MONITORING TUMOR VOLUME IN PROSTATE CANCER PATIENTS ON ACTIVE SURVEILLANCE IN A COHORT STUDY: IS THE APPARENT DIFFUSION COEFFICIENT ON MRI INDICATIVE OF TUMOR GROWTH?

Veronica A. Morgan, Christopher Parker, Alison MacDonald, Karen Thomas, Nandita M. deSouza

ABSTRACT

Aim: In prostate cancer patients on active surveillance, to measure longitudinal change in tumor volume of the dominant intraprostatic lesion and determine whether baseline ADC or change in ADC are indicative of tumor growth.

Methods: 151 men on active surveillance aged 68.1±7.4 years had 3D whole prostate, zonal and tumor volumetry documented on endorectal MRI done at 2 time-points (median interval 1.9 years). Tumor (location confirmed at TRUS or template biopsy) apparent diffusion coefficient (ADC) was measured on a slice with the largest lesion. Twenty randomly selected cases had the measurements repeated by the same observer after a 5-month interval and limits of agreement (LoA) of measurements were calculated. Tumor volume increases >upper LoA were designated "measurable growth"; their baseline ADCs and change in ADC were compared with those without measurable growth (independent samples t-test).

Results: Fifty-two (34.4%) tumors increased measurably in volume. Baseline ADC and tumor volume were negatively correlated (r=-0.42, p=0.001). Baseline ADC values did not differ between those with and without measurable growth (p=0.06) but change in ADC was significantly different (-6.8±12.3% for those with measurable growth vs. 0.23±10.1% for those without, p=0.0005). % change in tumor volume and % change in ADC were negatively correlated (r=-0.31, p=0.0001). A 5.8% reduction in ADC indicated a measurable increase in tumor volume with 54.9% sensitivity, 77.0% specificity (AUC=0.67).

Conclusion: Tumor volume increases measurably in 34% of men on active surveillance at 2 years. Change in ADC may be used to identify tumors with significant growth.

Key words: Prostate cancer, active surveillance, MRI, tumor volumetry apparent diffusion coefficient, reproducibility

INTRODUCTION

Active surveillance, the standard of care for managing low-risk prostate cancer, involves a programme of regular follow-up with serum prostate specific antigen (PSA) and Magnetic Resonance Imaging (MRI).[1] Although PSA measurements are notoriously unreliable, this serum biomarker continues to be routinely used to indicate progress of the disease[2] not only because it is easily obtainable but also because of the absence of other reliable or specific measurements. MRI, routinely used in prostate cancer staging, is increasingly being utilized to follow-up patients on active surveillance.[3-5] Although data is emerging regarding the use of multiple MRI metrics for risk stratifying patients selected for active surveillance,[6] the potential of these images for providing longitudinal tumor volume measurements in order to monitor growth rate, or quantitative metrics of disease progression remains under exploited.[7]

The Apparent Diffusion Coefficient is a quantitative biomarker that is derived from diffusion-weighted MRI. It is largely used qualitatively in conjunction with standard T2-W imaging to identify the dominant tumor nodule on the diagnostic scan.[8] Test-re-test studies of the repeatability of this quantitative metric are now available in a variety of tumor types,[9-13] including prostate cancer[14] and show that the measurement is remarkably robust with a variability of around 8% in single centre studies. ADC has been shown to be lower in poorly compared to well differentiated tumors, a fact that is borne out in prostate cancer where lower values are observed in higher Gleason grade tumors.[15, 16] The potential of this biomarker to indicate tumor growth rate in patients on active surveillance however, has not been established. The purpose of this study, therefore, was to measure longitudinal change in tumor volume of the dominant intraprostatic lesion and determine whether baseline ADC or change in ADC are indicative of tumor growth.

METHODS

Patients

Over a 32-month period June 2011 to Feb 2014, 157 consecutive patients selected for active surveillance who had undergone 2 MRI scans at least 1 year apart were included in this longitudinal cohort study performed at a single center. All of them were part of a large on-going active surveillance program at our institution which had ethical approval from our Committee for Clinical Research (CCR2492), where patients had given written informed consent for use of their data. 19 patients were recorded as being on Tamsulosin (alpha-blocker) to treat urinary symptoms due to benign prostatic hypertrophy. Criteria for inclusion on the active surveillance program include clinical stage T1/T2a, N0 (no nodal metastases), M0 (no metastatic disease) adenocarcinoma of the prostate with serum PSA < 15 ng/ml, Gleason score $\leq$ 7, primary Gleason grade $\leq$ 3, and % positive biopsy cores (pbc) $\leq$ 50%. These criteria are in accordance with the European Society of Medical Oncology guidelines[17]. Six patients were subsequently excluded, 4 because of significant artifact on the MRI from total hip replacements, and 2 because of pelvic surgery during the study period. The final study cohort comprised 151 patients aged 50-83 years (mean $\pm$ SD 68.1$\pm$7.4 years). Patients underwent PSA testing and endorectal MRI at baseline and at follow-up done after a median interval of 1.9 years (Lower Quartile [LQ] 1.2 years, Upper Quartile [UQ] 2.0 years), as a follow-up MRI at 2 years is the standard-of-care at our institution. All patients underwent biopsy to obtain histological confirmation of tumor: this was transrectal ultrasound (TRUS) guided in 145 cases with between 6 and 16 cores and a template biopsy in 6 where 26-100 cores were obtained. Biopsy had been done at a median interval of 1.7 years (LQ 0.4 years, UQ 4.2 years) prior to the baseline MRI of this study in all patients. The patients with longer intervals from biopsy to this baseline had scans elsewhere and were clinically and biochemically stable and therefore were deemed suitable to continue on active surveillance with MRI and PSA follow-up alone. Samples were obtained from lateral and medial locations at the base and mid-gland and at the apex from each hemi-prostate. Biopsy locations were matched with MRI abnormalities in order to define the location of tumor. Patients were not routinely re-biopsied, as this practice has changed over the time period of this study with re-biopsy indicated based on MRI uncertainty. Re-biopsy data was therefore variable and available after a >24-month interval in 47 patients.

MR Imaging Technique

Patients were scanned on a 3.0-T Achieva (Philips Medical Systems, Best, The Netherlands). In all cases an endorectal receiver coil (MedRad), inflated with 60mls of perfluorocarbon in combination with an external six-channel phased array coil was used.

An anti-spasmodic agent, 1ml hyoscine butylbromide (20mg/ml), was administered intra-muscularly to all patients prior to scanning. T2-W fast spin echo images were acquired in three orthogonal planes to the prostate, sagittal, axial and coronal. Following this, a reduced field of view ZOnal Oblique Multi-slice (ZOOM) diffusion-weighted sequence with 5 b values (0, 100, 300, 500, 800 s/mm^2) was acquired in the axial plane[18]. Slice thickness was 2.3 or 2.5 mm with 0.1 mm gap for all axial images depending on the coverage required. Image parameters are given in Table 1. Contrast-enhancement was not used in this context, as these were not staging examinations, but purely for the purpose of monitoring patients on active surveillance.

On completion of the endorectal imaging, axial T1- and T2-W images of the whole pelvis were acquired to determine nodal status. T1-W images were examined to assess the existence of any hemorrhage. Overall scan time was 30-40 minutes.

Data analysis

An experienced radiologist drew regions of interest (ROIs) around the whole prostate and transitional zone (TZ) on all T2-W axial slices to cover the prostate from apex to base. In addition, an ROI was placed around the dominant tumor nodule on all slices containing tumor (identified as an area of hypointense signal on the T2-W images, hyperintense on high b-value DW imaging with a low ADC value in a biopsy positive octant). Lesions not meeting these criteria were not considered to be tumor. In the TZ, tumors were differentiated from BPH nodules displaying similar signal-intensity characteristics by features such as homogeneity of signal-intensity of the lesion, irregular margins and mass effect. Images from the second time-point were viewed first, and on completion of the ROIs, the images from the first time-point were loaded on the workstation and the exercise repeated. This avoided bias from viewing both time-points together while ensuring consistency between the lesions selected and measured. Invisible tumors were excluded from tumor volume difference analyses. The tumor ROI was excluded from the PZ or TZ volume calculation. The summed areas of the regions of

interest of whole gland, TZ (and tumor where identified) were multiplied by slice thickness to obtain volume. The PZ volume was derived from the whole gland minus the TZ and PZ tumor volume.

ADC maps were generated from the diffusion weighted sequence using scanner software where a monoexponential fit of the data yielded a parameter map of calculated ADC values on a pixel-by-pixel basis. The ADC map slice that corresponded to the T2-W slice with the largest tumor ROI was selected. This ROI was copied onto the ADC map and adjusted manually if necessary to account for image distortions. The mean and standard deviation of the ADC of the pixels within this ROI was recorded using the scanner software.

Twenty cases were randomly selected by computer allocation for the purpose of measuring reproducibility. This number of patients has been used in previous studies of other tumor types to assess intraobserver repeatability.[19, 20] After a >4 month interval to avoid memorization, the baseline (first scan) images of these patients were presented to the same observer and the whole gland, TZ and tumor volumes re-drawn on all T2-W slices as before. The volumes for these regions and that of the PZ were calculated. Additionally, the slice with the largest tumor ROI was re-selected and the ROI copied onto the ADC map to obtain the mean and standard deviation for the ADC through the largest section of tumor.

Changes in volume and ADC were expressed as a percentage of the baseline measurement ([measurement at time-point 2- measurement at time-point 1)/ measurement at time-point 1] X 100). All change in volume and ADC analyses in this study used measurements made at specified time-points as it was not possible to assume a linear rate of change. However, in order to estimate the likely annual volume increase in these patients (as the time period over which the measurements were made was relatively short in the natural history of the cancer), the expected volume increase at 1 year was calculated by dividing the increase in volume by the time in years between scans and expressed as a growth rate per annum.

Statistical Analysis

Data were analyzed using MedCalc version 7 for Windows. A Kolmogorov-Smirnov test for normality indicated that data was normally distributed. Mean differences between tumor volumes for measurements 1 and 2 were calculated from the reproducibility cohort. The reproducibility of the

tumor volume measurements was established for whole gland, PZ, TZ and tumor. The Limits of Agreement were recorded as $\pm$ 1.96SD from the mean. A measurable increase or decrease in volume was taken to be one that lay above or below these limits.

An independent samples t-test was used to compare the difference in baseline ADC value between those that had a definite measurable (greater than upper limit of agreement variation in volume) increase in volume with those who did not. The change in ADC between baseline (time-point 1) and follow-up (time-point 2) was also compared between those that had a measurable increase in volume from those that did not. Receiver Operating curve analysis indicated the sensitivity and specificity with which a cut-off baseline ADC or change in ADC could detect a measurable increase in volume.

RESULTS

Patient Demographics:

PSA ranged from 1.3 - 16 ng/mL at baseline (mean $\pm$ SD 7.7 $\pm$ 4.0) and from 1.3 - 22 ng/mL (mean $\pm$ SD 9.2 $\pm$ 5.5) at follow-up. All patients had demonstrable tumor in at least 1 core (Figure 1). The number of positive cores was 1 (n=83), 2 (n=36), 3 (n=16), 4 (n=8) and >5 in the other 8. 144 cases had Gleason 3+3 histology, 7 had Gleason grade 3+4. Of the 47 patients who underwent re-biopsy, 22 remained as 3+3 and 3 remained as 3+4, 12 Gleason grade 3+3 were downgraded as negative for tumor, 7 were upgraded to 3+4 and 3 to 4+3.

Reproducibility of Volume and ADC Measurements:

In the 20 randomly selected patients, there was no visible tumor in 6. Tumor volumes for these patients were recorded as zero. The absolute volumes for WG, TZ, PZ and tumor and the reproducibility with the 95% CI are given in Table 2. Bland-Altman plots of the percentage difference in volumes for the 2 measurements is given in Figure 2. From these data a >23% change in whole gland volume, 11% in central gland volume, 50% in PZ volume and 62% in tumor volume was considered to be representative of a real increase or decrease over and above measurement variability.

ADC variability in the 14 patients with MR visible tumor was -0.6 ± 2.4% (Figure 2E). Limits of agreement were 5.8% from 0, therefore a >5.8% reduction in ADC was considered to represent a measurable reduction to serve as a threshold for indicating progression.

Longitudinal changes in volume of prostate zones and tumor:

Absolute volume measurements (cm^3) for the individual prostate zones and for tumor at baseline and at the second visit are given in Table 3. For WG, assuming a 23% change is within the Limits of Agreement (LoA) of the reliability of the measurement, 19 of 151 glands changed significantly in volume. Six of these were in a negative direction (likely measurement error beyond the upper LoA); of the other 13 that increased some are likely to be related to increases in TZ volume. For TZ, assuming an 11% variability in the measurement, 70 TZs changed significantly in volume, 4 in a negative direction (measurement error beyond the upper LoA). The other 66 had a 21.2 $\pm$ 8.6% increase in

volume (median 17.7%, LQ 15.7%, UQ 23.7%). For PZ, assuming a 49% variability in the measurement, 6 PZ's changed significantly in volume, 3 in the positive direction and 3 in the negative direction (likely measurement error beyond the upper LoA).

Nineteen patients (12.6%) had no measurable tumor nodule. The number of cores positive in these cases ranged from 1 to 4 and PSA was 6.7 ± 2.9 ng/L. None of these patients developed MRI visible tumor on the second follow-up visit; in one case, there was an equivocal abnormality on the T2-W images but there was no focal reduction of ADC in this region, so a definite identification of tumor was not made. Assuming ±62% variability of tumor volume measurements, volumes in 80 patients stayed stable within ± 62%, while in 52 (34.4%) tumors increased in size between the 2 measurements. Assuming a linear growth rate at these low tumor volumes in low risk disease, this would translate to 34 (22.5%) patients who would have experienced a measurable volume increase in the first year.

Of the 12 Gleason grade 3+3 tumors that were downgraded as negative for tumor on re-biopsy, 9 did not change in volume or ADC, 1 increased in volume and 2 increased on both volume and ADC. Of the 7 Gleason 3+3 cases upgraded to 3+4, 1 increased in volume and decreased in ADC, 2 decreased in ADC alone, 2 in volume alone and 2 in neither and of the 3 cases upgraded to 4+3, 2 decreased measurably in ADC, the third case did not change in volume or ADC. This reflects the inherent problems with sampling error when assessing prostate tumors with re-biopsy.

Tumor ADC variation and relationship to tumor volume change:

Baseline tumor ADC was 1053 ± 179 $X10^{-6}$ mm^2/s (median 1038 $X10^{-6}$ mm^2/s, LQ 912 $X10^{-6}$ mm^2/s, UQ 1166 $X10^{-6}$ mm^2/s). There was a significant negative correlation between baseline ADC and baseline tumor volume defined on T2-W images ($r = -0.42$, $p=0.001$, Figure 3A).

Differences in baseline ADC values between those that had a measurable increase in tumor volume (n=52) and those that did not (n=80) were not significant (1085 ± 172 $X10^{-6}$ mm^2/s vs 1032 ± 181 $X10^{-6}$ mm^2/s; $p=0.06$). The change in ADC value between both groups however, was significantly different (-6.8 ± 12.3% for those with a measurable change in T2-W volume vs. 0.23 ± 10.1% for those without, $p=0.0005$). There was a weak negative correlation between % change in ADC and % change in tumor volume ($r=-0.31$, $p=0.0001$, Figure 3B) but not between baseline ADC and % change in tumor volume ($r=0.1$, $p>0.05$).

On ROC curve analysis, a threshold baseline ADC of 1019 $x10^{-6}$ mm^2/s indicated a measurable (>62%) increase in tumor volume with 66.7% sensitivity, 56.4% specificity (area under curve, AUC =0.59, Figure 4A). A threshold reduction in ADC of 5.8% indicated a measurable increase in tumor volume with 54.9 % sensitivity, 77.0% specificity (AUC=0.67, Figure 4B).

Relating ADC and volume change to PSA change and progression to treatment

Serum PSA did not correlate with baseline ADC, change in ADC or change in tumor volume (r= 0.07, p=0.4; r=0.02, p=0.8; and r=-0.08, p=0.3 respectively). In addition, % change in serum PSA did not correlate with % change in tumor volume. As 95.4% of patients were Gleason grade 3+3 and 78.8% of patients had1 or 2 positive cores, a multivariate analysis incorporating these clinical factors and PSA with ADC was not done in this low-risk population.

Change in ADC and volume measurements were not considered in the decision-making process for progression to treatment. Twenty of 151 patients went on to treatment (13 with radiotherapy and 7 with prostatectomy). In the radiotherapy group, 3 had measurable (outside LoA) changes in both volume and ADC, 6 had measurable changes in volume, 1 had measurable changes in ADC and 3 had neither. In the prostatectomy group, 2 had measurable changes in both volume and ADC, 1 had measurable changes in volume, 2 had measurable changes in ADC and 2 had neither.

DISCUSSION

This study indicates that in men with low-risk prostate cancer about a third grow measurably on MRI over a 2-year period. However, the variability of the volume measurement even with one experienced observer in a single centre setting is greater than 60%; therefore, the variability of volume estimates across multiple readers and centres is likely to be much higher. In a clinical scenario, where tumor outlines from 2 visits are done alongside each other, it may be possible to reduce the error of the measurement to some extent. It was not feasible to perform repeatability measurements with a test-retest endorectal study, which would have been ideal. Also, inter-observer repeatability was not performed in this study, we have previously shown it to be around 30% in a prostatectomy cohort[21]. The reproducibility of the ADC measurement however, is more robust, varying by around 5%. This level of ADC variability is consistent with data from other tumor types,[9-13] both in single and multi-centre settings. Therefore estimating a change in ADC rather than in volume at a follow-up visit would be more reliable. However, the difficulty in identifying these small, low-risk cancers from which to extract an ADC measurement should not be underestimated.

In nineteen of our cases (12.6%) there was no MR visible lesion. This is in keeping with other series,[22] although a recent metaanalysis of >1000 patients indicated much higher rates of between 27 and 96% in patients on active surveillance.[23] Their study included all imaging techniques and radiologists with a wide range of expertise, whereas in our study done with an endorectal coil at 3T using a diffusion-weighted technique with high spatial resolution and a dedicated, experienced prostate radiologist ensured that our "MR-invisible" lesion rates were much lower. The clinical importance of these MR invisible lesions is a matter of debate. Several authors have concluded that they represent very low risk disease without risk of progression. In one study, a total of 8.3% (1 of 12) of men with MR-invisible tumor had adverse biopsy pathology (Epstein criteria of PSA density change >0.15ng/ml/g, Gleason score >6, >3 cores involved with >50% involvement in any one) as compared with 40.5% (34 of 84) of men with MR-visible tumors. The MR-invisibility of tumor was associated with a lower risk of adverse biopsy pathology.[22] However in another large study of 623 patients, 177 of whom had non-visible tumors on MRI and subsequently went to prostatectomy, pathological findings resulted in the upgrading of 49 (27.7%) patients to a Gleason score of 7 or more. Also, 101(57.1%) patients exhibited tumor volumes greater than 0.5cc.[24] We did not see a conversion from MR invisible to MR visible lesions in any patient in this cohort over the time period of the study. This means that

they may well have disease in a location not recognizable on MRI e.g. in the TZ, and not merely that they had very small tumors. Alternatively, it may well be that in this minority of patients, the biology of the lesion is such that it remains MR invisible despite an increase in volume. It may be argued that these patients are actually of greater concern as their disease is more difficult to recognize on MRI, posing a challenge to their follow-up. Moreover, the PSA in these 19 men in our study was 6.7 ng/mL and did not significantly differ from those with MR visible lesions, and their change in PSA was 0.33 $\pm$ 0.57 ng/mL, and was therefore not discriminatory at follow-up.

Difference in baseline ADC and change in ADC in tumors that were growing measurably indicates that factors that influence diffusion are changing as the tumor increases in size. This is not merely related to the components of the tumor (increased cell numbers, increased extracellular matrix), but is likely to be related to their composition and organization within the tumor. In pancreatic tumor xenografts ADC is lower in collagen-rich non differentiated tumors.[25] In patient tissues it correlates with the epithelial content of glandular tumors;[26] in human prostate cancer ADC has shown a positive correlation with percentage area of lumen and negative correlation with percentage area of nuclei.[27, 28] The significant correlation of change in ADC with change in tumor volume indicates that the pace of these changes is measurable within the time frame of follow-up scans in these patients on AS. Although previous studies have related baseline ADC to outcome in long-term follow-up studies,[29] this is the first time that a change in ADC has been related to change in volume, providing a measurable index of the change in tumor composition and organization as tumors grow. The 4 patients with an increase in ADC above the LoA in tumors that increased measurably in volume are likely to represent those outside the 95% confidence interval.

The repeatability of volume measurements of the prostate itself was worse for WG than the TZ primarily because of outlining at the extreme base and apex of the gland. Traditionally prostate volumes are estimated using tri-dimensional measurements and the formula for an ellipse as this suffices for volume approximations which are used to influence management decisions (surgery vs. brachytherapy vs. external beam radiotherapy). Volumes estimated by this method correlate well with the more detailed 3D volumetry measurements performed in our study,[30] both measurement schemes perform well in comparison to histopathology. Also the number of patients who changed over and above the negative CI indicated that our measurements were valid as they represented the 5% who were outside the 95% CI.

The patients selected for AS at our institution by and large had very large glands: the ratio of TZ to PZ in these cases meant that the PZ was often compressed and tumors within it were difficult to identify. We were effectively only visualizing tumors in 15% of the gland as the recognition of TZ tumors is poorer than in the PZ.[31] The utility of diffusion-weighted MRI for aiding the detection of TZ lesions has been long debated,[32] although used in conjunction with T2-W it remains the mainstay within the PIRADS-2 reporting system.[33] In our series we recognized TZ tumors in 12 cases but this is likely to be an underestimate as lesions will have been particularly difficult to identify in the very large TZs of the patients in our cohort. However, no lesions with T2 low signal and diffusion restriction were seen to increase in size, meaning that the TZ lesions missed were likely to have been those which were not growing within the time-frame of the study. There was no relationship between the TZ volume and the increase in tumor volume, indicating that mechanical reduction of the PZ volume by a large TZ did not affect tumor growth in the PZ.

Serum PSA remains the mainstay in the diagnosis and follow-up of patients with prostate cancer. PSA velocity, which potentially should indicate progressive disease has performed disappointingly.[34] This is borne out in this study where no correlation between change in PSA and change in MRI volume was documented. Also, as the decision to treat was based on a combination of a rise in PSA, MR appearance (but not formal measurements), clinical factors and other patient morbidity, we did not include it as an end-point of this study.

The use of an endorectal coil facilitated these measurements by providing high spatial resolution images with good SNR. It would not have been possible to obtain this quality of data without the endorectal coil as most tumors of the volume seen in this study would not have been identified. There is debate in the literature regarding the detectability of clinically significant cancers without and with an endorectal coil,[35] but in small, potentially initially clinically insignificant cancers, the use of an endorectal coil facilitated their recognition. This study did not aim to compare the use or not of an endorectal coil for lesion detection in these cases, as it is our routine clinical practice to scan these lesions with a ZOOM-DWI endorectal technique that allows a high-resolution (acquired voxel size 12.6 mm^3) single-shot DWI-EPI acquisition, with maximal achievable SNR.

Ideally, the segmentation of the whole tumor may have provided a more global assessment of tumor ADC.[36, 37] However, in these small tumors, it is unlikely that this would have altered the underlying conclusions, and may have introduced partial volume effects that obscured the results. A

further advantage of the technique we used ensured that it could be implemented quickly and easily at the scanner console at the time of reporting, making introduction into a clinical workflow feasible. Another limitation is having only 2 time-points of measurement, which meant that we had to assume a linear pattern of growth between them. Although tumor growth is more likely to be exponential, at these small tumor volumes in low-risk disease, the assumption of a linear increase in volume over the time frame studied compared with the natural history of the disease is not unreasonable. A previous small study in patients managed by active surveillance prior to prostatectomy versus those going straight to a surgical option showed no significant difference in tumor volume between groups,[38] thus confirming the validity of our assumptions. Future studies would benefit from multiple time points of measurement, but follow-up in these cases would require in excess of 6 years if monitoring 2-yearly as is our practice. Moreover, those lesions felt to be progressing would be diverted to a treatment pathway, thus biasing any analysis towards lesions with a more favourable biology. Our data has confirmed however that a measurable increase in volume is to be expected in approximately a quarter of patients at 1 year.

In summary, we have shown that the tumor volume measurements in patients on active surveillance measured using 3D volumetry can vary by 60%, and that approximately a quarter of men on active surveillance would show this level of increase at 1 year. As the change in T2-W volume correlates with a change in ADC, the latter may be used to identify patients with significant growth as it is a more reproducible measurement with a ~5% variability. Using a 5.8% reduction in ADC would identify tumors that grow measurably with 77% specificity, although sensitivity is low at 54.9%.

REFERENCES

1. van den Bergh RC, Ahmed HU, Bangma CH, Cooperberg MR, Villers A and Parker CC. Novel tools to improve patient selection and monitoring on active surveillance for low-risk prostate cancer: a systematic review. *European urology*. 2014; 65: 1023-1031.
2. Selvadurai ED, Singhera M, Thomas K, et al. Medium-term outcomes of active surveillance for localised prostate cancer. *European urology*. 2013; 64: 981-987.
3. 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. *European urology*. 2009; 56: 981-987.
4. Moore CM, Giganti F, Albertsen P, et al. Reporting Magnetic Resonance Imaging in Men on Active Surveillance for Prostate Cancer: The PRECISE Recommendations-A Report of a European School of Oncology Task Force. *European urology*. 2016.
5. 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. *Urologic oncology*. 2015; 33: 202.e201-207.
6. Salami SS, Ben-Levi E, Yaskiv O, Turkbey B, Villani R and Rastinehad AR. Risk stratification of prostate cancer utilizing apparent diffusion coefficient value and lesion volume on multiparametric MRI. *Journal of magnetic resonance imaging : JMRI*. 2016.
7. Recabal P and Ehdaie B. The role of MRI in active surveillance for men with localized prostate cancer. *Current opinion in urology*. 2015; 25: 504-509.
8. Jie C, Rongbo L and Ping T. The value of diffusion-weighted imaging in the detection of prostate cancer: a meta-analysis. *European radiology*. 2014; 24: 1929-1941.
9. Spick C, Bickel H, Pinker K, et al. Diffusion-weighted MRI of breast lesions: a prospective clinical investigation of the quantitative imaging biomarker characteristics of reproducibility, repeatability, and diagnostic accuracy. *NMR in biomedicine*. 2016.
10. Winfield JM, deSouza NM, Priest AN, et al. Modelling DW-MRI data from primary and metastatic ovarian tumours. *European radiology*. 2015; 25: 2033-2040.
11. Hoang JK, Choudhury KR, Chang J, Craciunescu OI, Yoo DS and Brizel DM. Diffusion-weighted imaging for head and neck squamous cell carcinoma: quantifying repeatability to understand early treatment-induced change. *AJR American journal of roentgenology*. 2014; 203: 1104-1108.
12. Bernardin L, Douglas NH, Collins DJ, et al. Diffusion-weighted magnetic resonance imaging for assessment of lung lesions: repeatability of the apparent diffusion coefficient measurement. *European radiology*. 2014; 24: 502-511.
13. Intven M, Reerink O and Philippens ME. Repeatability of diffusion-weighted imaging in rectal cancer. *Journal of magnetic resonance imaging : JMRI*. 2014; 40: 146-150.
14. Harvey H, Fromageau J, Morgan V, et al. Inter-modality correlation of prostatic microenvironmental tissue stiffness and water diffusivity using quantitative functional imaging techniques. *ISMRM Proceeding*. 2016.
15. Barbieri S, Bronnimann M, Boxler S, Vermathen P and Thoeny HC. Differentiation of prostate cancer lesions with high and with low Gleason score by diffusion-weighted MRI. *European radiology*. 2016.
16. Woo S, Kim SY, Cho JY and Kim SH. Preoperative Evaluation of Prostate Cancer Aggressiveness: Using ADC and ADC Ratio in Determining Gleason Score. *AJR American journal of roentgenology*. 2016; 207: 114-120.
17. Parker C, Gillessen S, Heidenreich A and Horwich A. Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2015; 26 Suppl 5: v69-77.
18. Wheeler-Kingshott CA, Hickman SJ, Parker GJ, et al. Investigating cervical spinal cord structure using axial diffusion tensor imaging. *NeuroImage*. 2002; 16: 93-102.
19. Letteboer MM, Olsen OF, Dam EB, Willems PW, Viergever MA and Niessen WJ. Segmentation of tumors in magnetic resonance brain images using an interactive multiscale watershed algorithm. *Academic radiology*. 2004; 11: 1125-1138.
20. Gong QY, Tan LT, Romaniuk CS, Jones B, Brunt JN and Roberts N. Determination of tumour regression rates during radiotherapy for cervical carcinoma by serial MRI: comparison of two measurement techniques and examination of intraobserver and interobserver variability. *The British journal of radiology*. 1999; 72: 62-72.
21. Harvey H, Orton MR, Morgan VA, et al. Volumetry of the Dominant Intraprostatic Tumour Lesion: Intersequence and Interobserver Differences on Multiparametric MRI. *The British journal of radiology*. 2017: 20160416.

22. Dianat SS, Carter HB, Pienta KJ, et al. Magnetic resonance-invisible versus magnetic resonance-visible prostate cancer in active surveillance: a preliminary report on disease outcomes. *Urology*. 2015; 85: 147-153.
23. Guo R, Cai L, Fan Y, Jin J, Zhou L and Zhang K. Magnetic resonance imaging on disease reclassification among active surveillance candidates with low-risk prostate cancer: a diagnostic meta-analysis. *Prostate cancer and prostatic diseases*. 2015; 18: 221-228.
24. Lee SH, Koo KC, Lee DH and Chung BH. Nonvisible tumors on multiparametric magnetic resonance imaging does not predict low-risk prostate cancer. *Prostate international*. 2015; 3: 127-131.
25. Wegner CS, Gaustad JV, Andersen LM, Simonsen TG and Rofstad EK. Diffusion-weighted and dynamic contrast-enhanced MRI of pancreatic adenocarcinoma xenografts: associations with tumor differentiation and collagen content. *Journal of translational medicine*. 2016; 14: 161.
26. Kyriazi S, Nye E, Stamp G, Collins DJ, Kaye SB and deSouza NM. Value of diffusion-weighted imaging for assessing site-specific response of advanced ovarian cancer to neoadjuvant chemotherapy: correlation of apparent diffusion coefficients with epithelial and stromal densities on histology. *Cancer biomarkers : section A of Disease markers*. 2010; 7: 201-210.
27. Langer DL, van der Kwast TH, Evans AJ, et al. Prostate tissue composition and MR measurements: investigating the relationships between ADC, T2, K(trans), v(e), and corresponding histologic features. *Radiology*. 2010; 255: 485-494.
28. Kobus T, van der Laak JA, Maas MC, et al. Contribution of Histopathologic Tissue Composition to Quantitative MR Spectroscopy and Diffusion-weighted Imaging of the Prostate. *Radiology*. 2016; 278: 801-811.
29. Henderson DR, de Souza NM, Thomas K, et al. Nine-year Follow-up for a Study of Diffusion-weighted Magnetic Resonance Imaging in a Prospective Prostate Cancer Active Surveillance Cohort. *European urology*. 2016; 69: 1028-1033.
30. Mazaheri Y, Hricak H, Fine SW, et al. Prostate tumor volume measurement with combined T2-weighted imaging and diffusion-weighted MR: correlation with pathologic tumor volume. *Radiology*. 2009; 252: 449-457.
31. 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: 715-723.
32. Hoeks CM, Hambrock T, Yakar D, et al. Transition zone prostate cancer: detection and localization with 3-T multiparametric MR imaging. *Radiology*. 2013; 266: 207-217.
33. Muller BG, Shih JH, Sankineni S, et al. Prostate Cancer: Interobserver Agreement and Accuracy with the Revised Prostate Imaging Reporting and Data System at Multiparametric MR Imaging. *Radiology*. 2015; 277: 741-750.
34. Loughlin KR. PSA velocity: a systematic review of clinical applications. *Urologic oncology*. 2014; 32: 1116-1125.
35. Bratan F, Niaf E, Melodelima C, et al. Influence of imaging and histological factors on prostate cancer detection and localisation on multiparametric MRI: a prospective study. *European radiology*. 2013; 23: 2019-2029.
36. Zhang YD, Wang Q, Wu CJ, et al. The histogram analysis of diffusion-weighted intravoxel incoherent motion (IVIM) imaging for differentiating the gleason grade of prostate cancer. *European radiology*. 2015; 25: 994-1004.
37. Donati OF, Mazaheri Y, Afaq A, et al. Prostate cancer aggressiveness: assessment with whole-lesion histogram analysis of the apparent diffusion coefficient. *Radiology*. 2014; 271: 143-152.
38. Khatami A, Damber JE, Lodding P, Pihl CG and Hugosson J. Does initial surveillance in early prostate cancer reduce the chance of cure by radical prostatectomy?--A case control study. *Scandinavian journal of urology and nephrology*. 2003; 37: 213-217.

FIGURE LEGENDS

Figure 1: *Patient with a measurable increase in tumor volume after 22 months on active surveillance:* Transverse T2-W (A) image through the prostate obtained with an endorectal receiver coil at 3.0T with the corresponding ADC map (B) at baseline shows a low-signal intensity lesion (outlined in A) with diffusion restriction (B, arrow)in the right mid peripheral zone laterally. A tumor was confirmed at this octant location on transrectal ultrasound-guided biopsy. A follow-up T2-W image (C) and corresponding ADC map (D) at the same level in the prostate at the second time-point shows the increase in size of the tumor (outlined in C) with a visible reduction in ADC (D, arrow).

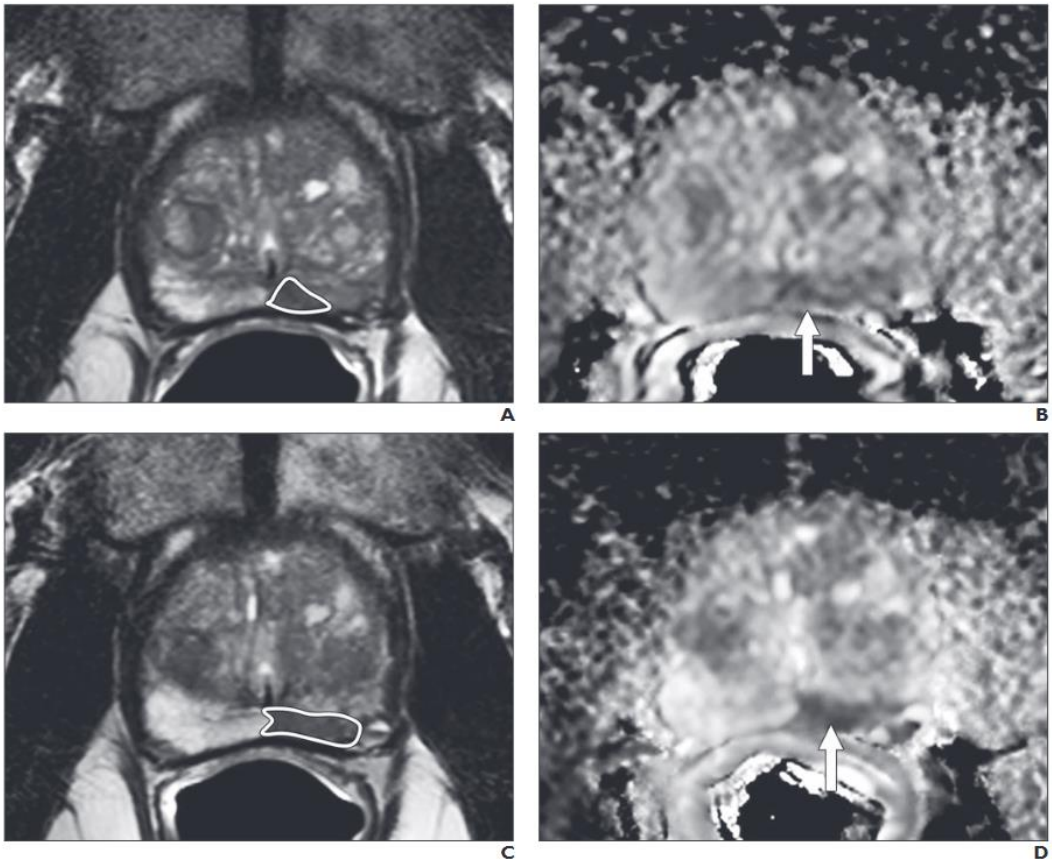

Figure 2: *Reproducibility of volume and ADC measurements in the prostate:* Bland- Altman plots (dashed lines = Limits of Agreement at ±1.96SD) for repeated volume measurements by a single observer for whole gland (A), peripheral zone (B), transitional zone (C) and tumor (D) indicate that transitional zone volumes are the most reproducible to measure and tumor volumes the least reproducible. By comparison the variability of the ADC measurement of the tumor is relatively low on the expanded percentage scale (E).

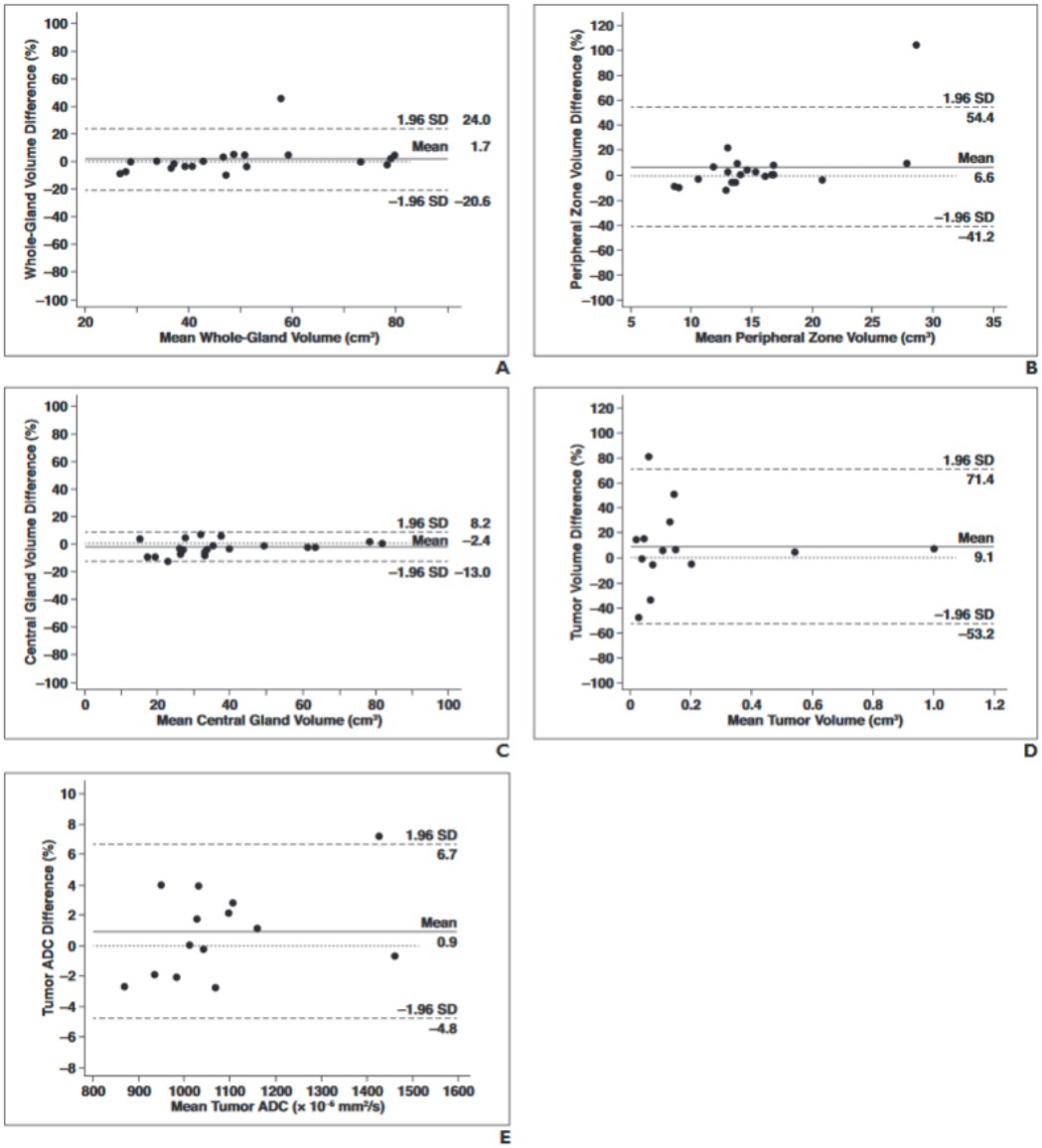

Figure 3: *Relationship between prostate tumor volume and ADC:* Scatter-plots between tumor volume and tumor ADC at baseline (A, left) and percentage change in tumor volume and percentage change in ADC between time-points 1 and 2 (A, right) indicate a weak correlation. Notched box and whisker plots (central line of box=median, upper and lower lines= 75th and 25 centiles, notches = 95% confidence interval of the median, whiskers=maximum and minimum values, [B]) show a small but significant difference in the percentage change in ADC in those that grew measurably vs. those that did not.

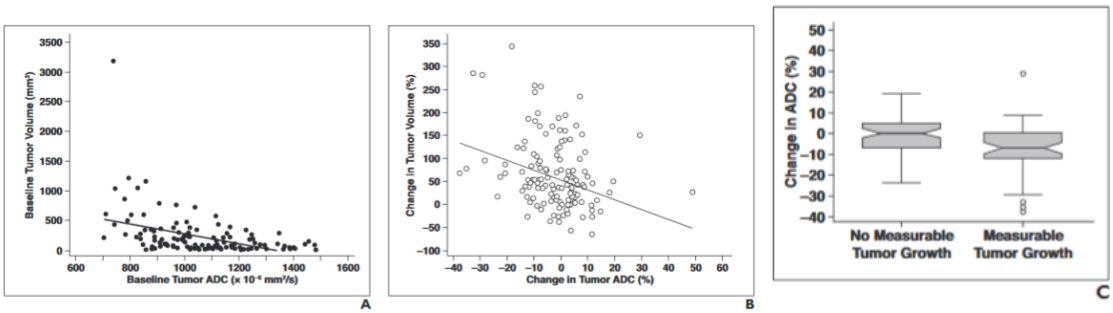

Figure 4: Receiver Operating Characteristic curves for baseline ADC (A) and change in ADC (B) for indicating measurable tumor growth.

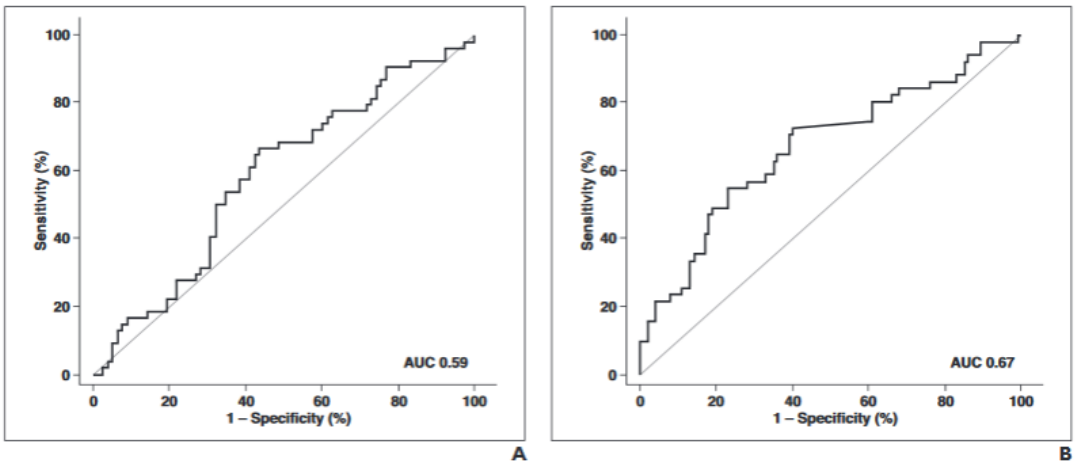

Table 1: *Sequence Acquisition parameters for endorectal prostate imaging in patients on active surveillance*

	T2W TSE	EP DWI
TR (msec)	3643	5129
TE (msec)	110	65
No. of slices	20	20
FA (deg)	90	90
Slice thickness (mm)	2.2	2.2
FOV (mm)	120	180
Matrix	Acq 220 x184 Recon 256	Acq 80 x 70 Recon 128
Voxel size (mm /mm/ mm)	0.55/0.76/2.2 (acq) 0.55/0.55/2.2 (recon)	2.25/2.54/2.2 (acq) 1.14/1.41/2.2 (recon)
SENSE factor	1.5	2
Scan time (min:sec)	4:48 x 3	3:20
Other	TSE factor13	b = 0, 100, 300, 500, 800 s/mm^2

Table 2: *Volume measurements and their reproducibility for the different prostate zones and for tumor*

N=20	Measurement 1 Mean ± SD [cm^3]	Measurement 2 Mean ± SD [cm^3]	Reproducibility Mean ± SD of difference between measurements	Coefficient of Variability SD/Mean (%)
Whole Gland	49.86 ± 18.16	48.49 ± 16.53	1.69 ± 11.37	6.7
Central Gland	37.61 ± 19.44	38.21 ±19.01	-2.42 ± 5.40	2.24
Peripheral Zone	16.16 ± 7.79	14.37 ± 3.95	6.62 ± 24.40	3.69
Tumor	0.14 ± 0.25	0.12 ± 0.23	9.12 ± 31.76	3.48

Table 3: *Baseline volume measurements for each prostate zone and for tumor and change in volume at follow up visit*

N=151	Baseline Mean ± SD [cm^3]	Baseline Median (LQ, UQ) [cm^3]	Follow-up Mean ± SD [cm^3]	Follow-up Median (LQ, UQ) [cm^3]	% increase in volume > measurement error
Whole Gland	58.82 ± 27.62	52.88 (38.80, 75.85)	62.52 ± 28.95	56.65 (41.31, 79.47)	No
Central Gland	50.90 ± 29.95	43.75 (28.59, 68.46)	56.64 ± 34.00	47.80 (31.52, 75.57)	21.2 ± 8.6 (n=66)
Peripheral Zone	15.52 ± 6.44	14.43(10.83, 19.25)	15.56 ± 6.59	14.13 (10.61, 19.91)	No
Tumor	0.20 ± 0.34	0.09 (0.03, 0.2)	0.31 ± 0.47	0.14 (0.06, 0.34)	140.1 ± 66.4 (n=52)