MRI and prostate cancer: a paradigm shift

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Résumé
L’IRM du cancer de la prostate : un changement de paradigme
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Un changement de paradigme de l’IRM de prostate dans le diagnostic, l’extension et la planification prémédiative du cancer modifie sensiblement sa pratique depuis le début des années 2000. Classiquement orienté vers la recherche d’une extension extra-prostatique, cet examen a aujourd’hui une place au moment du diagnostic (ciblage du site de métastase chez un patient à PSA anormal chez lequel on suspecte un cancer hors des sites habituels de biopsie), au moment de la planification thérapeutique (cartographie intra-prostatique), pour le suivi des patients après traitement (recherche de récidive locale ou suspi après ultrasons focalisés, radiothérapie, thérapie focale…). Les protocoles d’imagerie à 1,5 ou 3T combinent l’imagerie morphologique en T2 à des séquences fonctionnelles (imagerie de perfusion, imagerie de diffusion, spectroscopie) en utilisant des antennes pelviennes en réseau phasé de haute résolution ou « combinées » (en ajoutant une antenne endorectale). Pour être accepté par les cliniciens et plus largement accessible aux patients, cet examen doit préciser ses indications (notamment en se rapprochant des questions que se posent des urologues), devenir moins coûteux, plus reproductible, et standardiser la présentation de ses résultats.


Abstract
A shift in the use of prostate MR for diagnosis, staging, and pre-treatment planning over the last several years has modified the MR protocols. Classically used to detect extra-prostatic tumor, MR now plays a role for diagnosis (pre-biopsy evaluation in a patient with elevated PSA and suspected cancer in an unusual site), treatment planning (prostate mapping), and follow-up after treatment (evaluation for local recurrence or follow-up after HIFU, radiation therapy, or focal treatment…). Imaging protocols at 1.5T and 3.0T combine morphological T2W imaging with functional sequences (perfusion imaging, diffusion imaging, spectroscopy) using high-resolution phased array pelvic coils or “combined” coils (added endorectal coil). To promote acceptance by clinicians and increased access to patients, the indications for prostate MR must be better defined (and provide useful data to urologists), the cost must be reduced, and results must be more reproducible and standardized.

Key words: MRI. Prostate. Cancer. Diagnosis.


From its development in the 1990s until today, MRI has been a useful tool in the management of prostate cancer. Endorectal coils, initially alone, then combined with phased-array surface coils have enabled increasingly accurate evaluation of extra-prostatic extension of prostate cancer and T2W MRI has progressively established its role for local staging of prostate cancer (1-3), even though some have questioned its usefulness (4). However, MRI is increasingly being used for a different indication: detection and localization of intra-prostatic foci of tumor. This new interest for accurate tumor mapping is due in part to emerging clinical needs (guidance for biopsies in patients with normal digital exam and elevated PSA, follow-up of tumors too small to justify aggressive therapy, guidance for minimally invasive biopsies, etc.), and in part to the availability of newer imaging sequences enabling improved differentiation between tumoral and normal tissue (dynamic MRI (5-7), spectroscopy (8, 9), and recently, diffusion weighted MRI (10-12)). The availability of these new sequences has coincided with the arrival of a new generation of phased array surface coils, initially developed for cardiac imaging, with reduced field of view allowing the acquisition of high resolution T2W images of sufficient quality and homogeneity to evaluate the entire prostate now enabling mapping of lesions. The good results achieved in the detection and localization of cancer foci using these phased array surface coils (6, 13) has led some groups to discontinue the use of an endorectal coil (for multiple reasons (14), including its high cost). This new paradigm explains the particularity of what some had named the “French exception” (14), even though also practiced by foreign centers both at 1.5T and 3.0T MR imaging (15-18).

MRI and local staging: indications

The value of high resolution T2W imaging for pretherapeutic local staging of biopsy proven lesions was demonstrated...
(1, 19, 20), but several elements have impacted its usefulness for this indication alone:
- the variability of results with sensitivity values between 13% and 95% for detection of extracapsular spread and 25% to 71% for seminal vesicle invasion. The overall accuracy of MRI to differentiate between stages T2 (intraprostastic) and T3 (extraprostastic) varies between 54 and 93% (mean of about 70%) (20-22),
- microscopic criteria for extraprostastic extension of tumor remain the subject of discussions between pathologists (23-25). They differentiate between “focal” (rare extraprostatic neoplastic glandular tissue) and “established” prostatic capsular invasion (23, 24). While the accuracy of these criteria remains a subject of debate, the degree of extension is described based on the radial distance (perpendicular to the prostate surface) of tumor tissue extension with a 0.75 mm threshold for prognostic index. Tumor extension may be confluent or characterized by small islands of tumor within the periprostatic fat, further increasing difficulties in histological interpretation (26).
- the existence of more reliable prognostic factors, including tumor volume and presence or absence of positive surgical margins (28-31). The surgical margins can only be assessed after prostatectomy, but some authors have suggested that imaging could be helpful for surgical planning in order to reduce the rate of positive margins (32),
- good long term results from surgical management of advanced cancers (T3a or T3b) (33-36).

Several studies have demonstrated that local tumor staging with MRI for prostate cancer was only useful in patients with “intermediate” to “high” risk of recurrence after radical prostatectomy (table I) (37), because in patients with “low” risk (initial PSA ≤ 10 ng/ml, stages T1c to T2a disease and Gleason score 6 or less), the likelihood of pT3 cancer is low, and when present, it is usually microscopic and not detectable on imaging, irrespective of the modality or technique (3, 22, 38). In such cases, corresponding to most patients (39), the value of MRI for local staging is debatable.

Because of these limitations, MRI tends to be used for detection of “established” or “extended” extracapsular spread (fig. I). Results on MRI for macroscopic extracapsular extension are good: Jager, et al. (40) reported a sensitivity of 100% for detecting capsular penetration more than 3 mm, 67% for detecting capsular penetration 1-3 mm, and 14% for detecting capsular penetration less than 1 mm using endorectal MRI. As such, capsular penetration < 1 mm does not appear to be detectable on imaging, either MRI or US. However, minimal capsular penetration may not be a contra-indication to radical prostatectomy, and the absence of such minimal capsular penetration on MRI may not have an impact on the definitive prognosis. The situation of patients that are candidates to brachytherapy is different and it is preferable, in such cases, to have the most sensitive examination to detect the presence of capsular penetration, even minimal.

### Detection of cancer prior to biopsy: an emerging indication

#### Early diagnosis, “indolent” cancer and overtreatment

Prostate cancer is the most frequent cancer in males (over 40,000 cases per year in France). It is probable that its incidence will increase due to the aging population and PSA screening. Over the last 20 years, the profile of patients with prostate cancer has markedly changed. Screening with PSA has resulted in a drop in palpable cancers from 91% to 17% and a drop in mean tumor size on surgical specimens from 5 cc to less than 2 cc (39).

However, early diagnosis of cancers may lead to potential overdiagnosis (and overtreatment) of otherwise very slow growing tumor foci. Large series of total prostatectomy or cystoprostatectomy (30, 41, 42) have demonstrated the multifocal nature of prostate cancer and the large proportion of occult cancers of small volume, which, given the doubling time of such tumors [about 4 years for localized low grade tumors (43, 44)], will never have any clinical impact. Urologists have thus sought to define threshold values for tumor volumes to assist in therapy planning: above 4 cc (about 16 mm in diameter), it can be assumed that the tumor has outgrown its zone of origin, and has a metastatic potential with more than 3.2 cc of Gleason histologic pattern 4-5 cancer (30, 42). Above 0.5 cc (about 10 mm in diameter), the risk of morbidity and mortality significantly increases (30, 45, 46). Tumors smaller than 0.5 cc are thus considered indolent in the absence of Gleason histologic pattern 4-5 cancer. In the study by Cheng (47), small volume tumors were multifocal in 69% of cases and bilateral in 37% of cases. The threshold detection tumor volume by digital exam and imaging is 0.2 cc (about 7 mm in diameter) (6). All of these results raise questions about the significance of some cancers exposing patients to the risks of overdiagnosis and overtreatment, which has prompted the controversial approach of watchful waiting or active surveillance (45).

The challenge of imaging, especially MRI, is to offer a solution allowing early diagnosis while avoiding unnecessary overtreatment by detecting significant lesions (volume > 0.2-0.5 cc, Gleason score ≥ 6) and direct biopsies to suspicious lesions (48, 49), as suggested by some authors in the US literature (50). Do current advances open the way for MRI in the early detection of prostate cancer as a second line modality after biological diagnosis and prior to biopsy?

#### How can MRI allow early diagnosis of prostate cancer?

By improved detection of tumor foci?

Most studies evaluating the accuracy of MRI in detecting prostate cancer were based on correlation with prostatectomy specimens. The accuracy of detection on T2W images is disappointing, between 52 and 76% (40, 51, 52) for peripheral zone tumors. It is logical to believe that, due

| Table I Predicting the risk of local failure after prostatectomy (37). |
|---------------|------------------|------------------|------------------|
| Low risk      | Stage T1-T2 and PSA ≤ 10 ng/ml and Gleason score ≤ 6 |
| Intermediate risk | PSA between 10 and 20 ng/ml or Gleason score = 7 |
| High risk     | Stage T3 or PSA > 20 ng/ml or Gleason score ≥ 8 |
to the provided metabolic information, spectroscopy would improve the accuracy of MRI to detect cancers. A study of 53 patients treated by radical prostatectomy has suggested that the combination of T2W images and spectroscopy could provide positive and negative predictive values for the detection of cancer per sextant of 88-92% and 80-86% respectively, based on the reviewer (9). Such good results are not confirmed by all groups, and when strict interpretation criteria are used, the accuracy of T2W imaging and spectroscopy may be as low as 37% (53). It appears that MR spectroscopy would improve detection of more aggressive cancers: in the study by Zakian, et al., 89% of nodules with Gleason score ≥ 8 were detected by spectroscopy compared to 44% of tumors with Gleason score of 6 (54).

Dynamic contrast-enhanced MRI significantly increases the accuracy for localization of tumor foci compared to T2W imaging, either with integrated pelvic and endorectal coils (7) or without the use of an endorectal coil (55). This seems to relate to improved sensitivity without reduction in specificity. In a study on 49 patients prior to prostatectomy, the rate of detection of tumor foci > 0.3 cc was, based on readers, from 49.6% to 60.3% on T2W images and from 77.7% to 81% on dynamic MRI (13). Aggressive tumors are also better depicted: in the same study, the detection rate for tumors with Gleason score ≤ 6 was 30-34%, the detection rate for tumors with Gleason score of 7 was 77.5-81%, and the detection rate for tumors with Gleason score ≥ 8 was 96-97%. In a series of 93 patients with dynamic MRI (using a pelvic coil) prior to biopsy, evaluation of the prostatectomy specimens showed that the threshold volume to detect 95% of tumors was 0.33 cc for the peripheral zone and 0.52 cc for the transition zone (fig. 2) (56).

Diffusion weighted imaging, especially when combined with T2W, T2W and dynamic T1W, or T2W and spectroscopy improves the accuracy of MRI in the detection of cancers (12, 57-59); its exact role is not yet defined.

For biopsy guidance?

For this application, MRI must show good sensitivity to not miss aggressive cancers and good negative predictive value. Specificity is less of an issue since low specificity would lead to additional biopsies, which do not seem to increase the morbidity of the procedure (60). The Stanford technique of prostate mapping with 6 cores (61) was sufficient when most cancers were palpable, but this no longer is the case (62). Even currently proposed protocols with 10-12 cores (63) do not formally exclude the presence of cancer: 17-21% of patients with negative initial biopsies (10-12 cores) will show tumor at repeat biopsy (64). The addition of routine anterior zone biopsies only improves the accuracy by 2% (65). Recently, saturation prostatic biopsy (up to 45 cores) was proposed in patients after a first series of negative biopsies (66-68). Another approach could be to use imaging to direct biopsies towards suspicious lesions instead
of simply multiplying the number random biopsies (6): A recent study (69) using a high-resolution surface coil has shown that MRI could detect anterior tumors (fig. 3) typically undetected with random biopsies, thus confirming the work by Li (16). Several studies have also demonstrated that MRI could increase the sensitivity of biopsies in patients with abnormal PSA and negative biopsy, especially when T2W imaging was associated with at least one functional imaging technique: dynamic MRI (70) or spectroscopy (71). It would appear that multiparametric MRI (72) could become a valuable tool to direct prostate biopsies because of its higher sensitivity for aggressive tumors (large volume, high Gleason score), good negative predictive value (13) and its ability to detect anterior tumors that are frequently missed on random biopsies (69). Finally, the technique of MR-guided biopsy should also be discussed because when lesions detected on MRI are not visible on US, it may be difficult to guide the biopsy (fig. 4) to the site of lesion on MRI. Some false negative results may be due to such errors in guidance. To avoid this pitfall, some authors have proposed to perform MR-guided biopsies. While this technique is possible (71), it is technically challenging, requires a dedicated interventional MR unit, and would probably not be routinely available. The development of “co-registration” software for US and MR images seems to be a more realistic solution (73).

**Therapeutic planning**

MRI has been used for a long time to evaluate extraprostatic extension of cancers and triage patients to surgery, radiotherapy or palliative treatment. Accurate mapping of suspicious lesions on MRI or even gross estimation of tumor volumes were not felt to be priorities because they had no impact on the surgical technique of prostatectomy or radiotherapy. It was only performed from prostatectomy specimens (30) for morphometric tumor evaluation.

**Why lesion mapping?**

Tumor mapping may assist in surgical (selection of surgical technique, approach, type of dissection) and radiotherapy (conformal radiotherapy with higher dose on the tumor) planning by depicting the relation between tumor and neurovascular bundles for peripheral zone tumors and the bladder neck and anterior fibromuscular stroma for transition zone tumors. The purpose is to reduce morbidity (incontinence and erectile dysfunction) from these “radical” treatments while providing effective treatment (74). It was recently recognized that pretreatment
Fig. 3: PSA of 14.91 ng/ml in 2008 – negative digital exam – 2 series of negative biopsies in 2004 and 2005 (PSA of 9.4 ng/ml in 2005).
Prebiopsy MRI: detection of a suspicious T2W hypointense lesion in the anterior fibromuscular stroma (a), with abnormal enhancement (b) and reduced ADC value (c). Standard systematic biopsies were negative whereas 3 directed biopsies to the anterior fibromuscular stroma were positive (Gleason 3 + 3 = 6). Comparison of the localization, shape and size of the lesion on MRI and the tumor map generated from the radical prostatectomy specimen (d).

Fig. 4: PSA of 11 ng/ml; negative digital exam – prebiopsy MRI:
an Detection of a suspicious T2W hypointense lesion,
b-d early asymmetrical contrast enhancement (b: before injection; c: earlier postcontrast phase; d: postcontrast images 11 after c), 
e decreased ACD on the ADC map. Standard systematic biopsies showed microfocus of tumor (1 mm; Gleason 3 + 3) on the core obtained from the mid right lateral prostate whereas only one of two directed biopsies to the suspicious lesion was positive with a length of 4 mm of 12 mm and Gleason score of 7 (Gleason 3 + 4).
tumor mapping of intraglandular prostate cancer was needed for treatment planning, guidance, and mostly for early evaluation of treatment efficacy from emerging focal or subtotal treatments (75). These treatments (brachytherapy, HIFU, cryotherapy, phototherapy, thermotherapy, ...), with the sole objective of treating the tumor foci while avoiding a radical approach, have pushed further the limitations of imaging: evaluation of tumor size (diameter, surface or volume), localization and number of tumor foci (> 0.2 cc) within the gland are now necessary elements for both pre- and post-therapeutic assessment (76).

Is MRI accurate for tumor mapping?

To perform tumor mapping for lesion follow-up is more demanding than to simply guide biopsies because two conditions must be met: excellent sensitivity to detect all significant tumor foci to be treated or persisting after treatment; excellent negative predictive value to confidently exclude local tumor recurrence. Currently, only “blind” saturation prostate biopsy protocols from a transperineal approach (68) meet these requirements; transrectal biopsy protocols do not allow accurate sampling of the entire gland. Multiparametric MRI (72) is an attractive potential alternative by combining different morphological and functional techniques (10, 12, 57), it may achieve an accuracy (area under the curve) comparable to saturation prostate biopsy. MRI could thus become a comprehensive imaging modality that would allow diagnosis of cancer (biopsy guidance), selection of the best therapeutic option (local staging), as well as evaluation and follow-up of treatment response (comparison of pretreatment and follow-up tumor maps).

Detection of tumor recurrence

PSA surveillance after radical prostatectomy, radiotherapy or focal therapy (brachytherapy and HIFU) allows detection of patients at risk for recurrence. While imaging confirmation of local recurrence in patients with increasing PSA levels after radical prostatectomy may not be necessary (77), tumor localization may be achieved with MRI. After HIFU or radiotherapy, salvage therapy may be available (78, 79). This underscores the need for early detection of tumor recurrence and early mapping of tumor recurrence (fig. 5). After radiotherapy, the prostate appears diffusely T2W hypointense, with loss of zonal anatomy (80), reducing the usefulness of this sequence. On the other hand, dynamic MRI with pelvic coil alone (81) and spectroscopy with endorectal coil (82) show excellent results for early diagnosis and localization of local recurrence after radiotherapy. Preliminary results suggest that dynamic MRI would provide accurate localization of recurrent tumor after HIFU (83).

Methodological considerations

We believe that it is important to review such considerations to improve the quality and reproducibility of prostate MRI in order to meet the new objectives of prostate MRI.

Protocol standardization

Choice of coil

Latest generation pelvic coils allow reduced field of view examinations (16 cm), with spatial resolution of 0.55 × 0.7 × 3 or 4 mm on TSE T2W sequences (similar to an endorectal coil) (fig. 6), 1.25 × 1.31 × 4 mm on dynamic GRE T1W sequences, and 1.2 × 1.55 × 4 mm on diffusion weighted sequences. The acquisition time is less than 5 minutes for 15 T2W images, unlike what was previously reported (14) and a complete examination is about 30 minutes (excluding spectroscopy). Examinations performed using such coils cannot be compared to examinations obtained using first generation coils (84, 85) with some authors recently reporting mediocre results for local staging (14, 86), but results with both generations of coils are frequently confused. A recent study by Futterer, et al. (86) on 81 patients imaged on a 1.5 Tesla scanner has demonstrated the usefulness of combined endorectal and pelvic coils (integrated coil) for local staging, but imaging with the pelvic coil alone was acquired at low resolution (240 pixel matrix for a 280 mm field of view, for a voxel of 1.17 mm). The study by Heijmink (87) on 81 patients imaged on a 3.0 Tesla scanner demonstrated no significant difference between both coils for tumor localization, except in the transperineal zone, where the pelvic coil was clearly superior, in spite of a lower spatial resolution (half, or 0.44 × 0.44 × 4 mm). While awaiting results from rigorous comparison of both coil systems, mainly to ascertain the value of the added endorectal component compared to a high resolution pelvic coil (smaller field of view), the integrated endorectal-pelvic coil system should be considered as the gold standard for staging of posterior tumors and spectroscopy (86). For all other criteria (perfusion imaging, diffusion imaging, global gland evaluation...), pelvic coils are superior, which is why most groups recommend using the integrated endorectal-pelvic coil as opposed to an endorectal coil alone. This option seems logical when performing MR imaging of the prostate for local staging and/or perform multiparametric imaging including spectroscopy, as used in several centers across the Atlantic. On the other hand, it may not be necessary if MRI staging is not the primary goal and imaging is performed more for characterization of prostate cancer. As long as the pitfalls of the endorectal coil are not resolved (added cost of 100 euros per examination, technical failure in 10% for the rectal approach and failure rate of 10-30% for spectroscopy, discomfort, prostate compression that may interfere with post processing...), and that its added value is not convincingly demonstrated, we believe that if may be premature to draw conclusions on the “best” technique (14).

Coil position and imaging planes

Placement of a high resolution surface coil with field of view of only 160 × 160 is as important as placement of an endorectal coil to cover the gland from base to apex as well as seminal vesicles. Multiparametric evaluation relies on strict concordance between the imaging planes of the different sequences (morphological, dynamic and diffusion). The use of an axial oblique plane perpendicular to the posterior surface of the prostate facilitates comparison between MRI and prostatectomy specimen.

Limiting biopsy related artifacts

Hemorrhage (detected on noncontrast T1W images) may persist up to 8 weeks after biopsy (88) and it is suggested that MRI should only be performed after that time, which may not always be easy to achieve in clinical practice. Ideally, MRI

Fig. 5: 61 year old patient treated with combined radiotherapy-hormonotherapy 6 years previously for prostate carcinoma. The initial PSA was 23 ng/ml. The patient is referred for PSA failure at 2.6 ng/ml (after a nadir < 1 ng/ml). The rectal exam was normal. MRI is obtained prior to biopsy. T2W images (a-c) abnormal prostate signal with loss of zonal anatomy. A possible T2W hypointense nodule may be present in the transition zone on the right, at the border of the peripheral zone (arrow). Dynamic images (d-f) show that the nodule is clearly hypervascular, whereas the remainder of the prostate shows little enhancement. Directed biopsies to the right transition zone showed recurrent tumor Gleason 7; biopsies in other sextants were negative.

Fig. 6: Comparison of axial T2W (a and b) and noncontrast T1W (c and d) images obtained in a patient with a high-resolution pelvic coil (a and c) and an endorectal coil (b and d) at 3 months interval, in two different centers. Note the good depiction of the prostate margins and neurovascular bundles with both techniques, both also the differences in signal intensity and homogeneity on T2W and T1W images between both coils, as well as prostate compression by the endorectal coil.
would be performed prior to biopsy to avoid post-biopsy artifacts from hemorrhage and inflammation (6, 89).

**Quality control**

Accurate evaluation of the technical quality of the examination (presence of artifacts, quality of signal) could have an impact on the diagnostic confidence in patients with negative MRI.

**Interpretation criteria**

Reproducibility depends on the reviewers and their experience (90, 91), similar to other areas of imaging, and also on their level of clinical activity (92). The notion of reproducibility is discussed in publications describing the experience of reviewers by the number of years in a given area of imaging. The degree of subspecialization within groups is an important element. Reproducibility also raises a question about double reading when MRI is used for early diagnosis. An approach could be to develop a list of interpretation criteria with degree of suspicion similar to what is available for breast imaging (92, 94). A suspicion score on a scale of 1 to 5 (score 1: normal, score 2: probably benign, score 3: suspicious or indeterminate, score 4: probably cancer, score 5: cancer) is sometimes used in publications dedicated to the MRI evaluation of the prostate (53, 95). A scoring system could be proposed for prostate cancer based on morphological and functional criteria including perfusion (96), diffusion (10) and spectroscopy (97) after validation by the scientific community. Our group currently is working on developing computer-assisted diagnosis software integrating this type of approach (96). Similar criteria are proposed for MRI evaluation of seminal vesicle extension (98).

**Evaluation of results**

The first step in using MRI as a diagnostic tool not limited to TNM staging is to validate the value of the newer sequences (morphological, dynamic, diffusion, perfusion) individually or in combination (two, three or four). Validation requires correlation between MRI and prostatectomy specimens while not ignoring the limitations of histopathological analysis (26). This correlation requires the generation of tumor maps on MRI (example: 12 posterior sectors, 12 anterior sectors, and 1 sector for the anterior fibromuscular stroma) depicting the localization, imaging features, and volume of detected lesions duplicating what is done for transperineal biopsies (68). This could be reported using a standardized grid allowing easy correlation with pathological findings. This grid could be a tool in the interpretation of MR images. Evaluation of the specificity, as well as positive predictive value and negative predictive value, of MRI for prostate cancer remains problematic because prostate sampling from biopsies is too low. Theoretically, validation of the specificity and negative predictive value of MRI cannot be determined without correlation with radical prostatectomy specimens, even for patients without cancer. As a solution, complete mapping of the prostate from a transperineal approach may be proposed as an alternative gold standard (68). The definition of the sectors used for analysis would preferably be achieved by consensus both for imaging diagnosis and evaluation of response to focal therapies.

**Conclusion**

This paradigm shift of MRI for diagnosis, mapping and treatment planning modifies the practice of prostate MRI requiring this technique to become accessible, affordable and reproducible. The use of a high resolution phased array pelvic coil allows MRI to meet these requirements by easily combining morphological, perfusion and diffusion data (awaiting for spectroscopy to become widely available at 3T using surface coils). Some aspects must still be evaluated before justifying the role of MRI in the management of prostate cancer, and maybe, eventually consider MRI as a valuable tool for screening and active follow-up. The first aspect would be to determine the true negative predictive value of MRI from rigorous standardized comparison of all MRI techniques individually or in combination to biopsy maps of patients at risk. The second aspect would be to determine the sensitivity of MRI for detection based on tumor volume and localization, which can only be achieved by large series comparing MRI results to prostatectomy specimens.

**Conflict of interest**

None.

**References**


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