Long term survival and predictors of disease reclassification in patients on an active surveillance protocol for prostate cancer

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Introduction: *Up to 50% of patients will have disease reclassification while on active surveillance (AS) for their prostate cancer. Determining which patients will have reclassification that will impact their survival is difficult. We investigated clinicopathologic factors associated with disease reclassification and differences in both overall and metastasis free survival between those treated and those remaining on AS.*

Materials and methods: *We performed a retrospective review of patients who were enrolled in an AS protocol between 1994 and 2000. Inclusion criteria for AS were: < cT2a disease, PSA < 10 ng/mL, < 50% of single core involvement, and Gleason score < 7, as well as sufficient follow up for evaluation (at least 1 subsequent transrectal ultrasound guided biopsy after initial diagnosis).*

Results: *There were 102 patients that met the inclusion criteria with median age of 70 years (IQR 68-73), follow up of 9.25 years (IQR 6.1-12.2) and time to disease reclassification of 4.7 years (IQR 2.8-7.9). Only prostate-specific antigen (PSA) density ≥ 0.15 was a significant predictor of disease reclassification with a hazard ratio of 5.5 (95% confidence interval 2.3-13.4, p < 0.01). There was no significant difference in metastasis free and overall survival between patients who received treatment and those that continued on AS despite reclassification of disease; this remained true even while stratifying patients by age ≥ 70 compared to those < 70 years old.*

Conclusions: *PSA density is a significant predictor of disease reclassification and AS remains a safe option for patients with low risk prostate cancer with up to 10 years of follow up.*

Key Words: prostate cancer, active surveillance, PSA density, disease reclassification

Introduction

There will be 220,000 men diagnosed with prostate cancer in 2016, of which up to half will have low risk disease.[1] The National Comprehensive Cancer Network (NCCN) guidelines recommend that patients with very low risk and low risk disease should be offered active surveillance (AS) as an option for their prostate cancer. Between 70%-80% of patients with low risk disease are treated with either radical prostatectomy or radiation, while only 20%-30% will be on AS in the United States.[2] In a recent systematic review of AS series, the longest median follow up for any cohort was 7 years.[3-6] Longer follow up is necessary to determine the safety of AS as evidenced by the increased prostate cancer mortality observed

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in a randomized trial of radical prostatectomy versus watchful waiting which demonstrated a survival benefit for those with intermediate or high risk disease (which are not included in the cohort of men we studied) after 23 years of follow up in patients undergoing surgery compared to observation, and no benefit for those with low risk disease.[7]

In order to determine which patients to select for AS, traditional criteria such as Gleason score, prostate-specific antigen (PSA) at diagnosis, and age are utilized. However there is a 20%-30% risk of under staging a patient's disease utilizing these parameters.[8] More accurate diagnostic information is necessary in order to better select patients for AS and predict which patients will be more likely to have reclassification of their prostate cancer.

The primary aim of this study was to determine predictors of disease reclassification in a cohort of low risk prostate cancer patients with long term follow up. The secondary aim was to evaluate the safety of AS through survival analysis.

Materials and methods

After institutional review board approval, we retrospectively reviewed the charts of patients at Moffitt Cancer Center between 1994 and 2000 who met the inclusion criteria for AS: Gleason score < 7, PSA < 10 ng/mL, < 50% cancer volume in each biopsy core, and < clinical T2a disease and had at least one follow up visit and prostate biopsy after diagnosis. The following parameters were recorded: pre-diagnosis PSA in ng/mL, age at diagnosis, prostate volume as measured by transrectal ultrasound at initial biopsy, PSA velocity (all patients had a minimum of three PSA measurements), PSA density, PSA doubling time less than 3 years, time of follow up, cause of death, as well as time to metastasis , and Gleason score. Treatment-specific information was also obtained and included patients who underwent radical prostatectomy (none), external beam radiation or brachytherapy with or without androgen deprivation, primary chemotherapy, primary androgen deprivation therapy, or no treatment. Reclassification of disease was defined by either an increase in the volume of disease (> 50% of a biopsy core), increase in Gleason score, or both.

Surveillance was performed with PSA measurements and digital rectal exam (DRE) every 6 months, and TRUS-Bx of the prostate annually. AS interval was defined as the elapsed time from initial diagnostic biopsy to most recent date of surveillance. The total number and frequency of biopsies was also recorded.

Our primary objective was to determine predictors of disease progression amongst the following variables: PSA at time of diagnosis, age, PSA density, PSA velocity and PSA doubling time < 3 years. We performed Cox proportional hazards testing and determined which variable had the greatest effect on disease progression.

The secondary aim was to evaluate the safety of AS through survival analysis. We utilized Kaplan-Meier analysis to determine median survival and significance was set as $p < 0.05$, with the survival time being defined as the time from date of diagnosis to date of death or last follow up. We further stratified patients as ≥ 70 and < 70 years of age and determined overall survival. There was only 1 prostate cancer mortality in our cohort and this patient also had myocardial infarction listed on his death certificate, thus a competing risks analysis was not performed. In addition there was only 1 patient who progressed to metastatic disease, which occurred 9 years after diagnosis; this patient survived an additional 7 years after metastasis and died at the age of 93. Progression free survival was determined based on PSA density ≥ 0.15 versus < 0.15 as this was the only factor on Cox proportional hazards testing that was significant for predicting reclassification of disease.

Results

There were 102 patients that met the inclusion criteria for this study, with a median age of 70 years old (IQR 68-73). The median follow up was 9.25 years (IQR 6.1-12.2) and median PSA at diagnosis 6.4 ng/mL (IQR 4.6-8.8). Baseline patient characteristics are summarized in Table 1.

For our patients, the median number of years being on AS prior to reclassification of disease was 4.7 years (IQR 2.8-7.9) and approximately 63% of patients had reclassification of their disease as defined by increase in volume, Gleason score, or both. The median prostate

TABLE 1. **Patient demographics**

Variable	**Median (interquartile range)**
Total # of patients	102
Age	70 (68-73)
Follow up (years)	9.25 (6.1-12.2)
Time to progression (years)	4.7 (2.8-7.9)
PSA (ng/mL) at diagnosis	6.4 (4.6-8.8)
Gleason sum at diagnosis	6

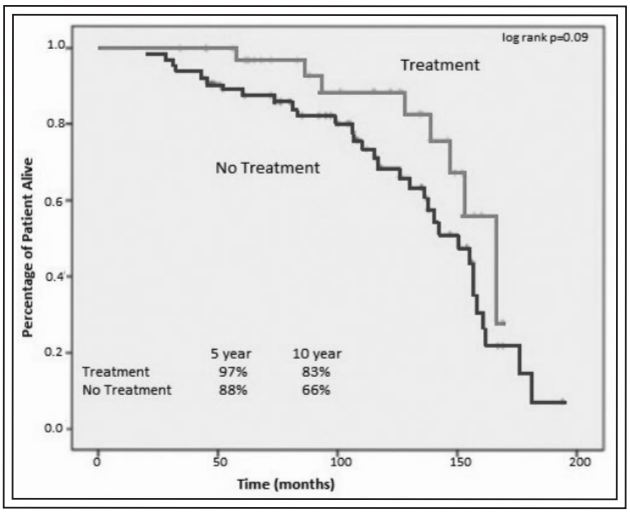

Figure 1. Overall survival for patients on active surveillance.

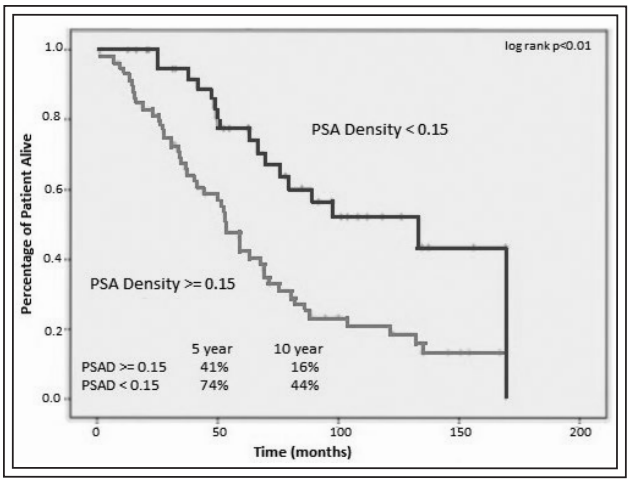

Figure 2. Progression free survival in patients on active surveillance.

volume was 34 grams (IQR 26.7-46.2), PSA density 0.18 (IQR 0.1-0.25), and PSA velocity 0.14 (IQR -0.83-0.64). Every patient received at least one active surveillance biopsy at year 1 on the protocol. There were 101 patients who underwent greater than one biopsy.

There were a total of 7 patients who experienced a PSA doubling time less than 3 years and all except 1 had reclassification of their disease. Of the patients with reclassification, 52% elected to have treatment. There were only 3 patients who elected treatment that did not demonstrate disease reclassification (2 had brachytherapy and 1 chose external beam radiation therapy).

The majority of those that chose treatment were younger than 70 years of age (44% less than 70 versus 29% above 70). Treatment consisted of radiation therapy (external beam or brachytherapy with or without androgen deprivation) in 45% of patients, primary androgen deprivation in 8% and primary cryotherapy in 13%. There was only 1 death attributed to prostate cancer.

The prostate cancer specific and metastasis free survival in our cohort was 99% as only 1 patient experience a prostate cancer related death and similarly only 1 patient experience radiographically confirmed metastasis. There was no significant difference in overall survival between those patients who had treatment and those without ($p = 0.09$), see Figure 1, even when stratified by age < 70 and ≥ 70 years old.

The variables of PSA doubling time < 3 years, PSA velocity, PSA at diagnosis, and age, were not significant predictors of disease progression on univariate analysis ($p > 0.05$). Only PSA density was a significant predictor of disease progression ($p = 0.01$). When placed in a Cox proportional hazards model, PSA density remained the only significant variable, see Table 2. As displayed in Figure 2, the progression free survival was also significantly worse in patients with PSA density ≥ 0.15 ($p < 0.01$).

TABLE 2. **Predictors of disease reclassification**

Variable	Odds ratio	95% confidence interval	p value
PSA velocity (all patients with at least 5 measurements) (ng/mL/year)	0.72	0.89-1.2	0.72
PSA density ≥ 0.15	5.5	2.3-13.4	< 0.01
PSA doubling time < 3 years	3.8	0.44-33.1	0.22
PSA (ng/mL) at diagnosis	0.98	0.92-1.03	0.39
Age (years)	1.1	0.99-1.2	0.08

Discussion

The 10 year safety of AS as an option for patients with low risk prostate cancer has been demonstrated regardless of age at diagnosis. Although 63% of patients went on to receive treatment at a median time of 4.7 years, there were no statistically significant differences in metastasis free and overall survival between patients who received treatment and those that remained on surveillance. Although not statistically significant, there is a clinically significant difference between the two groups, demonstrated by the early divergence of the survival curves, with those receiving treatment having longer survival ($p = 0.09$). This may be explained in that those receiving treatment had less comorbidities and better performance status rather than a treatment effect. In this cohort, the primary drivers of mortality were comorbid conditions and not their prostate cancer. This is consistent with a recent systematic review of large AS studies in which the prostate cancer specific mortality ranged from 0% to 1%.[3]

In our patient cohort, the median age was 70 years old which constitutes an older group of patients with prostate cancer. With the most recent AUA guidelines on prostate cancer screening, the majority of our patients would likely not get screened.[9] In addition to this, the median age at which patients experienced disease progression was 75 years old at which time no patients elected radical prostatectomy as a treatment option. The retrospective design of this study introduces bias with regard to patient selection and truly being able to capture an entire cohort of low risk prostate cancer patients. Thus, there is a need for prospective studies on the utilization of AS in younger patients with significantly longer follow up to determine its safety for those specific patients.

Additionally, all of our patients were diagnosed with prostate cancer prior to the change in pathological classification of prostate cancer in 2005, in which many of the previous Gleason 3+3 prostate cancers were reclassified as Gleason 3+4.[10] In a study of 97,168 men who were diagnosed with prostate cancer in Sweden between 1998 and 2011, there was a rise in Gleason score 7-10 amongst low risk tumors (clinical stage 1 and PSA 4-10 ng/mL) from 16% of tumors in 1998 to 40% in 2011.[11] With the finding in our study of no significant difference in survival in those that had disease progression and those that did not, it may be plausible that some Gleason 3+4 low volume cancers, that are otherwise low risk (PSA less than 10 ng/mL and clinical stage 1) may also be safely considered candidates for AS.

Most AS protocols will involve repeat prostate biopsy at some interval after the diagnosis. With the increasing rate of severe post prostate biopsy infections requiring hospitalization, limiting the number of TRUS-biopsies a patient undergoes is an increasingly important consideration.[12] Understanding which adverse clinicopathologic parameters are predictive of disease progression could help categorize patients into those requiring more frequent diagnostic testing with PSA, DRE, and TRUS-Bx and allow for those less likely to experience progression to have fewer invasive tests.

In our study, we found that PSA at diagnosis, age, PSA velocity, and PSA doubling time were not significant predictors of disease progression; with the only significant predictor being PSA density. Patients with a PSA density ≥ 0.15 were nearly five times more likely to experience disease progression compared to those with PSA density less than 0.15. In a large population based study of 13,159 men with low risk prostate cancer, Vellekoop et al observed that PSA density > 0.15 as well as the extent of cancer on a biopsy specimen were the only significant predictors of disease progression on multivariate analysis.[13] This PSA density threshold corresponds to the one in other studies determining cut off values for the detection of prostate cancer, where utilizing a PSA density of 0.15 or greater had an 86.4% cancer detection rate and also reduced the false negative biopsy rate by 54%.[14]

Further research into non-invasive testing to determine which patients are more likely to progress is needed. Recently, Park et al, found that if a lesion was present on MRI it was predictive of adverse pathological features at the time of prostatectomy when compared to those without any lesions on MRI despite positive biopsies for prostate cancer.[15] In addition to imaging technology, genetic markers are currently being prospectively evaluated for this purpose. In a recent review of tools for improving patient selection on AS, the authors determined that there is not enough evidence to rely solely on gene based assessments of a patient's disease in determining whether a patient is a good candidate for AS.[16]

Conclusion

AS is a viable option for older patients with low risk prostate cancer, this study demonstrates its long term safety. Primary drivers of patient mortality were their comorbid conditions and the only significant predictor of disease reclassification was PSA density at the time of diagnosis. Improved classification of patients who are candidates for AS will result in a more personalized approach limiting morbidity while improving cancer outcomes. □

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