Older Age at Diagnosis and Initial Disease Volume Predict Grade Reclassification Risk on Confirmatory Biopsy in Patients Considered for Active Surveillance

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OBJECTIVE To identify which active surveillance candidates benefit most from confirmatory biopsies to exclude grade underclassification.

MATERIALS AND METHODS This observational study includes 556 men diagnosed between 2002 and 2015 with Gleason 3 + 3 (GG1) disease on initial diagnostic biopsy, of whom 406 received a confirmatory biopsy within 12 months for active surveillance. Multivariable logistic regression analysis was performed to determine clinicopathologic features associated with Gleason 7 or higher (GG2+) on a confirmatory biopsy. Regression tree analysis was employed to stratify patients into select risk groups.

RESULTS Eighty-five of 406 patients (20.9%) with initially GG1 disease were reclassified to GG2+ on a confirmatory biopsy. On multivariable analysis, increasing age (per year odds ratio 1.07; 95% confidence interval 1.02-1.12; P <.01) and more positive cores at diagnosis (per core, odds ratio 1.37, 95% confidence interval 1.09-1.72; P <.01) were significantly associated with reclassification, independent of prostate volume, clinical stage, initial PSA, or confirmatory biopsy type (including magnetic resonance imaging-targeted approaches or transrectal saturation random sampling). Recursive partitioning demonstrated that age over 73 and 5 or more positive cores were factors associated with the greatest reclassification risk.

CONCLUSION In our cohort, both advancing age and additional positive cores were associated with increased odds of reclassification to GG2+ on confirmatory biopsy. In men over age 73 or with 5 or more positive cores, a repeat biopsy within 12 months may be particularly beneficial to minimize tumor grade underclassification. UROLOGY 130: 106–112, 2019. © 2019 Elsevier Inc.

Active surveillance (AS) is an increasingly accepted management strategy to minimize the overtreatment of favorable-risk prostate cancer. Large prospective cohorts have since shown that the overall long-term risk of adverse oncologic outcomes in patients on AS is low, particularly when considering proper patient selection and follow-up.[1,2] However, optimal practices for AS and guidelines for candidate selection continue to evolve and have yet to be fully delineated.[3] A major limitation related to current AS paradigms is the risk of diagnostic underclassification of occult unfavorable disease. Approximately 30% of men diagnosed with low risk disease are found to have higher grade or greater tumor volume on a repeat biopsy,[4,5] and prostate biopsy findings are often discordant with subsequent pathology on radical prostatectomy specimens.[6,7] Inadequate assessment of higher grade disease is of principal concern, given that tumor grade remains among the strongest predictors of prostate cancer-specific mortality.[8,9] Thus, surveillance protocols should ideally be risk-adapted among AS candidates to ensure proper detection of occult higher grade malignancy.[10,11] To this end, many AS protocols recommend obtaining a confirmatory biopsy within 12 months of diagnosis.[12] However, which patients benefit most from a repeat biopsy remains unclear. Importantly, a prostate biopsy is not entirely harmless,

Conflicts of Interest: *None.*

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being an invasive procedure that may be poorly tolerated or lead to complications ranging from self-limited bleeding to sepsis and other adverse consequences.[13,14] Therefore, we sought to identify baseline clinicopathologic features which predict for diagnostic underclassification among newly diagnosed Gleason 3 + 3 (GG1) patients, thereby helping to guide decisions on whether a repeat confirmatory biopsy is of value in this setting.

MATERIALS AND METHODS

Patient Population

Under institutional review board approval, we retrospectively identified all men who were managed on AS from 2002 to 2015 at a large tertiary care academic institution (Fig. 1). The composition, management strategies, and overall outcomes of this cohort have been previously described.[15] In brief, enrollment of patients on AS at our institution is determined by the treating physician, with eligibility based on the summative clinical characteristics (age, presence of medical comorbidities, and favorable disease features) as well as shared decision-making. Typical surveillance practices include periodic clinic visits every 6-12 months, involving routine digital rectal examinations and serum prostate-specific antigen (PSA) measurements, a repeat transrectal ultrasound (TRUS) or multi-parametric magnetic resonance imaging (mp-MRI)-targeted biopsy generally within 12 months of an initial diagnostic biopsy, and serial surveillance biopsies taken at a minimum of 12 cores generally every 1-2 years, with a rising PSA and/or an abnormal digital rectal examinations as a consistent trigger for earlier biopsy. Broad indications for definitive treatment include disease reclassification due to increased tumor grade or volume on a surveillance biopsy, or patient choice.

Clinicopathologic and Demographic Data

Patient clinicopathologic and demographic data were obtained related to age at diagnosis, race, serum PSA measurements, initial disease features and clinical staging, NCCN risk category, and prostate volume assessment by TRUS. Information from the initial diagnostic and confirmatory biopsy was determined, including highest Gleason grade group (GG), total number of cores sampled, number of cores involved with disease, percentage of cores with greater than 50% disease involvement, and whether the biopsy was targeted by mp-MRI (by MRI-TRUS fusion biopsy or cognitive fusion). A transrectal saturation biopsy was defined as a sampling of at least 20 tissue cores.[16] All prostate biopsies were reviewed by our institutional GU pathology team.

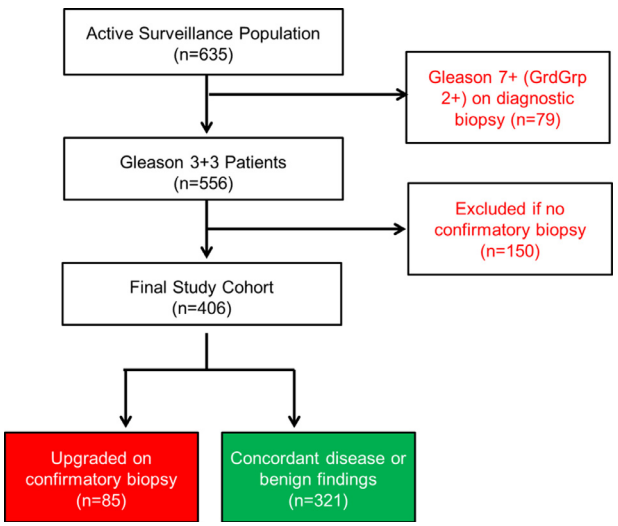

Figure 1. Cohort selection depicted on a consort diagram. (Color version available online.)

Inclusion and Exclusion Criteria

We initially determined a study cohort comprised of 556 patients on AS with GG1 disease, 406 of whom had received a confirmatory biopsy within 12 months of diagnosis (Fig. 1). Patients with any Gleason pattern 4 or higher at diagnosis (n = 79) and patients who did not receive a repeat biopsy within 12 months of diagnosis (n = 150) were excluded from the final analysis. Characteristics of patients excluded due to absence of a confirmatory biopsy are reported in a supplemental table (Table S1). In addition, a sensitivity analysis was performed to determine whether redefining our criteria for a confirmatory biopsy using repeat sampling within 15 months (rather than 12 months) influenced our findings, given the possibility of unanticipated delays in biopsies (Table S2). The study cohort was subsequently subdivided into 2 groups based on the presence or absence of reclassification to Gleason 7 (GG2) or higher on the confirmatory biopsy.

Statistical Analysis

The primary outcome was grade reclassification, defined as an increase in either primary or secondary Gleason pattern on confirmatory biopsy. Clinicopathologic and demographic differences between patients who were reclassified and not reclassified are reported as either a median with IQR and analyzed by Wilcoxon-rank sum test for continuous variables, or proportion analyzed by Fisher's exact test or chi-squared test, when appropriate, for categorical variables. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated by multivariable logistic regression analysis to determine independent predictors of reclassification on a confirmatory biopsy. Covariates were selected based on associations from previous literature and determined a priori. A LOWESS curve was generated, reflecting the unadjusted relationship between age and probability of reclassification. The assumption of linearity was tested with restricted cubic splines with knots at the tertiles. To further describe the relationship between potential predictors, we performed a recursive partitioning analysis to dichotomize patients into subgroups with a maximal difference in Gleason underclassification outcomes attained between pairs. In brief, a classification tree was constructed using an algorithm to determine an optimal sequence of classifications, with hierarchical splitting of data defined by a set of prespecified factors. We included all independent predictors as determined by our logistic regression model. Both PSA and prostate volume were included in the model while PSA density was omitted to avoid issues of colinearity. Statistical analyses were performed through the open source statistical computing software R (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org). An α of 0.05 was designated a priori for all statistical tests and were 2-sided.

RESULTS

In total, 406 patients with initial GG1 disease were identified who had received a confirmatory biopsy within 12 months

of diagnosis. In this cohort, 38.2% of men had NCCN very low-risk disease. Median age of diagnosis was 64 years (IQR 60-68), and a majority of patients self-identified as Caucasian (87.7%) and presented with clinical T1 stage (87.4%). Overall cohort characteristics are reported in Table 1. The median number of cores obtained on diagnostic biopsy was 12 (IQR 12-12), with <3 positive core detected on sampling in most cases (340/406, 83.7%). Median time to confirmatory biopsy was 3.5 months (IQR 1.6-6.4). Saturation-based confirmatory biopsies were performed in 27% of men. Guidance by mp-MRI was employed in 11.4% of confirmatory biopsies, most of whom were in the later stages of the study period when use of mp-MRI became standard management.

Within our cohort, 85 men (20.9%) were reclassified due to higher grade disease on a confirmatory biopsy. Among reclassified patients, 71 men (83.5%) were found to have GG2 disease, 1 (1.18%) had GG3, and 13 (15.3%) had GG4. Of note, among patients who were reclassified to GG2, 64/85 (75%) met criteria for NCCN favorable intermediate risk. Of men who were not reclassified, 155 (48.3%) demonstrated only benign tissue on repeat biopsy. Baseline differences between patients who were and were not reclassified are reported in Table 1. Patients who were reclassified tended to be older, have more positively involved cores on diagnostic biopsy, and went on to receive definitive treatment. On multivariable analysis, older age (per year OR 1.07; 95% CI 1.02-1.12; P <0.01) and a greater number of positive cores (per core OR 1.37, 95% CI 1.09-1.72; P <0.01) independently predicted grade reclassification odds on the confirmatory biopsy (Table 2), after adjusting for race, initial prostate volume, clinical stage, PSA, and use of mp-MRI-targeted or saturation biopsy approaches. These findings were not affected by extending the definition of confirmatory biopsy to 15 months from diagnosis (rather than 12 months) to account for possible delays in resampling. Of note, the unadjusted probability of grade reclassification was not linearly proportional with age and increased most dramatically in men with advanced age (Fig. S1). Regression tree analysis further identified age as the most important explanatory variable for grade reclassification risk and determined that age greater than 73, as well as 5 or more positive cores on diagnostic biopsy, as important factors associated with considerable reclassification risk compared to the general cohort (Fig. 2).

Table 1. Characteristics of patients who were reclassified on confirmatory biopsy

Characteristic	All Patients	Not Reclassified	Reclassified	*P* Value
No. of patients	406	321	85	
Age at diagnosis (years)	64 [60-68]	64 [60-68]	66 [61-72]	.01
Initial PSA (ng/mL)	5.05 [3.73-6.70]	5.01 [3.61-6.63]	5.07 [3.88-6.86]	.41
Initial prostate volume (cc)	38.0 [30.0-53.0]	37.8 [29.0-53.0]	38.0 [30.2-53.8]	.62
Initial PSAD (ng/mL/cc)	0.12 [0.08-0.17]	0.12 [0.08-0.17]	0.13 [0.09-0.19]	.17
Race				.21
Caucasian	356 (87.7%)	286 (89.1%)	70 (82.4%)	
African American	29 (7.14%)	21 (6.54%)	8 (9.41%)	
Other	21 (5.17%)	14 (4.36%)	7 (8.24%)	
Initial clinical stage				.30
cT1	355 (87.4%)	284 (88.5%)	71 (83.5%)	
cT2	51 (12.6%)	37 (11.5%)	14 (16.5%)	
Total no. of initially sampled cores	12 [12-12]	12 [12-13]	12 [12-12]	
Initial no. of positive cores				<.001
1	266 (67.2%)	215 (68.9%)	51 (60.7%)	
2	74 (18.7%)	65 (20.8%)	9 (10.7%)	
3+	56 (14.1%)	32 (10.3%)	24 (28.6%)	
Initial no. cores with >50% involvement				.55
0	369 (97.1%)	294 (97.4%)	75 (96.2%)	
1	10 (2.63%)	7 (2.32%)	3 (3.85%)	
2+	1 (0.26%)	1 (0.33%)	0 (0.00%)	
Initial NCCN risk category				.66
Very low risk	154 (38.2%)	126 (39.5%)	28 (33.3%)	
Low risk	225 (55.8%)	173 (54.2%)	52 (61.9%)	
Intermediate risk	19 (4.71%)	16 (5.02%)	3 (3.57%)	
High risk	5 (1.24%)	4 (1.25%)	1 (1.19%)	
No. of sampled cores on confirmatory biopsy	12 [12-20]	12 [12-20]	14 [12-20]	.12
Median time to confirmatory biopsy (months)	3.5 [1.6-6.4]	3.7 [1.7-6.4]	3.2 [1.1-6.3]	.09
Saturation confirmatory biopsy	109 (27%)	82 (25.8%)	27 (31.4%)	.30
MRI-targeted confirmatory biopsy	39 (11.4%)	30 (11.0%)	9 (12.9%)	.82
Gleason score on confirmatory biopsy				
Negative for disease	155 (38.2%)	155 (48.3%)	N/A	
3 + 3 (GrdGrp 1)	166 (40.9%)	166 (51.7%)	N/A	
3 + 4 (GrdGrp 2)	71 (17.5%)	N/A	71 (83.5%)	
4 + 3 (GrdGrp 3)	1 (0.3%)	N/A	1 (1.18%)	
3 + 5 (GrdGrp 4)	10 (2.5%)	N/A	10 (11.8%)	
4 + 4 (GrdGrp 4)	3 (1%)	N/A	3 (3.53%)	
Received definitive treatment	146 (35.9%)	80 (24.9%)	66 (77.6%)	<.001
Median time to treatment (months)	9.90 [5.13-25.6]	19.5 [7.8-48.6]	6.2 [3.1-11.8]	<.001

Values are reported as: median [interquartile range]; absolute number (percent total).

Table 2. Adjusted estimates for predictors of reclassification on confirmatory biopsy

Clinicopathologic Feature	Adjusted OR (95% CI)	*P* Value
Age at diagnosis (years)	1.07 (1.02-1.12)	.001
Initial PSA (ng/mL)	1.02 (0.95-1.09)	.60
Initial prostate volume (cc)	0.99 (0.98-1.01)	.30
Initial PSA density (ng/mL/cc)	1.41 (0.31-6.35)	.65
Race		
African American	1.53 (0.58-4.03)	.40
Other	[ref]	
Initial clinical stage		.67
cT1	[ref]	
cT2	1.17 (0.54-2.53)	
Initial no. of positive cores	1.37 (1.09-1.72)	.002
Saturation confirmatory biopsy	1.09 (0.60-1.95)	.78
MRI-targeted confirmatory biopsy	1.07 (0.46-2.48)	.88

DISCUSSION

Despite broader acceptance of AS in recent years, a persisting limitation related to current biopsy-based AS schemes remains the risk of diagnostic underclassification. Furthermore, an increasing number of surveillance modalities now exist,[17] which include but are not limited to serum markers,[18] serial biopsies, transperitoneal template mapping biopsy, mp-MRI with or without fusion,[19] and genomic testing.[20,21] Given the evolving paradigm in AS, the benefit of a repeat biopsy to guide decision-making should be weighed against the risk of biopsy-related complications and the appropriateness of other surveillance methods. We thus attempted to determine which patients among a large AS-eligible cohort may benefit most from a confirmatory biopsy-based approach to rule out occult higher-grade disease. In our institutional cohort of men with newly diagnosed GG1 disease who subsequently received a confirmatory biopsy, approximately 21% of patients were immediately reclassified to GG2 or higher on confirmatory biopsy. Among patients who were reclassified, the majority were found to have an increase in secondary rather than primary Gleason pattern 4, and a majority met NCCN favorable intermediate risk criteria. Furthermore, among these patients, older age at diagnosis and a greater number of positive cores on diagnostic biopsy were found to be the only independent factors associated with grade reclassification risk. On recursive partitioning analysis, advanced age (>73 years) was the strongest determinant of grade reclassification risk in our study population, although this analysis was limited by sample size and warrants replication in a larger series.

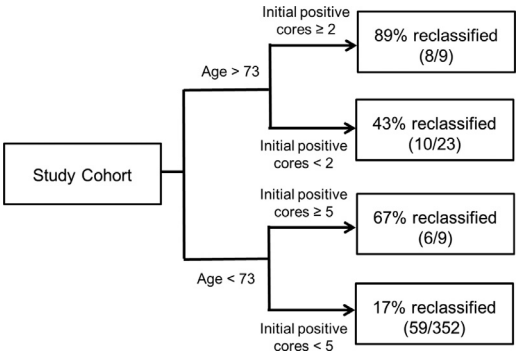

Figure 2. Recursive partitioning analysis reveals that age is the strongest predictor of grade underclassification on confirmatory biopsy and stratifies the population into 4 major risk groups. (Color version available online.)

The probability of upgrading on a first confirmatory biopsy among larger contemporary studies has been reported to range from 8% to 30%.[5,16,22] In results from the Canary Prostate Cancer Active Surveillance Study, 18% of 421 men were upgraded on a first AS biopsy obtained after a median of 11 months.[23] In contrast, a lower upgrading rate of 9% was reported among 646 low-risk patients at MSKCC undergoing confirmatory biopsy within the first 2 years.[22] Importantly, in the latter study, all patients received a prostate MRI prior to confirmatory biopsy per institutional protocol. Thus, differences in reclassification rates across cohorts likely reflect some variation in the practice of defining AS candidacy, as well as possibly the timing and methodology of obtaining confirmatory biopsies. Our higher rates of reclassification may indicate a more liberal representation of AS-eligible patients in our study population, for instance patients presenting with a greater volume disease at diagnosis.

The long-term success of surveillance relies on proper patient selection and risk assessment at time of enrollment. Although advanced age has frequently been recognized as a risk factor for biopsy upgrading,[2,22,24,25] the role of age towards determining surveillance biopsy scheduling is less well-defined.[10] Furthermore, while older men are generally thought to be better candidates for AS due to shorter life expectancy and/or death from competing causes of mortality, they are also more likely to be diagnosed with aggressive prostate cancer based on grade and pathologic stage,[26,27] less likely to be treated,[2] and at greater risk for prostate cancer-specific mortality.[28,29] For each year of increasing age, we noted a 7% increase in the odds of reclassification to GG2 or higher disease on the immediate following biopsy after diagnosis, which was not explained by differences in prostate volume. Conversely, younger men appear to be at lower risk for pathological upgrading over time, which was recently demonstrated in a large series involving over 1400 patients, where age ≤60 years was independently associated with decreased risk of Gleason core upgrading (hazard ratio 0.67; 95% CI 0.55-0.83), as well as a decrease in overall progression by either upgrading or an increase in tumor volume to >33% positive cores (hazard ratio 0.78; 95% CI 0.65-0.92).[24] Our findings similarly suggest that older men might benefit in particular from a repeat biopsy, which should be considered in the context of potential curability and alternative triggers for intervention. Of note, for every additional positive core on diagnostic biopsy, there was a

37% increase in the odds of reclassification on confirmatory biopsy. This finding has also been recently recapitulated by other studies, including Anderson et al, who also found an adjusted OR of 2.6 for reclassification on confirmatory biopsy with 2 positive cores (95% CI 1.4-5.1) and 3.9 for 3 positive cores (95% CI 1.6-9.7) compared to 1 positive core at diagnosis.[3,22,30,31] The association between tumor volume and grade reclassification may indicate sampling inadequacy of Gleason pattern 4 or 5 foci among larger tumors.

Notably, we did not observe a clear association between confirmatory biopsy sampling methodology by either saturation biopsy or mp-MRI utilization and overall grade reclassification risk, although our study may not have adequately captured these effects, given a low percentage of patients in our cohort who underwent these modalities. The role of these approaches toward routine AS biopsies in men with favorable-risk disease thus requires more rigorous prospective investigation. Importantly though, as the number of available modalities used in the contemporary AS space continues to expand and given the increasing diversity of surveillance options, a next frontier in AS requires integration of these data, comparison of performance characteristics across different modalities, and creation of personalized protocols for the detection of clinically significant prostate cancer. Along these lines, our findings posit that a confirmatory biopsy-based approach to detect occult higher-grade disease is most valuable in subpopulations of older men and younger men with a higher burden of disease at diagnosis. Reciprocally, in other subpopulations, alternative methods of surveillance could be more useful, although this hypothesis requires further validation.

This study is not without its limitations. Given its retrospective nature, our approach cannot fully capture and account for nonstandardized institutional AS approaches and evolving practices over the time period of analysis, including changes in Gleason score assignments, which could impact reclassification rates. Likewise, given limitations to available data, we were unable to define at a more granular level whether patients who underwent mp-MRI received a targeted fusion biopsy or biopsy by cognitive fusion, which may explain a lack of association between image guidance and risk of reclassification. Although we sought to investigate whether our data are generalizable specifically to African Americans as a risk group, this was unclear, given the limited sample size of our study. This remains a topic of interest for future study.

While our study addresses issues related to biopsy-based sampling, it does not assess long-term outcomes such as treatment failure or mortality, which would have relevance to the overall utility and safety of AS in the subpopulations which we identified. Nor were we able to rigorously determine the percent of high grade tissue within each core. Admittedly, the prognostic value of upgrading may be dependent on the extent of detected high grade disease involvement, which could not be ascertained. However, the observation that many patients who were reclassified met NCCN favorable intermediate risk criteria suggests that at least a subset of patients who are reclassified to higher grade disease are still candidates for AS. Nonetheless, our data support recent findings which suggest that surveillance biopsy scheduling should be adjusted based on patient age and disease volume to appropriately account for disease risk and potential morbidity of unnecessary biopsies. Prospective studies should further assess the clinical safety of less invasive and potentially adjuvant confirmatory testing such as mp-MRI and genomic stratifiers in this context.

CONCLUSION

Among patients with newly diagnosed GG1 disease who subsequently received a confirmatory biopsy for AS, older age and more positive cores at diagnosis were the only independent predictors for underclassification of GG2 or higher disease. Furthermore, advanced age appears to influence the performance characteristics of a confirmatory biopsy which are not explained by prostate volume alone. In men over age 73 or with 5 or more positive cores at diagnosis, a repeat biopsy within 12 months of diagnosis could be particularly beneficial to minimize diagnostic underclassification.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.02.050.

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EDITORIAL COMMENT

Active surveillance (AS) has been widely accepted as a first-line management approach in men with low-risk prostate cancer. While AS provides an avenue to reduce risk of overtreatment without compromising oncological safety, there remains a lack of consensus on the optimal approach to monitoring. An ideal surveillance strategy would be one that minimizes invasive testing such as prostate biopsy without conceding adverse oncologic outcomes. Thus, several studies have sought to identify men at higher risk of reclassification so as to more carefully select when biopsy is truly necessary.

In the current study, the authors explored predictors of reclassification on confirmatory biopsy in their institutional AS experience. Among 406 men with Grade Group 1 cancer who underwent confirmatory biopsy, 85 (21%) were reclassified to Grade Group ≥2. Multivariable analysis demonstrated that older age (odds ratio 1.07, P <0.01) and increased number of positive biopsy cores at diagnosis (odds ratio 1.37, P <0.01) were significantly associated with reclassification at confirmatory biopsy.

Consistent with these observations, previous studies have identified tumor volume (eg number or percentage of positive biopsy cores, bilateral cancer) as a risk factor for reclassification.[1-3] Similarly, while the practical utility of PSA and PSA kinetics appear limited in this setting,[4] measures of PSA likely do provide some additional information. In recent years, older age has been identified as a significant risk factor for biopsy reclassification in multiple AS cohorts.[5-8] The present analysis corroborates these findings that older men do, in fact, appear to be at increased risk of reclassification during AS. This represents a significant paradigm shift given that surveillance was initially considered a more reasonable strategy for older men.

These data yield many important practical and disease-specific questions. Practically, the frequency with which reclassification results in long-term adverse outcomes (eg metastatic disease, cancer-specific mortality), particularly in an older population, is likely to be limited. On the other hand, population-based data reveal that older men diagnosed with prostate cancer account for a disproportionately high rate of metastatic disease, and cancer-specific mortality, despite a higher risk of death from competing causes.[9] Finally, what is the biological mechanism underlying this relationship? Is it possible that decreased immunity with older age may account for these findings?[10] Understanding the biological mechanism of this relationship in the AS setting may provide insight as to the varied clinical aggressiveness of prostate cancer in general. For example, if reduced tumor immunity in older men contributes to progression on AS, could similar, individual-level variation in tumor immunity contribute to the wide range of cancer aggressiveness observed in the overall population?

Certainly, the intensity with which to monitor patients on AS merits a careful consideration of available data and patient-specific preferences. The current findings provide additional insight as we aim to advance toward more data-driven, risk-adapted surveillance strategies incorporating known risk factors. Ultimately, understanding the genetic and molecular changes that underlie the wide-ranging clinical behavior of prostate cancer remains a key step toward optimizing management of all patients diagnosed with this disease.

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