Review Article

Multi-parametric MRI imaging of the prostate—implications for focal therapy

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: The primary goal of a focal therapy treatment paradigm is to achieve cancer control through targeted tissue destruction while simultaneously limiting deleterious effects on peri-prostatic structures. Focal therapy approaches are employed in several oncologic treatment protocols, and have been shown to provide equivalent cancer control for malignancies such as breast cancer and renal cell carcinoma. Efforts to develop a focal therapy approach for prostate cancer have been challenged by several concepts including the multifocal nature of the disease and limited capability of prostate ultrasound and systematic biopsy to reliably localize the site(s) and aggressiveness of disease. Multi-parametric MRI (mpMRI) of the prostate has significantly improved disease localization, spatial demarcation and risk stratification of cancer detected within the prostate. The accuracy of this imaging modality has further enabled the urologist to improve biopsy approaches using targeted biopsy via MRI-ultrasound fusion. From this foundation, an improved delineation of the location of disease has become possible, providing a critical foundation to the development of a focal therapy strategy. This chapter reviews the accuracy of mpMRI for detection of "aggressive" disease, the accuracy of mpMRI in determining the tumor volume, and the ability of mpMRI to accurately identify the index lesion. While mpMRI provides a critical, first step in developing a strategy for focal therapy, considerable questions remain regarding the relationship between MR identified tumor volume and pathologic tumor volume, the accuracy and utility of mpMRI for treatment surveillance and the optimal role and timing of follow-up mpMRI.

Keywords: Focal therapy; prostate cancer; multi-parametric MRI (mpMRI); index lesion

Submitted Mar 15, 2017. Accepted for publication Apr 16, 2017.
doi: 10.21037/tau.2017.04.29
View this article at: http://dx.doi.org/10.21037/tau.2017.04.29

Introduction

Focal therapy for prostate cancer aims to address many of the critical limitations surrounding prostate cancer management. Many of these issues stem from the overtreatment of low-volume, low-grade disease by whole gland treatment and its subsequent impact on urinary continence and erectile function. One response to the overtreatment of low risk disease has been an increasing role for active surveillance (AS). While, AS aims to carefully select men who can consider deferring or avoiding active treatment, currently no formal selection criteria and follow up protocols exist. Furthermore, the results of the ProtecT trial indicate that almost 60% of men randomized to AS ultimately pursue active treatment. In addition, significantly more men randomized to AS experienced disease progression compared to those on active treatment (1). This is not surprising since over 50% of men with low risk disease based on SB harbor aggressive disease in radical prostatectomy surgical specimens (2). Accurate risk stratification is critical to selection for AS and employing

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mpMRI along with MR-US fusion biopsy has been shown to improve risk stratification (3,4). With increased utilization of mpMRI, men identified with MR visible disease that may qualify for focal therapy will likely increase.

Interest and utilization of focal treatment of clinically localized prostate cancer has increased. Multiple ablative technologies have been employed for focal therapy, including cryotherapy, high-intensity focused ultrasound (HIFU), electroporation, radiofrequency ablation, laser ablation and photodynamic therapy (5-15). Accurate disease risk stratification, precise tumor spatial localization and a reliable non-invasive, imaging-based treatment assessment are fundamental requirements to successful prostate cancer focal therapy.

Transrectal ultrasound (TRUS) imaging revolutionized prostate cancer (PCa) evaluation, diagnosis and monitoring by allowing the boundaries of the gland to be accurately demarcated and provided the foundation for systematic biopsies (16-21). However, TRUS imaging remains hindered by inadequate sensitivity and specificity for identifying precise tumor location, resulting in subpar negative predictive value and pathologic undergrading (22-25). These drawbacks have limited focal therapy approaches based solely on this imaging modality.

Multi-parametric MRI (mpMRI) vastly improves upon ultrasound prostate imaging by combining several MR sequences to improve tissue evaluation and differentiation, leading to improved cancer detection and tumor localization within the prostate (26-28). Utilizing software assistance, MRI image visible lesions can then be accurately sampled using targeted MR-US fusion techniques (29-32).

The inclusion of mpMRI in prostate cancer evaluation offers an imaging foundation that begins to address the critical challenges facing focal therapy strategies (33). This chapter reviews existing data supporting the role of mpMRI in providing information on the location and extent of disease within the prostate gland and the subsequent implications for identifying appropriate candidates for focal therapy and guiding the delivery of ablative energy to the treatment.

Multi-parametric MRI for prostate cancer disease detection and tumor volume

Imaging of the prostate using MRI has evolved from initial studies assessing the pelvis for staging purposes to dynamic, multi-parametric sequences aimed at characterizing disease within the gland itself (34). As mpMRI gains an increasing role as a triage test for disease detection it has been shown to be a useful tool for identifying men that may need a biopsy of the prostate (30,32,35). However, the ability of mpMRI to accurately identify and characterize disease depends upon size, location and aggressiveness of the cancer.

Disease detection on mpMRI

In a systematic review of data available in 2006, Kirkham *et al.* reported disease detection rates using early MRI referenced to disease detected whole mount pathology (36). This review reported on studies using unenhanced T2 weighted imaging (T2WI) with endorectal or pelvic phased array coils on 1.5T magnets and reported a sensitivity ranging from 37% to 96% and a specificity ranging from 21% to 67%. The authors concede that disease detection using T2WI alone can be confounded by hyperplasia, prostatitis, hemorrhage (post-biopsy) and the considerable signal heterogeneity of the transition zone (TZ). The accuracy of disease detection improved through addition of dynamic contrast enhancement (DCE). For example, in 1997, Jager *et al.* reported an increase in sensitivity from 57% to 73% and a specificity of 80% with the inclusion of DCE (37). In 2004, Schlemmer *et al.* reported an improvement in sensitivity for peripheral zone (PZ) tumor detection from 79% to 89% by combining T2 and DCE imaging (38). Emerging data suggested that 3T MRI as well as diffusion weighted imaging (DWI) would further impact imaging capabilities (39-42).

Diffusion weighted imaging (DWI) was initially used in neurologic imaging and evaluates the Brownian motion of protons (43). Restriction in this random motion correlates with increased cellular density associated with neoplasm (44-46). Jie *et al.* presented results of a meta-analysis of DWI on prostate cancer detection (47). They analyzed 21 studies and reported a sensitivity and specificity of 0.62 (95% CI: 0.61–0.64) and 0.90 (95% CI: 0.89–0.90) respectively.

In addition, Tan *et al.* performed a meta-analysis of the detection of prostate cancer with DCE (48). They demonstrated that the combination of DCE, DWI and T2WI provided the most accurate imaging on area under the curve (AUC) analysis. They also noted that DWI alone provided superior performance than DCE.

Recently, Hamoen *et al.* reported the results of a meta-analysis of T2WI combined with DCE and DWI on detection of prostate cancer using prostatectomy or biopsy as the reference standard (49). Of the 7 studies involving

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526 men, 4 used 1.5T magnets with pelvic phased array coil of which 2 utilized an endorectal coil, 2 utilized 1.5T and torso phased array coil and 1 utilized 3T. The authors report sensitivity and specificity of 74% and 88% respectively.

More recently, Fütterer *et al.* systematically reviewed the accuracy of mpMRI for identifying clinically significant disease including T2WI plus at least two functional sequences (DWI, DCE or MRSI) using prostate biopsy or radical prostatectomy specimens as reference standards (28). This review primarily analyzed studies using mpMRI employing 3T with pelvic phased array coils and reported a detection rate of clinically significant disease ranging from 44% to 87% and a negative predictive value of 63% to 98%. In addition, Thompson *et al.* reported disease detection in a prospective cohort of 150 men undergoing mpMRI followed by transperineal 30 core prostate biopsy with additional MR-US fusion biopsies or cognitive targeted biopsies obtained from MRI findings when deemed to be outside of the 30 core template (50). This study reported a positive predictive value ranging from 43% to 57% and negative predictive value of 92% to 96% depending on the definition of "clinically significant" disease.

Defining the absence of disease—the negative predictive value of mpMRI

MRI lesions identified on mpMRI are associated with varying probabilities of harboring disease based on imaging characteristics derived from the T2WI, contrast enhancement and diffusion weighted imaging sequences. While lesions noted on mpMRI with high suspicion often represent clinically significant cancer, the lack of high suspicion lesions carries importance for focal therapy strategies as a marker for absence of disease. A high negative predictive value (NPV) for significant cancer has the potential to rule-out significant disease and provides further confidence in treatment of only the disease identified on mpMRI.

The NPV for prostate mpMRI has been reported in a number of studies. Puech *et al.* reported a NPV of 85% for foci greater than 0.2 cm^3 and a NPV of 95% for foci greater than 0.5 cm^3 on radical prostatectomy specimens in 24 men with suspicious areas detected by pre-biopsy MRI (51).

Squillaci *et al.* reported cancer detection rates amongst 65 men undergoing mpMRI with spectroscopy (52). This study reported a NPV for overall cancer detection of T2W-MRI alone, MRSI alone, and combined mpMRI with MRSI as 77%, 78%, and 74%, respectively. Manenti *et al.* also reported NPV for T2W-MRI, MRSI, and mpMRI with MRSI on 39 men of 77%, 74%, and 74%, respectively (53).

Girometti *et al.* reported a NPV of 100% for a series of 8 men with prior negative biopsy using DWI in addition to T2WI and MRSI prior to biopsy (54). Pokorny *et al.* reported an NPV in 69% of men with a negative mpMRI prior to biopsy (31). Of those with cancer on biopsy, 90% had either low volume Gleason 3+3 or very low Gleason 3+4. In this study, the NPV for high risk disease was 94%.

Itatani *et al.* reported 5-year outcomes of men with initial negative mpMRI. This study demonstrated an NPV on initial TRUS-guided biopsy of 87%, with only 15% and 10% of men found to have any cancer and clinically significant cancer, respectively, on biopsy or radical prostatectomy within the 5-year period following MRI (55).

Finally, Wysock *et al.* reported an NPV of 91.7% and 97.9% for all cancers and Gleason ≥7 on men undergoing systematic 12-corebiopsy without a prior diagnosis of prostate cancer (56).

While these studies demonstrate a reliable NPV for prostate cancer, they remain small single series and lack consistency in the reference test utilized to confirm absence of disease. In fact, most of the studies rely upon biopsy data to serve as the reference standard which inflates the NPV. Additional follow-up data or prostatectomy data is needed to further strengthen reliability of the negative MRI results.

PROMIS

The PROMIS trial provides the highest level (Level 1b) of evidence at this time to address the accuracy of mpMRI for diagnosing prostate cancer (35). Ahmed *et al.* prospectively evaluated 576 men at risk for prostate cancer at 11 centers using a 1.5T mpMRI who underwent 5 mm transperineal template mapping biopsy and transrectal ultrasound guided standard 10–12 core biopsy. The study demonstrated a sensitivity for clinically significant cancer (Gleason dominant pattern 4 or greater) of 93% (95% CI: 88–96%) and a specificity of 41% (95% CI: 36–46%). One criticism of the study is that many Gleason 3+4 disease would merit at least consideration for focal or whole gland treatment. A strength of the study is that many of the 11 sites were not centers with high-level of experience with prostate MRI performance or interpretation, strengthening the external validity of these results.

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Prostate imaging reporting and data system (PI-RADS)

Due to the growing utilization of mpMRI, efforts to improve reporting standards led to the development of the PI-RADS (57). The PI-RADS system initially included T2WI, DWI, DCE and MR spectroscopy.

Hamoen *et al.* performed a meta-analysis of studies employing PI-RADS version 1 for prostate cancer diagnosis (49). This meta-analysis reviewed 14 studies, including 1,785 patients and using a variety of reference tests. Of the studies reviewed, 13 used biopsies as the reference standard and one used prostatectomy specimens. The authors reported sensitivity, specificity, negative predictive value, and value for cancer detection of 0.78 (95% CI: 0.70–0.84), 0.79 (95% CI: 0.68–0.86), 0.58–0.95 respectively. Of note, when these studies were analyzed for detection of only clinically significant cancer, the sensitivity increased to 0.84 (95% CI: 0.76–0.89) and specificity decreased to 0.75 (95% CI: 0.66–0.83). This meta-analysis reports an improvement in sensitivity from the meta-analysis on studies prior to publication of PI-RADS (49). However, only one study (58) utilized whole mount pathology as the reference standard, limiting the accuracy due to the potential of false-negative results based upon missed biopsies.

The PI-RADS system has recently been revised in order to further improve standardization of mpMRI interpretation and reporting by defining lesion scoring based upon sequence and prostate zonal anatomy (59). The revised PI-RADS version 2 redefines the analysis of DCE imaging, standardizes the 5 point scoring scale and removes spectroscopy. Future studies reporting on the results of PI-RADS version 2 will further define the accuracy for disease detection. It is also important to note that the PI-RADS system only applies to treatment naïve patients and thus does not apply for interpretation following therapy.

Disease detection summary

Overall, disease detection using mpMRI has significantly improved over the last 10 years. While these studies support an improvement in disease detection using mpMRI, they remain limited by lack of strict adherence to a common gold standard reference test. Using a gold standard reference of SB underestimates sensitivity and negative predictive value. Using a radical prostatectomy standard based on mpMRI coupled with MRFTB + SB detection is limited due to selection bias since the negative predictive value and sensitivity of the overall detection pathway is assumed to be 100%. Transperineal mapping biopsy is highly correlated with radical prostatectomy specimens and represents a preferred gold standard reference since it minimizes selection bias and maximizes disease detection. The results of the PROMIS trial address this criticism by providing a transperineal template mapping biopsy as the reference standard. Overall, these results serve as a strong argument for inclusion of mpMRI in the diagnostic paradigm for prostate cancer.

Currently, the reported specificity for clinically significant disease remains in the range of 50% (35). Given this level of specificity, precise disease localization requires biopsy confirmation. Further studies are necessary to define the optimal biopsy strategy to evaluate the findings on mpMRI. The ideal biopsy approach should serve to address not only confirmation of disease presence, but also accurately assess the boundaries of disease. An important converse to this concept, however, lies in the negative predictive value of mpMRI. Given that multiple studies demonstrate negative predictive values of 90% or greater, the role of biopsy to these negative regions requires further evaluation. From the perspective of focal therapy planning, confidence in the absence of disease within imaging negative regions is tantamount.

In summary, from the perspective of focal therapy, mpMRI is essential as an imaging study to identify men as candidates for focal therapy. Further confirmation with targeted biopsy is necessary for disease confirmation and also provides limited information on disease mapping. Current mpMRI technology can provide this necessary foundation for focal therapy and is recommended for selecting patients for this treatment option (59-61).

Tumor volume

The second critical requirement of focal therapy is to provide ablation energy to a volume of tissue that encompasses the tumor. Focal therapy strategies will rely upon these disease volume estimates in order to provide treatment margins. The ability of mpMRI to provide an accurate delineation of tumor volume is thus critical. However, the accuracy of mpMRI to estimate tumor volume remains to be clearly defined. *Table 1* summarizes studies reporting on tumor volume.

In their 2006 review, Kirkham *et al.* summarized existing whole mount analysis of MR tumor volume (MRTV) and histologic tumor volume (HTV) (36). Tumor volume

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Table 1 Summary of studies evaluating MR tumor volume compared to histologic tumor volume

Authors	Year	Study size	MR protocol	Pathology	MR TV compared to HTV	Comments
Kahn *et al.* (62)	1989	–	Unenhanced MRI	–	40%	–
Quint *et al.* (63)	1991	26	1.5T; body coil with spin echo pulse sequences; unenhanced	Whole mount prostatectomy	MRTV underestimated in 11/20 cases; Poor correlation (only 2 specimens MRTV within 10% of HTV)	5 tumors underestimated by >50%; 7 tumor overestimated by >50%
Sommer *et al.* (64)	1993	20	1.5T; pelvic coil with fast spin-echo (FSO); unenhanced	Whole mount prostatectomy	Overestimation of small tumors, underestimation of larger tumors; Correlation (r) =0.81 (slope 0.68)	Shrinkage factor of 33%; HTV = (0.3 + MRTV × 1.47)
Jager *et al*. (65)	1996	34	1.5T; endorectal coil; unenhanced	Whole mount prostatectomy	Poor correlation between MRTV and HTV; wide range of overestimation and underestimation	19 tumors overestimated by >25%; 8 tumors underestimated by >25%
Nakashima *et al.* (66)	2004	95	1.5T; endorectal and pelvic array; contrast enhanced	Whole mount prostatectomy	Poor correlation but improved with DCE: r=0.84	HTV = (0.1+ MR max diameter × 0.97)
Lemaitre *et al.* (67)	2009	27 tumors evaluated	1.5T; pelvic coil; T2WI, DCE	Whole mount prostatectomy	MRTV underestimated HTV up to 40%	Median MRTV 1.01 cc; Median HTV 2.84 cc
Turkbey *et al.* (68)	2012	135	3T; endorectal coil; T2WI, DCE, DWI, MRSI	Whole mount prostatectomy (3D mold)	MRTV underestimated 7% with shrinkage factor; MRTV overestimated by 7% without shrinkage factor	With shrinkage correction (1.15): mean MRTV 2.02 cm^3; mean HTV 2.18 cm^3
Baco *et al*. (69)	2015	135	1.5T and 3T; pelvic/body coil; T2WI, DCE, DWI	Whole mount prostatectomy	MRTV underestimated HTV ~5.7%	Mean MRTV 2.1 mL; mean HTV 2.2 mL; r=0.663
Radtke *et al.* (70)	2016	120	3T; pelvic coil; T2WI, DCE, DWI	Whole mount prostatectomy	MRTV underestimated HTV by 0.4 mL (36%)	r=0.42; underestimation decreased to 20% (0.3 mL)
Rud *et al.* (71)	2014	199	1.5T; body coil; T2WI, DCE, DWI	Whole mount prostatectomy	MRTV significantly lower than HTV for both Index Tumor as well as all tumors; MRTV for tumors <0.5 mL mean difference from HTV of 0.1 mL; MRTV for tumors >0.5 mL mean difference from HTV 2.8 mL	Index tumor: mean MRTV 2.8 mL; mean HTV 4.0 mL; all tumors: mean MRTV 2.3 mL; mean HTV 3.2 mL
Le Nobin *et al.* (72)	2015	33	3T; pelvic coil; T2WI, DCE, DWI	Prostatectomy reconstruction	MRTV underestimated HTV by 18.5% TV underestimation increasing as MR lesion suspicion score increased	Authors suggest 9 mm treatment margin in order to achieve complete HTV destruction in 100% of lesions
Cornud *et al.* (73)	2014	84	1.5T; endorectal coil; T2W1, DCE, DWI	Whole mount prostatectomy	MRTV on T2WI, DCE and DWI correlated poorly with HTV (underestimation and overestimation noted)	Median MRTV: 0.56 cc (T2W), 0.52 cc (DCE), 0.84 (DWI); median HTV: 0.85 cc
Priester *et al.* (74)	2017	114	3T; pelvic array and endorectal coil (47%); T2WI, DCE, DWI	Prostatectomy with 3D molds	Mean MRTV 0.8 cc; mean HTV 2.5 cc; underestimation ~30%	Authors note size best estimated in axial view; mean diameter underestimated by ~11 mm

MRTV, MRI tumor volume; HTV, histologic tumor volume; DCE, dynamic contrast enhancement; DWI, diffusion weighted imaging.

estimation improved with tumor size, however, they noted volume discrepancies of ~50% for tumor volume of 5 mL (62). Early estimations of tumor volume based on unenhanced T2 imaging was noted to be approximately 40% of HTV; these estimations appeared to improve slightly with DCE (63-66,75-77).

Lemaitre *et al*. compared morphologic features on mpMRI with whole-mount radical prostatectomy specimens for anterior prostate tumors in 27 specimens (67). These authors noted ill-defined tumor margins on T2W imaging in 89% and a median volume of 1.01 cc on MRI *vs.* 2.84 cc on histopathology. They also reported an underestimation of MRTV up to 40%.

Turkbey *et al.* further compared MRTV measurements to

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HTV in 135 index tumors on whole-mount pathology (68). These authors reported a MRTV of 2.02 cm^3 while mean HTV was 2.18 cm^3, correcting for shrinkage.

More recent studies have corroborated these findings. Baco *et al.* compared MRTV and HTV on 135 prostatectomy specimens (69). They demonstrated that mpMRI underestimated the HTV by approximately 5% (95% CI, −6–8%). Radtke *et al.* reported MRTV underestimated HTV by 0.4 mL (36%), which decreased to 20% (0.3 mL) when reevaluated applying shrinkage factor (70). Rud *et al.* reported MRTV was significantly smaller than HTV in 199 radical prostatectomy specimens (71). These authors noted that MRTV underestimated HTV (mean MRTV Index Tumor 2.8 mL *vs.* HTV Index Tumor 4.0 mL). For tumors <0.5 mL, mean MRTV was found to be 0.1 mL while mean HTV was 2.8 mL larger than MRTV for tumor >0.5 mL.

Le Nobin *et al.* compared MRTV to HTV on 46 histologically confirmed cancers on 33 radical prostatectomy specimens and reported an MRTV underestimated by 18.5%, with underestimation increasing as lesion suspicion score increased and Gleason score increased above 6. A 9 mm treatment margin was recommended in order to achieve complete HTV destruction in 100% of lesions (72).

Cornud *et al.* compared MRTV and HTV in 84 prostatectomy specimens and noted that tumor volume measured on T2W imaging and DWI correlated significantly with HTV (73). These authors noted that MRTV on DWI appeared to provide the best approximation of HTV, however volume underestimation was noted in 49% of cases. Furthermore, these authors attempted to provide a deliberate overestimation of tumor volume by using the largest tumor area on any sequence along with the number of slices demonstrating tumor. Using this technique, they reported an underestimation rate of 17%.

Utilizing customized tumor molds made from preoperative mpMRI T2 imaging, Priester *et al.* noted a mean volume of 0.8 cc for tumors on mpMRI and a subsequent tumor volume of 2.5 cc on whole mount pathology (74). Volume was best estimated in the axial view. These authors conclude that mpMRI may underestimate tumor volume by one third and that the mean diameter is approximately 11 mm greater on pathology than on T2 weighted imaging.

Ultimately, current data supports a systematic underestimation of HTV on mpMRI. In order to ensure adequate treatment margins, focal therapy treatment volumes must take this into consideration. At this time, focal therapy treatment zones utilizing a margin of approximately 9 to 10 mm, as proposed by Le Nobin *et al.*, appears reasonable as an initial estimate. Additional tumor mapping studies should serve to improve these estimations.

Utilization of mpMRI in treatment follow-up

Optimal strategies for focal therapy follow up remain to be defined. Utilizing mpMRI may offer a non-invasive method for estimating treatment success and post-treatment surveillance. However, the data to support this use is limited. The ideal timing of follow-up imaging also remains to be determined.

Follow up imaging approximately 2–3 weeks after focal treatment offers an opportunity to assess accuracy of ablation targeting. However, these results may only allow for identification of gross targeting as early post-treatment imaging results have failed to predict biopsy outcomes at 6 months post-ablation (78). The ability of early follow-up MRI to assess gross targeting may be useful during the initial adoption of an ablative treatment. Surveillance mpMRI using contrast enhancement assesses enhancement or viable tissue within or around the treatment site. Targeted biopsies using MRI-US fusion to regions of enhancement following ablation have been shown to improve detection of residual disease over non-targeted biopsies (79).

At this time, a clear post-ablation treatment protocol has yet to be defined in order to define oncological control. However, mpMRI is recommended for both treatment planning as well as follow up evaluation. One consensus panel has recommended post-treatment imaging with mpMRI at 6 months following treatment (59). The indications for biopsy of the ablation zone also remain highly controversial.

Defining the index lesion

Imaging basis of "index lesion"

The hypothesis of the "index lesion" represents the critical oncologic challenge to the focal therapy paradigm. Assuming the veracity of the biologic basis for the "index lesion", the ability to accurately locate and characterize this tumor focus remains a crucial component of a successful focal therapy strategy. Localized treatment thus requires precise mapping of the contours (80) and extent of this

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index tumor focus.

Transrectal ultrasound (TRUS) imaging revolutionized prostate cancer evaluation, diagnosis and monitoring by allowing the boundaries of the gland to be accurately demarcated and provided the footprint for systematic mapping biopsies (16-21). Since prostate cancer is multi-focal in 75% of radical prostatectomy specimens, successful focal therapy strategies mandate that a single tumor drives the biology of the disease. The concept of an "index" tumor that represented the primary malignant source was typically identified as the largest tumor visible by ultrasound (16,81,82). However, current TRUS imaging remains hindered by well-described limitations in the ability to identify and map disease (22-25). Consequently, defining an accurate index lesion using TRUS has remained elusive.

Recent evidence supports the ability of mpMRI to accurately localize the index tumor.

Rosenkrantz *et al.* retrospectively evaluated mpMRI of 51 men who underwent prostatectomy and identified an index lesion in 49 (96%). They reported a sensitivity of 74.8% for identification of the index lesion for Gleason >6 and 80.3% for lesions greater than 1 cm (83). A second analysis by Rosenkrantz *et al.* demonstrated improved sensitivity for index lesion detection using DWI, correlation between tumor diameter on ADC map with radical prostatectomy specimen, and greater sensitivity for higher Gleason scores on both DWI and ADC maps ranging from 80–100% (84). An evaluation by Reisaeter *et al.* reported similar findings, and further demonstrated decreased sensitivity and specificity for index tumor localization within the transition zone (85).

Delongchamps *et al.* evaluated prostatectomy surgical specimens from 125 consecutive men with preoperative mpMRI imaging available and identified 151 suspicious zones and 230 individual tumor foci. MRI-US fusion targeted biopsy demonstrated cancer in 126 (83%) of the mpMRI identified lesions. A total of 95 tumor foci were invisible on mpMRI, and 14 (15%) of these were significant disease. However, 13 of these 14 (93%) were secondary foci within gland where an index tumor was visible on mpMRI and detected on targeted biopsy. Furthermore, all Gleason >6 tumors not identified on mpMRI were Gleason 3+4 with less than 20% pattern 4 and 8, (57%) were less than 0.5 cm^3 in volume. Multivariate analysis of mpMRI target characteristics demonstrated that only PI-RADS score was associated with significant tumor foci. Interestingly, the size of mpMRI correlated with tumor volume and not Gleason score (86).

Le *et al.* evaluated 122 consecutive men undergoing radical prostatectomy with presurgical mpMRI imaging available. On whole mount evaluation, mpMRI identified 98 (80%) of index tumors and performed well for identifying higher grade and larger tumors (72% sensitivity, 75% positive predictive value) for Gleason >6 and diameter >1 cm. On multivariate analysis, index tumor status and lesion size were the strongest predictors of tumor detection. Multifocal disease was noted in 78 (64%) men and this did not significantly impact detection of the index tumor (86% in solitary tumors and 77% in multifocal tumors). Index tumor on mpMRI corresponded to highest grade tumor in 86% of cases, 20% of men had Gleason >6 non-index tumors, of which 15% were missed on mpMRI (87).

Baco *et al.* demonstrated a 95% concordance between the sites of mpMRI index lesion and histopathological index tumor on 135 prostatectomy specimens (69). Furthermore, they demonstrated that for all MR visible disease, MR-US targeted cancer location correlated with location of the index tumor on prostatectomy. Of seven MR invisible index tumors, 4 (3%) demonstrated any Gleason pattern 4 and only 1 (1%) demonstrated primary Gleason pattern 4.

Radtke *et al.* evaluated a cohort of 120 men undergoing transperineal fusion biopsy and 24 core systematic transperineal biopsy followed by radical prostatectomy. MRI detected 110 (92%) of index lesions, of which 89% harbored significant disease, and missed 86% of insignificant non-index lesions. Missed lesions demonstrated a median tumor volume of 0.6 cm^3 and 56% were Gleason 3+4 (75% of which harbored <11% Gleason pattern 4) (88).

Rud *et al.* evaluated 199 men undergoing radical prostatectomy with mpMRI imaging prior to surgery. Imaging detected the histologic index tumor in 92%.

While the index lesion hypothesis remains under investigation, the ability of mpMRI to accurately identify the index tumor ranges widely and appears to improve with the size and Gleason score of the tumor. From the perspective of focal therapy planning, these findings suggest that mpMRI reliably identifies the highest oncologic risk disease and thus allows for confirmation using targeted biopsy. Based upon the results of targeted biopsy, the presence and location of an index lesion can be determined, allowing for index lesion based treatment strategies. The high negative predictive value of mpMRI for significant disease is also important in order to ensure clinically

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significant cancers are not left untreated.

Conclusions

The ability of mpMRI to reliably identify clinically significant disease has enabled selection of candidates for focal therapy. Focal therapy success relies upon accurate tumor localization, tumor boundary definition, effective ablation targeting with adequate margin control and accurate follow-up protocols to assess oncological control. The current data reviewed above illustrate the capability of mpMRI to provide information valuable for each of these requirements. The use of mpMRI thus sets the necessary foundation to begin exploring focal therapy strategies. Future studies will serve to strengthen these data and provide further definition on the exact role of this imaging in disease management.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Wysock JS, Lepor H. Multi-parametric MRI imaging of the prostate—implications for focal therapy. Transl Androl Urol 2017;6(3):453-463. doi: 10.21037/tau.2017.04.29

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