Serial Anatomical Prostate Ultrasound during Prostate Cancer Active Surveillance

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Purpose: The growth potential of low grade prostate cancer is unknown and yet it is potentially impactful for the practice of active surveillance. We evaluated the incidence, growth dynamics and clinical significance of changes in prostate lesions on serial transrectal ultrasound among a large cohort of men with prostate cancer managed by active surveillance.

Materials and Methods: This retrospective study included men with prostate cancer treated with active surveillance at UCSF (University of California-San Francisco) from 2000 to 2014 who underwent a minimum of 2 transrectal ultrasound studies. Study inclusion criteria were prostate specific antigen 20 ng/ml or less, clinical stage T2 or less and biopsy Gleason grade 3 + 4 or less. Progression end points included an increase in imaging stage, a 50% or greater increase in volume and an increase in the number of sites (sextants) with apparent lesions. The relationship between transrectal ultrasound progression and biopsy Gleason upgrade was assessed by univariate and multivariate logistic regression models.

Results: The 875 identified patients underwent a median of 5 transrectal ultrasound studies (IQR 3–8). Median followup was 49 months (IQR 27–81). Of the patients 345 (39%) progressed on serial transrectal ultrasound, including 51 by size, 265 by the number of lesion sites and 279 by stage. Median time to progression was 14 months. Transrectal ultrasound progression was independently associated with biopsy upgrade (OR 1.8, 95% CI 1.3–2.5, $p < 0.01$).

Conclusions: Local progression on transrectal ultrasound was associated with Gleason upgrade at biopsy. These results suggest that stable imaging findings on transrectal ultrasound may allow for increased intervals between biopsies among men on active surveillance. A prospective study is required to evaluate the usefulness of such a practice.

Key Words: prostatic neoplasms, ultrasonography, biopsy, diagnostic imaging, disease progression

Abbreviations and Acronyms

AS = active surveillance
DRE = digital rectal examination
MRI = magnetic resonance imaging
PCa = prostate cancer
PSA = prostate specific antigen
TRUS = transrectal ultrasound

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THE detection of low grade, low risk PCa is a well recognized consequence of population based PSA screening efforts. Early definitive treatment in these men may offer little improvement in survival and potential detriment to health related quality of life.[1] AS has been embraced as an alternative to immediate treatment without meaningful risk to oncologic control.[2–5] No consensus exists regarding the optimal protocol for surveillance. However, most guidelines agree that PSA monitoring and periodic repeat

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biopsy are required to identify disease progression or reclassification.[6] Due to the burden of prolonged followup, interest has grown in refining AS protocols using a growing array of novel tools, including PSA isoforms, gene expression tests and multiparametric prostate MRI.[7–9]

Serial imaging during surveillance is a promising and noninvasive means to evaluate the occurrence of disease progression. A small number of MRI based series have identified indicators of imaging progression but they are limited by short followup and variations in imaging protocols.[10] TRUS has largely been used to ensure adequate sampling of the prostate sextants during biopsy. Compared to MRI, TRUS has been shown to be less specific and with lower negative predictive value to detect PCa.[11] The low cost and availability of TRUS make its use for monitoring prostatic lesions an attractive diagnostic staging modality.

We evaluated the stability and clinical significance of serial ultrasound during PCa AS.

MATERIALS AND METHODS

Under institutional review board approval we identified men with favorable risk prostate cancer managed by AS at the UCSF from the departmental Urological Oncology Database. All men consented to prospective data collection. Participants in this analysis enrolled on AS in 2000 to 2014 with diagnostic PSA 20 ng/ml or less, clinical stage T2 or less on DRE and TRUS, biopsy Gleason 3 + 4 or less (with a minimum of 6 biopsy cores sampled) and CAPRA (Cancer of the Prostate Risk Assessment) low (0 to 2) or intermediate (3 to 5) clinical risk.[12]

Patients underwent the first followup TRUS within 6 months after the first positive biopsy, which was considered the baseline. Surveillance after diagnosis entailed quarterly PSA testing and semiannual DRE. Confirmatory biopsy was recommended within 1 year of diagnosis and TRUS was advised at 6-month intervals. TRUS consisted of high resolution B-mode ultrasound. A lesion was defined as any area with decreased echogenicity. Lesion(s) volume and site were documented. Clinical stage was assigned according to the AJCC (American Joint Committee on Cancer) staging definition.[13] The diagnostic value of TRUS staging has been previously demonstrated with high staging accuracy.[14] All examinations were performed by a single experienced sonographer (KS).

We explored several definitions of TRUS progression, including any increase in stage (eg T1c to T2a and T2a to T2c), lesion volume and number of sites (sextants) with ultrasound apparent lesions. A threshold of 50% or greater was used to define a volume increase to account for interexamination variation. Biopsy Gleason upgrade was defined as any increase in Gleason score from initial diagnostic biopsy (ie Gleason 3 + 4 in 3 + 3 cases and Gleason 4 + 3 in 3 + 4 cases).

Demographics and clinical characteristics are described using frequency and mean tables as appropriate. We described rates of TRUS progression and the association with upgrade, and reported yearly progression-free survival rates using Kaplan-Meier methods. Logistic regression was done to test the association between TRUS progression and biopsy upgrade. Cox proportional hazards multivariable regression models were used to evaluate the risk of TRUS progression. All models were adjusted for age, PSA density, biopsy Gleason grade, percent of positive biopsy cores and stage at first TRUS. Model covariates were selected based on clinical relevance and evaluated for inter-item correlations. The log of PSA density was used to normalize value distributions. Significance was considered at $p < 0.05$ and analysis was done with SAS®, version 9.3 for Windows®.

RESULTS

Of 1,386 men initially treated with AS at UCSF between 2000 and 2014 who provided consent for research 1,252 met clinical criteria for study inclusion. A further 377 patients in whom first staging TRUS was done more than 6 months after baseline were excluded, resulting in a final cohort of 875. Mean ± SD age was 62 ± 7.61 years, median PSA was 5.3 ng/ml (IQR 4.2–7.2) and the median percent of positive core at diagnosis was 13% (IQR 7–20). There was a mean of 1.6 ± 2 months between diagnosis and the first TRUS, and 5.5 ± 1.28 months between the TRUS procedures. The median number of TRUS studies performed in each patient was 5 (IQR 3–8) and the median number of biopsies was 2 (IQR 3–4). Median followup was 49 months (IQR 27–81) (supplementary table, http://jurology.com/).

At diagnosis 417 cases (48%) were clinical stage T1c, 409 (47%) were T2a/b and 49 (6%) were T2c. On followup TRUS 265 men (30%) had an increased number of lesion sites, 51 (31%) had a 50% or greater increase in lesion volume, 279 (32%) had an increase in clinical stage and 345 (39%) experienced imaging progression by any definition. When stratified by baseline clinical stage, 210 T1c cases (50%) showed progression, including 185, 22 and 3 reclassified as T2a/b, T2c and T3a, respectively. Progression was less frequently observed among T2a/b cases (66 of 406 or 16%), including 60 and 6 with progression to T2c and T3a, respectively. Among T2c cases 3 (6%) progressed to T3a (fig. 1).

Regarding tumor focality, 376 patients had a single sextant harboring lesion at baseline, of whom 33 progressed to having a second sextant and 2 progressed to having 3 sextants involved. Of the 22 patients who had 2 sextants with visible lesions at diagnosis 1 progressed to having 3 visible lesions. Only 1 patient had 3 sextants harboring lesions at diagnosis. Median volume of the dominant lesion at diagnosis was 0.32 cc (IQR 0.21–0.55). Median volume of the dominant lesion at progression was 0.46 cc (IQR 0.26–0.70).