

# Comparison of Pathological Outcomes for Men with Low Risk Prostate Cancer from Diverse Practice Settings: Similar Results from Immediate Prostatectomy or Initial Surveillance with Delayed Prostatectomy

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**Purpose:** We compared pathological outcomes after radical prostatectomy for a population based sample of men with low risk prostate cancer initially on active surveillance and undergoing delayed prostatectomy vs those treated with immediate surgery in order to better understand this expectant management approach outside of the context of academic cohorts. We hypothesized that delays in surgery due to initial surveillance would not impact surgical pathological outcomes.

**Materials and Methods:** We performed a prospective cohort study of 2 groups of patients with NCCN low risk prostate cancer from practices in the Michigan Urological Surgery Improvement Collaborative, that is 1) men who chose initial active surveillance and went on to delayed prostatectomy and 2) men who chose immediate prostatectomy. Diagnoses occurred from January 2011 through August 2015. For these 2 groups we compared radical prostatectomy Gleason scores, and rates of extraprostatic disease, positive surgical margins, seminal vesicle invasion and lymph node metastases.

**Results:** During a median followup of 506 days 79 (6%) of 1,359 low risk men choosing initial surveillance transitioned to prostatectomy. Compared to those treated with immediate prostatectomy (778), men undergoing delayed surgery were more likely to have Gleason score 7 or greater disease (69.2% vs 48.8%, respectively,  $p=0.004$ ), but were no more likely to have positive margins, extraprostatic extension, seminal vesicle invasion or lymph node metastases.

**Conclusions:** Patients with low risk prostate cancer who enter active surveillance have higher grade disease at prostatectomy compared to those undergoing

## Abbreviations and Acronyms

AS = active surveillance  
MRI = magnetic resonance imaging  
MUSIC = Michigan Urological Surgery Improvement Collaborative  
NCCN® = National Comprehensive Cancer Network®  
PSA = prostate specific antigen  
RP = radical prostatectomy

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immediate surgery. However, the lack of difference in other adverse pathological outcomes suggests preservation of the window of curability.

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**Key Words:** neoplasms, prostate, prostatic neoplasms, watchful waiting, treatment outcome

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ACTIVE surveillance for prostate cancer is an expectant management strategy that aims to address concerns about overtreatment by deferring upfront local therapy (eg surgery or radiation) in favor of close clinical monitoring, including followup PSA testing coupled with intermittent biopsy and/or imaging. There is a growing body of evidence indicating that a substantial number of appropriately selected patients can delay or avoid treatment and associated morbidity without adversely impacting cancer related outcomes.<sup>1-5</sup> Accordingly, several recent reports indicate that the use of AS is increasing in varied practice settings.<sup>6,7</sup>

Despite encouraging study results and the more broad use of AS, the impact of AS applied at scale across diverse populations is less well understood. Notably, when promising academic findings are translated to more general clinical strategy, the outcomes are not always equivalent.<sup>8</sup> In the face of increasingly rapid adoption, there has been little investigation of AS outcomes when used outside of academic centers. It is important to determine whether results from more varied clinical settings will differ from those already achieved among more standardized academic cohorts. Given the protracted course of most prostate cancer cases,<sup>9</sup> appropriate survival information from diverse practice settings may not be available for many years. As such data accumulate, comparisons of more intermediate outcomes between patients on AS and those receiving definitive local therapy may allow for earlier insight regarding the implications of this approach for cancer control.

In this context we examined pathological outcomes following RP for patients with low risk prostate cancer who underwent immediate surgery vs initial AS with delayed prostatectomy in the diverse academic and community practices comprising MUSIC. Once available, these data will provide a better understanding of the impact of AS on immediate cancer control outcomes in real-world practice settings. We hypothesized that delays in surgery due to initial surveillance would not impact surgical outcomes.

## MATERIALS AND METHODS

### Data Source

The Michigan Urological Surgery Improvement Collaborative was established in 2011 in partnership with Blue

Cross Blue Shield of Michigan. The quality improvement collaborative currently comprises 42 diverse community and academic urology practices representing nearly 85% of the urologists in the state.

For all men seen in MUSIC practices with newly diagnosed prostate cancer, trained data abstractors prospectively enter a standardized set of demographic and clinicopathological data elements related to diagnosis, treatment and followup care into a web based clinical registry. Prior reports have described MUSIC's data quality control activities, including annual data audits at each practice and validation analyses based on insurance claims.<sup>7,10</sup> Each MUSIC practice obtained an exemption or approval for collaborative participation from a local institutional review board.

### Patients

The cohort for this study included 3,288 patients in the MUSIC registry diagnosed with low risk prostate cancer according to NCCN criteria (ie Gleason score 6 or less, PSA less than 10 ng/ml and clinical stage T2a or less) from January 2011 through August 2015.<sup>11</sup> Patients were excluded if longitudinal followup was outside of a MUSIC practice (430), or if primary management after diagnosis was something other than RP or AS (721). The 2 groups of interest we defined for the comparisons in this analysis were men who underwent initial AS with delayed RP and men who underwent immediate RP.

### Outcomes

For patients on initial AS we reported details of followup during surveillance, including the frequency of repeat PSA testing, changes in PSA and the frequency of repeat prostate biopsy. We supplemented data from the registry by using retrospective chart review to identify the reasons for transitions in management from AS to RP. Our primary outcomes included the adverse surgical pathology outcomes of Gleason score 7 or greater, positive surgical margins, extracapsular extension, seminal vesicle invasion and lymph node metastases.

### Statistical Analyses

We first performed univariate comparisons of demographic and cancer specific characteristics for patients undergoing immediate RP vs those on initial AS with delayed surgery. We then compared RP pathological outcomes for the same 2 groups. In addition, we performed subgroup analyses of patients meeting NCCN very low risk criteria (ie clinical stage T1c, Gleason score 6 or less, PSA less than 10 ng/ml, less than 3 positive biopsy cores, 50% or less cancer in any core and PSA density less than 0.15 ng/ml/gm), which are included.<sup>11</sup>

Wilcoxon rank sum tests were used to compare continuous measures while chi-squared and Fisher's exact tests were used for categorical outcomes. All statistical

testing was performed using Stata® v.14 at the 5% significance level.

**RESULTS**

We identified 2,858 men diagnosed with NCCN low risk prostate cancer and continuously followed in a MUSIC practice during the study period. Among this group 778 (27.2%) patients underwent immediate RP while AS was the primary strategy for 1,359 (47.6%) patients. There were 721 patients (25.2%) excluded from further analysis due to another primary strategy (radiation 241, watchful waiting 161, primary androgen deprivation 27, cryoablation 12 and primary treatment decisions yet to be documented after diagnosis 280).

After a median followup of 506 days (IQR 280–793) 79 of the men (5.8%) who initially entered AS transitioned to RP, 40 (2.9%) went on to receive radiation and 1 received cryotherapy, while 1,239 (91.2%) remained on surveillance. In the group eventually undergoing surgery 47 of 79 (59.5%) underwent at least 1 repeat biopsy while on surveillance and this rate was significantly higher than the repeat biopsy rate for those remaining on AS (389 of 1,239 [31.4%],  $p < 0.001$ ).

As highlighted in the table, patients choosing immediate RP were younger at diagnosis (median age 60.4 vs 64.1 years,  $p < 0.001$ ) and more commonly had clinical stage T2a disease (14.5% vs 5.1%,  $p = 0.02$ ). There were no differences in median PSA or PSA density at diagnosis, but men in the initial AS group had fewer positive cores on diagnostic biopsy (median 1 vs 2,  $p < 0.001$ ), lower

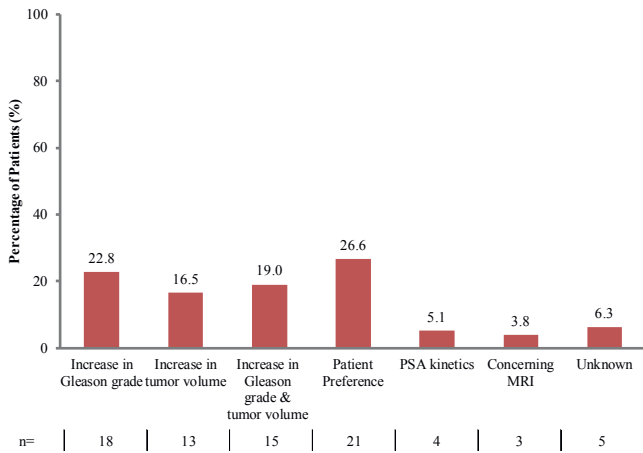
maximum percent involvement of the most involved biopsy core containing cancer (10.0% vs 20.0%,  $p = 0.001$ ) and more frequently met very low risk criteria (see table). MRI was used in the interval between diagnosis and surgery for 6 men (7.6%) in the initial AS group vs 13 (1.7%) in the immediate RP group ( $p < 0.001$ ). The rate of use of other novel diagnostics (eg genomic testing) was not measured. The median time from diagnosis to surgery was 404 days in the initial AS group, which was significantly longer than the median of 79 days in the initial RP group ( $p < 0.001$ ).

For the group of men who entered AS but later transitioned to RP a median of 2 PSA tests (IQR 1–4) was performed between diagnosis and RP. Median change in PSA from diagnosis to immediately before treatment was +0.9 ng/ml (IQR –0.5 – +2.1). For patients undergoing repeat biopsy the median time to repeat biopsy was 353 days from diagnosis (IQR 202–399). Figure 1 summarizes the reasons for transition from AS to RP. The majority of patients (58.3%) moved on to RP after followup biopsy reclassified tumor grade and/or volume.

In terms of pathological outcomes at radical prostatectomy, patients who underwent initial AS with delayed RP were more likely to have a pathological Gleason score of 7 or greater (54 men [69.2%] vs 370 [48.8%] undergoing immediate RP,  $p = 0.004$ , fig. 2, A). Despite this more frequent upgrading, there was no increased likelihood of extraprostatic disease, positive surgical margins or seminal vesicle invasion for patients who underwent RP after a period of surveillance (fig. 2, B). Two patients (0.3%) in the immediate RP group had positive lymph

*Characteristics of patients undergoing immediate RP vs initial AS with delayed RP*

	Immediate RP		Initial AS		p Value
No. pts	778		79		
No. practices with at least 1 pt in group	34		20		
Median pt age (IQR)	60.4 (54.9–65.3)		64.1 (59.7–68.0)		<0.001
Median kg/m <sup>2</sup> body mass index (IQR)	28.1 (25.6–31.3)		27.8 (25.7–30.8)		0.93
No. race (%):					
Caucasian	616 (79.2)		62 (78.5)		0.97
African-American	80 (10.3)		8 (10.1)		
Other	22 (2.8)		2 (2.5)		
Unknown	60 (7.7)		7 (8.9)		
No. Charlson comorbidity index (%):					
0	606 (77.9)		55 (69.6)		0.17
1	114 (14.6)		14 (17.7)		
2+	58 (7.5)		10 (12.7)		
Median ng/ml PSA (IQR)	4.8 (3.7–6.1)		5.1 (4.1–6.3)		0.08
Median cm <sup>3</sup> prostate vol (IQR)	36.0 (26.0–49.8)		38.6 (28.0–52.6)		0.25
Median ng/ml/gm PSA density (IQR)	0.13 (0.09–0.18)		0.13 (0.09–0.18)		0.77
Median max % involvement of any pos core (IQR)	20.0 (9.0–40.0)		10.0 (5.0–26.0)		0.001
Median pos cores (IQR)	2 (1–4)		1 (1–3)		<0.001
Median cores obtained on diagnostic biopsy (IQR)	12 (12–12)		12 (12–12)		0.54
No. clinical T stage (%):					
Any T1	665 (85.5)		75 (94.9)		0.02
T2a	113 (14.5)		4 (5.1)		
No. meeting very low risk criteria (%)	192 (24.7)		30 (38.0)		0.01
Median days diagnosis to RP (IQR)	79 (60–109)		404 (250–505)		<0.001



**Figure 1.** Reasons for transition to RP among men initially entering AS. All increases in Gleason grade or tumor volume were determined on followup surveillance biopsy.

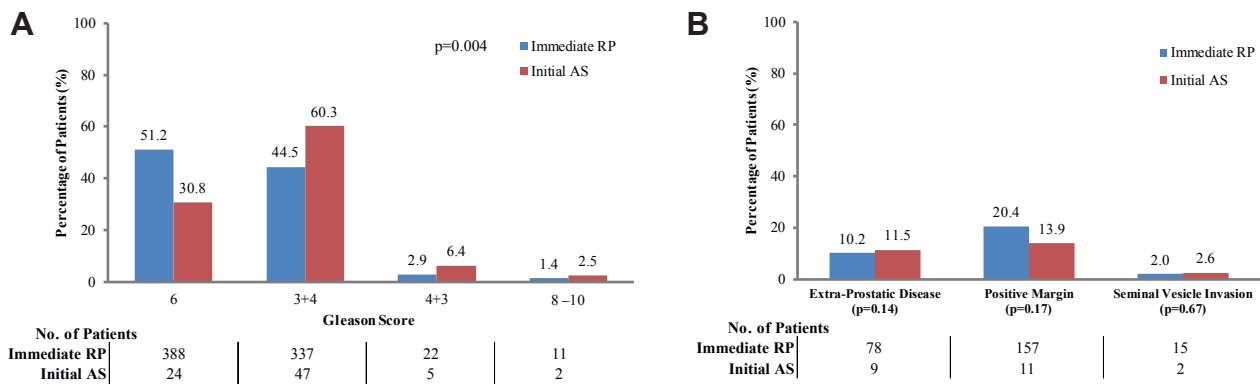
nodes at surgery. Nodal involvement was not identified for any patients in the initial AS cohort, and there were no differences in the rate of lymph node dissection across groups with 386 (49.6%) in the immediate RP group and 43 (54.4%) in the initial AS group undergoing dissection ( $p=0.15$ ). There were no nonnodal metastases or cancer related deaths in either group.

A subgroup analysis compared pathological outcomes for the subset of men from the immediate RP and initial AS groups meeting NCCN very low risk criteria. There were 192 men in the immediate RP group and 30 men in the initial AS group who met these criteria. Similar to the primary analysis, patients who underwent RP after initial AS more often had a Gleason score of 7 or more at RP (19 men [65.6%] vs 62 [33.3%] in the immediate RP group,  $p=0.001$ ), but were no more likely to have other adverse pathology (fig. 3).

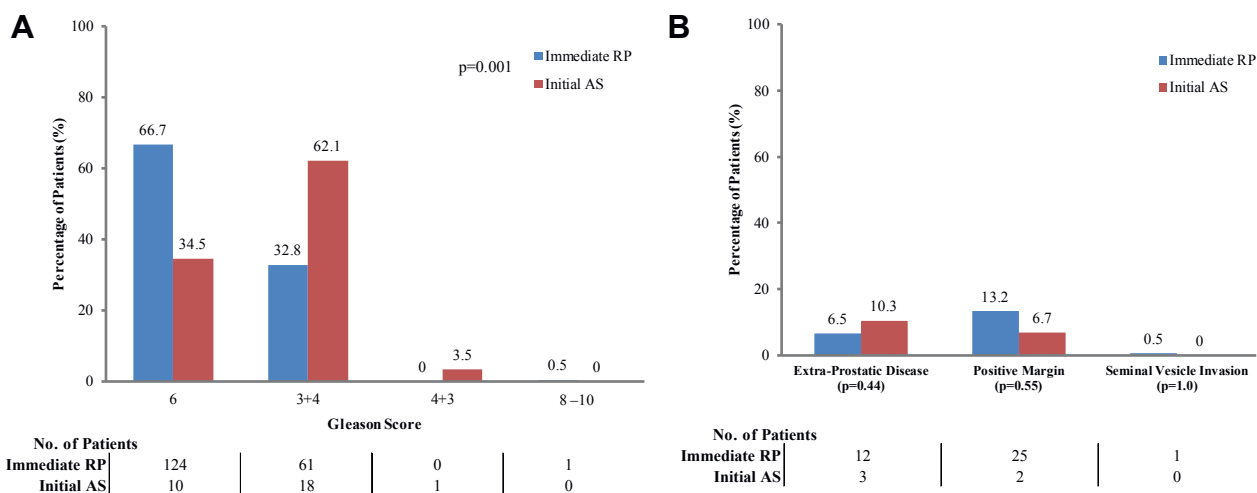
## DISCUSSION

Among a large sample of men with NCCN low risk prostate cancer treated at academic and community urology practices across Michigan, 48% were initially placed on AS and 27% were treated with immediate RP. Of those starting on AS 6% transitioned to treatment with RP after a median followup of 506 days. The most common reason for proceeding with treatment was pathological evidence of higher grade or higher volume tumor on followup biopsy. Compared to patients undergoing immediate RP, men who had surgery after a period of initial AS were more likely to have a Gleason score of 7 or higher in the surgical pathology specimen, but no more likely to have extraprostatic tumor extension, seminal vesicle invasion, positive surgical margins or lymph node metastases. Findings were similar in subgroups with NCCN very low risk disease.

Our findings build on previous reports from several academic medical centers. Investigators at Johns Hopkins compared surgical pathology for patients undergoing delayed RP to those choosing immediate surgery and found no differences in Gleason score, the likelihood of nodal metastases or other adverse pathological features.<sup>3</sup> Other large single institution series have reported similar surgical pathology outcomes with immediate vs deferred prostatectomy after accounting for upgrading on surveillance biopsies performed before surgery.<sup>1,12</sup> In our cohort the rate of Gleason upgrading to primary pattern 4 or greater was 4.3% for the immediate surgery group and 8.9% for the delayed RP group. Similar rates of 5% for immediate RP vs 12% for delayed RP were reported in a cohort from the University of California.<sup>1</sup> However, Johns Hopkins has reported significantly higher rates of primary pattern 4 or more at RP (14% for immediate RP and 20% for delayed RP).<sup>3</sup> It is unclear if this variation represents differences in patient risk in



**Figure 2.** Comparison of pathological Gleason score (A) and adverse pathological parameters (B) for NCCN low risk patients undergoing immediate RP vs initial AS with delayed RP (778 for immediate RP and 79 for initial AS). Patients with missing data excluded for percentage calculations.



**Figure 3.** Comparison of pathological Gleason score (A) and adverse pathological parameters (B) for NCCN very low risk patients undergoing immediate RP vs initial AS with delayed RP (192 for immediate RP and 30 for initial AS). Patients with missing data excluded for percentage calculations.

the Hopkins cohort unappreciated by clinical stratification, differences in pathological reporting or some other phenomenon. Consistent with our findings, the recently published multi-institutional Canary PASS study reported Gleason score upgrading to 7 or greater in 80% of patients with NCCN very low and low risk tumors who transitioned from AS to radical prostatectomy. Only 33% of patients had other adverse surgical pathology.<sup>13</sup> The consistency of results from these academic cohorts and the broader population of patients treated at diverse MUSIC practices provide reassurance around the short-term safety of active surveillance as it diffuses from selected academic centers to the broader urological community.

This analysis should be considered in the context of several limitations. The duration of followup was somewhat short, and pathology outcomes from prostatectomy represent only an intermediate end point in the natural history of prostate cancer. Therefore, longer term followup of the MUSIC cohort will be important to evaluate for differences in biochemical recurrence, development of metastatic disease and other cancer control outcomes. Nonetheless, adverse surgical pathology outcomes are relevant to consider because they are associated with more frequent recurrence and potential use of adjuvant treatments.<sup>14,15</sup> In addition, AS followup regimens were left to the discretion of managing urologists, yielding variation in the frequency of repeated PSA and biopsy evaluations across patients and providers in our cohort. Although such variable practice patterns may impact the probability of transitioning to other treatments, it remains reassuring that pathological outcomes across the study groups were similar despite heterogeneity

in surveillance regimens. Given minor cross-group differences in biopsy tumor volume, clinical T stage and proportion of patients meeting very low risk criteria, all favoring slightly lower baseline risk in the initial AS group, it is possible there is some confounding of measured outcomes due to baseline differences (see table). Although this deserves mention, our suspicion is that the statistically significant differences likely are of minimal clinical impact given the magnitude of these differences is very small.

These limitations notwithstanding, our findings have important implications in the context of more widespread use of AS. In a cohort that may more closely estimate the expected outcomes for broad populations of men entering AS, we found that despite having a greater proportion of Gleason 7 cancers, other pathological indicators of local disease progression were no more common in men who underwent prostatectomy after a surveillance period. Although the time on surveillance delayed surgery, the lack of stage migration in the initial AS group suggests that deferred treatment does not appear to diminish the curative potential of more aggressive therapy if deemed necessary in followup. Although still early in the history of this cohort, it is also encouraging that 91% of patients choosing initial surveillance have not transitioned to other therapy. Greater use of AS has likely limited over-treatment for many of these men in Michigan.

Moving forward, continued followup of patients in the MUSIC registry who are on AS will allow us to examine important, longer term cancer control outcomes. In addition, the high level of provider engagement and quality improvement focus of the collaborative will facilitate timely changes in practice



patterns in the event that adverse outcomes are identified for patients on longer term surveillance. External validation of these results from other large population based cohorts would be valuable.

It is also important to optimize the actual implementation of AS. Within the collaborative, specific initiatives are under way to improve patient selection for AS, to develop tailored surveillance pathways that take into account patient preferences for different monitoring regimens and outcomes, and to define the optimal role of novel diagnostics (eg MRI, genomics) in the selection and monitoring of patients on AS. Given that the majority of conversions to surgery in this cohort were driven by a change in biopsy findings and also appreciating that there was nearly a 30% difference in the rate of repeat biopsy for patients on AS who went on to surgery vs those who did not, focusing on decreasing barriers to repeat biopsy is a key priority. Similar work is ongoing at many other centers.<sup>16–20</sup> As this collective knowledge develops, more precise application of AS when appropriate and avoidance of AS when inappropriate should further mitigate risk and maximize benefits for men diagnosed with early stage prostate cancer.

## CONCLUSIONS

Compared to similar men who underwent immediate prostatectomy, men with low risk prostate cancer who chose AS for primary management and went on to delayed prostatectomy had more frequent upgrading to Gleason 7 or higher but no increases in other measures of local disease burden. The absence of stage migration indicates that appropriately selected men choosing AS in diverse practice settings maintain similar opportunities for cure even if more aggressive treatment is initiated after a period of delay.

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## EDITORIAL COMMENTS

Auffenberg et al describe pathological outcomes for men with low/very low risk prostate cancer treated with immediate or delayed RP after a period of AS. These results, from a statewide collaborative that includes many community hospitals, offers beneficial insight into real-world practice over the current, largely academic AS series. The authors found no differences in many oncologic outcomes between the 2 groups but a higher rate of Gleason 7 tumors in the delayed RP group. Confirmatory biopsy identified most Gleason 7 tumors that were presumably not sampled at initial diagnosis. We can say that for low/very low risk disease, delayed treatment (median 506 days) has no apparent negative pathological consequences in well surveilled men. However, the reasons why patients

Whether evaluating medications, surgical techniques or clinical management strategies, results from strict, protocol driven studies performed in isolated laboratory or academic settings are not always more broadly generalizable. Auffenberg et al evaluated data from MUSIC, a multicenter quality registry in Michigan, to determine if pathological outcomes for patients on active surveillance treated with delayed radical prostatectomy are comparable to those who undergo immediate surgery. Not only did the authors demonstrate similar proportions of adverse pathological staging in those 2 groups, but Gleason upgrading was in the range of outcomes reported from large protocol based cohorts at the

came off AS to undergo treatment deserves further attention, as 21 patients (26.6%) preferred RP rather than further AS, presumably due to anxiety. While this was the third most common reason for treatment after an increase in grade and volume, it suggests a need to improve counseling and shared decision making strategies to assuage prostate cancer related anxiety. Thus, we congratulate the authors on a large, multicenter work that helps us identify our strengths and generates further direction for treating our patients.

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University of California-San Francisco and Johns Hopkins University (references 1 and 3 in article).

These results support the real-world applicability of active surveillance for men diagnosed with low risk prostate cancer across a diverse spectrum of urology practices. From here, an assessment of the long-term outcomes and impact of novel risk stratification strategies (eg multiparametric MRI, genomic testing) within this quality collective will be eagerly anticipated.

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