Prognostic Value of a Cell-cycle Progression Score in Men with Prostate Cancer Managed with Active Surveillance after MRI-guided Prostate Biopsy - A Pilot Study

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Abstract. *Background/Aim: Initial inaccurate staging is a common problem associated with active surveillance (AS) for patients detected by transrectal ultrasound-guided prostate biopsy (TRUS-GB). Subsequently, repeated biopsies are necessary to monitor such patients. Thus, in addition to the already established clinicopathological criteria, there is a considerable demand for new, objective decision criteria to more accurately select AS candidates. Recently, a novel RNA expression signature derived from 31 cell-cycle progression (CCP) genes has been shown to be a strong predictor of outcome in patients after radical prostatectomy or radiotherapy. This is a qualitative pilot study to evaluate the prognostic value of the CCP-score (CCP-S) for the first time in men managed with AS after MRI-guided prostate biopsy (MRI-GB). Patients and Methods: Nine patients previously diagnosed with prostate cancer during an ongoing, prospective trial assessing MRI-GB with additional TRUS-GB and were subsequently managed with AS. CCP-S were retrospectively derived from biopsy specimens. The CCP-S is defined as the expression level of 31 CCP genes, normalized to 15 housekeeping genes, and is clinically validated in a range between –1.3 and 4.7. To assess the estimated 10-year mortality risk (without curative treatment), the CCP-S from each patient was combined with the individual CAPRA (Cancer of the Prostate Risk Assessment) score (CAPRA-S). Results: Median patient age was 72 (range=58-77) years. Mean pre-biopsy PSA level was 6.33±1.94 (range 4.23-9.97) ng/ml. Eight cases had Gleason score 6 (3+3) and one cancer had Gleason score 7 (3+4). Median CCP-S was –0.9 (range=–1.5 to 0.0). Combining CCP-S with CAPRA-S [CAPRA-S: 1 (n=4), 2 (n=4), 3 (n=1)] the estimated 10-year mortality risk was not calculable for three patients because their CCP-S [CCP-S -1.4 (n=2) and –1.5 (n=1)] was outside the validated range. For the other 6 patients the estimated 10-year mortality ranged from 1.0-3.0%. Conclusion: The CCP-S confirms accurate staging of AS patients detected by MRI-based biopsy strategies and may significantly reduce inaccurate staging of AS patients and subsequent unnecessary re-biopsies. The CCP score may help to more accurately select for active surveillance candidates.*

Over-diagnosis and subsequent over-treatment in terms of radical prostatectomy or radiotherapy are important side-effects of the early detection of prostate cancer (PCa). Meanwhile active surveillance (AS) has become an established alternative choice to curative treatment options in patients with low-risk PCa. However, initial inaccurate staging and Gleason grading are common problems associated with AS patients detected by systematic transrectal ultrasound (TRUS)-guided prostate biopsy. At repeat-biopsy approximately 30% of patients show re-classification, regarding cases being of higher risk and in need of curative treatment (1, 2). Therefore, an annual prostate biopsy is recommended in most AS programmes. But this leads to considerable anxiety and restricted quality of life for the patient. Thus, there is an urgent need for better disease staging at initial diagnosis to more accurately select for AS candidates. Multi-parametric magnetic resonance imaging (mpMRI) of the prostate and targeted-biopsy strategies are promising tools to help minimize the risk of underestimation (3, 4). Biomarkers instead of – or in addition to – the current clinical and biopsy-based decision criteria, represent another approach for optimal selection of AS candidates (5, 6).

Recently, a novel RNA expression signature derived from 31 cell-cycle progression (CCP) genes has been shown to be a stronger predictor of outcome in different PCa cohorts than

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classic prognostic parameters like Gleason grading, prostate-specific antigen (PSA) level and clinical tumor stage. Higher CCP scores (CCP-S) were strongly predictive of biochemical recurrence after radical prostatectomy (7, 8) or external-beam radiation therapy (9). Higher CCP-S were also highly predictive of death from PCa in a watchful waiting population (10) or in men with clinically-localized PCa diagnosed by use of transurethral resection of the prostate (7). Additionally, CCP-S showed independent prognostic utility beyond clinical prognostic factors like the CAPRA score (Cancer of the Prostate Risk Assessment) which includes five clinical variables – PSA level, Gleason score, clinical tumor stage, percentage of positive biopsies and patient age. The predictive value of the combined CCP-S and CAPRA score (CAPRA-S) outperformed the individual scores (8).

The objective of the present pilot study was to evaluate the prognostic value of the CCP-S for the first time in men managed with AS after MR-guided prostate biopsy.

Patients and Methods

Study population. Subjects of this retrospective pilot study were previously enrolled in an ongoing, prospective trial assessing MRI-guided in-bore prostate biopsy with additional TRUS-guided prostate biopsy in biopsy-naive men with elevated PSA levels at our Institution (ClinicalTrials.gov identifier: NCT01553838). The trial was approved by our Institutional review board and written informed consent was obtained from all patients. The detailed design of this prospective trial has been reported elsewhere (11). The CCP and CAPRA scores were retrospectively derived from 9 PCa patients who were previously diagnosed during this prospective trial, and who were subsequently managed with AS.

Imaging. All patients were previously submitted to a diagnostic 3.0-T mpMRI of the prostate with a six-channel phases-array body coil (Magnetom Trio; Siemens Healthcare, Germany). The mpMRI of the prostate included T2-weighted imaging (T2WI), diffusion-weighted imaging (DWI) and dynamic contrast-enhanced imaging (DCE-MRI), as previously described (11, 12). Prostate lesions were then defined and scored along the standardized PI-RADS (Prostate Imaging Reporting and Data System) classification of the European Society of Urogenital Radiology (ESUR) (13) by two experienced genitourinary radiologists in consensus. For reporting the localization of prostate lesions, a standardized MRI prostate reporting scheme was used dividing the prostate gland into 27 regions (14). A maximum of three lesions was defined for each patient and all lesions were rated on a 5-point Likert-scale for grading the findings obtained with different MRI techniques (T2WI, DWI, DCE-MRI) according to the ESUR guidelines (PI-RADS). Additionally, each lesion was given an overall PI-RADS score (1-5 points) as previously described (15).

In-bore MRI-guided biopsy. After the diagnostic mpMRI, all patients underwent a MRI-guided biopsy performed by an interventional radiologist using the same 3.0-T scanner. Patients were placed in a prone position and a needle guide fixed to a portable biopsy device (DynaTRIM) was introduced rectally (Invivo, Gainesville, USA). Image data were transferred to a DynaCAD workstation (Invivo) for biopsy planning. In accordance with the study, protocol biopsy cores were obtained from each predefined prostate lesion irrespective of its PI-RADS score, *i.e.* unsuspicious lesions were also biopsied. Biopsies were taken with an MRI-compatible, 18-gauge, fully-automatic biopsy gun (Invivo).

TRUS-guided biopsy. Subsequently, all patients underwent an additional, standard 12-core TRUS-guided prostate biopsy performed by an urologist who was blinded to the mpMRI findings.

CCP score and CAPRA score. For calculation of the individual CCP-S, specimens of all 9 patients were processed in the Myriad Genetics commercial laboratory (Myriad Genetics, Salt Lake City, USA), as previously described (7-10). Briefly, the tumor was dissected from the formalin-fixed, paraffin-embedded (FFPE) needle biopsy blocks. Total RNA was extracted and then converted into single-strand cDNA with the High-capacity cDNA Archive Kit (Applied Biosystems, Foster City, USA). Expression levels of 31 pre-determined CCP genes and 15 housekeeping genes were determined by a pooled reaction containing TaqMan assays (Applied Biosystems). The detailed description of CCP-S calculation has been reported (7). Briefly, the CCP-S is defined as the expression level of 31 CCP genes in each triplicate, normalized to 15 housekeeping genes. Thus, over- and under-expression of the 31 CCP genes results in positive and negative CCP-S, respectively. The CCP-S is clinically validated in a range between -1.3 and 4.7.

To calculate the CAPRA-S of each patient, PSA level at diagnosis, Gleason score on biopsy, clinical tumour stage, percentage of positive biopsies and patient age were recorded and provided to the Myriad Genetics commercial laboratory.

The combined analysis of CCP and CAPRA scores uses the equation 0.57*CCP-S + 0.39*CAPRA-S. Its ability to assess 10-year PCa-specific mortality has been validated on 349 FFPE prostate tumor biopsy samples from a cohort of conservatively managed (watchful waiting) patients with clinically-localized PCa (10). To generate the estimated 10-year mortality risk (without curative treatment) in this study population, the derived CCP-S from each patient was combined with the individual CAPRA-S. Estimated 10-year mortality risk, together with the CCP-S, was reported by the Myriad Genetics commercial laboratory.

Follow-up. Patients were followed-up clinically and by PSA, at least every three months.

Statistical analysis. The Shapiro-Wilk test was used to assess the normal distribution of variables. The Mann-Whitney *U*-test was used for comparisons of non-normally distributed continuous variables.

Results

Patients' characteristics and multi-parametric MRI findings. Table I shows patients' characteristics and the diagnostic mpMRI findings of 9 patients. Median patient age was 72 (range=58-77) years, and the pre-biopsy PSA level ranged from 4.23 to 9.97 (mean 6.33±1.94) ng/ml. Median prostate volume measured by MRI was 49.0 (range 41.0-83.4) cm^3. This produced a PSA density from 0.09 to 0.19 ng/ml^2.

Table I. *Patients' characteristics and diagnostic mpMRI findings.*

Patient	Age (years)	Pre-biopsy PSA (ng/ml)	Prostate volume (cm^3)	PSA density (ng/ml^2)	Regions prostate lesions (mpMRI)	Longest diameter prostate lesions (mm)	Overall PI-RADS score
01	58	4.40	51.7	0.09	9a/9p	13	3
					15as	11	4
02	72	4.71	49.0	0.10	5a	8	3
					11a	11	3
					12a	5	3
03	72	4.61	42.0	0.11	3a	12	3
					12a	8	5
					12a	10	5
04	68	4.23	47.0	0.09	2p	14	4
					3a	12	4
					9a/10a	13	4
05	74	7.65	41.0	0.19	9a/10a	8	4
					3a	8	2
					9p	9	5
06	77	7.10	83.4	0.09	3a	9	2
					9a	9	3
07	62	6.76	60.0	0.11	13as	21	4
					9a	6	4
					6p	12	3
08	73	7.68	46.0	0.17	12a/12p	11	3
09	77	9.79	61.2	0.16	7a	12	3
					7a	9	4
					14as	8	4

Three out of 9 patients had a PSA density >0.15 ng/ml^2. Overall, prior to targeted-biopsy, 23 prostate lesions were pre-defined and rated according to PI-RADS. The longest diameter of these 23 prostate lesions ranged from 5 to 21 (median 10) mm. Twelve prostate lesions were ≥10 mm in the longest diameter. Overall, two lesions were classified as PI-RADS category 2 (probably benign), 9 lesions were classified as PI-RADS category 3 (indeterminate), 9 lesions were classified as PI-RADS category 4 (probably malignant) and three lesions were classified as PI-RADS category 5 (highly suspicious of malignancy).

Biopsy results. Table II shows histopathological biopsy results of the 9 patients distinguished by MRI-guided biopsy and TRUS-guided biopsy. Five patients were detected by MRI-guided biopsy only, 2 patients by TRUS-guided biopsy-only and 2 patients were detected both by MRI-guided and TRUS-guided biopsy. Seven out of the 23 MRI prostate lesions revealed PCa on histopathological assessment (30.4%). The positivity rate per PI-RADS category was as follows: PI-RADS 2=0% (0/2), PI-RADS 3=22.2% (2/9), PI-RADS 4=44.4% (4/9), PI-RADS 5=33.3% (1/3). Positivity rate per core was significantly higher in the MRI-guided prostate biopsy (12/52=23.1%) as compared to TRUS-guided biopsy (5/108=4.6%; p=0.019). Eight cancers had a 3+3=6 Gleason score and one cancer had a 3+4=7 Gleason score. There was no difference in the Gleason sum in the two patients detected both by MRI-guided and TRUS-guided biopsy (patients 07 and 08). The tumor involvement of biopsy cores ranged from <5% to 50%. As an example, Figure 1 shows the findings of diagnostic mpMRI and subsequent in-bore MRI-guided biopsy of patient 04.

CAPRA score, CCP score and estimated 10-year mortality. Table III summarizes the clinical parameters to generate the individual CAPRA-S for each patient. The CAPRA-S were distributed as follows: 0 (n=0); 1 (n=4), 2 (n=4), 3 (n=1), 4-10 (n=0). Thus, 8 patients were in the low-risk category (CAPRA-S 0-1) and 1 patient was in the intermediate-risk category (CAPRA-S 2-5). The median CCP-S was –0.9 (mean=–0.83±0.55) (range=–1.5-0.0). Combining the CCP-S with the CAPRA-S according to the equation 0.57*CCP-S + 0.39*CAPRA-S, the estimated 10-year mortality risk without any curative treatment for 6 of the 9 patients ranged from 1.0% to 3.0% (1.0% (n=1); 2.0% (n=3); 3.0% (n=2). Estimated 10-year mortality was not calculable for three patients because their CCP-S (CCP-S –1.4 (n=2) and –1.5 (n=1)) was outside the clinically validated range (–1.3 to 4.7).

Follow-up. Median follow-up time was 7 months. Currently, 7 out of 9 patients have lower PSA levels compared to pre-biopsy values. After biopsy, patient 01 and 04 initially

Table II. *Biopsy results separated for MRI-guided biopsy and TRUS-guided biopsy.*

Patient	Regions prostate lesions (mpMRI)	Positive cores MRI-guided biopsy only	Gleason Score MRI-guided biopsy only (max. tumor involvement)	Positive cores TRUS-guided biopsy only	Gleason Score TRUS-guided biopsy only (max. tumor involvement)
01	9a/9p	0/2		0/12	
	15as	2/3	3+3=6 (50%)		
02	5a	2/2	3+3=6 (<5%)	0/12	
	11a	0/2			
	12a	0/2			
03	3a	0/2		1/12	3+3=6 (40%)
	12a	0/3			
	12a	0/4			
04	2p	2/2	3+3=6 (40%)	0/12	
	3a	0/2			
	9a/10a	0/2			
05	9a/10a	0/2		0/12	
	3a	0/2			
	9p	1/2	3+3=6 (20%)		
06	3a	0/3		1/12	3+3=6 (10%)
	9a	0/2			
07	13as	0/2		2/12	3+4=7 (35%)
	9a	1/2	3+4=7 (40%)		
	6p	0/2			
08	12a/12p	2/3	3+3=6 (20%)	1/12	3+3=6 (5%)
09	7a	0/2		0/12	
	7a	0/2			
	14as	2/2	3+3=6 (15%)		

showed an increase in their PSA levels up to 14.7 and 6.8 ng/ml, respectively. Further PSA controls in these two patients showed declining values, as demonstrated in table IV. To date no patient has left the AS strategy – neither due to tumor progression nor for any other reason. However, none of the patients has undergone re-biopsy until now.

Discussion

The concept of AS represents an excellent tool to address the problem of over-treatment of low-risk PCa. First long-term data from several large AS series show low PCa-specific mortality rates of 0-3% (16, 17). But with the longest reported median follow-up being only 6.8 years, AS still remains an experimental strategy to treat patients with low-risk PCa (2). In contrast to PCa-specific mortality rates, AS shows much poorer rates for progression-free survival ranging from 54% to 86% (16). Up to 1/3 of patients have to undergo secondary, curative treatment after a median AS period of 2.5 years (17). In most cases this is due to higher re-classification after repeat biopsy. Data from patients who immediately undergo radical prostatectomy after PCa diagnosis, as well as data from AS patients with immediate re-biopsy (within 3 months), indicates that 20-30% of AS patients are underestimated in terms of grading and/or tumor volume at initial diagnosis (18, 19, 20). In contrast to this tissue under-sampling at initial diagnosis, only a small amount of AS patients probably will have a true progress due to tumor de-differentiation and/or tumor growth over the time. Tissue under-sampling is mainly caused by the restricted inter-observer reproducibility of Gleason grading (21, 22) among pathologists and more importantly by the undirected character of systematic TRUS-guided needle biopsy. Increasing the number of biopsy cores on TRUS-guided biopsy does not only improve the overall cancer detection rate, but also that of clinically significant cancers (23).

Finally, judgement of the performance of AS is hindered by varying inclusion criteria among the different AS cohorts. This leads to extreme variations in eligibility rates (in the range of 4-82%) (17), which subsequently leads to varying progression-free survival rates. Additionally, some of the inclusion criteria (*i.e.* clinical tumor stage) are of subjective and tentative character. These obstacles with current management of AS patients show that, in addition to the already established clinicopathological criteria, there is a considerable demand for new, objective decision criteria.

With respect to the results of our pilot study, we believe that the combined use of the CCP-S with mpMRI at initial diagnosis could overcome these challenges of AS. MpMRI

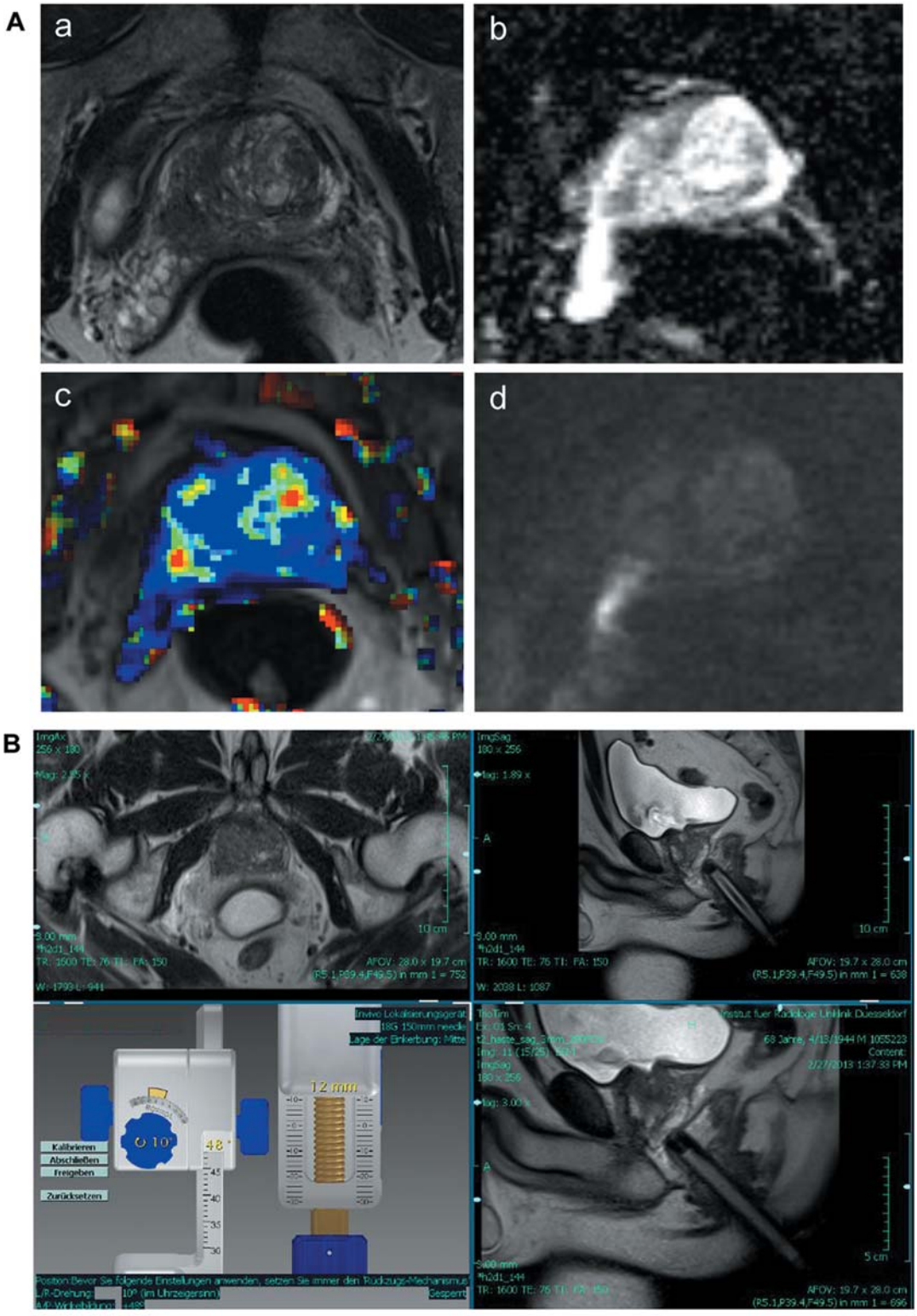

Figure 1. *A: Example of a diagnostic mpMRI. a: Axial T2WI with a suspicious peripheral lesion located in the right peripheral zone; b: ADC map showing a corresponding reduced signal; c: DCI-MRI showing a focal and asymmetric contrast media washout of this lesion. d: DWI on high b-value (1000 s/mm²) showing an increased signal; Histological result after targeted in-bore MRI-guided biopsy (e) was a tumour with a Gleason score of 3+3=6. B: Setting of a targeted in-bore MRI-guided biopsy planning using the DynaCAD. Lower images: Calibration and settings of the needle guide; upper images: Targeting of a suspect lesion.*

Table III. *CAPRA and CCP scores and individual estimated 10-year mortality rates.*

Patient	Age (years)	Pre-biopsy PSA (ng/ml)	Total positive cores (percentage)	Max. Gleason Score (max. tumour involvement)	Clinical tumor stage	CAPRA score	CCP score	Estimated 10-year mortality
01	58	4.40	2/17 (11.7%)	3+3=6 (50%)	T1cN0MX	1	–1.4	not calculable
02	72	4.71	2/18 (11.1%)	3+3=6 (<5%)	T2aN0MX	1	–1.5	not calculable
03	72	4.61	1/21 (4.8%)	3+3=6 (40%)	T1cN0MX	1	–1.4	not calculable
04	68	4.23	2/18 (11.1%)	3+3=6 (40%)	T1cN0MX	1	–0.9	1.0%
05	74	7.65	1/18 (5.6%)	3+3=6 (20%)	T2cN0MX	2	0.0	3.0%
06	77	7.10	1/17 (5.9%)	3+3=6 (10%)	T1cN0MX	2	–1.1	2.0%
07	62	6.76	3/18 (16.7%)	3+4=7 (40%)	T1cN0MX	3	–0.3	3.0%
08	73	7.68	3/15 (20.0%)	3+3=6 (20%)	T1cN0MX	2	–0.5	2.0%
09	77	9.79	2/18 (11.1%)	3+3=6 (15%)	T1cN0MX	2	–0.4	2.0%

Table IV. *Follow-up by PSA.*

Patient	Pre-biopsy PSA (ng/ml)	Date Biopsy	Last PSA (ng/ml)	Date last PSA	Time follow-up (months)
01	4.40	02/2013	8.23	08/2013	6
02	4.71	01/2012	4.17	10/2013	9
03	4.61	09/2012	2.89	09/2013	12
04	4.23	02/2013	5.90	09/2013	7
05	7.65	05/2012	6.91	08/2013	15
06	7.10	01/2013	6.37	08/2013	7
07	6.76	04/2013	6.69	08/2013	4
08	7.68	08/2013	4.01	11/2013	3
09	9.79	04/2013	9.05	10/2013	6

is able to detect more than 90% of significant PCa, and there is sufficient evidence to suggest that mpMRI can also be used to assess the eligibility of patients for AS, as well as to monitor AS patients (24-26). On the other hand, lower CCP-S have been shown to be predictive for better outcome in different PCa populations (7-10).

This retrospective pilot study was a feasibility study to evaluate the CCP-S in patients managed with AS who were well-defined by modern imaging with standardized reporting of the examinations (PI-RADS) and targeted biopsies to the mpMRI findings. Due to the high sensitivity and specificity of mpMRI for significant cancers, and the combined use of targeted biopsies with 12-core TRUS-guided biopsies we felt certain that these patients did not exhibit significant cancers that were missed by biopsy. Consequently, we anticipated low CCP-S in this population.

The calculation of a CCP-S from needle biopsies was technically feasible and confirmed previous feasibility results from two other needle biopsy cohorts (9, 10). Even from biopsy cores with very low tumor involvement (<5%), generation of a CCP-S was feasible. With a median CCP-S of –0.9 in this well-defined AS population our expectations were confirmed. This score was much lower as compared to the median CCP-S reported for two other needle biopsy cohorts. In a watchful waiting cohort of 349 patients, and in a cohort of 141 patients undergoing external beam radiation therapy, the median CCP-S was 1.03 (interquartile range 0.41 to 1.74) and 0.12 (interquartile range=–0.43-0.66), respectively (9, 10). The CCP-S in these 9 patients were at the lower end of the clinically-validated range of the CCP-S. In fact, the CCP-S of three patients were below the validated range.

Certainly, our study has several limitations. First, the overall number of patients included in this retrospective study was low. Also, we did not evaluate the CCP-S in a control group, *i.e.* patients who were submitted to AS after a standard 12-core TRUS-guided biopsy without previous mpMRI. And finally, patient follow-up was short.

Despite these limitations, we believe that the results of our pilot study indicate that the CCP-S has prognostic value in AS patients, and should be explored to serve as an independent parameter for selection of patients to undergo AS. The use of the CCP-S at initial diagnosis may help the urologist to counsel patients who fit clinical and histological criteria for AS, but who fear under-treatment. The combination of the CCP-S with subsequent control mpMRI

examinations could replace repeat biopsies which are currently necessary and represent the state-of-the-art. This would have a major impact on quality of life and cancer-related anxiety in AS patients. We believe that the results of our pilot study warrant further evaluation of the CCP-S in AS patients within a multi-center trial. Such a multi-center trial is currently in preparation.

Conclusion

The CCP-S confirms accurate staging of AS patients detected by mpMRI and MRI-guided biopsy strategies shown by the excellent, low mortality risk profile in this AS population. The combined use of mpMRI and the CCP-S at initial diagnosis may significantly reduce inaccurate staging of AS patients and subsequent unnecessary re-biopsies.

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