Tumor Volume on Biopsy of Low Risk Prostate Cancer Managed with Active Surveillance

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Abbreviations and Acronyms

AS = active surveillance

JHU = Johns Hopkins University

MRI = magnetic resonance imaging

PSA = prostate specific antigen

PSAD = PSA density

RP = radical prostatectomy

Accepted for publication October 19, 2017.

No direct or indirect commercial incentive associated with publishing this article.

The corresponding author certifies that, when applicable, a statement(s) has been included in the manuscript documenting institutional review board, ethics committee or ethical review board study approval; principles of Helsinki Declaration were followed in lieu of formal ethics committee approval; institutional animal care and use committee approval; all human subjects provided written informed consent with guarantees of confidentiality; IRB approved protocol number; animal approved project number.

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Editor's Note: This article is the second of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 1074 and 1075.

Purpose: Contemporary clinical guidelines recommend active surveillance of men with low risk prostate cancer. Low risk disease spans any potential volume of Gleason score 6 cancer without sufficient attention to tumor volume in the past. Therefore, we compared tumor characteristics in men at low risk on active surveillance to men treated with radical prostatectomy.

Materials and Methods: We evaluated an institutional cohort of 1,633 men with very low risk disease (clinical stage T1c, prostate specific antigen density less than 0.15 ng/ml/cm^3, 2 or more positive cores and 50% or greater core involvement) and low risk disease (clinical stage T2a or less, prostate specific antigen less than 10 ng/ml and Gleason score 6 or less). Among patients at low risk we calculated the proportion who failed to meet very low risk volume criteria (greater than 2 positive cores or greater than 50% core involvement). Clinical and pathological metrics in the active surveillance cohort were compared to those in a cohort of men at low risk who underwent radical prostatectomy in the current era of 2011 to 2016.

Results: In the active surveillance cohort 1,119 men (69%) met very low risk criteria and 514 (31%) had low risk disease. In the low risk population only 138 men (27%) harbored higher volume cancer exceeding very low risk criteria compared to 815 (82%) at low risk who underwent radical prostatectomy ($p < 0.001$). Overall the low risk active surveillance population had fewer positive biopsy cores (median 1 vs 3, $p < 0.001$) and a lower maximum percent of core involvement (median 10% vs 40%, $p < 0.001$) compared to patients at low risk who underwent radical prostatectomy.

Conclusions: Data supporting the safety of active surveillance in men at low risk at our institution were derived from a distinct subgroup harboring a limited cancer volume. Until acceptable outcomes are confirmed for higher volume tumors it is important to remain mindful of these limitations before broadly recommending active surveillance to all low risk men.

Key Words: prostatic neoplasms, watchful waiting, prostatectomy, risk, safety

Although AS of localized prostate cancer has been formally used since the mid 1990s, many areas of uncertainty remain. For example, there is wide variation among the criteria for patient selection, monitoring and initiation of curative intervention.[1] Therefore, patients and providers must consider the risks and benefits of AS through shared decision making, and acknowledge the uncertainties that persist despite available data.

0022-5347/18/1994-0954/0
THE JOURNAL OF UROLOGY®

https://doi.org/10.1016/j.juro.2017.10.029
Vol. 199, 954-960, April 2018
Printed in U.S.A.

The 2 largest and most mature prospective AS cohorts are those at JHU and Sunnybrook Health Sciences Centre.[2,3] Along with randomized controlled studies considering monitoring and observation, data from these programs have driven contemporary clinical guidelines that recommend AS in most or all men with low risk disease.[4–7] However, there are important caveats to the literature describing AS. Most notably the methods of patient selection are such that the clinical characteristics of these cohorts do not represent the overall population diagnosed with low risk disease. As such, broadly applying AS to the low risk population could result in unacceptable oncologic outcomes, particularly among patients with high volume cancer who may be underrepresented. Thus, recommendations to use AS in most or all low risk men may be misleading.

Therefore, we sought to better characterize the population of men at low risk treated with AS at our institution. We suspected they may represent a select group with low volume disease that is not representative of the overall pool potentially eligible for AS. We aimed to determine the proportion of men on AS who met very low risk criteria and specifically compare tumor volume in the remaining men at low risk (ie those not meeting very low risk criteria) to tumor volume in a contemporary cohort of men at low risk who underwent surgery. We hypothesized that those at low risk treated with AS would harbor less extensive disease compared to men who elected immediate surgery.

MATERIALS AND METHODS

A total of 1,633 men with low risk or very low risk prostate cancer were enrolled in the prospective JHU AS program from 1995 through January 2017. Institutional review board approval was obtained and all patients provided informed consent. Very low risk prostate cancer was defined by clinical stage T1c, PSA less than 10 ng/ml, PSAD less than 0.15 ng/ml/cm^3, Gleason score 6 or less, 2 or fewer biopsy cores with cancer and 50% or less involvement of any positive biopsy core with cancer.[8] Low risk cancers were Gleason score 6 or less, clinical stage T2a or less and PSA less than 10 ng/ml that failed to meet very low risk criteria.

All patients were prospectively monitored with routine PSA measurements, digital rectal examination and surveillance prostate biopsies as previously described.[2] Men could elect to enroll after an initial diagnostic biopsy but a confirmatory biopsy is generally recommended within 18 months for all patients. Enrollment data on all men were obtained to determine the proportion who met very low risk criteria. Among men who did not meet very low risk criteria the reasons for failing to meet the criteria were explored, including clinical stage, PSAD and tumor extent on biopsy.

We also sought to evaluate whether men with low risk prostate cancer who underwent monitoring on AS were clinically representative of the overall low risk population. To do this we evaluated similarly assessed men with low risk cancer who underwent RP at our institution in the current era of 2011 to 2016. All men with clinically localized prostate cancer are counseled about RP as a management option with AS favored for very low risk and most low risk cancers. Additional evaluation with confirmatory biopsy and the decision to elect RP are determined through shared decision making. All men with low risk prostate cancer who underwent RP were included. Patient demographics, PSA, PSAD and tumor volume were compared between the AS and RP populations.

The primary outcome assessed was tumor volume on biopsy compared to the pathological threshold for very low risk disease (greater than 2 biopsy cores with cancer or greater than 50% involvement of any positive biopsy core with cancer). To maintain homogeneous comparisons of biopsy pathology only systematic biopsy cores from the patient diagnostic biopsy were used for risk classification and comparisons between the AS and RP cohorts. Targeted or MRI-fusion biopsy cores were not considered. Analyses were performed with SAS®, version 9.4 and STATA®, version 13.1.

RESULTS

Active Surveillance

Of the 1,633 men enrolled in AS 1,119 (69%) met the criteria for very low risk prostate cancer. The remaining 514 men (31%) did not meet very low risk criteria and enrolled in AS with low risk disease. Among the low risk AS population 376 men (73%) met biopsy parameters for very low risk disease (Gleason score 6 or less, 2 or fewer positive biopsy cores and 50% or less cancer involvement of any positive biopsy core) but failed to meet all very low risk criteria due to elevated PSAD or clinical stage. Specifically 245 men, representing 48% of the low risk AS cohort, had PSAD greater than 0.15 ng/ml/cm^3, 105 (20%) had unknown prostate volume precluding a PSAD calculation and 26 (5%) had clinical stage T2a disease (fig. 1).

The remaining 138 men at low risk, representing 27% of the low risk AS cohort, harbored higher volume cancer than the very low risk threshold (ie greater than 2 positive biopsy cores or greater than 50% cancer involvement of any biopsy core). Of these men 24 (17%) had 2 or fewer positive biopsy cores but were classified as having higher volume based on harboring greater than 50% involvement of a positive core. An additional 73 men (53%) had 3 positive cores, 30 (22%) had 4 positive cores and only 11 (8%) had 5 or more positive cores. Patients with greater than 2 positive biopsy cores were at increased risk for grade reclassification while on AS (HR 2.8, $p < 0.001$, supplementary figure, http://jurology.com/).