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Comparison of pathologic 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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Abstract

Purpose—We compare pathologic outcomes following radical prostatectomy for a population-based sample of men with low-risk prostate cancer managed with initial active surveillance and delayed prostatectomy versus 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.

Material and Methods—We performed a prospective cohort study of two groups of patients with National Comprehensive Cancer Network low-risk prostate cancer from practices in the Michigan Urological Surgery Improvement Collaborative (MUSIC): men who chose initial active surveillance and went on to delayed prostatectomy and those who chose immediate prostatectomy. Diagnoses occurred from January 2011 through August 2015. For these two groups, we compared radical prostatectomy Gleason scores, and rates of extra-prostatic disease, positive surgical margins, seminal vesicle invasion, and lymph node metastases.

Results—During median follow-up of 506 days, 79 (6%) of 1,359 low-risk men choosing initial surveillance transitioned to prostatectomy. Compared to those treated with immediate prostatectomy (n=778), men undergoing delayed surgery were more likely to have Gleason score 7 (69.2% vs 48.8% respectively, p=0.004), but no more likely to have positive margins, extra-prostatic extension, seminal vesicle invasion, or lymph node metastases.

Conclusions—Patients with low risk prostate cancer that enter active surveillance have higher grade disease at prostatectomy compared to those undergoing immediate surgery. However, the lack of differences in other adverse pathologic outcomes suggests preservation of the window of curability.

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Keywords

cancer; prostate; prostate neoplasms; active surveillance; treatment outcome

Introduction

Active Surveillance (AS) for prostate cancer is an expectant management strategy that aims to address concerns about overtreatment by deferring upfront local therapy (e.g. surgery or radiation) in favor of close clinical monitoring, including follow-up prostate specific antigen (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.¹⁻⁵ Accordingly, several recent reports indicate that utilization of AS is increasing in varied practice settings.^{6,7}

Despite encouraging study results and the more broad utilization 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.⁸ In the face of increasingly rapid adoption, there has been little investigation of AS outcomes when utilized 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,⁹ appropriate survival information from diverse practice settings may not be available for many years. As such data accumulates, comparisons of more intermediate outcomes between patients undergoing 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 radical prostatectomy (RP) for patients with low-risk prostate cancer who underwent immediate surgery versus initial AS with delayed prostatectomy within the diverse academic and community practices comprising the Michigan Urological Surgery Improvement Collaborative (MUSIC). Once available, these data will provide 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 clinicopathologic data

elements related to the diagnosis, treatment, and follow up 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.^{7,10} 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 (i.e. Gleason score ≤ 6 , PSA <10 ng/mL, and Clinical Stage $\leq T2a$)¹¹ from January 2011 through August 2015. Patients were excluded if longitudinal follow-up was outside of a MUSIC practice ($n=430$), or if primary management following diagnosis was something other than RP or AS ($n=721$). We defined two groups of interest for the comparisons in this analysis: men who underwent initial AS with delayed RP and men who underwent immediate RP.

Outcomes

For patients undergoing initial AS, we report details of follow-up during surveillance, including the frequency of repeat PSA testing, changes in PSA levels, 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 following adverse surgical pathology outcomes: Gleason score ≥ 7 , positive surgical margins, extra-capsular 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 versus those undergoing initial AS with delayed surgery. We then compared RP pathologic outcomes for the same two groups. Additionally, we performed sub-group analyses of patients meeting NCCN very-low risk criteria (i.e. clinical stage T1c, Gleason score ≤ 6 , PSA <10 ng/mL, <3 positive biopsy cores, 50% cancer in any core, and PSA density <0.15 ng/mL/g)¹¹ which are included.

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 (StataCorp, College Station, TX, USA) 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. AS was the primary management strategy for 1,359 (47.6%) patients; 721 patients (25.2%) were excluded from further analysis due to receiving another primary management (241 received radiation, 161 watchful waiting, 27 primary

androgen deprivation, 12 cryoablation, and primary treatment decisions were yet to be documented after diagnosis for 280 men).

After median follow-up of 506 days (IQR 280-793 days), 79 of the men (5.8%) that 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 receiving surgery, 47 of 79 men (59.5%) received at least one repeat biopsy while on surveillance and this rate was significantly higher than the re-biopsy rate for those remaining on AS (389 of 1,239 (31.4%) ($p<0.001$)).

As highlighted in Table 1, 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 (Table 1), 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 (Table 1). Magnetic resonance imaging (MRI) was utilized in the interval between diagnosis and surgery for 6 men (7.6%) in Initial AS group vs. 13 (1.7%) immediate RP patients; $p<0.001$. The rate of utilization of other novel diagnostics (e.g. genomic testing) was not measured. The median time from diagnosis to surgery was 404 days in the initial AS group; this was significantly longer than the median of 79 days in the initial RP group ($p<0.001$). (Table 1).

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

In terms of pathological outcomes at radical prostatectomy, patients that underwent initial AS with delayed RP were more likely to have a pathological Gleason score ≥ 7 (54 men (69.2%) vs 370 (48.8%) men undergoing immediate RP, $p=0.004$) (Figure 2). Despite this more frequent upgrading, there was no increased likelihood of extra-prostatic disease, positive surgical margins, or seminal vesicle invasion for patients that underwent RP after a period of surveillance (Figure 3). Two patients (0.3%) in the immediate RP group had positive lymph 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%) of immediate RP patients and 43 (54.4%) of initial AS patient undergoing a dissection ($p=0.15$). There were no non-nodal metastases or cancer related deaths in either group.

A sub-group analysis compared pathologic 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 above, patients who underwent RP after Initial AS more often had Gleason score of 7 or more at RP (19 men (65.6%) vs. 62 (33.3%) immediate RP patients; $p=0.001$), but were no more likely to have other adverse pathology (Figures 4 & 5).

Discussion

Among a large sample of men with NCCN low-risk prostate cancer treated in academic and community urology practices across Michigan, 48% were managed initially with AS, and 27% with immediate RP. Among those starting on AS, 6% transitioned to treatment with RP after median follow-up of 506 days. The most common reason for proceeding with treatment was pathological evidence for higher grade or higher volume tumor on follow-up 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 extra-prostatic 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 pathologic features.³ Other large single-institution series have reported similar surgical pathology outcomes with immediate versus deferred prostatectomy, after accounting for upgrading on surveillance biopsies performed prior to surgery.^{1,12} 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.¹ 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)³. It is unclear if this variation represents differences in patient risk in the Hopkins cohort unappreciated by clinical stratification, differences in pathologic reporting, or some other phenomenon. Consistent with our findings, the recently published multi-institutional Canary PASS study reported Gleason score upgrading to 7 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.¹³ The consistency between results from these academic cohorts, and the broader population of patients managed in diverse MUSIC practices, provides reassurance around the short-term safety of AS as it diffuses from selected academic centers to the broader urological community.

This analysis should be considered in the context of several limitations. First, the duration of follow-up is somewhat short, and pathology outcomes from prostatectomy represent only an intermediate end-point in the natural history of prostate cancer. Longer-term follow up of the MUSIC cohort will therefore 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 both more frequent recurrence and potential use of adjuvant treatments.^{14,15} Second, AS follow-up 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 pathologic outcomes across the study groups were similar despite heterogeneity in surveillance regimens. Third, given minor cross-group differences in biopsy tumor volume, clinical T stage, and proportion of patients meeting very-low risk criteria (Table 1) 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. 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 utilization of AS. Within 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 GS 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 follow-up. Although still early in 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 overtreatment for many of these men in Michigan.

Moving forward, continued follow-up of patients in the MUSIC registry that 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 underway 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 (e.g. MRI, genomics) in both the selection and monitoring of patients on AS. Given 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 AS patients who went on to surgery versus those who did not, focusing on decreasing barriers to repeat biopsy is a key priority. Similar work is ongoing at many other centers.¹⁶⁻²⁰ 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 management is initiated after a period of treatment delay.

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Key of Definitions for Abbreviations

AS	Active Surveillance
PSA	prostate specific antigen
RP	Radical Prostatectomy
MUSIC	Michigan Urological Surgery Improvement Collaborative

Figure 1. Reasons for transition to radical prostatectomy (RP) among men initially entering active surveillance (AS)

(PSA – prostate specific antigen; MRI – magnetic resonance imaging) All increases in Gleason grade or tumor volume were determined on follow-up surveillance biopsy

Figure 2. Comparison of pathological Gleason score for NCCN low-risk patients undergoing immediate RP versus initial AS with delayed RP (n=778 for immediate RP and 79 for initial AS)
Patients with missing data excluded for percentage calculations

Figure 3. Comparison of adverse pathologic parameters for NCCN low-risk patients undergoing immediate RP versus initial AS with delayed RP (n=778 for immediate RP and 79 for initial AS)
 Patients with missing data excluded for percentage calculations

Figure 4. Comparison of pathological Gleason score for NCCN very low-risk patients undergoing immediate RP versus initial AS with delayed RP (n=192 for immediate RP and 30 for initial AS)
Patients with missing data excluded for percentage calculations

Figure 5. Comparison of adverse pathologic parameters for NCCN very low-risk patients undergoing immediate RP versus initial AS with delayed RP (n=192 for immediate RP and 30 for initial AS)

Patients with missing data excluded for percentage calculations

Table 1

Characteristics of patients undergoing immediate radical prostatectomy (RP) versus initial active surveillance (AS) with delayed RP.

	Immediate RP	Initial AS	p value
No. of Patients	778	79	
No. of Practices with at least 1 patient in group	34	20	
Median Age (IQR) (years)	60.4 (54.9-65.3)	64.1 (59.7-68.0)	<0.001
Median Body Mass Index (IQR) (kg/m²)	28.1 (25.6-31.3)	27.8 (25.7-30.8)	0.93
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)	
Charlson Co-morbidity 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 PSA (IQR) (ng/mL)	4.8 (3.7-6.1)	5.1 (4.1-6.3)	0.08
Median Prostate volume (IQR) (cm³)	36.0 (26.0-49.8)	38.6 (28.0-52.6)	0.25
Median PSA density (IQR) (ng/mL/g)	0.13 (0.09-0.18)	0.13 (0.09-0.18)	0.77
Median of maximum % involvement of any positive core	20.0 (9.0-40.0)	10.0 (5.0-26.0)	0.001
Median No. pos cores	2 (1-4)	1 (1-3)	<0.001
Median No. cores obtained on diagnostic biopsy (IQR)	12 (12-12)	12 (12-12)	0.54
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 from Diagnosis to RP (IQR)	79 (60-109)	404 (250-505)	< 0.001

(IQR – interquartile range)