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TOPIC PAPER

The role of MRI for detection and staging of radio- and focal therapy-recurrent prostate cancer

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Abstract
Local recurrent prostate cancer after radical treatment is found in the majority of men with a rising PSA. Salvage treatment procedures for recurrent disease, such as radiation therapy and ablative procedures, can provide long-term responses in well-selected cases. Prostate magnetic resonance imaging (MRI) allows diagnosis and staging, and the value provides information on treatment selection, treatment planning and treatment guidance in local recurrent prostate cancer.

Keywords Prostate cancer · Radiorecurrent · mpMRI · Salvage · Prostatectomy · Focal therapy · Cryotherapy · HIFU

Introduction

Radical prostatectomy, external-beam radiation therapy and brachytherapy are the most widely used treatments for localized prostate cancer. Following non-surgical treatments including radiation therapy and focal ablative procedures, approximately 30–50% of patients experience local recurrence within 10 years [1–3]. For these patients, focal salvage therapy can be an alternative treatment option, in addition to salvage radical prostatectomy [4]. High-resolution imaging is pivotal in detection, staging and treatment guidance in local recurrent prostate cancer.

For the detection of local recurrent prostate cancer, prostate-specific membrane antigen positron-emission tomography (PSMA-PET) is generally considered to provide superior staging performance for lymph node and bone metastases, compared to (11)C-choline and (18)F-fluoromethylcholine PET [5–9], and conventional imaging modalities, such as computed tomography (CT) [10–14]. However, the resolution of the PSMA-PET/CT is limited and thereby smaller lesions in prostate and lymph nodes, seminal vesicle invasion and extracapsular growth may still remain undetected [15].

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Prostate MRI has high spatial resolution and may aid in this void. The PSMA-PET and magnetic resonance imaging (MRI) for local tumor detection in the primary diagnostic setting showed a promising correlation between these tests in men with high-risk primary prostate cancer [16], but a combination of both imaging tests provided an even higher detection rate of recurrence [17]. Moreover, accurate local staging is crucial for the planning of salvage local treatment. The number of studies on the value of local staging in recurrent prostate cancer is limited [18, 19]. The aim of this review is to summarize the available literature on the role of MRI for the detection and staging of locally recurrent prostate cancer after primary radiotherapy and ablative treatments.

Methodology

A non-systematic review was performed based on a medline literature search on PubMed from 1 January 2010 till 1 January 2018 using the following search terms: (Prostate cancer [MedSH terms] and recurrent disease [MeSH]) (OR) (Prostate cancer [MedSH terms] and salvage treatment therapy [MeSH] (OR) (Prostate cancer [MeSH terms] and magnetic resonance imaging (MRI) [MeSH]). Non-English studies were excluded.

Results

MRI in local staging of recurrent disease

Only those patients with recurrent prostate cancer who would benefit from salvage therapy should be identified and distinguished from those with advanced disease, not benefiting from salvage treatment. Furthermore, unnecessarily exposure to side effects and toxicities associated with local salvage therapy can be avoided. Clinical staging of locally recurrent prostate cancer is important since the recurrent clinical stage (rcT) and detection of seminal vesicle invasion were the strongest predictors of survival outcome after salvage treatments [3].

Prostate MRI in men suspected with recurrent disease may identify localized from advanced recurrent prostate cancer, and may indicate seminal vesicle invasion. High-resolution MR imaging is pivotal for accurate anatomical and functional information. For the detection of local recurrences after radiotherapy, T2-weighted sequences alone are considered for limited diagnostic value; both recurrent prostate cancer as well as irradiated prostatic tissue may appear hypointense on T2w images, reducing the ability to detect recurrent disease [19]. Still, high-resolution T2w imaging is the most important anatomical sequence in staging, and subsequently is pivotal in discriminating between locally and advanced recurrent prostate cancers. The additional functional imaging sequences of diffusion-weighted imaging (DWI) and dynamic contract-enhanced (DCE) imaging improve the diagnostic accuracy in detecting recurrent disease [18, 20].

Furthermore, staging in men after radiation therapy with multiparametric MRI is even more challenging than in primary staging (before treatment) [21]. Most studies use Likert scale readings for MRI-based local staging after radiotherapy, since the PI-RADS scoring is designed for primary tumor assessment only [22]. The staging accuracy of MRI in radiorecurrent prostate cancer was reasonable but slightly lower than reported in primary cases [23]. For the detection of seminal vesicle invasion, the sensitivity and specificity range from 61.5–76.9% and 66.6%, respectively, in a study on 19 patients with radiorecurrent prostate cancer [18]. For the detection of extracapsular extension, the diagnostic accuracy was even lower [18]. Table 1 summarizes the diagnostic accuracy of MRI in staging recurrent prostate cancer, in different population definitions. Reported interobserver agreement in one study was moderate with a kappa of 0.51–0.57 for SVI and EPE prediction in 19 patients [18].

Table 1 MRI in radiorecurrent prostate cancer

Study	*N*	MRI sequences	Population	Accuracy
Zattoni 2017 [17]	19	3T, T2, DCE, DWI	Patients after external beam radiotherapy	Sens/Spec: SVI: 61.5–76.9%/66.6% EPE: 50–71.4%/80–100%
Panebianco 2010 [54]	242	T2, DCE, DWI	Patients after external beam radiotherapy	T2 and DCE/DWI: Sens/Spec: 98%/94%
Donati 2013 [28]	53	T2, DCE, DWI	Rising PSA (Phoenix criteria) suspicious for a local recurrence at least 6 months after external beam radiotherapy	T2 and DWI Reader-dependent AUC varying from 0.46 to 0.81
Panebianco 2014 [33]	50	3T MRS	Patients after external beam radiotherapy	Spectra could distinguish responders from non-responders better than PSA
Akin 2011 [20]	24	T2, DCE, DWI	Patients after external beam radiotherapy with rising PSA, 67% positive biopsies	mpMRI outperformed T2 sequences. ADC lower in tumor-containing areas. Ktrans significantly higher
Luzurier 2018 [27]	52	T2, W, DCE, DWI	Biological suspected PCa recurrence after radiotherapy	Addition of DCE imaging slightly improved the sensitivity for less-experienced readers but not for experienced readers
Alonzo 2016 [55]	45	T2, DCE, DWI	Rising PSA after external beam radiotherapy	Use of DCE increased sensitivity and decreased specificity
Rouviere 2010 [31]	59	T2, DCE	Biochemical recurrence after HIFU treatment	41 of 77 (53%) MRI-detected lesions contained cancer. Majority of lesions (67% detected in DCE sequence)
Rosset 2017 [32]	81	T2	Comparing MRI readings before and after primary HIFU treatment	3-tier Likert tissue destruction score on MRI after HIFU predicted outcome in 1 of 3 readers only
Lotte 2018 [29]	45	T2, DCE, DWI	Clinical and biological suspected PCa recurrence after HIFU	Accuracy of mpMRI was not significantly improved by adding DCE to T2w + DWI

The contribution of additional functional imaging sequences such as diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) imaging in radio-recurrent prostate cancer is a matter of debate. Histologic changes of normal prostatic tissue after irradiation such as fibrosis, atrophy and acinar distortion do affect DWI sequences resulting in a decrease in ADC values, whereas tumor regions may show an increase in ADC values [24]. An interval of at least 3 months between radiotherapy and MRI is recommended when using DCE sequences because the radiation can induce blood pooling and inflammation reaction may result in false positive results [25].

Some studies have shown that the utilization of DCE imaging can facilitate a better distinction between post-radiotherapy fibrosis (often presented with low and slow homogenous enhancement) and recurrent cancer (that can be recognized as more hypervascular early enhancing nodi) [26, 27]. However, studies results demonstrate contradictory findings on the significance of DCE imaging in the detection of recurrent prostate cancer; while some studies showed improved diagnostic accuracy by the additional use of DCE imaging to T2w imaging and DWI [28]; other studies did not show improved diagnostic accuracy [29, 30].

Furthermore, in guidance to biopsy suspected recurrent disease, combining T2-weighted and DCE imaging after HIFU treatment [31] found to be correlated with positive targeted biopsies with the majority of lesions detected on the DCE sequences [32]. The size of the dominant lesion on post-HIFU treatment MRI was correlated with recurrence risk: Rosset et al. [33] found the size of the dominant lesion on MRI to predict recurrence in addition to clinical factors such as pre-HIFU PSA levels and destruction scores after treatment in 81 men that underwent HIFU.

MR spectroscopy, although now only rarely performed, may indicate metabolic information, based on choline-to-creatinine ratio; voxels with increased risk of a local recurrence that contain a ratio > 1.5:1. However, MR spectroscopy is not routinely based in clinically practice, mostly in experimental setting [25, 34].

MRI in treatment planning and follow-up

Early data suggest that MRI can aid in planning of focal salvage treatment for radio-recurrent prostate cancer [35]. Independent of the salvage method a recent consensus panel recommended MRI-guided biopsies for diagnoses and treatment planning in ablative salvage procedures [36]. MRI-guided biopsies were shown to improve the delineation of focal salvage brachytherapy in 30 men with radio-recurrent prostate cancer [37] (Table 2).

Moreover, the panel recommended mpMRI in the follow-up of these patients. In light of the investigational nature of any focal therapy for prostate cancer, the recommendation to apply imaging during follow-up is important in particular due to the lack of reliable PSA criteria of progression after focal salvage therapy [4]. Ongoing studies on salvage (focal) therapy for radiorecurrent prostate cancer implement mpMRI in most ablative options [38, 39].

MRI in treatment guidance

Salvage external radiation therapy Targeted external beam radiotherapy was shown to result in a high local control rate (89%) with minimal gastrointestinal toxicity and moderate genitourinary toxicity [40]. MRI-guided re-irradiation using stereotactic radiotherapy was shown to result in a BCR-free survival of 55.6% after 14.5 months follow-up with one patient developing prostatic necrosis but no grade 3 or higher bowel toxicity [41] indicating that targeted radiotherapy of radiorecurrent prostate cancer is feasible.

Salvage brachytherapy, compared to external beam salvage radiotherapy, is more extensively studied using either low-dose-rate (LDR) or high-dose-rate (HDR) techniques. Although methods of implantation and MRI sequences differed among studies, the efficacy of MRI-guided salvage brachytherapy on radio-recurrent prostate cancer is generally high with acceptable toxicity [42] in particular when compared to that of other salvage options [43, 44].

MRI-guided biopsies were shown to improve the delineation of focal salvage brachytherapy in 30 men with radio-recurrent prostate cancer [37]. Salvage LDR iodine-125 brachytherapy under MRI guidance resulted in low toxicity and improved BCR-free survival in 14 of 20 patients

Table 2 MRI in treatment planning and follow-up

Study	*N*	MRI sequences	Population
Moman 2010 [35]	31	T2, DCE, DWI	Salvage brachytherapy, treatment planning
Menard 2015 [37]	28	T2, DCE, DWI	Radiorecurrent prostate cancer, MRI targeted biopsies excluded false positives for MRI in 26% and false negatives in 11%
Kanthabalan 2015 [38]	150	T2, DCE, DWI	MRI in the follow-up of HIFU salvage treatment

[45]. Hsu et al. [46] reported that two local recurrences after MRI-guided salvage LDR brachytherapy were successfully retreated with a second salvage procedure with no grade 3 or higher toxicity. Maenhout et al. [47] reported that when a second salvage MRI-guided HDR-brachytherapy was applied in four patients, no more than grade 2 toxicity was recorded while three patients showed biochemical progression.

Focal salvage cryotherapy Focal salvage cryotherapy is generally performed under ultrasound guidance [48, 49]. Compared to re-irradiation options, cryotherapy provides an alternative approach of ablation. Tumor ablation can be obtained with several freeze–thaw cycles under transrectal ultrasound guidance. Interestingly, MRI-guided focal cryotherapy in the primary setting was shown to be feasible and has the potential to further improve outcome in the salvage setting [50]. In 23 men, Valerio et al., found no ipsilateral progression and only two men developed progression on MRI in contralateral disease. MRI assessed the ice ball size during percutaneous focal salvage cryotherapy for radio-recurrent prostate cancer which revealed the need for a 5-mm safety margin beyond the MRI-detected tumor margin for reliable tumor ablation [51].

Focal salvage HIFU Focal salvage high-intensity focused ultrasound (sHIFU) is generally performed by ultrasound or MRI guidance. Advantages of MRI guidance consist of heat monitoring, tumor boundary assessment and reduction of toxicity to adjacent organs. Disadvantages of sHIFU treatment are the fact that apical lesions are less readily targeted due to proximity of the urethral sphincter and the fact that more anterior tumors in larger tumors cannot be ablated. An anterior lesion on pre-sHIFU MRI was an independent predictor of sHIFU-failure with a risk ratio of 2.51 [32, 52].

MRI and salvage prostatectomy

MRI in treatment selection and planning

Salvage prostatectomy is considered in men with local recurrent disease and obstructive voiding complaints or tumor locations not amenable to ablative options. Extensive extracapsular tumor growth, ingrowth into the pelvic floor and rectum as well as extensive tumor ingrowth into the seminal vesicles are all relative contraindications of salvage prostatectomy. Accurate clinical staging, therefore, is crucial for patient selection. Interestingly, reports on the use of MRI for clinical staging prior to salvage prostatectomy are rare. Sala et al. [19] reported reasonable accuracy of endorectal coil-MRI for the prediction of EPE and SVI as found on final pathology (Fig. 1).

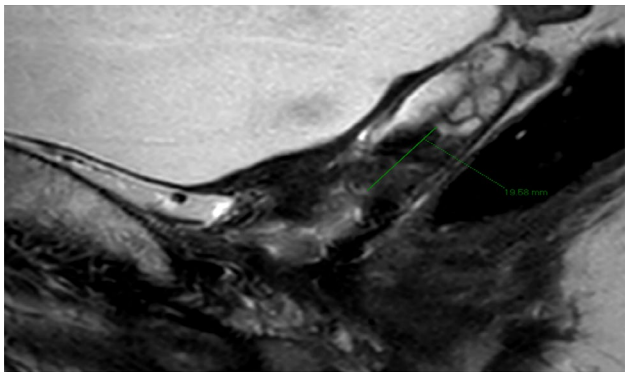

Fig. 1 Seminal vesicle invasion of radiorecurrent prostate cancer 9 years after LDR-brachytherapy with iodine125 seeds

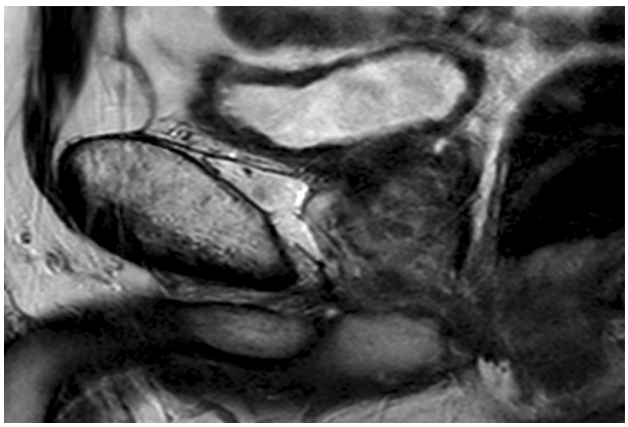

Fig. 2 Recto-prostatic plane as assessed by MRI prior to salvage prostatectomy

Besides the role for MRI in identifying EPE and SVI, MRI may also aid in selecting patients for salvage prostatectomy in predicting postoperative continence, by imaging the recto-prostatic plane (Fig. 2). Contrary to primary prostatectomy where MRI can improve the prediction of continence outcome after prostatectomy based on membranous urethral length (MUL) and inner-levator distance [47, 48], in a retrospective analysis we were unable to confirm an association of MUL and outcome after salvage prostatectomy (data unpublished). Primary treatment was predictive of continence outcome: men after brachytherapy were more likely to experience urinary incontinence after salvage prostatectomy, whereas men after HIFU had the lowest incidence of postsurgical urinary incontinence. Earlier studies found shrinkage of both the prostate [53] as well as the membranous urethral length, in particular after brachytherapy. These findings may possibly explain the observations that brachytherapy patients have an increased risk of urinary incontinence after salvage prostatectomy.

Discussion and conclusion

Use of radiotherapeutic and ablative options for localized prostate cancer do require accurate detection and where needed early treatment of residual or recurrent disease. As opposed to surgery, ablative salvage treatment options were shown to result in less toxicity in several series. Focal salvage treatment options may further limit toxicity. However, emerging (focal) salvage treatment options do require accurate tumor imaging of (radio)recurrent prostate cancer within the prostate. Review of the literature shows that MRI is widely applied for diagnosis and staging of recurrent prostate cancer after primary radiotherapy or ablative therapy but standardized approaches are lacking. T2 and DCE sequences are considered essential by some but not confirmed in other studies. Although the use of mpMRI shows promising results, due to a lack of larger scale comparative studies the precise value of MRI in salvage treatment remains unclear. Using mpMRI for the prediction of functional and oncological outcomes after salvage treatment needs further study. This is relevant considering the potential toxicity of any salvage treatment.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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