Variation in Guideline Concordant Active Surveillance Followup in Diverse Urology Practices

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Purpose: We examined the frequency of followup prostate specific antigen testing and prostate biopsy among men treated with active surveillance in the academic and community urology practices comprising MUSIC (Michigan Urological Surgery Improvement Collaborative).

Materials and Methods: MUSIC is a consortium of 42 practices that maintains a prospective clinical registry with validated clinical data on all patients diagnosed with prostate cancer at participating sites. We identified all patients in MUSIC practices who entered active surveillance and had at least 2 years of continuous followup. After determining the frequency of repeat prostate specific antigen testing and prostate biopsy, we calculated rates of concordance with NCCN Guidelines® recommendations (ie at least 3 prostate specific antigen tests and 1 surveillance biopsy) collaborative-wide and across individual practices.

Results: We identified 513 patients who entered active surveillance from January 2012 through September 2013 and had at least 2 years of followup. Among the 431 men (84%) who remained on active surveillance for 2 years 132 (30.6%) underwent followup surveillance testing at a frequency that was concordant with NCCN® (National Comprehensive Cancer Network®) recommendations. At the practice level, the median rate of guideline concordant followup was 26.5% (range 10% to 67.5%, $p < 0.001$). Among patients with discordant followup, the absence of followup biopsy was common and not significantly different across practices (median rate 82.0%, $p = 0.35$).

Conclusions: Among diverse community and academic practices in Michigan, there is wide variation in the proportion of men on active surveillance who meet guideline recommendations for followup prostate specific antigen testing and repeat biopsy. These data highlight the need for standardized active surveillance pathways that emphasize the role of repeat surveillance biopsies.

Key Words: prostatic neoplasms, prostate-specific antigen, watchful waiting, biopsy, quality improvement

Abbreviations and Acronyms

AS = active surveillance

MRI = magnetic resonance imaging

PSA = prostate specific antigen

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Active surveillance is increasingly used as a primary treatment strategy for patients with low risk prostate cancer[1–4] because it allows many men to avoid the risks of more aggressive therapy (eg surgery or radiation therapy).[5,6] However, because a proportion of patients who initially enter AS may ultimately prove to have more aggressive cancer, optimal

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application of surveillance necessitates a plan for regular followup with repeat clinical and laboratory evaluations for evidence of disease progression.

Although specific details of established AS regimens vary, all advise close urological followup with some combination of scheduled laboratory, radiographic (MRI) and/or pathological examinations.[7–9] Among the widely recognized clinical guidelines in this area, most recommend at least semiannual PSA tests and prostate biopsies at scheduled intervals.[7,8,10–13] For example, the NCCN Guidelines have recommended PSA testing at least as often as every 6 months and repeat biopsy as often as annually for men on active surveillance.[8,14–16] With no clear consensus on the best AS followup regimen, there is likely significant variability in how these patients are followed in routine clinical practice.[17] Recent publications from administrative data sets have demonstrated low rates of adherence with active surveillance regimens, although these data sets have been limited to Medicare beneficiaries and may not reliably distinguish AS from watchful waiting.[18,19]

In this context, we examined variation in active surveillance followup testing among patients treated in the diverse academic and community practices comprising MUSIC. We specifically assessed levels of adherence with NCCN Guidelines recommendations for followup PSA testing and prostate biopsy during the first 2 years on surveillance.

MATERIALS AND METHODS

Michigan Urological Surgery Improvement Collaborative

Established in 2011 with support from Blue Cross Blue Shield of Michigan, MUSIC aims to improve the quality and cost-efficiency of care for men with prostate cancer in Michigan. Currently, the collaborative includes 42 urology practices comprising nearly 85% of urologists in the state. In each participating practice, trained abstractors prospectively enter a standardized set of demographic and clinicopathological data on every patient with a new prostate cancer diagnosis into an electronic clinical registry. Abstractors also enter data related to treatment and followup at fixed intervals in the patient course.

Previous reports have outlined quality assurance measures taken within the collaborative to confirm the accuracy of registry data, including annual random sample audits of each practice with manual validation of registry cases and cross-validation with administrative data.[1,20] Each MUSIC practice obtained an exemption or approval by the local institutional review board for participation in the collaborative.

Study Population

For this analysis, we first identified all patients with newly diagnosed prostate cancer at participating MUSIC practices in whom active surveillance was initiated as primary disease management from January 2012 through September 2013. In the MUSIC data abstraction policies, AS is defined distinctly from watchful waiting.[4] Patients were excluded from study if they did not have at least 2 years of continuous followup in the same practice.

Outcomes

We evaluated the frequency of PSA testing and repeat prostate biopsy for each patient during the first 2 years of AS. As the primary outcome measure, we calculated the proportion of patients enrolled in AS who met the minimum recommended followup testing based on the 2011 NCCN Guidelines.[16]

The NCCN Guidelines state that patients on AS should undergo PSA testing "at least as often as every 6 months" and "repeat prostate biopsy should be considered as often as annually."[16] Therefore, we defined care concordant with the guideline during a 2-year period as including at least 3 PSA tests and 1 repeat biopsy. The rate of guideline concordant care was evaluated at the patient and practice levels. For practice level analyses, we only included patients from practices with 10 or more patients on AS who had at least 2 years of continuous followup. We also determined the frequency with which guideline discordant followup was due to a lack of repeat biopsy vs less frequent PSA testing.

Statistical Analysis

Descriptive baseline demographic and clinical data are reported. Cross-practice comparisons were performed using the chi-square test. Results were considered statistically significant at $\alpha \leq 0.05$. All analyses were performed using STATA®, version 14.1.

RESULTS

From January 2012 through September 2013, 593 men were diagnosed with prostate cancer who selected AS for primary management. We excluded 80 patients because they were not continuously followed in the collaborative during the 2 years subsequent to AS initiation. The remaining 513 men comprised the final analytical cohort. The supplementary table (http://jurology.com/) lists baseline clinical and demographic data on this cohort.

These patients were treated by a total of 111 urologists across 30 practice sites. Median patient age at AS enrollment was 66 years and median PSA was 5.3 ng/ml (IQR 4.1–7.5). At diagnosis, the majority of patients had Gleason score 6 or less, clinical stage T1c disease and they met NCCN very low or low risk criteria (supplementary table, http://jurology.com/).[16]

In the 2 years following the initiation of AS, 431 patients (84.0%) had remained on AS for the entire period, 80 (15.6%) had transitioned to other therapies and 2 (0.4%) had died of causes unrelated to prostate cancer. Of the 431 men who remained on

AS for a full 2 years only 132 (30.6%) underwent followup PSA and biopsy testing that was concordant with NCCN recommendations while the remainder had guideline discordant followup (fig. 1).

Biopsy followup was guideline discordant during the first 2 years of AS for 231 patients (53.6%). In the group of patients lacking repeat biopsy, 135 had sufficient PSA followup while 96 also had fewer than 3 repeat PSA tests over 2 years. Followup in 68 patients (15.8%) was guideline discordant only due to the receipt of fewer than 3 PSA tests (fig. 1).

At each of 16 MUSIC practices there were 10 or more patients with 2 years of continuous followup after initial treatment with AS and they were included in the practice level analyses. The number of urologists treating patients with prostate cancer at these sites ranged from 3 to 13. Of the 513 patients in the larger cohort 474 were treated at these 16 sites, including 399 who remained on surveillance for the full 2 years. The median number of men on AS for 2 years by site was 16 (range 8 to 68). At the practice level, the median rate of guideline concordant care was 26.5% (range 10.0% to 67.5%, $p < 0.001$, fig. 2). Among patients with guideline discordant followup at each practice, the absence of repeat biopsy was common and similar across all sites (median rate of biopsy driven guideline discordance 82.0%, range 54.2% to 100%, $p = 0.35$, fig. 3).

DISCUSSION

Of patients treated with AS in a large group of diverse academic and community practices across Michigan, only 30.6% received followup testing during the first 2 years on surveillance that was concordant with NCCN Guidelines recommendations. In addition, the proportion of patients with guideline concordant surveillance testing varied widely across MUSIC practices. The most common reason for guideline discordance was lack of a recommended repeat biopsy during the followup interval.

Our results are consistent with prior studies examining the nature and frequency of followup testing in men entering active surveillance. Recently, a study using SEER (Surveillance, Epidemiology and End Results)-Medicare data demonstrated only 11.1% and 5% of men enrolled in AS met followup recommendations depending on which guidelines were analyzed.[18] Likewise, prior population based analyses indicate that only 1 of 10 Medicare beneficiaries with prostate cancer who deferred initial treatment underwent repeat biopsy and PSA test in the first 2 years after diagnosis.[19] Finally, a recent publication from a large multicenter cohort in Europe showed that rates of rebiopsy were less than 30% even in men with more

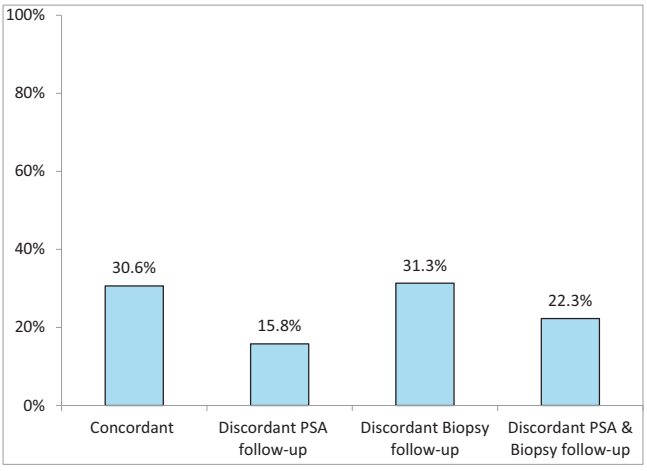

Figure 1. Frequency of guideline concordant followup among patients on AS for at least 2 years.

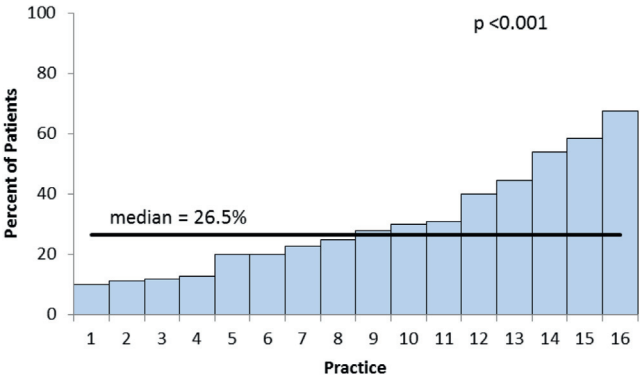

Figure 2. Variation in guideline concordant AS followup across MUSIC practices.

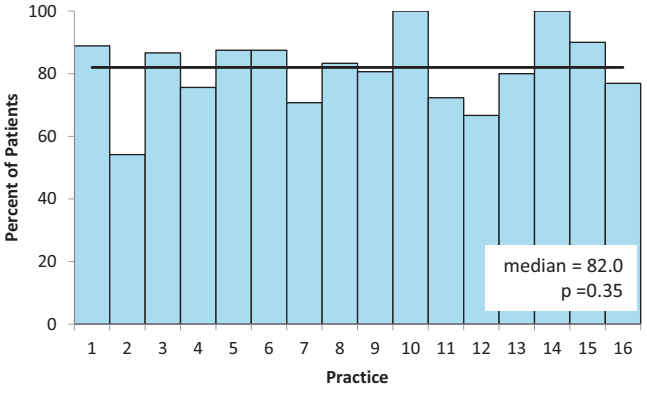

Figure 3. Proportion of patients with guideline discordant followup who did not undergo repeat biopsy.

rapidly rising PSA.[21] Taken together, our results from diverse community and academic practices in Michigan further underscore opportunities to optimize followup processes as more men elect surveillance as the initial management strategy.

Our findings should be considered in the context of several limitations. 1) Although we observed variation in followup testing in men on surveillance, we did not evaluate associations between the frequency of testing and patient outcomes. Therefore, further studies are needed to examine the impact of intensity of AS followup on cancer specific outcomes and patient reported outcomes.

2) Our data are limited to a sample of practices and patients across Michigan and may not be entirely representative of a broader population. Nonetheless, the data represent patients from a variety of practices ranging from small solo practices to large academic centers. Therefore, our results likely highlight important challenges when considering the implementation of AS on a large scale.

3) An additional limitation is our operationalization of the NCCN Guidelines specifying that PSA testing should be performed "as often as every 6 months" and biopsy "should be considered as often as annually."[16] Although this language does not set a true minimum evaluation threshold for guideline concordance, we thought that it was important to establish a pragmatic benchmark to evaluate performance against a guideline. In defining this benchmark, we thought that 3 PSA tests and 1 repeat biopsy in 2 years would be a conservative threshold that remains consistent with the guideline statements.

4) A final limitation is that we did not systematically evaluate the use of MRI or genomic tests throughout the collaborative, which may potentially be used instead of biopsy. Although limitations of current data collection prevent us from commenting further on the utilization or results of these newer diagnostic tests, we can report that only 18 men (4.2%) in our population underwent prostate MRI in the first 2 years of followup, indicating that MRI use in this cohort was infrequent during the study interval.

Despite these limitations, our findings have important implications for patients and providers. As it is defined, active surveillance implies routine reassessment of prostate cancer risk via followup PSA testing, repeat biopsy, and possibly other radiographic (eg MRI) and/or genomic evaluations. Lack of consistent followup may lead to delays in detecting disease reclassification or progression to higher risk cancer. Prolonging the time to detection of disease progression and subsequent transition to more aggressive management may increase the risk of unfavorable cancer related outcomes. When initiating AS, patients must be made aware of the need for close followup with repeat biopsy and PSA testing. Given the variation in followup testing observed in this analysis, it appears that standardized clinical pathways and novel implementation strategies (eg electronic medical record based tracking systems)[22] may be a helpful step toward more consistent AS followup.

Our data specifically highlight the need to improve rates of prostate biopsy in men enrolled in AS. Biopsies can be painful and carry a risk of complications, which may decrease the likelihood of adherence with serial biopsy recommendations. Nonetheless, biopsy remains the gold standard for reevaluating the tumor burden in patients on AS.[7,8,10] For this reason, repeat biopsy is a component of all AS protocols regardless of other clinical factors such as PSA or digital rectal examination. These expectations must be set for all patients prior to enrollment in AS.

In the near term, work to understand the strategies used by high performing practices can provide a foundation for population based quality improvement to increase biopsy adherence. Future investigation to determine the optimal interval between repeat biopsies that balances the necessity for serial pathological evaluation with risks and patient preferences will be important. Furthermore, work to better understand the role of emerging technologies, such as MRI and biomarkers, that could potentially replace some or all invasive biopsies required for AS monitoring is warranted and may improve adherence with AS protocols in the future.

CONCLUSIONS

In summary, there is significant variation in AS followup strategies on the practice and patient levels. Moving forward, a better understanding is needed of outcomes in patients receiving guideline concordant vs nonconcordant AS followup. Moreover, establishment and dissemination of pragmatic clinical pathways may be a strategy for increasing followup biopsy rates in patients enrolled in AS as a primary management strategy.

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EDITORIAL COMMENTS

Favorable long-term outcomes for patients on active surveillance have been derived from protocols that incorporate repeat biopsies to confirm the presence of low risk disease. The real-world results reported by these authors from a diverse array of practices in Michigan suggest that this approach may be the exception, rather than the rule.

Traditional transrectal ultrasound guided prostate biopsies are imperfect with an under grading rate exceeding 40%.[1] Newer methods of risk stratification with prostate MRI alone are inadequate as they cannot rule out higher grade disease without tissue sampling[2] and accuracy relies on the experience of those interpreting the images.[3] The long-term implications of forgoing a repeat prostate biopsy during active surveillance remain unknown but place patients at risk for harboring occult lethal tumors.

The collaborative providing these data has a proven track record of demonstrating the benefits of the audit-feedback approach to quality improvement. I eagerly anticipate followup studies examining outcomes and future use of followup testing and repeat biopsy among these practices.

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This study found that among patients on AS followed for 2 years in the MUSIC registry only 30.6% had 3 PSA tests and 1 followup biopsy, ranging from 10% to 67.5% across practices. These findings agree with SEER-Medicare data showing that only 22% of men underwent 10 or more PSA tests and 2 or more biopsies during 5 years of AS (reference 18 in article).

We recently completed a qualitative study to explore the factors that influence physician decision making during AS, which might help explain such heterogeneous practice patterns.[1] Key themes that emerged included trade-offs between the desire to reduce harm from multiple repeat biopsies vs the risk of missing disease reclassification, insufficient education on AS during training and lack of a single international standard protocol.

Overall, reliance on serial biopsies during AS represents a major source of risk and noncompliance.[2] Hopefully, in the future continued improvements in markers and imaging will allow a shift toward more personalized, less invasive AS protocols.

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