Journal of Lifestyle Diseases and Management

Open Access Research Article

Prostate Cancer Progression Defined by MRI Correlates with Serum PSA in Men Undergoing Lifestyle and Nutritional Interventions for Low Risk Disease

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Received: 27 Jul 2015
Accepted: 05 Dec 2015
Published: 07 Dec 2015

Competing interests: The authors declare that no competing interests exist.

Access This Article

Abstract

Background: Men with low-risk prostate cancer are often offered active surveillance (AS), sparing them the toxicities of radical therapies and providing them with the opportunity to embark on healthy lifestyle and nutritional strategies. Annual magnetic resonance imaging (MRI) is increasingly being used to help monitor disease progress although its precise role has not been fully established. Hitherto no study has correlated changes in MRI disease status with Prostate Specific Antigen (PSA) dynamics among men managed with AS.

Methods: We correlated 346 serum PSA levels with 346 MRIs of 138 men who had at least two prostate MRI scans, and who had prostate cancer managed with AS. All men were given lifestyle information guidance and 102 were also were also taking, long term, a polyphenol rich food supplement following initial recruitment in the UK's Pomi-t study.

Results: Men with progression seen on MRI had a mean 39.78% rise in PSA (confident interval (CI) 28 to 52%), compared to those whose disease shrunk (-16.05%, CI 14 to -46%), remained stable (1.62% CI -3 to 5%), or was not visualised (-1.62%, CI -14 to 11%) (ANOVA, P-value <0.0001). Of the 142 (68.6%) with paired scans with stable disease 54.1% involved men taking polyphenol rich food supplement as opposed to 14.49% not taking it (chi squared test of $p < 0.01$).

Conclusions: This strong link between PSA dynamics and MRI tumour progression provides reassurance to men on AS that their PSA dynamics reflect underlying tumour status as seen on MRI, especially in this group keen on lifestyle and nutritional self help strategies.

Cite as: Thomas R, Shaikh M,Cauchi M, et al. Prostate Cancer Progression Defined by MRI Correlates with Serum PSA in Men Undergoing Lifestyle and Nutritional Interventions for Low Risk Disease. J Lifestyle Dis Management. 2015;1(1):1-8.

Keywords: Active surveillance, Multiparametric MRI, Prostate cancer, PSA

Introduction

Increased public awareness and widespread use of the prostate-specific antigen (PSA) test has resulted in increased detection of low-risk localised prostate cancer.[1] As most of these tumours undergo an indolent rate of progression,[2] national guidelines support active surveillance (AS), reserving radical intervention for those with evidence of significant progression. This spares many men the toxicities of radical therapies, which for this type of disease would not confer a survival advantage. Moreover, AS provides men with the opportunity to embark on healthy lifestyle strategies, which have been shown to further slow PSA progression.[3,4] PSA is a useful tool for monitoring disease progression or response to treatment, but men on AS are also usually monitored with digital rectal examination (DRE), repeat biopsy, and, more recently, serial magnetic resonance imaging (MRI). The role of prostate MRI in particular has gained importance with the development of higher-resolution diffusion-weighted imaging (DWI).[1,5]

There is evidence that findings from MRI can be accurate predictors of disease progression found on re-biopsies[6,7] and of tumour size found on pathological analysis after prostatectomy.[8] There is also evidence that the presence and size of diffusion-weighted MRI (DW-MRI) abnormalities are correlated with PSA level both at initial diagnosis [6] and after radiation or hormone therapy.[9] The purpose of this evaluation was to correlate PSA dynamics with changes in MRI-defined tumour status in men managed with AS, for which, to the best of our knowledge, there has been no published report to date.

Materials and methods

Patients

Although this data was collected prospective we retrospectively analysed the MRI-defined disease status from 346 scans and correlated it with the PSA dynamics of 138 men with histologically confirmed prostate cancer. This represents the complete cohort of men managed with AS at our community Oncology Unit who had undergone at least two MRI scans by April 2015. All men were given verbal and written lifestyle information which included reducing intake of processed sugar, exercising more than three hours a week, tips to stop smoking (if relevant), tips to lose weight (if relevant) and eating more healthy rich foods such as herbs, spices, fruit and vegetables based on evidence from previous studies.[3,4] The cohort also included 102 men (74%) who had been recruited into a previous polyphenol rich food supplement study.[4] The baseline characteristics of the patient cohort are summarised in Table 1. Age and tumour grade (Gleason score) did not differ significantly between the radiological categories defined below. The study protocol conformed to the guidelines of the Department of Health Research Governance Framework for Health and Social Care and was approved by the Bedford Hospital NHS Trust Research and Development Department.

PSA and MRI analysis

Men managed with AS in our unit were clinically reviewed every four to six months, and from mid-2012 the policy of annual MRI was gradually introduced. MRI was performed with a 1.5 Tesla scanner and a body matrix coil. Sequences included T2-weighted, T1-weighted, and diffusion-weighted imaging. The quality of MRI did not change over the course of this study. Of the 138 men evaluated, 81 had two MRI scans and 57 had more than two. For this study, consecutive MRIs were analysed as separate pairs. The serum PSA levels at the time of the first and second MRI scans were compared, and the MRI scans were compared with each other. All MRIs had an initial report from a consultant radiologist, and the images were further reviewed in our

Specialist Multidisciplinary Team (SMDT) meeting. If disease status remained unclear, images were reviewed a third time in our regional SMDT meeting. Disease on consecutive MRI scans were categorised into four groups (Figure. 01):

- No disease: No signs of the disease seen on either image.
- No change: No differences in disease volume or intensity between images.
- Progression: Increased size of lesion, new lesion, invasion into prostatic capsule or seminal vesicles.
- Improvement: Smaller or less intense disease seen

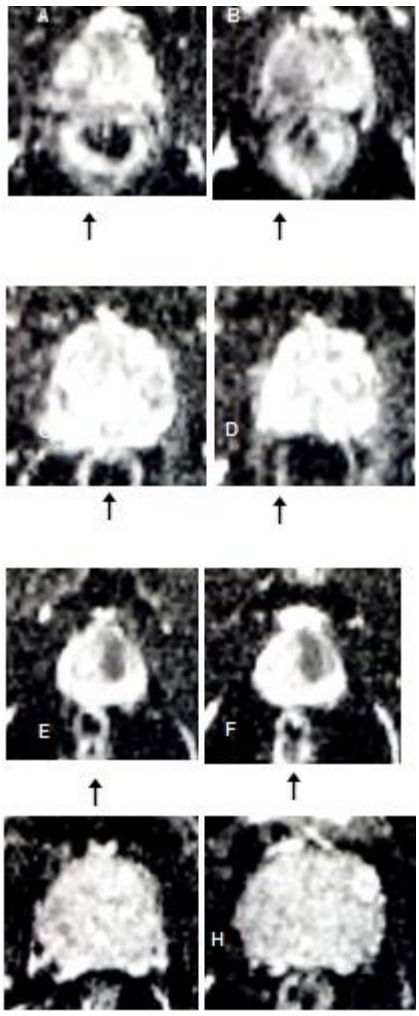

Figure. 01 *Apparent diffusion coefficient (ADC) maps obtained from consecutive DW-MRIs of four different patients, illustrating changes in disease.*

Areas of low signal abnormality are indicated with black arrows. (A-B) Progression. On (A), an 11 mm x 8 mm area of restricted diffusion can be seen in the right peripheral zone. This lesion has increased to 18 mm x 13 mm on the second scan (B). (C-D) Improvement. There is a small area of restricted diffusion (C) which can no longer be seen on the scan taken one year later (D). (E-F) No change. The low signal region of abnormality has not changed significantly between consecutive MRI scans, and there are no other signs of progression or change. (G-H) No disease.

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There are features suggestive of benign prostatic hyperplasia, including diffuse enlargement of the prostate gland with barely distinguishable peripheral zones. However, there are no areas of restricted diffusion or foci suspicious for prostate cancer on either scan.

Statistical analysis

MATLAB R2011a (MathWorks Inc., USA) and GraphPad Prism 6 (GraphPad Software, USA) were employed. The difference in PSA levels at first and second MRI scan within each MRI category was evaluated using the paired t-test. One-way ANOVA was used to compare age, PSA, and PSA percentage change between the MRI categories, and the chi-squared test was used to assess differences in Gleason score. Differences with calculated P-values < 0.05 were considered statistically significant. Significant P-values obtained with one-way ANOVA were further evaluated by making multiple comparisons using Tukey's test.

Results

The results as distributed across the MRI categories are summarised in Table. 01. There was no difference in the baseline characteristics between the four MRI categories namely Initial PSA (one way ANOVA P<0.191), age (one way ANOVA p<0.531) and Gleason grade (Chi2 p<0.898). Overall, the mean PSA remained stable over one year for the whole cohort (7.1 to 7.3 µg/l, paired t-test p<0.72). Disease was seen on 78.6% of the total MRI scans, and the majority of paired MRIs (68.6%) showed stable disease, no disease was seen on 15.9% of images.

Total (N) = 138 men		MRI Category				
		Improved	No change	No disease	Progressed	Calculated P-value
Number of paired MRIs (%)	207	8	142	33	24	NA
Age (years, mean [sd] (range)*	69.7 [6.1] (52-83)	67.8 [6.8] (57-76)	70.0 [6.0] (52-80)	68.6 [6.8]	70.0 [5.3]	0.531
Gleason 6 (%)*	115 (83%)	6 (75%)	120 (85%)	27 (82%)	20 (83%)	0.898
Gleason 7 (%)*	23 (17%)	2 (25%)	22 (15%)	6 (18%)	4 (17%)	
PSA at first MRI (µg/l, mean [sd])*	7.1 [3.1]	6.0 [2.5]	7.3 [2.9]	6.2 [3.6]	7.3 [3.3]	0.191

PSA at second MRI (µg/l, mean [sd])#	7.3 [3.7]	4.8 [2.6]	7.4 [3.3]	5.9 [4.0]	9.9 [4.4]	0.0001
Percentage change in PSA	3%	-16.05% CI 14 to -46%	1.62% CI 5 to -3%	-1.62% CI 11 to -14%	39.78% CI 28 to 52%	

Table. 01 *Summary of patient baseline demographics and results*

** For these baseline characteristics, there was no statistical difference between the four MRI categories; sd is standard deviation.*

 # PSA at second MRI was significantly higher (ANOVA)for the group that progressed compared to the other three categories combined (p<0.0001) or individually compared to those that showed improvement (P<0.01), no change, (P<0.01) or no disease (P<0.01)

The difference between the PSA at first MRI and the PSA at second MRI was statistically significant for the group that progressed on MRI as it rose from 7.3 to 9.9 µg/l (39.78%, CI 28 to 52%, paired t-test p value 0.023). This was a significantly greater PSA increase compared to men whose disease was stable (7.3 to 7.4 µg/l), not seen (6.2 to 5.9 µg/l), or improved on MRI (6.0 to 4.8µg/l) (One way ANOVA, P<0.0001) (Figure. 02). Only one man (0.7% of entire group) who had an MRI showing disease progression had a PSA that fell. Figure. 02 also demonstrates that the best PSA dynamics occurred in the 8 men (3.9%) whose disease improved on MRI for whom the average PSA fell from a mean of 6.0 to 4.8µg/l but this percentage fall of 20% had wide confidence intervals in view of the small number in the group (CI +14 to -46%).

Of the 102 men who were taking the polyphenol rich food supplement either continuing from the previous RCT[4] or subsequently starting taking it at their own accord, all 8 (3.9%) of paired MRI scans showing disease improvement included men who were taking the supplement (3.9%). Of the 142 men (68.6%) with paired scans with stable disease 112 (54.1%) involved men taking the supplement as opposed to 14.49% not taking it (chi squared test of p< 0.01).

Discussion

This study of all men in our institute managed with AS reassures us that average PSA progression was very low 7.1 to 7.3 µg/l (3%) and only 11.6% had MRI progression which promoted intervention to radical interventions including surgery, radiotherapy or brachytherapy. These figures are on a par or generally better than the large published AS series internationally,[2,3,10] although men in our centre receive evidence based lifestyle advice.[3]

More and more men are now opting to be managed with AS to avoid treatment toxicities with radical interventions but it is important to remember even in this group with indolent disease some progress and require intervention so accurate follow up is required including cost effective imaging.[2,10]

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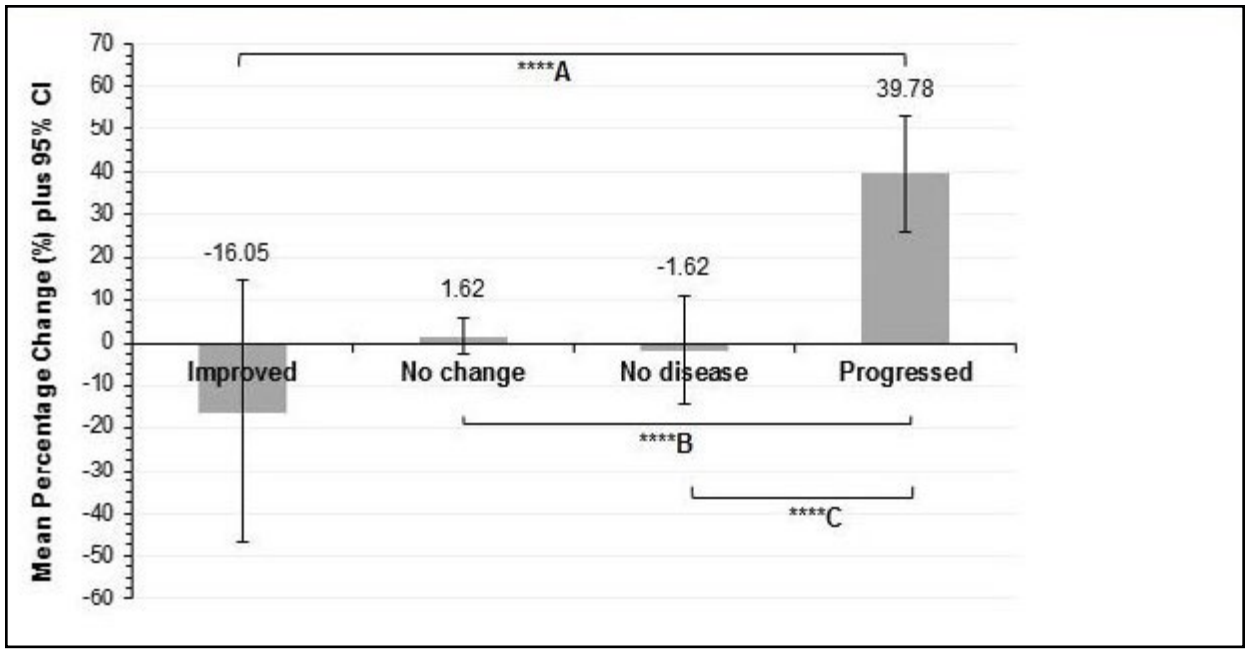

Figure. 02 *Mean percentage change in PSA associated with the different MRI categories.*

***** P-value <0.0001 calculated by one-way ANOVA. A compares "Improved" with "Progressed"; B compares "No change" with "Progressed"; C compares "No disease" with "Progressed".*

Several studies have reported a useful role for MRI staging of prostate cancer to detect capsular, seminal vesicle or nodal involvement, in order to advise treatment modalities.[11] MRI also accurately predicts the location and volume of intra-prostatic disease,[12] the presence of high-grade disease,[13] and can be used to direct transrectal and transperineal biopsies.[14,15] Although it has been reported that men with more significant intra-prostatic lesions on MRI are more likely to progress on AS,[6,16] there have been no previous reports correlating MRI progression with changes in PSA over time.

We believe that this study is important for men managed with AS, as PSA is a significant component in monitoring disease, together with DRE and repeat biopsy. Indeed, many men monitor their own disease by plotting their PSA levels, often using online and mobile device applications. They frequently rely on PSA dynamics as a trigger for deciding whether to remain on AS or leave for radical interventions.[4] Our findings provide some reassurance that PSA dynamics represents underlying disease, or at least that defined by MRI. This correlation appears most helpful among men at both ends of the radiological spectrum, with MRI progression being associated with a significant rise in PSA. While the fall in PSA associated with MRI improvement was not found to be statistically significant, most likely due to the small number of cases of improvement, we also found falling PSA to be associated generally with improvement or no disease seen on MRI.

The weakness of this study is that it is open, non-randomised, and from a single centre. Its strength is that it studies an entire group of men, rather than a selected cohort, within a busy community hospital, which avoids potential selection bias and suggests that the data is very relevant to routine UK practice. This study also adds bearing to some of the AS lifestyle intervention studies that have been published which were not able to fund regular MRI in their design.[3,4,17] Our link between PSA dynamics and MRI-defined disease status makes it

more likely that the significant PSA changes produced by the lifestyle interventions in these studies were clinically relevant, at least in this setting of early, localised disease.

The benefits of the polyphenol rich food supplement were previously evaluated by a double blind RCT which showed a 64% reduction in PSA progression compared to placebo.[4] Like all other lifestyle studies evaluating its effects on PSA, MRIs were too prohibitively expensive to be included as a primary end point. Baring in mind the retrospective nature of this analysis, albeit on prospectively recorded data, it is reassuring all men with MRI disease improvement were taking Pomi-T as well as a significantly higher proportion of men taking it in the stable disease category than not.

Prostate cancer is now the most common cancer in men, and at least 40% of men diagnosed with favourable-risk disease are offered AS often involving regular monitoring for many years.[10] Although multiparametric MRI is now available in most UK hospitals, standardised protocols determining whether to use it for all men and at what intervals have not been established. Further research, especially in terms of cost-effectiveness and in relation to repeat prostatic biopsy, is clearly needed. Our study provides more data to help plan a potential trial design, which would be of national significance in view of the large number of potential MRIs involved. It suggests that, for men managed with AS for low-risk disease, a falling PSA provides reassurance that MRI-defined disease is not growing, and within the safeguards of a trial design the intervals between scans could be extended, reducing costs. On the other hand, a significantly rising PSA suggests that the intervals between MRIs should be shortened or further investigations triggered especially if the man is keen to continue AS. Such a trial would further contribute to determining the optimal usage of PSA and MRI as tools of disease monitoring for men managed with AS.

Acknowledgement

We are most grateful to the members of the Bedford Hospital Urology SMDT for their contributions to MRI interpretation. This work was supported by the Primrose Oncology Research Fund.

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