; same slice. g) Enhancement curves obtained on this slice; in red on the lesion in the hypervascular right peripheral zone; in green, on the contralateral peripheral zone.

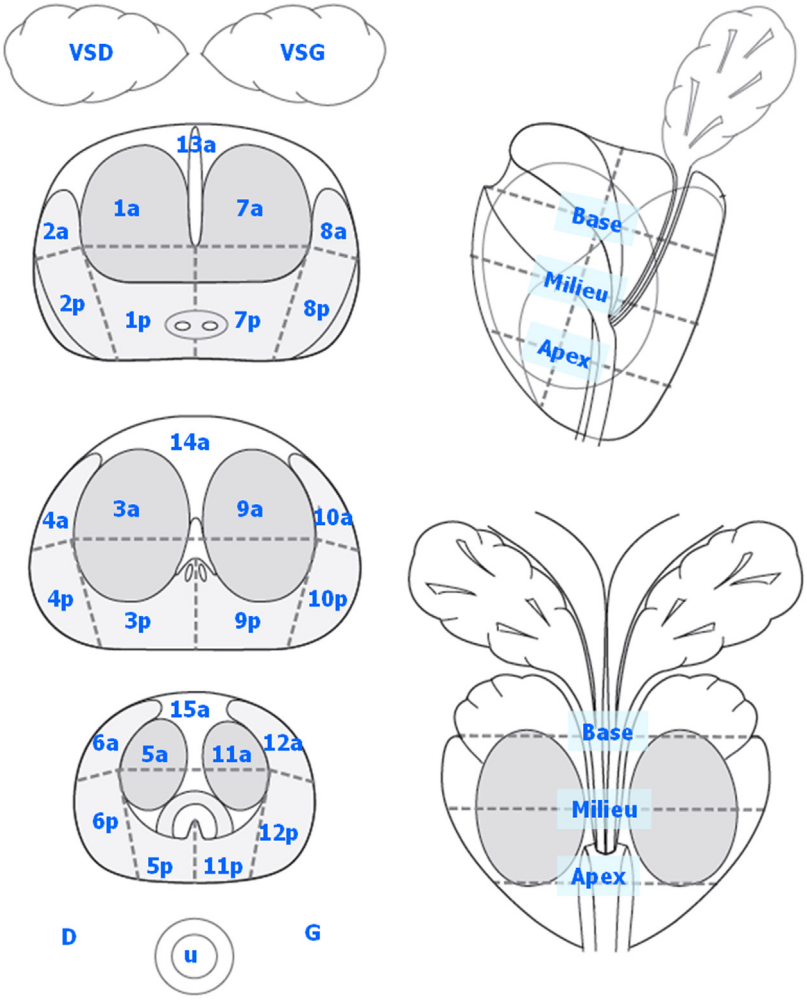

Figure 6. Recommended prostate partitioning scheme.

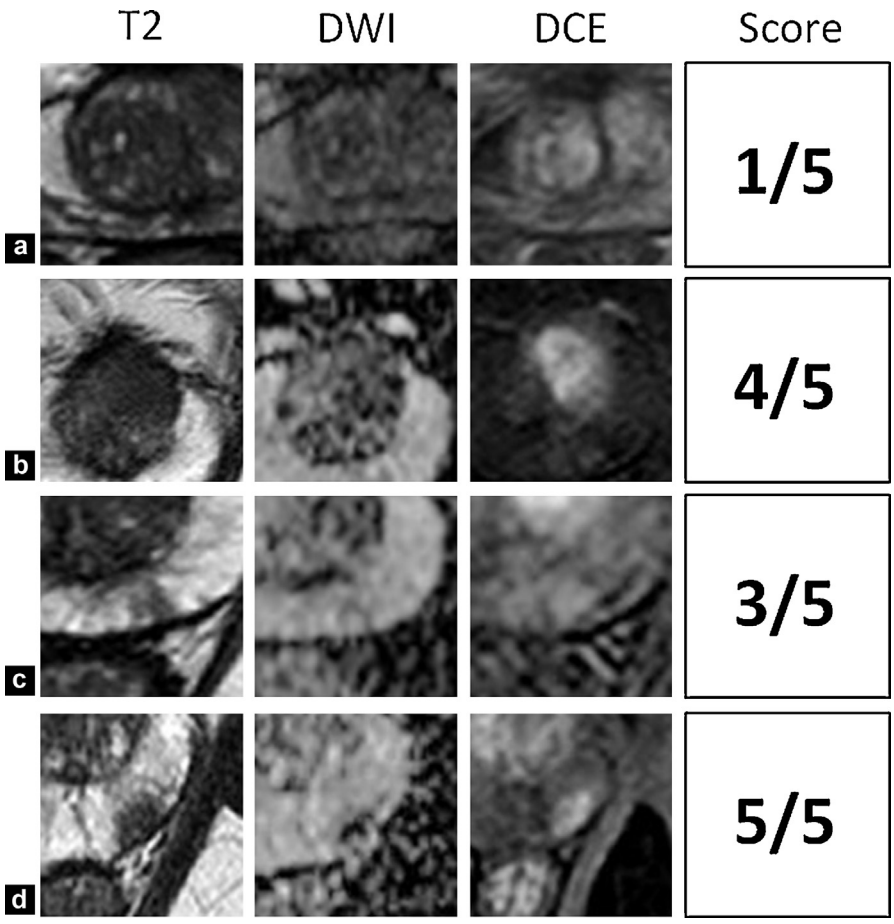

Figure 7. Evaluation of prostate lesions according to a score of from 1 to 5 (78). a) Nodular lesion of transition zone which is non-suspicious (1/5) despite its high vascularity due to a ''ringed'' appearance of the nodule by T2-WI and the absence of signal loss on the ADC map. Negative biopsies. b) Highly suspicious lesion (4/5) of left transition zone, because of its anterior location, homogeneous and asymmetric appearance relative to the rest of the adenoma by T2-WI and vascularity and despite the low restricted diffusion. If the diffusion image had been consistent, a score of 5/5 would be logical. Cancer confirmed by prostatectomy. c) Equivocal lesion (3/5) of the left peripheral zone, despite its isolated position in the peripheral zone, making it similar to the lesion visible in d). The hypo-intense T2 signal is unclear and not nodular; restriction of diffusion is low and contrast uptake is unpronounced with respect to the rest of the parenchyma. These findings are discordant. Finally, the perfusion and T2 sequences showed that this was a ''low suspicion'' lesion, so no decision could be made and it was deemed ''equivocal''. Prostatectomy confirmed the benign nature of this image. d) Very highly suspicious lesion of the left peripheral zone (5/5) due to its isolated nature in a normal peripheral zone, its nodular form and the deep and homogeneous hypo-intense signal on T2-weighted images. The restriction of diffusion and contrast enhancement is pronounced and nodular. All these findings are consistent and tend to impose a score 5/5 instead of 4/5. Lesion demonstrated by prostatectomy.

Disclosure of interest

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

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