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Quantified Clinical Risk Change as an End Point During Prostate Cancer Active Surveillance

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Abstract

For men with low-stage prostate cancer (PCa) managed with active surveillance (AS), clinical thresholds for intervention have not been definitively established. We aimed to evaluate whether the magnitude of quantitative risk change may serve as a refined end point. We identified 735 men managed with AS at our institution who received a minimum of two biopsies and who were followed for a median of 52 mo. We described the relative changes in the Cancer of the Prostate Risk Assessment (CAPRA) score from diagnosis to last follow-up and evaluated the proportion of patients experiencing changes in constituent clinical variables. Among patients treated with radical prostatectomy (RP), the association between change in CAPRA score and the occurrence of adverse pathology (pT3a or higher and/or primary Gleason pattern ≥ 4) was assessed using logistic regression models. Among patients ultimately treated with RP ($n = 196$), unit increases in CAPRA score from diagnosis were associated with the occurrence of adverse pathology (odds ratio: 1.60; 95% confidence interval, 1.25–2.04; $p < 0.01$). On this basis, disease reclassification should be regarded from the vantage of multiple parameters.

Patient summary: In this study of men with favorable-risk prostate cancer on active surveillance, we evaluated the change in risk status from initial diagnosis to last biopsy using a readily tabulated clinical instrument. Unit change in the Cancer of the Prostate Risk Assessment (CAPRA) score was associated with increasing risk of adverse pathologic findings at delayed prostatectomy. This framework may be useful to stratify men based on the degree of clinical change from baseline over time.

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For men with favorable-risk prostate cancer (PCa) managed with active surveillance (AS), firm end points have not been prospectively evaluated. As a result, definitive intervention is often undertaken in the setting of changes in biopsy grade, prostate-specific antigen (PSA), tumor volume estimates, or personal preference [1]. While periodic monitoring of such

clinical characteristics offers numerous opportunities for risk appraisal, it is unclear whether changes in individual parameters offer equal value in informing the necessity of treatment. Furthermore, it is unknown if changes in multiple relevant characteristics may serve as an improved end point for men managed with surveillance. Consequently, we

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sought to evaluate whether the change in clinical risk, assessed from initial biopsy to final surveillance biopsy, predicted the presence of adverse pathologic findings at delayed radical prostatectomy (RP).

We identified study participants under a prior University of California, San Francisco (UCSF) institutional review board–approved protocol. Most men were selected based on strict UCSF AS criteria: PSA ≤ 10 ng/mL, clinical stage T2 or lower, $\leq 33\%$ positive biopsy cores, and $\leq 50\%$ positivity within a single core. Patients with relatively favorable risk profiles outside of strict AS criteria (eg, higher volume Gleason 3 + 3, low-volume Gleason 3 + 4) desiring surveillance were also included. All pathology slides obtained from outside institutions were reviewed by experienced academic pathologists. Men on AS between 1993 and 2013 who consented to prospective data collection and who did not receive definitive treatment for a minimum of 6 mo were included and participated in a surveillance program, as previously reported [2]. The Cancer of the Prostate Risk Assessment (CAPRA) score, an extensively validated risk assessment instrument, was calculated, as described previously, for all patients at initial diagnosis and following most recent biopsy (Supplementary Table 1) [3,4]. Patients with high-risk PCa (CAPRA >5 and/or Gleason score $\geq 4 + 3$) at diagnosis and those without subsequent clinical follow-up at our institution were excluded.

We evaluated the change in CAPRA score and its constituent components among all patients from diagnosis to last follow-up biopsy, using descriptive statistics and contingency tables with *p* values based on chi-square tests. Definitive treatment included RP, radiation therapy, androgen deprivation therapy alone, or ablative therapy. Among patients who received RP, adverse pathology was defined as the presence of primary Gleason pattern $\geq 4 + 3$, pathological T stage T3a or higher, and/or lymph node positivity—pathologic end points demonstrated to predict significant future clinical events [5]. The difference in CAPRA score from diagnosis to last biopsy was then used as a primary explanatory variable. A patient with, for example, a CAPRA score of 1 on diagnostic biopsy and 4 on a third surveillance biopsy would experience a net change of 3 points. Other covariates that could affect the response variable were included in the models, including PSA density, CAPRA score at the time of last biopsy, and time from diagnosis to prostatectomy. Among patients ultimately receiving delayed RP, we used receiver operating characteristic analysis to compare the effect of individual clinical parameter reclassification with CAPRA score change on the prediction of adverse pathology. Mann-Whitney *U* statistics were used to compare the area under the curve (AUC).

Overall, 735 patients met the inclusion criteria and were followed for a median of 52 mo. Mean age at diagnosis was 62 yr, and the median PSA was 5.2 ng/mL. At diagnosis, 577 patients (79%) met strict UCSF AS criteria, and 85% were low risk (CAPRA 0–2), whereas 15% were classified as intermediate risk (CAPRA 3–5). The complete baseline clinical and demographic characteristics of the cohort are shown in Supplementary Table 2. When assessed on

a continuous scale, CAPRA score was unchanged in 192 patients and decreased in 74. Shift in CAPRA score occurred due to multidirectional changes in biopsy Gleason score in 413 patients (56%), in PSA in 297 (40%), and in percentage of positive cores in 278 (38%). Moreover, 97 (13%) experienced reclassification by Gleason score alone, 156 (21%) by PSA alone, and 29 (4%) were reclassified based on changes in tumor volume. In total, 282 (38%) had a change in one parameter alone, 166 (23%) had changes in two parameters, and 42 (5.7%) had changes in three parameters (Fig. 1). In a multivariable logistic regression model, unit increases in CAPRA score were significantly associated with the occurrence of adverse pathology (odds ratio [OR]: 1.60; 95% confidence interval [CI], 1.25–2.04; *p* < 0.001). In addition, clinical risk (CAPRA) following last biopsy was also independently associated with adverse pathology (OR: 1.52; 95% CI, 1.21–1.92; *p* < 0.001) (Table 1). Magnitude of CAPRA score change (AUC: 0.72) outperformed individual PSA progression (AUC: 0.64; *p* = 0.03), and change in percentage of cores positive for cancer (AUC: 0.64; *p* = 0.04) for the prediction of adverse pathology at delayed RP.

Numerous surrogate end points during surveillance have been proposed to identify individuals at risk for harboring sufficiently aggressive disease warranting treatment. Changes in biopsy Gleason grade or tumor volume are widely regarded by surveillance protocols as an indication to pursue treatment; these events occur in a reliable proportion of men with each successive biopsy [6,7]. The occurrence of Gleason grade reclassification has been attributed to several factors including the detection of higher grade or volume tumor as a consequence of initial biopsy inaccuracy and the contribution of genuine cancer progression over time; however, the directionality of sampling limitations does not uniformly favor underdetection. This has been reflected in RP series in which misclassification at initial biopsy has resulted in both pathologic upgrade and downgrade [8]. Consequently, reclassification metrics based solely on a single clinical parameter may incompletely account for an individual's risk of clinically significant disease progression and expose many to early treatment.

We evaluated the change in clinical risk among men with low- and intermediate-risk PCa managed with AS at a single

Table 1 – Multivariable logistic regression models of adverse surgical pathology among men treated with radical prostatectomy following initial active surveillance (*n* = 169)

Variable	OR	95% CI	<i>p</i> value
CAPRA score at last biopsy (per 1 U)	1.52	1.21–1.92	<0.001
Log PSA density	0.83	0.44–1.58	0.57
Age (per 5 yr)	1.15	0.89–1.49	0.29
Time to RP (yr)	1.17	0.99–1.39	0.07
Magnitude of CAPRA change (per 1 U)	1.60	1.25–2.04	<0.001
Log PSA density	0.96	0.52–1.80	0.91
Age (per 5 yr)	1.24	0.96–1.61	0.10
Time to RP (yr)	1.18	0.99–1.39	0.06

CAPRA = Cancer of the Prostate Risk Assessment; CI = confidence interval; OR = odds ratio; PSA = prostate-specific antigen; RP = radical prostatectomy.

Fig. 1 – Relative frequency of variables reclassified over time among men on active surveillance.
 %Pos = percentage of positive biopsy cores; PSA = prostate-specific antigen.

institution and examined the significance of change in risk status from diagnosis as a predictor of adverse pathology among those receiving surgical treatment. In multivariable models composed of men ultimately treated with RP, the magnitude of risk change (CAPRA) from baseline was significantly associated with high-grade and/or non-organ-confined disease. Notable limitations of this analysis include noncontrolled decisions to pursue definitive treatment and the use of multiple genitourinary pathologists, reflecting the longitudinal nature of the surveillance cohort. To our knowledge, no other multivariable risk prediction tool has similarly been evaluated following a period of surveillance and suggests that risk stratification may be valuable following repeated clinical assessments. Such an approach may be meaningful for men experiencing reclassification of Gleason grade or PSA status alone and in whom clinical risk assessment may offer more comprehensive insight into an individual's broader status. These findings indicate that gradations of change in clinical risk occur over time and suggest that the magnitude of risk change, rather than unifactorial reclassification thresholds, may better inform triggers for intervention during AS.

Author contributions: Michael S. Leapman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Leapman, Ameli, Shinohara, Cooperberg, Carroll.

Acquisition of data: Leapman, Ameli.

Analysis and interpretation of data: Leapman, Chu, Hussein.

Drafting of the manuscript: Leapman, Cooperberg, Carroll.

Critical revision of the manuscript for important intellectual content: Leapman, Cooperberg, Carroll.

Statistical analysis: Ameli, Cooperberg.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eururo.2016.04.021>.

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