Age is Associated with Upgrading at Confirmatory Biopsy among Men with Prostate Cancer Treated with Active Surveillance

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Purpose: Active surveillance is increasingly recommended for older men with low risk prostate cancer. Although older men have higher all cause mortality, they also have higher prostate cancer specific mortality. We hypothesized that older age is associated with an increased risk of Gleason score upgrading at confirmatory biopsy when controlling for prostate volume.

Materials and Methods: We retrospectively reviewed data on 1,130 patients with prostate cancer who were treated with active surveillance from 1991 through 2011. We included 646 patients with clinical Gleason 6 or less, stage T2a or less prostate cancer, a confirmatory biopsy within 2 years of diagnostic biopsy and prostate magnetic resonance imaging before confirmatory biopsy. The primary outcome was Gleason score upgrading to 7 or greater on confirmatory biopsy. We used logistic regression to estimate the effect of age on upgrading, adjusting for magnetic resonance imaging prostate volume and other potential confounders.

Results: Median age was 66 years (IQR 61–72) and median magnetic resonance imaging prostate volume was 41 ml (IQR 29–55). At confirmatory biopsy disease was upgraded in 55 of 646 patients (9%) and unchanged in 290 (45%) and biopsy was negative in 297 (46%). Older age was associated with higher odds of upgrading (adjusted OR 1.05, 95% CI 1.01–1.09, p = 0.009). Larger prostate volume was associated with lower odds of upgrading (adjusted OR 0.80/10 ml increase, 95% CI 0.7–0.9, p = 0.012).

Conclusions: Our findings suggest that older age is associated with an increased risk of misclassification on diagnostic biopsy. Older men who are interested in active surveillance should be counseled about the risks and benefits of confirmatory biopsy.

Key Words: prostatic neoplasms, biopsy, watchful waiting, magnetic resonance imaging, age factors

Abbreviations and Acronyms

AS = active surveillance

MRI = magnetic resonance imaging

PSA = prostate specific antigen

RP = radical prostatectomy

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Prostate cancer is a disease of age and approximately half of the men are older than 65 years at diagnosis.[1–3] National guidelines support using AS to treat patients who are unlikely to die of prostate cancer, including those with low risk disease and those with limited life expectancy due to older age or significant medical comorbidity.[4] Among appropriately selected patients intermediate term outcomes for AS demonstrate high disease specific survival and avoidance of radical treatment in the majority of patients.[5]

While older men have shorter life expectancy and are at higher risk for

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competing causes of mortality, they are still at significant risk for prostate cancer specific mortality.[6–8] In an analysis of the SEER (Surveillance, Epidemiology and End Results) database older age was associated with higher grade at diagnosis and men older than 75 years accounted for almost half of prostate cancer deaths and those with metastatic disease.[2] Contemporary AS cohorts appropriately include older men[9] but older men with prostate cancer who are treated with noncurative intent may have higher cancer specific mortality.[10] This may be due to age related differences in disease biology, the ability to risk stratify patients at diagnosis or a trend toward less aggressive treatment in older men.

Selection for AS depends on accurate disease classification at diagnosis based on tumor stage, PSA, biopsy grade and tumor volume. Confirmatory biopsy within 1 year of diagnosis is strongly recommended as part of AS since approximately 30% of men with low risk disease are found to have higher grade or volume disease at confirmatory biopsy and may no longer be candidates for AS.[11–13]

We hypothesized that among men with prostate cancer who were treated with AS older age is associated with upgrading at confirmatory biopsy. We included prostate volume as a confounder of the main effect because it has been associated with biopsy under sampling and older men are expected to have a larger prostate.[14,15]

MATERIALS AND METHODS

Patient Cohort

After receiving institutional review board approval we retrospectively reviewed data from a prospectively maintained clinical database to identify all 1,130 men diagnosed with prostate cancer who were treated with AS from 1991 through 2011 at our institution. The analytical cohort included 646 patients with Gleason score 6 or less, clinical stage T2a or less, any number of positive biopsy cores at diagnostic biopsy, confirmatory biopsy within 2 years of diagnostic biopsy and prostate MRI prior to confirmatory biopsy. There were 369 patients who were excluded from study due to an absent confirmatory biopsy within 2 years of diagnostic biopsy.

Multiplanar MRI was done, including T1-weighted and T2-weighted sequences, which were interpreted by experienced radiologists.[16] Prostate volume on MRI was measured on T2-weighted images and calculated by assuming an ellipsoid shape of the gland using the formula, (transverse diameter × anteroposterior diameter × craniocaudal diameter)/2. Men with abnormalities detected by MRI underwent biopsies under direct vision using cognitive documentation of suspicious lesions on T2-weighted images. All biopsy specimens were reviewed at our institution by an experienced genitourinary pathologist. The criteria for low risk prostate cancer were defined as clinical stage T2a or less, Gleason score 6 or less, 2 or fewer positive cores and 50% or less single core positivity.[17]

Statistical Analysis

The primary outcome was Gleason score 7 or greater on confirmatory biopsy. Clinical and demographic characteristics are presented as the median and IQR for continuous variables and the frequency and percentage for categorical variables. Differences in percentages were compared using the chi-square test. We present the unadjusted relationship between age and upgrading using a LOWESS curve. Logistic regression was used to examine the independent association between age and upgrading on confirmatory biopsy. Model covariates included race, PSA at diagnosis, clinical tumor stage at diagnosis (T2a vs T1c or less), number of positive biopsy cores on diagnostic biopsy (1 vs 2 vs 3) and prostate volume measured on MRI (in 10 ml increments). We used restricted cubic splines with knots at the tertiles to test for a nonlinear association between age and upgrading at confirmatory biopsy. However, the test was nonsignificant ($p = 0.8$) and we present the model of results with linear age.

We performed sensitivity analysis after restricting our cohort to men who underwent repeat biopsy within 1 year of diagnostic biopsy. However, our conclusions were unchanged (data not shown). In addition because our regression model carried a risk of overfit, we repeated the analysis after excluding race from our model and then excluding clinical stage but results were unchanged. Finally because many AS protocols use an increase in tumor volume as a treatment trigger, we used logistic regression to examine whether age was associated with any increase in tumor volume on repeat biopsy. Statistical significance was considered at $p < 0.05$.

RESULTS

Most of the 646 patients included in study were white and had low risk disease on diagnostic biopsy (table 1). Only 70 patients (11%) had diagnostic biopsies performed at our institution while the rest were performed elsewhere. Of biopsies done elsewhere 87% were reviewed by our pathologists.

Table 1. *Demographic and clinical characteristics of 646 patients in analytical cohort*

Median age at diagnosis (IQR)	66	(61–72)
Median ng/ml PSA at diagnosis (IQR)	4.6	(3.4–6.2)
Median ml prostate vol on MRI (IQR)	41	(29–55)
Median max % pos single core on initial biopsy (IQR)	5%	(3–13)
No. race (%):		
White	569	(88)
Nonwhite	77	(12)
No. clinical stage at diagnosis (%):		
T1c or less	561	(87)
T2a	85	(13)
No. pos cores on initial biopsy (%):		
1	465	(72)
2	138	(21)
3 or Greater	41	(7)
No. low risk criteria at diagnostic biopsy (%):		
Yes	588	(91)
No	58	(9)
No. repeat biopsy (%):		
Upgraded	55	(9)
Unchanged	293	(45)
Neg	298	(46)