Magnetic resonance imaging detected prostate evasive anterior tumours: Further insights

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Abstract

Introduction: Clinical confusion continues to exist regarding the underestimation of cancers among patients on active surveillance and among men with repeated negative prostate biopsies despite worrisome prostate-specific antigen (PSA) levels. We have previously described our initial experience with magnetic resonance imaging (MRI)-based detection of tumours in the anterior prostate gland. In this report, we update and expand our experience with these tumours in terms of multiparametric-MRI findings, staging, and grading. Furthermore, we report early treatment outcomes with these unique cancers.

Methods: We reviewed our prostate MRI dataset of 1117 cases from January 2006 until December 2012 and identified 189 patients who fulfilled criteria for prostate evasive anterior tumors (PEATS). Descriptive analyses were performed on multiple covariates. Kaplan-Meier actuarial technique was used to plot the treatment-related outcomes from PEATS tumours.

Results: Among the 189 patients who had MRI-detectable anterior tumours, 148 had biopsy proven disease in the anterior zone. Among these tumours, the average PSA was 18.3 ng/mL and most cancers were Gleason 7. In total, 68 patients chose surgical therapy. Among these men, most of their cancers had extra prostatic extension and 46% had positive surgical margins. Interestingly, upgrading of tumours that were biopsy Gleason 6 in the anterior zone was common, with 59% exhibiting upgrading to Gleason 7 or higher. Biochemical-free survival among men who elected surgery was not ideal, with 20% failing by 20 months.

Conclusion: PEATS tumours are found late and are disproportionally high grade tumours. Careful consideration to MRI testing should be given to men at risk for PEATS.

Introduction

Prostate cancer is the most common male malignancy and the second leading cause of cancer death among men in the western world.[1] Detection of prostate cancers has changed over the past 30 years from digital rectal examination (DRE) findings to prostate-specific antigen (PSA) based case identification. The key in using the DRE to find prostate cancers is based on the seminal observations by McNeal and colleagues, who defined the zonal anatomy of the prostate.[2] It has been observed that the vast majority of prostate cancers originate in the peripheral zone of the gland and thus over time most men with prostate cancers will exhibit an abnormal DRE. It has been recognized however that historically some men died of metastatic prostate cancer with a normal DRE.[3] Many of these tumours are felt to have arisen in the transition zone of the prostate, although these tumours are classically lower grade than peripheral zone cancers.[4]

Use of PSA as a screening tool has led to an increased detection of prostate cancer on transrectal biopsy with stage migration towards early and low-risk disease. This has come with the risk of overdiagnosis since many of the cancers detected on transrectal ultrasound (TRUS) biopsy are low-risk prostate cancer. On the other hand, anterior tumours tend to be missed by TRUS biopsy until they grow to a substantial size and reach within 2 cm from the posterior prostatic capsule, leading to delayed or missed diagnosis. Multiparametric magnetic resonance imaging (mp-MRI) has been extensively studied in recent years and, when used in conjunction with PSA for targeted biopsies, provides a better diagnostic pathway to detect cancer and assign appropriate treatment.[5-9]

In 2009, our group published a series of 19 cases of men either on active surveillance or who had repeated negative prostate biopsies and rising PSA and were later deemed to have large sized and high-grade tumours in the anterior prostate on mp-MRI (Fig. 1).[10] The origin of these tumours may be the anterior lateral horn of peripheral zone, transition zone or the anterior fibromuscular zone. The latter, if true, challenges the findings of McNeill and colleagues who claimed that epithelium was devoid in this area.

Since the publication of our original paper, our clinical suspicion of the prostate evasive anterior tumours (PEATS)

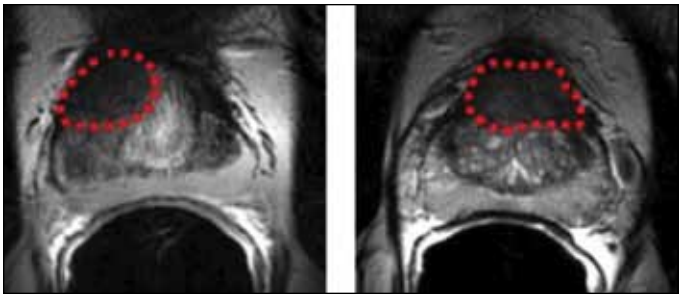

Fig. 1. Magnetic resonance imaging reveals large anterior tumour. Dotted outline indicates the tumour.

has increased and we have subsequently performed more MRI scans among patients in whom we would not have traditionally. This paper describes our recent experience and the increasing role of mp-MRI to detect and stage these tumours; we also report our initial treatment results with these unique tumours.

Methods

Cohort assembly

We retrospectively reviewed our prostate MRI (2006–2012) database, including cases from January 2006 to December 2012. All reports were reviewed. We selected cases where an anterior lesion (defined as lesions at a distance of >20 mm from the posterior prostate capsule, >4 mm in largest dimension on mp-MRI) (n = 225). Among these selected files, we then identified 189 men who had targeted biopsies (cognitive co-registration by an experienced uro-radiologist [AT]). Of these 189 patients, those with positive targeted biopsies were further identified. Chart review was then carried out on all cases and the following covariates were measured: age, PSA, MRI lesion size, total prostate volume by ultrasound, DRE findings, anterior zone biopsy Gleason score, staging results, and surgical findings (including pathological stage, grade, margins as well as biochemical treatment outcomes). We also noted the indication for the initial MRI which included active surveillance (AS), prior negative biopsy, failed local treatment, and staging.

MRI technique

Our mp-MRI has been previously published.[11] All patients underwent a diagnostic mp-MRI (Siemens Avanto or GE Excite HD 1.5T or Siemens, MAGNETOM, Verio 3T) using a 4-channel phased-array surface coil coupled to an endorectal coil, to aid tumour localization. Sequences included axial, sagittal and coronal Turbo Spin Echo T2-weighted images in relation to the orientation of the prostate gland (slice thickness, 3 mm; gap, 0 mm), axial diffusion-weighted imaging with the same slice locations as the T2-axial sequence (B-values: 0, 100,400,800 s/mm^2), axial 2D-Flash in and out of phase T1-weighted images, and axial 2D Flash in- and out- of phase imaging, followed by axial 3D flash dynamic contrast-enhanced T1-weighted imaging, using Magnevist (Bayer Healthcare) as contrast agent.

MRI scans were reviewed by one of two experienced uro-radiologists (SG/MH). All MRIs were done at least 6 weeks from biopsy to minimize the effect from hemorrhage. Diagnostic features for malignancy were low T2 signal and specifically an erased charcoal appearance in the transition zone, a relatively low apparent diffusion coefficient calculated from diffusion-weighted imaging (DWI), early enhancement and washout on dynamic contrast-enhanced (DCE) MRI.[10,12,13]

Tumours were confirmed on biopsy if they were displayed on MRI in the anterior zone, if they were greater or equal to 4 mm in dimension, or if patients had significant abnormalities in different anatomical locations other than the original diagnostic biopsy.

Prostate biopsies were taken within 12 weeks of the MRI so that a correlation was possible between biopsy and imaging findings. Confirmatory biopsy consisted of a standard biopsy (minimum 12 cores), plus additional cores aimed at anterior MRI identified locations. Abnormal sites on MRI were annotated into zones and given to the radiologist taking the TRUS biopsy for targeting. The MRI scans were available allowing "real time" comparison of the methods and zones of interest. All prostate biopsies were reviewed by dedicated uro-pathologists at our institution. Specific biopsies from anterior regions were correlated based on MRI scans in which there was a high suspicion for cancer, as in previous studies.[14-16]

Analyses

Descriptive analyses were performed on the above-mentioned covariates. The Kaplan-Meier actuarial technique was used to plot treatment-related outcomes from PEATS tumours. For surgical and radiation-related therapies, any PSA >0.2 ng/mL or Phoenix criteria (PSA nadir plus 2 ng/mL) were utilized, respectively.

Results

In total, 148 (78.3%) of the 189 patients with suspicious anterior MRI lesions underwent targeted biopsy. The clinical characteristics of this cohort are shown in Table 1. The targeted biopsy area Gleason score distribution was as follows: 6, 43.2%; 7 (3+4), 31.2%: 7 (4+3), 14.2% and 8-10, 11.4%. Five patients had nodal Mets at presentation.

The reasons for performing the mp-MRI of the prostate were: active surveillance 53.3% (79 patients); prior negative biopsy 29% (43 patients); failed non-surgical local therapy,

Table 1. Baseline clinical characteristics among 148 patients with PEATS tumours

Variable	No.	Proportion
Mean age, years	64	NA
Median PSA (range)	18.26 ng/mL (4.2–559.33)	NA
PSA distribution		
<10	73	49.3%
10–20	47	31.7%
20–50	21	14.2%
>50	7	4.7%
Indication for MRI		
Surveillance	79	53.3%
Negative biopsy	43	29%
Staging	16	10.8%
Failed local therapy	10	6.7%
Biopsy Gleason score		
6	64	43.2%
7 (3+4)	46	31.2%
7 (4+3)	21	14.2%
8–10	17	11.4%
MRI lesion size distribution		
≤5 mm	10	6.7%
6–10 mm	13	8.7%
11–15 mm	44	29.7%
16–20 mm	43	29%
>21 mm	38	25.6%
Elected therapy		
Radical prostatectomy	68	45.9%
Radiotherapy	12	8.1%
Radiotherapy plus hormones	20	13.5%
HIFU	10	6.7%
Watchful waiting/lost to follow-up	31	20.9%
Waiting for therapy	7	4.7%

PEATS: prostate evasive anterior tumours; PSA: prostate-specific antigen; MRI: magnetic resonance imaging; HIFU: high-intensity focused ultrasound; NA: not applicable.

such as radiation or high-intensity focused ultrasound (HIFU) 6.7% (10 patients); and 10.8% (16 patients) had their PEATS tumours discovered when they underwent staging (Table 1).

In terms of elected therapies, 68 (45.9%) patients underwent radical prostatectomy (RP), 12 patients (8.1%) had radiotherapy alone, 20 patients (13.5%) had radiotherapy in combination with androgen deprivation therapy (ADT), 10 patients (6.7%) had HIFU, and 31 patients (20.9%) elected for watchful waiting (Table 1). Seven patients were awaiting therapy at time of manuscript preparation. Among the RP patients, an additional 7 had adjuvant radiotherapy and 3 had radiotherapy in combination with ADT.

Pathological stages and Gleason score among men who underwent RP are listed in Table 2. Other surgical outcomes included 1 patient who was N+ and 31 with positive margins (45.5%). Three patients (4.4%) had detectable postoperative PSA (Table 2).

Biochemical and salvage therapy free survival from patients treated with RP is noted in Figure 2, with about 70% of patients free of either PSA failure or salvage treatment.

Table 2. Initial surgical outcomes

Surgical outcomes (n = 68)	No.	Proportion
Pathological stage		
T2	27	39.7%
T3a	31	45.5%
T3b	7	10.2%
T4	3	4.4%
Nodal status		
N0	42	62.7%
N1	1	1.5%
Nx	25	35.8%
Margins		
Positive	31	45.5%
Negative	37	54.5%
Final Gleason score		
6	12	17.6%
7 (3+4)	29	42.6%
7 (4+3)	17	25%
8–10	8	11.7%
ADT effect	2	2.9%
Detectable postoperative PSA	3	4.4%

PSA: prostate-specific antigen.

A total of 5 patients either died of disease or had known metastatic progression.

Discussion

The diagnosis of prostate cancer continues to be a topic that elicits strong passions and great debate, particularly in the context of screening. Conventionally, PSA, DRE and TRUS biopsy remain the main tests used by clinicians to determine the presence of significant disease. We have previously identified a series of clinical scenarios which have historically puzzled clinicians who diagnose and treat men with prostate cancer.[11] Two major scenarios include: (1) men with rising levels of PSA despite multiple negative biopsies and (2) men who otherwise fulfill criteria for active surveillance but develop seemingly rapid disease progression. PEATS were first described by our group as large and disproportionately high-grade MRI detectable lesions among men within these two clinical scenarios. Their significance is emphasized as these tumours almost always present after considerable delay. The true prevalence of PEATS remains unknown in the negative biopsy scenario, but is in the range of about 10% among unselected active surveillance patients.[11]

It must be stressed that historically we "reserved" prostate MRI for patients off protocol to those with PSA levels >10 ng/mL. In this setting, the average PSA was high and only 22% of cancers were Gleason 6. Once we learned of PEATS tumours, our awareness increased and we have more recently performed MRIs earlier than in the original cohort. As a result, it becomes important to reanalyze this entity and its clinical characteristics.

In this retrospective study, we reviewed our new experi-

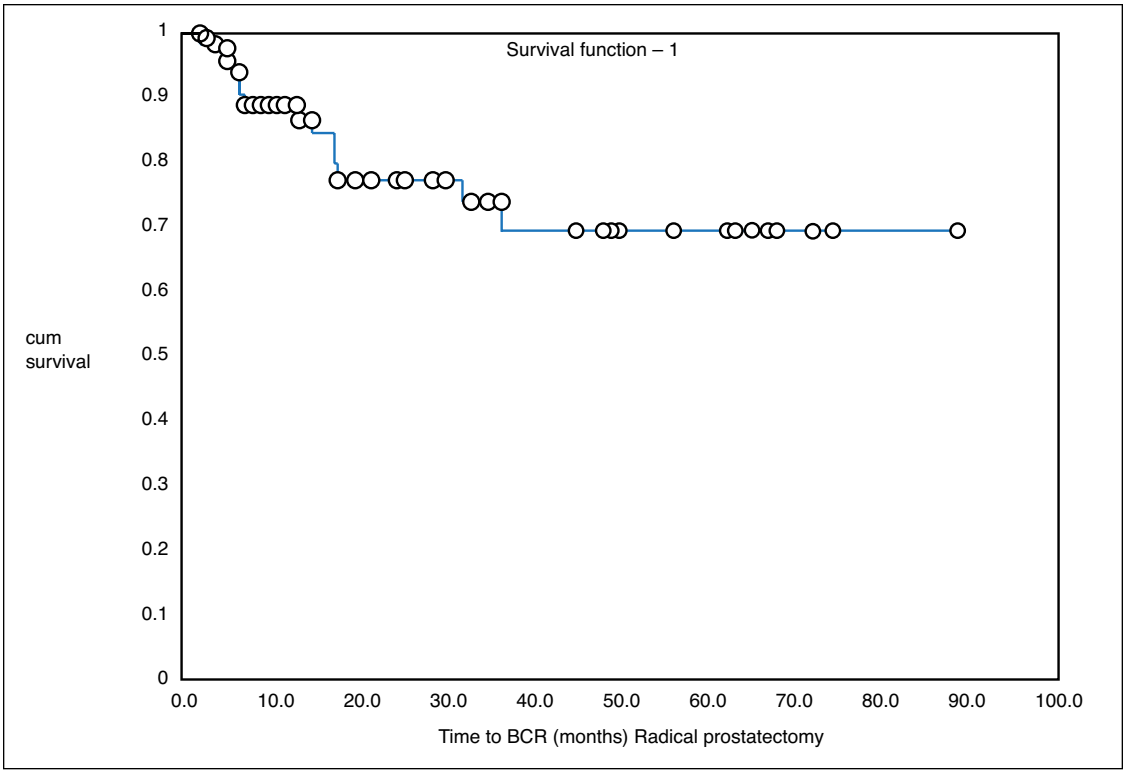

Fig. 2. Kaplan-Meier survival function curve for radical prostatectomy patients.

ence with anterior prostatic tumours. We started the cohort by analyzing our MRI database and selecting men with positive prostate biopsy in the anterior zone. By analyzing the data this way, we were able to capture the clinical relevance of these tumours. This is in contrast with prior histopathology-based studies which have analyzed these tumours purely based on their anatomic location.[17] In these cases, the vast majority of tumours were found in the peripheral zone first and hence those descriptive papers do not capture the clinical entity.

In this paper we have identified 148 patients with MRI-detected anterior biopsy confirmed tumours among the 189 patients with actual lesions. Therefore about 21.7% of patients with MRI-detected lesions did not have a positive confirmatory biopsy. This is lower than our original manuscript and either represents falsely positive scans or missed biopsies. As we have noted, our biopsies to date have largely been via cognitive coregistration and thus can be theoretically prone to misses, particularly as we identify smaller lesions. Also, since these anterior lesions may be directly anterior to the urethra, smaller lesions may be difficult to target via a TRUS approach. Novel software for MRI/TRUS fusion are now coming online (including at our centre) and it will be interesting to see how these predictive values change over time. On the other hand, heterogenous appearance makes an assessment for cancer more difficult in the transition zone.

Additional benefit of functional imaging over T2 weighted images in assessing the transition zone tumour is limited, as areas of benign stromal hyperplasia may show enhancement on DCE and restricted diffusion on DWI.[18,19] Suspicion of cancer on mp-MRI in the transitional zone is mostly limited to morphological features on T2WI, such as an 'erased charcoal' appearance, indistinct margins of the nodule, extension of low signal into peripheral zone, lenticular shape, and extension to fibromuscular stroma. This may have also partially accounted for some false positive interpretations on mp-MRI. Several studies have shown that targeted biopsy following mp-MRI is more likely to detect clinically significant disease in comparison to systematic TRUS biopsy,[20] which by its random nature may detect low grade 'sparse' or low volume tumour, which are usually not identified on mp-MRI.[21] This may account for a Gleason score of 7 or higher in >50% of tumours identified in our study.

Although PEATS tumours tend to have worse outcomes than earlier detected peripheral zone tumours, the Gleason score distribution of these lesions are now approaching peripheral zone tumours, with 43.2% of tumours possessing low-grade (Gleason 6) features. This number is similar to our in-house data (data not shown), although the risk of high-grade disease (Gleason 8–10) is about double that of de novo diagnosed peripheral zone tumours (4.8% in-house data not shown). One observation that must be stressed relates to pathological upgrading. In our cohort, 43.2% of patients

had a Gleason 6 biopsy, but only 17.6% had Gleason 6 at final pathology in those who had RP. Although upgrading is not uncommon at RP,[22] 59.2% of Gleason 6 cancers were upgraded in our series. This likely reflects two phenomena: difficulty with sampling in PEATS tumours and the fact that higher volume Gleason 6 tumours have a tendency to harbour foci of pattern 4 disease.[22]

It should be noted that with average PSA values approaching 20 ng/mL, many of these patients have a later diagnosis than traditionally diagnosed patients. As a consequence, many patients have adverse stage, operative findings, and an adverse clinical course.

The zonal origin of PEATS tumours remains unknown. They may represent high lateral horn peripheral zone tumours or transition zone lesions which invade the anterior prostate. Furthermore, as some of these tumours seemingly have no radiological connection to the lateral horn or transition zone, it remains plausible that they are truly anterior fibromuscular in origin. If so, this would contradict the seminal studies of McNeal and colleagues who claimed that epithelial glands were devoid in this era.[2] Molecular characterization of these tumours could help clarify their zonal ontogeny and whether they represent a distinct biological entity. It should be noted that the utility of other diagnostic tests, such as prostate cancer antigen (PCA)-3, remain unknown in these tumours.

As this paper represents a retrospective albeit important case series, we must be aware of bias. In our view, the major bias in this study is that many of these lesions are found late. A more rigorous use of MRI, especially among men with first negative biopsies, would help clarify the true incidence of these tumours. We of course cannot comment on the incidence/prevalence of these lesions without offering MRI to a consecutive group of unselected men. We have previously published our experience with consecutive MRI among non-selected men with very low-risk PCA and found that 10% of men who otherwise are active surveillance candidates harbour PEATS tumours. This proportion is unknown in the post-first negative biopsy setting. Another bias is that perhaps not all physicians at our centre had the same trigger for ordering MRI. In this case, the generalizability of the findings should be tempered.

It is important to recognize PEATS as distinct clinical entity of prostate cancer.[23,24] Careful attention should be given to men with rising PSA and negative biopsies and men with rising PSA on active surveillance.[25] Men with smaller volume prostates appear to be at an increased risk for PEATS.[4] Although biopsy may reveal Gleason 6 disease, few patients are truly Gleason 6 at surgery. MRI is the best way to detect PEATS with a positive predictive value approaching 80%. Clinicians need a high sense of awareness to diagnose these lesions.

Conclusion

PEATS are a distinct clinical entity in prostate cancer characterized by tumour in the anterior aspect of the gland that is difficult to diagnose by traditional methods. MRI remains the mainstay in the detection of these lesions. Very few of these lesions are true Gleason 6 tumours.

Notes: Presented in part as podium poster at the 68th Annual Meeting of the Canadian Urological Association, June 2013, Niagara Falls, Ontario Canada; and as moderated poster at the AUA Annual Meeting, May 2014, Orlando FL.

Competing interests: Dr. Al Edwan, Dr. Ghai, Dr. Margel, Dr. Hamilton, Dr. Toi, and Dr. Haider declare no competing financial or personal interests. Dr. Kulkarni has received a grant from Astellas and he is currently participating in a clinical trial with Spectrum Pharmaceuticals. Dr. Finelli has participated in clinical trials in the past 2 years for Amgen, Astellas, Janssen and Ferring. He is also Chair of the CUA Guidelines Committee. Dr. Fleshner is a member of the advisory boards for Amgen, Janssen, Astellas and Eli Lily. He has received honoraria from Amgen, Janssen, Astellas, and Eli Lily. He is and has participated in clinical trials for Amgen, Janssen, Medivation, OICR, and Prostate Cancer Canada.

This paper has been peer-reviewed.

References

1. Sanda MG, Dunn RL, Michalaski J, et al. Quality of life and satisfaction with outcome among prostate cancer survivors. *N Engl J Med* 2008;358:1250-61. http://dx.doi.org/10.1056/NEJMoa074311
2. McNeal JE. The zonal anatomy of the prostate. *Prostate* 1981;2:35-49. http://dx.doi.org/10.1002/pros.2990020105
3. Stamey TA, Dietrick DD, Issa MM. Large, organ confined, impalpable transition zone prostate cancer: Association with metastatic levels of prostate specific antigen. *J Urol* 1993;149:510-5.
4. Noguchi M, Stamey TA, Neal JE, et al. An analysis of 148 consecutive transition zone cancers: Clinical and histological characteristics. *J Urol* 2000;163:1751-5. http://dx.doi.org/10.1016/S0022-5347(05)67535-0
5. Panebianco V, Barchetti F, Sciarra A, et al., Multiparametric magnetic resonance imaging vs. standard care in men being evaluated for prostate cancer: A randomized study. *Urol Oncol* 2015;33:17.e1-7. http://dx.doi.org/10.1016/j.urolonc.2014.09.013. Epub 2014 Nov 11.
6. Puech P, Rouvière O, Renard-Penna R, et al. Prostate cancer diagnosis: Multiparametric MR-targeted biopsy with cognitive and transrectal US-MR fusion guidance versus systematic biopsy–prospective multicenter study. *Radiology* 2013;268:461-9. http://dx.doi.org/10.1148/radiol.13121501
7. de Rooij M, Hamoen EHJ, Fütterer JJ, et al. Accuracy of multiparametric MRI for prostate cancer detection: A meta-analysis. *AJR Am J Roentgenol* 2014;202:343-51. http://dx.doi.org/10.2214/AJR.13.11046
8. Abd-Alazeez M, Ahmed HU, Arya M, et al. The accuracy of multiparametric MRI in men with negative biopsy and elevated PSA level–can it rule out clinically significant prostate cancer? *Urol Oncol* 2014;32:45.e17-22.
9. Shakir NA, George AK, Siddiqui MM, et al. Identification of threshold prostate specific antigen levels to optimize the detection of clinically significant prostate cancer by magnetic resonance imaging/ultrasound fusion guided biopsy. *J Urol* 2014;192:1642-9. http://dx.doi.org/10.1016/j.juro.2014.08.002
10. Lawrentschuk N, Haider MA, Daljeet N, et al. "Prostatic evasive anterior tumors": The role of magnetic resonance imaging. *BJU Int* 2010;105:1231-6. http://dx.doi.org/10.1111/j.1464-410X.2009.08938.x
11. Margel D, Yap SA, Lawrentschuk N, et al. Impact of multiparametric endorectal coil prostate magnetic resonance imaging on disease reclassification among active surveillance candidates: A prospective cohort study. *J Urol* 2012;187:1247-52. http://dx.doi.org/10.1016/j.juro.2011.11.112
12. Kurhanewicz J, Vigneron D, Carroll P, et al. Multiparametric magnetic resonance Imaging in prostate cancer: Present and future. *Curr Opin Urol* 2008;18:71-7. http://dx.doi.org/10.1097/MOU.0b013e3282f19d01

13. Weinreb JC, Blume JD, Coakley FV, et al. Prostate cancer: Sextant localization at MR imaging and MR spectroscopic imaging before prostatectomy—results of ACRIN prospective multi-institutional clinicopathologic study. *Radiology* 2009;251:122-33. http://dx.doi.org/10.1148/radiol.2511080409
14. Haider MA, van der Kwast TH, Tanguay J, et al. Combined T2-weighted and diffusion-weighted MRI for localization of prostate cancer. *AJR Am J Roentgenol* 2007;189:323-8. http://dx.doi.org/10.2214/AJR.07.2211
15. Akin O, Sala E, Moskowitz CS, et al. Transition zone prostate cancers: Features, detection, localization, and staging at endorectal MR imaging. *Radiology* 2006;239:784-92. http://dx.doi.org/10.1148/radiol.2392050949
16. Futterer JJ, Heijmink SW, Scheenen TW, et al. Prostate cancer localization with dynamic contrast-enhanced MR imaging and proton MR spectroscopic imaging. *Radiology* 2006;241:449-58. http://dx.doi.org/10.1148/radiol.2412051866
17. Al-Ahmadie HA, Tickoo SK, Olgac S, et al. Anterior-predominant prostatic tumors: Zone of origin and pathologic outcomes at radical prostatectomy. *Am J Surg Pathol* 2008;32:229-35. http://dx.doi.org/10.1097/PAS.0b013e31812f7b27
18. Hoeks CM, Vos EK, Bomers JGR, et al. Diffusion-weighted magnetic resonance imaging in the prostate transition zone: Histopathological validation using magnetic resonance-guided biopsy specimens. *Invest Radiol* 2013;48:693-701. http://dx.doi.org/10.1097/RLI.0b013e31828eeaf9
19. Oto A, Kayhan A, Jiang Y, et al., Prostate cancer: Differentiation of central gland cancer from benign prostatic hyperplasia by using diffusion-weighted and dynamic contrast-enhanced MR imaging. *Radiology* 2010;257:715-23. http://dx.doi.org/10.1148/radiol.10100021
20. Schoots IG, Roobol MJ, Nieboer D, et al. Magnetic resonance imaging-targeted biopsy may enhance the diagnostic accuracy of significant prostate cancer detection compared to standard transrectal ultrasound-guided biopsy: A systematic review and meta-analysis. *Eur Urol* 2014; http://dx.doi.org/10.1016/j.eururo.2014.11.037
21. Langer DL, van der Kwast TH, Evans AJ, et al. Intermixed normal tissue within prostate cancer: Effect on MR imaging measurements of apparent diffusion coefficient and T2–sparse versus dense cancers. *Radiology* 2008;249:900-8. http://dx.doi.org/10.1148/radiol.2493080236
22. Kulkarni GS, Lockwood G, Evans AJ, et al. Clinical predictors of Gleason score upgrading: Implications for patients considering watchful waiting, active surveillance, or brachytherapy. *Cancer* 2007;109:2432-8. http://dx.doi.org/10.1002/cncr.22712
23. Koppie TM, Bianco FJ, Kuroiwqa K, et al. The clinical features of anterior prostate cancers. *BJU Int* 2006;98:1167-71. http://dx.doi.org/10.1111/j.1464-410X.2006.06578.x
24. Bott SR, Young MP, Kellett MJ, et al. Contributors to the UCL Hospitals' Trust Radical Prostatectomy Database. Anterior prostate cancer: Is it more difficult to diagnose? *BJU Int* 2002;89:886-9. http://dx.doi.org/10.1046/j.1464-410X.2002.02796.x
25. Lieberman D, Jeldres C, Trinh Q-D, et al. Suspected clinical T3 prostate cancer is associated with high rate of negative extended biopsies: Clinical implications. Presented at: Québec Urological Association Annual Meeting; November 14-16, 2008; Québec, Canada.

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