Validity of prostate-specific antigen as a tumour marker in men with prostate cancer managed by watchful-waiting: correlation with findings at serial endorectal magnetic resonance imaging and spectroscopic imaging

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OBJECTIVE

To investigate the validity of prostate-specific antigen (PSA) as a tumour marker in men with clinically localized prostate cancer who have selected watchful waiting, by determining if serial PSA level measurements are correlated with findings of malignancy or benign prostatic hyperplasia (BPH) at serial endorectal magnetic resonance imaging (MRI) and magnetic resonance spectroscopic imaging (MRSI).

PATIENTS AND METHODS

We retrospectively identified 69 men with biopsy-proven prostate cancer being managed by watchful waiting, who underwent serial endorectal MRI/MRSI and who had contemporaneous serial PSA measurements. The mean (range) follow-up was 392 (294–571) days. A panel of three experienced readers reviewed the initial and follow-up MRI/MRSI studies, and classified findings of prostate cancer as stable or progressive. Another reader assessed BPH by calculating total gland and central gland volumes on all studies.

RESULTS

At the follow-up MRI/MRSI, 51, 17 and one patient had stable, progressive, or unevaluable prostate cancer, respectively. The mean PSA velocity was significantly greater in patients with radiologically progressive disease (1.42 vs 0.42 ng/mL/year, $P = 0.04$). A PSA velocity of >0.75 ng/mL/year identified those with radiologically progressive disease with a true-positive fraction of 0.71 and a false-positive fraction of 0.39. PSA levels were not correlated with changes in total or central gland volumes ($P > 0.05$).

CONCLUSIONS

In men with clinically localized prostate cancer who select watchful waiting, serial PSA levels are correlated with findings of malignancy but not BPH at serial endorectal MRI/MRSI, suggesting that PSA is a useful longitudinal tumour marker in this population.

KEYWORDS

PSA, biological markers, prostatic neoplasms, prostatic hyperplasia, MRI

INTRODUCTION

The identification of serum PSA as a tumour marker revolutionized both the diagnosis and therapeutic monitoring of prostate cancer. At high levels, PSA is clearly associated with the presence of cancer and serial changes can be used to follow tumour progression or regression [1,2]. For example, preliminary results from the prospective Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial show that 35.7% of men with a PSA level of 4–10 ng/mL have prostate cancer on biopsy, rising to 72.8% of men with a PSA level of >10 ng/mL [1]. However, the role of PSA as a cross-sectional tumour marker at the lower levels typically encountered in the North American population has recently been questioned; Stamey *et al.* [3] showed that PSA levels in North American men currently being diagnosed with prostate cancer are correlated only with the presence of BPH and not with the presence of prostate cancer. In that study, the mean serum PSA for the period 1999–2003 was 8.14 ng/mL, vs 24.74 ng/mL for 1983–88. Six histological cancer variables (volume of largest cancer, capsular penetration, lymph node involvement, seminal vesicle invasion, Gleason grade 4/5 of largest cancer, and prostate size) were significantly related to serum PSA level in 1983–88, but in 1999–2003 serum PSA level was related only to prostate size. The authors controversially declared that the 'PSA era' was over in the USA [4], and suggested that better tumour markers are needed for the diagnosis of early-stage prostate cancer. Because the study focus was cancer diagnosis rather than tumour monitoring, and because the study design was cross-sectional rather than longitudinal, it did not address the question of whether serial changes in low levels of PSA are correlated with tumour development. This question is critically important for patients being managed by watchful waiting, in whom objective and agreed criteria to define progression are controversial [5]. Over the last two decades, combined endorectal MRI and magnetic resonance spectroscopic imaging (MRSI) has emerged as a relatively accurate and powerful new method of evaluating

the local extent and aggressiveness of prostate cancer [6–9]. To our knowledge, the relationship between serial PSA levels and serial MRI/MRSI findings has not been explored. Therefore, in the present study we investigated the validity of PSA as a tumour marker in men with prostate cancer managed by watchful waiting, by determining if serial PSA measurements are correlated with findings of malignancy or BPH at serial endorectal MRI/MRSI.

PATIENTS AND METHODS

Using the University of California at San Francisco Prostate Cancer Database, we retrospectively identified 69 men with biopsy-proven and clinically localized prostate cancer who selected management by watchful waiting, and who had serial endorectal MRI/MRSI at our institution between 1998 and 2001 with contemporaneous serial PSA measurements. Patients were recruited as part of an ongoing National Institute of Health (NIH) study investigating the use of MRI/MRSI in prostate cancer. In addition to informed consent obtained prospectively for the NIH trial, this retrospective study was approved by our Committee on Human Research and was compliant with the Health Insurance Portability and Accountability Act (HIPAA) regulations. The mean (range) patient age was 68 (53–87) years; the mean baseline serum PSA was 6.9 (3.1–18.6) ng/mL; the median Gleason score was 6 (2–7). The clinical stage was T1 in 19 patients and T2 in 12 (data on clinical stage was unavailable in the other 38). The mean interval between the initial and follow-up MRI/MRSI studies was 392 (294–571) days, and the mean interval between each MR study and the contemporaneous PSA measurement was 37 (0–90) days.

MR studies were performed on a 1.5-T whole-body MR scanner (Signa; GE Medical Systems, Milwaukee, WI, USA). Patients were scanned while supine, using the body coil for excitation and a pelvic phased-array coil (GE Medical Systems) in combination with a commercially available balloon-covered expandable endorectal coil (Medrad, Pittsburgh, PA, USA) for signal reception. MRI sequences acquired included thin-section high spatial resolution axial and coronal T2-weighted fast spin-echo images of the prostate and seminal vesicles, with the following parameters: TR/effective TE, 5000/96 ms; echo train length, 16; slice thickness, 3 mm, interslice gap, 0 mm; field of view, 14 cm; matrix, 256 × 192, frequency direction anteroposterior (to prevent obscuring the prostate by endorectal coil motion artefact), and three excitations. After reviewing the axial T2-weighted images, a MRSI volume was selected to maximize coverage of the prostate, while minimizing the inclusion of periprostatic fat and rectal air. Three-dimensional MRSI data were acquired using a water and lipid-suppressed double-spin echo point-resolved spectroscopy sequence that used spectral spatial pulses for the two 180° excitation pulses. The spectral-spatial pulses allowed both sharp volume selection and frequency selection, to reduce the water resonance and suppress lipid resonance. Data sets were acquired as 16 × 8 × 8 phase-encoded spectral arrays (1024 voxels with a spatial resolution of 0.24–0.34 cm), TR/TE 1000/130 ms, and a 17-min acquisition time. The spectroscopic imaging data was zero-filled from 8 to 16 in both the anteroposterior and craniocaudal directions to increase the likelihood of optimal alignment between spectroscopic voxels and the peripheral zone. The total examination time was 1 h, including coil placement and patient positioning. MRSI data were overlaid on the corresponding axial T2-weighted images, including the raw spectra and the choline to creatine ratio, and the choline plus creatine to citrate ratio.

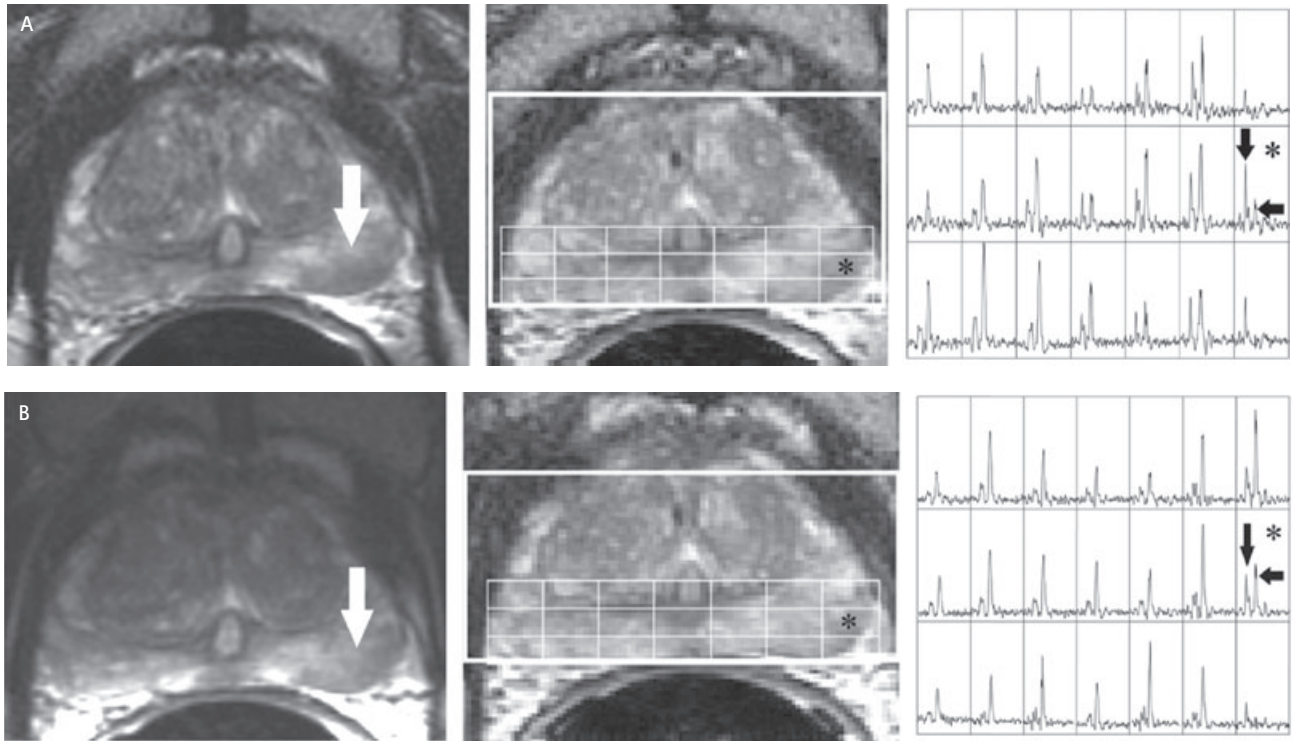
For MRI/MRSI interpretation an expert consensus panel composed of three experienced readers (F.V.C, A.Q., J.K.) compared the follow-up and initial MRI/MRSI studies and classified findings of malignancy as stable or progressive. Readers used their professional judgement and experience to identify tumour, rather than using fixed objective criteria, but in general tumour was defined at MRI as a mass-like nodule of low T2 signal intensity and at MRSI as a cluster of voxels showing abnormal metabolism (choline elevation or citrate reduction, or both) [10]. Stable disease was considered present if there was no appreciable change in MRI and MRSI findings. Progressive disease was considered present if either MRI or MRSI showed an appreciable increase in tumour extent or if MRSI showed an increase in metabolic abnormality. The expert panel was unaware of the PSA or biopsy results. BPH was evaluated by calculating both total gland volume and central gland volume. One experienced reader (I.C.) measured the total and central gland volumes on each of the initial and follow-up endorectal MRI studies using the ellipsoid formula (volume = 0.52 × anteroposterior diameter × transverse diameter × craniocaudal diameter).

Statistical analyses were used to determine if PSA velocity, defined as (follow-up PSA – initial PSA)/(time interval between initial and follow-up PSA in years), was correlated with prostate cancer development (as determined by consensus panel review of serial MRI/MRSI studies) or with changes in BPH (as determined by measurement of total and central gland volumes). The nonparametric Wilcoxon rank-sum test was used to determine whether PSA velocity was significantly different between patients with or with no progression. Using different thresholds of PSA velocity to define progressive or stable disease, and using serial MRI/MRSI as the reference standard, we calculated the area under (AUC) the receiver operating characteristic (ROC) curve to estimate the accuracy of PSA velocity as a longitudinal tumour marker. Multivariate linear regression analysis was used to identify the subset of variables from prostate cancer progression and BPH that were most predictive of the changes in PSA. A ROC curve was constructed for PSA velocity by plotting the pairs of (1 – specificity, sensitivity) for varying threshold points on a unit square. The AUC of the ROC curve and the associated standard error were calculated using the trapezoidal method.

RESULTS

At follow-up MRI/MRSI, 51 men had stable and 17 had progressive prostate cancer (in one disease progression could not be assessed because of extensive haemorrhage after biopsy on the initial MR study, and this case was excluded from further analysis). A representative example of radiologically progressive disease is shown in Fig. 1. Using the Wilcoxon rank-sum test, the PSA velocity was significantly greater in men with radiologically progressive disease (1.42 vs 0.42 ng/mL/year, $P = 0.04$). Using a different threshold of PSA velocity to define progressive or stable disease, and using serial MRI/MRSI as the reference standard, the AUC (SEM) was 0.67 (0.08) (Fig. 2). In particular, a PSA velocity of >0.75 ng/mL/year identified those with radiologically progressive disease with a true-positive fraction of 0.71 and a false-positive fraction of 0.39. The mean total

FIG. 1. (A) Photomontage of an axial T2-weighted MR image through the base of the prostate (left panel), the same image with the overlaid MRSI volume and grid (central panel), and the corresponding spectra from the grid (right panel) in a 60-year-old man with a PSA level of 4.0 ng/mL and biopsy-proven Gleason 6 prostate adenocarcinoma. An ill-defined focus (white arrow) of low T2 signal intensity in the left side of the prostate is associated with metabolic signs of malignancy on MR spectroscopy; for example, the voxel indicated with an asterisk shows elevation of the choline peak (vertical black arrow) and reduction of the citrate peak (horizontal black arrow). (B) Similar photomontage at the same level 13 months later. The focus of low T2 signal (white arrow) is more pronounced and the metabolic abnormalities have increased in extent and magnitude. For example, the voxel indicated by an asterisk (corresponding to the labelled voxel in Fig. 1A) shows a greater elevation of the choline peak (vertical black arrow) and a greater reduction in the citrate peak (horizontal black arrow). Interval increases in choline are also seen in adjacent voxels. These findings of radiological disease progression were associated with an increase in the PSA level to 6.3 ng/mL over the same period.



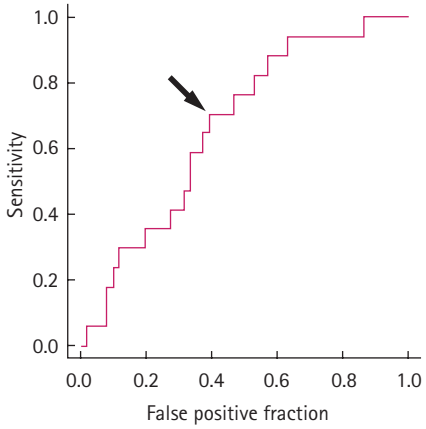
gland volume did not change significantly (41.6 mL at baseline vs 43.5 mL at follow-up). Similarly, the mean central gland volume did not change significantly (23.2 mL at baseline vs 24.6 mL at follow-up). PSA levels were not correlated with changes in total or central gland volume ($P > 0.05$).

DISCUSSION

The present results suggest that, despite recent controversy about the use of PSA as cross-sectional tumour marker for population screening [3,4], PSA remains a valid tumour marker for the longitudinal follow-up of men with prostate cancer managed by watchful waiting. We found that PSA levels increased faster in men with radiologically progressive disease than in men with radiologically stable disease, using state-of-the-art endorectal MRI/MRSI for tumour visualization. Based on the present findings, patients on watchful-waiting can be reassured that PSA remains a legitimate tool for therapeutic monitoring. However, the present study also illustrates that other endpoints might be required, as we found PSA velocity to be a relatively crude instrument to distinguish stable from progressive disease; even the optimum threshold of 0.75 ng/mL/year was associated with a limited true-positive fraction of 0.71 and a substantial false-positive fraction of 0.39. Interestingly, we found no correlation between total and central gland volumes and PSA changes over time, perhaps because BPH is too indolent to affect PSA levels over the relatively short-term follow-up in our cohort. This suggests that BPH is not a confounding factor when using PSA for following men who have selected watchful waiting.

The use of PSA to monitor patients selecting watchful waiting has been widely studied. A short PSA doubling time correlates with clinical progression, disease progression on repeat biopsy and DRE, and progression to treatment [11–13]. This approach is not without problems, because the threshold PSA doubling time considered to define progression varies considerably between studies, and because PSA doubling time might be a poor proxy for progression, with a substantial overlap of PSA doubling times between men with organ-confined tumour and men with metastatic disease [14,15]. Other options to define progression in this population include an increase in disease on DRE or TRUS, development of obstructive symptoms, or upgrade in Gleason score on repeat biopsy [16–19]. All of these criteria can be easily criticized, as DRE and TRUS might be unreliable and subjective, bladder outlet symptoms are more likely to be due to BPH than cancer, and histological progression on repeat biopsy could be due to sampling variation rather than true tumour dedifferentiation. 'Progression to treatment' is equally problematic, as it might be driven by

FIG. 2. ROC curve showing the performance of PSA velocity at different thresholds to define progressive or stable disease, using serial MRI/MRSI as the standard of reference. The AUC is 0.67, indicating reasonable accuracy (1.0 indicates a perfect test while 0 indicates a useless test). A PSA velocity of >0.75 ng/mL/year (arrow) identified those with radiologically progressive disease with a true-positive fraction of 0.71 and a false-positive fraction of 0.39.



these other poor markers of disease status, or by patient preference in the absence of objective data. Clearly, an additional method of tumour monitoring could be of great benefit in these patients, and imaging is a natural choice given the widespread use of radiological endpoints in oncological practice. Unfortunately, serial TRUS has been shown to be unhelpful in this regard [20]. Our preliminary results suggest that endorectal MRI/MRSI might be able to fill this need for an imaging method that can reliably follow untreated localized prostate cancer. We suspect the superiority of MRI/MRSI reflects the ability of this method to provide a precise and permanent volumetric record of the anatomical and metabolic status of the prostate.

The present study has several limitations. First, and probably foremost, is the use of endorectal MRI/MRSI as the standard of reference to define tumour progression or stability. Endorectal MRI/MRSI remains an emerging technology, and the legitimacy of using this to evaluate prostate cancer stability or progression would have to be considered novel and unvalidated. Because the subjects of this study elected to undergo watchful waiting rather than surgery, step-section histopathological correlation is impossible. Step-section histopathological validation of tumour progression is also impossible, as previous prostatectomy would have precluded serial measurements of tumour volume. Ultimately, a long-term follow-up to investigate whether imaging or biochemical progression is a better indicator of prostate cancer-specific morbidity and mortality would be required to validate MRI/MRSI as an appropriate tool for therapeutic monitoring, and establish whether it is better than PSA testing. Second, the preliminary nature of the present study leaves many practical questions unanswered; e.g. is it feasible, realistic, or cost-effective to use MRI/MRSI for surveillance of patients on watchful waiting? Is such monitoring superior to PSA testing for ultimate patient outcome? How should discrepancies between serial MRI/MRSI and PSA results be arbitrated? All of these are valid questions and concerns that will probably only be resolved after larger, longer and more detailed studies. Third, the mean follow-up interval was only 392 days. Given the indolent nature of prostate cancer in men with low-risk tumours, this might be considered a short time. Despite this, and despite the relatively few patients in the present study, we found a significant association between MRI progression and biochemical progression. Arguably, our ability to detect such association in a small study group over a short time is of itself supportive evidence that the association is probably valid. However, a longer follow-up in a larger population studied prospectively would clearly be preferable, and can be addressed in future studies. Fourth, the study was retrospective at one academic institution, using a relatively small and selected population of patients seen and treated at this centre. The extent to which the present results can be extrapolated to other institutions and populations is unknown. Fifth, tumour progression was evaluated by the consensus judgement of an independent expert panel. Despite our best efforts to bring as much experience and objectivity as possible to the definition of tumour progression, there is undoubtedly some subjectivity in this. Sixth, we suggested a PSA velocity of ≥0.75 ng/mL/year to define progression, but this was associated with a limited true-positive fraction of 0.71 and a substantial false-positive fraction of 0.39. The extent to which the imperfections of this threshold reflect limitations of the MRI/MRSI technique vs other factors such as 'noise' and non-malignant causes of variation in serum PSA levels is unknown. It is possible that a more precise threshold could be established with a longer follow-up interval.

In conclusion, in men with clinically localized prostate cancer who select watchful waiting, serial PSA levels are correlated with findings of malignancy but not BPH at serial endorectal MRI/MRSI, suggesting that PSA is a useful longitudinal tumour marker in this population.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **ROC**, receiver operating characteristic; **AUC**, area under the (ROC) curve; **MRSI**, magnetic resonance spectroscopic imaging; **NIH**, National Institutes of Health.