The role of 3T MRI in the detection of prostatic cancer local recurrence after radical prostatectomy and radiotherapy

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Purpose

Prostatic cancer is the most frequent malignant tumor in over-50 male population. It is the second cause of cancer-related deaths in the US, right after lung cancer. Over the past 20 years, therapeutic strategies against localized prostate cancer have developed considerably. Classic treatment methods, as radical prostatectomy and external radiotherapy, have been associated with new ones, as brachytherapy, cryotherapy, focused ultrasound ablation and photodynamic therapy. [1-3].

The most frequently used local therapies for prostate cancer are radical prostatectomy and external beam radiation therapy. While these primary therapies are associated with a significantly high cancer control rate for localized disease, up to 33% of these patients will incur in a biochemical recurrence after local therapy [4].

Biochemical recurrence

Biochemical recurrence is characterized by a rising serum prostate-specific antigen (PSA), with or without evidence of clinical or radiological metastasis. Prostate-specific antigens are evaluated every 3 months after surgery. Serum PSA should reach undosable levels within 4 weeks in patients undergoing radical prostatectomy. A detectable PSA level may indicate the presence of benign prostatic tissue left after surgery, and a serial evaluation of PSAs can help to understand its clinical significance. Patients with biochemical recurrence can present a variable clinical course, from indolent course with no adverse long-term effect on their survival, to a rapid clinical progression, with bone metastasis and increased mortality risk.

Since an isolated detectable PSA level after radical prostatectomy does not indicate biochemical recurrence, several studies have evaluated if specific PSA cut-offs could define it. The European Association of Urology guidelines define biochemical recurrence with both a post-surgical PSA cut-off of 0.2 ng/ml, and two sequential PSA values # 0.2 ng/ml. The PSA Working Group defined biochemical recurrence with a PSA cut-off # 0.4 ng/ml with a subsequent higher level [5]. Following radiation therapy, PSA levels may not decrease to undosable levels and may settle at a stable detectable level. Further, PSA fluctuations are common in the first 2 years after radiotherapy, and the median time to PSA nadir is 18 months: the Phoenix criteria for post-radiotherapy biochemical recurrence indicate a PSA increase # 2 ng/ml above nadir [6].

Biochemical recurrence may be sign of local or metastatic recurrence: patients with localized recurrence may be managed with localized salvage therapies, while patients with metastatic recurrence need a systemic approach. For these reasons, the evaluation of patients with biochemical recurrence is primarily aimed at differentiating between local and metastatic recurrence, by analyzing absolute PSA level, PSA kinetics and time to recurrence, and by using multivariable prediction tools, bioptic tools and, of course,
imaging. A limitation in evaluating patients for salvage therapy is the absence of a reliable imaging modality to accurately select men with locally recurrent disease. New imaging modalities such as radioimmunoscintigraphy have shown disappointing results, and PET data are still limited and evolving. Magnetic resonance imaging is a modality which seems to be capable to define locally recurrent disease.

MRI recurrence after radical prostatectomy and after radiation therapy

In T2-weighted images of patients who underwent radical prostatectomy, peri-urethral fibrosis appears as a layer giving a homogeneous hyposignal. however, it is dynamic MRI that differentiates well between local recurrences and postoperative fibrosis.

A T2-weighted MR image of patients who underwent radiotherapy shows the prostate with a diffuse area of low signal intensity, with loss of differentiation between the peripheral and transition zones, and detection of recurrences (which also appear as an area of low signal intensity) remains difficult. On the other hand, dynamic MRI, that presents excellent contrast between the recurrence (which is often hypervascular) and post-radiation fibrosis (hypovascular) has given very promising results: indeed, it correlates well with biopsy result and has a good inter-reader agreement [7]. Spectroscopy (MRSI) could be of assistance, as the reappearance of a choline peak seems to be a good sign of recurrence. Diffusion imaging (DWI) also appears to show recurrence. Its association with T2-weighted MRI increases the detection sensitivity from 25% to 62% and specificity from 92% to 97% [8,9].

Purpose

The purpose of our study was to achieve an early and precise detection of local recurrence following radical therapy using MRI, and to correlate such radiological findings to Gleason score and to seriate PSA serum values.
Methods and Materials

This was a retrospective single-institution study approved by our institutional Committee on Human Research with waiver of the requirement for informed consent. We performed a computerized search of our institutional prostate cancer patients database and identified all patients who had biopsy-proven cancer prior to radiotherapy and/or radical prostatectomy between May 2010 and May 2012 (n = 62). Age of patients ranged from 50 to 84 years (mean age 69 years). All patients underwent histological (Gleason Score) and biochemical (seriat PSA) evaluation. 26 patients underwent radical prostatectomy; 36 were treated with external beam radiotherapy (60-70 Gy on the prostate and 40-50 Gy on regional lymphnodes). All patients showed evidence of biochemical recurrence.

MR studies were performed with a 3-Tesla whole-body MR scanner. Patients were scanned in a supine position using a multichannel phased-array coil. MR imaging sequences included thin-section high spatial resolution sagittal, axial and coronal T2-weighted fast spin-echo images (thickness: 4mm; FOV 260mm; matrix: 320x512; TR 3000ms; TE: 120ms), axial DWI images (b-value: 50-350-800) and axial GRE 3D T1-weighted FS dynamic images (FOV: 260mm; matrix: 192x256; high temporal resolution: 4.9sec) of the prostate and seminal vesicles. Two radiologists with 15 years of experience in the interpretation of MR imaging of the prostate, reviewed all images. Readers were aware that patients had biopsy-proven prostate cancer treated with radical prostatectomy or radiotherapy and also aware of all clinical and histopathological findings. Readers reviewed MR images in consensus and recorded the presence, location and size of unequivocal dominant recurrent tumors and pathological lymphnodes.
Results

We detected local recurrence in 20 patients (6 treated with radical prostatectomy and 14 treated with external beam radiotherapy) out of 62 (26 underwent surgery, 36 underwent radiation therapy). Diagnostic criteria for lymphnodes included their size (we considered lymphnodes with diameter>10mm as expression of local recurrence) and restricted diffusion on DWI sequences.

The group of patients who underwent radical prostatectomy showed local recurrence in 23% (6 out of 26 patients) of cases: early relapses were more often associated with an aggressive primary tumor and showed an higher risk of metastatic disease with subsequent worst outcome. Risk of local recurrence was higher in patients with an elevated Gleason score at first diagnosis.

Radiation therapy is intended to be a radical and definitive treatment: however, the group of patients who underwent external beam radiotherapy showed a biochemical increase of PSA serum level followed by a radiological recurrence in 39% (14 out of 36 patients) of cases. In addiction, in the remaining 61% of the patients with biochemical recurrence and negative MR, a systemic micro-metastatic recurrence couldn't be excluded.
Fig. 1: 70-years-old patient with previous prostate cancer, presenting with increasing PSA level after radical prostatectomy. Axial T2-weighted MR image (A) shows a slightly hyperintense nodular finding (arrow) on right-posterior side of the urinary bladder. Axial DWI MR image (B) confirms the presence of an area with restricted diffusion (arrowhead). These findings are consistent with local recurrence of disease.

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**Fig. 2:** 72-years-old patient with previous prostate cancer and presenting with increasing PSA level after radical therapy. Axial T2-weighted MR image (A) shows a nodular hypointense finding (arrow) in the peri-rectal space. Axial dynamic contrast-enhanced T1-weighted MR image (B) confirms the presence of a nodular area (arrowhead). These findings are consistent with recurrence of disease in a local lymphnode.

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**Fig. 3:** 76-years-old patient with biochemical recurrence after radiotherapy for prostate cancer. Axial T2-weighted MR image (A) shows a slightly hyperintense area on the right side of the prostate (arrow). Axial DWI MR image (B) confirms the presence of an area with restricted diffusion (arrowhead). These findings are consistent with local recurrence of disease.

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**Fig. 4:** 72-years-old patient who underwent external beam radiation therapy for prostate cancer, now presenting with increased PSA serum level. Axial dynamic contrast-enhanced T1-weighted MR image shows increased contrast enhancement on the right side of the prostate (arrow), suspicious for tumor recurrence.

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Table 1: Local recurrence shown at MRI examination in patients with biochemical recurrence.

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Conclusion

Biochemical recurrence has to be considered as an expression of tumor relapse. Evaluation of relapse location and extension is fundamental to outline a correct therapeutic strategy: local recurrence usually leads to salvage prostatectomy, brachiteraphy or criotherapy, while a systemic recurrence requires hormonal therapy or systemic chemotherapy.

MR has a central role in the management planning of patients with prostatic cancer: more and more frequently it is involved in the follow-up of patients who underwent radical therapy and present a rise of PSA serum levels, in order to exclude the presence of local recurrence. Increase of spatial resolution in high-field magnetic resonance systems led to a substantial improvement of anatomic detail, essential for the patient's management. Integration of images obtained from different MR modalities (morphologic images, diffusion-weighted images, perfusion dynamic images) allowed an increase of sensitivity and specificity of radiological diagnosis.

Prostatic cancer local recurrence shows low signal intensity in T2-weighted images; dynamic (after administration of paramagnetic contrast media) GRE T1-weighted images help discriminate normal tissue from tumoral relapse; in diffusion-weighted images, neoplastic tissue usually presents a restricted diffusion, due to its high cellular density.

The knowledge of surgical techniques allows an easier detection of local recurrence, as it helps distinguish between an asymmetrical anastomotic thickening (due to fibrotic and adherential phenomena) and a real recurrence of neoplastic tissue. Dynamic perfusional sequences are fundamental in differential diagnosis between fibrotic result and local recurrence, as fibrotic tissue presents late wash-in and absence of wash-out, while local recurrence presents rapid wash-in and relatively early wash-out.

In accordance with literature, our study pointed out that positive margins of resection present a radiological local recurrence much more frequently compared to patients with negative surgical margins. [10 - 12].

On the other side, in all irradiated patients, prostate showed evidence of atrophic and fibrotic changes, leading to a decrease in volume and in signal intensity in T2-weighted images, causing a loss of identification of normal zonal anatomy: that is why morphologic MR imaging had to be completed with a dynamic evaluation, in which all patients with local recurrence showed areas of contrast enhancement compared to surrounding normal prostatic tissue [13].

In conclusion, MR has to be considered as an important tool for the evaluation of prostate bed, in order to assess the new post-surgical anatomical arrangement and it plays a central role in the diagnosis of local recurrence.
References


