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Variation in guideline concordant active surveillance follow-up in diverse urology practices

Amy N. Luckenbaugh, MD¹, Gregory B. Aufferberg, MD¹, Scott R. Hawken, MS¹, Apoorv Dhir, BBA¹, Susan Linsell, MHSA¹, Sanjeev Kaul, MD², and David C. Miller, MD, MPH¹ for the Michigan Urological Surgery Improvement Collaborative

¹Department of Urology, University of Michigan, Ann Arbor, Michigan

²Comprehensive Urology, William Beaumont Hospital, Royal Oak, Michigan

Abstract

Purpose—We examined the frequency of follow-up prostate-specific antigen (PSA) testing and prostate biopsy among men managed with active surveillance (AS) in academic and community urology practices comprising the Michigan Urological Surgery Improvement Collaborative (MUSIC).

Materials and Methods—MUSIC is a consortium of 42 practices that maintains a prospective clinical registry with validated clinical data for all patients diagnosed with prostate cancer at participating sites. We identified all patients in MUSIC practices who entered AS and had at least two years of continuous follow-up. After determining the frequency of repeat PSA testing and prostate biopsy, we calculated rates of concordance with NCCN guideline recommendations (i.e., at least three PSA tests and one surveillance biopsy) both collaborative-wide and across individual practices.

Results—We identified 513 patients entering AS from 1/2012–9/2013 with at least two years of follow-up. Among the 431 men (84%) that remained on AS for two years, 132 (30.6%) had follow-up surveillance testing at a frequency that was concordant with NCCN recommendations. At a practice-level, the median rate of guideline concordant follow-up was 26.5% (range 10–67.5%, $p < 0.001$). Among patients with discordant follow-up, the absence of follow-up 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 that meet guideline recommendations for follow-up PSA testing and repeat biopsy. These data highlight the need for standardized AS pathways that emphasize the role for repeat surveillance biopsies.

Corresponding Author: David C. Miller, University of Michigan Department of Urology, NCRC Building 16, Room 108E, 2800 Plymouth Road, Ann Arbor, MI 48109, Phone: 734-936-0054, Fax: 734-232-2400, dcmiller@med.umich.edu.

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Keywords

prostate cancer; active surveillance; guidelines; quality improvement

Introduction

Active surveillance (AS) is increasingly employed as a primary management strategy for patients with low-risk prostate cancer^{1–4} because it allows many men to avoid the risks of more aggressive therapy (e.g. surgery or radiation therapy).^{5,6} However, because a proportion of patients that initially enter AS may ultimately prove to have more aggressive cancers, optimal application of surveillance necessitates a plan for regular follow-up with repeated clinical and laboratory evaluations for evidence of disease progression.

Although specific details of established AS regimens vary, all advise close urologic follow-up with some combination of scheduled laboratory, radiographic (MRI), and/or pathologic examinations.^{7–9} Among the widely recognized clinical guidelines in this area, most recommend at least semi-annual prostate specific antigen (PSA) tests and prostate biopsies at scheduled intervals.^{7,8,10–13} For example, the National Comprehensive Cancer Network (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 follow-up 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; however, 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 follow-up testing among patients managed in the diverse academic and community practices comprising the Michigan Urologic Surgery Improvement Collaborative (MUSIC). We specifically assessed levels of adherence with NCCN guideline recommendations for follow-up PSA testing and prostate biopsy during the first two years on surveillance.

Materials and Methods

Michigan Urologic 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 the state of Michigan. At present, 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 clinicopathologic data for every patient with a new prostate cancer diagnosis into an electronic clinical registry. Abstractors also enter data related to treatment and follow-up at fixed intervals in a patient's course. Previous reports have outlined quality assurance measures taken within the collaborative to confirm 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 their local institutional review board for participation in the collaborative.

Study Population

For this analysis, we first identified all patients with newly-diagnosed prostate cancer from participating MUSIC practices who initiated active surveillance as primary disease management from January 2012 through September 2013. In the MUSIC data abstraction policies, AS is defined distinctly from watchful waiting.²¹ Patients were excluded if they did not have at least two years of continuous follow-up in the same practice.

Outcomes

We evaluated the frequency of PSA testing and repeat prostate biopsy for each patient during the first two years of AS. As the primary outcome measure, we calculated the proportion of patients enrolled in AS who met the minimum recommended follow-up testing based on the 2011 NCCN guidelines.¹⁶

The NCCN guidelines state that AS patients should receive PSA testing “at least as often as every 6 months” and “repeat prostate biopsy should be considered as often as annually”.¹⁶ We therefore defined care concordant with the guideline over a two year period as including at least three PSA tests and one repeat biopsy. The rate of guideline concordant care was evaluated at both the patient- and practice-level. For practice-level analyses, we only included patients from practices with 10 or more AS patients having at least two years of continuous follow-up. We also determined the frequency with which guideline-discordant follow-up was due to lack of repeat biopsy versus less frequent PSA testing.

Statistical Analysis

Descriptive baseline demographic and clinical data are reported. Cross-practice comparisons were performed using Chi-Squared testing. Results were considered statistically significant when $\alpha = 0.05$. All analyses were performed using commercially available statistical software (STATA, version 14.1, StataCorp, College Station, TX).

Results

From January 2012 through September 2013, 593 men were diagnosed with prostate cancer and selected AS for primary management. We excluded 80 patients because they were not continuously followed in the collaborative over the two years subsequent to AS initiation. The remaining 513 men comprised the final analytic cohort. Baseline clinical and demographic data for this cohort are summarized in Table 1. These patients were managed by 111 urologists across 30 practice sites. The median age at the time of AS enrollment was 66 years, and the median PSA was 5.3 ng/mL (IQR 4.1–7.5 ng/mL). At diagnosis, the majority of patients had Gleason Scores ≤ 6 , clinical stage of T1c, and met NCCN very-low or low risk criteria (Table 1).¹⁶

Over the two years following initiation of AS, 431 (84.0%) patients remained on AS for the entire period; 80 (15.6%) transitioned to other therapies, and 2 (0.4%) died of causes

unrelated to prostate cancer. Of the 431 men that remained on AS for two full years, only 132 (30.6%) had follow-up PSA and biopsy testing that was concordant with NCCN recommendations while the remainder had guideline discordant follow-up (Figure 1).

Biopsy follow-up was guideline discordant over the first two years of AS for 231 patients (53.6%). Within the group of patients lacking repeat biopsy, 135 had sufficient PSA follow-up while 96 also had less than 3 repeat PSA tests over 2 years. The follow up for 68 patients (15.8%) was guideline discordant only due to receipt of fewer than 3 PSA tests (Figure 1).

Sixteen MUSIC practices had 10 or more patients with two years of continuous follow-up after initial management with AS and were included in the practice-level analyses. The number of urologists managing patients with prostate cancer at these sites ranged from 3–13. 474 of the 513 patients in the larger cohort were managed in these 16 sites, and 399 of those patients remained on surveillance for the full two years. The median number of men managed on AS for two years by site was 16 (range 8–68). At a practice level, the median rate of guideline concordant care was 26.5% and ranged from 10.0–67.5% ($p<0.001$) (Figure 2). Among patients with guideline discordant follow-up from each practice, the absence of repeat biopsy was common and similar across all sites (median rate of biopsy driven guideline discordance = 82.0% (range 54.2–100%, $p=0.35$) (Figure 3).

Discussion

Among patients managed with AS in a large group of diverse academic and community practices across Michigan, only 30.6% received follow-up testing during the first two years on surveillance that was concordant with NCCN guideline 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 follow-up interval.

Our results are consistent with prior studies examining the nature and frequency of follow-up testing among men entering active surveillance. Recently, a study using SEER-Medicare data demonstrated only 11.1% and 5% of men enrolled in AS met follow-up recommendations depending on which guidelines were analyzed.¹⁸ Likewise, prior population-based analyses indicate that only 1 in 10 Medicare beneficiaries with prostate cancer who deferred initial treatment underwent repeat biopsy and PSA test in the first two years after diagnosis.¹⁹ Finally, a recent publication from a large multicenter cohort in Europe found that rates of re-biopsy were <30% even for men with a more rapidly-rising PSA.²² Taken together, our results from diverse community and academic practices in Michigan further underscore opportunities to optimize follow-up processes as more men select surveillance as their initial management strategy.

Our findings should be considered in the context of several limitations. First, although we observed variation in follow-up testing for men on surveillance, we did not evaluate associations between frequency of testing and patient outcomes. Therefore, further studies are needed to examine the impact of intensity of AS follow-up on cancer-specific outcomes and patient-reported outcomes. Second, our data are limited to a sample of practices and

patients across the state of 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 implementation of AS on a large scale. An additional limitation is our operationalization of the NCCN guidelines specifying that PSA should be performed “as often as every 6 months” and that biopsy “should be considered as often as annually”.¹⁶ Although this language does not set a true minimum evaluation threshold for guideline concordance, we felt it was important to establish a pragmatic benchmark for evaluating performance against a guideline. In defining this benchmark, we felt that 3 PSA tests and 1 repeat biopsy over two years would be a conservative threshold that remains consistent with the guideline statements. 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 in lieu 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 eighteen men (4.2%) in our population received a prostate magnetic resonance imaging (MRI) in the first two years of follow-up indicating the utilization of MRI in this cohort was infrequent during the study interval.

Despite these limitations, our findings have important implications for both patients and providers. As it is defined, active surveillance implies routine reassessment of prostate cancer risk via follow-up PSA testing, repeat biopsy and possibly other radiographic (e.g., MRI) and/or genomic evaluations. Lack of consistent follow-up 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 follow-up with both repeat biopsy and PSA. Given the variation in follow-up testing observed in this analysis, it appears that standardized clinical pathways and novel implementation strategies (e.g. electronic medical record based tracking systems)²³ may be a helpful step toward more consistent AS follow-up.

Our data specifically highlights the need to improve rates of prostate biopsy for men enrolled in AS. Biopsies can be painful and carry risks of complications, which may decrease the likelihood of adherence to serial biopsy recommendations. Nonetheless, biopsy remains the gold-standard for re-evaluation of tumor burden for 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 DRE. These expectations must be set for all patients prior to enrollment in AS. In the near term, work to understand the strategies employed 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 pathologic 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 of the 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 follow-up strategies on both a practice and patient level. Moving forward, a better understanding of the outcomes for patients receiving guideline concordant versus non-concordant AS follow-up is needed. Moreover, establishment and dissemination of pragmatic clinical pathways may be one strategy for increasing follow-up biopsy rates for patients enrolled in AS as a primary management strategy.

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Key of Definitions for Abbreviations

PSA	Prostate-specific antigen testing
AS	Active surveillance
MUSIC	Michigan Urological Surgery Improvement Collaborative
NCCN	National Comprehensive Cancer Network

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

Figure 2.
Variation in NCCN guideline concordant AS follow-up across MUSIC practices

Figure 3.
Proportion of patients with guideline discordant follow-up that did not undergo repeat biopsy

Table 1

Characteristics of patients entering AS in MUSIC practices.

No. patients	513
Age (years), median [IQR]	66 [62–71]
Body mass index (kg/m ²), median [IQR]	27.6 [25.2–31.0]
Race , n (%)	
Caucasian	376 (73.3)
African-American	46 (9.0)
Other	16 (3.1)
Unknown	75 (14.6)
Charlson co-morbidity score , n (%)	
0	323 (63.0)
1	93 (18.1)
2	63 (12.3)
3+	33 (6.4)
Unknown	1 (0.2)
Family history of prostate cancer , n (%)	
None	350 (68.2)
First degree relative	103 (20.1)
Non-first degree or unknown relation	28 (5.5)
Unknown	32 (6.2)
PSA level (ng/mL), median [IQR]	5.3 [4.1–7.5]
PSA density (ng/mL/g), median [IQR]	0.12 [0.08–0.17]
No. cores positive for cancer , median [IQR]	1 [1–2]
No. cores sampled on diagnostic biopsy , median [IQR]	12 [12–13]
Maximum % involvement of any positive core , median [IQR]	10 [5.0–24.5]
Clinical Stage , n (%)	
T1	351 (68.4)
T2a	34 (6.6)
T2b	8 (1.6)
T2c	6 (1.2)
Unknown	114 (22.2)
NCCN risk categories , n (%)	
Very low	128 (25.0)
Low	138 (26.9)
Intermediate	106 (20.6)
High	8 (1.6)
Unknown	133 (25.9)
Gleason Score at diagnosis , n (%)	
6	383 (74.7)
3+4	88 (17.2)
4+3	12 (2.3)

8 – 10	5 (1.0)
unknown	25 (4.9)

* IQR= inter-quartile range