Nine year follow-up for a study of diffusion-weighted MRI in a prospective prostate cancer active surveillance cohort.

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Abstract

Background: In active surveillance (AS) for prostate cancer there is little data on long-term outcomes associated with novel imaging markers.

Objective: To determine long-term outcomes with respect to apparent diffusion coefficient (ADC) derived from diffusion-weighted MRI (DW-MRI) in a prospective AS cohort. Early results were previously published; we now present findings with long-term follow-up.

Design, Setting, and Participants: A subset of patients (86) had pre-enrolment DW-MRI in a prospective research study of AS, 2002-2006. Inclusion criteria: untreated prostate cancer, clinical T1/T2a/N0M0, Gleason $\leq$ 3+4, PSA < 15. Protocol follow-up was by biopsy at 18-24 months, then every 24 months, with regular PSA.

Intervention(s): Men had baseline DW-MRI in addition to standard sequences. ADC was measured from the index lesion on T2-weighted images. To avoid influencing treatment decisions, results of DW-MRI sequences were not available to the AS study investigators.

Outcome Measurements and Statistical Analysis: Baseline ADC was analysed with respect to time to radical treatment (TRT) and time to adverse histology (TAH). Kaplan-Meier analysis, univariate and multivariate regression was performed.

Results and Limitations: Median follow-up: 9.5 years (IQR: 7.9-10.0). On univariate analysis, ADC below the median was associated with shorter TAH and TRT with hazard ratios of 2.13 (CI: 1.17-3.89; p <0.014) and 2.54 (CI: 1.49-4.32; p <0.001), respectively. Median TRT in patients with ADC above the median was 9.3 years (CI: 7.0-11.6) but 2.4 years (CI: 1.5-6.0) for those below the median. For TRT, addition of ADC to a multivariate model of baseline variables resulted in a significant improvement in model fit (HR: 1.33, CI: 1.14-1.54, p<0.001). ROC analysis for TRT: AUC 0.80 (CI: 0.70-0.88). The number of variables included in the multivariate model was limited by sample size.

Conclusions: Long-term follow-up for this study provides strong evidence that ADC is a useful marker when selecting patients for AS. Routine DW-MRI is now being evaluated in our ongoing AS study for initial assessment and as alternative to repeat biopsy.

Patient summary: Before entering a study of close monitoring for the initial management of prostate cancer, patients in this study had a type of MRI scan that looks at the movement of water within cancers. These scans may help predict whether patients should receive close monitoring or whether immediate treatment should be given.

Introduction

Active surveillance (AS) is a standard of care for localised prostate cancer [1,2]. A successful AS programme requires two processes: first, the accurate selection of patients who may safely defer or avoid radical treatment and, secondly, the effective monitoring of patients, with institution of radical treatment for clinically significant progression.

In the major reported cohort studies, selection and monitoring has been based on serum PSA, biopsy Gleason score, and rectal examination findings [3-8]. Although these cohorts have demonstrated medium-term outcomes consistent with other radical treatment approaches, a significant proportion of patients develop progression requiring treatment. More importantly, a small group of patients may develop more advanced disease while on AS, and might have benefited from "upfront" radical treatment. It therefore appears that these baseline investigations cannot fully explain the behaviour of prostate cancer. Furthermore, regular biopsy for AS is invasive and patients are often understandably reluctant to undergo this.

In response to this need for improved selection and monitoring, there has been increasing use of MRI in AS [9]. MRI aims to improve initial staging, and may be useful during monitoring to guide biopsies, or avoid them if imaging is stable. Diffusion-weighted MRI (DW-MRI) measures the movement of water molecules within tissues. The apparent diffusion coefficient (ADC) is derived from these measurements[10]. ADC is relatively high in normal prostate tissue, but low in cancerous prostate tissue due to increased cellularity restricting diffusion [10-12]. We

have previously published outcome data with a median follow-up of 29 months for a cohort of AS patients having baseline DW-MRI [13]. This demonstrated that tumours with lower ADC values were associated with a more aggressive phenotype, as measured by repeat biopsy findings and time to radical treatment. However, given that patients can remain on AS for many years, long-term follow-up is essential for patients and clinicians to make fully informed treatment decisions. There is also a relative lack of AS studies with median follow-up significantly beyond 5 years [14]. In this setting we now present the findings of our study of DW-MRI in AS with the benefit of 9.5 years median follow-up.

Patients and Methods

The methods for this study have been published previously [13]. The Royal Marsden prospective active surveillance study was commenced in 2002 [3]. Eligibility criteria were: clinical stage T1/T2a N0/Nx M0/Mx prostate adenocarinoma with serum PSA <15ng/ml, Gleason score 3+3 or 3+4, and percentage of positive biopsy cores (pbc) ≤50%. Patients were monitored with serial PSA (minimum 3 monthly) and prostate biopsies (first between 12 and 24 months, then every 24 months). Criteria for initiating radical treatment were[15]: PSA velocity >1 ng/ml per year, primary Gleason grade ≥4 on repeat biopsy, or pbc > 50% on repeat biopsy.

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Although MRI was not mandated for active surveillance study entry, a number of patients had prostate MRI scans as part of their assessment for deciding between radical treatment and AS. All patients in this study had DW-MRI in addition to standard sequences. These DW-MRI studies were performed as research scans and results were not available to the managing clinicians in order to minimise influence on decision-making. Although not specified in the AS study protocol, some patients did have repeat MRI during AS follow-up (see Results). When these were reported, the reporting radiologist would have had access to the DW-MRI taken at baseline, although managing clinicians remained blinded.

Initial and repeat biopsies were done using a standard transrectal ultrasound (TRUS) systematic approach. At the date of original analysis (2007), there were 326 patients enrolled in our active surveillance study, 160 of whom had had DW-MRI imaging at baseline. At the time of recruitment to this study, patients had to be eligible for initial repeat biopsy (i.e. not declined biopsy, been treated, or been withdrawn from study)

and have an MRI-visible index lesion from which ADC could be calculated. In addition, for index lesions in the peripheral zone, a positive biopsy in that octant was required. For central gland tumours a homogenous low signal with evidence of mass effect was required. In total, 86 patients fulfilled these criteria and were included in the study. The current analysis was performed in August 2014.

DW-MRI was performed according to a standard protocol, which has been previously described[13]. A single region of interest was defined, and mean ADC calculated. Interpretation was performed by an experienced prostate radiologist (NMdS).

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Baseline clinical variables included: age, initial PSA, Gleason score, clinical stage, free PSA to total PSA ratio, PSA velocity, percentage maximum core involvement, and percentage of positive cores. These were analysed with respect to time to adverse histology (TAH) and time to deferred radical treatment (TRT). ADC was analysed as both a continuous variable and dichotomised about the mean. The unit of measure for ADC was 100 mm^2/s. Kaplan-Meier analysis along with univariate Cox regression was performed for TAH and TRT with date measure from consent to first event. Patients with no event were censored at date of last biopsy or last clinic follow-up for TAH and TRT, respectively. Hazard ratios (HR) and 95% confidence intervals were calculated (1/HR was presented for ADC as lower ADC is associated with more aggressive disease). A multivariate model incorporating selected baseline variables was fitted to the data. The addition of ADC to this model was analysed to determine its independent predictive value. As biopsies are not always performed at exactly regular intervals in AS studies, for TAH, an additional analysis using logistic regression was performed for comparison. This analysis used the binary outcome of

adverse histology at 4 years (the majority of eligible patients had at least two biopsies in the first 4 years). ROC (receiver operating characteristic) analysis was also performed to allow comparison with our original publication[13]. For ROC analysis, repeat biopsy result was treated as a binary outcome.

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Results

Median clinical follow-up was 9.5 years (IQR: 7.9-10.0). Median follow-up for patients who had not had radical treatment at time of analysis was 9.2 years (IQR: 8.2-9.6). Baseline characteristics are displayed in Table 1. Seventy seven (90%) patients had Gleason grade 3+3 at baseline while the remaining nine (10%) were Gleason grade 3+4. Seventy four (86%) patients were clinical stage T1 and 12 (14%) clinical stage T2a. With regard to D'Amico risk group, 72 (84%) were low risk, while 14 (16%) were intermediate risk (in 4 patients this was solely due to a PSA above 10 – range 11-13). Eighty one (94%) patients had an index lesion in the peripheral zone (PZ), while 3 had index lesions involving both the PZ and central gland, and 2 patients had index lesions in the central gland.

Thirty patients (35%) had at least one repeat MRI (see Patients and Methods). The median time to first repeat MRI in this group was 2.8 years (IQR: 2.3-3.6). These investigations were not mandated by the study protocol and were done on an individual patient basis.

Eighty two patients had at least one repeat biopsy and were included in the TAH analysis. The other four patients had treatment due to clinical factors or biochemical progression alone. Median length of biopsy follow-up was 5.4 years, measured from consent to most recent repeat biopsy. Median TAH was 4.1 years (95% CI: 2.5-5.4). The results of univariate analysis are displayed in Table 2. Among other factors, continuous and dichotomised ADC were significant predictors for the development of adverse histology: HR: 1.30; $p < 0.0001$; 95% CI: 1.13-1.50, and HR: 2.13; $p = 0.014$; 95% CI: 1.17-3.89, respectively. For patients whose ADC value was below the

median ADC value, median TAH was 2.20 years (95% CI: 1.67-2.73), for those above the median ADC reading, median TAH has not yet been reached (Figure 1).

All patients were included in the analysis of TRT. Median follow-up was 9.5 years (IQR 7.9-10.0), with 69 (80%) patients having at least 7 years of follow-up. At the time of analysis 59 patients had received deferred treatment. Of these 35 had treatment for adverse histology on repeat biopsy, 15 for biochemical progression alone, 4 due to patient choice and one for worsening clinical features. In addition, 4 patients had radical treatment for PSA or biopsy progression not meeting the criteria for treatment within the study, but supported by repeat MRI findings of volume progression. These repeat MRI scans were done for clinical concern, and were not part of the active surveillance protocol. Radical treatments given were: radiotherapy (42), prostatectomy (13) and, brachytherapy (3). One patient declined radical treatment and was treated with androgen deprivation therapy alone. Univariate analysis for time to deferred radical treatment is shown in Table 3. Again, continuous and dichotomised ADC were significant predictors for time to deferred radical treatment: HR: 1.40; $p < 0.001$; 95% CI: 1.22-1.61, and HR: 2.54; $p = 0.001$; 95% CI: 1.49-4.32, respectively. For patients whose ADC value was below the median ADC reading, median time to deferred radical treatment was 2.40 years (95% CI: 1.5-6.0), compared with 9.33 years (95% CI: 7.0-11.6) for those above the median (Figure 2).

A baseline multivariate model of initial PSA, clinical T stage and percentage of positive cores was fitted to the data. Gleason grade was not included, as this was not a significant predictor on univariate analysis. No further clinical factors were included in view of the limited sample size. The addition of continuous ADC to models for both TAH and TRT resulted in a significant improvement in model fit

247 (Tables 4 and 5): HR: 1.23; p =0.002; 95% CI: 1.06-1.44 and, HR: 1.33; p <0.001;
248 95% CI: 1.14-1.54, respectively. For TAH, similar results were obtained with both
249 logistic and Cox regression approaches (Table 4). The results of the ROC analysis are
250 shown in Table 6.
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Discussion

We have shown that baseline ADC is strongly predictive of both time to adverse histology and deferred radical treatment in an AS cohort with long-term follow-up. Building on our initial findings, the additional multivariate analysis is evidence that ADC has independent predictive value. Therefore, DW-MRI appears to provide further information about disease biology than that provided by standard investigations. Our findings are in keeping with previous studies of DW-MRI in AS, which have shown an association between low ADC and clinically significant prostate cancer[16,17].

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The potential predictive value of DW-MRI, makes it an appealing method for monitoring patients on AS. This may allow men with findings unchanged from baseline to avoid re-biopsy. It may also permit targeted biopsy in those with new areas of low ADC. In a recent systematic review Schoots *et al* assessed the use of MRI in AS. MRI imaging was typically multi-parametric (mpMRI), incorporating DW, T2-weighted, and contrast-enhanced sequences [18]. They concluded that while baseline mpMRI was a good predictor of clinically significant disease, there was relatively little data for its use in monitoring on AS. They also emphasised the need to determine radiological significance and radiological progression for monitoring. We would suggest that the development of areas of reduced ADC while on surveillance is likely to prove useful in this regard. Even more recently, Walton *et al* reported a cohort of 58 men undergoing AS [19]. These patients had mpMRI (including DW-MRI) at baseline and prior to repeat biopsy. They found that unchanged mpMRI

had a negative predictive value of 80% for biopsy upgrade (Gleason 6 to ≥7), suggesting that these patients could safely have avoided re-biopsy.

An unexpected finding in our cohort was the high rate of progression to radical treatment. In our original report, at 29 months follow-up, 39 of 86 patients had received deferred radical treatment[13]. Now, with 9.5 years follow-up, this has risen to 59 patients (with estimated deferred radical treatment rates at nine years of 45% and 81% for patients with ADC above and below the median, respectively; Figure 2). The major reported series (including our own) have 5 year deferred radical treatment rates between 15-40% [3]. Klotz *et al* have reported the series with the longest follow up (819 patients with 6.4 years median follow-up), estimating deferred radical treatment rates of 24%, 36%, and 45% at 5, 10, and 15 years, respectively [4]. A possible explanation is selection bias. Patients were required to have an MRI-visible index lesion from which to calculate ADC. Given that pathological cancer volume is associated with outcome[20], patients with visible lesions on T2-weighted MRI may be more likely to progress than those without visible disease. It should also be remembered that our initial T staging was based on clinical findings rather than MRI.

This study has a number of limitations. First, the relatively small numbers limited the number of variables that could be included in the multivariate analysis and ideally requires validation in a larger cohort. Second, actual ADC values will be dependent on the data acquisition parameters and the model used to derive ADC. In this regard, published ADC values for cancer vary significantly[21]. Therefore, reproducibility between centres is challenging and requires further work to be generalisable. Furthermore, the ADC values of cancer and inflammation can overlap[21]. However,

in our study, the majority of patients had peripheral zone index lesions with a positive biopsy in the corresponding octant. Third, 35% of patients had at least one repeat MRI. As the reporting radiologist for the repeat scans was not blinded to the initial DW-MRI, this may have introduced an element of bias via their report (although the AS investigators remain blinded). However, the median time to repeat imaging was 2.8 years (IQR: 2.3-3.6), where as it can be seen from Figures 1 and 2 that wide separation of curves had occurred by two years. Together with the fact that 65% of patients did not have repeat MRI, this fact makes it less likely that repeat MRI influenced the results significantly. Fourth, the duration of biopsy follow-up is significantly shorter than the clinical follow-up. This is likely due to a combination of factors including: increased interval between biopsies in those with stable features, the increased use of MRI for follow-up, men declining further biopsy, and men who become less fit transferring to a "watchful waiting" strategy. Fifth, we acknowledge that the use of TRUS biopsy has limitations with regard to under-sampling[22]. This may have been improved by using trans-perineal template biopsies[23]. However, these techniques were not our practice at the time of embarking on the study. Finally, an AS strategy incorporating DW-MRI may be less informative for patients who have no index lesion from which to measure ADC at baseline, but a baseline MRI remains a useful comparator for future follow-up.

In order to validate the DW-MRI approach, we are currently conducting a prospective cohort study of AS incorporating mpMRI. The study protocol mandates mpMRI at baseline, 12 months, then every 24 months. In patients with no significant changes in mpMRI findings, repeat biopsy is not mandated. This study will help to generate the prospective evidence required in this setting.

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Conclusions:

Long term follow-up for this study of DW-MRI in AS provides strong support for its value in predicting adverse histology and the need for radical treatment. The evaluation of DW-MRI in large prospective AS studies to improve patient selection and potentially replace biopsy-based monitoring is justified.

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Data access and responsibility

Dr Nicholas van As had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. EAU. European Association of Urology: Guidelines on Prostate Cancer. 2015. http://uroweb.org/guideline/prostate-cancer/. Accessed 11/06/2015.
2. NCCN. National Comprehensive Cancer Network - Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 1.2015. 2014; http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed 24/10/2014.
3. Selvadurai ED, Singhera M, Thomas K, et al. Medium-term outcomes of active surveillance for localised prostate cancer. *Eur Urol.* Dec 2013;64(6):981-987.
4. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. *J Clin Oncol.* Jan 20 2015;33(3):272-277.
5. Tosoian JJ, Trock BJ, Landis P, et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. *J Clin Oncol.* Jun 1 2011;29(16):2185-2190.
6. Cooperberg MR, Cowan JE, Hilton JF, et al. Outcomes of active surveillance for men with intermediate-risk prostate cancer. *J Clin Oncol.* Jan 10 2011;29(2):228-234.
7. Bul M, Zhu X, Valdagni R, et al. Active surveillance for low-risk prostate cancer worldwide: the PRIAS study. *Eur Urol.* Apr 2013;63(4):597-603.
8. Soloway MS, Soloway CT, Eldefrawy A, Acosta K, Kava B, Manoharan M. Careful selection and close monitoring of low-risk prostate cancer patients on active surveillance minimizes the need for treatment. *Eur Urol.* Dec 2010;58(6):831-835.
9. van den Bergh RC, Ahmed HU, Bangma CH, Cooperberg MR, Villers A, Parker CC. Novel tools to improve patient selection and monitoring on active surveillance for low-risk prostate cancer: a systematic review. *Eur Urol.* Jun 2014;65(6):1023-1031.
10. Van As N, Charles-Edwards E, Jackson A, et al. Correlation of diffusion-weighted MRI with whole mount radical prostatectomy specimens. *Br J Radiol.* Jun 2008;81(966):456-462.
11. Sato C, Naganawa S, Nakamura T, et al. Differentiation of noncancerous tissue and cancer lesions by apparent diffusion coefficient values in transition and peripheral zones of the prostate. *J Magn Reson Imaging.* Mar 2005;21(3):258-262.
12. Morgan VA, Kyriazi S, Ashley SE, DeSouza NM. Evaluation of the potential of diffusion-weighted imaging in prostate cancer detection. *Acta Radiol.* Jul 2007;48(6):695-703.
13. van As NJ, de Souza NM, Riches SF, et al. A study of diffusion-weighted magnetic resonance imaging in men with untreated localised prostate cancer on active surveillance. *Eur Urol.* Dec 2009;56(6):981-987.
14. Simpkin AJ, Tilling K, Martin RM, et al. Systematic Review and Meta-analysis of Factors Determining Change to Radical Treatment in Active Surveillance for Localized Prostate Cancer. *Eur Urol.* Jan 21 2015.
15. Venkitaraman R, Norman A, Woode-Amissah R, et al. Predictors of histological disease progression in untreated, localized prostate cancer. *J Urol.* Sep 2007;178(3 Pt 1):833-837.

16. Somford DM, Hoeks CM, Hulsbergen-van de Kaa CA, et al. Evaluation of diffusion-weighted MR imaging at inclusion in an active surveillance protocol for low-risk prostate cancer. *Invest Radiol.* Mar 2013;48(3):152-157.

17. Morgan VA, Riches SF, Thomas K, et al. Diffusion-weighted magnetic resonance imaging for monitoring prostate cancer progression in patients managed by active surveillance. *Br J Radiol.* Jan 2011;84(997):31-37.

18. Schoots IG, Petrides N, Giganti F, et al. Magnetic Resonance Imaging in Active Surveillance of Prostate Cancer: A Systematic Review. *Eur Urol.* Apr 2015;67(4):627-636.

19. Walton Diaz A, Shakir NA, George AK, et al. Use of serial multiparametric magnetic resonance imaging in the management of patients with prostate cancer on active surveillance. *Urol Oncol.* Mar 5 2015.

20. Turkbey B, Mani H, Aras O, et al. Prostate cancer: can multiparametric MR imaging help identify patients who are candidates for active surveillance? *Radiology.* Jul 2013;268(1):144-152.

21. Giannarini G, Petralia G, Thoeny HC. Potential and limitations of diffusion-weighted magnetic resonance imaging in kidney, prostate, and bladder cancer including pelvic lymph node staging: a critical analysis of the literature. *Eur Urol.* Feb 2012;61(2):326-340.

22. Ukimura O, Coleman JA, de la Taille A, et al. Contemporary role of systematic prostate biopsies: indications, techniques, and implications for patient care. *Eur Urol.* Feb 2013;63(2):214-230.

23. Lecornet E, Ahmed HU, Hu Y, et al. The accuracy of different biopsy strategies for the detection of clinically important prostate cancer: a computer simulation. *J Urol.* Sep 2012;188(3):974-980.