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Multiparametric Magnetic Resonance Imaging-Transrectal Ultrasound Fusion-Assisted Biopsy for the Diagnosis of Local Recurrence after Radical Prostatectomy

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Abstract

Objective—Approximately 15% of patients who undergo radical prostatectomy (RP) for prostate cancer develop local recurrence which is heralded by a rise in serum prostate specific antigen (PSA) levels. Early detection and treatment of recurrence improves the outcome of salvage treatment. We investigated the ability of multiparametric (mp) MRI -Transrectal Ultrasound (TRUS) fusion-guided biopsy combined with “cognitive biopsy” to confirm local recurrence of prostate cancer after RP.

Materials and Methods—In this retrospective study conducted between January 2010 and December 2014, patients with rising PSA levels after RP who had no known evidence of distant metastases underwent mpMRI including T2 weighted imaging (T2WI), Diffusion Weighted Imaging (DWI), Dynamic Contrast Enhanced (DCE) MRI at 3 Tesla and subsequent MRI-Ultrasound fusion biopsy with cognitive assistance. The detection rate of locally recurrent disease was determined.

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Results—10 patients (mean age 67y, mean PSA 3.44ng/ml) met the inclusion criteria. Of the 10 patients, all had positive findings suspicious for local recurrence on mpMRI per entrance criteria. The most important features on mpMRI were early enhancement on DCE MRI and hypointensity on T2WI. Average lesion diameter on mpMRI was 1.12 cm (range 0.40cm – 2.20cm). All suspicious lesions (16/16, 100%) were positive on T2W MRI, 14 (89%) showed positive features on ADC maps of DWI, and 16 (100%) were positive on DCE-MRI. MRI-TRUS fusion-guided biopsies were positive in 10/16 lesions (62.5%) and 8/10 (80%) patients.

Conclusion—MRI-TRUS fusion-guided biopsy with cognitive assistance is able to detect and diagnose locally recurrent lesions after RP, even at low PSA levels. This may facilitate early detection of recurrent disease, and improve salvage treatment outcomes.

Keywords

Prostate cancer; biochemical recurrence; MRI; MRI-ultrasound fusion guided biopsy

1.0 Introduction

Prostate cancer is the most common solid organ malignancy in men with an estimated 238,590 new diagnoses and 29,720 deaths in the United States of America (USA) in 2014 [1]. In 2007, 79,875 patients underwent radical prostatectomy (RP) as a definitive treatment of prostate cancer in the USA [2]. While RP provides long-term cancer control in the majority of patients with localized prostate cancer [3] approximately 15–20% of patients have a rise in PSA indicating recurrence of their disease after RP[4]. Early detection of disease recurrence after RP leading to early salvage therapy is associated with improved outcomes whereas delayed diagnosis may limit the opportunity for salvage treatment [5]. A landmark study by Stephenson in 2004 demonstrated a survival benefit for salvage radiation therapy when treatment was initiated when the PSA was still below 2ng/mL [6]. Others have confirmed these findings suggesting improved outcomes with earlier treatments [7]. Furthermore, when the recurrent lesions can be localized, targeted dose escalation radiotherapy can be performed [8].

Over the last decade, the diagnostic accuracy of multiparametric MRI (mpMRI) of the prostate has dramatically improved. Technology improvements and standardized acquisition and interpretation protocols have contributed to the increasing value of mpMRI [9]. However, the majority of clinical research has been performed in preoperative patients. MRI-TRUS fusion guided biopsy has been used to confirm the findings on the mpMRI and is rapidly being adopted [10]. However after surgery, the anatomic landmarks commonly used to register the MR and TRUS for fusion biopsy are absent and it is thus more difficult to properly align and fuse the two data sets. Several studies have reported the value of mpMRI in the early detection of local recurrence after RP but there is a paucity of data on the use of MR-TRUS fusion biopsy in the setting of biochemical recurrence [11–15]. In this study, we investigate the ability of MRI-TRUS fusion biopsy to confirm sites of local recurrence suspected by mpMRI.

2.0 Materials and Methods

2.1 Study design and population

This retrospective single institution study was approved by the local institution review board and was compliant with the Health Insurance Portability and Accountability Act: informed consent was obtained for each patient. Inclusion criteria included documented serum PSA elevations (above 0.2 ng/dl) after RP in the absence of known distant metastases, and a mpMRI examination of the prostatic fossa. Exclusion criteria included insufficient pre-operative medical history, prior or current history of Androgen Deprivation Therapy (ADT) and the presence of metastatic disease in bones or lymph nodes on bone scan or computed tomography.

2.2 Multiparametric MR imaging

All MR imaging studies were performed using a combination of an endorectal coil (BPX-30; Medrad, Pittsburgh, PA, USA) tuned to 127.8 MHz and a 16-channel cardiac coil (SENSE; Philips Medical Systems, Best, the Netherlands) with a 3T magnet (Achieva; Philips Medical Systems, Best, the Netherlands), without prior bowel preparation. The endorectal coil was inserted using a semi-anesthetic gel (xylocaine, Lidocaine, Astra-Zeneca, Wilmington, DE, USA) while the patient was in the left lateral decubitus position. The balloon surrounding the coil was distended with 3-mol/L perfluorocarbon (Fluorinert; 3M, St Paul, MN, USA) to a volume of approximately 45mL, to reduce susceptibility artefacts induced by air in the coil's balloon. The MR imaging protocol included triplanar T2-weighted turbo spin echo imaging, DW MRI imaging, axial three-dimensional fast-field-echo DCE MRI. Axial DCE images were obtained before, during, and after a single- dose of gadopentetate dimeglumine (Magnevist; Berlex, Wayne, NJ, USA), administered at a dose of 0.1 mmol per kilogram of body weight through a peripheral vein at a rate 3 mL/sec using a mechanical injector (Spectris MR injection System; Medrad, Pittsburgh, PA, USA). Sequence parameters were defined in previous studies [16, 17].

2.3 mpMRI Evaluation

mpMRI studies were evaluated by two radiologists (BT and PLC with a cumulative experience of 8 and 15 years in prostate mpMRI, respectively), who were blinded to clinicopathologic information. Each mpMRI sequence was evaluated separately in a commercially available picture archiving and communication system (PACS) (V.11.3, Carestream Health, Inc. Rochester, NY, USA). On T2W MRI and ADC maps of DW MRI, the criteria for a suspicious lesion were: presence of an isointense or hypointense focus at the urethral anastomosis within the prostatectomy fossa. For DCE-MRI evaluation, the raw images were reviewed visually and the criterion for a suspicious lesion was the presence of an early enhancing focus within the prostatectomy fossa. A patient was called "negative for local recurrence" if no lesion was detected within the prostatectomy fossa, "low suspicion for local recurrence" in the presence of a lesion positive on T2W MRI or ADC maps alone and "positive for local recurrence" in the presence of a lesion positive on T2W MRI or ADC maps and DCE MRI.

2.4 Fusion guided biopsies

MR-TRUS fusion guided biopsies of target lesions were performed on a now commercially available platform which was developed in our institution (UroNav, InVivo Corp, Gainesville, FL, USA) [18–20]. Since the device became commercially available in May 2013, the first 5 patients were biopsied using the research version of the device (biopsied before May 2013). First, T2 weighted MR images of the suspected lesion were segmented. The patient received prophylactic antibiotics prior and after biopsy. On the day of the biopsy, the prostatectomy fossa was scanned with transrectal ultrasound (TRUS) and MR-TRUS fusion was attempted using visualized anatomic landmarks such as the bladder neck, vessels, areas of calcification, etc. Because such fusions are necessarily inexact without the prostate as a landmark, the actual biopsy was performed by identifying lesions on TRUS that corresponded to the location of the lesion on the MRI. We termed this “cognitive assistance” to differentiate it from routine MR-TRUS fusion biopsies which rely exclusively on the fusion image. The lesion identified on TRUS was segmented manually and the processed MRI and TRUS images were registered to each other using the software fusion platform. Finally, lesions that were suspicious for recurrence were displayed as targets on real time

TRUS, and were sampled in the axial and in the sagittal plane, resulting in two cores per target [21]. Needle trajectories were mapped with real time electromagnetic tracking which is part of the biopsy platform (Northern Digital Inc., Ontario, Canada).

3.0 Results

The initial study population consisted of 39 patients who had mpMRI between January 2010 and December 2014 (Table 1). All patients had a rising PSA above nadir. Out of these 39 patients, 21 (54%) had positive findings on mpMRI. Among these 21 patients, 4 had metastatic disease and were treated with androgen deprivation therapy and 7 patients chose to undergo radiation therapy without biopsies. Thus, 10 patients consented to undergo MRI-ultrasound fusion guided biopsies and they constitute our final patient population (figure 1). Patient characteristics are presented in Table 1. Their average age was 67 years (range: 61y–75y). The time interval between the RP and PSA recurrence averaged 107 months (range: 7 months – 259 months). Initial Gleason score varied between 3+2 and 4+5 and 4 patients (40%) had positive surgical margins after RP (Table 2).

All 10 patients had positive findings on mpMRI as part of study entry criteria. In total, 16 suspicious lesions were found. The most common features used for detection were early enhancement on DCE MRI, and a hypointense signal pattern on T2WI. A hypointense focal signal pattern on ADC maps was considered supportive evidence of recurrence. Average lesion diameter on mpMRI was 1.12 cm (range 0.40cm – 2.20cm). Sixteen (100%) of these suspicious lesions were positive on T2W MRI (figure 1), 14 (89%) were positive on ADC maps and 16 (100%) of the suspicious lesions were positive on DCE.

The targeted MRI/TRUS fusion biopsy with cognitive assistance revealed adenocarcinoma of prostatic origin in 10 out of 16 biopsies (63%). Two (12%) lesions proved to be healthy prostatic tissue. MRI/TRUS fusion biopsy showed fibromuscular tissue in 4 lesions. On a per-patient basis, the cancer detection rate was 80% (8/10 patients) (table 3).

4.0 Discussion

Biochemical recurrence (BCR) after RP occurs in 15–20% of the patients [4, 22, 23]. Salvage therapy is an important mode of therapy for these patients, since it improves patient survival [24, 25]. A study by Stephenson, demonstrated that early detection and therapy of recurrent prostate cancer is associated with improved outcomes. In their analysis there was no difference between the progression rates for patients with a recurrence PSA level of 1.0 ng/mL or less and of 1.1 through 2.0 ng/mL ($P=0.22$). However, a PSA level greater than 2.0 ng/mL was associated with a higher rate of progression ($P<0.001$) [6]. Therefore, the goal of this study was to test whether lesions detected by mpMRI could be confirmed histologically using combined MR-TRUS fusion-guided biopsy even at PSA levels below 2 ng/mL, which was the case in 8 of our 10 patients

In this study, 10 consecutive patients underwent mpMRI after referral for evaluation of rising PSA post RP. Findings suspicious for recurrence included early enhancement on DCE-MRI and focal hypointensity on T2 weighted images. mpMRI combined with MR-TRUS fusion-guided biopsy demonstrated recurrent disease in 8 out of 10 patients (80%) with a PSA range from 0.14 ng/mL to 21.74 ng/mL. If we restrict the study patients to those with a PSA level below 2 ng/mL, the biopsy technique demonstrated recurrent disease in 6 out of 8 patients (75%) (Mean PSA: 0.90, range: 0.14–1.35). The prostatic fossa is notoriously difficult to biopsy and these early results suggest that MR-TRUS fusion-guidance may aid in the localization of targets compared to TRUS-guidance alone.

Several studies have investigated the topic of MRI in the setting of local recurrence. Rischke et al evaluated 33 patients with PSA rise after RP who had response after salvage radiotherapy. All patients underwent prostate MRI prior to and after salvage radiation therapy. The authors used a cut-off value of PSA (0.54 ng/mL) above which the lesion was always visible on MRI [13]. Verma et al. did a similar study in 90 patients with PSA rise after RP. They found that 20% of these patients had positive MRI findings, of whom 80% had PSA values <1 ng/mL. Positive surgical margins at RP was a predictor of positive MRI findings [14]. Wassberg et al. analyzed 51 patients with suspicious T2W MRI findings and 33 (63%) of the biopsies were positive for recurrent prostate cancer [15]. Another study with 22 patients demonstrated superior accuracy of mpMRI over F-18 Choline or C11 acetate PET. MRI identified recurrent prostate cancer in 85% of the cases [26]. Thus, previous studies have documented the ability of MRI to detect recurrences but subsequent validation has been made difficult by poor visualization of the prostatic fossa with TRUS alone.

In our study, a combination of DCE MRI and T2WI were the most helpful sequences in localizing suspicious foci for recurrence compared DW MRI. The key feature of DCE MRI for localizing the recurrent foci was early strong enhancement consistent with earlier studies [15, 27, 28]. However, the high resolution T2W MRI was indispensable for planning the MR-TRUS fusion-guided biopsy. Even though the final placement of the biopsy needle was under the control of the operator under direct TRUS visualization, the MR-TRUS fusion was extremely helpful in guiding the operator to the correct region to be biopsied.

Detection rates of recurrent disease using ultrasound or MRI guided biopsies are reported to be low (range 30%–66%) with a positive biopsy in less than 30% in patients with PSA levels <1ng/ml [29, 30]. The increased sensitivity (80%) of MR-TRUS fusion is in part because the spatial accuracy of such biopsies is 2.4 ± 1.2 mm [31], whereas the mean lesion size in our population was 8.4mm (IQR 5mm–9mm). One additional implication of accurately localizing recurrences is that it enables targeted boost radiotherapy to confirmed lesions which is thought to improve response [32]. In theory, recurrent lesions at the bladder neck, should also be able to be biopsied and even treated using TUR, however no studies about this could be found.

This study has several limitations. First, the study size is limited and the results clearly must be validated in larger trials. It proved difficult to identify patients who had MRI-visible lesions who were willing to undergo biopsy as the standard of care does not require biopsy. Additionally, the patients described here were highly selected for having a positive mpMRI. However, these preliminary results may encourage physicians to study BCR patients PSA <2.0ng/ml with imaging and image fusion guided biopsy in order to deliver early precision radiotherapy to sites of local recurrence.

Conclusion

In conclusion, in the setting of biochemical recurrence after RP, lesions detected by mpMRI can be biopsied using a combination of MR-TRUS fusion-guided biopsy and cognitive guidance even at PSA levels <2.0ng/ml. This hybrid method utilizing MRI-ultrasound fusion guidance and direct ultrasound targeting can be helpful to validate the MRI findings histopathologically even at low PSA levels. This approach may improve salvage treatment outcomes.

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Figure 1.

Flow chart shows the initial accrual and exclusion steps applied for the whole study population.

Figure 2.

72 y/o male who presented after RP with a slowly progressing PSA recurrence (1.22ng/mL at time of scan). There is a hypointense lesion visible at 11 o'clock at the level of the anastomosis on the T2W MRI (A). ADC map shows low signal intensity pattern in this region (B) and the lesion shows early focal contrast enhancement on DCE MRI (arrow) (C). Targeted TRUS/MRI fusion biopsy (D) confirmed recurrent prostate cancer.

Table 1

Patient characteristics of the total study population.

Patient Characteristics: All patients	n=39	
	Mean/ number	Median (range)
Age (years) at PSA recurrence Median (range)	63	63 (56–68)
Age (years) at RP	59	58 (54–63)
T Stage at surgery		
<i>pT2</i>	<i>n</i> = 19	
<i>pT3a</i>	<i>n</i> = 13	
<i>pT3b</i>	<i>n</i> = 4	
<i>pT4</i>	<i>n</i> = 1	
<i>Missing data</i>	<i>n</i> = 2	
Gleason Score at surgery		
<i>3+2</i>	<i>n</i> = 1	
<i>3+3</i>	<i>n</i> = 4	
<i>3+4</i>	<i>n</i> = 12	
<i>4+3</i>	<i>n</i> = 3	
<i>4+4</i>	<i>n</i> = 9	
<i>4+5</i>	<i>n</i> = 7	
<i>Missing data</i>	<i>n</i> = 2	
Surgical Margins		
<i>Positive</i>	<i>n</i> = 19	
<i>Negative</i>	<i>n</i> = 17	
<i>Missing data</i>	<i>n</i> = 3	
Pre-op PSA	13.94	13.29 (2.40 – 57.00)
<i>PSA Nadir</i>	0.21	0.37 (<0.01 – 1.71)
PSA at suspicion of recurrence	0.63	0.39 (0.02 – 21.74)
Time to PSA recurrence (<i>months</i>)	43.97	55.49 (3 – 259)
Positive MRI	21/39	
Mean PSA (range) positive MRI	1.79 (0.02 – 21.74)	
Negative MRI	18/39	
Mean PSA (range) negative MRI	0.54 (0.04 – 1.95)	
# of MRI positive in PSA range < 1	14/28 (50%)	
# of MRI positive in PSA range 1 < PSA < 2	4/8 (50%)	
# of MRI positive in PSA range >2	3/3 (100%)	

Table 2

Patient characteristics of the final study population, only biopsied patients.

Patient Characteristics (n=10)	
Age (years) at PSA recurrence: Mean (range)	67 (61–75)
Age (years) at RP: Mean (range)	58 (50–69)
T Stage at surgery: n (percentage)	
<i>pT2</i>	7 (70%)
<i>pT3a</i>	3 (30%)
Gleason Score at surgery: n (percentage)	
<i>3+2</i>	1 (10%)
<i>3+3</i>	2 (20%)
<i>3+4</i>	3 (30%)
<i>4+3</i>	1 (10%)
<i>4+4</i>	1 (10%)
<i>4+5</i>	2 (20%)
Surgical Margins: n (percentage)	
<i>Positive</i>	4 (40%)
<i>Negative</i>	4 (40%)
<i>Unknown</i>	2 (20%)
Pre-op PSA in ng/mL: Mean(range) <missing values>	14.98 (2.70 – 46.50) <4>
<i>PSA Nadir in ng/mL: Mean (range) <missing values></i>	0.25 (<0.01 – 1.35) <3>
PSA at suspicion of recurrence in ng/mL: Mean (range)	3.44 (0.14 – 21.74)
Time to PSA recurrence in months: Mean (range)	107 (7 – 259)

Table 3

Lesion characteristics of the final study population.

	Number/mean
Total positive MRI's: n (percentage)	10 (100%)
Number of lesions per patient: mean (range)	1.70 (1 – 3)
Total number of lesions: n	16
Lesion largest diameter in centimeters: Mean (range)	1.12 (0.40 – 2.20)
Total # lesions positive on T2W MRI: n (percentage)	16 (100%)
Total # lesions positive on ADC maps: n (percentage)	14 (89%)
Total #lesions positive on DCE MRI: n (percentage)	16 (100%)
Total # of lesions positive on T1W MRI: n (percentage)	0 (0%)
Pathology on MRI/US fusion guided biopsy	
Fibromuscular tissue: n (percentage)	4 (25%)
Benign prostatic tissue: n (percentage)	2 (13%)
Adenocarcinoma of prostatic origin: n (percentage)	10 (63%)
Lesions positive on FGB in patients: PSA < 1.00	3/8
Lesions positive on FGB in patients: 1.00 < PSA < 2.00	4/4
Lesions positive on FGB in patients: PSA > 2.00	3/4
Mean lesion diameter (range) positive lesions (cm)	1.2 (0.4 – 2.2)
Mean lesion diameter (range) negative lesions (cm)	0.9 (0.5–1.8)