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The Use and Short-term Outcomes of Active Surveillance in Men With National Comprehensive Cancer Network Favorable Intermediate-risk Prostate Cancer: The Initial Michigan Urological Surgery Improvement Collaborative Experience

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Study Need and Importance: There is a lack of real-world evidence on the use of active surveillance (AS) for favorable intermediate-risk prostate cancer (FIRPC) from diverse clinical practice settings. Further, little is known about the short-term oncologic outcomes for men with FIRPC who receive up-front treatment vs those who delay radical prostatectomy (RP). We retrospectively reviewed the Michigan Urological Surgery Improvement Collaborative data to assess the use of AS for men diagnosed with FIRPC and investigated short-term outcomes including adverse pathology and time to biochemical recurrence for those who underwent radical prostatectomy from 2012 to 2020.

What We Found: We found considerable variability in the use of AS for men with FIPRC by practice ranging from 8% to 65% (23% to 85% for Grade Group [GG] 1 and 8% to 57% for GG2 disease). The 5-year treatment-free probability for those managed with AS was 63% overall and 73% for GG1 and 57% for GG2 disease. In risk-adjusted models, men with delayed RP had a higher risk of adverse pathology (46% vs 32%) but had similar rates of biochemical recurrence (22% vs 14%) to those who received immediate treatment (see Figure).

Limitations: The present study has limitations that are inherent to observational designs, including selection bias. Since the Michigan Urological Surgery Improvement Collaborative is a relatively new surgical registry, we were limited to reporting short-term oncologic outcomes for surgical patients only. Other limitations include lack of standardization in AS follow-up care as well as the inconsistent criteria for transition from AS to treatment.

Interpretation for Patient Care: Our study shows that men who delayed RP had similar oncologic outcomes to men undergoing up-front treatment suggesting many men with FIRPC can safely avoid radical treatment for years without compromising the survival benefit associated with radical treatment.

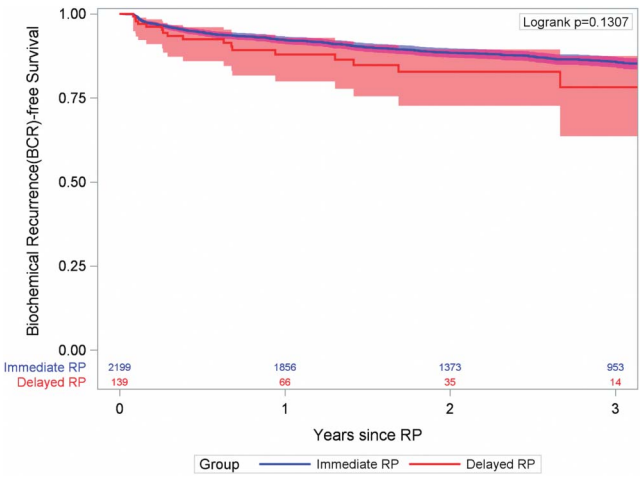

Figure. Kaplan-Meier survival curves estimating biochemical recurrence-free survival for men with favorable intermediate-risk prostate cancer undergoing immediate and delayed radical prostatectomy (RP).

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The Use and Short-term Outcomes of Active Surveillance in Men With National Comprehensive Cancer Network Favorable Intermediate-risk Prostate Cancer: The Initial Michigan Urological Surgery Improvement Collaborative Experience

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Purpose: National Comprehensive Cancer Network favorable intermediate-risk prostate cancer is a heterogeneous disease with varied oncologic and survival outcomes. We describe the Michigan Urological Surgery Improvement Collaborative's experience with the use of active surveillance and the short-term oncologic outcomes for men with favorable intermediate-risk prostate cancer.

Materials and Methods: We reviewed the Michigan Urological Surgery Improvement Collaborative registry for men diagnosed with favorable intermediate-risk prostate cancer from 2012-2020. The proportion of men with favorable intermediate-risk prostate cancer managed with active surveillance was calculated by year of diagnosis. For men selecting active surveillance, the Kaplan-Meier method was used to estimate treatment-free survival. To assess for the oncologic safety of active surveillance, we compared the proportion of patients with adverse pathology and biochemical recurrence-free survival between men undergoing delayed radical prostatectomy after a period of active surveillance with men undergoing immediate radical prostatectomy.

Results: Of the 4,275 men with favorable intermediate-risk prostate cancer, 1,321 (31%) were managed with active surveillance, increasing from 13% in 2012 to 45% in 2020. The 5-year treatment-free probability for men with favorable intermediate-risk prostate cancer on active surveillance was 73% for Gleason Grade Group 1 and 57% for Grade Group 2 disease. More men undergoing a delayed radical prostatectomy had adverse pathology (46%) compared with immediate radical prostatectomy (32%, $P < .001$), yet short-term biochemical recurrence was similar between groups (log-rank test, $P = .131$).

Conclusions: The use of active surveillance for men with favorable intermediate-risk prostate cancer has increased markedly. Over half of men with favorable intermediate-risk prostate cancer on active surveillance remained free of treatment 5 years after diagnosis. Most men on active surveillance will not lose their window of cure and have similar short-term oncologic outcomes as men undergoing up-front treatment. Active surveillance is an oncologically safe option for appropriately selected men with favorable intermediate-risk prostate cancer.

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Ethics Statement: This study was deemed exempt from Institutional Review Board review.
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Key Words: watchful waiting, prostatic neoplasms, treatment outcome, survival rate, prostatectomy

ACTIVE surveillance (AS) is the preferred management strategy for men with low risk prostate cancer as reflected by multiple guideline organizations.[1-3] Given significant gains in quality of life and excellent oncologic outcomes for men with Grade Group (GG) 1 disease on AS,[4] there is increasing interest in expanding AS to select men with favorable intermediate-risk prostate cancer (FIRPC). Intermediate-risk prostate cancer is a heterogeneous disease.[5-7] Some men with intermediate-risk prostate cancer will have a benign disease course while others may develop metastasis or death from prostate cancer despite treatment.

Many treatment guidelines recommend AS for a subset of intermediate-risk patients.[8] Given most of the evidence for FIRPC stems from academic centers, little is known about the adoption of AS for FIRPC in a diverse, real-world setting.[9] Furthermore, the lack of oncologic outcomes for men with FIRPC on AS compared with men electing for up-front treatment has not been extensively described.

Herein, we describe the Michigan Urological Surgery Improvement Collaborative's (MUSIC's) initial experiences with AS for men with intermediate-risk prostate cancer. The objectives of this study are to assess for factors associated with the selection of AS, quantify practice-level variability in the use of AS, and describe the short-term oncologic outcomes for men with FIRPC on AS.

METHODS

Study Design

This is a retrospective review of MUSIC's prospectively maintained prostate cancer registry. MUSIC is a statewide quality improvement collaborative consisting of more than 250 urologists and 46 diverse practices. Each practice obtained exemption or approval from their Institutional Review Board prior to participation in MUSIC, and this study was deemed exempt from review by the Wayne State University Institutional Review Board.

Study Population

We identified men with newly diagnosed FIRPC seen in MUSIC practices between 2012-2020. FIRPC was defined per National Comprehensive Cancer Network guideline criteria.[3]

Study Objectives

The primary objectives of our study were to estimate the proportion of patients with FIRPC that were managed with AS, and to evaluate for characteristics associated with the selection of AS among patients with FIRPC. Additionally, we assessed for variation in the selection of AS by contributing practice. Per MUSIC criteria, patients were considered to be on AS if both of the following criteria were met: (1) affirmative selection of AS as the primary management strategy and (2) the absence of treatment within 12 months of diagnosis. Patients with AS selected as the primary management strategy but underwent treatment within 12 months of diagnosis were considered as having immediate treatment. Men who did not have treatment within 12 months of diagnosis but had other treatments selected as primary management strategy (such as watchful waiting) were excluded. Patients had to have at least 12 months of follow-up and continued to be actively followed at the time of data analysis to be included in the study.

Secondary objectives were to assess for surveillance and oncologic outcomes among men undergoing AS. First, we assessed for treatment-free survival for men with FIRPC who selected AS. Second, to assess the oncologic safety of AS for men with FIRPC and quantify the difference in oncologic outcomes for men choosing AS vs up-front treatment, we compared the proportion of patients with adverse pathology and time to biochemical recurrence (BCR). Men were stratified by initial treatment: immediate radical prostatectomy (RP) vs delayed RP after a period of AS. Adverse pathology was defined as any of the following on RP pathology: $\geq$GG3; $\geq$pT3; pN+ disease.[10,11] BCR was defined as a PSA $\geq$0.2 and/or receipt of a secondary treatment (adjuvant/salvage radiotherapy and/or androgen deprivation therapy).

Statistical Analysis

Clinical, demographic, and oncologic factors were summarized as counts and proportions or medians with IQR. The proportion of patients with FIRPC who selected AS by year of diagnosis was calculated. We fit a mixed-effects logistic regression model with urology practices included as random intercepts to assess for factors associated with being managed with AS vs immediate treatment. Variables included were race, Charlson comorbidity index, family history of prostate cancer, Gleason GG, clinical T stage, practice type, age at diagnosis, PSA, number of cores positive for cancer, and maximum percent of an individual core involved with cancer. The multivariable model was used to estimate the risk-adjusted probability of men with FIRPC at each practice being managed with AS vs immediate treatment. Based on the model, predicted probability of being on AS was obtained for each patient using the best linear unbiased predictors. We obtained the risk-adjusted probability of AS by averaging the best linear unbiased predictors of patients from each practice.

Among all men in the study, RP-free probability was calculated using the Kaplan-Meier method from the date of the diagnostic biopsy. Men undergoing treatments other than RP were censored at the date of treatment. Men which remained on AS were censored at the date of last clinical contact. For the subset of men selecting AS, Kaplan-Meier survival curves were used to estimate treatment-free probability calculated from the date of the diagnostic biopsy. Men remaining on AS at their last follow-up were censored at the date of their last clinical contact. Men were stratified by GG1 vs GG2 disease and survival curves were compared with the log-rank test. Among men undergoing RP, the proportion of men with adverse pathology was compared with the chi-squared test. To test for an association between immediate/delayed RP and adverse pathology, we fit a mixed-effects multivariable logistic regression model using the same set of covariates described above. The Kaplan-Meier method and the log-rank test was used to

compare time to BCR between men undergoing immediate vs delayed RP after AS. The date of RP was considered time zero for the analysis of time to BCR.

RESULTS

We identified 4,275 men diagnosed with FIRPC from 2012 to 2020, of whom 1,321 (31%) were managed with AS as their primary management strategy (supplemental Figure 1, https://www.jurology.com). Median follow-up was 2.9 years from diagnosis for men undergoing immediate treatment (IQR 1.8-4.3). Among the 1,321 men who were initially managed with AS, median follow-up was 2.9 (IQR: 1.7-4.4) years. The median follow-up for men who remained on AS at last follow-up was 2.6 years (IQR 1.6-4.1), and the median time to treatment initiation was 1.8 years (IQR 1.3-2.8) for men who have transitioned to treatment. The median age of the whole cohort was 65 years (IQR 59-69) and 84% (n = 3,596) had GG2 disease (Table 1). Of the 1,321 men selecting AS, 429 (32%) had GG1 disease and 892 (68%) had GG2 disease. The use of AS for men with FIRPC gradually increased from 13% in 2012 to 45% in 2020 (Figure 1). The mean number of positive cores for the entire cohort was 2.8.

We fit a multivariable model to identify factors associated with the selection of AS vs immediate treatment (Table 2). We noted that increasing age (per 10 year increase: OR 2.02; 95% CI: 1.81-2.25, $P < .001$) was associated with increased odds of being managed with AS, while the presence of GG2 disease (OR 0.26, 95% CI 0.20-0.33, $P < .001$) was associated with decreased odds of being managed with AS. As disease volume increased (number of positive cores: OR 0.71, 95% CI 0.67-0.75, $P < .001$; and for each 10% increase in the maximum percent cancer involved of an individual core: OR 0.86, 95% 0.83-0.89, $P < .001$), the odds of being managed with AS decreased.

There was notable variability in the risk-adjusted probability of being managed with AS at each practice, ranging from 8% to 65% (Figure 2, A). Furthermore, this variability persisted when patients were stratified by GG1 (23% to 85%) and GG2 disease (8% to 57%) for each contributing practice (Figure 2, B and Figure 2, C, respectively).

Of men with FIRPC who were managed with AS, 63% were free of treatment 5 years after diagnosis (Figure 3, A). Stratifying by GG, the estimated 5-year treatment-free probability was 73% for men with GG1 and 57% for men with GG2 prostate cancer ($P < .001$, Figure 3, B).

In our cohort, 2,338 men underwent RP, consisting of 2,199 men undergoing immediate RP and 139 men undergoing delayed RP after a period of AS (supplemental Figure 1, https://www.jurology.com). Median time to prostatectomy for those who had immediate RP was 85 days (IQR 63-119), while those who delayed treatment had a median time to RP of 673 days (IQR 481-979). Kaplan-Meier plots of RP-free survival for patients undergoing immediate and delayed RP are shown in supplemental Figure 2, A and B (https://www.jurology.com). Median time to RP for men undergoing immediate RP calculated via the Kaplan-Meier method was 99 days and not reached for patients undergoing delayed RP.

We noted more men with a delayed prostatectomy had adverse pathology (46%) compared with

Table 1. *Characteristics of Men With Favorable Intermediate-risk Prostate Cancer in the Michigan Urological Surgery Improvement Collaborative Registry (2012-2020)*

Variable	Cohort		Active surveillance		Treatment	
Patients, No. (%)	4,275		1,321		2,954	
Race						
White	3,252	(76)	1,026	(78)	2,226	(75)
African American	584	(14)	179	(14)	405	(14)
Other	106	(2.5)	34	(2.6)	72	(2.4)
Unknown	333	(7.8)	82	(6.2)	251	(8.5)
Charlson comorbidity, No. (%)						
0	3,041	(71)	919	(70)	2,122	(72)
1	735	(17)	224	(17)	511	(17)
≥2	497	(12)	178	(13)	319	(11)
Family history of PCa, No. (%)						
Yes	1,316	(31)	350	(26)	966	(33)
No	2,739	(64)	908	(69)	1,831	(62)
Unknown	220	(5.1)	63	(4.8)	157	(5.3)
Gleason grade, No. (%)						
GG1	679	(16)	429	(32)	250	(8.5)
GG2	3,596	(84)	892	(68)	2,704	(92)
Clinical tumor stage, No. (%)						
T1	3,627	(85)	1,132	(86)	2,495	(84)
T2	648	(15)	189	(14)	459	(16)
Age, median (IQR)	65.0	(59.0-69.0)	67.0	(62.0-72.0)	64.0	(58.0-68.0)
PSA, median (IQR)	5.5	(4.4-7.5)	6.2	(4.6-10.1)	5.3	(4.3-6.9)
Percent of positive cores, median (IQR)	21.4	(12.5-33.3)	16.7	(8.3-25.0)	25.0	(16.7-33.3)

Abbreviations: GG, Grade Group; IQR, interquartile range; PCa, prostate cancer; PSA, prostate specific antigen; T, tumor stage.

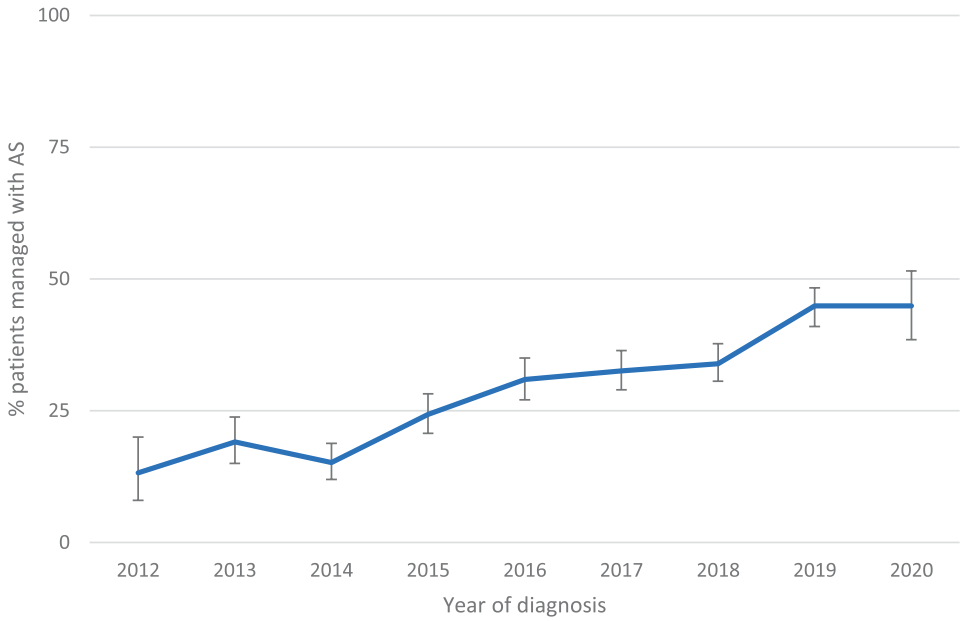

Figure 1. Proportion of patients with favorable intermediate-risk prostate cancer managed with active surveillance by year of diagnosis. Error bars display 95% confidence interval.

immediate RP (32%, $P < .001$). After adjustment, men with delayed RP had a higher risk of adverse pathology compared to immediate RP (OR 2.14; 95% CI 1.48, 3.10; $P < .001$, Table 3). Despite an increase in adverse pathology, men undergoing delayed RP had similar short-term BCR compared to men undergoing immediate RP ($P = .13$, Figure 3, C). BCR within 3 years of RP was 14% for patients undergoing immediate RP and 22% for patients undergoing delayed RP.

Table 2. *Mixed-effects Multivariable Logistic Regression Model With Practice as Random Intercepts for the Association of Clinical, Demographic, and Oncologic Factors With the Use of Active Surveillance vs Immediate Treatment*

	OR	95% CI	*P* value
Race			.678
White	Reference	Reference	
Black	0.99	(0.79, 1.26)	
Other	1.21	(0.74, 1.97)	
Unknown	0.86	(0.62, 1.19)	
Charlson index			.158
0	Reference	Reference	
1	0.86	(0.70, 1.05)	
≥2	1.12	(0.88, 1.41)	
Family history			.050
No	Reference	Reference	
Yes	0.82	(0.70, 0.97)	
Unknown	0.80	(0.56, 1.15)	
Biopsy Gleason grade			< .001
GG1	Reference	Reference	
GG2	0.26	(0.20, 0.33)	
Clinical tumor stage			.221
T1	Reference	Reference	
T2	0.86	(0.68, 1.09)	
Practice type			.414
Private/community	Reference	Reference	
Academic	1.62	(0.78, 3.35)	
Hybrid	1.22	(0.71, 2.07)	
Age (per 10-year increase)	2.02	(1.81, 2.25)	< .001
PSA (log)	0.91	(0.76, 1.08)	.290
No. positive cores (per 1-core increase)	0.71	(0.67, 0.75)	< .001
Maximum percent cancer involvement of an individual core (per 10% increase)	0.86	(0.83, 0.89)	< .001

Abbreviations: CI, confidence interval; GG, Gleason Grade; OR, odds ratio, PSA, prostate specific antigen; T, tumor stage.

DISCUSSION

Due to the heterogeneous nature of intermediate-risk prostate cancer, choosing a management strategy is challenging. Data from randomized trials comparing radical therapy with observational strategies, often watchful waiting, offer scant clinical guidance for the optimal management strategy for men with FIRPC given the modest survival advantage to men receiving treatment.[12-14] There is a growing opportunity with AS to safely delay and/or avoid treatment in many men with FIRPC while still maintaining the benefits in survival seen with radical therapies.

The use of AS continues to rise nationally among men with low-risk (LR) prostate cancer and select men with FIRPC.[15] At the inception of MUSIC in 2012, only 13% of men with FIRPC were managed on AS, similar to the relatively stable 10% of men with intermediate-risk prostate cancer managed with AS in the United States between 2010 and 2015.[15] Importantly, the proportion of men with FIRPC managed with AS in MUSIC rose to above 40% in 2019 and 2020. There are several possible explanations for the increased use of AS. First, these data may mirror national patterns and trends within MUSIC in the management in LR prostate cancer, which similarly has increased with time. Increasing comfort and utilization of AS for men

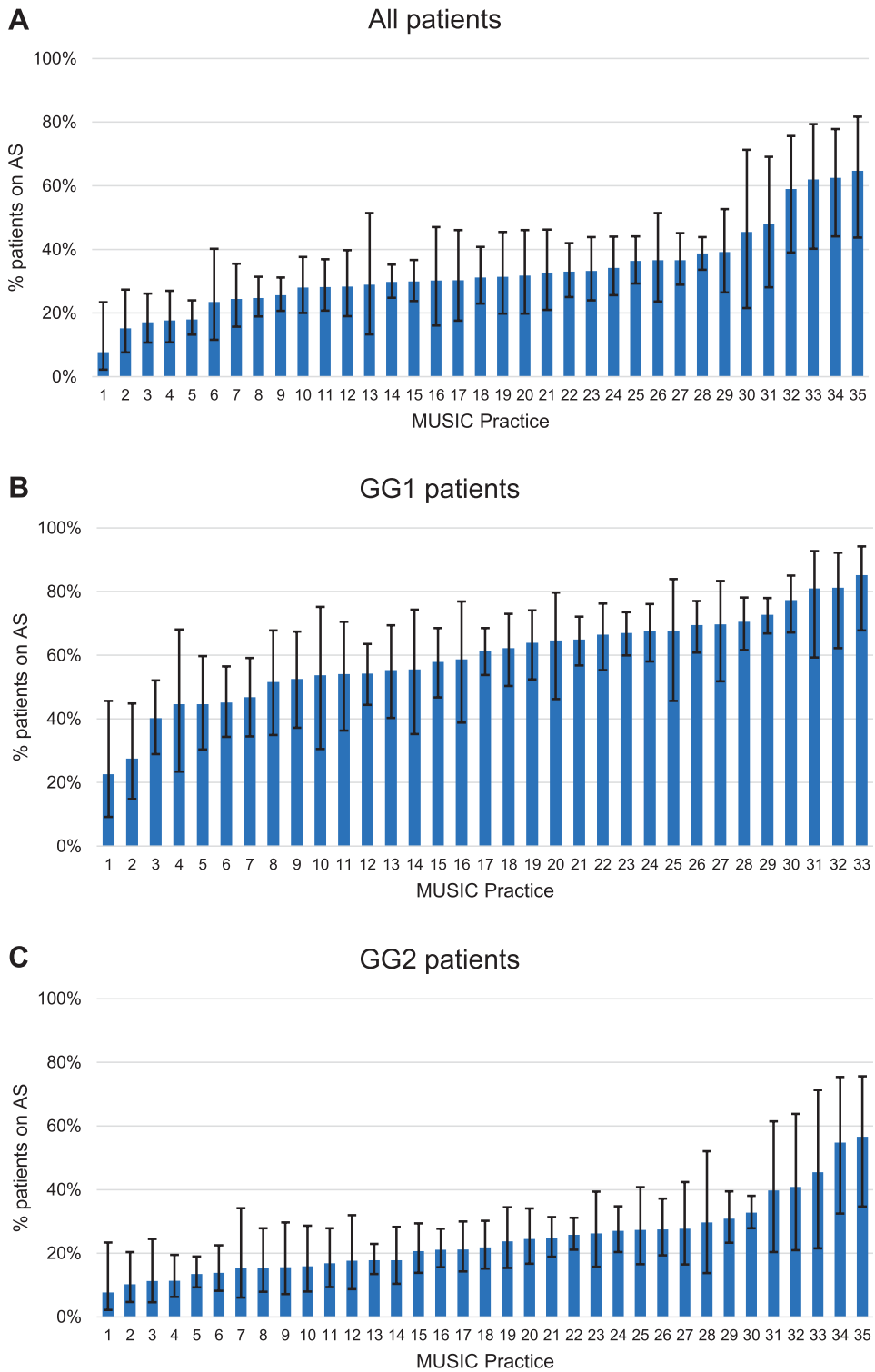

Figure 2. A, Risk-adjusted proportion of patients with favorable intermediate-risk prostate cancer selecting active surveillance (AS) for each Michigan Urological Surgery Improvement Collaborative (MUSIC) contributing practice, with error bars representing 95% confidence interval. B, Risk-adjusted proportion of patients with Grade Group (GG) 1 favorable intermediate-risk prostate cancer selecting AS for each MUSIC contributing practice, with error bars representing 95% confidence interval. C, Risk-adjusted proportion of patients with GG2 favorable intermediate-risk prostate cancer selecting AS for each MUSIC contributing practice, with error bars representing 95% confidence interval.

with LR, which carries an absolute prostate mortality risk similar to FIRPC,[13,16,17] may translate into increased comfort and utilization of AS for men with FIRPC. Second, MUSIC has made concerted efforts aimed to encourage the use of AS in LR and low-volume FIRPC.[18] Third, since 2016, MUSIC has

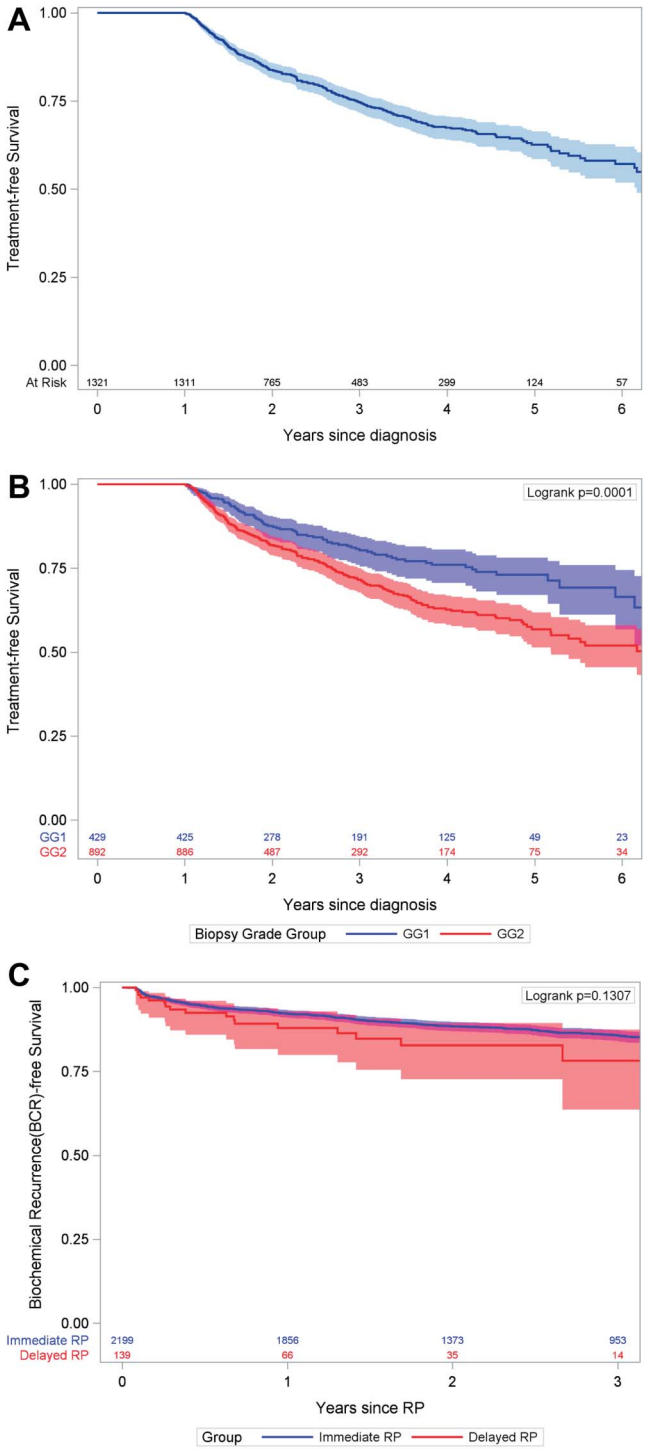

Figure 3. A Kaplan-Meier survival curve estimating treatment-free survival for patients on active surveillance. B, Kaplan-Meier survival curves estimating treatment-free survival for Grade Group (GG) 1 and GG2 patients on active surveillance. C, Kaplan-Meier survival curves estimating time to biochemical recurrence-free survival for men with favorable intermediate-risk prostate cancer undergoing immediate and delayed radical prostatectomy (RP).

stressed the use of an early confirmatory test within 6 months of diagnosis to support shared decision making.[19] This additional datapoint and further risk stratification may offer assurances and increase confidence that the patient is appropriate for AS.[20]

Table 3. *Multivariable Logistic Regression Model of Factors Associated With Adverse Pathology*

	OR	95% CI	*P* value
Radical prostatectomy			< .0001
Immediate	Reference	Reference	
Delayed	2.14	(1.48, 3.10)	
Race			.835
White	Reference	Reference	
Black	0.92	(0.69, 1.22)	
Other	0.85	(0.48, 1.51)	
Unknown	1.07	(0.77, 1.49)	
Charlson index			.364
0	Reference	Reference	
1	1.05	(0.81, 1.35)	
≥2	1.25	(0.92, 1.70)	
Family history			.467
No	Reference	Reference	
Yes	0.89	(0.73, 1.08)	
Unknown	0.93	(0.62, 1.39)	
Biopsy Gleason grade			.018
GG1	Reference	Reference	
GG2	1.58	(1.08, 2.30)	
Clinical tumor stage			.002
T1	Reference	Reference	
T2	1.49	(1.16, 1.92)	
Practice type			.562
Private/community	Reference	Reference	
Academic	1.00	(0.65, 1.53)	
Hybrid	1.15	(0.86, 1.54)	
Age (per 10-year increase)	1.21	(1.05, 1.38)	.008
PSA (log)	1.87	(1.46, 2.40)	< .001
No. positive cores (per 1-core increase)	0.94	(0.89, 1.00)	.060
Maximum percent cancer involvement of an individual core (per 10% increase)	1.13	(1.08, 1.17)	< .001

Abbreviations: CI, confidence interval; GG, Gleason Grade; OR, odds ratio, PSA, prostate specific antigen; T, tumor stage.

Among men choosing AS in the MUSIC cohort, most men remained treatment-free 5 years after diagnosis. This is similar to other AS cohorts reporting approximately half of men with FIRPC or GG2 disease on AS will transition to treatment between 5 and 10 years after diagnosis.[10,21-24] Importantly, regarding the oncologic safety of AS in men with FIRPC, we noted a larger proportion of men undergoing delayed RP had adverse pathology (AP; 46% vs 32%), similar to the incidence of AP seen among men with GG2 prostate cancer undergoing delayed RP in the Canary PASS cohort (53%).[10] While AP is a convenient intermediate endpoint for patients undergoing delayed RP, it likely does not reflect the absolute oncologic risk of the patient after RP. Although most men with metastasis and/or death from prostate cancer will have AP at RP, the converse is not true: most men with AP will not develop metastasis or die of prostate cancer.[5,11,25] In our study, men undergoing delayed RP had a similar risk of short term BCR as men undergoing immediate RP. Encouragingly, we did not see a strong signal that men who underwent delayed RP had notably worse oncologic outcomes, suggesting many men with FIRPC will not lose their window of cure and will have similar outcomes to men undergoing up-front treatment.

Much as we would expect patients undergoing radical therapy for FIRPC to have worse outcomes compared with LR prostate cancer, it is not surprising that men with FIRPC undergoing AS are at an increased risk for worse outcomes compared with men with LR prostate cancer on AS as shown in previous studies.[10,22] A novel strength of this analysis is comparing men with FIRPC undergoing up-front treatment vs AS, as this mimics the decision a patient will face clinically shortly after diagnosis: "Am I worse off if I avoid or delay my treatment?" This clinical uncertainty likely underpins the noted variability seen in the use of AS for men with FIRPC seen in this study.

These data and similar studies from other groups on the use of AS for select men with FIRPC are encouraging that many men can safely avoid treatment for years. Given current diagnostic and technological limitations, there is some overtreatment or undertreatment that will exist in the management of FIRPC. Are we comfortable overtreating many to avoid undertreating the few (such as the 8% more men which may experience BCR after a delayed RP compared with immediate RP as in this study) or are we more comfortable undertreating a few to avoid overtreating the many (such as the >50% of men who remain on AS 5 years after diagnosis)?

Our study has limitations inherent to an observational study. First, patients were not randomized and selection bias may underpin these results. Second, short-term follow-up limits our ability to make a longer-term assessment of oncologic safety. Third, follow-up testing type and interval of testing on AS was not standardized. Fourth, criteria for progression from AS to treatment were at the discretion of the patient and physician. Fifth, MUSIC is a surgical registry with limited follow-up information on patients undergoing radiation or ablative therapies after initial AS. We are limited to comparing immediate vs delayed treatment after AS in the surgical subset of this cohort. Sixth, men who are on AS at last follow-up remain at risk to undergo future treatment and the association of treatment delay with BCR in this population cannot be assessed, which may be a source of bias. Despite these limitations, the present study is one of the largest experiences with AS for men with FIRPC and may be useful to patients and physicians as they consider the risks and benefits of management options.

CONCLUSIONS

The use of AS for FIRPC increased from 13% to 45% during the 9-year study period. There was notable variability in the use of AS by contributing practice. Patients undergoing AS with FIRPC did well on AS with >60% remaining free of treatment at 5 years after diagnosis. Among men undergoing RP, short-term oncologic data appear safe as rates of BCR were similar between men undergoing immediate vs delayed RP. These data suggest AS is a reasonable option for appropriately selected men with FIRPC wishing to avoid or delay the side effects of radical treatment.

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EDITORIAL COMMENT

The authors present a review of the Michigan Urological Surgery Improvement Collaborative (MUSIC) experience and variability of uptake of active surveillance (AS) for favorable intermediate-risk prostate cancer (FIRPC) across practices. They also examine outcomes between men with FIRPC who chose upfront radical prostatectomy (RP) compared to those who underwent delayed RP on AS.

In approximately two-thirds of the 35 practices, the rate of AS in Grade Group (GG) 2 patients is under 25%. In 5 of the 35 practices, AS is used in 40%-50% of GG2 patients. This latter number is surprisingly high. The MUSIC group has published their experience with use of confirmatory tests such as repeat biopsy, MRI, and/or genomic classifiers in low risk disease.[1] This high patient acceptance rate in GG2 FIRPC probably also requires innovative and intensive patient counseling processes. I am sure there are valuable lessons to be learned from these practices.

In addition to the 139 men who underwent delayed RP, there is a group of 180 men who had "other treatment." The outcomes of this group are not described as the registry does not track those men. It would be helpful to know about this group. There was a difference in adverse pathology between the immediate RP group (32%) and the delayed RP group (46%). If the "other treatment" group had more adverse features or perhaps less adverse, this could bias the pathology results of the delayed group.

With 3 years of follow-up, there was only an 8% difference in biochemical recurrence rates favoring immediate RP (22% vs 14%). This is reassuring, but perhaps not yet long enough to conclude that AS in GG2 is oncologically safe except for carefully selected patients. Nonetheless, these data may be useful for counseling our patients with GG2 FIRPC who are interested in AS and those facing long waiting lists. This is timely considering pandemic-related surgical backlogs.

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REPLY BY AUTHORS

We thank Dr Morash and appreciate his thoughtful comments. As Dr Morash notes, there is noticeable variability in the use of active surveillance (AS) in men with favorable intermediate-risk prostate cancer among contributing practices. We believe this reflects the clinical uncertainty regarding the optimal management strategy in this population. The high use of AS for men with Grade Group 2 disease in the Michigan Urological Surgery Improvement Collaborative likely indicates a general increasing comfort

with AS as well as broader acceptance of AS for certain men with favorable intermediate-risk prostate cancer among urologists in the Michigan Urological Surgery Improvement Collaborative.

As mentioned by Dr Morash, we are limited to studying short-term oncologic outcomes (risk of biochemical recurrence 3 years postoperatively) in the present study. We would note most biochemical recurrence events happen within 5 years of surgery and early biochemical recurrences tend to be more clinically meaningful and track with prostate cancer mortality compared with late biochemical recurrences.[1] For these reasons, we believe the results provided in the current analysis are still informative and clinically relevant. Although we note a small difference in biochemical recurrence rates 3 years postoperatively among those who had immediate vs delayed radical prostatectomy, importantly, this difference was not statistically significant. We agree that longer follow-up from this cohort is needed. We are nonetheless encouraged that these initial results do not show a strong signal suggesting that men who select AS and go on to have treatment will have compromised oncologic outcomes.

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