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Diffusion-weighted MRI for detecting prostate tumour in men at increased genetic risk

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Abstract

Background: Diffusion-weighted (DW)-MRI is invaluable in detecting prostate cancer. We determined its sensitivity and specificity and established interobserver agreement for detecting tumour in men with a family history of prostate cancer stratified by genetic risk.
Methods: 51 men with a family history of prostate cancer underwent T2-W + DW-endorectal MRI at 3.0 T. Presence of tumour was noted at right and left apex, mid and basal prostate sextants by 2 independent observers, 1 experienced and the other inexperienced in endorectal MRI. Sensitivity and specificity against a 10-core sampling technique (lateral and medial cores at each level considered together) in men with >2× population risk based on 71 SNP analysis versus those with lower genetic risk scores was established. Interobserver agreement was determined at a subject level.
Results: Biopsies indicated cancer in 28 sextants in 13/51 men; 32 of 51 men had twice the population risk (>0.25) based on 71 SNP profiling. Sensitivity/specificity per-subject for patients was 90.0%/86.4% (high-risk) vs. 66.7%/100% (low-risk, observer 1) and 60.0%/86.3% (high-risk) vs. 33.3%/93.8% (low-risk, observer 2) with moderate overall inter-observer agreement (kappa = 0.42). Regional sensitivities/specificities for high-risk vs. low-risk for observer 1 apex 72.2%/100% [33.3%/100%], mid 100%/93.1% [100%/97.3%], base 16.7%/98.3% [0%/100%] and for observer 2 apex 36.4%/98.1% [0%/100%], mid 28.6%/96.5% [100%/100%], base 20%/100% [0%/97.3%] were poorer as they failed to detect multiple lesions.
Conclusion: Endorectal T2W + DW-MRI at 3.0 T yields high sensitivity and specificity for tumour detection by an experienced observer in screening men with a family history of prostate cancer and increased genetic risk.

Keywords: Prostate cancer; MRI; Diffusion-weighted; Genetic risk; Screening; Detection

1. Introduction

Men with a strong family history of prostate cancer (defined as a first degree relative with histologically or death certificate proven prostate cancer diagnosed at <70 years or 2 relatives on the same side of the family where at least one is diagnosed at <70 years or ≥3 relatives on the same side of the family diagnosed at any age) carry an increased risk of the disease compared to the general population [1,2]. Seventy-six single nucleotide polymorphisms have been shown to be significantly associated with

Abbreviations: ADC, apparent diffusion coefficient; DW, diffusion-weighted; FoV, field of view; HIPAA, Health Insurance Portability and Accountability Act; iCOGS, Illumina Collaborative Oncological Gene-Environment Study; MRI, magnetic resonance imaging; PSA, prostate specific antigen; SNP, single nucleotide polymorphism; STARD, Standards for the Reporting of Diagnostic Accuracy Studies; TR, repetition time; TE, time to echo; TRUS, transrectal ultrasound.

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prostate cancer in these men [3,4]. The detection of prostate cancer in this population however, remains reliant on random, non-targetted multiple biopsies of the gland, which are painful and carry a significant morbidity whilst not necessarily sampling a relevant lesion. Diffusion-weighted MRI, when used in conjunction with T2-W MRI has been shown to be sensitive at detecting clinically significant prostate cancers [5] especially when random sampling in men with raised prostate specific antigen (PSA) is initially negative [6]. Moreover, the quantified apparent diffusion coefficient (ADC), which reflects the water diffusivity in the extracellular space, is increasingly restricted as tumours increase in cellularity [7] so that ADC correlates with Gleason grade [8,9] and is invaluable in detecting significant cancers. DW-MRI is easy to implement as a standard technique on current MRI platforms, and an ADC map derived using scanner software can be visually assessed for the presence of tumour as an area of restricted diffusion, as well as being quantifiable. The purpose of this study therefore was to determine the sensitivity and specificity of T2W + DW-MRI as a screening tool in men with a family history of prostate cancer stratified by genetic risk and establish interobserver agreement for detecting tumour.

2. Methods

2.1. Subjects

This pilot diagnostic accuracy study had Institutional Review Board approval and was performed as a single institution study at a National Cancer Centre. Ethical standards complied with the Helsinki Declaration of 1975 as revised in 2013. Between January 2010 and July 2012, men aged 41–68 years (mean 53.4 ± 8.5 years) with a positive family history of prostate cancer defined as (i) one first degree relative with histology or death-certificate proven prostate cancer at <70 years, (ii) 2 relatives on the same side of the family with prostate cancer where one is diagnosed at <70 years or (iii) ≥3 relatives on the same side of the family of any age, were invited into the study. Those with a previous cancer and with a terminal prognosis of <5 years or with a previous diagnosis of prostate cancer but with a current negative biopsy were excluded. Fifty-four patients were approached to undergo MRI within this study: 2 declined because of claustrophobia, the third had a high body mass index and had previously experienced discomfort being positioned in an MRI scanner, so declined. Fifty-one consecutive men willing to undergo endorectal MRI followed by a 10-core transrectal ultrasound guided biopsy therefore were prospectively recruited. All subjects were imaged following written informed consent. PSA was 1.9 ± 1.7 ng/mL (mean ± standard deviation). The median interval between imaging and subsequent biopsy was 15 days (lower quartile 6.5 days, upper quartile 29 days). Although limited by the non-targetted approach to biopsy, transrectal ultrasound guided random sampling of the prostate remains the gold-standard for prostate cancer diagnosis.

2.2. SNP analysis and scores

The participant's DNA was genotyped on the iCOGS (Illumina, Collaborative Oncological Gene-Environment Study) chip. iCOGS is a custom Illumina iSelect genotyping array, designed to test genetic variants related to three hormone related cancers of which prostate cancer is one [3]. Data was available for 71 of the 76 previously identified known prostate cancer susceptibility SNPs; 61 were directly genotyped and for 10 loci we used data for a proxy SNP with a linkage disequilibrium >0.75 (3). The cumulative SNP risk score for each patient was calculated by summing 71 risk alleles using the weighted effect (log-additive model) as estimated in previous studies [10]. Patients were divided into those having a low risk (score <0.25) or high risk (score ≥0.25), where 0.25 represented twice the lifetime risk of 1 in 8 (0.125) in a normal population [11].

2.3. Imaging methods

Images were acquired on a 3 T Philips Achieva (Best, Netherlands) using an endorectal coil (Medrad Inc., PA, USA) in combination with an external phased array coil. The endorectal balloon was inflated with 60 ml of perfluorocarbon. Hyoscine butyl bromide was administered routinely as an antiperistaltic agent. T2-W images were obtained in 3 planes orthogonal to the prostate (FSE, TR 2500 ms, TE 110 ms, FoV 14 cm, slice thickness 2.2 mm, matrix 220 × 184 extrapolated to 256 × 256) and were complemented by diffusion weighted images in the transverse plane (single shot EPI, TR 5243 ms, TE 72 ms, $b = 0$, 100, 800 s/mm^2, FOV 180 mm, slice thickness 2.2 mm, matrix 80 m × 71 m, extrapolated to 128 × 128). Whole pelvis imaging was not deemed to be a requirement in this cohort.

2.4. Biopsy procedure and histology analysis

Ten cores were obtained using a random sampling technique (lateral and medial gland base, lateral and medial mid gland and apex from right and left lobes) under transrectal ultrasound (TRUS) guidance. The systematic biopsies were not formally registered to the MR data, although the MR images and reports were available to the operator performing the biopsies, so that visual account could be taken of the position of any identified lesions. Routine antibiotic prophylaxis was administered with Ciprofloxacin 500 mg twice daily and intrarectal Metronidazole 1 g capsule 1–2 h prior to the procedure.

Sections obtained using 18-G Tru-cut needles were stained with haematoxylin and eosin and the presence or absence of cancer and its Gleason grading were noted by a specialist uropathologist. For the purposes of comparison with imaging the lateral and medial cores at the base and mid gland of each side were scored together as either positive or negative for tumour.

2.5. Data analysis

Apparent diffusion coefficient (ADC) maps were derived for every voxel in the image using all b-values and a monoexponential fit of the data. Images were assessed by 2 observers; the